Diploma thesis

Comparison of clinical and pathological parameters between clinically localised prostate cancer diagnosed in the first biopsy and saturation-rebiopsy

Vergleich klinischer und pathologischer Parameter bei klinisch lokalisierten Prostatakarzinomen, welche in der Erstbiopsie bzw. Saturations-rebiopsie diagnostiziert wurden

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Robert C. Peteani

Matr.Nr.: 0211601

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Ao. Prof. Dr. med. Herbert Augustin

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Graz, im Juni 2008 ……

This work is dedicated to all patients, who suffered from this terrifying disease.

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Abstract

Comparison of clinical and pathological parameters between patients with clinically localised prostate cancer diagnosed in the first biopsy and saturation-rebiopsy

Robert C. Peteani, Marco Auprich, Karl Pummer and Herbert Augustin
Department of Urology, Medical University of Graz, Graz, Austria

Objective:
To compare clinical and pathological parameters between clinically localised prostate cancer (PC) diagnosed in the first biopsy and saturation-rebiopsy.

Patients and methods:
Between January 2005 and December 2007, a consecutive series of 428 men with clinically localised PC underwent retropubic radical prostatectomy (RRP) and pelvic lymphadenectomy at the Department of Urology, University Hospital of Graz, Austria. Patients with PC were diagnosed by first core-biopsy (group1) or by 24-core-saturation-rebiopsy (group 2). Clinical and pathological parameters were entered into a computer database and analysed using SPSS 14.0.

Results:
Overall, 256 patients were eligible for analysis. Men were separated into two groups. 201 patients with a mean age of 61.1 years were included in group 1. Group 2 consisted of 55 patients with a mean age of 61.7 years (P=0.633).The median serum PSA was 5.9 ng/mL in group 1 and 7.8 ng/mL in group 2 (P=0.372), respectively. The median PSA ratio was 11% in both groups (P=0.596). In the initial biopsy set the number of cores ranged between 6 and 12 (mean 8.6). In group 2 patients underwent between 1 and 8 rebiopsies (mean 2.5). 37.7% of cores in group 1 and 17.6% in group 2 were diagnosed with PC (P=0.000). 33.6% of DRE in group 1 and 10.6% in group 2 were suspicious (P=0.002). The present study showed exact agreement of needle biopsy Gleason Scores and RRP Gleason Score in 45.7% in group 1 and 51.9% in group 2. Under-grading in group 1 (47.2%) and in group 2 (34.6%) was more frequent than over-grading with 7.1% and 13.5%, respectively. Cohen's kappa coefficient was in group 1 0.250 and

0.356 in group 2. Kendall τ b coefficient confirmed low agreement in group 1 (0.390) as well as a moderate one in group 2 (0.496).

Conclusion:

Group 2 showed a decreased rate of positive cores, even though more prostatic tissue was taken. The majority of suspicious DRE was registered in patients with first core-biopsy. Cohen's kappa coefficient of Gleason Scores between biopsy specimen and RRP specimen was higher in group 2.

Key words:

Prostate Cancer, saturation-rebiopsy, first core-biopsy, Gleason Score.

Zusammenfassung

Vergleich klinischer und pathologischer Parameter bei Patienten mit klinisch lokalisierten Prostatakarzinomen, welche in der Erstbiopsie bzw. Saturations-rebiopsie diagnostiziert wurden

Robert C. Peteani, Marco Auprich, Karl Pummer und Herbert Augustin
Abteilung für Urologie, Medizinische Universität Graz, Graz, Austria

Ziel:
Vergleich klinischer und pathologischer Parameter bei klinisch lokalisierten Prostatakarzinomen (PC), welche in der Erstbiopsie bzw. Saturations-rebiopsie diagnostiziert wurden.

Patienten und Methoden:
Zwischen Jänner 2005 und Dezember 2007 wurde bei einer konsekutiven Gruppe von 428 Männern mit klinisch lokalisiertem PC eine radikale retropubische Prostatektomie (RRP), sowie eine pelvine Lymphadenektomie an der Universitätsklinik Graz, Abteilung für Urologie durchgeführt. Das PC wurde mit einer Feinnadel-Erstbiopsie (Gruppe 1) bzw. mit einer Saturations-rebiopsie (Gruppe 2) diagnostiziert. Die klinischen und pathologischen Daten wurden in eine Computerdatenbank eingegeben und mit SPSS 14.0 analysiert.

Ergebnisse:
Insgesamt 256 Patienten eigneten sich für eine Analyse. 201 Patienten mit einem Durchschnittsalter von 61 Jahren befanden sich in Gruppe 1. In Gruppe 2 waren 55 Patienten mit durchschnittlich 62 Jahren (P=0.633). Das mediane Serum PSA war 5.9 ng/mL in Gruppe 1 und 7.8 ng/mL in Gruppe 2 (P=0.372). Die mediane PSA-Ratio war in beiden Gruppen 11% (P=0.596). Die Anzahl der Zylinder bewegte sich bei den Erstbiopsien zwischen 6 und 12 (durchschnittlich 8.6). Patienten der Gruppe 2 hatten zwischen 1 und 8 Rebiopsien (durchschnittlich 2.5). In 37.7% der Zylinder in Gruppe 1 und in 17.6% in Gruppe 2 befand sich ein PC (P=0.000). 33.6% der DRE in Gruppe 1 und 10.6% in Gruppe 2 waren auffällig (P= 0.002). Diese Studie zeigte in 45.7% der Gruppe 1 und in 51.9% der Gruppe 2 eine exakte Übereinstimmung der Biopsie- und RRP-Gleason Scores. Ein “Under-

grading” in Gruppe 1 (47.2%) und in Gruppe 2 (34.6%) war häufiger als ein “Over-grading” mit 7.1% und 13.5%. Der Kappa Koeffizient nach Cohen war in Gruppe 1 0.250 und 0.356 in Gruppe 2. Der Rangkorrelationskoeffizient Kendall τ b bestätigte eine niedrige Übereinstimmung in Gruppe 1 (0.390), sowie eine moderate in Gruppe 2 (0.496).

Schlussfolgerung:

Gruppe 2 zeigte eine geringere Rate an positiven Zylindern, obwohl mehr Prostatagewebe entnommen wurde. Der Großteil an auffälligen DRE befand sich bei Patienten mit einer Erstbiopsie. Der Kappa Koeffizient nach Cohen der Gleason Scores zwischen Biopsie- und RRP-Präparaten war in Gruppe 2 höher.

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Glossary and abbreviation

ACTH	Adreno-Cortico-Tropic Hormone
ASAP	Atypical Small Acinar Proliferation
BPH	Benign Prostatic Hyperplasia
CT	Computed Tomography
CZ	Central Zone
DCO	Death Certificate Only
DHT	Dihydrotestosterone
DRE	Digital Rectal Examination
ED	Erectile Dysfunction
EBRT	External Beam Radiotherapy
FISH	Fluorescence-In-Situ-Hybridisation
HDR	High Dose Rate
HGPIN	High Grade Prostatic Intraepithelial Neoplasia
IIEF	International Index of Erectile Function
IPSS	International Prostate Symptom Score
LDR	Low Dose Rate
LGPIN	Low Grade Prostatic Intraepithelial Neoplasia
LH	Luteinising Hormone
LHRH	Luteinising-Hormone Releasing-Hormone
LUTS	Lower Urinary Tract Symptoms
MAB	Maximal Androgen Blockade
MRI	Magnetic Resonance Imaging
MRSI	Magnetic Resonance Spectroscopic Imaging
NK-cells	Natural Killer cells
NSAID	Non Steroidal Anti-Inflammatory Drugs
PAP	Prostatic Acid Phosphatase
PC	Prostate Cancer
PET	Positron Emission Tomography
PIN	Prostatic Intraepithelial Neoplasia
PSA	Prostate Specific Antigen
PSAD	PSA Density
PSMA	Prostate Specific Membrane Antigen

PZ	Peripheral Zone
RIS	Radio-Immuno-Scintigraphy
RRP	Radical Retropubic Prostatectomy
SPECT	Single Photon Emission Computed Tomography
STI	Sexual Transmitted Disease
TRUS	Trans-Rectal Ultrasound
TURP	Trans-Urethral Resection of the Prostate
TZ	Transition Zone
UICC	International Union Against Cancer
WHO	World Health Organisation

1 Introduction

Prostate Cancer is the most frequent malignant disease and represents the second cancer related cause of death in Austrian men under the age of 75. Accordingly, physicians and the health care system are confronted with the challenge to diagnose and treat PC timely. The incidence rate of PC increased in the past two decades, because of better diagnostic methods (e.g. PSA) and a higher prevalence of this malignancy (general aging of the male population). By contrast, the mortality rate stayed almost at the same level. A study from L.M. Franks' reported that 40% of men beyond middle-age developed latent PC and 9% of them presented a clinical manifest stage. Only 3 % of elderly men died with the disease and not of this ([1]).

Nowadays, the most common propagated diagnostic techniques in 45-50 year-old men are the digital rectal examination (DRE) and serum PSA testing. PSA is the most important parameter in the follow-up too.

Furthermore, prostatic fine-needle-core biopsy is the standard procedure in detecting PC, when DRE and PSA testing indicate malignancy. The classical systemic sextant biopsy by Hodge et al. was replaced by 8-, 10- and 12 -core biopsy, since studies certified a better significance as the sextant biopsy technique ([2]). A 24-core-saturation-rebiopsy is indicated after a negative prostatic biopsy set in case of clinical suspicion [high grade prostatic intraepithelial neoplasia (HGPIN), atypical small acinar proliferation (ASAP) as well as an increasing serum PSA level].

PC, a multifactorial disease, rarely shows characteristic symptoms. Therefore, a European screening study (ERSPC) demonstrated that screening may even lead to a quick diagnosis of PC. As a result, over-detection of insignificant PC might be its consequence ([3]).

Differences between clinical and pathological parameters could point to a diverse prognosis after curative therapy. Patients with PC diagnosed after several prostatic fine-needle-core biopsies, might have a smaller tumour volume and therefore a lower stage with a better prognosis. The aim of the present study was to compare clinical and pathological parameters between patients with clinically localised PC diagnosed in the first biopsy and saturation-rebiopsy in a consecutive series of 428 men from January 2005 to December 2007.

1.1 Anatomy of the prostate

1.1.1 Introduction

The prostate is located between the posterior side of the bladder and the rectum. Both spermatic ducts and seminal vesicles are surrounded by the rectovesical septum, which merges in the urinary bladder's fascia.

1.1.2 Form and Constitution

The prostate represents an adenomatous organ with smooth muscles enclosing the prostatic urethra. The gland of the prostate is built by several singular glands anastomosing into the prostatic part of the urethra as well as to both sides of the seminal colliculi. In general the prostatic shape looks like a walnut.

The apex of the prostate is directed downwards to the upper surface of the urogenital diaphragm and the prostatic base is building the bladder neck. The posterior side is in front of the rectum and the lateral sides are touched by the levator muscle. For clinical purposes the zonal anatomy of the prostate has replaced the systemical anatomy. According to the latter, the prostate is divided into lobes. The right and left lobe are connected in front of the urethra. This connection is called isthmus, or anterior lobe. A medial lobe is described between the prostatic urethra and ejaculatory ducts. The posterior lobe lies behind both ejaculatory ducts and is amenable for the digital rectal palpation. The prostate is fixed by the urethra and urogenital diaphragm as well as by the prostatic fascia and the puboprostatic ligaments. The prostatic consistency changes from strong, during the infantile to smooth in the adolescent age, getting stronger in older ages.

The seminal vesicles are embedded in the rectovesical septum. They are about 5 cm long and send off excretory ducts coalescing with the spermatic ducts to the ejaculatory ducts.

The ductus deferens enters the abdomen through the abdominal inguinal ring, surrounded by the spermatic cord. It follows the inferior epigastric vein and artery deep downwards on the lateral side of the pelvic wall and finally loops next to the seminal vesicles to the prostate, where it dilates to the ampulla of the ductus deferens, before both ducts enter the prostate. The prostate is vascularised similar to the urinary bladder by the inferior vesical artery and by medial rectal artery from

dorsal. The prostatic venous plexus (Plexus Santorini) is located above the ventral part of the prostate. The lower part of the bigger vesical prostatic plexus transfers venous blood to the internal iliacal vein.

There are several lymph nodes in the pelvic area. Internal iliacal and inferior gluteal lymph nodes follow the inferior vesicle and medial rectal artery. Next to the perineal flexure of the rectum are regional anorectal lymph nodes. Regional lymph nodes include pelvic, hypogastric, obturator and sacral lymph nodes. The pelvic plexus, containing sympathetic and parasympathetic bundles of nerves, is responsible for the vegetative innervation. It reaches the prostate as prostatic plexus and is situated mainly on both dorsolateral sides of the prostate. These nerve fibres are responsible for ED, when removed by RRP.

The seminal vesicles are vascularised by the inferior vesical arteries and by small branches of the medial rectal artery. The pelvic plexus is responsible for their innervation. The spermatic ducts are vascularised by the spermatic ducts arteries, followed by several lymph nodes in the way of the spermatic cord.

1.1.3 Zonal anatomy

The zonal anatomy is based on studies by McNeal and reflects the functional and oncological differences of prostatic areas ([4]). The prostate gland is divided into three zones: the peripheral zone, the transition zone and the central zone.

The peripheral zone (PZ) is the largest zone and contains 65% of the prostatic volume in young adults. It is situated on the posterolateral part of the prostate and extends from the apex to its base. Its histological characteristics are small acinar spaces and secretory epithelial cells.

The central zone (CZ) is the second largest zone and contains 25% of the prostatic volume. It is discharged by the ejaculatory ducts from dorsal and characterised by large acini with irregular contours as well as by low columnar cuboidal epithelial cells. The smooth muscles seem more compact than that of the PZ.

In the young adult, the transition zone (TZ) is the smallest zone and contains approximately 5-10% of the prostatic volume. It surrounds the urethra and the acini are similar to the ones of the PZ as well as the smooth muscles to these of the CZ.

1.2 Embryology

On the one hand the urorectal septum divides the cloaca in the anorectal canal and on the other hand in the urogenital sinus. This happens from the 4th to the 7th week of development.

The primitive urogenital sinus builds the urinary bladder, the prostatic part and the membranous part of the urethra. The phallic part of the urogenital sinus forms the male penile urethra.

The mesonephric ducts are getting closer and finally discharge into prostatic part of the urethra. They are building the ductus deferens, the ejaculatory ducts and the seminal vesicles.

The urethra's epithel is endodermic origin. It proliferates in the end of the 3rd month of development and builds buds, of which the prostate develops.

1.3 Physiology

1.3.1 Introduction

The secretions of the accessory sex glands dilute the sperm. They prevent from prostatitis by flushing urine and bacteria from the urethra. In addition, they buffer spermatozoa in the acidic vaginal milieu and give them energy for movement. Furthermore, the prostatic fluid maintains the sperm in a reversibly quiescent state.

1.3.2 Prostatic fluid

Prostatic fluid contains a lot of immunosuppressive components and protects the sperm from the female's immune system. Protecting components of the ejaculate are high proportions of natural killer cells (NK-cells), T-cells and CD8+ T-cells. These components hold off the intrusion of microorganism ascending from the urethra in the prostate gland.
The normal ejaculation volume is about 2-6mL ([5]) and contains 40-240 million ([5]) sperms per mL. Its pH amounts 6.5 ([5]), which is slightly acidic. No elsewhere in the human body are high rates of bivalent cations of Calcium 2+, Zinc 2+ and Magnesium 2+ as in the ejaculate. Proteins, such as PSA and prostatic acid phosphatase (PAP) may have immunoprotective function.

1.3.3 Neurophysiology of the prostate

The prostate has a dual innervation from the sympathetic and parasympathetic nerve system. The sympathetic nerves are responsible for the gland's contraction and secretion, the role of the parasympathic nerves is unclear.

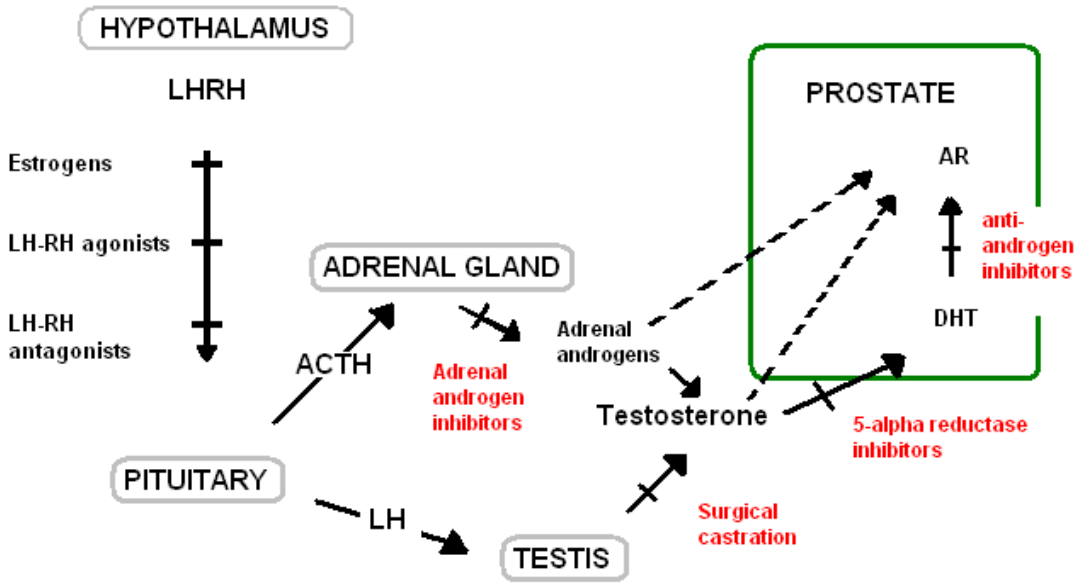
1.3.4 The role of androgens in the normal prostate

The prostate gland develops and grows under the influence of androgens. In the adolescence the prostate undergoes major enlargement, initiated at the beginning of the puberty by increasing testosterone levels. The size of the prostate during this time amounts about 20 grams and increases in the following decades.

The most important androgen is dihydrotestosterone (DHT). It is split up from testosterone by 5-alpha-reductase. DHT has a larger affinity to androgen receptors in the gland than testosterone. Furthermore, it stimulates the expression of proteins, especially of PSA.

Finally, the development of PC is induced and supported by several more factors, such as positive and negative growth factors and angiogenesis factors that make the prostate's pathophysiological mechanisms difficult to detect.

Figure 1 Hypothalamic-pituitary-testicular axis (modified from [6])



The Hypothalamic-pituitary-testicular axis is responsible for about 95% of androgen stimulus to the prostate. Only 5% of androgens originate from the adrenal glands. The hormone system is regulated by a negative feedback mechanism that works by releasing LHRH from the pituitary gland, influenced by gonadotropin-releasing hormone (GNRH) from the hypothalamus. Pituitary glands produce more of luteinising hormone (LH) and adrenocorticotropic hormone (ACTH) after stimulation of LHRH agonists. LH and ACTH stimulate the Leydig cells of the testis and the adrenal glands to produce testosterone and adrenal androgens, respectively.

1.4 Epidemiology and Aetiology

1.4.1 Introduction

PC is the most frequent malignant disease in Austrian men and represents the second cancer related cause of death under the age of 75. In the year 2004 PC was detected in about 5.500 men. In detail, the average incidence was 91.1/100.000 ([7]) and the mortality rate was 18.1 / 100.000 ([7]), respectively. For PC, the ratio of all malignant diseases adds up to 30% ([7]).

1.4.2 Incidence and mortality rates

Table 1 Incidence of prostate cancer, Austria 1983 – 2004 (modified from [7])

Prostate – Incidence of Cancer, Austria from 1983 – 2004									
Year	**absolute numbers[1])**			**Age-adjusted numbers[2])**			**Cumulative numbers[3])**		
	total	men	women	total	men	women	total	men	women
1983	-	1.787	-	-	37.7	-	-	3.4	-
1984	-	1.901	-	-	39.9	-	-	3.7	-
1985	-	1.966	-	-	41.4	-	-	3.8	-
1986	-	1.852	-	-	38.6	-	-	3.5	-
1987	-	1.992	-	-	41.7	-	-	3.9	-
1988	-	2.117	-	-	43.9	-	-	4.0	-
1989	-	2.317	-	-	48.5	-	-	4.8	-
1990	-	2.297	-	-	47.3	-	-	4.4	-
1991	-	2.284	-	-	46.4	-	-	4.2	-
1992	-	2.427	-	-	49.0	-	-	4.5	-
1993	-	2.743	-	-	55.2	-	-	5.4	-
1994	-	3.230	-	-	64.4	-	-	6.6	-
1995	-	3.548	-	-	69.6	-	-	7.3	-
1996	-	3.743	-	-	72.3	-	-	7.8	-
1997	-	4.087	-	-	77.9	-	-	8.6	-
1998	-	4.352	-	-	81.6	-	-	9.1	-
1999	-	4.638	-	-	85.5	-	-	9.7	-
2000	-	5.305	-	-	96.4	-	-	11.3	-
2001	-	5.302	-	-	94.5	-	-	11.2	-
2002	-	5.297	-	-	92.8	-	-	11.1	-
2003	-	5.789	-	-	99.6	-	-	12.0	-
2004	-	5.416	-	-	91.1	-	-	11.0	-
Q: STATISTIK AUSTRIA, Austrian Cancer Index (from 11.09.2007). 1) Malign invasive cases, incl. DCO-cases (Death Certificate Only). 2) each on 100.000 persons / men / women, standard population = WHO-world population, 2001. 3) risk of morbidity till age of 75 in percent.									

Since 1983, the total number of men diagnosed with PC raised from 1787 patients to 5416 in the year 2004. PSA testing was introduced around the year 1990, its more and more frequently use in clinical practise represents the major cause for an increasing detection rate.

Table 2 Mortality of prostate cancer, Austria 1983-2004 (modified from [7])

Prostate - Mortality, Austria from 1983 – 2004									
Year	**Absolute numbers**			**Age-adjusted numbers[1])**			**Cumulative numbers[2])**		
	total	men	women	total	men	women	total	men	women
1983	-	898	-	-	19.2	-	-	1.3	-
1984	-	903	-	-	19.3	-	-	1.3	-
1985	-	981	-	-	20.4	-	-	1.2	-
1986	-	995	-	-	20.4	-	-	1.3	-
1987	-	1.071	-	-	22.1	-	-	1.5	-
1988	-	1.012	-	-	20.8	-	-	1.4	-
1989	-	1.058	-	-	21.9	-	-	1.4	-
1990	-	1.110	-	-	22.3	-	-	1.3	-
1991	-	1.206	-	-	24.3	-	-	1.5	-
1992	-	1.139	-	-	22.7	-	-	1.3	-
1993	-	1.177	-	-	23.3	-	-	1.4	-
1994	-	1.088	-	-	21.2	-	-	1.3	-
1995	-	1.202	-	-	23.0	-	-	1.3	-
1996	-	1.170	-	-	22.2	-	-	1.3	-
1997	-	1.184	-	-	22.2	-	-	1.3	-
1998	-	1.139	-	-	21.1	-	-	1.2	-
1999	-	1.222	-	-	22.4	-	-	1.2	-
2000	-	1.229	-	-	21.7	-	-	1.2	-
2001	-	1.184	-	-	20.3	-	-	1.2	-
2002	-	1.138	-	-	19.1	-	-	1.2	-
2003	-	1.160	-	-	19.1	-	-	1.1	-
2004	-	1.139	-	-	18.1	-	-	1.0	-
Q: STATISTIK AUSTRIA, Austrian statistic of causes of death . 1) each on 100.000 persons / men / women, standard population = WHO-world population, 2001. - 2) risk of mortality till the 75th year of life in percent.									

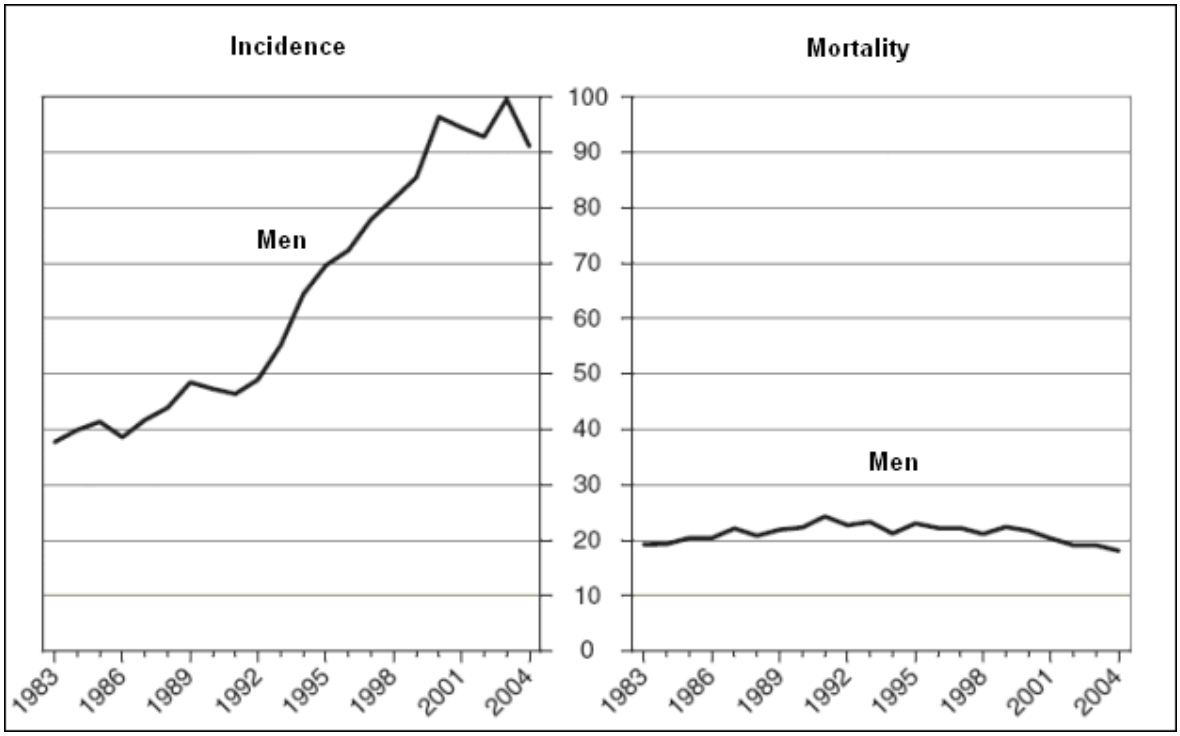
The absolute numbers of death cases raised a little bit from 898 patients in 1983 to 1.139 men in 2004, but the age-adjusted numbers went down from 19.2 /100.000 in 1983 to 18.1 /100.000 in the year 2004. The risk of death fell down from 1.3% to 1%, too.

Table 3 Incidence of prostate cancer stage, Austria 2002/2004 (modified from [7])

Prostate – Incidence of cancer stage, average (2002/2004)			
Tumour stages in %	**total**	**men**	**women**
Total	**-**	**100,0**	**-**
Carcinoma in Situ	-	0.3	-
Localised	-	59.0	-
Locally advanced	-	12.8	-
Disseminated	-	3.8	-
Unknown	-	19.8	-
DCO-cases[2])	-	4.2	-

In 2004, 59% of newly diagnosed PC showed clinically localised disease. Locally advanced disease was detected in 12.8% and 19.8% of patients were not classified.

Figure 2 Incidence and mortality rate in Austria between 1983 and 2004 (modified from [7])



Interestingly, the incidence of PC increased from 1983 to 2004, while the mortality rate stayed almost at the same level.

1.4.3 Risk factors and life style

The western nutrition, characterised by a high fat and low fibres intake, may stimulate the development of PC. Tomatoes, cereals, vegetables and soy, containing isoflavonoids as protective factors, might explain the low incidence in eastern Asia. Moreover, migrating populations tend to take on the incidence and risk of mortality of the host country, if they modify their life style, accordingly.
There exists some controversy of clinical significance for the development of PC for obesity, physical inactivity, occupation, environmental containments, cigarette smoking, alcohol drinking, sexual transmitted diseases and prostatitis.

Nutrition

Andersson et al. found in 1997 that the risk of mortality from PC was significant higher in all BMI categories than in the reference category ([8]).
In 2007, Wright et al. described a positive correlation between an increasing risk of death from PC and a higher BMI and adult weight gain, respectively. Furthermore, the authors could not testify a positive relation to an increasing incidence rate ([9]).
In contrast, Giovannucci et al. showed that energy restriction in the growth period lowers the height and therefore an increasing incidence of PC. Tallness was a marker of increased risk while even greater adiposity between the ages of 5 and 20 years was associated with a lower risk of PC ([10]).
In Western Countries, where the intake of animal fats, proteins and processed carbohydrates are high, the total intake of red meat is positively associated with PC-mortality ([11]).
Tomato based foods, containing selenium and vitamin E may have some cancer protective effects ([12]).
Also in Asian Countries, where the intake of soy products is very high, the rates of PC are very low. Soy, metabolised in estrogens, arrests the growth of the prostate and induces apoptosis of malign cells ([13]).

Life-style factors

Some studies examined physical activity that showed a controversial decreased as well an increased outcome ([14],[15],[16]).
In general, cigarette smoking is not a very important risk factor for developing PC, but mutations can be caused by smoking ([17]). Drinking alcohol did not show an increased rate of risk too ([18]).
Sexual activity plays maybe an important role; associations with sexually transmitted diseases were stronger than for overall sexual activity ([19]).
In some cases, bacterial infection can cause prostatitis. Studies reported a positive association with PC ([20]).
Aspirin and NSAID's (non-steroidal-anti-inflammatory-drugs) may have a modest reduction in risk ([21]).

Genetic patterns

Hereditary accumulations of PC were reported several times. Smith et al. detected on chromosome 1 a genetic mutation in case of familial PC, called HPC 1 (hereditary prostate cancer 1) ([22]). Relatives of patients with HPC 1 have a threefold-increased-risk to develop PC in contrast to men of the same age ([23]). Further defects of tumour suppressor genes on chromosome 7, 10 and 16 were detected by fluorescence-in-situ-hybridisation (FISH) ([23]).
Overall, approximately 6% of all PC may be hereditary.

Androgens

Androgens play an important role in the development of PC. In early stages of PC, the presence of androgens is necessary for its growth. Due to this, prepuberal castrates do not develop PC without sufficient testicular androgen stimulation ([23]).

Demographic Patterns

The Western “industrialised” Countries have much more higher rates of PC than the Far East and the Indian Subcontinent. The highest rates of the Western Countries have Western Europe, Australia and North America.

- In China, the incidence of prostate cancer is 2.9 per 100.000 persons, while in the United States the rate is 107-185 per 100.000 white and black men ([24]).
- China’s mortality lies by 1 per 100.000 men annually and in the US by 17.9 per 100.000 in the year 2000 ([24]).

Race and ethnicity

African Americans have the highest rate of incidence with 185 / 100.000 and mortality with 75.1 / 100.000 ([25]). Compared with other Africans, Trinidad and Tobago has the highest mortality among 45 countries ([26]). US-Studies showed that African Americans have more distant metastases [18%] than white Americans [10%], too ([25]).

1.5 Pathology

1.5.1 Introduction

Adenocarcinoma is the most common histological type of primary PC. The histological patterns are described by the Gleason-Grading-System. The Gleason Score is an important prognostic factor for the prediction of the natural history of PC and for the estimation of recurrence after total prostatectomy or radiotherapy.
Primary non-adenocarcinomatous tumours of the prostate are rare.

1.5.2 Premalignant lesions of the prostate

1.5.2.1 Prostatic Intraepithelial Neoplasia (PIN)

Prostatic intraepithelial neoplasia is discussed as a precursor lesion for prostatic adenocarcinoma and commonly related to high grade PIN (HGPIN). It is difficult to differentiate low grade PIN (LGPIN) from benign lesions, such as prostatic hyperplasia.

- LGPIN: Its histopathological appearance is characterised by minimal stratification, preserved polarity, mildly increased nuclear size, normal or mild focal hyperchromasia and absence of nucleoli.

- HGPIN: Its histopathological appearance is characterised by mild to moderate stratification, mild to marked disarray of polarity, moderate-focal to marked extensive hyperchromasia and finally few small to multiple prominent nucleoli.

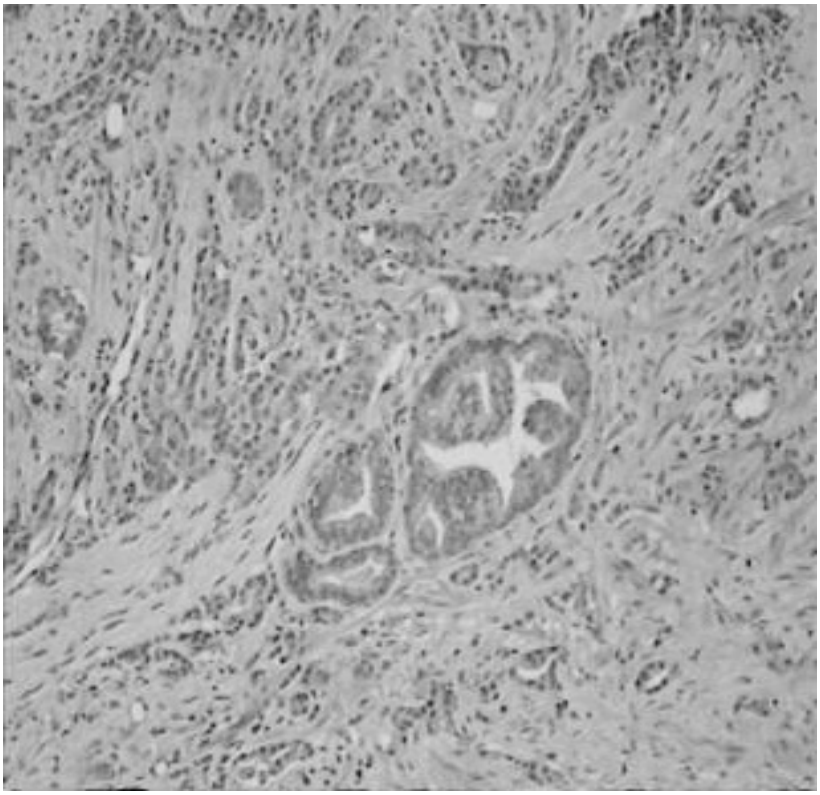
Most HGPIN's are localised in the PZ of the prostate, in which adenocarcinoma is detected most frequently.
The identification of HGPIN is based on the presence of cytological atypical cells with prominent nucleoli within a prostatic duct/acinus. The amount of cytological atypia or the number or size of nucleoli is required for HGPIN to be reliably diagnosed, but there are no precise guidelines. As a result, a significant inter-observer variation in the incidence of isolated HGPIN on biopsy specimens is reported from various institutions (from less than 1% to over 20%) ([27]).

Furthermore, LGPIN on biopsy does not appear to increase the risk for PC ([27]). For this reason, most pathologists do not report the presence of LGPIN on prostatic biopsies.

1.5.3 Histological classification and differentiation

As outlined above, the most frequently histological type of primary PC is adenocarcinoma. Beneath the adenocarcinoma, the acinic adenocarcinoma is in 95% ([23]) of cases the most frequent type. Mucinous- and ductal adenocarcinoma are rare forms. Other infrequent cancer types are cribriform carcinoma and anaplastic carcinoma.

Figure 3 Acinic adenocarcinoma of the prostate (modified from [28])



The following primary non-adenocarcinomatous tumours of the prostate are described by the World Health Organisation (WHO):

- Epithelial tumours: - urothelial carcinoma
  - adenosquamous carcinoma
  - squamous cell carcinoma
  - basal cell carcinoma

- Neuroendocrine tumours: - carcinoid tumour
  - small cell carcinoma
  - paraganglioma
  - neuroblastoma

- Prostatic stromal tumours: - stromal tumour of uncertain malignant potential
  - stromal sarcoma

- Mesenchymal tumours: - leiomyosarcoma
  - rhabdomyosarcoma
  - chondromyosarcoma
  - malignant fibrous histiocytoma
  - malignant peripheral nerve sheath tumour

- Hematolymphoid tumours: - lymphoma
  - leukaemia

- Miscancellaneous tumours: - nephroblastoma
  - rhabdoid tumour
  - germ cell tumours
  - yolk sac tumour [seminoma, embryonal carcinoma and teratoma, choriocarcinoma, melanoma] ([29])

The most secondary cancers of the prostate are direct extensions of vesical urothelial carcinoma and metastatic spreads of leukaemia.

1.5.4 Clinical manifestations of PC

There are 4 types of clinical manifestations of PC:

- **Clinical manifest PC**
  diagnosed because of suspect DRE;
- **Latent insignificant PC**
  diagnosed post-mortem by autopsy; without clinical findings;
- **Incidental PC**
  diagnosed by transurethral resection of the prostate (TURP) as a result of symptomatic BPH;
- **Occult PC**
  diagnosed because of symptomatic metastasis, with inconspicuous DRE;

This classification does not divide between treatable or none treatable PC.

1.5.4.1 Incidental PC

Incidental PC is a rare tumour with two different stages:
T1a stage describes an involvement of less than 5% of the prostatic glands volume. It is the most common form and well-differentiated too.
T1b tumours are less well-differentiated than “T1a’s” with a volume of more than 5%.

1.5.5 Tumour invasion and metastasis

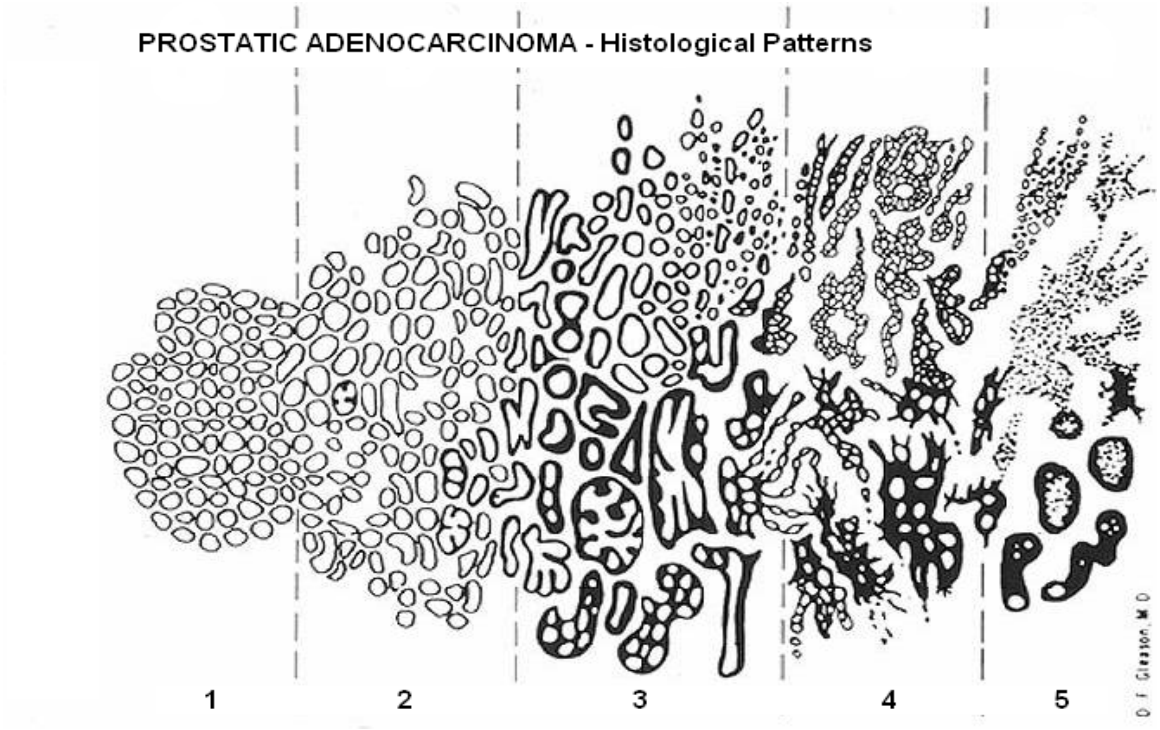
95% of PC grows in the PZ and shows multifocal focuses in 85% ([23]). Only 3% of PC develops in the TZ ([23]).
The invasion of the tumour starts from central to the periphery. After crossing the capsule, it penetrates seminal vesicles as well as both ductus deferens. The ureter and rectum is invaded less frequently than the base of the bladder. The capsule of the prostate is a very important borderline, which has the function of a barrier. Transcending the prostatic capsule happens via nerval- and vessel sheathes, often located in the prostate’s apex and basis. PC metastasises in the regional

obturatoric and iliacal lymph nodes as well as in the retroperitoneal lymph nodes. Retrograde bloodstream over paravertebral veins causes hematogenic metastases. The most common hematogenic metastases are found in the skeletal system, especially in the lumbar spinal column. PC invades almost all organs, but most common infiltrated structures are bone, lungs and liver.

1.5.6 Gleason-Grading-System of prostatic adenocarcinoma vs. WHO-Grading by Mostofi

In 1966, Dr. Donald F. Gleason first published the prostatic carcinoma grading system, in collaboration with the Veterans Administration Cooperative Research Group. The Gleason-Grading-System had an increasing acceptance during the 1980's. Finally, in 1993 it was recommended by a WHO Consensus Conference on prostatic carcinoma. Today, it is the most common used grading system for prostatic adenocarcinoma worldwide. Multiple studies showed that the Gleason-Grading-System is a powerful prognostic factor for the prediction of the natural history of PC and for the assessment of the risk of recurrence after RRP or radiotherapy ([30]).

Figure 4 Histological patterns of prostatic adenocarcinoma (modified from [31])



The Gleason-Grading-System is based on architectural pattern as well as on the least differentiated pattern within the tumour. The standard histological diagram separates architectural characteristics into 5 histological patterns of decreasing differentiation. Pattern 1 is the most differentiated and pattern 5 the least differentiated. The most prostatic adenocarcinoma show several histological patterns. In fact, Gleason detected that the prognosis of prostatic carcinoma was intermediate between the most predominant pattern of carcinoma and the second most predominant pattern.

In the Gleason-Grading-System the most prevalent and the second most prevalent pattern are added together to obtain a Gleason Score - e.g. Gleason grade 5+4=9.

If the tumour shows only one histological characteristic, the primary and the secondary pattern are doubled and added together to obtain the Gleason Score - e.g. pattern 3, would be 3+3=6 ([30]).

Gleason Scores range from 2, according to high differentiated, to 10, according to absolutely undifferentiated tumours.

WHO's grading system by Mostofi was used, before the Gleason-Grading-System was established in the department of pathology of Graz in 1999. This system has four different grades: grade 1 (G1), to grade (G4). It evaluates the tumour's glandular differentiation and the nuclear aplasia.

1.6 Clinical diagnosis and staging of PC

1.6.1 Introduction

In earlier decades of the last century, clinical significant symptoms of PC were commonly a complex of weight loss, bone pain, anaemia and uraemia as well as bladder outflow symptoms. They accord to tumours, which were very huge and in an advanced stage. Nowadays, most PC are detected in men beyond middle-age, with asymptomatic signs and symptoms as well as a lower stage of PC. The most common propagated diagnostic techniques are the DRE and serum PSA testing. PSA, an organic marker, is the most important parameter in the follow-up, too.

Furthermore, prostatic fine-needle-core biopsy is the standard procedure in detecting PC, when DRE and PSA testing indicate malignancy.

The International Union Against Cancer (UICC) changed in 2002 the 6th revision of TNM-Staging-System from 1997 into the current issue. The TNM-Staging-System combines clinical staging techniques as well as pathologic staging. Clinical staging techniques are used to diagnose tumour extension and metastasis, while pathological staging informs the surgeon about the border of resection, invasion and penetration of the prostatic capsule as well as affection of the seminal vesicles and finally of lymph node status. Following clinical staging techniques are explained below: Digital rectal examination (DRE), prostatic specific antigen testing (PSA), transrectal-ultrasound-guided (TRUS) prostatic biopsy, endorectal magnetic resonance imaging (MRI), magnetic resonance spectroscopic imaging (MRSI), positron emission tomography (PET) and radio-immuno-scintigraphy (RIS).

1.6.2 Presenting symptoms of local prostatic invasion

The presenting symptoms of men with localised PC and/or local invasion are the following:

Local PC:

- Poor stream
- Hesitancy
- Sensation of incomplete emptying
- Frequency
- Urgency
- Urge incontinence

Local invasive PC:

- Hematuria
- Dysuria
- Pain
- Impotence
- Incontinence
- Loin pain (ureteric obstruction)
- Symptoms of renal failure
- Rectal symptoms including bleeding hemospermia ([32])

Symptoms of bladder outflow obstruction are related to benign prostatic hyperplasia (BPH). BPH develops in the TZ. Due to compressions of the prostatic urethra, advanced PC may also cause bladder outflow obstruction. Only a few prostatic tumours are detected by TURP for clinical BPH. These tumours are incidental carcinomas.

The symptoms of bladder outflow obstruction are usefully divided into two groups: obstructive and irritative. Obstructive symptoms, namely reduced uroflow, hesitancy and incomplete emptying, result from narrowing of the prostatic urethra by tumour.

Urinary retention is the ultimate obstructive symptom in locally advanced PC. It necessitates urgent decompression by either urethral or suprapubic

catheterisation. In addition, irritative symptoms may occur in PC because of invasion of the trigone of the bladder and pelvic nerves. Bladder outflow obstruction may lead to secondary problems such as recurrent urinary tract infections, which in turn result in frequency, dysuria and sometimes also hematuria. Hemospermia is a symptom that is only occasionally associated with PC. The description of this by a patient should prompt both a DRE with PSA determination and transrectal ultrasonography, together with prostatic biopsy if indicated on other clinical grounds ([32]).

The American Urologic Association, endorsed by the WHO, designed an evaluation score, to detect BPH in patients. It can be used also in patients with PC presenting obstructive and irritative lower urinary tract symptoms:

1.6.3 International Prostate Symptom Score (IPSS)

Table 4 International Prostate Symptom Score IPSS (modified from [33])

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	**Your score**
1. Incomplete emptying Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5	
2. Frequency Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5	
3. Intermittency Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency Over the last month, how difficult have you found it to postpone urination?	0	1	2	3	4	5	
5. Weak stream Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
	None	1 time	2 times	3 times	4 times	5 times or more	**Your score**
7. Nocturia Over the past month, many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?	0	1	2	3	4	5	
Total IPSS score							

Quality of life due to urinary symptoms	Delighted	Pleased	Mostly satisfied	Mixed – about equally satisfied and dissatisfied	Mostly dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?	0	1	2	3	4	5	6

Total score: 0-7 mildly symptomatic; 8-19 moderately symptomatic; 20-35 severely symptomatic.

Local carcinomatous invasion of the urethra may cause hematuria associated with dysuria. Erectile dysfunction (ED) results from neurovascular infiltration and expansion. Pain is produced by extracapsular extension of other nerves, located in perineum and suprapubic areas.
Urinary incontinence is a symptom of local infiltration of the distal urethral sphincter that may make the use of a permanent catheterisation necessary. Chronic retention, caused by prostatic tissue hypertrophy, may be treated by TURP or intraprostatic stent insertion.

1.6.4 Presenting symptoms of metastasis

The following symptoms are characteristic for local and systemic metastases:

Local metastases:

- Bone pain
- Paraplegia
- Lymph node enhancement
- Lymphedema
- Loin pain

Systemic metastases:

- Lethargy
- Weight loss, cachexia
- Anaemia and uraemia
- Haemorrhage

Bone pain is the most common local symptom caused by bone infiltration, which is detectable in a quarter (^{32}) of men with PC. Bone metastases, localised within pelvic bones and lumbar spine, destroy the architecture of the bone matrix. Pathological fractures under mechanical pressure are its consequences. Broad invasion of the bone marrow causes anaemia as well as neurological deficits, which are symptoms of spinal cord compression.
Lymph node metastasis appears not that dramatic as the bone invasion. Oftentimes an enlargement of lymph nodes can be seen. Due to the size of

swollen lymph nodes, many patients suffer from loin pain and a lymphomatous lower limb swelling.

1.6.5 Tumour classification - TNM-System UICC 2002 7th revision

Primary tumour clinical staging (cT)

cTX: Primary tumour unable to be assessed

cT0: No evidence of primary tumour

cT1: Tumour not apparent palpation or imaging
- T1a: incidental finding at TUR (<5%)
- T1b: incidental finding at TUR (>5%)
- T1c: Tumour identified at time of biopsy (PSA elevation)

cT2: Tumour confined within prostate*
- T2a: Tumour involves 50% or less of one lobe
- T2b: Tumour involves more than 50% of one lobe but not both lobes
- T2c: Tumour involves both lobes

cT3: Tumour not confined to the prostate**
- T3a: Extra capsular extension (unilateral or bilateral)
- T3b: Tumour invades seminal vesicle(s)

cT4: Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall

*Note: Tumour that is found in one or both lobes by needle biopsy, but is not palpable or reliably visible by imaging is classified as T1c.

** Note: Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified as T2 not T3.

Primary tumour pathologic staging (pT)

pT2: organ confined

pT2a/b: unilateral involvement

pT2c: bilateral involvement

pT3: extra prostatic extension

pT3a: capsular invasion

pt3b: seminal vesicle invasion

pT4: invasion of contiguous structures

Regional lymph nodes (N)

NX: Regional lymph nodes were not assessed

N0: No regional lymph node metastasis

N1: Metastasis in regional lymph node(s)

Distant metastasis (M)

MX: Distant metastasis not assessed

M0: No distant metastasis

M1: Distant metastasis

M1a: Non-regional lymph node(s)

M1b: Bone(s)

M1c: Other site(s) with or without bone disease ([34])

Residual tumour (R)

RX: Presence of residual tumour cannot be assessed

R0: No residual tumour

R1: Microscopic residual tumour

R2: Macroscopic residual tumour

1.6.6 DRE

DRE is a very important component of the health prevention program in men at the age of 45-50 ([35]) or for patients with lower urinary tract symptoms (LUTS). It is a fast and simple diagnostic method for prostatic anomalies, provided that the tumour exists in the PZ, because only the dorsal part of the prostate can be palpated. In Europe, the patient lies during the DRE on the left side with inflected legs. During the DRE, anus, rectum, seminal vesicles and Douglas' space should be estimated too.

The normal size of the prostate is like a walnut. It is plane, its consistency is smooth to solid and the gland is circumscribable on lateral sides.

In case of painful palpation, prostatitis or prostatic abscess could be its cause.

BPH often shows a sturdy-elastic consistency of the prostatic surface. Indurations and/or rigidification of the prostate are suspicious for the existence of PC.

The positive predictive value (PPV) of DRE ranges from 4% to 11% in men with PSA levels of 0-2.9 ng/mL and from 33% to 83% in men with PSA levels of 3.0-9.9 ng/mL or more ([36]). The variability of these numbers depends on the experience of the examiner and on preselected patients.

TRUS guided biopsy follows a suspicious DRE or an increased PSA score.

1.6.7 PSA testing

PSA is the most important serum marker for diagnosing PC and course control after RRP. It was isolated and first described in 1979 by Wang et al.

PSA, a neutral serine protease is produced by acinic and ductal epithelial cells. It has a molecular weight of about 33 kD ([37]). It divides in the seminal plasma seminogelin 1 and seminogelin 2 as well as fibronectin, which liquefies ejaculate and increases spermatic motility. PSA, an organic marker, is detected in several other tissues or organs too. It is not a tumour specific marker, because it can be elevated by benign hyperplastic prostatic cells and by malignant cells, respectively. The general estimated cut off is PSA < 4.0 ng/mL ([38]). The existence of a "diagnostic grey zone" between PC and BPH at a PSA level of 4.0 and 10.0 ng/mL entailed the development of PSA-derivatives in the diagnosis of PC. PSA-derivatives are the following ones:

PSA-Density (PSAD)

The serum PSA divided by gland volume is called density of PSA. PSAD combined with total PSA should increase the percentage of specificity, but there are several errors by measuring the prostatic volume, depending on the examiner ([39]).

PSA-Velocity

The rate of change over time is called PSA-Velocity. Carter et al. reported that an annual increase of 0.75 ng/mL per year may indicate men who would develop or who have developed PC ([40]).
An important landmark is the doubling time of PSA, which is on focus of many studies.

Age-Specific PSA

PSA score and the mass of BPH increase with the cumulative age of men. While the assimilated age-specific PSA rate increases the test sensitivity in young men, it also decreases the older men's sensitivity.
The age-specific PSA score after Oesterling et al. is in use on the Department of Urology, University Hospital of Graz, Austria.

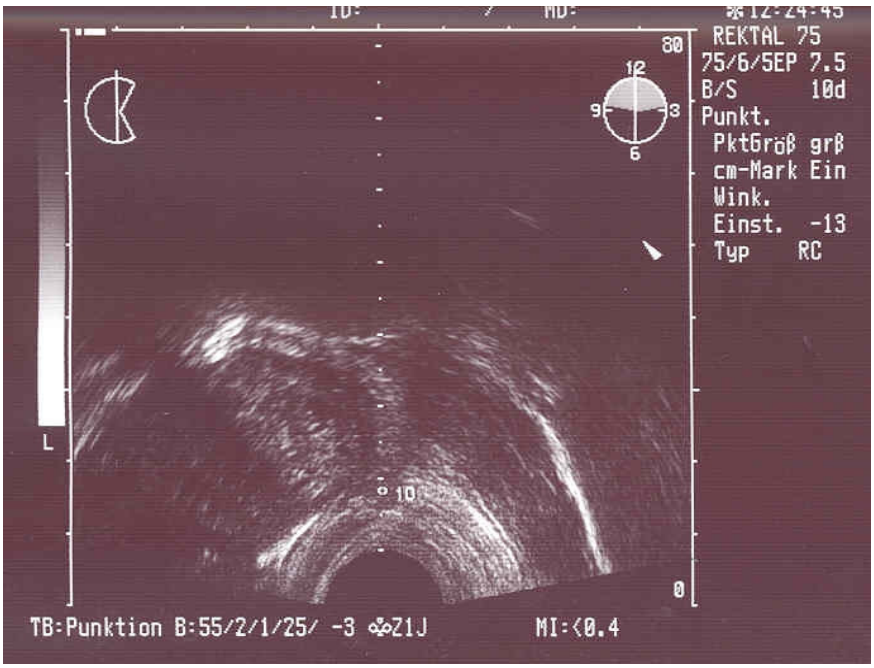
Table 5 Age-specific PSA score ([41])

Age	PSA (ng/mL)
40-49	- 2.5
50-59	- 3.5
60-69	- 4.5
70-79	- 6.5

1.6.8 Transrectal-ultrasound-guided biopsy (TRUS) of the prostate

DRE and serum PSA testing are performed for confirming suspicion of PC. When these diagnostic methods indicate PC, ultrasound-guided biopsy will be indicated.
In general there are two major biopsy techniques operated: transrectal- and transperineal-ultrasound-guided biopsy of the prostate. The first biopsy technique is used more often then the second one. Directed and/or systematic random fine-needle-core biopsies are standard. Directed biopsy is used for sonographic suspicious areas, while random systematic biopsy scans the prostate upon a pattern. The classical systemic sextant biopsy was described in 1989 by Hodge et al. ([2]). Meanwhile, 10- and 12 -core laterally directed biopsies have replaced the sextant biopsy technique.
Rebiopsies are indicated either when HGPIN-lesions or atypical small acinar proliferations (ASAP) are shown by previous biopsies, or when clinical suspicion of PC exists. After negative prostatic biopsies a 24 or more-core-saturation rebiopsy may be indicated. Presti et al. reported that sextant biopsy detects 78%, lateral sextant 83%, 8-core 92% and finally 10-core 96% of lesions of the prostate ([42]).
Common biopsies are taken from peripheral zones, while cores of TZ and seminal vesicles are not generally performed.

Figure 5 TRUS-guided biopsy



Contraindications to prostate biopsy are recent or active acute prostatitis, uncorrected coagulopathy and colorectal diseases.

Antibiotic prophylaxis is a standard practise before TRUS-guided biopsy is performed. The patient gets either a singular dose of oral broadband antibiotics before the biopsy or medication for several days. The average duration for administrating antibiotics varies from physician to physician. Antibiotic prophylaxis in combination with fine needles (18 G) reduce blooding and septic complications. These complications are quite rare nowadays < 2% ([43]). Hematuria (60%) and hemospermia (10%) are more frequent complications as listed above ([43]).

As local anaesthesia, topical lidocain can be used, but does not provide optimal pain.

TRUS uses a grey-scale mode and a transducer frequency in a range from 6 to 10 MHz. The prostate should be measured in the sagittal and transverse plane to calculate its volume.

1.6.9 Endorectal magnetic resonance imaging (MRI) and magnetic resonance spectroscopic imaging (MRSI)

Magnetic resonance imaging (MRI) is used with computed tomography (CT) for detecting metastases, but it is not a standard procedure in staging local tumour infiltration. Current MRI magnets generate up to 3 tesla. New technical features combine endorectal and body coils for a higher resolution. Most PC demonstrates a low signal intensity in contrast to the normal PZ showing a high signal on T2-weighted images.

A study reported that MRI compared with TRUS showed no difference in detecting apical tumours, but MRI had a better localisation of tumour in all other prostatic areas ([44]).

Metabolic reaction of PC is different from tumour to tumour. Magnetic resonance spectroscopic imaging (MRSI) detects its metabolism and helps to distinguish different dignities. Spectroscopy detects citrate and choline. The PZ of the prostate has a higher level of citrate than CZ or TZ and a low level of choline. The detection of PC with MRSI depends on the choline to citrate ratio, in which choline is increased and citrate deceased.

1.6.10 Positron emission tomography (PET) and radio-immuno-scintigraphy (RIS)

Positron emission tomography (PET) and single photon emission computed tomography (SPECT) are functional techniques for detecting enhanced metabolic activity in PC. These detecting techniques are combined with MRI and CT, allowing an exact location of an area with enhanced metabolism. PET is based on showing enhanced metabolic activity using 2-F18-fluoro-deoxy-D-glucose FDG as the marker of hypermetabolism. Contrary to PET, SPECT imaging of prostatic tumour detects the uptake of monoclonal antibodies, marking prostate specific membrane antigen (PSMA). PSMA is commonly associated with PC.
These methods are useful for staging metastatic lymph nodes too.

1.7 Treatment of clinically localised PC and management of metastatic disease

1.7.1 Introduction

Since better diagnostic methods were developed, the most common cancers of the prostate show a localised stage (T1 or T2 tumours).
Nowadays, the surgical standard in the treatment of localised PC is the anatomic radical retropubic prostatectomy (RRP) by Walsh and Donker. The first description of RPE was by Millin in 1947. The 7-year prostate cancer specific survival rate after RRP is 97% ([45]). In addition, radical prostatectomy can also be performed by a perineal access, laparoscopically and with robotic assistance.
Around this development, many alternative therapy procedures for clinically localised PC were created, such as watchful waiting or expectant management and radiation therapy (EBRT, Brachytherapy). Androgen deprivation is a therapy with a non curative intent. Cryotherapeutic ablation, hyperthermia or laser therapy and high intensity focused ultrasound (HIFU) are experimental alternatives.
In general, metastatic diseases are not curable and need another management of treatment than clinically localised PC. First line treatment of metastasis is totally androgen deprivation, either with bilateral orchidectomy or the use of LHRH analogues.
The prognosis of long time survival depends on PSA level, Gleason Score and on the number of positive biopsy cores as well as the biological age of the patient, comorbidity and patient decision sharing.

1.7.2 Anatomic radical retropubic prostatectomy (RRP)

The radical retropubic prostatectomy (RRP) by Walsh is the most common performed procedure. It is the surgical standard in the treatment of clinically localised PC. The retropubic approach also allows pelvic lymphadenectomy.
The most common localised stages are T1 and T2 diseases. This means a low-to-moderate stage. T3 diseases with or without minimal lymph node metastases are rarely curable. RRP is the treatment for PC stage T1a-c and T2a-c. It can also be

performed in cT3 cancers, as 25% of these tumours show an organ-confined disease on histological examination ([46]).

The criteria for the selection of patients for this major operation are a life expectancy of more than 10 years, histological evidence of PC as well as clinically localised stage. Furthermore, patients must not have any contradicting surgical comorbidities and they have to be well informed about the risks, the morbidity and mortality.

The aim of RRP is a complete excision of the prostate, seminal vesicles and adjacent tissue. In case of a nerve-sparing technique, neurovascular bundles are saved. The caudal landmark of the operation area is the membranous urethra and the cranial is the bladder's neck. The posterior landmark is the Denonvillier's fascia, and the anterior one the fibroadipose tissue of the Retzius' cave. The lateral margin is formed by the prostatic plexus, next to the neurovascular bundle.

Radical retropubic prostatectomy can be reliably performed in 2-3 hours with minimal morbidity. The patient is situated on the operating table in dorsosacral position. To increase the distance between the pubis and xiphosternum the patient is hyperextended 10-20° at its midpoint. A 20F urethral catheter is placed in the penile urethra and balloon inflated. The excess to the extraperitoneal space is made by an abdominal-lower-midline laparotomy.

In general, a bilateral pelvic lymphadenectomy of internal iliac nodes as well as of obturatoric nodes is performed, but frozen section histology is no longer recommended (unless in case of suspicious lymph nodes, i.e. PSA <10ng/ml). After division of the endopelvic fascia, avascular puboprostatic ligaments close to the pubis are divided and attention is then paid to secure the dorsal venous complex. If this is performed successfully, blood loss from the complete operation is rarely more than 700 ml ([47]). Afterwards, the dorsal vein complex is ligated with a strong absorbable suture to expose the urethra after its division. The use of a Gil-Vernet renal retractor for dissection increases the length of urethra for subsequent anastomosis to the bladder neck. The proximal end of the catheter is used as a tractor to enable the 'peeling back' of the prostate with the division of the rest of the urethra and the lateral vascular pedicles of the prostate.

After this procedure seminal vesicles and ampullary portions of both vasa come into view and are prepared. Attention should be paid on the securement of small arteries, supplying the medial side of each seminal vesicle.
The prostate is then carefully prepared away from the bladder neck by the use of a bladder-neck sparing technique. The catheter is used as a retractor to divide the junction of the trigone and the prostate. RRP-specimen together with the seminal vesicles are removed. For preventing anastomotic stricture, the mucosa of the bladder is everted and then an anastomosis is created between the bladder neck and urethra over an 18 or 20F urethral catheter. The anastomosis varies between four to six absorbable Vicryl or Dexon sutures. Finally, a tube wound drain is inserted and the wound is closed in layers.

1.7.2.1 Advantages of RRP

RRP has the advantage to cure patients with a clinically localised stage. RRP also reduces anxiety in men during the follow-up, because they have an exact diagnosis achieved by definitive staging. Patients with LUTS, implicated by BPH, can be cured and symptoms can be reduced too. Nerve-sparing-techniques by Walsh preserve 'aging males' between 55 and 65 years of erectile dysfunction.
However, the advancement of RRP by Walsh and other pioneers reduced the loss of blood (important for 'Zeugen Jehovas'), and other complications, which are described below.

1.7.2.2 Disadvantages and complications of RRP

Early complications of RRP are:

- Mortality
- Pulmonary embolisms
- Sepsis
- Wound infections
- Lymphocele
- Stricture of anastomosis

Mortality fall under 1% ([23]), pulmonary embolisms are between 0.5 -1% ([23]) and cases of sepsis are less than 0.5% ([23]). Furthermore, wound infections reach from

1% to 3% ([23]), lymphocele from 2% to 3% ([23]) and stricture of anastomosis is between 5% and 8% ([23]).

Long-term complications of RRP are:

- Urinary incontinence
- Erectile dysfunction (ED)

Urinary incontinence and ED are the most important long-term complications of RRP. These complications are in most clinics under 5% ([23]). A nerve-sparing anatomic RRP reduces urinary incontinence and ED. An effective treatment of major or total urinary incontinence is only available by implanting an artificial bulbar sphincter. The commitment of sildenafil in patients with ED was effective in around 42% of cases ([23]). Before the RRP, the patient's erectile function should be evaluated by the International Index of Erectile Function (IIEF).

Table 6 International Index of Erectile Function IIEF- 5 (modified from [48])

Scores	**1**	**2**	**3**	**4**	**5**
1. How do you rate your confidence that you could get and keep an erection?	very low	low	moderate	high	very high
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	never or almost never	a few times	sometimes	Most times	almost always or always
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	never or almost never	a few times	sometimes	Most times	almost always or always
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	extremely difficult	very difficult	Difficult	slightly difficult	not difficult
5. When you attempted sexual intercourse, how often was it satisfactory for you?	never or almost never	a few times	sometimes	Most times	almost always or always

IIEF-5 score is the short form and is used more often. The IIEF-5 score is the sum of questions 1 to 5. The lowest score is 5 and the highest score 25. According to the IIEF-5 score, ED is classified into 4 groups of mild (17 to 21), mild to moderate (12 to 16), moderate (8 to 11), and severe (5 to 7).

1.7.3 Radiation therapy

In case of presence of contradicting surgical comorbidities, radiation therapy of localised PC is an alternate curable treatment strategy as well. External beam radiotherapy (EBRT) is an alternative curable treatment strategy for clinically localised PC. PC is not that radiosensitive than other tumours, but it can be well handled with a high radiation dose. The success of treatment depends on histological grading, tumour volume, radiation type and technique of applied dose.

There are different forms of radiation therapy used for clinically localised and metastatic PC:

- External beam radiation therapy (EBRT)
- Brachytherapy
- Adjuvant radiation therapy after radical prostatectomy
- Radiation therapy of local relapse after RRP
- Palliative radiation therapy

1.7.3.1 EBRT

The radiation therapy is an alternate therapy strategy for patients with surgical contraindications. The primary curative radiation therapy is used for very small tumours and for locally progressive cancer, respectively. Further indications of radiation therapy are advanced age, comorbidities and the patient's denial of surgery.

Contraindications of radiation therapy include the possibility of exceeding the radiation-dose-limit, when another tumour was treated before or in case of predamage of bladder and rectum by chronic phlogistic diseases.

Medical criteria for this treatment are histological evidence of PC, clinically localised disease, sufficient life expectancy, absence of lower urinary tract disorder

and colorectal disease as well as recent TURP and an adequate informed patient. A significant advantage in patients, treated by EBRT, is to avoid the risks of surgery. Disadvantages of radiation therapy are treatment time and morbidity, including rectal injury, bladder damage, incontinence, impotence and hematuria. Further problems are patient's anxiety because of an unknown status of potentially persisting carcinoma.

Hormonal therapy neoadjuvant to EBRT as well as adjuvant HT show benefits in high-risk patients (benefits are described below). There are two techniques used for radiation therapy: external-beam radiation and brachytherapy.

The 7 year relapse free survival rate for clinically localised T1-T2 PC after EBRT <72 gray and ≥ 72 gray is 48% and 81%, respectively ([49]). The treatment of local progressive tumours compared with the localised stage is very bad. The relapse rate after 5 years is 50-80% ([23]). The combination of radiation therapy and hormone therapy may achieve a better local tumour control, but this treatment strategy is subject of current studies.

1.7.3.2 Brachytherapy

Transperineal brachytherapy is a modern therapy procedure for clinically localised PC ([50]). Radioactive sources are applicated over simultaneous TRUS. There are two different techniques used: low dose rate (LDR) and high dose rate applications. LDR uses radioisotopes like Iodine-125, and Palladium-103 (gamma ray). HDR uses Iridium-192. LDR brachytherapy is used for low risk patients with a serum PSA ≤ 10 ng/ml (≤T2b). High risk patients are treated with HDR brachytherapy. Brachytherapy minimises radiation dose in uninvolved organs and maximises the tumouricidal dose within the prostate. PSA failure-free rates are between 80 and 95% at 5 years ([51]).

1.7.3.3 Adjuvant radiation therapy and radiation of local relapse

A possible indication for postoperative radiation therapy is a positive surgical margin. Furthermore a local relapse of PC after radical prostatectomy can undergo radiation treatment.

1.7.3.4 Palliative radiation therapy

In advanced stages of PC, bone metastases cause heavy pain, which might not be controlled only by medication. Aim of palliative radiation treatment is an efficient pain control. Painful bone metastases, coming along with a high risk of pathological factures, can be treated by this method. A study reported that pain was reduced in about 90% of patients receiving EBRT for painful bone metastases ([52]). Thereby, pain can be reduced or totally eliminated within three months. Radiation therapy is also very useful, when brain metastases cannot be operated.

1.7.3.5 Systemic radionuclides

Systemically-applied radionuclides such as strontium-89, samarium-153 and rhenium-186 show a good palliation of painful bone metastases too. The advantage of this method is to treat multiple focuses of metastases with a single intravenous administration. 65% to 80% of patients receiving samarium-153 obtain pain relief within 1 week of therapy ([53]).

1.7.4 Watchful waiting or expectant management

Watchful waiting describes an abandonment of treatment in the diagnosis of PC. Aim of this treatment option is to control closely meshed biochemical and clinical markers to avoid a progression to a not curable disease.
Incidental or T1a tumours, detected at TURP, show a progression over eight years as low as 3% ([54]).
This treatment strategy is an alternative option in patients with a life expectancy of less than ten years. It includes PSA-monitoring and involves therapy by clear evidence of progression.

1.7.5 Neoadjuvant and adjuvant hormonal treatments

Some studies showed that a number of patients receiving radical prostatectomy, had a very low risk of disease progression ([55]) and mortality from PC ([56]). For this reason, additional hormonal treatment plays a little role in clinically localised PC's therapy.

There are no studies that neoadjuvant hormonal treatment prior to radical prostatectomy show benefits on localised or on locally advanced tumours.
Unlike this, hormonal therapy adjuvant to radical prostatectomy demonstrated benefits in progression ([57]) and data analysis showed an improvement of overall survival with immediate therapy ([58]) in patients with lymph node metastases.
Subset analysis of Pilepich et al. reported that patients with a Gleason Score from 2-6 had also benefits receiving hormonal neoadjuvant therapy prior to EBRT ([59]).
Locally advanced or high-risk localised tumours had a better outcome under adjuvant hormonal therapy combined with EBRT ([57],[60],[61]).

Types of hormonal therapies

LHRH

Luteinising hormone-releasing hormone agonists cause deprivation of androgen because of LHRH-receptor down regulation. They are applied subcutaneous and work for three months (Zoladex®, Profact®, Trenantone®). It is standard procedure in hormone ablative therapy and works equally as bilateral orchidectomy.

Antiandrogens

Antiandrogens annihilate the effect of androgens by a competitive antagonism. Bicalutamide 150 mg per day is used as a single treatment regimen. After a median follow-up of three years, adjuvant bicalutamide reduced the risk of disease progression compared to standard care alone (i.e. radical prostatectomy, radiotherapy) of about 42% ([62]). Patients with locally advanced disease (stage M0), given bicalutamide showed positive effects after a median follow-up of 5.4 years. In contrast, patients with clinically localised PC, treated with bicalutamide appeared to have a reduced survival compared to those given placebo ([63]).
Finally, high dose bicalutamide has become an alternative therapy to castration in patients with locally advanced cancers (stage M0) as well as selected M1 cancers, but it is not recommended in patients with clinically localised disease ([66]).

Maximal androgen blockade (MAB)

MAB is the combination of surgical or medical castration and antiandrogens. Surgical or medical castration reduces serum testosterone levels up to 95%, while antiandrogens inhibit the action of circulating androgens at the level of their receptor in the prostate. Several studies reported that MAB compared to hormonal monotherapies showed a small advantage in survival (< 5%) at a follow up of 5 years ([64],[65]).

Following adverse effects are caused by luteinising hormone-releasing hormone agonists (LHRH):

- Hot flushes
- Loss of libido
- Impotence

By non-steroidal antiandrogens:

- Gynecomastia
- Breast pain
- Hot flushes
- Diarrhoea
- Hepatotoxicity
- Interstitial pneumonia
- Delayed adaptation to darkness
- Alcohol intolerance
- Loss of libido/impotence

By steroidal antiandrogens:

- Cardiovascular events
- Adverse changes in serum lipids
- Impotence

Patients with a good performance status and a reasonable volume of metastatic disease may stay longer in remission and have an expanded survival under MAB than treated by LHRH single treatment regimen.

1.7.6 Management of metastatic disease

In general, metastatic diseases are not curable and they need another management of treatment than clinically localised PC. First line treatment of metastases is totally androgen deprivation, either with bilateral orchidectomy or the use of LHRH analogues.
Another useful palliative treatment regimen is the use of radiation therapy against painfully metastases.
The goal of palliative therapy is to reduce symptomatic disease. Urinary retention is a bothersome complication caused by obstruction of the urethra. This symptom can be treated by TURP.

1.7.7 Follow-up regimen of primary curative and metastatic PC

Most patients who fail treatment for PC do so early, even if failure only becomes clinically obvious after years. The patient should therefore be followed-up more closely during the first years after treatment, when the risk of failure is highest. PSA measurement, disease-specific history and DRE are recommended at 3, 6 and 12 months postoperatively. After one year the follow-up interval extends to every 6 months until 3 years, and then annually.
After initiation of hormonal treatment, it is recommended that patients should be followed-up at 3 and 6 months ([66]).
The oncological aftercare is individually, dependent on clinical staging, histopathological grading, and the performance status. The most important parameter is PSA testing.

Guidelines for follow-up (clinically localised, advanced and metastatic PC)

- In general:
  Disease-specific history, serum PSA and DRE should be evaluated after 3, 6 and 12 months after treatment, then every 6 months until 3 years, and then annually. Symptoms, response and the side-effects of hormonal treatments given should be evaluated too ([66]).

- A serum PSA level ≥ 0.2 ng/mL is associated with residual or recurrent disease after RRP or radiotherapy ([66]).

- TRUS and biopsy is only recommended after recurrence if it will affect the treatment plan ([66]).

- Metastases are detected by pelvic CT/MRI or bone scan. These techniques are recommended between 20-30 ng/mL PSA level. M1 diseases should have a scheduled follow-up every 3 – 6 months ([66]).

- Routine bone scans and other imaging studies are not recommended in asymptomatic patients ([66]).

2 Study design and participation criteria

2.1 Patients and methods

2.1.1 Study design and population

Between January 2005 and December 2007, 428 men with clinically localised PC underwent RRP and pelvic lymphadenectomy (described by Walsh and Donker [67]) at the Department of Urology, University Hospital of Graz, Austria. 9 Patients were excluded from the study because of neoadjuvant hormonal treatment, which may result in a regressive molecular and pathological stage ([68]). A further 172 men were eliminated because PC was either diagnosed in initial 24-core-saturation-biopsy or in repeated 6, 8, 10, or 12-core-biopsies. A small part of these exclusions (n=7) were patients with incidental PC diagnosed by TURP.

Overall, 256 selected patients were eligible for analysis. Men were separated into two groups. In 201 patients PC was diagnosed in the initial biopsy (group1), and in 55 patients PC was detected in a 24-core-saturation-rebiopsy (group 2), respectively.

In general, PC was diagnosed preoperatively with 6, 8, 10, or 12 systematic random fine-needle-core biopsies, or with a 24 core-saturation-rebiopsy.

In clinical staging PSA and DRE were performed routinely. Serum PSA levels were defined by the Roche immunoassay (Roche Diagnostics, Mannheim, Germany). Clinical and pathological stages were determined using the 7th edition of TNM Classification of Malignant Tumours. The surfaces of RRP specimens were inked and processed by using serial transverse sections (Stanford protocol [69]). The specimens were graded histologically according to the Gleason-Grading-System by Gleason et al. ([31]).

2.1.2 Statistical analysis

Data were analysed using the SPSS package version 14.0 (SPSS INC., Chicago, IL, USA). Clinical and pathological parameters were matched using Student's t-test for continuous variables. The statistical difference in the frequency distribution of tumour characteristics was compared using the Chi-squared test for categorical variables. Pearson's product moment correlation coefficient was used to analyse if there was a significant trend in tumour features and to evaluate correlations between clinical and pathological parameters. A probability level $(P) < 0.05$ was referred statistically significant.

Cohen's kappa (k) coefficient was used to measure the agreement of Gleason scores of the fine-needle-core biopsies and RRP specimen. It is a measure of concordance between observations with values of - 1 to 1; a k of <0.40 represents low, 0.41–0.60 moderate, 0.61 – 0.80 full and >0.81 – 1 almost perfect agreement. Kendall τ b rank correlation coefficient was used for its confirmation. All statistical tests were two-sided.

3 Results

3.1 Clinical characteristics

Table 7 Statistical parameters after separation in two groups

	Pts.	Mean number of cores	Mean number of rebiopsy	Mean number of positive cores
Total (n)	256			33.4%
Group 1	201	8.6		37.7%
Group 2	55		2.5	17.6%
Standard deviation		2.1	1.4	
P				.000

Table 7 shows characteristic parameters of the first core-biopsy group (group 1) as well as of the 24-core-saturation-rebiopsy group (group 2). In the initial biopsy set the number of cores ranged between 6 and 12 (mean 8.6). In group 2 patients underwent between 1 and 8 rebiopsies (mean 2.5).
37.7% of cores in group 1 and 17.6% of cores in group 2 were diagnosed with PC. The result is significant (P=0.000).

Table 8 Clinical features of patients undergoing fine-needle-core biopsies

	Pts. (n)	Mean age (years)	Median serum PSA (ng/ml)	Median f/t-PSA ratio	Median RRP time (min)
Total	256	61.6	6.12	11.1	155
Group 1	201	61.2	5.9	11.1	150
Group 2	55	61.7	7.8	10.9	165
P		.633	.372	.596	.044

Table 8 shows clinical features of 256 patients undergoing fine-needle-core biopsies between January 2005 and December 2007. PC was diagnosed in both groups almost at the same mean age. Group 1 and Group 2 showed a mean age of 61.2 years and of 61.7 years, respectively. The median serum PSA level was 5.9 ng/mL in group 1 and 7.8 ng/mL in group 2.

The median PSA ratio of Group 1 and Group 2 was 11.1% and 10.9%, respectively. PSA level and ratio were not significant (P= 0.372; P=0.596). By contrast, the median time of RRP in group 2 took with a total of 165 minutes 15 minutes longer than in group 1 (P=0.044).

Table 9 Comparison of DRE between both groups

%(n)	unsuspicious	suspicious	P
Total*	72.3% (133)	27.7% (51)	
Group 1	66.4% (91)	33.6% (46)	
Group 2	89.4% (42)	10.6% (5)	
			0.002

In 72 pts. data missing

Table 9 demonstrates the correlation of DRE between both groups. DRE was divided into suspicious and unsuspicious findings. Physiological parameters of the normal prostate are: size of a walnut, a plane surface, a smooth to solid consistency and the gland is circumscribable on lateral sides. Pathological structural abnormalities or asymmetry of the prostate indicate a suspicious DRE.
33.6% of DRE in group 1 and 10.6% of DRE in group 2 were suspicious, representing a significant difference (P= 0.002).
Overall, DRE was negative in 72.3%.

3.2 Pathological characteristics

Table 10 Comparison of Gleason Scores between biopsy and RRP specimen

	Biopsy - Gleason Score				RRP – Gleason Score			
(%)		≤ 6	7	≥ 8		≤ 6	7	≥ 8
Group 1		70.2	24.1	5.8		34.5	56.5	9.0
Group 2		69.2	23.1	7.7		39.6	56.6	3.8
P	.874				.415			

The Gleason-Grading-System by JF Gleason is used for histological grading. Table 10 compares the Gleason Score between prostatic fine-needle-core biopsy and RRP specimen of group 1 and group 2.

The Gleason Score of prostatic biopsy specimen most frequently diagnosed was ≤ 6 in 70.2% in group 1 and 69.2% in group 2, respectively. Furthermore a Gleason Score of 7 and ≥ 8 was graded in 24.1% and in 5.8% in group 1 as well as 23.1% and 7.7% in group 2. Gleason Score was equally distributed in both groups (P= 0.874).

The spreading of Gleason Score in RRP specimen was also nearly the same (P=0.415).

Table 11 Correlation between Gleason Scores of biopsy and RRP specimen

(n) %	All	Group 1	Group 2
N	251*	199	52
Exact correlation	47.1% (118)	45.7% (91)	51.9% (27)
Under-grading	44.6% (112)	47.2% (94)	34.6% (18)
Over-grading	8.3% (21)	7.1% (14)	13.5% (7)
k coefficient		.250	.356
Kendall τ b		.390	.496

In 5 pts.data missing

There exists a difference between the Gleason Score of biopsy and RRP specimen by a higher part of Gleason Score ≤ 6 in prostatic biopsies and the higher part of Gleason Score 7 in RRP specimen.

Table 11 compares the Gleason Score of prostatic fine-needle-core biopsies and RRP specimen with the k coefficient and the Kendall τ b coefficient. The present study showed exact agreement in 47.1% of all carcinoma. Under-grading was more frequent with 44.6% than over-grading with 8.3%.

The Gleason Score between biopsy specimen and RRP specimen in group 2 showed a higher kappa coefficient (0.356) than in group 1 (0.250). The alternate Kendall τ b coefficient showed a low agreement in group 1 (0.390) and a moderate in group 2 (0.496), respectively.

Table 12 Comparison of pathological tumour stages in RRP specimen

(%)	pT	2a	2b	2c	3a	3b	N	0	1	R	0	1
Group 1		3.0	1.0	73.0	15.5	7.5		98.0	2.0		92.0	8.0
Group 2		5.5	1.8	78.0	9.1	5.5		100.0	0.0		92.7	7.3
P	.618						.295			.859		

Table 12 shows pathological cancer stages, lymph node status as well as resection status of prostatectomy specimen.

The most common pathological tumour stage is T2c with 73% in group 1. The data are almost similar in group 2 (78.2%).

There were no pathological lymph nodes in group 2 and only 2% in group 1.

The resection status was in almost all cases negative. The result is not significant (pT: P= 0.618; N: P=0.295; R: P=0.859).

4 Discussion

Prostatic random fine-needle-core biopsy is the standard procedure for the histological diagnosis of PC and basis for further treatment. A suspicious DRE and/or a serum PSA level of more than 4ng/ml ([38]) as well as an average increase of 0,75ng/ml ([40]) per year should lead to prostatic fine-needle-core biopsy. In addition, especially in the rebiopsy set, the saturation technique represents a valuable tool. Stewart et al. found that saturation biopsy is a useful diagnostic method in men with previous negative fine-needle-core biopsies. This technique has a detection rate of 34% ([70]).

The median serum PSA was 5.9 ng/ml in group 1 and 7.8 ng/ml in group 2 (P=0.372), respectively. A study from Stamey reported that preoperative serum PSA levels between 2 and 10 ng/mL fail to predict postoperative cure rates of PC after treatment with RRP ([71]). Positive prostatic needle biopsy rates increase with age at total PSA levels between 4 and 10 ng/ml in men with normal DRE ([72]). Furthermore, a study from Catalona et al. demonstrated that measurement of percentage of free to total PSA (f/t-PSA ratio) can help to distinguish between BPH and PC in patients with serum PSA levels between 4 and 10 ng/mL. In detail, men with a total PSA level between 4 to 10 ng/mL and a f/t-PSA ratio higher than 25% have only a 8% chance of detecting cancer with a needle biopsy. Patients with a f/t-PSA ratio of less than 10% have a 56% chance of finding PC ([73]). The median PSA ratio in this study was in both groups 11%.

The most common pathological tumour stage of RRP specimen in this study was an organ-confined bilateral involvement of the prostate (pT2c) with a percentage between 73.1% and 78.3% (table 12). Locally advanced T3 tumours were detected in 15 to 22% in RRP specimen. A study by Augustin et al. showed a shift towards non-palpable PC and a significant migration towards higher rates of organ-confined tumour stages ([74]). There exists a low correlation between serum PSA level and tumour stage. These results are concordant with trends observed in centers of the US about 8-10 years earlier ([75]).

37.7% of cores in group 1 were positive. By contrast, group 2 showed with 17.6% a decreased rate of positive cores. Interestingly, even though more prostatic tissue was taken by 24-core-saturation-rebiopsy, the rate of detection was lower than by first-core biopsy. Every third core showed PC in group 1, while in group 2 every 6th

core was positive. A study proposed the concept of “insignificant PC”, which accompanies the patient a lifetime and does not influence his life expectancy ([76]). An insignificant carcinoma has a tumour volume less than 0.5 cm³ and a Gleason Score ≤ 6 in RRP specimen ([77]). Boccon-Gibod et al. might provide an explanation for the decreased rate of positive cores in 24-core-saturation-rebiopsy specimen. They studied pathological features of RRP specimen of patients operated of a potentially insignificant PC. 42% of 56 patients had a cancer volume less than 0.5mL and therefore it is more difficult to detect PC by using a saturation-rebiopsy ([78]). However, we were not able to assess the rate of insignificant PC due to the missing of cancer volumes.

Other data of this study showed that the DRE of the prostate in group 1 was in 33.6% suspicious. By comparison, patients with PC detected by using a 24-core-saturation-rebiopsy presented in only 10.6% a suspicious finding (table 9). A suspicious DRE shows the existence of structural abnormalities or prostatic asymmetry. Flanigan RC et al. reported that DRE is a helpful instrument in concordance with serum PSA testing for further biopsies, but it has limited accuracy in identifying localised PC ([79]).

The Gleason Score of fine-needle-core biopsies is an important prognostic parameter. A good correlation with that of the RRP specimens is warranted in clinical practice. Some studies reported a complete agreement between Gleason Scores of fine-needle-core biopsies and surgical specimens in 28–58% of cases, when using 18 G biopsy needles ([80],[81],[82]). The present study showed exact agreement in 47.1% in the whole study cohort. Under-grading was distinctly more frequent with 44.6% than over-grading with 8.3%. Notably, Group 2 showed a higher percentage (51.9%) of exact agreement of Gleason Score than group 1 (45.7%). The rate of under-grading was higher in group 1 (47.2%) than in group 2 (34.6%). In detail, the correlation between fine-needle-core biopsy Gleason Scores and RRP specimen Gleason Score showed in group 1 a lower kappa coefficient (0.250) than in group 2 (0.356). The alternate Kendall τ b rank correlation coefficient confirmed a low agreement in group 1 (0.390) as well as a moderate one in group 2 (0.496).

The most frequent Gleason Score of prostatic biopsy specimen was a score of ≤ 6 in about 70 % in both groups. Furthermore, a Gleason Score of 7 and ≥ 8 in RRP

specimen was graded in about 24% and in about 7 %, respectively. RRP specimen showed a higher part of Gleason Score 7.

Furthermore, RRP was performed by several surgeons and staging lymphadenectomy was not a standard procedure in each patient. This might explain the different time of RRP between group 1 and 2, taking 15 minutes longer in group 2 than in group 1 (table 8).

Obturatoric lymph nodes, carried out routinely during RRP, presented in almost all patients (98-100%) no evidence of metastases. By contrast, extended pelvic lymphadenectomy may reveal a higher rate of positive lymph nodes, because more lymph nodes are removed. Burkhard et al. suggest a meticulous lymphadenectomy for correct staging in all patients undergoing radical prostatectomy for PC. Patients with a WHO grade 1 and a PSA ≤10 ng/mL are excepted from the study ([83]).

Stamey et al. observed a significant reduction of positive surgical margins from 30% to 14% between 1988 and 1996 (p=0.0001) ([84]). In the present study, the rate of positive surgical margins was low. Hereby, group 1 and 2 showed no statistical difference with a percentage of 8% and 7.3%, respectively.

The limitations of the present study are the lack of data on tumour volumes. Patients with PC diagnosed after several prostatic fine-needle-core biopsies, could have a smaller tumour volume and probably a better prognosis.

Unfortunately, we were not able to assess the rate of insignificant cancers, and subsequently possible differences between the groups.

5 Conclusion

Patients with PC detected in the first biopsy set presented with 33.6% a significant higher rate of suspicious DRE findings.

Men undergoing 24-core-saturation-rebiopsy showed a lower rate of positive cores compared to those with cancer diagnosed in the initial biopsy.

Interestingly, Cohen's kappa coefficient of Gleason Scores between biopsy specimen and RRP specimen was higher in group 2.

We found no statistical differences between the groups for age, PSA level, PSA ratio, Gleason Score of biopsy as well as RRP specimen. Furthermore, tumour stage, lymph nodes and surgical margins of RRP specimen in the groups did not differ too.

Curriculum Vitae

Personal information

Name:	Robert Christian Peteani
Address:	Ragnitzsztr. 62 D Top 18 A-8047 Graz, Austria
Mobile phone:	0043 6641386486
Email:	robert.peteani@hotmail.com
Date of birth:	10.08.1983
Place of birth:	Salzburg
Nationality:	Austria

Academic and educational studies

10-2002 - 07-2008:	humane medicine Medical University of Graz, Austria degree, major: Dr. med. univ. end of academic studies: 4th of July 2008 diploma thesis: comparison of clinical and pathological parameters between clinically localised prostate cancer diagnosed in the first biopsy and saturation-rebiopsy
09-1993 - 06-2001:	general qualification for university entrance: “Matura” Certificate undergraduate institution: private grammar school of Herz-Jesu-Missionare, Salzburg-Liefering, Austria
09-1989 - 07-1993:	elementary school Liefering I, Salzburg, Austria

Clinical practise during academic studies

04-2008 - 07-2008:	Clinical practise during the practical year (PY) Department of Gastroenterology and Hepatology University Clinic of Internal Medicine, Graz, Austria
12-2007 - 04-2008:	Clinical practise during the practical year (PY) Department of Urology University Clinic of Urology, Graz, Austria
11-2007 - 12-2007:	Clinical practise during the practical year (PY) General Family Doctor Dr. med. univ. Herbert Ederer, Weiz, Austria
10-2007 - 11-2007:	Clinical practise during the practical year (PY) Department of General Otorhinolaringology, Head and Neck Surgery University Clinic of Otorhinolaryngology, Graz, Austria
02-2007 - 03-2007:	Clinical elective (CE) Department of Vascular Surgery University Clinic of Surgery, Graz, Austria

09-2006 - 10-2006:	Clinical elective (CE) Department of Nephrology and Haemodialysis University Clinic of Internal Medicine, Graz, Austria
07-2005 - 08-2005:	Clinical elective (CE) Department of Accident Surgery AUVA Emergency Hospital, Graz, Austria
08-2004 - 09-2004:	Clinical elective (CE) Department of Orthopaedic Surgery University Clinic of Orthopaedics, Oberndorf, Austria

Experience of working

10-2005 - 07-2007:	Tutor Institute of Anatomy, Medical University of Graz, Austria Teaching lessons in autopsy
10-2002 - 10-2006:	job/ gastronomy Tea and Coffeeshop Heißenberger GesmbH, Graz, Austria
07-2000 - 08-2000:	job/ administrative assistance Department of General Paediatrics University Clinic of Paediatrics and Adolescent Medicine, Salzburg, Austria

Civil work

10-2001 - 09-2002:	Civil work; operative assistance Department of Vascular Surgery University Clinic of Surgery, Salzburg, Austria

Compulsory optional subjects

Problem based learning, Internal Medicine, BHB Graz, Austria
Clinical exercises in anaesthesia and emergency medicine aid,
University Clinic of Anaesthesia and Intensive Care Medicine, Graz, Austria

Languages

German (native)
English (fluent in spoken and written)
French (basics)
Italian (basics)
Latin

Computer skills

MS-Office
medical software

Interests and skills

Hobbies	Playing the guitar, sailing, golfing, hiking, cooking

Bibliography

1. Kirby RS et al. Prostate Cancer – Principles and Practice. Taylor and Francis. 2006
2. Kirby RS et al. Prostate Cancer. Mosby. 2001, 2nd edition
3. Jocham D et al. Praxis der Urologie. Thieme. 2003, 2nd edition I + II
4. Hafferl A. Lehrbuch der topographischen Anatomie. Springer. 1969, 3rd edition
5. Waldeyer AJ. Anatomie des Menschen. Walter de Gryter. 2003, 17th edition
6. Sadler TW. Medizinische Embryologie. Thieme. 1998, 9th edition
7. Bucher O et al. Cytologie, Histologie und mirkoskopische Anatomie des Menschen. Verlag Hans Huber. 1997, 12th edition
8. Böcker, Denk, Heitz. Pathologie. Urban & Fischer. 2004, 3rd edition
9. Forth, Henschler, Rummel. Allgemeine und spezielle Pharmakologie und Toxikologie. Urban & Fischer. 2001, 8th edition
10. EAU Guidelines Prostate Cancer 2007. http://www.uroweb.org/professional-resources/guidelines
11. UICC: International Union Against Cancer http://www.uicc.org/index.php?option=com_content&task=view&id=14317&Itemid=251

References

[1] Franks LM. Latent carcinoma of the prostate.
J Pathol Bacteriol 1954; 2nd **68**:603-616

[2] Hodge KK et al. Random systematic versus directed ultrasound guided transrectal core biopsies of the prostate.
J Urol 1989;**142**:71-75.

[3] Draisma G et al. Lead times and over-detection due to prostate-specific antigen screening: estimates from the European Randomised Study of Screening for Prostate Cancer.
J Natl Cancer Inst 2003;**95**:868-878.

[4] McNeal JE. Regional morphology and pathology of the prostate.
Am J Clin Pathol 1968;**49**:347-357.

[5] Kirby RS et al. Prostate Cancer – Principles and Practice.
Taylor and Francis. 2006;**2**:60- 90.

[6] Kirby RS et al. Prostate Cancer – Principles and Practice.
Taylor and Francis. 2006;**2**:99.

[7] Statistik Austria Prostata.
http://www.statistik.gv.at/web_de/statistiken/gesundheit/krebserkrankungen/prostata/index.html

[8] Andersson SO et al. Body size and prostate cancer: a 20-year follow-up study among 135006 Swedish construction workers.
J Natl Cancer Inst 1997;**89**:385–389.

[9] Wright ME et al. Prospective study of adiposity and weight change in relation to prostate cancer incidence and mortality.
Cancer 2007;**109**:675-684.

[10] Giovannucci E et al. Height, body weight, and risk of prostate cancer.
Cancer Epidemiol Biomarkers Prev 1997;**6**:557–563.

[11] Kushi L et al. Dietary fat and cancer.
Am J Med 2002;**113**:63-70.

[12] Heinonen OP et al. Prostate cancer and supplementation with alpha-tocopherol and beta-carotene: incidence and mortality in a controlled trial.
JNCI 1998;**90**:440-446.

[13] Kolonel LN et al. Vegetables, fruits, legumes and prostate cancer: a multiethnic case-control study.
Cancer Epidemiol Biomarkers Prev 2000;**9**:795-804.

[14] Polednak AP. College athletics, body size, and cancer mortality.
Cancer 1976;**38**:382-387.

[15] Whittemore AS et al. Early precursors of site-specific cancers in college men and women.
J Natl Cancer Inst 1985;**74**:43-51.

[16] Paffenbarger RS et al. Physical activity and incidence of cancer in diverse populations: a prelimenary report.
Am J Clin Nutr 1987;**45**:312-317.

[17] Hsing AW et al. Diet, tobacco use, and fatal prostate cancer: results from the Lutheran Brotherhood Cohort Study.
Cancer Res 1990;**50**:6836-6840.

[18] Dennis L. Meta-analysis for combining relative risks of alcohol consumption and prostate cancer.
Prostate 2000;**42**:56-66.

[19] Dennis LK et al. Meta-analysis of measures of sexual activity and prostate cancer.
Epidemiology 2002;**13**:72-79.

[20] Roberts RO et al. Prevalence of physician-assigned diagnosis of prostatitis: the Olmsted County Study of Urinary Symptoms and Health Status among Men.
J Urol 1998;**51**:578-584.

[21] Habel LA et al. Daily aspirin use and prostate cancer risk in a large, multiracial cohort in the US.
Cancer Causes Control 2002;**13**:427-434.

[22] Smith JR et al. Major susceptibility locus for prostate cancer on chromosome 1 suggested by genome-wide search.
Science 1996;**274**:1371-1374.

[23] Jocham D et al. Praxis der Urologie.
Thieme. 2003; **2nd II**:174-220.

[24] Parkin DM et al. Cancer Incidence in Five Continents.Lyon: International Agency for Research on Cancer.
IARC Scientific Publications 2003;No.**155**.

[25] Jemal A et al. Cancer Statistics, 2003; CA Cancer.
J Clin Med 2003;**53**:5-26.

[26] American Cancer Society. Cancer Facts and Figures, 2003. Atlanta, GA, 2003.

[27] Kirby RS et al. Prostate Cancer – Principles and Practice.
Taylor and Francis. 2006;**2**:121.

[28] Department of Laboratory Medicine & Pathology. 2005
http://www.lmp.ualberta.ca/resources/pathoimages/PC-A.htm

[29] Eble JN et al. Tumours of the Urinary System and Male Genital Organs. From Tumours of the Prostate.
Lyon, France: IARC Press, 2004;159 – 214.

[30] Gleason Grading of Prostatic Carcinoma; Copyright © 2004 Johns Hopkins University;
http://pathology2.jhu.edu/gleason/patterns.cfm

[31] Gleason DJ et al. Veterans Administration Cooperative Urological Research Group: Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging.
J Urol 1974;**111**:58-64.

[32] Kirby RS et al. Prostate Cancer.
Mosby International Limited. 2001;2:49-57.

[33] International prostate symptom score (IPSS).
http://www.gp-training.net/protocol/docs/ipss.doc

[34] Kirby RS et al. Prostate Cancer – Principles and Practice.
Taylor and Francis. 2006;**2**:460.

[35] Jocham D et al. Praxis der Urologie.
Thieme. 2003;**2nd I**:13.

[36] Schroder FH et al. Evaluation of the digital rectal examination as a screening test for prostate cancer. Rotterdam section of the European Randomized Study of Screening for Prostate Cancer.
JNCI 1998;**90**:1817-1823.

[37] Bombardieri E et al.: Heterogeneity and specificity of cancer associated mucins.
J. Nucl. Med. Allied Sci. 1990;**34**:163-169.

[38] Myrtle JF et al. Clinical Utility of Prostate Specific Antigen (PSA) in the Management of Prostate Cancer.
Hybritech Inc. San Diego, CA 1986;1-4.

[39] Benson MC et al. Prostate specific antigen density: a means of distinguishing benign prostatic hypertrophy and prostate cancer.
J Urol 1992;**147**:815 – 816.

[40] Carter HB et al. Estimation of prostatic growth using serial prostate-specifis antigen measurements in men with and without prostate disease.
Cancer Res 1992;**52**:3323-3328.

[41] Oesterling JE et al. Standard Versus Age-Specific Prostate Specific Antigen Reference Ranges. Among Men With Clinically Localized Prostate Cancer: A Pathological Analysis.
J Urol 1996;**155**:1336-1339.

[42] Presti JC et al. the optimal systematic prostate biopsy scheme should include 8 rather than 6 biopsies: results of a prospective clinical trial.
J Urol 2000;**163**:163-167.

[43] Djavan B et al. Safety and morbidity of first and repeat transrectal ultrasound guided prostate needle biopsies.
J Urol 2001;**357**:1849-1850.

[44] Mullerad M et al. Comparison of endorectal magnetic resonance imaging, guided prostate biopsy and digital rectal examination in the preoperative anatomical localization of prostate cancer.
J Urol 2005;**174**:2158-63.

[45] Catalona WJ et al. Cancer recurrence and survival rates after anatomic radical retropubic prostatectomy for prostate cancer intermediate-term results.
J Urol 1998;**160**:2428-2434.

[46] Ward JF et al. Radical prostatectomy for clinically advanced (cT3) prostate cancer since the advent of PSA-testing: 15 year outcome.
BJU Int 2005;**95**:751-756.

[47] Kirby RS et al. Prostate Cancer.
Mosby International Limited. 2001; **2**:117-119.

[48] Rosen RC et al. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction.
Int J Impot Res. 1999;**11**:319-26.

[49] Kupelian PA et al. Radical prostatectomy, external beam radiotherapy <72 Gy, external beam radiotherapy ≥72 Gy, permanent seed implantation, or combined seeds/external beam radiotherapy for stage T1–T2 prostate cancer.
Int J Radiat Oncol Biol Phys 2004;**58**:25-33.

[50] Stone NN. Brachytherapy or radical prostatectomy: is there a preferred method for treating localized prostate cancer?
BJU Int 2004;**93**:5.

[51] Blasko JC et al. Palladium 103 brachytherapy for prostate carcinoma.
Int J Radiat Oncol Biol Phys 2000;**46**:839-850.

[52] Arcangeli G et al. Radiation therapy in the management of symptomatic bone metastases: the effect of total dose and histology on pain relief and response duration.
Int J Radiat Oncol Biol Phys 1998;**42**:1119-1126.

[53] Collins C et al. Samarium 153 EDTMP in bone metastases of hormone refractory prostate carcinoma: a phaseI/II trial.
J Nucl Med 1993;**34**:1839-1844.

[54] Cantrell BB et al. Pathological factors that influence prognosis in stage A prostatic cancer: the influence of extend versus grade.
J Urol 1981;**125**:516-521.

[55] D'Amico AV et al. Biochemical outcome after radial prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer.
JAMA 1998;**280**:969-974.

[56] Lu-Yao GL et al. Population-based study of long-term survival in patients with clinically localised prostate cancer.
Lancet 1997;**349**:906-910.

[57] Wirth M et al. Bicalutamide (Casodex) 150 mg in addition to standard care in patients with localized or locally advanced prostate cancer: results from the second analysis of the Early Prostate Cancer program at 5.4 years' median follow-up.
J Urol 2004;**172**:1865-1870.

[58] Messing E et al. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node positive prostate cancer: results at 10 years of EST 3886.
J Urol 2003;**169**:396 [abstract 1480].

[59] Pilepich MV et al. Phase III Radiation Therapy Oncology Group (RTOG) trial 86-10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate.
Int J Radiat Oncol Biol Phys 2001;**50**:1243-1252.

[60] D'Amico AV et al. 6-month androgen suppression plus radiation therapy vs.radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial.
JAMA 2004;**292**:821-827.

[61] Bolla M et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin.
N Engl J Med 1997;**337**:295-300.

[62] Wirth MP et al. Casodex Early Prostate Cancer Trialists' Group. Bicalutamide 150 mg in addition to standard care in patients with localized or locally advanced prostate cancer: results from the analysis of the early prostate cancer programme at median followup of 5.4 years.
J Urol 2004;**172**:1865-1870.

[63] McLeod DG et al. Casodex Early Prostate Cancer Trialists' Group. Bicalutamide 150 mg plus standard care vs standard care alone for early prostate cancer.
BJU Int. 2006;**97**:247-254.

[64] Schmitt B et al. Maximal androgen blockade for advanced prostate cancer.
Cochrane Database Syst Rev 2000;**2**:D001526.

[65] Samson DJ et al. Systematic review and meta-analysis of monotherapy compared with combined androgen blockade for patients with advanced prostate carcinoma.
Cancer 2002;**95**:361-376.

[66] EAU Guidelines Prostate Cancer 2007.
http://www.uroweb.org/professional-resources/guidelines

[67] Walsh PC et al. Impotence following radical prostatectomy: insight into etiology and prevention.
J Urol 1982;**128**:492-497.

[68] Kollermann J et al. Nondetected tumor (pT0) after prolonged, neoadjuvant treatment of localized prostatic carcinoma.
Eur Urol 2000;**38**:714-720.

[69] MC Neal JE et al. Zonal distribution of prostatic adenocarcinoma. Correlation with histologic pattern and direction of spread.
Am J Surg Pathol 1988;**13**:897-906.

[70] Stewart S et al. Prostate cancer diagnosis using a saturation needle biopsy technique after previous negative sextant biopsies.
J Urol 2001;**166**:86-92.

[71] Stamey TA. Preoperative serum prostate-specific antigen (PSA) below 10 microg/l predicts neither the presence of prostate cancer nor the rate of postoperative PSA failure.
Clin Chem 2001;**47**:631.

[72] Orozco R et al.: Positive prostate biopsy rate consistently increases with age at the same prostate-specific antigen level in patients with normal digital rectal examination.
J Urol 1998;**51**:531.

[73] Catalona WJ et al. Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial.
JAMA 1998;**297**:1542-1547.

[74] Augustin H et al. Shift of tumor features in patients with clinically localized prostate cancer undergoing radical prostatectomy since the beginning of the PSA era.
Wiener Klinische Wochenzeitschrift. 2006;**118/11-12**: 348-354.

[75] Stamey TA et al. The prostate specific antigen era in the United States is over for prostate cancer: what happened in the last 20 years?
J Urol 2004;**172:** 1297–1301.

[76] Stamey TA et al. Localized prostate cancer. Relationship of tumor volume to clinical significance for treatment of prostate cancer.
Cancer 1993;**71**(3):933-938.

[77] Epstein JI et al. Pathologic and clinical findings to predict tumour extend of nonpalpable (stage T1c) prostate cancer.
JAMA 1994; **271**:368-374.

[78] Boccon-Gibod LM et al. Micro-Focal Prostate Cancer: A Comparison of Biopsy and Radical Prostatectomy Specimen Features.
Eur Urol 2005;**48**:895-899.

[79] Flanigan RC et al. Accuracy of digital rectal examination and transrectal ultrasonography in localizing prostate cancer.
J Urol 1994;**152**:1506-1509.

[80] Cookson MS et al. Correlation between Gleason score of needle biopsy and radical prostatectomy specimen: accuracy and clinical implications.
J Urol 1997;**157**:559–562.

[81] Bostwick DG. Gleason grading of prostatic needle biopsies. Correlation with grade in 316 matched prostatectomies.
Am J Surg Path 1994;**18**:796–803.

[82] Spires SE et al. Gleason histologic grading in prostate carcinoma. Correlation of 18-gauge core biopsy with prostatectomy.
Arch Path Laboratory Med 1994;**118**:705–708.

[83] Burkhard FC et al. Reliability of Preoperative Values to Determine the Need for Lymphadenectomy in Patients with Prostate Cancer and Meticulous Lymph Node Dissection.
Eur Urol 2002;**42**:84-92.

[84] Stamey TA et al. Histological and clinical findings in 896 consecutive prostates treated only with radical retropubic prostatectomy: epidemiologic significance of annual changes.
J Urol 1998;**160**:2412-2417.