POPULATION BASED SCREENING FOR PROSTATE CANCER

the pathology of early detected tumors

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The pathology of early detected tumors

BEVOLKINGSONDERZOEK NAAR PROSTAATKANKER

De pathologie van vroeg gedetecteerde tumoren

PROEFSCHRIFT

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	Prof. dr. F.H. Schröder
Overige leden:	Prof. dr. C.H. Bangma
	Prof. dr. ir. J.D.F. Habbema
	Prof. dr. D.J. Ruiter

The studies reported in this thesis were performed at the departments of Pathology, Urology and Public Health of the Erasmus University Rotterdam, the Netherlands. The studies form an integrated part of the European Randomized study of Screening for Prostate Cancer (ERSPC), an international multicenter study that investigates the effects of population based screening for prostate cancer on mortality and quality of life.
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Voor mijn ouders
Voor Ingeborg

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List of Contributing Authors

Theodorus. H. van der Kwast	Department of Pathology in the Rotterdam Dijkzigt Hospital and the Erasmus University Rotterdam
Fritz H.Schröder	Department of Urology Rotterdam Dijkzigt Hospital and the Erasmus University Rotterdam Study coördinator of the European Randomized study of Screening for Prostate Cancer (ERSPC)
John.B.W. Rietbergen	Department of Urology Rotterdam Dijkzigt Hospital and the Erasmus University Rotterdam
Arto E. Boeken Kruger	Department of Urology Rotterdam Dijkzigt Hospital and the Erasmus University Rotterdam
André N. Vis	Departments of Pathology and Urology in the Rotterdam Dijkzigt Hospital and the Erasmus University Rotterdam
Ries Kranse	Department of Urology Rotterdam Dijkzigt Hospital and the Erasmus University Rotterdam
Monique Roobol	Department of Urology Rotterdam Dijkzigt Hospital and the Erasmus University Rotterdam
Harry J. de Koning	Department of Public Health, Erasmus University Rotterdam
Rob Boer	Department of Public Health, Erasmus University Rotterdam

List of abbreviations

AAH	Atypical Adenomatous Hyperplasia
AAP	Atypical Acinar Proliferation
ASAP	Atypical Small Acinar Proliferations
DRE	Digital Rectal Examination
ERSPC	European Randomized study of Screening for Prostate Cancer
LH	Luteinizing Hormone
LHRH	Luteinizing Hormone Releasing Hormone
PIN	Prostatic Intraepithelial Neoplasia
PAP	Prostate Acid Phosphatase
PSA	Prostate Specific Antigen
TRUS	Trans Rectal Ultrasonography

GENERAL INTRODUCTION

The prostate is notorious for its relatively high occurrence of malignant tumors (prostatic adenocarcinomas) in older men. The incidence of prostatic adenocarcinoma - or as it is generally referred to - prostate cancer, increases with age. The increased life expectancy of men and the use of new, more sensitive methods to detect prostate cancer have led to the observation that prostate cancer is now the second most diagnosed malignant tumor in males after non-melanotic skin cancer. In the United States, prostate cancer mortality is second only to mortality caused by lung cancer [1].

The increasing incidence of prostate cancer has led to the question whether early detection by systematic screening of the general population at risk would be beneficial with respect to overall survival and quality of life. To address this question, several large randomized trials on screening for prostate cancer are in progress. A randomized trial entails that the studied population is randomly divided into two groups. One of the two groups, also called the screening arm is offered periodical tests for prostate cancer, while the other group (the control arm) is not. At the end of the study period, the two groups are compared with regard to differences in survival and quality of life.

The European Randomized study of Screening for Prostate Cancer (ERSPC), a joint effort by several European hospitals and health centers in nine different European countries, is such a randomized trial [2]. By randomizing 200.000 European males of ages ranging from 50 to 75 years into screened and non-screened groups, the ERSPC strives to answer the question whether systematically screening the male population for prostate cancer leads to a health benefit. One of the main participating centers of ERSPC is the Rotterdam University Hospital, which is responsible for the randomized study of 40.000 residents of the city of Rotterdam and its surroundings. The effects of population-based screening for prostate cancer are not a subject of this thesis, as the first overall evaluations of the randomized trial are not expected until 2008.

Meanwhile, however, especially in large scale programs, such as the ERSPC, the determination of intermediate endpoints, which facilitate an evaluation of the feasibility of systematic screening, is of great importance. Apart from the observation of the detection rates of prostate cancer in the different rounds of screening, the assessment of the efficiency of the different screening tests, and the determination of screening-related morbidity and mortality, the histopathologic assessment of the characteristics of the detected tumors is important during the evaluation of the screening process. Histopathologic examination provides a way to continuously interpret and check the

possible clinical significance of the detected tumors in the screened population, and serves as an early alarm system, when too many small and possibly harmless tumors would be found. Besides this, it provides a way to investigate which if any effect the efforts for early detection have on features associated with the biological behavior of the detected tumors and thereby on the prognosis of the screened participants.

In this thesis, the outcomes of various studies of the histopathologic characteristics of tumors and premalignant lesions that were detected in the screening arm of the Rotterdam section of ERSPC are presented and discussed.

An optimal interpretation of the studies in this thesis requires some general knowledge of the normal anatomy, morphology and function of the prostate, as well as some insight in general aspects of prostate cancer, its epidemiology, diagnosis, assessment and treatment options. Chapter 1 was written to provide a general overview of these matters, and in addition the problems and controversies of screening for prostate cancer are discussed.

A reliable histopathologic documentation of tumor features requires consistent protocols for processing and reporting prostate tissue specimens. In Chapter 2, the methodology of the processing and reporting of needle biopsy sets and radical prostatectomy specimens is presented and discussed.

The definite diagnosis of prostate cancer or one of its precursor lesions requires histopathologic examination of prostatic tissue. For this reason, approximately 20% of participants in the screened group are selected to undergo the sextant biopsy procedure. Histopathologic examination of prostatic biopsies does not always lead to conclusive results. In Chapter 3, the frequencies of prostate cancer and lesions that require repeated biopsies (e.g. precursor lesions and biopsies that lack a conclusive diagnosis) are described in screened participants of the ERSPC. The frequencies of precursor lesions and inconclusive biopsies are of great importance in large screening programs for prostate cancer, since too many indications for repeat biopsies would hamper their feasibility. Besides a description of the frequency of repeat biopsy indications, in Chapter 3 the outcome of performed repeat biopsies is discussed and compared to the available literature.

During screening in the ERSPC, participants are offered three tests, namely digital rectal examination (DRE), transrectal ultrasonography and the measurement of serum levels of prostate specific antigen (PSA). An indication for biopsies is established if one or a combination of these tests show abnormal results. Especially tumors detected after an

elevated serum PSA level only (i.e. impalpable and invisible tumors) have raised some concern in the literature, since their clinical significance was unclear. Chapter 4 outlines a study in which the general histopathologic characteristics of screen-detected tumors in radical prostatectomy specimens obtained after surgical treatment are documented. A special emphasis is placed on tumors that are detected by elevated serum PSA levels only (i.e. impalpable and ultrasonographically invisible tumors). The assessment of the clinical significance of tumors depends on a mixture of various tumor characteristics. In addition, age and life expectancy of the individual patient will strongly influence the clinical outcome. To estimate the possible clinical significance of these tumors, we introduced an arbitrary model, which combines tumor extent and grade.

The clinical significance of tumors detected and surgically treated in the screening arm of the Rotterdam section of the ERSPC is discussed further in Chapter 5. In this chapter, the characteristics of a larger series of screen detected and treated prostatic tumors in participants of the ERSPC are compared to a historic series of conventionally detected prostate cancer (in a time period before the introduction of serum PSA measurements). It is discussed whether such a comparison is able to predict whether systematic screening will lead to an improvement in the prognosis of treated participants.

As is outlined in Chapter 1, systematic screening for prostate cancer entails a risk of detecting a large number of clinically insignificant tumors (i.e. tumors that will not pose a threat to their host's health during his lifetime). Although the purpose of an early detection program for malignant tumors is to detect and subsequently treat at an early stage thereby improving prognosis and life-expectancy of the screened population, the frequency of mostly small and well differentiated prostate cancers that are found incidentally (at autopsy or surgery for bladder cancer) is very high. Therefore, an increased detection of clinically insignificant tumors may lead to high rates of unnecessary treatment and the question remains whether every malignant prostatic tumor requires treatment. Chapter 6 discusses whether small and well differentiated prostate cancers can be predicted with combinations of clinical parameters. An accurate predictability of this kind of tumors could enable additional future studies to establish possible ways to deal with this problem.

The effects of a periodical screening program for prostate cancer rely on a large number of different parameters. An important factor for the efficiency of screening is the length of the interval that lies in between different screens. After an initial screen (prevalence

screen), participants of the Rotterdam section of ERSPC were screened at intervals of 4 years. Chapter 7 discusses the histopathologic characteristics of tumors in needle biopsies in the second screening round and compares them to the characteristics of the tumors detected at the first round (prevalence screen). The efficiency of the chosen screening interval at ERSPC is discussed.

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Chapter 1

PROSTATE CANCER AND SCREENING FOR PROSTATE CANCER

Robert F. Hoedemaeker

1. The Normal Prostate

1.1 Anatomy

The prostate consists of groups of exocrine glands that are packed in dense fibromuscular tissue and surround the proximal part of the urethra. For practical purposes, it is best to consider the prostate as a pyramid-shaped organ with, its point (apex) pointing downward and its base facing upward and slightly forward (figure 1A). At the base, three different structures border the prostate: the bladder neck borders the anterior end of the base and two seminal vesicles and two deferential ducts extend at the posterior end. Each seminal vesicle consists of a long convoluted tubular structure surrounded by a well-defined muscular wall. On each side, a deferential duct that arrives from the epididymis joins the seminal vesicle at its base. The seminal vesicles and deferential ducts are connected to the urethral lumen by two ejaculatory ducts that lie within the prostatic stroma and join the urethra in the center of the prostate gland (figure 1B).

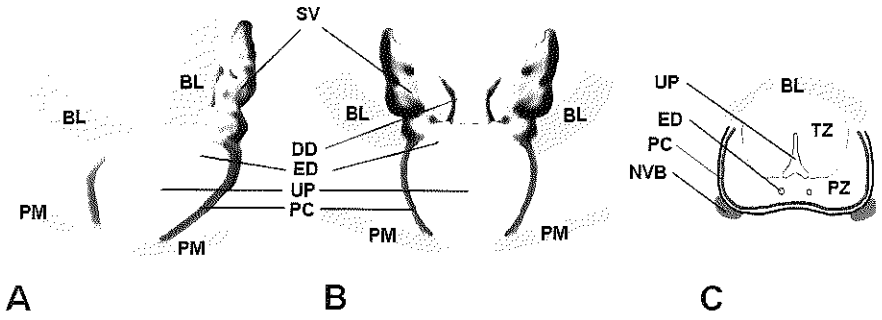


Figure 1. Schematic drawing of the prostate showing its lateral (A) and frontal (B) aspect as well as a transverse section (C). The prostatic capsule is shown in red. These drawings show the different boundaries of the prostate. (Abbreviations :BL: bladder neck; PM: pelvic musculature; SV: seminal vesicles; DD: ductus deferens; ED: ejaculatory ducts; UP: prostatic urethra; NVB: neurovascular bundles; TZ: transition zone; PZ: peripheral zone; PC: periprostatic (pseudo-) capsule).

At its apical end, the prostate is surrounded by the striated musculature of the pelvis. At its posterior, lateral and - to a lesser extent- its anterior side, the prostate is surrounded by loosely packed connective and fatty tissue, in which two neurovascular bundles are located at the posterolateral side of the gland (figure 1C). The demarcation between the prostate and its surrounding loose connective and fatty tissue is sharpest at the rectal and

lateral sides of the gland. In these areas, the prostatic stroma forms a sheet at the circumference of the glandular tissue. This structure of dense fibromuscular stroma has often been referred to as the prostatic capsule. A few studies, however, provide arguments that it rather should be regarded as a mere extension of the prostatic stroma[1,2].
The glandular tissue of the prostate can be divided into different regions in various ways. Traditionally, five different lobes of glandular tissue were recognized, an anterior, a middle and a posterior lobe flanked by two lateral lobes. Besides this division based on anatomy, prostatic glandular tissue can be divided functionally into a more centrally and peri-urethrally located transition zone and a more posteriorly and laterally located peripheral zone (figure 1C). The glands in the transition zone are the main sites for the development of benign prostate hyperplasia, while the glands in the peripheral zone are more prone to malignant transformation[3,4]. Furthermore, the two zones show different morphologic changes after hormone deprivation[5]. Therefore, in addition to being simpler, a functional approach to the division of prostatic glandular tissue also reflects several aspects of normal prostate physiology and prostatic disease better than the anatomical approach.

1.2 Histology and function

Together with the seminal vesicles, the prostate produces substances that are added to the spermatozoa that arrive at the prostate through the ductus deferens (figure 1B). Approximately 60% of the semen consists of seminogelin, which is produced by the seminal vesicles. The prostate roughly contributes 30% by adding proteins and enzymes that control and regulate the liquidity of the semen. The bulbourethral and urethral glands that lie further, i.e. 'downstream' along the urethra produce the other 10% of the semen. Morphologically, the glandular tissue of the prostate is similar in all zones and consists of ducts and acini lined by a double epithelial layer. The inner or luminal secretory epithelial cells have a cuboidal and sometimes columnar shape. They are separated from the basal membrane by a continuous layer of mostly flattened, but sometimes cuboidal basal epithelial cells. Scattered throughout the glands, neuroendocrine cells are present, mostly in or just above the basal cell layer. A dense stroma, rich in smooth muscle fibers, surrounds the glands (figure 2).

The luminal epithelial cells of both acini and ducts produce an array of proteins that are released in the semen. Among these proteins are prostate acid phosphatase (PAP) and prostate specific antigen (PSA). PSA digests the protein seminogelin and seems to have an important role in regulating the degree of liquidity of the semen and thereby influencing the motility of the sperm. Both PAP and PSA are – given only a few exceptions of mostly background expression in other tissues[6] – exclusively produced by prostate epithelium[7-9]. For their maintenance and functional activity, luminal cells are dependent on androgen hormones. Androgen receptors are mostly located in the nuclei, as can be demonstrated immunohistochemically[10].

The basal cells in the human prostate do not have a connection to the lumen of the glands and they do not produce PSA or PAP. Focally, however, basal cells do express androgen receptor[10-12]. The contractile elements that can be found in myoepithelial cells in other glandular organs such as the breast, are not present in human prostatic basal cells. With the high content of smooth muscle tissue in the prostatic stroma taken into consideration, contractile qualities of the basal cells would indeed seem redundant. In contrast to luminal epithelial cells, the cytoskeleton of basal cells contains high molecular weight keratin molecules. This has proven of great value in diagnosing prostate cancer, because basal cells are absent in prostate cancer, which can be confirmed with specific stains for high molecular weight keratins such as 34β12[13,14].

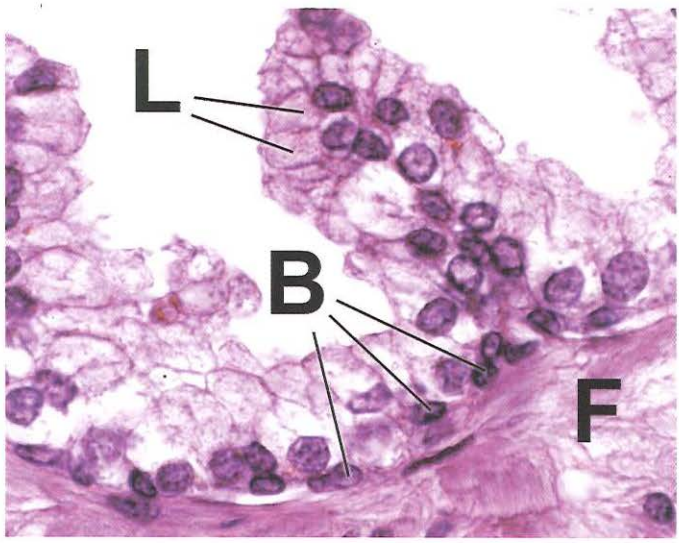


Figure 2. Benign prostatic tissue showing part of the wall of a glandular structure (H&E stained x400). (Abbreviations :**L**: Luminal (secretory) cell; **B**: basal cell; **F**: Fibromuscular stroma).

The exact role of the basal cell population is not yet known. Some investigators have provided evidence that prostatic basal cells act as a reserve population for the renewal of luminal cells[15]. They are thought to hold a stem cell compartment, from which by multidirectional differentiation, luminal secretory cells and neuroendocrine cells emerge[16]. However, a recent study showed that basal cells have ultrastructural features of differentiated and active cells[17]. Basal cells have been shown to produce enzymes that are able to convert inactive adrenal steroid precursors into active androgens[18]. These observations implicate that basal cells in the human prostate, apart from acting as the main proliferative cell compartment in the prostatic epithelium, also form a differentiated and functional cell layer that functions as a barrier between luminal cells and the prostatic stroma, thus regulating growth and differentiation of the epithelium.

Other observations that indirectly support the theory, that basal cells are not a merely a reserve cell population for the renewal of the luminal epithelial cell layer, include the high proliferative activity of luminal cells under circumstances of androgen deprivation or post-inflammatory atrophy. This "self-renewal-capacity" of the luminal cells implicates that the renewal of luminal epithelial layer does not rely entirely on the proliferative capability of the basal cells[19,20].

Neuroendocrine cells in the prostate epithelium also produce a large variety of peptides. Among these are chromogranin A, serotonin, and neuron-specific enolase[21]. The exact function of these secretory products is unknown, but it is likely that they are secreted as part of a paracrine system, and that they have a signaling function to the surrounding epithelial cells. A minority of neuroendocrine cells produces PSA, which implies a kinship to the luminal epithelial cells. They, however, consistently lack expression of androgen receptor[22,23].

The prostatic stroma is made up of connective tissue and smooth muscle fibers. The smooth muscle tissue in the prostatic stroma probably exerts its main function during ejaculation, when prostatic products are ejected together with the semen. Development and differentiation of smooth muscle fibers in the prostate depends on the presence of androgens, which is reflected by their nuclear expression of androgen receptor.

2. Prostate Cancer

2.1 Introduction

More than 95% of malignant prostatic tumors are adenocarcinomas that often show a morphologic and immunohistochemical resemblance to normal prostatic glandular tissue. Other, rare epithelial malignancies that primarily occur in the prostate include basal cell carcinoma arising from the basal cell population[24], and urothelial carcinoma arising from the prostatic urethra[25,26]. Malignant tumors of the prostatic stroma (most often leiomyosarcoma, solitary fibrous tumor and rhabdomyosarcoma) are occasionally reported[27-29]. Even less frequent are mixed neoplasms containing both stromal and epithelial cells[30,31]. Very rarely, hematological malignancies and germ cell tumors that seem to have originated in the prostate have been reported in the literature[32-34]. In general, the term prostate cancer is used to designate primary adenocarcinomas with morphologic and immunohistochemical resemblance to the luminal epithelial cells of the prostate.

2.2 The epidemiology of prostate cancer

2.2.1 Clinical incidence

The occurrence of prostatic adenocarcinoma is reported almost exclusively in men and dogs and has rarely been described in primates and other mammals[35-38]. In man, prostate cancer is rarely diagnosed before the age of forty. The cumulative chance for a fifty year old male to be diagnosed with prostate cancer during the rest of his lifetime, is estimated at 9.9 %[39]. The clinical incidence of prostate cancer increases rapidly with age. In the Netherlands it is the most frequently diagnosed malignancy with the highest mortality rate in males over 85 years old, even surpassing mortality by lung cancer[40].

As the general life expectancy of man continues to rise, the incidence of prostatic adenocarcinoma is expected to rise accordingly. During the last decade, the incidence of prostate cancer has risen dramatically in Western countries. Most of this rise is attributed to the increased use of serum PSA measurements, a relatively new clinical tool to detect men at risk for prostate cancer[41].

2.2.2 'Latent' prostate cancer

The already high clinical incidence of prostate cancer is by far surpassed by the prevalence of mostly small adenocarcinomas that are incidentally found at autopsy or in prostatic tissue that is surgically removed in patients with bladder cancer or with urinary outflow obstruction. In several studies, the prevalence of these "clinically latent" prostate adenocarcinomas is estimated to lie between 30 and 50% in males over fifty years old[42-44]. Apparently, human prostatic epithelial cells are very susceptible to malignant transformation. However, not every prostatic adenocarcinoma will lead to clinical morbidity or mortality, and men seem to have a higher chance of dying with prostate cancer than of dying of it. This poses a significant clinical problem, especially in early detection programs for prostate cancer where the high prevalence of clinically unimportant tumors could result in an increased risk for unnecessary treatment. Studies made in effort to distinguish clinically important tumors from clinically unimportant ones have shown that volume and volume doubling times are important predictors of biologic behavior[45,46]. On the other hand, recent studies show that some small prostatic adenocarcinomas may sometimes show evidence of potentially aggressive behavior[47,48]. The clinical significance of prostatic adenocarcinoma cannot yet be predicted on an individual patient basis, and it seems likely and logical that patient characteristics such as age and co-morbidity are important factors in such a prediction[49].

2.2.3 Geographical distribution and environmental factors

The variation of the incidence of clinically detectable prostate adenocarcinoma by geographic region is striking. The highest incidence is found in the United States and Scandinavian countries, whereas the lowest incidence is reported in Japan and the Mediterranean countries[50-52]. Prostatic adenocarcinoma incidence also differs by ethnic group within countries. The incidence of prostate cancer in Afro-American males is markedly higher than its incidence in Caucasian, native Chinese, and native Japanese American males[53]. In contrast to the incidence of clinically detectable prostate cancer, the prevalence of latent adenocarcinomas of the prostate shows little or no variation between different geographic regions or ethnic groups[54,55].

The observation that the prostate cancer risk rises in Japanese males who move to Western countries, implies that environmental factors such as nutrition play an important role in the development of prostate cancer into a clinically detectable and sometimes life-

threatening disease[50,56]. A high intake of fat has been implicated to cause an increased chance for the development of clinically detectable prostatic adenocarcinoma[57,58]. Possible protective effects of other nutrition such as soy beans, vitamin D, and green tea, have not yet been conclusively demonstrated and are currently still being researched[59-61].

2.3 Pathogenesis and precursor lesions of prostate cancer

2.3.1 The pathogenesis of prostate cancer

Very little is known about the mechanisms by which prostate cancer originates and evolves. In the normal prostate, the basal cell compartment is thought to be the cell compartment for renewal of epithelial and neuroendocrine cells, and thereby constitutes the cell population with the highest proliferative activity within the prostate[62]. One would think that cell compartments with the highest proliferative activity would be the ones most likely to undergo malignant transformation. However, prostatic adenocarcinomas do not show any resemblance to the basal cell compartment of the benign prostate. They for instance do not express high molecular weight keratins[13,14], but do express both PSA and PAP, which demonstrates that the malignant cells in prostatic adenocarcinomas are closely related to the luminal secretory cell compartment in the benign prostate[9,63]. Moreover, most prostatic adenocarcinomas widely express androgen receptor[64], whereas androgen receptor is only focally expressed by basal cells in the normal prostate[11,12]. Finally, fully differentiated neuroendocrine cells are present in prostatic adenocarcinomas[65,66]. Taking these observations into account, a stem cell model for the pathogenesis of prostate cancer was proposed by Bonkhoff et al. in 1996[16]. This model contends that an androgen-dependent stem cell population located in the basal cell layer gives rise to all epithelial cell lineages in the normal prostate. According to the model, prostate cancer would eventually originate from this stem cell compartment which partly differentiates into cells with the characteristics of secretory luminal cells and for another part into neuroendocrine cells. Although the correctness of this model has never been proven, it has never been refuted either.

Alternative hypotheses on the pathogenesis of prostate cancer however cannot be ruled out either. The observation, that the luminal epithelial cells are capable of self-renewal implies, that they also could represent a target for oncogenic events[19]. The fact that

conventional prostatic adenocarcinomas never show morphologic or immunohistochemical characteristics of basal cells supports this alternative hypothesis. In view of this hypothesis, the presumed regulatory role of the basal cell population in the development and differentiation of the luminal cell compartment in benign prostatic glandular tissue[18] becomes interesting. The progressive loss of basal cells in precursor lesions for prostate cancer (prostatic intraepithelial neoplasia, mentioned below) and their absence in prostatic adenocarcinomas could imply that the loss of basal cells would render the luminal epithelial cells prone to malignant transformation.
Prostate cancer is often multifocal, which may indicate that it results due to a "field" effect of carcinogenic factors[67,68].

2.3.2 Prostatic Intraepithelial Neoplasia (PIN)

To get insight in prostatic carcinogenesis, a search was made for premalignant lesions. Apart from the view, that premalignant lesions might reflect some of the mechanisms by which prostate cancer develops, their identification could be of help in the development of methods for prostate cancer prevention.
A premalignant lesion in the prostate was first described by McNeal 1965[69]. Initially, this lesion was called intraductal dysplasia[70] and later, the name prostatic intraepithelial neoplasia (PIN) was proposed by Bostwick and Brawer[71]. According to the severity of the histologic and cytologic changes, PIN was originally divided into three grades (I, II and III). In 1989, it was recommended that these three grades were compressed into two (low grade PIN for grade I, and high grade PIN for grades II and III)[72].
Histologically, PIN is characterized by a cellular proliferation within the pre-existing lining of prostatic ducts, ductules and acini. The proliferating cells show cytologic changes that are similar to those observed in invasive prostate cancer, such as nuclear and nucleolar enlargement and an increased density of the cytoplasm of the cells[70]. The basal cell layer is typically discontinuous, especially in high grade PIN (figure 3). The proliferative activity in PIN lesions is essentially different from that in normal glands. In PIN, most of the proliferative activity is seen in the (dysplastic) layer of luminal secretory cells[16], whereas physiologically, most of the proliferation in prostatic ducts occurs in the basal cell layer[62]. The observed morphologic and functional changes in high grade PIN could fit into the concept of the pathogenesis of prostate cancer that is proposed in Bonkhoff's stem cell model[16]. However, they could also fit in the above-mentioned

alternative hypothesis for prostate cancer carcinogenesis, which contends that the observed changes are caused by the loss of basal cells.

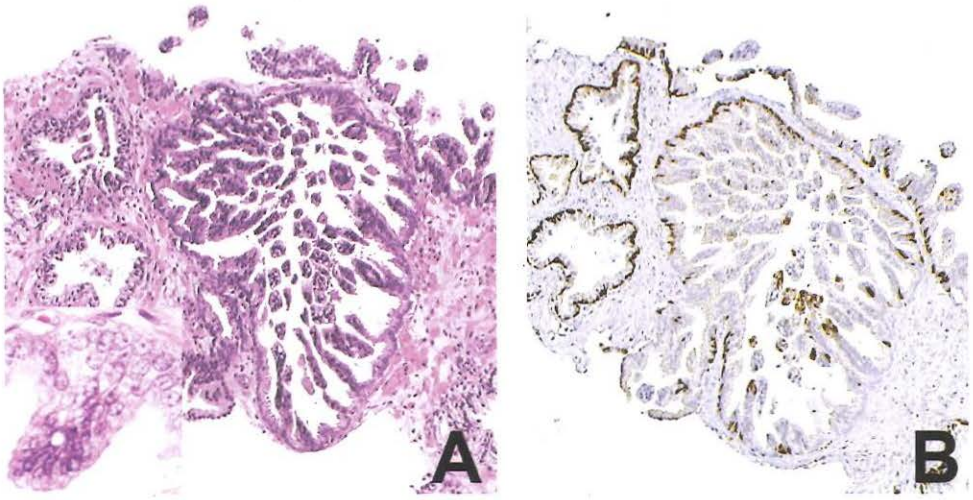


Figure 3 High grade PIN of the prostate. A: PIN presents itself mostly as large ducts with clearly enlarged nuclei and prominent nucleoli (inset) of the lining cells (H&E, 100x). B: Immunohistochemical stain of the same lesion with 34β12, a monoclonal antibody directed specifically against basal cells, showing the characteristically discontinuous basal cell layer opposed to the continuous layer in the benign glands on the left side (34β12 immunohistochemical stain, 100x).

The evidence for an association of high grade PIN with prostate cancer is overwhelming. In about 80% of cases, high grade PIN is found to co-exist with adenocarcinoma[44,70]. Like adenocarcinomas, most high grade PIN lesions are found in the peripheral (outer) zone of the prostate[73]. Cytogenetic aberrations in high grade PIN have been found to be similar to those found in adjacent adenocarcinomas[74-76]. Differences in the incidence of high grade PIN in Afro-American and Caucasian males might partly explain the difference of the incidence of clinically detectable adenocarcinoma between these two groups in the population[77]. Still, a fraction of about 24% of adenocarcinomas is found in the absence of high grade PIN[44]. Whether PIN is overgrown by adenocarcinoma in some cases, or whether alternative precursor lesions of prostatic adenocarcinomas exist, is not yet clear. Its strong association with prostatic adenocarcinoma has raised the question whether high grade PIN might form a suitable target lesion for some kind of preventive therapy, including chemoprevention [78,79]. Several reports mention a reduction of the extent and the prevalence of high grade PIN after androgen deprivation[5,80,81]. One study, however, shows that high grade PIN persists even after long-term androgen deprivation, which suggests

that endocrine manipulation by androgen deprivation seems less suitable for the chemoprevention of prostate cancer[82]. Currently, it is recommended that the finding of isolated high grade PIN in needle biopsies does warrant repeat biopsies to exclude concurrent or later evolving adenocarcinoma[83-87]. The clinical relevance of high grade PIN detected in early detection programs is discussed in Chapter 3 of this thesis.

2.3.3 Other premalignant lesions

A few other types of lesions have been proposed as being premalignant. They include atypical adenomatous hyperplasia (AAH) and atrophic lesions. The evidence of their premalignant nature is, however, much less convincing than for high grade PIN[20,88-90].

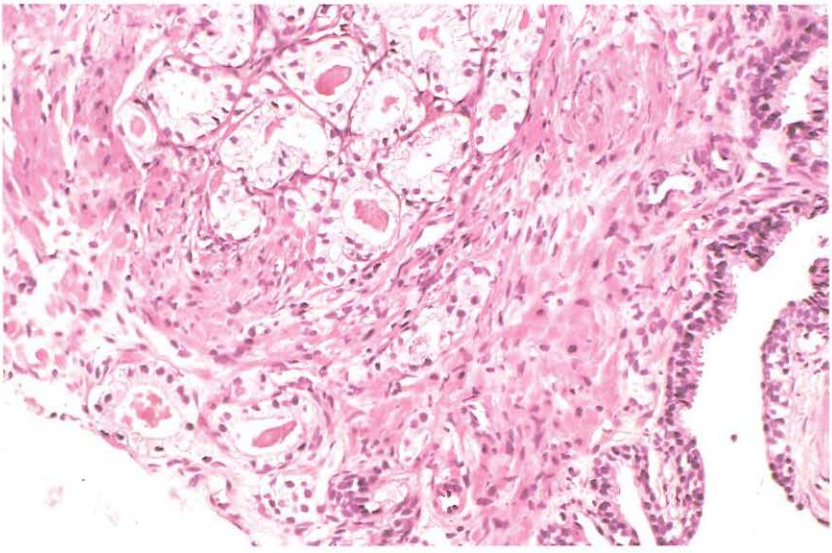


Figure 4. Atypical adenomatous hyperplasia (AAH) of the prostate. The picture shows a compact proliferation of small to medium sized glands. Nuclei are not clearly enlarged.

AAH (shown in figure 4) consists of reasonably well circumscribed proliferations of small, closely packed, uniform glands, often with an discontinuous layer of basal cells. It is often found in the transition zone of the prostate[91]. It seems loosely associated with the occurrence of prostate cancer, especially with well-differentiated adenocarcinomas that occur in the transition zone of the gland[91,92]. AAH closely resembles well-differentiated prostate cancer, and is therefore a known source of overdiagnosis[93]. Direct transitions from AAH to invasive adenocarcinoma, comparable to those observed in high grade PIN, have not been reported for AAH. Genetic alterations in AAH are infrequent, although they

seem to be comparable to genetic alterations observed in well-differentiated prostate cancer[94].Overall, the evidence that AAH can be considered a premalignant lesion remains insufficient.

It is important to stress that small lesions that are suspicious for, but not diagnostic of prostate cancer -sometimes referred to as atypical small acinar proliferations (ASAP) or borderline lesions- do not qualify for the specification of a premalignant lesion. These lesions are discussed elsewhere in this introduction and in Chapter 3 of this thesis.

2.4 The clinical detection of prostate cancer

2.4.1 Introduction

To identify men at risk for prostate cancer, three clinical methods exist and are often used in various combinations. Until thirty years ago, palpation via digital rectal examination (DRE) was the only way to evaluate the prostatic gland. Later developments enabled visualization of the prostate by transrectal ultrasonography (TRUS)[95]. A decade ago, measurement of serum PSA proved another important clinical tool to detect men at risk for prostate cancer[41,96].

2.4.2 Digital rectal examination (DRE)

Prostate cancer most frequently develops in the peripheral or outer zone of the prostate[3]. Because of their location, tumors can often grow for a considerable amount of time without giving rise to clinical symptoms such as urethral compression or bleeding. As a result of this long symptomless tumor expansion, prostate cancer used to be diagnosed either at a very late stage, or at a routine DRE in men who presented for conditions unrelated to the prostate. For a long period of time, routine examination of the prostate by DRE was the only possibility for an early recognition of prostate cancer[97]. Compared to combinations of DRE with either TRUS or serum PSA measurements, however, DRE as a single detection tool leads to relatively low detection rates and the detection of relatively advanced disease[98,99]. Something that might partly explain this is the fact that at DRE only part of the prostatic gland can be examined, namely the part that borders the rectal wall. Nowadays, the performance of DRE as a single screening tool is considered ineffective in prostate cancer early detection programs.

2.4.3 Transrectal ultrasonography (TRUS)

Adenocarcinoma of the prostate can present itself as a hypoechoic area at ultrasonography[100](figure 5). Because not every prostatic adenocarcinoma presents with abnormal findings at DRE, the introduction of ultrasonographic imaging of the prostate meant an valuable tool for the detection of impalpable tumors. However, as several studies have shown, only about half of prostatic adenocarcinomas are visible as hypoechoic lesions on transrectal ultrasonography[101,102]. The value of TRUS in detecting prostate cancer is therefore limited, even in combination with DRE. On the other hand, TRUS has proven valuable for visualization of the entire prostatic gland, which is useful in guiding biopsy needles.

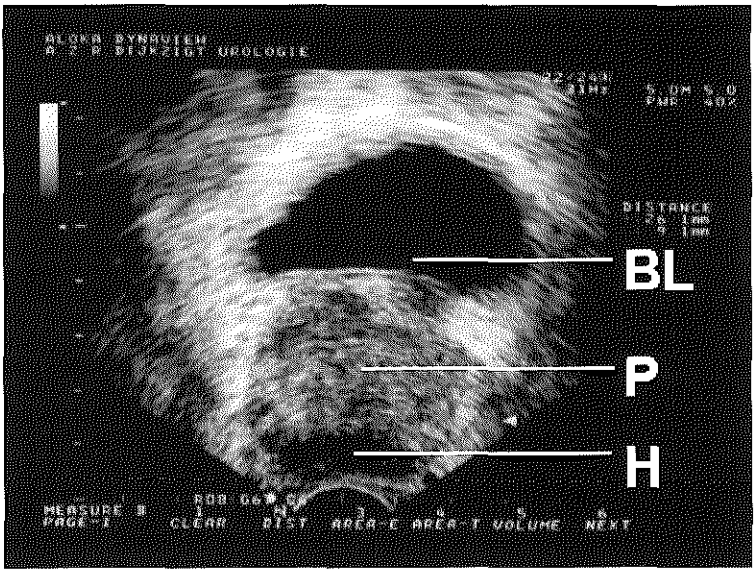


Figure 5. Transrectal ultrasonography (TRUS) showing a transverse section of the prostate. A part of the bladder is also visible. In this case a prostatic adenocarcinoma is visible as a hypoechoic lesion (dark) at the bottom. (Abbreviations :BL: bladder; P: prostate; H: hypoechoic lesion)

2.4.4 Serum Prostate Specific Antigen (PSA) measurement

The introduction of serum PSA measurement as a tool for detecting men at risk for prostate cancer did have a major impact on prostate cancer detection rates. The substantial rise in the incidence of prostate cancer that occurred in Western countries during the last decade has been mainly attributed to its increased use[103-105]. Prostatic adenocarcinomas often cause an elevation of serum PSA levels. Although the exact mechanism by which

this happens is not yet clear, it is generally assumed that PSA leaks through the walls of imperfectly built cancerous glands, and eventually enters the bloodstream by way of capillaries in the prostatic stroma. PSA leakage into the bloodstream is not a process that is exclusively related to prostatic adenocarcinomas, and an elevation of serum PSA also occurs in benign conditions such as inflammation or benign prostatic hyperplasia[106,107]. Serum PSA measurements have proven to be a useful tool in the detection of prostatic adenocarcinomas that are neither palpable at DRE, nor visible at TRUS. Its use has led to an increased detection of tumors that proved to be confined to the prostate at surgery, and therefore are likely to have a favorable prognosis[108]. The increased detection and subsequent treatment of this new subset of non-palpable and invisible prostatic adenocarcinomas has become a major subject of much discussion, since it was not clear whether they were different from the majority of latent carcinomas found at autopsy. Some studies, however, have put forward that a large majority of PSA-detectable tumors has to be considered clinically significant[109]. The clinical significance of PSA-detectable adenocarcinomas in early detection programs is discussed in Chapter 4 of this thesis.

2.5 The histology of prostate cancer

2.5.1 Introduction

The above-mentioned clinical tools represent various ways of selecting men that are at risk of having prostate cancer. To establish a definite diagnosis, the obtainment and the subsequential examination of prostatic tissue samples is essential for the establishment of a definite diagnosis. Basically, the histologic diagnosis of prostate cancer is made on two types of tissue samples. Most frequently, in cases with a clinical suspicion for prostate cancer, one or more prostate biopsies are taken. It is, however, not uncommon that prostate cancer is unexpectedly diagnosed in therapeutically resected prostate tissue for other conditions (e.g. transurethral resections for benign prostatic hyperplasia or cystoprostatectomies for bladder cancer).

2.5.2 Systematic sextant prostate biopsies

It is now generally accepted that obtaining six systematic transrectal ultrasound-guided biopsies (systematic biopsies from each side of the apex, middle, and base of the prostate)

constitutes a highly effective method for the detection of prostate cancer that should be preferred above the performance of separate biopsies that are directed towards palpable or echographically abnormal areas in the prostate[110-112] (Fig 6).

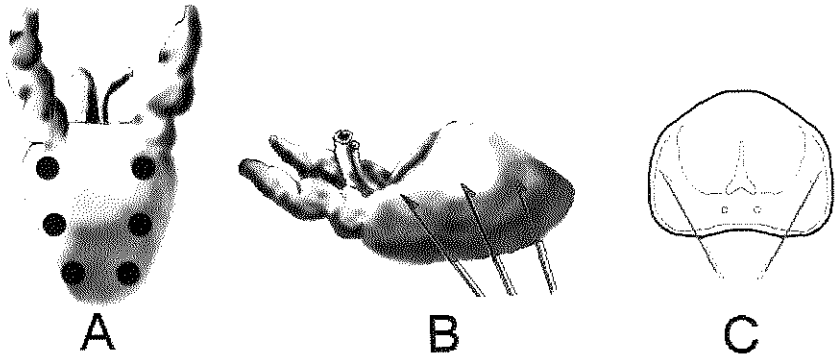


Figure 6. Systematic sextant prostate biopsy scheme A: dorsal view; B: lateral view; C: transverse section. Biopsies are directed laterally to preferentially sample the peripheral zone.

Apart from providing a way to establish the definite diagnosis of prostate cancer, the histologic examination of biopsy specimens is probably the best way to assess prognostic prostate cancer characteristics (such as grade, stage, and extent) before treatment. The interpretation of prostate cancer characteristics on biopsies therefore partly influences the choice of treatment. To a certain extent, sometimes in combination with the value of serum PSA, biopsy-derived cancer characteristics show a clear relationship to prognostic cancer characteristics in the prostate[113]. However, this has been shown not to hold true for individual prostate cancer cases. Whether prostate biopsies can be used to predict cancer characteristics on an individual basis is still questionable[114]. The main reason for this is the high likelihood to underestimate and underdiagnose prostatic disorders on biopsies. Because biopsy specimens only represent a very limited fraction of the tumor and of the total prostatic tissue, sampling error, which leads to underestimation, is likely to occur. Three major categories of underestimation are known to occur and are extensively described in the literature. These are: (1) underestimation of the grade of the tumor ('undergrading')[115,116], (2) underestimation of the extent of the tumor[114,117,118], and (3) underestimation of the diagnosis, for when sextant biopsies are repeated in patients with prostate cancer, approximately a third of the tumors are not redetected[119,120]. To improve pretreatment evaluation of prostate cancer and to reduce underestimation, one could

increase the number of biopsies in the diagnostic session. Recently, a study was performed by Eskew et al., who reported that by adding seven biopsies to the traditional sextant biopsies, cancer detection rates increased by a remarkable 35%[121]. This increase might largely be attributable to the more lateral placement of some of the additional biopsies. Placing sextant biopsies as lateral as possible was previously recognized to have advantages in cancer detection rates, because more of the peripheral zone is sampled[112], (Fig 6c). Another recent study, conducted by Onder et al., focussed on the value of adding transition zone-directed biopsies to the sextant biopsy scheme[122]. They concluded that transition zone biopsies did not substantially increase cancer detection rates. A small study on prostate cancer detection in biopsies performed on radical prostatectomy specimens of men with sextant biopsy-detected prostate cancer was performed in our own institution. The results showed that by tripling the number of biopsies, cancer redetection rates in the radical prostatectomy specimens only moderately increased (from 68% to 80%), while the grading error did not decrease significantly[120].
The effect of a substantial increase in the number of initial biopsies therefore appears to be limited. To avoid the high costs and the increased amount of effort associated with an increased number of initial biopsies, the performance of repeat biopsies in selected cases, such as lesions that are suspicious for, but not diagnostic of prostate cancer, a minimal cancer focus in the initial biopsy or a benign diagnosis in combination with a strong clinical suspicion of prostate cancer, seems to be preferable[119,123].

2.5.3 The histologic diagnosis of prostate cancer

In oncologic pathology, the benign or malignant nature of tissue is estimated on the basis of architectural features, its relation to the surrounding preexisting tissue, and the morphologic aspect of individual tumor cells. Tumors always tend to mimic the structure of the tissue from which they arise. The extent in which they are able to do this depends on their degree of differentiation. The histologic diagnosis of prostate cancer is based on a number of criteria. The three major criteria of which at least two should be clearly present for a definite diagnosis are based on (1) architectural changes, (2) the absence of basal cells and (3) nuclear abnormalities[124]. These three major criteria for the diagnosis of prostate cancer are shown in figure 7.

Well differentiated adenocarcinoma of the prostate forms glandular structures that are very similar to benign prostatic glandular tissue. The malignant glands, however, are often smaller and as a result of infiltrating growth show a haphazard distribution in the

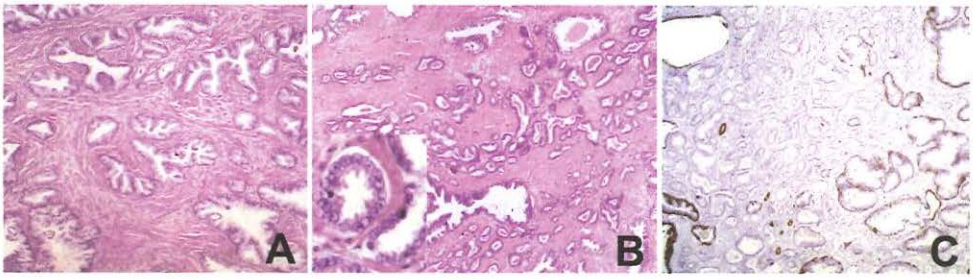


Figure 7. Illustration of the major criteria for the histologic diagnosis of prostate cancer. A: Benign prostatic tissue. The glands in the picture are evenly branched and form relatively circumscript structures (H&E 100x). B: Well differentiated prostatic adenocarcinoma, characterized by the presence of small to medium sized glands that show haphazardly infiltrative growth between the preexisting benign glands (H&E 100x). An inset shows the enlarged nuclei with prominent nucleoli (H&E 400x). C: Immunohistochemical staining with 34β12, an antibody specifically directed against basal cells. While basal cells are clearly present around preexisting benign prostatic ducts (mainly lower right), they are absent in prostatic adenocarcinoma (upper left, 34β12 stain 400X).

surrounding tissue. This architectural feature is best assessed at low power magnifications where a clear contrast to benign glands, which tend to form evenly branched and more circumscript structures, can be assessed (figure 7 a and b). A second important diagnostic feature that distinguishes malignant from benign glands is the complete absence of the basal cell in the former. The absence of basal cells can be confirmed with specific immunohistochemical staining techniques for high molecular weight cytokeratines which are specifically expressed by basal cells[125,126] (fig 7c). The appliance of these markers, however, must be performed with caution, as some benign prostatic lesions such as high grade PIN and AAH, have an attenuated and discontinuous basal cell layer, which can be difficult to demonstrate immunohistochemically[13]. Characteristic changes of the individual cells in prostatic adenocarcinoma are their slightly enlarged nuclei in which often a clearly enlarged nucleolus can be found (figure 7b).

The above-mentioned histologic features of prostatic adenocarcinoma form the major criteria for its diagnosis. Other, less important criteria include mitoses, nuclear hyperchromasia, and the presence of a eosinophilic, amorphous substance in the lumina. Most or all of the major criteria, and one or more of the minor criteria are often clearly present in adenocarcinoma, so that a histopathologic diagnosis can be made without great difficulty in most cases. In some cases, however, histologic features are insufficient for a

definite diagnosis of adenocarcinoma. The lack of a sufficient number of criteria most often results from a very small number of glands, which mainly occurs in the assessment of prostate needle biopsies. In this thesis, lesions that lack the required criteria for a definite diagnosis of prostate cancer are referred to as borderline lesions. Their incidence and clinical importance is discussed in Chapter 3 of this thesis.

2.5.4 Histologic grade

The degree of differentiation of malignant tumors (commonly the degree in which malignant tumors show features that are similar to the benign tissue from which they arise) is often highly predictive of their biologic behavior. Tumor-related features that determine the biologic behavior, including clinical aggressiveness and prognosis, incorporate a large variety of different parameters which can be assessed in many different ways (histology, biochemistry, electron microscopy, molecular biology etc). Routine histologic examination of tumor tissue is probably the most accepted and most easy way to determine the main prognostic features of a malignant tumor.

Histologic grading is based on the notion that tumors which retain many histologic features and functions of their benign counterparts, tend to be less aggressive than tumors that poorly resemble the benign tissue from which they arise. To assess, quantitate, and report the degree of differentiation of tumors, various histologic grading systems have been developed. These systems subdivide malignant tumors into a number (most often three or four) categories or grades, based on histologic tumor characteristics. For adenocarcinomas in general, a grading system based on the amount of glandular formation was first proposed by Broders in 1926[127]. However, although adenocarcinomas that arise in different organs do show common features, they also exhibit differences in terms of architecture and cell morphology. Therefore, in subsequent years, different grading systems for adenocarcinomas arising in particular organs were designed.

The ones that are most commonly used are the Gleason score system[128] and the MD Anderson system[129], both of which are based on architectural features. Adenocarcinoma of the prostate can exhibit many different architecturally different patterns of growth. Generally, more than one of these growth patterns is observed within the same tumor (intratumor heterogeneity). In the Gleason score system, intratumor heterogeneity is accounted for by combining the most prominent pattern of growth with the second most common pattern of growth as criteria for the overall grade. To this purpose, Gleason

divided the possible growth patterns that can be observed in prostate adenocarcinoma into five categories (fig 8). The total score is obtained by adding the growth pattern of the most dominant pattern to that of the second most dominant pattern (in cases of only one growth pattern, this pattern is doubled to obtain the total score). In this way, a nine-tiered categorization system is created with scores ranking from 2 to 10. An earlier proposed version of the Gleason system that is not commonly used, is the "Gleason sum" method in which the clinical stage (ranging from 1 to 4) was added to the Gleason score[130].
The Gleason score method is now the most commonly used grading system in the world. It, however, retains a few weak spots that require discussion. By averaging the two most prominent growth patterns of a tumor, the Gleason score method asserts that adenocarcinomas exhibit a clinical behavior that corresponds to their average degree of histologic differentiation. Following this argument, a person with a small but poorly differentiated tumor would have a worse prognosis than someone with a comparable tumor in combination with an additional focus of well differentiated tumor. Recent reports in the literature have shown that the amount of a high grade cancer component (Gleason pattern 4 or 5) is proportional to the overall tumor size[131,132] and that the proportion of high grade cancer indeed has a prognostic value superior to that of the original Gleason score system[133-135]. The use of the Gleason score system in relation to the changing histopathologic characteristics of early detected prostate cancer is discussed in Chapter 5 of this thesis. In the MD Anderson grading system, the relative proportion between gland forming adenocarcinoma and non-gland forming adenocarcinoma is assessed. In this system, cribriform carcinoma (similar to Gleason pattern 3c), is considered gland forming adenocarcinoma. However, predominantly cribriform carcinomas are termed grade 2 tumors. The MD Anderson system contains four categories, although a modified version reduces this number to three by combining grades 2 and 3 of the original version[129].
Other less commonly used systems are the World Health Organization (Mostofi) grading system, the Bocking grading system[136,137], and the Mostofi-Schröder grading method[138-140]. In contrast to the architecturally-based grading systems, these systems include nuclear features of individual tumor cells to assess tumor grade.

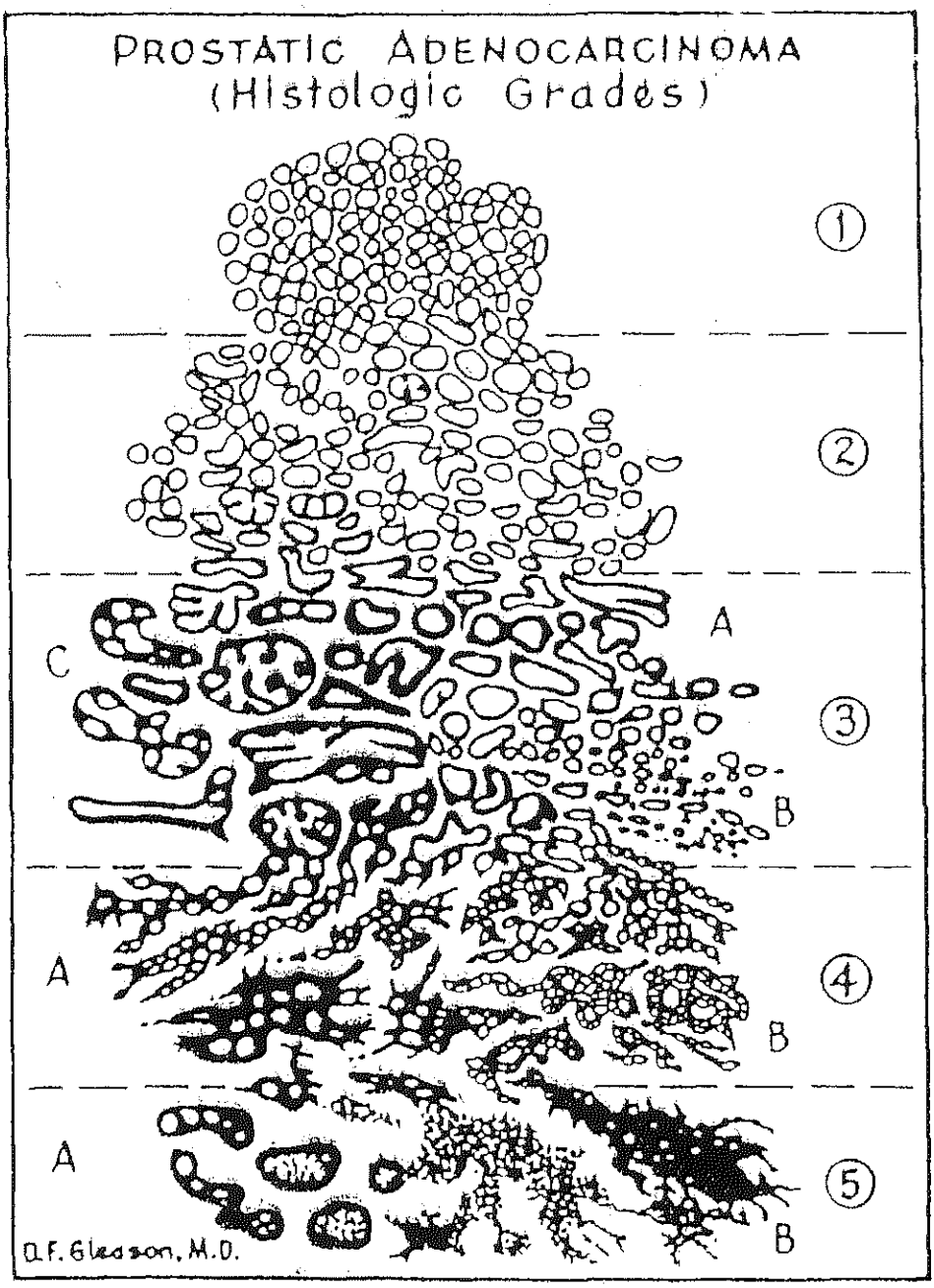
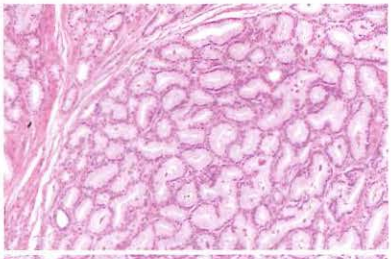
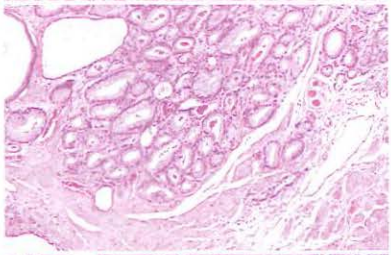
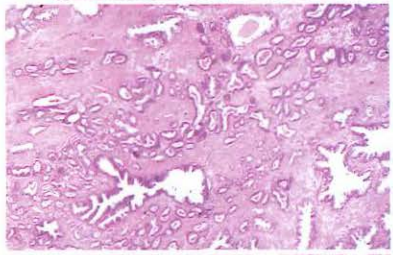
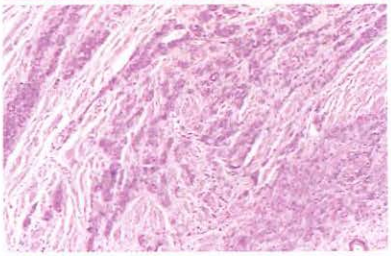
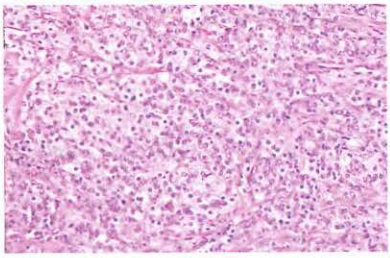


Figure 8. The Gleason score system, designated by a drawing of the different histologic growth patterns and subpatterns.A short description of their morphology with histologic examples of each pattern show is shown on the opposite page.

Pattern	Subpattern	Description	Example
1		Simple uniform round glands, closely packed with well-defined margins	 1
2		Simple rounded glands, loosely packed in vague rounded masses with loosely defined margins	 2
3	A	Medium-sized, single glands of irregular shape and irregular spacing with ill-defined, infiltrating margins	 3A
	B	Very similar to 3a, but small to very small glands, which must not form significant chains or chords	
	C	Papillary and cribriform epithelium in smooth rounded cylinders and masses; no necrosis	
4	A	Small, medium or large glands fused into chords, chains, or ragged infiltrating masses	 4A
	B	Very similar to 4a, but with many large clear cells, sometimes resembling "hypernephroma"	
5	A	Papillary and cribriform epithelium in smooth rounded masses, more solid than 3c and with central necrosis	 5B
	B	Anaplastic adenocarcinoma in ragged sheeths	

In order to be of practical clinical use, histologic grading systems should fulfill certain criteria. Most importantly, grading systems must have a strong correlation with the clinical behavior of the tumor. Since the development of all the above mentioned grading systems has been largely based on a relation with clinical behavior and prognosis, this objective is met by all, and the general usefulness of histologic grading of prostate cancer with either system is undoubted[141]. Gallee et al. compared five different histologic grading systems (Broders, Gleason, MD Anderson Mostofi and Mostofi-Schröder). In this comparison, the Gleason score system had the lowest predictive capacity, whereas the predictive ability of the Broders system and the Mostofi-Schröder system were reasonable[142].

Another important criterion that should be met by histologic grading systems is a good reproducibility of their results between different observers. Numerous studies on this subject have been performed, often with varying results[143-148]. However, it can be said in general that the difficulty in establishing clear criteria for nuclear features and the problems that arise because of tumor heterogeneity seem to account for a poor agreement between different observers in the Bocking, Mostofi and Mostofi-Schröder systems[143]. Both the MD Anderson and the Gleason score system have clearer defined and more easily assessable criteria, and have shown to have a relatively high interobserver reproducibility[143,147], although the relatively high number of categories in the Gleason score accounts for a higher degree of interobserver variation[143,144]. To decrease the interobserver variation of the Gleason score system, the categories are sometimes compressed into a smaller number[144,148]. A disadvantage of this simplification is that a decreased number of categories lead to a smaller amount of prognostic information. Therefore, compression diminishes the prognostic value of the Gleason score system[147].

2.6 Clinical and pathologic stage

2.6.1 Introduction

The determination of clinical and pathologic tumor stage provides a systematic way to describe the amount and the extent of a tumor at a certain point in time. The extent of a tumor strongly predicts its natural course. Therefore, in combination with grade and patient characteristics such as age and co-morbidity, tumor stage may strongly influence therapeutic decisions.

2.6.2 Staging systems for prostate cancer

The first reported staging system for prostate cancer essentially dates back to 1956, and was slightly adapted in 1975[149]. During the late sixties and early seventies, a TNM classification (T = primary tumor, N = lymph node status and M = distant metastasis) for prostate cancer was developed[150]. It became internationally established during the early nineties[151-153]. In the TNM system, tumor stage can essentially be approached in two circumstances: firstly when the patient is clinically evaluated (i.e. clinical stage) and secondly at microscopic evaluation after surgical removal of the organ or part of it (i.e. pathologic stage). Clinically, primary tumor characteristics (T) are assessed by findings at DRE, TRUS and sometimes by other imaging techniques (stages T2 to T4). Lymph node status (N) and the possible presence of distant metastases (M) are evaluated by histologic sampling (retropelvic lymph node dissection) or imaging techniques such as bone scintigraphy. Pathologic stage is determined at microscopic examination of tissue samples. The 1992 TNM staging system for prostate cancer and their 1997 revisions are shown in table 1. Clinical stage T1 refers to cases with a clinically unexpected diagnosis of prostate cancer in the absence of any of the above findings, after transurethral resection for benign hyperplasia (T1a or b). An additional group of clinical stage T1 tumors comprises cases in which the diagnosis of prostate cancer was made on needle biopsies prompted by an elevated serum PSA in the absence of other clinical abnormalities (T1c). Tumors that transgress the boundaries of the prostatic gland have shown to result in a higher chance of lymph node metastasis and a markedly worse prognosis after radical prostatectomy than tumors that respect the organ's boundaries[154-156]. The reasons for this can be easily understood. Tumors that ignore anatomic boundaries will exhibit a more aggressive pattern of invasive growth and will more likely be able to penetrate vascular and perineural spaces, which they can utilize as a vehicle to extend beyond surgical margins and to metastasize. In the 1997 revision of the TNM system the distinction between TNM'92 T2a and 2b has been abandoned and TNM'92 stage T2c tumors have been reassigned to the T2b category. The same holds true for stage T3, in which the distinction between stage T3a and T3b has been abandoned and T3c tumors are now assigned to T3b (table 1). It is very important to note that these changes could result in misunderstandings and it would therefore be recommendable to indicate the version of the TNM system used ('92 or '97), especially when reporting TNM'97 T2b or T3b tumors.

Table 1. The TNM system for prostate cancer: its 1992 version and 1997 revision.

	The 1992 TNM version			The 1997 TNM revision	
T0	No pathologic evidence of tumor. (note that clinical stage T0 does not exist)		T0	No pathologic evidence of tumor. (note that clinical stage T0 does not exist)	
T1	No clinical evidence of tumor. Tumor is an "incidental finding". (note that a pathologic stage pT1 does not exist)		T1	No clinical evidence of tumor. Tumor is an "incidental finding". (note that a pathologic stage pT1 does not exist)	
	T1a	Tumor found incidentally at transurethral resection in ≤ 5% of tissue		T1a	Tumor found incidentally at transurethral resection in ≤ 5% of tissue
	T1b	Tumor found incidentally at transurethral resection in > 5% of tissue		T1b	Tumor found incidentally at transurethral resection in > 5% of tissue
	T1c	Tumor found incidentally at needle biopsy		T1c	Tumor found incidentally at needle biopsy
T2	Tumor is confined to the prostatic gland		T2	Tumor is confined to the prostatic gland	
	T2a	Tumor in one side of the prostate, smaller than half a lobe		T2a	Tumor in one side of the prostate
	T2b	Tumor in one side of the prostate, larger than half a lobe		T2b	Tumor in both sides of the prostate
	T2c	Tumor in both sides of the prostate			
T3	Extraprostatic extension		T3	Extraprostatic extension	
	T3a	Tumor extends into the periprostatic tissue on one side		T3a	Tumor extends into the periprostatic tissue
	T3b	Tumor extends into the periprostatic tissue on both sides		T3b	Seminal vesicle invasion on one or both sides
	T3c	Seminal vesicle invasion on one or both sides			
T4	Invasion of other organs		T4	Invasion of other organs (no substages)	
	T4a	Bladder neck or rectal wall invasion			
	T4b	Levator musculature or pelvic wall invasion			
N	Invasion of regional lymph nodes		N	Invasion of regional lymph nodes	
NX	Regional lymph node invasion cannot be assessed		NX	Regional lymph node invasion cannot be assessed	
N0	No regional lymph node invasion		N0	No regional lymph node invasion	
N1	Metastasis in a single regional lymph node ≤ 2 cm in diameter		N1	Metastasis in a single regional lymph node ≤ 2 cm in diameter	
N2	Metastasis in a single regional lymph node > 2 cm in diameter		N2	Metastasis in a single regional lymph node > 2 cm in diameter	
N3	Metastasis in regional lymph nodes, either multiple or > 5 cm		N3	Metastasis in regional lymph nodes, either Multiple or > 5 cm	
M	Presence of distant metastases		M	Presence of distant metastases	
Mx	Presence of distant metastasis cannot be assessed		Mx	Presence of distant metastasis cannot be assessed	
M0	No distant metastasis		M0	No distant metastasis	
M1	Distant metastasis		M1	Distant metastasis	
	M1a	Non-regional lymph nodes		M1a	Non-regional lymph nodes
	M1b	Bone metastasis		M1b	Bone metastasis
	M1c	Metastasis to other site		M1c	Metastasis to other site

2.6.3 Comparison of clinical and pathologic stage

The clinical primary tumor (T) stage of prostate cancer is divided into two categories, namely tumors that are clinically apparent and those that are not. This general division brings on a number of difficulties, especially since the clinical stage of the primary tumors is assessed with DRE and TRUS, both of which have shown not to be very sensitive clinical tools[98,99,101]. Stage T1 is essentially a clinical stage that is based on an unexpectedly discovered tumor that is in the absence of clinical abnormalities at DRE or TRUS. The diagnosis of prostate cancer is made after histopathologic examination of transurethral resection material or needle biopsies. The amount of tissue in these specimens is limited. Because they do not provide sufficient oversight of the tumor – and especially its relation to the boundaries of the prostate, these specimens are insufficient for a proper assessment of the pathologic stage. Therefore, although the pathologist is required for making the diagnosis of a clinical stage T1 prostate cancer, the T1 category does not have a pathologic equivalent (i.e. pT1 does not exist). Several studies have shown that clinically unapparent (stage T1) tumors do not form a separate group with a different prognosis[109,157-159]. However, in the current system, by definition all clinical stage T1 tumors are clinically understaged as they are invariably upgraded after histopathologic examination of radical prostatectomy specimens[160,161]. The clinical significance of T1c tumors is discussed in Chapter 4 of this thesis.

Table 2. Comparison of clinical and pathologic stage in 114 radical prostatectomies of ERSPC patients with clinical stage T2 or higher.

	Pathologic stage				
	pT2ab(c)	pT3a(b)	PT3c	pT4(ab)	Total
Clinical stage					
cT2ab(c)	**30**	24	8	13	75
cT3 a(b)	7	**15**	4	12	38
cT3c	0	0	**0**	0	0
cT4(ab)	0	0	0	**1**	1
Total	37	39	12	26	114

In only 46 of the 114 cases (40%), clinical and pathologic stage match. Correct stages are shown in bold typeface. Clinical understaging (shown in light grey) occurs in 61 cases (53%). Clinical overstaging is less frequent as it occurs in only 7 cases(6%).

At histopathologic examination, a substantial number of clinically prostate-confined tumors are upstaged because of microscopic evidence of extraprostatic growth. It is obvious that microscopic examination of prostate borders and extraprostatic tissue has a

higher sensitivity for the detection of extraprostatic growth than palpation or ultrasonographic imaging. Moreover, at microscopic examination of tissue, all prostatic boundaries can be properly evaluated, while at DRE only the posterior and lateral borders can be assessed. This difference in sensitivity results in clinical understaging. In practice, tumors are clinically understaged in more than half of the cases. Even when T1 tumors, which are by definition understaged, are excluded, reported frequencies of clinical understaging range from 54% to 59%[161,162] (Table 2). Importantly, preoperatively assessable features such as the amount of cancer present in systematically taken biopsies and the level of serum PSA are reported to have a predictive capacity at least as powerful as the findings at DRE and TRUS[113,163,164]. Future revisions of the prostate cancer TNM systems might therefore consider biopsy-related and biochemical features as additional preoperative criteria for staging. Their implementation might decrease the frequency of clinical understaging and might render the use of a separate stage for clinically impalpable and invisible tumors unnecessary.

2.6.4 Assessment of pathologic stage

The pathologic equivalent of the T category in the TNM staging system (the pT category) requires translation of clinical findings based on palpation and imaging techniques to useful and reproducible microscopic criteria concerning tumor extent in relation to the prostate gland and its boundaries. An accurate assessment of the pathologic stage requires the availability of all prostatic and periprostatic tissue for sampling and microscopic examination. Consequently, a reliable assessment of the pathologic stage can only be achieved after examination of complete radical prostatectomy specimens. The number of histologic slides has been shown to correlate directly with the sensitivity to detect extraprostatic extension[165]. Therefore, sampling of all[165,166] or at least alternate sections[167,168] of the gland is generally recommended for an optimal assessment of the pathologic stage.

Problems may arise when clinical criteria are translated into histopathologic ones. In the 1992 TNM system, stage T2 tumors are subdivided into three subcategories that delineate different levels of tumor extent inside the prostate gland. T2a is reserved for one-sided tumors that are smaller than half of a prostatic lobe, T2b designates one-sided tumors that are bigger than one half of a lobe and T2c is reserved for tumors that are present in both lobes of the prostate (table 1). These criteria are useful at DRE, but problems arise in

translating them to report findings at TRUS or at histopathologic examination. This is mainly due to the fact that the human prostate gland does not have a clearly definable anatomically distinct equivalent of a lobe. Clear rules on what to consider the histologic equivalent of an anatomical lobe have never been constructed. Also, clear and reproducible methods of assessing the amount of involvement of what should be considered the equivalent of a lobe have not been established. Various interpretations by different pathologists can therefore lead to differences in staging outcome. In partially embedded radical prostatectomies, it is often impossible to make a histopathologic distinction between the various pT2 substages.

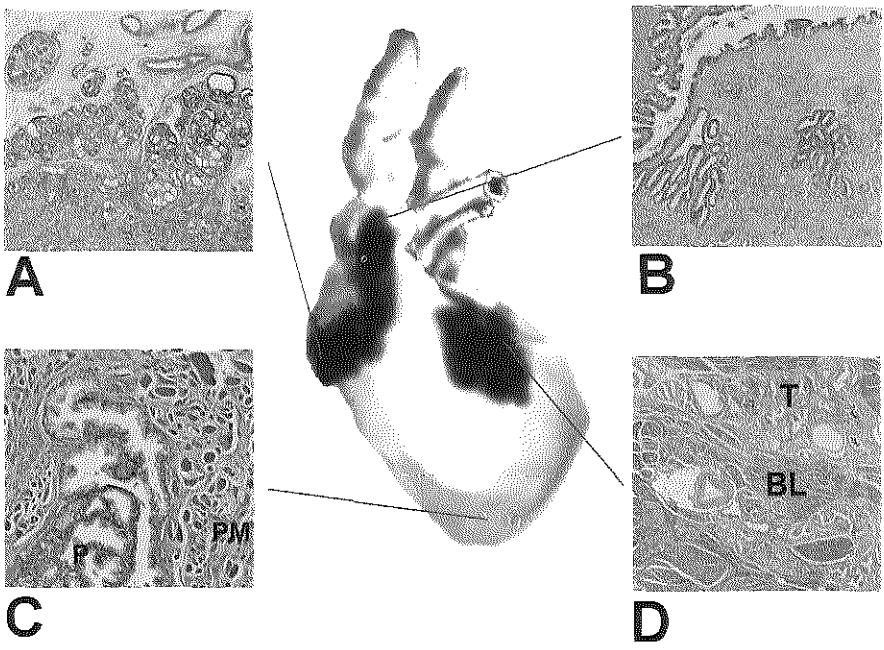


Figure 9. Histologic evidence of tumor transgressing the prostatic boundaries. A:Pathologic Stage pT3ab (TNM '92); tumor is present in the periprostatic fatty tissue or lies outside reasonable boundaries of the prostate. B: Pathologic Stage pT3c (TNM '92); tumor is present in the muscular wall of the seminal vesicles. C: The apex of the prostate, where striated muscle tissue of the pelvic floor (PM) interdigitates with benign prostatic tissue (P). In this area, it is impossible to assess tumor invasion in striated muscle tissue. D: Pathologic stage pT4a (TNM'92); tumor (T) is present between the large distinct bundles of smooth muscle tissue of the bladder wall (BL).

Another problem in distinguishing T2 substages lies in the fact that about 67% of prostate cancers are multifocal[67,68]. No clear guidelines on the approach towards multifocal tumors have been established. Two prostate-confined, small, and separate tumor foci that are

present at either side of the prostate gland would result in a TNM '92 stage pT2c or a TNM '97 stage pT2b when the total topographic distribution of tumor would be considered. In this way, multifocal localization of a relatively small amount of cancer could lead to an overestimation of actual tumor stage. Further studies are required to provide clear guidelines to the problems arising as a result of tumor multifocality[161].
The histologic criteria for extraprostatic extension, seminal vesicle invasion, and bladder neck invasion are well-defined and do not form major problems in assessing the pathologic stage[161](fig 9). The only exception is the evaluation of invasion into the levator-musculature (stage T4b in the 1992 TNM system), which is histologically impossible. Striated muscle tissue of both the levator musculature and the external sphincter of the urethra are histologically undistinguishable, and interdigitate with the prostatic stroma. Because of this, benign prostatic glandular tissue is usually found surrounded by the pelvic striated musculature, and therefore, the prostatic borders are impossible to evaluate histologically(fig 9). Especially with the limited amount of surrounding striated muscle tissue in radical prostatectomies, it is in our opinion impossible to accurately assess tumor invasion in the pelvic musculature in radical prostatectomy specimens.

2.7 The clinical management of prostate cancer

2.7.1 Conservative management

The main question that is raised in the clinical management of prostate cancer, and especially in early detected prostate cancer, is whether to treat it or not to treat immediately[169-171]. Prostate cancer is generally known as an "old man's disease", and patients by definition have a limited life expectancy, while the chance of dying of concurrent diseases is relatively high[49].
Conservative management, also referred to as deferred treatment or "watchful waiting", is an approach where patients enter a clinical follow-up program, in which the size and spread of the tumor is monitored carefully (for instance by regular serum PSA measurements). In cases with evidence of tumor progression, curative or palliative treatment options can be considered. Conservative management might be the better option

for a substantial number of prostate cancer patients, especially older patients with small and well differentiated tumors[172].

It has never been conclusively proven that conservative management of prostate cancer has a lower overall or disease-specific survival. A study that was performed to compare radical prostatectomy with 'placebo' showed no significant difference in overall survival after 15 years of follow-up[173]. The study was, however, tampered by the fact that many patients were lost to follow-up and by an age imbalance between the studied groups. Furthermore, it lacked the necessary statistical power, and was never completed. A survey of almost 60.000 prostate cancer patients treated with either radical prostatectomy, radiotherapy, or conservative management showed that relative and disease-specific survival were higher in patients who were treated with curative intent[174]. A large randomized trial that compares radical prostatectomy with deferred treatment is currently underway, but results are not expected for another decade[175].

2.7.2 Treatment with curative intent

Most men diagnosed with clinically localized prostate cancer (i.e. without clinical evidence of extraprostatic spread or metastasis) are offered therapy with a curative intent. The most frequently used forms of curative therapy are radical prostatectomy[176] and external beam radiotherapy[177], which - in cases with evidence of tumor progression after irradiation - can be followed by a "salvage" radical prostatectomy[178,179]. The choice between these two treatment options has been the subject of debate[180-185]. As of now, no conclusive evidence for a better outcome for either option has been presented. A randomized trial of limited size suggests that progression free survival is slightly higher in men that undergo radical prostatectomy, and therapy-related adverse side-effects are lower in men treated with radiation therapy[186]. Both radical prostatectomy and radiotherapy are associated with a relatively high rate of adverse side effects. For radical prostatectomy, these are impotence (between 32% and 91%), urethral stricture (between 12% and 32%), and incontinence (around 6%)[187-191]. For radiotherapy, bowel injury (between 11% and 35%), impotence (between 41 - 55%) and urethral stricture (around 5%) are the main reported adverse effects[187,191]. Progression rates after treatment with curative intent are substantial, as biochemical evidence of tumor recurrence (i.e. elevation of serum PSA levels) reported after radical prostatectomy in patients with clinically detected prostate cancer ranges up to 40%[192,193].

2.7.3 Treatment of metastasized disease

It has been known for a long time that androgens play a crucial role in the development and progression of prostate cancer. Eunuchs that are castrated before puberty never develop prostate cancer in their lifetimes. Most prostatic adenocarcinomas of the prostate depend on the availability of androgens for their growth. The hormone dependence of prostate cancer offers an important target for therapeutic or palliative measures, especially in the case of metastatic disease. The aim of these measures is to deprive prostate tumor cells of their growth-stimulating androgen hormones, testosterone and its active metabolite 5α-dihydroxytestosterone. This can be achieved in a number of ways. Surgical castration by bilateral orchidectomy removes the primary source of testosterone (which is produced by Leydig cells in the testicles). In 1941, Huggins et al. first introduced hormonal treatment for prostate cancer in the form of surgical castration[194]. Later developments enabled pharmacologic castration.

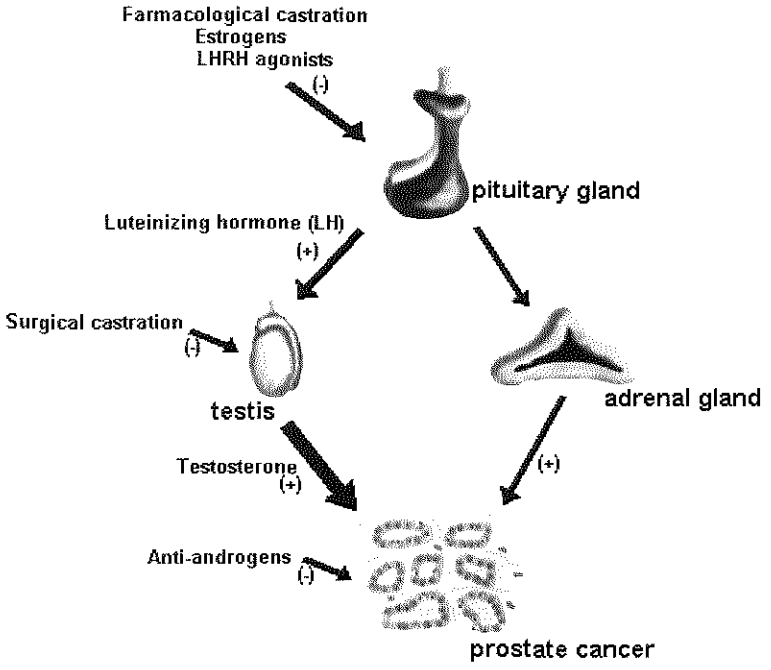


Figure 10. Hormonal dependence of prostate cancer

The production of testosterone in the testicles is stimulated by luteinizing hormone (LH), which in its turn is produced in the pituitary gland. Chronic administration of luteinizing hormone-releasing hormone(LHRH) agonists, eventually suppresses the production of luteinizing hormone(LH) by down-regulation of its receptors in the pituitary gland, thereby indirectly suppressing the testosterone production in the testicles. Estrogens have a similar effect as they too suppress LH production by the pituitary gland. A third mechanism is the administration of anti-androgens, substances that interfere with the activation of androgen receptors by androgens. The concept of total androgen blockade is to block the testicular androgen production by surgical or pharmacologic castration in combination with a blockade of the androgen receptor by the administration of anti-androgens. The additional blockade of the androgen receptor is thought to be nessecary to diminish the effects of the adrenal androgen production (the adrenal glands are reponsible for about 5% of the total production of androgen hormones in the body)[195]. The advantage of total androgen blockade over more conventional methods of castration, however, has never been conclusively proven, and its administration in a neo-adjuvant setting still remains controversial[196-198]. About 70% of prostate cancer patients initially respond well to hormonal treatment[199]. However, the median time to tumor progression and the median survival after hormonal therapy are limited[200,201], and most tumors will eventually acquire mechanisms for hormone independent growth (hormone-refractory prostatic adenocarcinomas). The prognosis of hormone refractory prostatic adenocarcinomas is poor, with a median survival time of 5 to 10 months[199]. Although new chemotherapeutic strategies may look promising, their effect is expected to be limited[202-204].

3. The early detection of Prostate Cancer

3.1 Screening for malignant tumors

Screening for the prevalence of malignant diseases, with the aim to cure them at early stages and to prevent costly and potentially incurable late stages, has become increasingly integrated into the medical practice of the western world during the second half of the past century. The first examples of malignant tumors for which screening was introduced were cervical cancer[205] and lung cancer[206]. Guidelines were laid down by the World Health Organization, defining principles that must be demonstrable before population-based screening for certain diseases can be introduced. They include the following key principles: (1) the disease is an important public health problem; (2) a screening test is available that is safe, acceptable, and valid; (3) an early stage of the disease can be recognized; and (4) effective therapy is available for early disease and treatment, given in the absence of symptoms, improves the prognosis[207].

The above-mentioned principles do not explicitly include the cost-effectiveness of screening and the quality of life of the screened participants. Both could also play a prominent role in the decision whether population-based screening would or would not be acceptable. Cervical cancer has proven to have a long period of pre-clinical disease and screening by relatively simple and cheap cervical smears has reduced the mortality of cervical cancer by an estimated 75%[208]. In lung cancer screening programs, however, chest X-rays did not detect the disease at a stage in which treatment would have resulted in an improved prognosis. A reduction of lung cancer mortality as a result of screening could not be found, and screening for lung cancer therefore seemed to have insufficient effect on the health of the screened population[209]. Although screening for breast cancer seems to have an effect on mortality[210,211], the cost-effectiveness of a population-wide implementation has not yet been conclusively proven[212].

3.2 Screening for prostate cancer

The relatively high relapse rate after initial treatment with curative intent in patients with prostate cancer[192,193] and the difficulties that are encountered with the clinical management of advanced prostate cancer are major incentives for attempts to detect

prostate cancer at an early stage. Indeed, the introduction of serum PSA measurements seems to lead to the detection of a higher fraction of organ-confined tumors with a more favorable prognosis[108]. However, to make serum PSA measurements a successful tool for early detection of prostate cancer (including non-palpable and invisible adenocarcinomas), they must be performed in men who have no clinical evidence of prostate cancer. Launching early detection programs that are designed to screen the population at risk for prostate cancer is the only way to do this. With the previously mentioned high prevalence of latent prostate cancer[42-44], systematic screening of men without clinical symptoms of prostate cancer, could increase the risk of detecting patients who do not have life threatening cancer and therefore will not benefit from treatment.

Therefore, the question whether population-based screening for prostate cancer would benefit the population at risk, has been the matter of much debate[213-215]. Considering the guidelines of the World Health Organization, prostate cancer certainly meets the first criterium of being an important health problem. In the USA, prostate cancer mortality is now second only that of lung cancer[216]. And as lung cancer mortality is declining and the age-expectancy of humans is expected to rise, prostate cancer mortality is destined to become the leading cause of male cancer death. The second criterium, i.e. the availability of a relatively simple, and reasonably effective test for prostate cancer is met by serum PSA measurement. The third criterium is also met, since early stage prostatic adenocarcinomas that do not give rise to clinical symptoms can be detected by a rise in serum PSA, while they are not palpable by DRE or visible on TRUS. These could be considered to represent an early stage, although a portion of asymptomatic disease shows unfavorable prognostic features[108]. Early detection of prostate cancer, therefore, is possible. The question to screen or not to screen for prostate cancer seems to depend on the fourth criterium, i.e. the issue of the effectiveness of early treatment, because, as mentioned above, a beneficial effect of early treatment over deferred treatment has not yet been shown.

In 1993, annual screening by PSA measurements was nevertheless recommended for men over 50 in the USA[217]. Since then, considerable changes in the epidemiology of prostate cancer have been witnessed in the population-based registry data of the Surveillance, Epidemiology and End Results (SEER) program, that covers about 10% of the population of the United States of America. After a marked increase in the incidence of prostate cancer that started in the late 1980s, the incidence trend peaked in 1992, and started to

decline afterwards[105]. This pattern of rise and subsequent decline in incidence may be in line with the notion that through PSA-based screening, an additional number of prostatic adenocarcinomas were detected that had accumulated as a result of lower previous years' clinical incidences. Incidences are now believed to decline back to the rate of newly occurring disease. Together with the incidence rates, also prostate cancer mortality rates first showed an increase and declined after 1992[218,219]. The observed trends are consistent with the notion that prostate cancer screening reduces prostate cancer mortality rates[105]. However, two important biases apply to screening for prostate cancer, namely lead time bias and length time bias. Lead-time bias entails that early detection of prostatic adenocarcinomas leads to a seemingly prolonged life span, while the life span of the involved patients is not genuinely prolonged, since their tumors would have been detected later without screening. Lead time bias may therefore result in the observation that early detection leads to improved survival, while in fact it does not. Some of the reported observations of improved prostate cancer survival after early detection may have been caused by lead-time bias[220]. Length time bias associated with active screening, results in the detection and subsequent treatment of tumors that would not have posed a threat to the life-expectancy of their host. The detection of these indolent tumors would have a seemingly beneficial effect on a screened group, while a true beneficial effect does not in fact exist. Apart from considering these biases, it must be realized, that prostate cancer predominantly occurs in a subgroup of men in which generally advanced age and the relatively high rate of comorbidity probably have a substantial effect on the overall effect on prostate cancer related mortality and quality of life. The only way to avoid these biases and to prove a beneficial effect of systematic screening for prostate cancer in the general population is to perform a randomized trial[221]. Randomized trials on screening for prostate cancer evaluating the effects of systematic screening for prostate cancer on mortality and quality of life are underway, but final results are not expected until 2008[222,223].

Apart from the question whether systematic population-based screening will benefit the population at risk for prostate cancer, the manner in which screening tools are implemented and the interval at which subsequent rounds of screening should occur have not been extensively studied yet. It is obvious, that differences in the screening procedure will lead to differences in the end result.

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Chapter 2

PROCESSING AND REPORTING PROSTATIC NEEDLE BIOPSIES AND RADICAL PROSTATECTOMY SPECIMENS

Robert F. Hoedemaeker
Theodorus H. van der Kwast

Based on

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1. Summary

The first part of this chapter describes some general guidelines for processing and reporting of prostatic needle biopsies. The reported detection rates of prostate cancer, lesions suspicious for prostate cancer, and prostatic intra-epithelial neoplasia (PIN) in needle biopsies varies considerably among participants of different early prostate cancer detection programs. In addition to differences in the investigated populations, other factors that may account for this variation include the adequacy of prostate biopsies, the quality of tissue processing methods, and the detailedness of histopathologic reporting. An analysis of prostate needle biopsies from the participating centers of the European Randomized Screening study of Prostate Cancer (ERSPC) revealed that both number and length of biopsies correlated with the detection rate of prostate cancer. It was suggested that standardization of tissue processing might reduce the differences in detection rates, and would be helpful in the development of quality control parameters. Consensus among the members of the Pathology Committee of the ERSPC was reached concerning the optimal methodology of tissue embedding. This resulted in a number of guidelines for prostatic needle biopsy processing. The establishment of an unequivocal and uniform method for reporting lesions encountered in prostatic needle biopsies is considered an important aid in decisions taken by the clinician. In addition, standardized reporting will facilitate clinical epidemiologic multicenter studies of prostate cancer.
In the second part of this chapter, a standardized protocol for processing radical prostatectomy specimens is described. The protocol features methods for the total embedding of radical prostatectomy specimens. Standardization of methods for the processing of prostate needle biopsies and radical prostatectomy specimens is considered extremely important, since each can have considerable effects on the outcome of routine histopathologic examination.

2. Introduction

In early detection programs for prostate cancer such as the ERSPC, the histopathologic assessment of tissue specimens plays a crucial role. Apart from being an essential tool for

establishing a final diagnosis of prostate cancer, the examination of prostate needle biopsies also provides a way to assess certain tumor characteristics such as grade and tumor extent. Radical prostatectomy specimens probably offer the best opportunities for precise documentation of tumor characteristics such as tumor volume, grade, and stage. Next to these, tumor heterogeneity and the presence of multiple, anatomically distinct cancer lesions can be assessed in radical prostatectomy specimens. As of yet, pathologic stage and grade are considered the two most important prognostic factors that predict clinical outcome after radical prostatectomy [1].

Reporting tumor characteristics may help the clinician in choosing the appropriate therapy. The reproducibility and consistency of the assessment and the reporting of prostatic tissue specimens can therefore be considered essential for proper patient care. In turn, the quality of histopathologic reports strongly depends on procedures of tissue handling, processing, and reporting.

The Pathology Committee of the ERSPC was installed to obtain uniformity in histopathologic reporting of prostatic tissue and to enhance the quality of tissue processing. In this chapter, its recommendations with regard to processing and reporting of prostatic needle biopsies are outlined. In addition, a standardized protocol for the processing of radical prostatectomy specimens is described. This protocol is used in the Rotterdam section of the ERSPC and it was adopted as the standard protocol in the Biomed II Markers for Prostate Cancer study, an international multicenter study that evaluates new prognostic markers for prostate cancer.

3. General guidelines for processing and reporting prostate needle biopsies

3.1 Guidelines for adequate histopathologic processing

The following points have proven to be relevant for adequate processing of prostatic needle biopsies in order to achieve a maximum amount of available prostatic tissue:

3.1.1. The number of biopsies embedded in one cassette.

The knowledge of the exact site of prostate cancer within the prostate gland can be important in various situations. In clinically higher stage cancers, this information may help in the decision whether unilateral nerve sparing prostatectomy is possible. In the case of a very small amount of prostate cancer, it is sometimes difficult to find the tumor in the radical prostatectomy specimen[2]. In these cases deeper cuts of the tissue blocks are necessary and detailed knowledge of the site at which prostate cancer was present in the diagnostic biopsy cores can facilitate the search for prostate cancer.
For the above reasons, it is considered preferable that each biopsy is embedded separately and marked according to its origin. The consensus of the ERSPC Pathology Committee minimally requires that biopsies should be embedded in separate sets of left and right. If a biopsy is specifically taken from a clinically suspect lesion, based on digital rectal examination (DRE) or transrectal ultrasonography (TRUS) findings, this biopsy should also be embedded separately.

3.1.2. Paraffin-embedding

Since needle biopsies tend to become curved after fixation, the achievement of the maximum amount of tissue for histopathologic evaluation requires flat embedding of biopsy cores. This can be achieved by stretching the needle biopsy cores between two nylon meshes [3,4]. Alternatively, needle biopsy cores may be streched and fixed on a small piece of paper. In our experience, stretching of needle biopsy cores is possible after formalin fixation. Therefore, it is not necessary that urologists insert biopsy cores between nylon meshes immediately after obtaining the biopsy cores. If multiple cores are embedded in a single cassette, it is necessary to take care that they are well separated from

each other. This will prevent that multiple, entangled biopsies are only partially represented in the mounted sections.

3.1.3. Needle biopsy sectioning

Easy visualization of the biopsy core in paraffin blocks greatly helps the laboratory technician to cut sections without much loss of tissue. In some laboratories it is therefore practice to add eosin or another color solution to the biopsies during embedding. When darkly colored nylon meshes are used, the addition of a color solution is not necessary, as the yellowish needle biopsies generally contrast well with the dark nylon mesh background.

3.1.4. The number of sections from each specimen (levels of sectioning)

Some reports in the literature [3,5] demonstrated that in order not to miss small foci of adenocarcinoma, and to allow a definite diagnosis of malignancy when at one level only a small borderline lesion is found, it is important to take sections from various levels of each biopsy core. Since these reports do not mention whether the cores were flattened appropriately prior to embedding, the recommendation to cut at three different levels may be superfluous in the case of adequately flattened cores. The ERSPC Pathology Committee, however, recommends that a few subsequent sections of a biopsy core of at least two different levels with an interval of at least 50µ should be mounted on 1 or 2 glass slides.

3.1.5. The preservation of sectioned biopsy ribbons

It is recommended that ribbons of the levels between the mounted sections are preserved. Preservation of sectioned ribbons of biopsy cores facilitates the production of additional routine H&E slides at specific section levels, a procedure that is indicated if at the original levels a lesion suspect for adenocarcinoma is observed. Furthermore, preservation of ribbons of the sectioned biopsy cores facilitates the performance of additional specialized immunohistochemical stainings (such as basal cell staining) at specific section levels, should they be needed. A recent study reports a significant decay of immunoreactivity in prostate biopsy ribbons, which are stored for longer periods of time[6]. Therefore, immunohistochemical assessment of prognostic tissue markers on longer stored ribbons must be considered with care.

3.2 Guidelines for reporting prostate lesions on needle biopsies

In screened populations, men generally lack clinical signs of prostate cancer at DRE or TRUS. Moreover, PSA measurement, DRE, and TRUS have proven to be relatively unreliable methods for prostate cancer detection. A well-known example of a benign lesion that clinically mimics prostate cancer is granulomatous prostatitis, which leads to a suspect lesion at DRE and very high PSA levels[7]. Therefore, we and others [8] recommend that pathologists evaluate needle biopsies without knowledge of the outcome of previous clinical examinations.

Reporting on prostatic needle biopsies in a screening setting should be as unequivocal and concise as possible. This means that the nomenclature of prostatic lesions should be entirely uniform among reporting pathologists. Terms such as "atypical glands", "glandular atypia", "probably malignant, but benignity not excluded" should be avoided, since it is unclear to the urologist which, if any, action should be undertaken.

The underlying terms are recommended by the ERSPC, as they seem to have proven their value and consistency in the past several years:

1. *Benign, no abnormality.*
   This also includes foci of chronic (lymphocytic) inflammation, as it is very common in prostatic needle biopsies.
2. *Acute inflammation.*
   This may be a cause of increased PSA levels.
3. *Chronic granulomatous inflammation*
   This also includes xanthomatous inflammation. This lesion can cause highly elevated PSA levels as well as a positive DRE
4. *Extensive atrophy, no malignancy.*
   Particularly multiple biopsies with post-atrophic lobular hyperplasia may be reported as such, although in itself this finding has no clinical consequence.
5. *Atypical adenomatous hyperplasia*
   This lesion is fortunately a very rare finding and is also known as adenosis
6. *High grade Prostatic Intra-epithelial Neoplasia (PIN).*
   The histologic criteria of high grade PIN are described by Bostwick [9]. The single most important criterion for high grade PIN is the presence of prominent nucleoli in

at least 5% of the luminal cells. The location(s) of PIN should also be reported. It should be noted that low grade PIN (formerly PIN grade I) is no longer considered to be of clinical value and therefore not mentioned in the conclusion of the pathology report.

7. *Suspicious for adenocarcinoma*

   Lesions that are too small and/or lack sufficient criteria to lead to a definite diagnosis of adenocarcinoma are called suspicious for adenocarcinoma, or borderline lesions. The Pathology Committee of the ERSPC does not recommend any of the acronyms that have been proposed recently, such as atypical acinar proliferation (AAP) or atypical small acinar proliferation (ASAP). Firstly, these lesions do not represent a separate entity and secondly, their morphology may vary from a few single atypical cells to strands of abnormal cells or glands with atypical features.

8. *Adenocarcinoma*

   It should be indicated whether adenocarcinoma is present left, right, or bilateral. In addition, it is common practice to report if perineural invasion of the adenocarcinoma is present, although its clinical impact is controversial[10,11]. By indicating the location of adenocarcinoma, the number of positive biopsies is implicitly known to the clinician. An important issue is the quantity of cancer found in an individual. The Pathology Committee does not consider it necessary that an estimation of the proportion of carcinoma in the needle biopsies should be provided. Certainly, for study reasons, this information may be interesting[12], but it does not as yet seem to have clinical consequences. Combinations of adenocarcinoma and high grade PIN or lesions suspect for adenocarcinoma should also be reported, and the location of each lesion should be indicated.

9. *Other malignancies*

   These include carcinosarcoma, sarcoma, malignant non-Hodgkin lymphoma, adenocarcinoma of the colon etc.

It is important to mention the adequacy of the prostatic needle biopsy cores. An inadequate prostatic core biopsy is defined as a core lacking epithelial structures, either benign or malignant. For review in case of a later occurring carcinoma, it is important to know to which extent the sextant core biopsies were adequate for diagnostic purposes. Generally, a separate biopsy is taken from areas suspect for malignancy at DRE or

transurethral rectal ultrasonography. If this is inadequate, it is of particular importance to mention this in the report.

3.3 Guidelines for reporting prostate cancer grade on needle biopsies

Although several grading systems are employed, it is recommended to use the Gleason grading system. Advantages of this grading system are its general use and the large amount of literature data on its prognostic impact. Furthermore, this grading system is based on architectural features, which are more easily comprehensible than for instance histomorphologic features based on nuclear polymorphy. An additional important feature of the Gleason system is that it takes into account the two most important growth patterns of prostate cancer (i.e. gland formation or not). In sextant needle biopsies, the two growth patterns with the highest Gleason graded growth patterns (i.e. Gleason growth pattern 4 and 5) should be separately mentioned in the Gleason score. Of the two growth patterns reported in the Gleason score, the one with the highest quantity should be mentioned first. For example, needle biopsies that contain Gleason growth patterns 2, 3 and 4 would receive a Gleason score of seven, irrespective of the amount of growth pattern 2. The final report would read "3 + 4 = 7" if the amount of growth pattern 3 exceeds the amount of growth pattern 4, and "4 + 3 = 7" if the situation was vice versa. In addition to the Gleason score, the location of a separate area of high grade (Gleason 4 or 5 pattern) should be mentioned.

3.4 Guidelines for reporting prostate cancer stage on needle biopsies

Although the predictive value for the determination of pathologic stage is considered to be very limited because of the small amount of tissue present in needle biopsies, it is recommended to mention any clear parameters of pathologic stage whenever they can be assessed. Such parameters may include the bilateral presence of prostate cancer, the presence of clear extraprostatic growth, or the presence of seminal vesicle invasion.

4. Guidelines for processing and reporting radical prostatectomy specimens

4.1 Processing radical prostatectomy specimens

4.1.1 Specimen collection and general inspection

Immediately following surgical excision, radical prostatectomy specimens are transported to the Pathology laboratory. A pathologist or an experienced resident pathologist carries out a general inspection of the specimen. Specimens are weighed, measured in three dimensions, and fixed for 24 hours in a 10% neutral-buffered formalin solution.

4.1.2 Sectioning and embedding

The optimal method for cutting and total embedding of radical prostatectomy specimens was first described by Stamey et al. in 1988[13]. Prior to sectioning, surgical margins are inked. It is recommended to use different colors for each side. This prevents accidental flipping over of the laterally symmetrical tissue slices and allows for an optimal orientation throughout sectioning and embedding of the specimen.

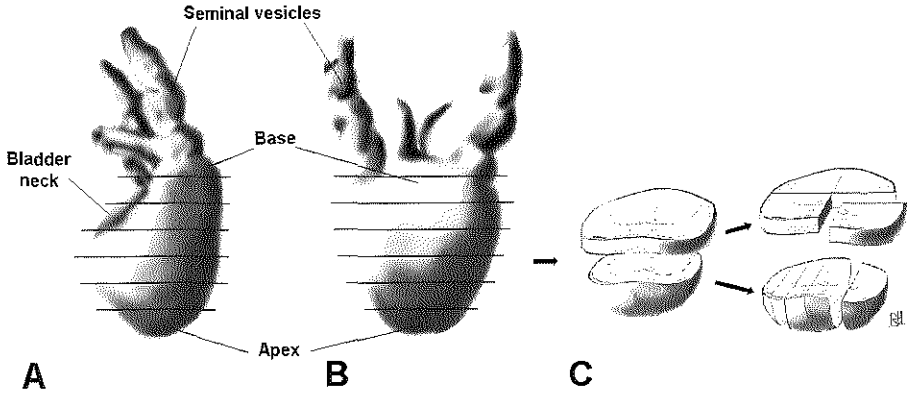

Figure 1. Cutting scheme for radical prostatectomy specimens. **A** lateral view. **B** dorsal view. **C** Slices are divided into four quadrants and the apical slice is cut parasagittaly at 4-mm intervals.

After inking the specimen is inked, it is cut into 4 to 10 slices (depending on its size) at 4mm intervals perpendicular to the rectal surface (Fig 1A and B). Cuts perpendicular to

the rectal surface provide an optimal orientation for assessing the relation of tumor to the periprostatic tissues and rectal surgical margins. To enhance precise spacing and parallel orientation of each cut, the use of an electrical cutting machine is highly recommended. Each transverse section is sequentially numbered according to its origin in relation to the apex, and subsequently divided in quadrants or halves that fit routine sized cassettes used for paraffin embedding (Fig 1C). To enhance the accuracy of determining tumor extension in the apical surgical margins, the apical slice is cut parasagittally at 4mm intervals (Fig 1C). In this way, an optimal histologic view of the relation of a tumor to the inked surgical margin on one side of the section is obtained. Parasagittal cuts of the apical slice are preferred over obtaining thin shaved sections of the apical margin, because the exact relation of a tumor to the inked surface cannot be viewed in a thin shaved section, and false-positive surgical margins could be reported in cases in which a tumor extends close to, but not actually *in* the margin of the specimen.

The surgical margin of the bladder neck has a 45-degree angle to the rectal surface of the prostate (Fig 1A). Because of this, cuts perpendicular to the rectal surface provide a good view of the surgical margins in this area. Additional parasagittal cuts of this part of the prostate do not enhance the overview of these margins, and are therefore considered unnecessary. To determine seminal vesicle invasion, representative slices of the base of each seminal vesicle are taken separately.

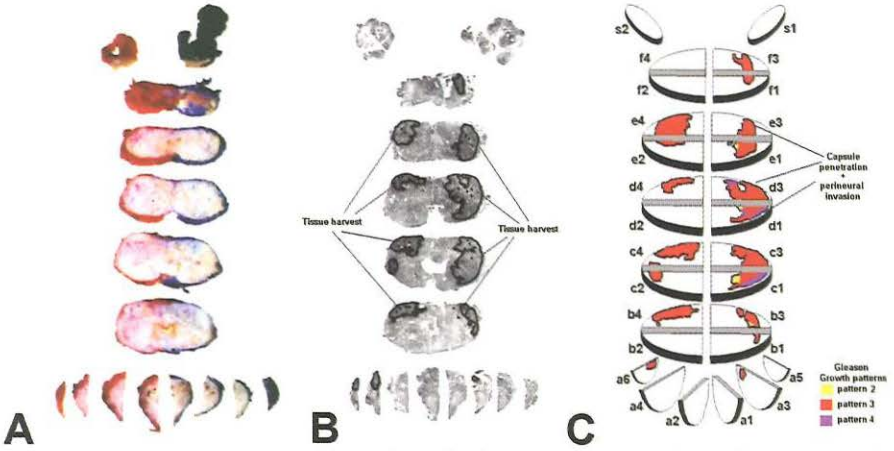

Figure 2. Whole organ representations of a radical prostatectomy specimen that was cut and processed according to the described protocol. **A** Macrophotograph of the specimen after it was step-sectioned at 4-mm intervals. **B** Whole mount reconstruction of grayscale images of H&E stained routine histologic slides. Tumor areas were outlined on the slide coverslips. **C** Schematic drawing of the specimen showing grade heterogeneity, tumor multifocality and sites with extraprostatic extension.

4.1.3 Histologic examination and documentation

Of each of the tissue blocks, 5μ H&E-stained histologic slides are prepared. Each slide of the prostatectomy specimen is microscopically examined for the presence, extent, and growth pattern of carcinoma. Histologic grading is performed according to the Gleason score system [14].

Invasion of tumor into perineural or vascular spaces, the presence and extent of capsule invasion or penetration into surrounding extraprostatic tissue, the presence of seminal vesicle or bladder neck invasion and involvement of surgical margins are carefully marked on the slide coverslip. After outlining all tumor areas, the slides can be used to establish tumor volume by measuring tumor areas (e.g. by computer-assisted morphometric analysis or by manual measurement two-dimensionally on the slides in millimeters) and then subsequently multiplying them by 4 (the thickness of the original slices).

Digital grayscale images of each histologic slide can be used to reconstruct 'virtual' whole-mounts of the specimen (Fig 2B). A diagrammatic representation of the entire specimen is created in which histologic findings of carcinoma lesions are carefully documented (Fig 2C). In these maps, the presence, the extent, and the multifocality of the tumor can easily be assessed. Sites of extraprostatic extension and positive surgical margins can be assessed. In addition, grade heterogeneity (different Gleason growth patterns) and the percentage of high grade cancer (Gleason growth pattern 4 and 5) can reported.

4.2 Reporting radical prostatectomy specimens

Reports on radical prostatectomy specimens should include the type, the location, and the extent of prostate cancer, its grade and the status of the surgical margins. Mentioning the presence of vascular invasion or perineural invasion could provide the clinician with additional prognostic information. The presence and extent of precursor lesions such as high grade PIN is considered less important as it mainly serves research purposes. Below, the clinical relevance of issues that should always be mentioned in radical prostatectomy reports is briefly discussed.

4.2.1. Histologic tumor type

Although most prostate cancers are adenocarcinomas, other types of cancer that occur in the prostate have different prognoses and may call for a different clinical management (see chapter 1).

4.2.2. Location and extent

Prostate adenocarcinomas that arise in the transition zone usually have a better prognosis than adenocarcinomas that arise in the peripheral zone. Adenocarcinomas that arise in the transition zone are smaller and of lower grade than peripheral zone tumors[15,16]. Furthermore, because of their location, transition zone tumors are less likely to exhibit perineural growth into the neurovascular bundles located at the posterolateral margins of the prostate.

The extent of adenocarcinoma throughout the prostate, including the extension outside the boundaries of the prostate, forms the basis for the determination of the pathologic stage. Together with grade, pathologic stage is considered one of the most important prognostic factors that predict clinical outcome after radical prostatectomy[1]. The criteria for the determination of the pathologic stage are discussed in detail in chapter 1. Reports on radical prostatectomies should mention each criterion, such as sidedness, extraprostatic extension, and invasion of the seminal vesicles and/or bladder neck, separately.

4.2.3. Grade

Because of its strong prognostic value, tumor grade should be regarded an essential part of the report. However, because of the high frequency of tumor multifocality and grade heterogeneity between and within different tumor foci within the radical prostatectomy specimen, determining tumor grade is not always easy. Reports on tumor grade in radical prostatectomy specimens should mention the overall tumor grade. The most frequently used systems for grading prostate cancer are the Gleason score method[14] and the MD Anderson system[17].

The occurrence of small foci of high grade cancer is, however, not always reflected in these grading systems. The relative amount of high grade cancer has been shown to have a high prognostic value, which, in a recent report, even overrules the Gleason and the MD Anderson grading method[18]. When their occurrence is not reflected by the overall tumor

grade, the presence of small foci of high grade cancer should, therefore, be mentioned in the report.

4.2.4. Surgical margin status

Because of its location deep within the pelvis, and because it is surrounded by vulnerable structures such as the urogenital diaphragm, the trigonum, and the rectal wall, surgical removal of the prostatic gland is not easy. As a rule, the surgical margins of a radical prostatectomy specimen will lie within a few millimeters from the boundaries of the gland. Because of this, reported frequencies of positive surgical margins are high, ranging from 33%[19] to as high as 57%[20]. Positive surgical margins require tumor cells to touch the inked surface of the prostate. Frequently, ink leaks into crevices created by interoperative or postoperative damage to the gland. It is important, but sometimes difficult, not to interpret these crevices as true surgical margins[16]. It has been shown that close, but negative surgical margins do not have an adverse prognostic impact[21]. Furthermore, the prognostic value of positive surgical margins seems to depend on the site of the margins. Several studies have shown that a positive surgical margin at the base of the prostate has a considerable adverse prognostic effect, while a positive surgical margin at the apex is not an indication of a bad prognosis[22,23]. Finally, it is important to distinguish positive surgical margins from extraprostatic extension. Although positive surgical margins do occur at sites of extraprostatic extension of a tumor, they sometimes occur at places where there is little or no periprostatic tissue. In the absence of other sites of extraprostatic extension, these tumors should be regarded as organ-confined (stage pT2) with positive margins.

5. Concluding remarks

The methods for processing of prostatic needle biopsies and radical prostatectomy specimens have been shown of considerable influence on the determination of various prognostic parameters. It has been described that procedures for processing prostatic needle biopsies can influence the sensitivity of prostate cancer detection[4,24]. Likewise, several studies on radical prostatectomy specimens have shown that the amount of tissue that is embedded and processed for histologic examination is directly proportional to the

reported presence of positive surgical margins and extraprostatic extension in radical prostatectomy specimens [25,26].

The above mentioned guidelines for the processing and reporting on prostatic needle biopsies and radical prostatectomy specimens have been implemented in all the studies that are reported in this thesis. They allow thorough comparisons of cancer features on needle biopsies with characteristics of tumors in radical prostatectomies and thereby facilitate the assessment of the clinical importance of early detected prostate cancer.

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Chapter 3

EVALUATION OF PROSTATE NEEDLE BIOPSIES IN POPULATION-BASED SCREENING

The clinical importance of borderline lesions

Robert F. Hoedemaeker
Ries Kranse
John B.W. Rietbergen J.B.
Arto E. Boeken-Kruger
Fritz H. Schröder
Theodorus H. van der Kwast

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1. Summary

The finding of isolated high grade prostatic intraepithelial neoplasia (PIN) or borderline lesions (lesions suspicious for malignancy) in prostate needle biopsies warrants repeat biopsies. The reported frequency of these lesions in prostate needle biopsies varies considerably. We evaluated the frequency and clinical impact of high grade PIN and borderline lesions in sextant prostate needle biopsies obtained from screened participants in the European Randomized study of Screening for Prostate Cancer (ERSPC).

A total of 8763 participants in the Rotterdam section of the ERSPC ages 55 to 75 years were screened systematically for prostate cancer. Systematic sextant prostate needle biopsies were prompted by an abnormal digital rectal examination and/or abnormal transrectal ultrasonography findings at serum prostate specific antigen (PSA) levels ≥ 1.0 ng/mL, or a PSA-level ≥ 4.0 ng/mL. Repeat biopsies were obtained within 6 months after initial biopsy.

Of 1824 biopsied men 384 (21.1%) were found to have prostate cancer on initial biopsy. Twelve participants (0.7%) had isolated high grade PIN and 43 (2.4%) had borderline lesions. Repeat biopsies yielded no cancer in seven participants with initial high grade PIN and 15 tumors (38.5%) in 39 participants with borderline lesions. In prostate needle biopsies obtained from a screened population, indications for repeat biopsy such as high grade PIN and borderline lesions do not represent large diagnostic subsets. Borderline lesions comprise the most important indication for a repeat biopsy. The low frequency of equivocal biopsy diagnoses in the current study supports the clinical applicability of sextant needle biopsies in population-based screening for prostate cancer.

2. Introduction

Screening techniques such as digital rectal examination (DRE), transrectal ultrasonography (TRUS) and measurement of serum prostate specific antigen (PSA) can identify men with an increased risk of having prostate cancer. The definite diagnosis of prostate cancer can however only be established after histopathologic examination of prostate needle biopsies. Prostate needle biopsies are very small and occasionally contain lesions in which a conclusive diagnosis of cancer or non cancer can be very difficult if not impossible. Lesions of this kind have been typed "suspicious for, but not diagnostic of prostate cancer"[1]. They exhibit some, but not all diagnostic criteria necessary for the diagnosis of prostate cancer, making it impossible to distinguish prostate cancer from one of its known mimics, that include atypical adenomatous hyperplasia (adenosis)[2], postatrophic hyperplasia[3], basal cell hyperplasia[4], and paraganglia[5]. To emphasize the fact that they do not form a clearly confined group of morphologic entities, but represent a variety of proliferations, we will call these lesions "borderline lesions".

Since its description in 1965 by McNeal[6] and its further characterization[7], prostatic intraepithelial neoplasia (PIN) has become widely accepted as being related directly to prostate cancer[8]. Both borderline lesions and the finding of isolated high grade PIN warrant the performance of repeat biopsies to exclude prostate cancer.

This report focuses on the effectiveness of prostate biopsies and repeat biopsies in population-based screening. The study population referred to was comprised of screened participants in the Rotterdam section of the European Randomized study of Screening for Prostate Cancer (ERSPC), an international multicenter population based screening study, that investigates the impact of screening on prostate cancer related mortality and quality of life[9]. This study will focus on the frequencies of cancer, high grade PIN and borderline lesions in systematic sextant needle biopsy sets obtained from this population. We also report on the frequency and outcome of repeat biopsies performed for high grade PIN and borderline lesions.

3. Methods

3.1 Screening Protocol

Between June 1994 and March 1997, a total of 8763 participants aged 55-75 years in the Rotterdam section of the ERSPC was systematically screened for prostate cancer. No participant had a previous diagnosis of prostate cancer. Written informed consent was obtained from every participant and the study was approved by the local medical ethics committee.

In the screening protocol of the ERSPC, participants had an indication for biopsy by either an elevated serum PSA (≥ 4.0 ng/mL, Hybritech Tandem E assay) or a combination of serum PSA levels ≥ 1.0 ng/mL and either an abnormal digital rectal examination (DRE) or abnormal findings on transrectal ultrasonography (TRUS).

Systematic sextant biopsies were obtained during longitudinal ultrasonographic scanning of the prostate by two resident urologists (JBWR and AEBK). A Bard 18 gauge biopsy-needle driven by a spring-loaded biopsy gun (Manan pro-mag) was used in all cases. Biopsies were directed cranial at an angle of approximately 45° from the transversal plane and were directed outward at approximately 30° from the sagittal plane. Biopsy cores were inked at their capsular end, numbered according to their site of origin and sent to the pathology department.

3.2 Histopathologic examination and biopsy review

After routine fixation in a 4% buffered formalin solution, biopsy cores were separately embedded in paraffin blocks. Biopsy cores were longitudinally sectioned at three levels with a thickness of 5μm and standard hematoxylin and eosin stained histologic slides were prepared. Routine histologic examination was performed by the regular pathologists of the Rotterdam University Hospital pathology department. Diagnostic criteria established by McNeal and Bostwick were used to distinguish between low grade PIN and high grade PIN[7]. A low threshold for consultation with the uropathologic reference pathologist of the department (Th.vd K.) was maintained in case of doubt. Occasionally, adenocarcinoma could be ruled out with a basal cell specific high molecular weight keratin

immunohistochemical assay[10]. In addition to all cases initially diagnosed as prostate cancer, the reference pathologist reviewed all cases with atypical adenomatous hyperplasia, postatrophic hyperplasia, low and high grade PIN and all biopsy sets that contained borderline lesions.

To assess possible missed diagnoses by the general pathologists, the uropathologic reference pathologist also reviewed a randomly selected sample of 100 sextant biopsy sets classified as having no abnormalities.

3.3 Categorization of diagnoses

Needle biopsy diagnoses were categorized as follows: All biopsy sets containing no abnormalities were categorized as benign. The benign category also included biopsy sets that contained benign prostatic hyperplasia (BPH), atrophy, prostatitis, atypical adenomatous hyperplasia and low grade PIN. Separate categories were made for biopsy sets containing isolated foci of high grade PIN and for biopsy sets containing borderline lesions, because both of these conditions were considered an indication for a repeat biopsy procedure. Biopsy sets containing borderline lesions were termed borderline, even if foci of high grade PIN were present concurrently. Biopsy sets that contained evident prostate cancer foci were termed malignant, even if additional foci of high grade PIN or borderline lesions were present. All adenocarcinomas were graded with the Gleason score method[11]. In each biopsy core, the percentages of involvement with high grade PIN, borderline lesions and cancer were recorded by comparing the length of the biopsy core in mm with the length of the lesion.

3.4 Repeat biopsy strategy

In cases of isolated high grade PIN or borderline lesions, biopsy was repeated within 6 months. Repeat biopsies for isolated high grade PIN involved systematic sextant biopsies. In participants that had borderline lesions, four new biopsies were obtained from the region with the initial borderline lesion.

3.5 Statistical analysis

Clinical parameters such as age and outcome of DRE, TRUS and PSA-measurement were compared for all different diagnosis categories. Statistical analysis was done with a Mann Whitney *U* two-tailed test for continuous variables such as age and serum PSA and with a Pearson chi-squared test for discontinuous variables such as DRE and TRUS.

4. Results

4.1 Frequency distribution of diagnoses

Of 8763 systematically screened men 1824 (20.8%) underwent sextant biopsies of the prostate. Histopathologic examination and subsequent review revealed 384 cases of adenocarcinoma (21.1% of all biopsy sets), leading to an overall detection rate of 4.4% in the studied population. Thirteen hundred and eighty-four benign biopsy sets (75.9% of all biopsy sets) included 50 low grade PIN lesions (2.7% of all biopsy sets) and 7 lesions with atypical adenomatous hyperplasia (0.4% of all biopsy sets). High grade PIN was found in 62 cases (3.4% of all biopsy sets). In four of these cases concurrent borderline lesions were found. In 46 cases, high grade PIN was found with foci of evident prostate cancer, leaving 12 cases with isolated high grade PIN (19.4% of all high grade PIN lesions and 0.7% of all biopsy sets). Forty-three biopsy sets (2.4%) contained borderline lesions. Finally, in one case, a leiomyosarcoma originating from the rectal wall was found. A summary of all biopsy diagnoses is given in Table 1.

4.2 Extent of adenocarcinoma, borderline lesions and high grade PIN

In needle biopsy sets with adenocarcinoma, the median percentage of involvement of biopsy cores with tumor was 13% (range 1.7% - 97%). In contrast to prostate adenocarcinoma, foci with high grade PIN and borderline lesions were much smaller with a median percentage of involvement of 1.7% (range 1.7% - 15%) for high grade PIN and of 1.7% (range 1.7% - 6.7%) for borderline lesions. The percentage of involvement with

Table 1. Diagnosis in 1824 sextant prostate needle biopsies

Diagnosis	Number of Cases (%)	
Benign	1384	(75.9)
Isolated high grade PIN	12	(0.7)
Borderline lesions	43	(2.4)
Cancer	384	(21.1)
Other malignancy	1	(< 0.1)
Total	1824	(100.0)

high grade PIN did not differ between cases with isolated high grade PIN and cases with high grade PIN and concurrent carcinoma.

4.3 Relationship of diagnoses with clinical parameters

Clinical parameters are summarized in Table 2. Participants diagnosed with cancer on initial biopsy were older than participants with benign diagnoses (Mann Whitney *U* test two-tailed $P = 0.001$). Serum PSA for participants with cancer was significantly higher compared to the ones in the category with benign diagnoses (Mann Whitney *U* test two-tailed $P < 0.001$), with high grade PIN ($P = 0.003$) and borderline lesions ($P = 0.005$). PSA-levels in participants with high grade PIN or borderline lesions did not differ significantly from those in participants with benign diagnoses.

Participants with cancer more frequently had an abnormal DRE and TRUS than participants with benign diagnoses (Pearson chi-squared test two-tailed $P < 0.001$ in both cases). An unexpected observation was the high percentage of abnormal DRE in participants with high grade PIN when compared to participants in the benign category ($P = 0.009$) and the low percentage of abnormal TRUS in participants with borderline lesions ($P < 0.001$ compared to participants in the malignant category)(Table 2).

Table 2.Clinical findings in 1823 patients undergoing needle biopsy

	Biopsy diagnosis			
	benign (n = 1384)	high grade PIN (n = 12)	Borderline lesion (n = 43)	cancer (n =384)
Age[a] median (range)	66 (55 – 76)	67.5 (63 – 75)	67 (55 – 74)	67 (56 – 76)
PSA (ng/mL)[b] median (range)	4.0 (1.0 – 49.4)	3.7 (1.0 – 16.3)	4.2 (1.3 – 61.5)	5.7 (1.0 – 315.7)
% abnormal DRE (95% CI)	37.7 (35.2 – 40.3)	66.7 (40.0 – 93.3)	48.8 (33.9 – 63.8)	56.0 (51.0 – 61.0)
% abnormal TRUS (95% CI)	35.9 (33.4 – 38.4)	41.7 (13.8 – 69.6)	27.9 (14.5 – 41.3)	53.6 (48.7 – 58.6)

PIN: prostatic intraepithelial neoplasia; PSA: prostate specific antigen; DRE: digital rectal examination; 95%CI: 95% confidence interval; TRUS: transrectal ultrasonography

[a] Mann Whitney *U* two-tailed test: cancer vs benign $P = 0.001$
[b] Mann Whitney *U* two-tailed test: cancer vs benign $P < 0.001$; cancer vs high grade PIN $P = 0.003$; cancer vs borderline lesions $P = 0.005$
[c] Pearson chi-squared two-tailed test: cancer vs benign $P < 0.001$; high grade PIN vs benign $P = 0.009$
[d] Pearson chi-squared two-tailed test: cancer vs benign $P < 0.001$; cancer vs borderline lesions $P < 0.001$

4.4 Pathology review

All needle biopsy diagnoses described earlier were established by regular pathologists. The reference pathologist reviewed all cases that were initially diagnosed with prostate cancer, borderline lesions, PIN and atypical adenomatous hyperplasia. In three cases the original diagnosis of prostate cancer was reverted to normal on review. A review of a random sample of 100 sextant biopsy sets that initially were diagnosed with no abnormalities revealed one additional case of isolated high grade PIN (1%).

4.5 Repeat biopsies

A total of 55 men (3.1%) had an indication for repeat biopsy because of the presence of isolated high grade PIN or borderline lesions. Nine participants refused; repeat biopsies therefore were performed in 46 participants (83.6%), seven for high grade PIN and 39 for borderline lesions. In four additional cases, systematic sextant biopsies were repeated

because of a combination of a high PSA and prostatitis and one additional case of prostate cancer was discovered. The results of repeat biopsies are summarized in Table 3. None of the seven repeat sextant biopsies performed after an initial diagnosis of high grade PIN showed prostate cancer. In one case, a renewed diagnosis of high grade PIN was made on repeat biopsy.

Table 3.Diagnosis frequency in 46 repeat biopsies

	Number of Cases (%)							
	Repeat biopsy for high grade PIN (not performed: 4)		Repeat biopsy for borderline lesions (not performed: 5)		Repeat biopsy for a high PSA		Repeat biopsy (total) (not performed: 9)	
Benign	6	(85.7)	23	(58.9)	3	(75.0)	32	(64.0)
High grade PIN	1	(14.3)	0	(0.0)	0	(0.0)	1	(2.0)
Borderline lesion	0	(0.0)	1	(2.6)	0	(0.0)	1	(2.0)
Cancer	0	(0.0)	15	(38.5)	1	(25.0)	16	(32.0)
Other Malignancy	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Total	7	(100.0)	39	(100.0)	4	(100.0)	50	(100.0)

PIN: prostatic intraepithelial neoplasia; PSA: prostate specific antigen

Of 39 subjects who were rebiopsied because of a borderline lesion, 15 (38.5%) were found to have prostate cancer (Table 3). Participants found to have cancer after repeat biopsies had higher serum PSA levels than participants with a benign diagnosis after repeat biopsy. However, this difference did not reach statistical significance (Mann Whitney U test two-tailed $P = 0.07$). One case had a renewed diagnosis of a borderline lesion after repeat biopsies. A comparison of Gleason score distributions between cancer detected on primary biopsy and cancer detected after repeat biopsy showed no apparent differences (Table 4). In total, repeat biopsies raised the prostate cancer detection rate in the studied population from 4.4% to 4.5%. In the two participants, in whom high grade

PIN and a borderline lesion were found on repeat biopsy, no prostate cancer has been found at the time of the last follow-up.

Table 4. Gleason score distribution of cancer on initial biopsies and repeat biopsies

	Number of Cases (%)							
Gleason Score	Cancer detected on initial biopsy		Cancer detected on repeat biopsy for borderline lesions		Cancer detected on repeat biopsy for a high PSA		Cancer detected on repeat biopsy (total)	
4	13	(3)	1	(7)	0	(0)	1	(6)
5	40	(10)	2	(13)	0	(0)	2	(13)
6	175	(46)	9	(60)	0	(0)	9	(56)
7	105	(27)	2	(13)	1	(100)	3	(19)
8	42	(11)	1	(7)	0	(0)	1	(6)
9	6	(2)	0	(0)	0	(0)	0	(0)
10	3	(1)	0	(0)	0	(0)	0	(0)
Total	384	(100)	15	(100)	1	(100)	16	(100)

PSA: prostate specific antigen

5. Discussion and review of the literature

Histopathologic examination of prostate needle biopsies plays a central role in diagnosing prostate cancer. Previous reports on prostate needle biopsies show varying frequencies of cancer[1,12-21] and isolated PIN[1,13,14,17,18,20-22] (Table 5). The variability of these frequencies can be explained in part by factors such as biopsy indication and technique and histologic processing methods[23]. The number of biopsies obtained and the anatomical prostatic regions targeted for biopsy prove to be of considerable influence on the detection rates of prostate cancer[19]. Differences in the type of population being studied (the general population in early detection programs versus a referred urologic patient population) also may substantially influence the detection frequencies of cancer and isolated high grade PIN in prostate needle biopsies. Indeed, the frequencies of prostate cancer and isolated

high grade PIN in our study (21.1% for cancer and 1.5% for high grade PIN) are more in line with frequencies found in the American Cancer Society National Prostate Cancer Project (15.8% for cancer and 5.2% for high and low grade PIN)[14] than with the results of a study regarding a referred urologic patient population (40.5% cancer and 16.5% high grade PIN)[1].

Table 5. Reported frequencies of cancer, high grade PIN and borderline lesions in prostate biopsies

Reference	Number of biopsies	Number of cases with cancer (%)	Number of cases with isolated PIN (%)	Number of cases with borderline or "atypical" lesions (%)
Lee et al. [12]	248	103 (41)	27 (11)[a]	-
Devonec et al. [13]	226	45 (20)	23 (10)[a]	-
Mettlin et al. [14]	330	52 (16)	17 (15)[a]	-
Terris et al. [15]	816	442 (54)	-	-
Catalona et al. [16]	860	296 (34)	-	-
Richie et al. [17]	163	24 (15)	14 (8)[a]	-
Bostwick et al. [1,3]	400	157 (39)	52 (13)[c]	8 (2)
Khan et al. [18]	3300	1487 (45)	62 (2)[c]	139 (4)
Eskew et al. [19]	119	48 (40)	-	-
Wills et al. [20]	439	160 (36)	12 (2.7)[c,d]	18 (4)
Cheville et al. [21]	1009	360 (36)	15 (1)	48 (5)
Current study	1823	384 (21)	12 (0.7)[c]	43 (2)

PIN: prostatic intraepithelial neoplasia
[a] prostatic intraepithelial neoplasia not otherwise specified (presumably low and high grade PIN).
[b] Combined numbers from two hospitals
[c] High grade prostatic intraepithelial neoplasia
[d] The number of cases with isolated high grade PIN was doubled upon review

Participants that were found to have isolated high grade PIN in our study did not show any specific clinical parameters, except a high percentage of abnormal DRE, for which we have no clear explanation (Table 2). As judged from several recent studies on

interobserver variation, the agreement of general pathologists in the diagnosis of high grade PIN can be considered "moderate"[23,24]. A higher level of agreement is reported among pathologists with expertise in urologic pathology[23].

In our study, the frequency of isolated high grade PIN was surprisingly low (0.7%) compared with results in other studies (Table 5). After a review of 100 normal biopsy sets in our study, one additional case of high grade PIN was discovered. This suggests, that the true frequency of isolated high grade PIN in our study can be estimated to be around 1.5%, and that about 50% of all cases with isolated high grade PIN may have been missed by the general pathologists. This is in keeping with findings in a recent study, in which the initial number of cases with high grade PIN was doubled on review[20].

Data regarding the frequency of borderline lesions in prostate needle biopsies have been published in only a few previous reports[1,18,20,21]; they range from 2-5% which is similar to our results (2.4%)(Table 5). Participants with borderline lesions in our study did not show any indicative clinical parameters except a remarkably low percentage of abnormal TRUS (Table 2).

The criteria for the diagnosis of prostate cancer are discussed in detail in chapter 1. Borderline lesions are diagnosed when some suspicious features (such as a distorted architecture enlarged nuclei and prominent nucleoli)[21,25] are present in a lesion, while a lack of sufficient criteria for an unequivocal diagnosis of adenocarcinoma remains. Features that raise suspicion for adenocarcinoma vary from case to case and borderline lesions therefore do not form a separate morphologic entity. To avoid confusion, refraining from terms that imply morphologic features is preferable. In our opinion, the recently introduced term "atypical small acinar proliferations (ASAP)"[21,25] is not suitable to designate a separate diagnostic category because it can only be used to indicate only part of the lesions that are suspicious for, but not diagnostic of adenocarcinoma (i.e. glandular or acinar proliferations). A more general term, such as "borderline lesions" would be more adequate, also because these lesions do not form a large diagnostic subset. Although general agreement regarding the type of criteria that are important for the diagnosis of prostate cancer exists (small infiltrating glands, nuclear enlargement, nucleolar prominence and the absence of a basal cell layer) [26], uncertainties remain regarding their exact application. Therefore we anticipated that the threshold for a definite diagnosis of prostate cancer is likely to vary markedly between different pathologists, leading to different numbers and types of borderline lesions. However, judged from

several other studies, the variation in the frequency of borderline lesions is less than would be expected (Table 5).

It is generally agreed that the presence of isolated high grade PIN in prostate needle biopsies warrants repeat biopsies, either to exclude concurrent adenocarcinoma or to detect subsequent adenocarcinoma that could originate from this lesion. Several studies on the results of repeat biopsies for initial isolated high grade PIN have been published[27-33]. The frequency of cancer on repeat biopsy for high grade PIN in these studies varies considerably and ranges from 28%[31] up to 100%[29,34] (Table 6). It should be noted that different procedures for repeat biopsies were applied in these studies. These varied from biopsies that were solely directed at the site of the initial PIN-lesion[29] to systematic quadrant or sextant biopsies[31]. Surprisingly, of the7 cases with isolated high grade PIN lesions in our study, none showed cancer on repeat systematic sextant biopsy. Although this observation may be attributed to the small number of cases, there could be other explanations. In our series nearly 75% of the initial biopsy sets with high grade PIN also contained cancer. A recent autopsy study showed that about 20% of all prostates with high grade PIN do not harbor concurrent adenocarcinoma[35]. It is possible that systematic sextant biopsies provide a higher chance of detecting high grade PIN with concurrent cancer. If so, this could explain the low frequency of isolated high grade PIN in our study. Also, the tumor yield on repeat biopsies after isolated high grade PIN would decrease, because most of the repeat biopsies would be performed in cases with high grade PIN and no concurrent cancer. Longer follow-up would then be needed to detect cancer that would eventually originate in these cases. This theory is supported by the findings of a recent study, in which it was shown that repeat biopsies for isolated high grade PIN were more likely to show cancer at longer follow-up intervals [28].

In our experience, reports on repeat biopsies for borderline lesions are less frequent and of a more recent date than reports on repeat biopsies for isolated high grade PIN[18,21,25,29,36,37]. The frequency of cancer in repeat biopsies after an initial borderline lesion in these reports ranges from to 29%[29] to 60%[21] (Table 6). Unfortunately, in each study some uncertainty remains regarding how repeat biopsies were performed (systematic sextant biopsies versus biopsies directed at the borderline lesion). In our study, a definite diagnosis of cancer on repeat biopsy consisting of 4 biopsy cores directed at borderline lesions was established in 38.5% of the cases.

Methods for repeat biopsies should depend on the diagnosis made on the initial biopsy. In the case of isolated high grade PIN, despite its close relationship with prostate cancer[8] some doubt always has remained regarding whether high grade PIN represents a direct precursor of adenocarcinoma or results of a coexisting field effect reflecting carcinogenic injury to the prostatic gland as a whole[38]. In view of this uncertainty and in view of the results of several other studies[31,32], cases with isolated high grade PIN are probably best managed with systematic sextant repeat biopsies. Borderline lesions, however, reflect quite a different situation, because the lesion itself raises questions regarding its nature.

Table 6. Reported frequencies of adenocarcinoma, detected in repeat biopsies

	Repeat biopsy indication	
Reference	Isolated high grade PIN	Borderline or "atypical" lesions
Brawer et al. [34]	10 / 10 (100%)	-
Weinstein and Epstein [27]	10 / 33 (31%)	-
Aboseif et al. [30]	21 / 36 (58%)	-
Davidson et al. [28]	35 / 100 (35%)	-
Ellis et al. [29]	5 / 5 (100%)	5 / 17 (29%)
Shepherd et al. [32]	26 / 45 (58%)	-
Raviv et al. [33]	23 / 48 (48%)	-
Langer et al. [31]	15 / 53 (28%)	-
Iczkowski et al. [25]	-	15 / 33 (45%)
Cheville et al. [21]	-	15 / 25 (60%)
Khan et al. [18]	9 / 24 (38%)	21 / 36 (58%)
Chan and Epstein [36]	-	45 / 92 (49%)
Allen et al. [37]	-	56/124 (45%)
Current study	0 / 7 (0%)	15 / 39 (38%)

PIN: prostatic intraepithelial neoplasia

Additional samples of the lesion itself are needed and repeat biopsies should therefore be directed specifically toward the site of the lesion. Of course, cancer may be found far away from the initial borderline lesion [37], but this would most probably constitute a chance finding.

Especially in large scale prostate cancer detection programs such as our study, a high frequency of repeat biopsies would be unfeasible. In a recent study conducted by Bostwick et al., judging by the combined frequencies of isolated high grade PIN and borderline lesions, indication for repeat biopsy would have occurred in up to 15% of all biopsied men in a referred urologic patient population[1]. Fortunately, of all biopsied men in our study, only 3.1% had an indication for repeat biopsy because of isolated high grade PIN or borderline lesions. The majority of the repeat biopsy indications were comprised of borderline lesions, making this diagnostic entity the most important repeat biopsy indication in our population.

An important issue in assessing the need for performing repeat biopsies for high grade PIN and borderline lesions is the clinical significance of tumors detected by those repeat biopsies. A comparison of cancers that were detected on initial biopsy and cancers that were detected on repeat biopsy shows that they have similar Gleason score distributions (Table 4). However, a more thorough characterization of prostate cancer detected on repeat biopsy (including tumor volume and pathologic stage) is needed and will require careful examination of radical prostatectomy specimens. Because to date radical prostatectomy was only performed in two cases within this study, these findings will be presented at a later date.

The results of this population-based screening study show that repeat biopsy indications such as high grade PIN and borderline lesions do not represent major diagnostic subsets, yet appear to yield significant additional tumors. To assess the clinical value of pursuing these lesions further, a better understanding of the clinical significance of tumors found after repeat biopsies is needed. When performing repeat biopsies, we have to realize that not all borderline lesions and foci with high grade PIN will have been detected on initial biopsy and that some therefore will remain unmanaged. Evaluation of the contributive value of repeat biopsies in prostate cancer detection should include consideration of these factors.

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Chapter 4

ARE IMPALPABLE AND INVISIBLE TUMORS CLINICALLY IMPORTANT?

Robert F. Hoedemaeker
John B. W. Rietbergen
Ries Kranse
Theodorus H. van der Kwast
Fritz H. Schröder

The Naming of Cats is a difficult matter,
It isn't just one of your holiday games;
You may think at first I'm as mad as a hatter
When I tell you, a cat must have three different names……

From T.S. Eliot - The Naming of Cats

Original title:

Comparison of pathologic characteristics of T1c and non-T1c cancers detected in a population-based screening study, the European Randomized Study of Screening for Prostate Cancer.

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1. Summary

In recent years, the introduction of serum prostate specific antigen (PSA) determination as a screening tool for early detection of prostate cancer in asymptomatic men has led to a markedly increased detection of prostate cancers that are neither palpable nor visible with transrectal ultrasonography (stage T1c). In this study we assessed pathologic features and aspects that are indicative for clinical significance in T1c tumors and tumors with palpable or visible lesions (non-T1c tumors).

Between June 1994 and December 1995, 51 consecutive radical prostatectomies were performed on screened participants in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer (ERSPC). After determination of pathologic stage and Gleason score, morphometric analysis was performed to determine tumor volume. Radical prostatectomy specimens were divided into three mutually exclusive subsets: T1c tumors, non-T1c tumors with preoperative PSA below 4 ng/mL and non-T1c tumors with PSA equal or greater than 4 ng/mL. These subsets were compared for differences in the distribution of tumor volume, pathologic stage and Gleason score. An arbitrarily constructed categorization model was used to assess clinical significance.

In all, 17 (33%) of the patients had clinical stage T1c disease. In our categorization model, 88% of the T1c tumors fit the criteria for clinically significant tumors. T1c tumors however were significantly smaller (Mann Whitney U test, two-tailed $P < 0.01$) and were more likely to be organ-confined (Pearson chi-squared test two-tailed $P = 0.01$) as compared to non-T1c tumors in patients with an elevated preoperative serum PSA level. In contrast, tumors detected at preoperative PSA levels below 4 ng/mL had comparably the lowest pathologic stages and tumor volumes in our series. In our categorization model, 42% of these tumors fit the criteria for minimal tumor. This group of radical prostatectomies was therefore most likely to harbor clinically insignificant cancer, a finding that was consistent in two other categorization models derived from earlier reports. T1c-tumors comprise a large fraction of the tumors found in population based screening. As judged by their pathologic characteristics T1c tumors are clinically significant tumors. The overall low pathologic stage and Gleason score of these tumors make these patients excellent candidates for curative treatment by radical prostatectomy or radiotherapy.

In contrast, some concern should be raised on the detection of tumors at low serum PSA levels by means of digital rectal examination and transrectal ultrasound only, since a

substantial proportion of these tumors could be considered clinically insignificant. Long-term follow-up, however, is necessary to substantiate this view.

2. Introduction

In recent years, extensive systematic screening for the presence of prostate cancer in asymptomatic men has become widespread in the western world. The relatively high rate of recurrence after curative treatment such as radical prostatectomy[1,2] warrants the attempt to detect prostate cancer at an earlier stage, thereby improving the chances of curative treatment. On the other hand, it should be noted that the incidence of unsuspected prostate cancer in a number of cystoprostatectomy and autopsy studies is very high (30-60% in men > 50 years old)[3-5]. A substantial proportion of prostatic neoplasms therefore seems to have an indolent biological behavior[6]. It is obvious, that in screening programs for prostate cancer the detection of too many of these mostly insignificant tumors should be avoided. It is likely that the clinical significance of prostate cancer can be partly derived from histopathologic tumor characteristics. In addition, the life expectancy and co-morbidity of the patient should be taken into consideration[7].

In early detection programs for prostate cancer it is pertinent to find a way to distinguish the clinically important tumors from the clinically unimportant ones. Without sufficient follow-up data available to provide good insight into these matters, screening for prostate cancer remains a controversial topic.

The application of serum prostate specific antigen (PSA) measurements as a screening test for the presence of prostatic adenocarcinoma[8] has led to an increased discovery of organ-confined prostate cancer[9]. It has also led to the discovery of an increasing number of clinically impalpable and echographically invisible tumors. The clinical relevance of these T1c tumors has been scrutinized in a number of recent studies[6,10-12]. After careful judgement of their histopathologic features the majority of these tumors has been delineated as being clinically significant. To determine the extent and the clinical significance of T1c tumors in a population-based screening study, we investigated the pathologic characteristics of 51 radical prostatectomies that were performed between June

1994 and December 1995 in screened patients of the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer (ERSPC). We determined various pathologic features and compared subsets of tumors that were classified by their properties of palpability and echographic visibility and preoperative serum PSA levels. A categorization model that was based on tumor characteristics was constructed for the determination and comparison of their clinical significance.

3. Methods

3.1. Patients

The ERSPC is an international multicenter study that investigates the effects of systematic screening for prostate cancer on prostate cancer mortality and quality of life[13]. In the ERSPC the male population aged 55-75 years is randomized to screened and not-screened groups. Between June 1994 and December 1995 at the University Hospital Rotterdam, 51 radical prostatectomies, all of which are included in this report, were performed on participants in the screening arm of the ERSPC. In all subjects, the diagnosis of prostate cancer had been established with ultrasound-guided random sextant biopsy of the prostate. Biopsy indication was based on either an elevated serum PSA level (Hybritech Tandem E Assay ≥ 4 ng/mL) or an abnormal digital rectal examination (DRE) and/or transrectal ultrasonography (TRUS). None of the participants had a previous diagnosis of prostate cancer or prostatic surgery.

3.2. Tissue

Radical prostatectomy specimens were fixed for 24 hours in a 4% saline buffered formalin solution. After fixation, each specimen was totally embedded in paraffin blocks. The scheme by which the specimens were cut was based mainly on the Stanford technique[14]. In short, after fixation the specimens were inked and cut at 4mm intervals in the transversal plane perpendicular to the rectal surface. Each transversal slice was divided into two dorsal and two ventral quadrants. To enhance the accuracy of the determination

of tumor extension in the apical surgical margins the apical part of the prostate was cut parasagittally at 4mm intervals. Additional representative slices of the base of the seminal vesicles were prepared and each slice was totally embedded in paraffin. From each paraffin block, hematoxylin-eosin stained histologic slides were prepared for routine pathologic examination. For each radical prostatectomy specimen the pathologic stage (TNM '92) [15] and the Gleason Score [16] were determined.

3.3.Volumetric measurements

After histologic examination, all cancer areas were outlined on the hematoxylin-eosin stained slides. Grey scale digital images of each histologic section were made using a digital camera, and digital morphometric analysis was subsequently performed to measure each tumor area using computer software for morphometry (Kontron Imaging System (KS400), Kontron Elektronik GmbH, Eching, Germany) . Tumor volume was determined by totaling all measured tumor areas and total slide areas (in square millimeters) and their multiplication by 4 (the thickness in mm of the original slices). Prior experiments had shown that no correction factor was required for the effects of fixation and paraffin embedding.

3.4. Preoperative criteria for subdivision of radical prostatectomy specimens

On the basis of the different biopsy indications in the ERSPC, we could distinguish three mutually exclusive groups of radical prostatectomy specimens, i.e., tumors detected by an abnormal DRE and/or TRUS finding in patients with an elevated PSA level ($\geq$ 4 ng/mL), tumors, detected by an abnormal DRE and/or TRUS finding in patients with a normal PSA level (< 4ng/mL) and tumors detected by an elevated PSA level only (Table 1). We compared these three groups for the presence of various parameters that previously proved to be of prognostic value (i.e., tumor volume, pathologic stage, Gleason score and surgical margin status).

Table 1. Subsets of tumors

Subset	Criteria
Group 1	Tumors detected by an abnormal DRE or TRUS at normal PSA (< 4ng/mL)
Group 2	Tumors detected by an elevated PSA (> 4ng/mL) only
Group 3	Tumors detected by both an abnormal DRE or TRUS and an elevated PSA

3.5. Categorization of tumors

Whereas the prognosis after radical prostatectomy depends on a combination of tumor characteristics and outcome of surgery, the clinical significance of a detected prostate cancer depends on a very complex mixture of tumor characteristics and patient features (life expectancy and co-morbidity). Given the current lack of follow-up data, categorization of radical prostatectomy series based on tumor characteristics is the only way to assess different subsets of radical prostatectomies for their clinical significance. In a few recent studies, two different categorization systems based on tumor characteristics were proposed [6,10]. These categorizations were based on the outcome of earlier series of radical prostatectomies in the institutions of the respective authors. Because of the current lack of follow-up data available in our series of radical prostatectomies, we constructed an arbitrary model for categorization that was in part based on the above-mentioned models (Table 2).

Minimal tumors - Tumors smaller than 0.5 mL, lacking a Gleason growth pattern 4 or 5 and confined to the prostate (stage pT2) were categorized as minimal tumors. Minimal tumors are generally considered to have an excellent prognosis after radical prostatectomy.

Moderate tumors - Tumors with a Gleason growth pattern of 4 or 5 confined to the prostatic gland in addition to well differentiated tumors (no Gleason patterns 4 or 5) larger than 0.5 mL or showing capsular penetration were assigned to this group. The prognosis after radical prostatectomy in this group is expected to be less favorable than the prognosis in minimal tumors; nonetheless, it is expected to be acceptable. Patients with moderate tumors are expected to gain a maximum benefit from initially curative treatment such as radical prostatectomy or radiotherapy.

Advanced tumors - Either lesions with capsular penetration and a Gleason growth pattern 4 or 5 or tumors invading adjacent structures such as the seminal vesicles or bladder neck were considered to be advanced tumors. It is expected that a large fraction of patients with advanced tumors will have tumor recurrence after radical prostatectomy or radiotherapy.

Table 2. Categorization of tumors

Category	Tumorvolume	Gleason	Tumor extent
Minimal	< 0.5 mL	No pattern 4 or 5	Confined
Moderate	Any	Any	Confined
	Any	No pattern 4 or 5	Extracapsular extension
Advanced	Any	Pattern 4 or 5	Extracapsular extension
	Any	Any	Seminal vesicle invasion
	Any	Any	Bladder neck invasion
	Any	Any	Positive Lymph nodes

To get some insight in differences in the clinical significance and prognosis of T1c and non-T1c tumors detected with and without an elevated PSA level, the frequency of the various categories (minimal, moderate and advanced) was evaluated in the above-mentioned three groups of radical prostatectomies.

3.6. Statistical analysis

To test the dependence of tumor group classification on pathologic stage, Gleason score and tumor categorization, the Pearson chi-squared test was used. The null hypothesis (statistical independence assumed) was rejected for P values under 0.05. Because of the limited number of radical prostatectomies in our series, comparison of pathologic stage was limited to the two categories of confined (pT2) and non-confined (> pT2).
Since tumor volume did not show a normal distribution, a non-parametric statistical test (Mann Whitney U test) was used for comparison. The null hypothesis (equal distribution) was rejected for P values under 0.05 (two-tailed test).

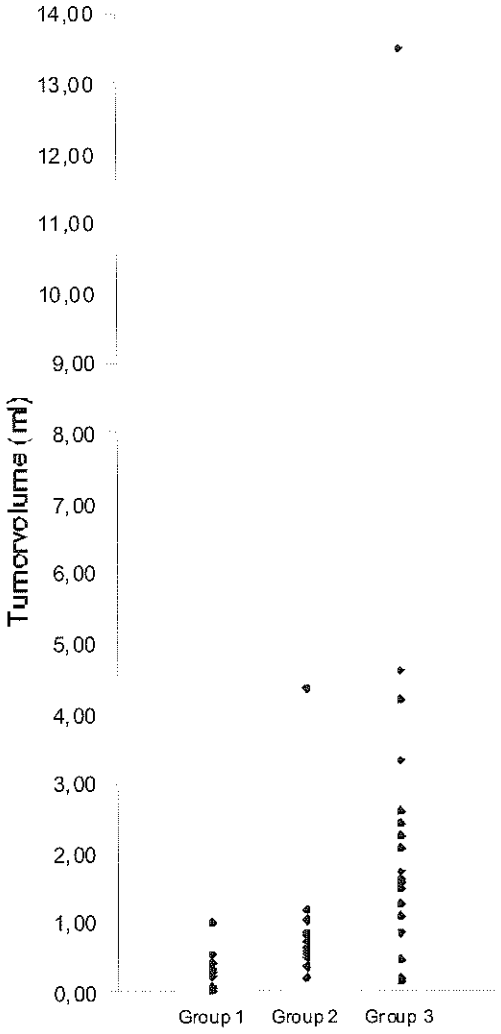


Figure 1. Distribution of tumor volume among the three different groups of radical prostatectomies. T1c tumors (group 2) lie intermediate between non-T1c tumors with (group 3) and those without (group 1) an elevated PSA level. Mann Whitney *U* test (two-tailed): group 1 vs group 2 $P < 0.001$, group 1 vs group 3 $P < 0.001$, group 2 vs group 3 $P < 0.001$.

4. Results

4.1. General features

The mean age of the 51 patients at surgery was 63.5 (median 64, range 55-73) years. Preoperative serum PSA levels ranged from 0.0 to 16.0 ng/mL (mean 6.1 median 5.0). A total of 34 tumors (67%) had been detected after abnormal DRE or TRUS. Detection of the remaining 17 tumors (33%) was based on an elevated serum PSA level only (stage T1c). Tumor volume ranged form 0.02 to 13.48 mL (mean 1.31mL, median 0.63mL). Assessment of the pathologic stage revealed 33 (65%) organ-confined tumors (combined stages pT2a and pT2c). Of 51 tumors, 16 (31%) had capsular penetration and 2 (4%) invaded the seminal vesicles. Bladder neck invasion was seen in 5 cases (9%). In 37% of the specimens tumor was found in the surgical margins. In none of the cases positive lymph nodes were found.

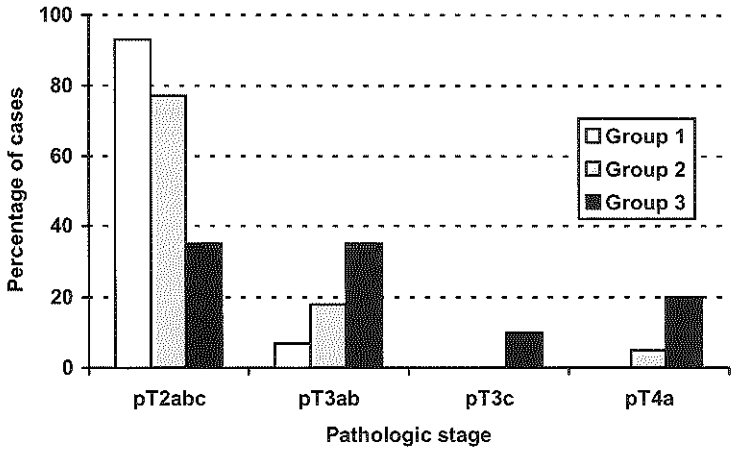


Figure 2. Distribution of pathologic stage among three groups of tumors. The pathologic stage of T1c tumors lies intermediate between that of non-T1c cancers with and those without an elevated PSA level. Pearson chi-squared test (two-tailed): group 1 vs group 2 nonsignificant, group 1 vs group 3 $P < 0.001$, group 2 vs group 3 $P = 0.01$

4.2. Prognostic features in different groups of radical prostatectomies

The distribution patterns of tumor volume recorded for the three different groups are shown in Fig 1. Group 2 tumors (T1c tumors) were intermediate with regard to tumor volume, whereas group 3 tumors were generally the largest (Mann Whitney *U* test, two-tailed $P < 0.01$ as compared to group 2 tumors and < 0.001 as compared to group 1 tumors; Fig. 1).

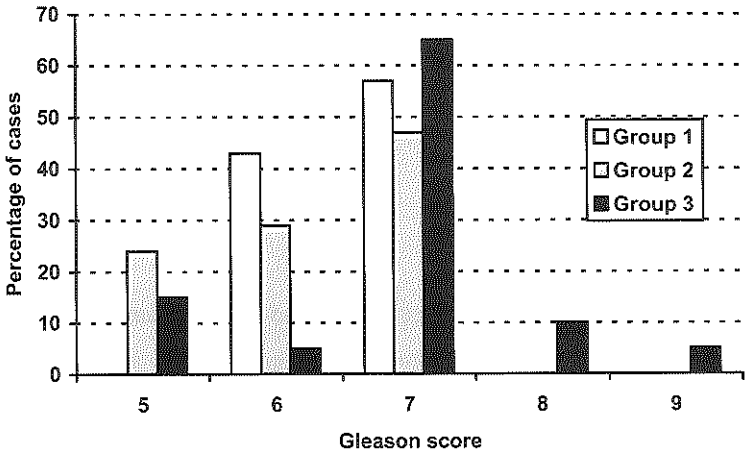
Figure 2 shows the distribution of pathologic stage. Again, group 3 tumors had the highest pathologic stage (only 35% was organ-confined; Fig. 2, Table 3). Group 1 and group 2 tumors were more likely to be organ-confined than group 3 tumors (Pearson chi-squared test, two-tailed $P < 0.001$ for group 1 tumors and $P < 0.001$ for group 2 tumors; Fig. 2, Table 3).

Table 3. Prognostic parameters in subsets of radical prostatectomies

	Number of cases (%)		
	Group 1 (Non-T1c, PSA below 4 ng/mL)	Group 2 (T1c, PSA 4 ng/mL or above)	Group 3 (Non-T1c, PSA 4 ng/mL or above)
Number of Cases (%)	14 (27)	17 (33)	20 (40)
Patient age mean / median	62.9 / 63.5	62.5 / 63.0	64.6 / 65.5
Organ confined No. (%)	13 (93)	13 (77)	7 (35)
Capsule penetration No. (%)	1 (7)	3 (18)	12 (60)
Seminal vesicle invasion No. (%)	0 (0)	0 (0)	3 (15)
Bladder neck invasion No. (%)	0 (0)	1 (6)	4 (20)
Positive surgical margins No. (%)	2 (14)	6 (35)	11 (55)

The Gleason score in was lowest in group 1 tumors (Pearson chi-squared test, two-tailed $P = 0.04$ as compared to group 3 tumors; Fig. 3). The distribution of Gleason score was not significantly different between group 2 and group 3 tumors, although it should be noted that all tumors with Gleason scores above 7 were group 3 tumors (Fig.3).

Some prognostic features in the three mutually exclusive groups of radical prostatectomy specimens are shown in Table 3. Patient age did not differ much between the three groups. Patients with T1c tumors were generally the youngest as compared with both non-T1c groups (Table 3). Group 3 tumors had the worst prognostic parameter distribution; 60% showed capsular penetration and 55% had positive surgical margins (Table 3). Group 1 tumors were almost always organ-confined (there was only one case of capsule penetration), and radical prostatectomies for these tumors had positive surgical margins least often (14%). Group 2 tumors were intermediate between group 1 and group 3 tumors, with 77% being organ-confined tumors, 35% having positive surgical margins and one



case involving bladder neck invasion.

Figure 3. Distribution of Gleason score in three groups of radical prostatectomy specimens. Pearson chi-squared test (two-tailed): group 1 vs group 2 nonsignificant, group 1 vs group 3 $P = 0.04$, group 2 vs group 3 nonsignificant

4.3. Categorization of tumors

The distribution of tumors along the various categories of our categorization model (described in Table 1) are shown in Table 4. Overall, 18% of tumors in our series fit the criteria for minimal tumor. Most of the tumors (55%) could be considered to be moderate and 27% were advanced. The different groups of tumors showed different distributions along the various categories. In group 1 a substantial proportion (43%) of minimal tumor

was present whereas none of the tumors in group 1 was advanced (Table 4). T1c tumors were more likely to be moderate (70%), with a small percentage of minimal (12%) and advanced (18%) tumors being observed (Table 4). The majority of group 3 tumors were advanced (55%). Differences in category distributions in the three groups reached statistical significance only in comparison of group 1 tumors with group 3 tumors, where group 1 tumors were more likely to have a lower categorization (Pearson chi-squared test, two-tailed $P < 0.001$, Table 4). Group 3 tumors were also more likely to be advanced than group 2 tumors, although this difference was not statistically significant. For comparison, the categorization models that were constructed by Epstein et al.[10] and Ohori et al.[6] are given in Tables 5 and 6, respectively. No great difference was found except for the tendency toward a relatively higher frequency of advanced tumors in the model of Epstein et al. (Table 5) and toward relatively more curable tumors in the categorization model by Ohori et al. (Table 6).

5. Discussion

To determine the features of clinical significance for T1c and non-T1c tumors, we constructed a model for the categorization of tumors based on a combination of tumor volume, pathologic stage and Gleason score (Table 1). In our categorization model we tried to distinguish the 'moderate' tumors, which are most likely to benefit from curative treatment such as radical prostatectomy or radiotherapy, from minimal tumors and advanced tumors. Although patients with minimal tumors probably have an excellent prognosis after curative therapy, a substantial proportion of them most likely harbor tumors which have an indolent biologic behavior. For a substantial proportion of these patients, therefore, conservative treatment perhaps would be a better alternative. On the other hand, the category of advanced tumors is meant to identify the group of patients who will have a high risk for progression after initial treatment. It is however questionable how 'advanced' the tumors in this category really are. These questions can be answered only after follow-up of significant duration.

Table 4. Categorization of tumors with different biopsy indications[a]

Category	Number of cases (%)			
	Group 1 (Non-T1c, PSA below 4 ng/mL)	Group 2 (T1c, PSA 4 ng/mL or above)	Group 3 (Non-T1c, PSA 4 ng/mL or above)	Total
Minimal	6 (43)	2 (12)	1 (5)	9 (18)
Moderate	8 (57)	12 (70)	8 (40)	28 (55)
Advanced	0 (0)	3 (18)	11 (55)	14 (27)
Total	14 (100)	17 (100)	20 (100)	51 (100)

[a]Pearson chi-squared test (two-tailed): group 1 vs group 2 nonsignificant, group 1 vs group 3 $P <$ 0.001, group 2 vs group 3 nonsignificant

Table 5. Categorization of tumors according to Epstein et al.[10]

Category	Number of cases (%)			
	Group 1 (Non-T1c, PSA below 4 ng/mL)	Group 2 (T1c, PSA 4 ng/mL or above)	Group 3 (Non-T1c, PSA 4 ng/mL or above)	Total
Insignificant	3 (21)	0 (0)	0 (0)	3 (6)
Minimal	3 (21)	3 (17)	0 (0)	6 (12)
Moderate	8 (58)	10 (59)	6 (30)	24 (47)
Advanced	0 (0)	4 (24)	14 (70)	18 (35)
Total	14 (100)	17 (100)	20 (100)	51 (100)

Table 6. Categorization of tumors according to Ohori et al. [6]

Category	Number of cases (%)			
	Group 1 (Non-T1c, PSA below 4 ng/mL)	Group 2 (T1c, PSA 4 ng/mL or above)	Group 3 (Non-T1c, PSA 4 ng/mL or above)	Total
Minimal	6 (43)	2 (12)	1 (5)	9 (18)
Curable	8 (57)	14 (82)	13 (65)	36 (68)
Advanced	0 (0)	1 (6)	6 (30)	7 (14)
Total	14 (100)	17 (100)	20 (100)	51 (100)

The construction of categorization models based on tumor characteristics has been done before in a few recent studies[6,10]. Because of the current lack of follow-up data in our series of radical prostatectomies, our arbitrary model for tumor categorization was in part based on the above-mentioned models. When we compared categorization of our series according to our model with the categorizations used by Epstein et al.[10] and Ohori et al. [6], there were no substantial differences in distribution of cancers among the comparable categories (Tables 4-6). Constructing of our own categorization model therefore seems pointless at first view. There is, however, an important reason why we did so.
In both earlier models, surgical margin status was partly used to establish extensive capsular penetration. In our opinion, surgical margin status must be seen as a characteristic of surgery and tumor localization rather than of tumor extent or aggressiveness and, therefore, cannot be used as a parameter of clinical significance. From a practical point of view this feature can never be determined preoperatively. Also the value of surgical margin status in describing the extent of capsular penetration is limited, since the amount of extraprostatic tissue varies considerably. For these reasons we omitted surgical margin status and the difference between focal and extensive capsule penetration in our arbitrary categorization model (Table 1).
As judged by the distribution of clinical stages in our group of radical prostatectomies, the number of T1c-tumors detected in the screened general population is considerable. No less than 33% of all radical prostatectomies and 46% of radical prostatectomies performed for tumors detected on the basis of an elevated PSA level were performed in stage T1c patients. On the basis of our data it can generally be said that T1c tumors are smaller (Fig. 1) and of lower pathologic stage (Fig.2) as compared with palpable and visible tumors detected with preoperative PSA levels ≥ 4ng/mL. Also, no Gleason score higher than 7 was seen in T1c tumors, although the Gleason score distribution of these tumors was not significantly different from that of non-T1c tumors with an elevated PSA level (Fig. 3). T1c tumors were mostly present in the moderate category, with only 2 of 17 T1c tumors fitting the criteria for minimal tumor (Table 4). Also T1c tumors were less likely to be advanced than non-T1c tumors with an elevated PSA level (18% versus 55%, Table 4). Considering the independent prognostic values of pathologic stage[1,17], we should expect that the long-term outcome after radical prostatectomy would be relatively favorable for T1c tumors as compared with non-T1c tumors with elevated serum PSA levels. A recent

study with limited follow-up indeed showed that T1c-tumors seem to have a more favorable outcome than non-T1c tumors detected at similar preoperative serum PSA concentrations[18]. The detection of impalpable and echographically invisible tumors in a population-based screening study therefore seems of great importance in reducing prostate-cancer-related mortality. Some concern should be raised on the characteristics of tumors detected by DRE and TRUS in patients with PSA levels < 4 ng/mL. This group contains the smallest tumors with the lowest pathologic stages (Table 3) and is therefore most likely to harbor clinically insignificant tumors. A considerable fraction (43%) of these tumors fit our criteria for minimal tumor and none of them was advanced (Table 4). As judged by their tumor volume (86% were smaller than 0.5 mL), it is likely, that a substantial proportion of these non-T1c tumors were detected on the basis of a false positive DRE or TRUS finding.

It is important to realize that according to our categorization model the percentage of patients with moderate tumors, who are most likely to benefit from curative treatment was limited (55%, Table 4). Furthermore, be it with some variation, the three categorization models would predict that a substantial proportion (27%, Table 4) of the patients may currently be at risk for recurrence. In all, 18% of radical prostatectomies were done in patients with minimal tumor (Table 4). These findings stress the importance of the use of serum PSA as a screening tool for early detection and preoperative assessment of prostate cancer. The value of clinical stage, which is solely based on the outcome of DRE and TRUS, is decreasing with the rapidly changing tumor characteristics due to early detection. Our data show that an elevated preoperative serum PSA concentration is associated with larger, more aggressive tumors. In combination with elevated serum PSA levels, abnormalities in DRE or TRUS are associated with more advanced tumors. In combination with a normal PSA level (< 4 ng/mL), however, this association disappears. The additive value of the outcome of DRE or TRUS therefore seems limited to patients with elevated PSA levels.

Finally, it is important to realize that all of the screen-detected tumors discussed in this report were detected in the first round of screening. They therefore merely resemble tumors that are to be found in a general asymptomatic population using the described screening protocol. The characteristics of tumors that are detected in systematic, 4-year interval screening therefore remain unknown. In subsequent screening rounds of the

ERSPC it is likely that the morphology of the discovered tumors will change further, probably leading to a yet higher proportion of small, organ-confined tumors.

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Chapter 5

THE CHANGING CHARACTERISTICS OF PROSTATE CANCER IN RADICAL PROSTATECTOMY SPECIMENS

Robert F. Hoedemaeker
John B.W. Rietbergen
Ries Kranse
Fritz H. Schröder
Theodorus H. van der Kwast

Original title:

Histopathologic prostate cancer characteristics at radical prostatectomy after population based screening.

J Urol 2000;164:411-5.

1. Summary

Although early detection of prostate cancer by prostate specific antigen (PSA) based screening results in a shift towards more clinically organ-confined tumors, changes in prostate cancer characteristics after radical prostatectomy are less clear.
We studied 121 totally embedded radical prostatectomy specimens that were obtained from consecutive participants of the European Randomized study of Screening for Prostate Cancer who were systematically screened and treated surgically. In each specimen pathologic stage, Gleason score, and proportion of high grade cancer (Gleason pattern 4 or 5) were determined. Lymph node status at operation, stage and grade were compared to a historical series of 72 surgical procedures performed for clinically localized prostate cancer at our hospital before the introduction of serum PSA measurements as a diagnostic tool.
Although none of the screen detected cancers had positive lymph nodes at surgery, operation was discontinued in 13 (18%) of the 72 historical cases because of positive lymph nodes. Compared with the remaining 59 historical radical prostatectomy specimens, the screen-detected series showed a definite increase in the frequency of pathologically organ-confined tumors and a relative decrease in Gleason score 8 to 10 tumors. However, 60% of screen detected tumors contained areas with high grade cancer (Gleason pattern 4 or 5) and 50% had a Gleason score of 7. The relative amount of high grade cancer in each tumor was related to its volume (Kruskal Wallis test $P < 0.001$).
Screening for prostate cancer leads to an increase in surgical treatment for relatively small tumors that have a higher probability of being pathologically organ-confined. The frequency of positive lymph nodes at operation decreases dramatically and the proportion of organ-confined cancers after surgery increases. In addition, there is a shift from Gleason 8 to 10 tumors towards lower grade tumors. Still, judged by the high frequency of focal dedifferentiation in screen-detected tumors, most of them are likely to be clinically important. The observed accumulation of tumors in the Gleason 7 category is of some concern, because it could lead to a decrease in the clinical usefulness of the Gleason score system.

2. Introduction

The introduction of serum prostate specific antigen (PSA) measurements as a diagnostic tool for the detection of prostate cancer and the increased efforts for its early detection are probably the main causes of the recent dramatic increase of prostate cancer incidence rates in the western world. The main objective of early detection is to improve clinical outcome by increasing the frequency of succesful initial curative treatment. However, screening for prostate cancer also entails a risk of detecting increased numbers of clinical unimportant prostate cancer. Several past studies on prostates removed at autopsy or during surgery for bladder cancer have shown a high frequency of clinically latent prostate cancer[1-3]. These studies imply that the actual prevalence of prostate cancer in the general male population older than 55 years can be estimated to lie between 30 and 50%. In the Netherlands the cumulative risk for a 55 year old man to be diagnosed with prostate cancer during the rest of his lifetime without screening is estimated to be 9.9%[4]. Using these two percentages, it can be easily calculated, that 66-80% of prostate tumors that are actually present in the male population older than 55 years will not lead to morbidity or mortality. In early detection programs it is of critical importance to detect and treat only those cancers that will result in morbidity and mortality without treating too many clinically unimportant tumors. Therefore, the increasing effort for early detection of prostate cancer remains a controversial issue.

To understand the impact of prostate cancer screening, it is mandatory to gain more insight into the resulting changes in prostate cancer stage, grade and volume. This information could provide us with clues with regard to the clinical importance of early detected tumors, while comparisons with series of non-screened cases would allow us to gain more insight into prostate cancer evolution and progression. Recent reports have shown a dramatic increase in the frequency of radical prostatectomy since the introduction of serum PSA[5-7]. The increased frequency of treatment with curative intent is most likely due to an increase in the detection of non-palpable prostate cancer, resulting in a higher number of clinically confined tumors. Whether any changes have occurred in volume, stage and grade of the tumors in radical prostatectomy specimens is much less clear, as different reports show conflicting results[6,8]. These conflicting results might have arisen because of differences in the study populations, the processing of radical prostatectomy

specimens and pathologic review.

We determined whether histopathologic characteristics of prostate cancer in patients treated with radical prostatectomy changed due to systematic screening for prostate cancer. We recorded prostate cancer characteristics in a series of consecutive radical prostatectomies performed for cancer detected in systematically screened participants of the screening arm of the Rotterdam section of the European Randomized study of Screening for Prostate Cancer (ERSPC), which is a population-based screening study. Lymph node status at surgery, stage and grade characteristics were compared to a historical series of radical prostatectomy operations performed on patients with a similar age distribution who had clinically localized prostate cancer at our institute between 1980 and 1989 before the introduction of serum PSA measurements as a diagnostic tool. In both series complete radical prostatectomy specimens were submitted for histopathologic examination and reviewed by a single pathologist (Th.vd K.). A detailed analysis of prostate cancer characteristics in the screened series allowed us to study how some of the observed changes between the two series might have occurred.

3. Methods

3.1. Patients

3.1.1. Screened group

Between June 1994 and March 1997, a total of 8763 participants in the Rotterdam section of the ERSPC aged 55-75 years old underwent first-time systematic screening for prostate cancer. None of the screened participants had a previous diagnosis of prostate cancer. Written informed consent was obtained from every participant before randomization and the study was approved by the local medical ethics committee. Participants in the screening arm underwent a PSA determination (Hybritech Tandem E assay, Hybritech Beckman-Coulter Corp., San Diego, California, USA), digital rectal examination, and transrectal ultrasonography. Biopsy was recommended for each participant who had either an elevated serum PSA level (≥ 4.0 ng/mL), an abnormal digital rectal examination or abnormal findings on transrectal ultrasonography. Systematic sextant biopsies were obtained during longitudinal ultrasonographic scanning of the prostate. Biopsies were

directed cranially at an angle of approximately 45° from the transversal plane and outward at approximately 30° from the sagittal plane.

Prostate biopsies were obtained in 1824 men (25%) and prostate cancer was discovered in 399 (22%) of the biopsy sets. All patients were referred to their general physicians who in turn referred to a urologist of their choice. After treatment options were thoroughly discussed with all patients, 194 elected radical prostatectomy, of which 121 (62%) were performed at our hospital. During operation, regional lymph node status was evaluated by the examination of frozen sections. Operation was discontinued when lymph nodes were positive.

3.1.2. Historical reference series

As the number of radical prostatectomies performed on patients in the reference series of ERSPC is still too small for adequate comparison, we compared radical prostatectomies from the screened group to a historical series of consecutive surgical procedures. Between 1980 and 1989, before the introduction of serum PSA measurement as a screening test, 100 consecutive operations for prostate cancer were performed at our institute in a referred patient population. In these men prostate cancer had been discovered by needle biopsies or at transurethal resection. Since the introduction of serum PSA measurements, the selection procedures for surgery at our institute have changed substantially. For example, operation is not performed on patients with clinical evidence of locally extended prostate cancer (T3) and serum PSA levels above 20 ng/mL. To avoid bias introduced by differences in age, only patiens older than 55 years were selected for study. Eventually, 72 patients with clinically localized prostate cancer who underwent surgery were used for this study. Similar to the screended group, regional lymph node status was evaluated during the operation by the examination of frozen sections and surgery was discontinued if lymph nodes were positive.

3.2. Histopathologic examination of radical prostatectomy specimens

In each case of radical prostatectomy performed in the Rotterdam University Hospital specimens were sent to the Pathology department immediately after surgery. The protocol for the processing of radical prostatectomy specimens at the pathology department has

been described previouslyin this thesis (Chapter 2). Briefly, radical prostatectomy specimens were fixed for 24 hours and cut at 4mm intervals perpendicular to the rectal surface. All specimens were submitted entirely for histopathologic examination.
For each radical prostatectomy specimen, pathologic stage (TNM '92 classification) and Gleason score[9] were evaluated by a single pathologist (Th.vd K.). Extracapsular extension was determined when tumor was present in the fatty periprostatic tissue. Seminal vesicle invasion required tumor invading the muscular wall of the seminal vesicles and bladder neck invasion was called when tumor tissue was present between the smooth muscle bundles of the bladder wall. Separate Gleason patterns were included in the Gleason score calculation in cases in which the growth pattern was estimated to comprise 5% or more of the total tumor.
An additional evaluation was performed on radical prostatectomy specimens obtained from the screened series. All tumor areas in the radical prostatectomy specimens were carefully mapped. When tumor areas were separated by more than 4mm., prostate cancer was assumed multifocal. The site of origin in the prostate gland (transitional zone or peripheral zone) was recorded for each separate tumor focus. Gleason scores were assessed for each separate tumor focus and for each entire radical prostatectomy specimen. Tumor volumes of all separate tumor foci in each radical prostatectomy specimens were measured using computer assisted morphometric analysis. Additionally, volume measurements of high grade cancer areas (Gleason pattern 4 or 5) were performed and percentages of high grade cancer in each tumor focus and in each entire radical prostatectomy specimen were calculated. Unfortunately, data on tumor volume were not available for the historical series and comparisons of tumor volume could not be performed.

3.3. Statistical analysis

The frequencies of tumor characteristics were compared between various subsets of tumors. Statistical analyses of comparisons of characteristics of subsets of tumors that were based on noncontinuous variables, such as pathologic stage and Gleason score were performed with a Pearson chi-squared test. The null hypothesis (an equal distribution of the tested variables between different series) was rejected for $P \leq 0.05$. Statistical analyses

of comparisons of characteristics, based on continuous variables with a skewed distribution, such as tumor volume, were performed with a two-tailed Mann-Whitney *U* test for two and with a Kruskal-Wallis test for more than two subsets of tumors. In both tests, the null hypothesis was rejected for $P \leq 0.05$. Correlations between grade characteristics and not continuous variables, such as tumor volume, were measured using the Spearman correlation coefficient.

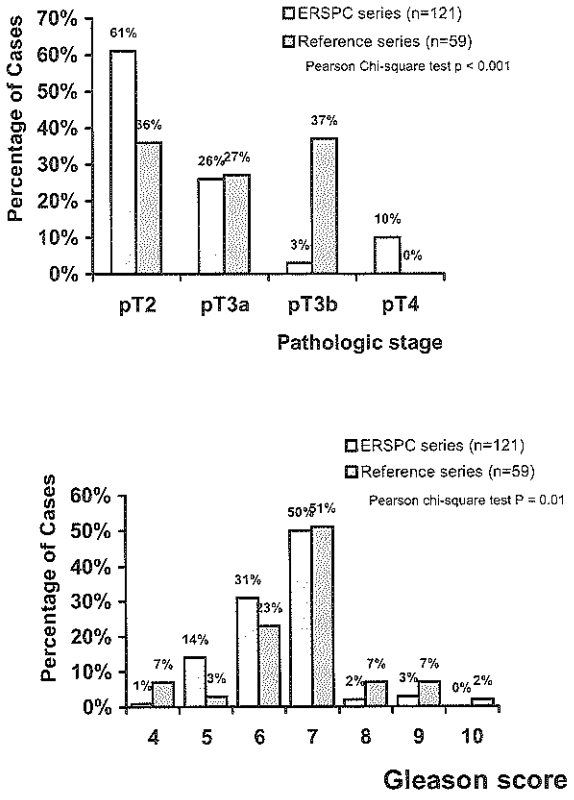


Figure 1 Comparison of pathologic stage (top) and Gleason score (bottom) distributions of 121 tumors found in the ERSPC series to a historical series of 59 consecutive radical prostatectomies performed in the Rotterdam University hospital between 1986 and 1989. Comparison reveals significant differences in both distributions.

4. Results

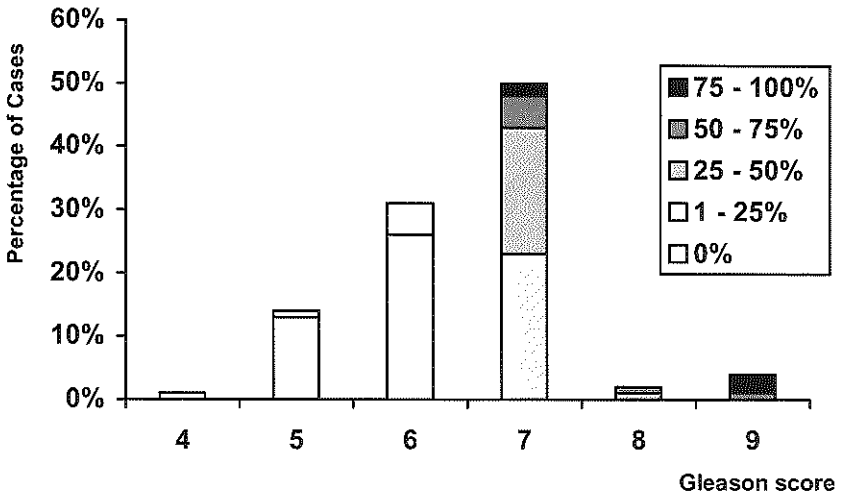
4.1. Prostate cancer characteristics

The distribution of patient age in the screened group (mean 63.7 years, standard deviation 4.7) was similar to the historical reference series (mean 63.3 years, standard deviation 4.5). Preoperative serum PSA in the screened group ranged from 0.8 to 29.5 ng/mL (mean 6.1, median 5.2). At surgery none of the 121 screened participants of the ERSPC had positive lymph nodes, and so radical prostatectomy was performed in all cases. In the historical reference series, however, operation was discontinued because of positive lymph nodes in 13 patients (18%). Pathologic stage of surgically treated tumors in the screen detected series was significantly lower than in the historical series (Pearson chi-squared $P < 0.001$, Fig. 1A). Although positive surgical margins were less frequent in screened patients (31% versus 41% in the historical series), this difference was not statistically significant. Prostate cancer in screened participants also had significantly lower Gleason scores than the historical series (Pearson chi-squared $P = 0.01$, Fig. 1B). The difference in Gleason score distribution between the two series was mainly the result of a relative decrease in tumors with Gleason scores 8, 9 and 10 in the screened group. Total tumor volume of the 121 radical prostatectomy specimens from the screened group ranged from 0.002 to 13.84 mL (mean 1.09, median 0.63). Areas with high grade cancer (Gleason pattern 4 or 5) were present in 73 of the 121 radical prostatectomies (60%), including 35 (48%) in which high grade cancer areas comprised less than 25% of the total tumor volume. In 61 of the 121 radical prostatectomy specimens (50%), this resulted in a Gleason score of 7. Most of these Gleason score 7 tumors had a score of 3 + 4. In only 9 of the 61 cases with a Gleason score of 7 (15%), pattern 4 outweighed pattern 3, which resulted in a score of 4 + 3.

Figure 2 shows the relative proportion of high grade cancer in the Gleason score distribution. There was a marked heterogeneity of overall Gleason score 7 tumors with regard to relative proportion of high grade cancer. In addition to high grade cancer in Gleason score 7 tumors, 6 radical prostatectomies with an overall Gleason score of 6 and one with an overall Gleason score of 5 contained small amounts of high grade cancer (Fig.2). For the Gleason score 6 tumors, the relative proportions of high grade cancer were considered to be too small (comprising less than 5% of the total tumor volume) to

influence the overall Gleason score. In the case with the Gleason score 5, the components of Gleason pattern 2 and 3 outweighed the amount of Gleason pattern 4 or 5.

Figure 2. Distribution of Gleason scores and percentages of high grade cancer. Note that Gleason score tumors form a highly heterogeneous group.



4.2. Multifocality and heterogeneity

Of the 121 radical prostatectomy specimens in the screened series 81 (67%) contained multifocal tumor. In total, 259 separate tumor foci were identified in 121 radical prostatectomies in these series (an average of 2.14 tumor foci per radical prostatectomy specimen). The maximum number of tumor foci per radical prostatectomy specimen was five in five cases (4.1%). Volumes of separate tumor foci ranged from 0.001 to 13.84mL (mean 0.52mL; median 0.17mL). In 54 of the 81 radical prostatectomy specimens with multifocal tumor (67%), separate foci showed differences in Gleason score among each other (*inter*-tumor heterogeneity). In all, 132 of 259 tumor foci (51%) exhibited more than one Gleason growth pattern themselves (*intra*-tumor heterogeneity).

Thus, 91 out of 121 radical prostatectomies (75%), contained two or more Gleason growth patterns. More than two Gleason growth patterns were found in 24 (20%) cases and four

different growth patterns were noted in 3 radical prostatectomies (3%). High grade cancer areas (Gleason growth patterns 4 or 5) were found in 97 of 259 separate tumor foci (37.6%). High grade cancer areas were more commonly found in tumor foci in the peripheral zone (42%) than in tumor foci in the transiton zone (9%). High grade cancer areas were often located at the center of otherwise well differentiated tumor foci (Fig 3). Most of the tumor foci with high grade cancer components were heterogeneous with regard to grade. Only two small tumor foci(0.07 and 0.12mL, respectively) consisted entirely of high grade cancer (in both cases Gleason growth pattern 4).

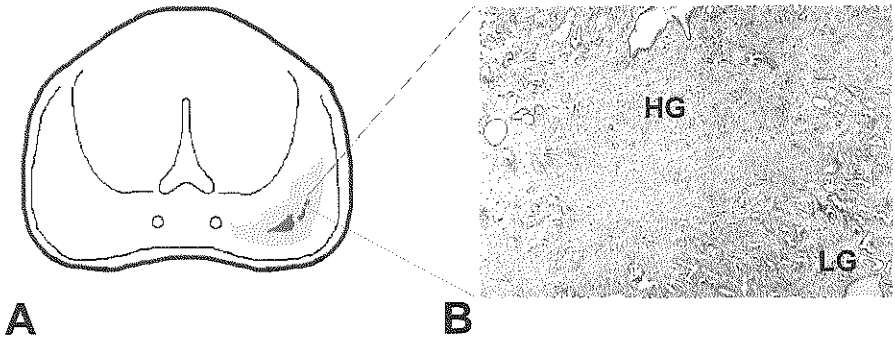


Figure 3. Representation of a focus with high grade cancer in an otherwise well-differentiated tumor area. **A** The schematic representation of a transverse prostate section shows a tumor area (light grey) with dedifferentiated areas (dark grey) at its center. **B** Photomicrograph showing a part of the dedifferentiated area (HG), which consists of small strings of infiltrating tumor cells (Gleason growth pattern 4). At the edges of the photomicrograph, some of the well differentiated gland-forming part of the tumor, showing small irregular glands (Gleason growth pattern 3) can also be seen (LG) . H&E, reduced from x400.

4.3. High grade cancer areas and tumor volume

In the screened series a clear correlation was found between grade and size of separate tumor foci. Of 112 tumor foci with volumes smaller than 0.1 mL., 16 (14%) contained areas with high grade cancer. Of 76 foci with volumes between 0.1 and 0.5 mL., 27 (36%) contained some Gleason pattern 4 or 5. The frequency of high grade cancer areas increased to 22 out of 37 foci (59%) with volumes between 0.5 and 1.0 mL and the chances of high grade cancer areas were highest in foci that were larger than 1.0 mL (25

of 34, 74%). Figure 4 depicts a box and whiskers plot of the volumes of all 259 separate tumor foci stratified for increasing percentage of high grade cancer. The correlation between volume and percentage of high grade cancer was highly significant, as was the correlation between volume and Gleason score (Kruskal Wallis test $P < 0.001$ for both Gleason score and high grade cancer percentage). Despite these highly significant relations, correlation coefficients of were low (Spearman's *Rho* was 0.40 for the Gleason score and 0.45 for high grade cancer percentage).

With regard to the total amount of tumor per radical prostatectomy specimen, overall high grade cancer percentage and overall Gleason score showed a similar significant correlation with total tumor volume (Kruskal Wallis test $P < 0.001$ for overall high grade cancer percentage and $P = 0.001$ for overall Gleason score), although also with low correlation coefficients (Spearman's *Rho* was 0.33 for the Gleason score and 0.35 for high grade cancer percentage).

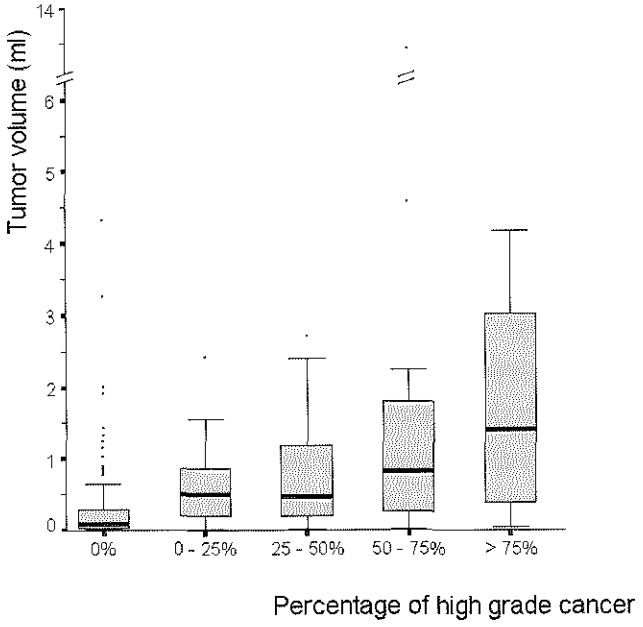


Figure 4. Volumes of 259 separate tumor foci stratified for increasing percentage of high grade cancer.

5. Discussion

Since the capacity of current clinical tools to predict prostate cancer characteristics and extent is still limited, totally embedded radical prostatectomy specimens provide the best opportunity to study prostate cancer in detail. Studying radical prostatectomy specimens also has its limitations. In the first place, it should be realized that patients that undergo radical prostatectomy represent a highly selected subpopulation of prostate cancer patients. The characteristics of the tumors in radical prostatectomy specimens are obviously influenced by criteria used to select patients for operation. Different selection criteria for surgery could hamper reliable comparisons between different series of radical prostatectomies reported in the literature. Besides these difficulties, comparisons of tumor characteristics in reported radical prostatectomy series are often complicated by incomplete data, the combining of Gleason scores into categories, and by the use of different protocols for volume measurement and grading.

A number of changes in prostate cancer stage attributed to early detection have been reported recently. A shift in stage was first reported in 1993 when Catalona et al. described a substantial increase in the frequency of organ-confined prostate cancer after PSA based screening[8]. This shift towards earlier stage was reflected in clinical stage and pathologic stage after radical prostatectomy. While some reports confirm an increased frequency of pathologically organ-confined tumors at radical prostatectomy[5], others report no change in pathologic stage[6].

The reported changes in prostate cancer grade that are attributable to early detection are more univocal. Most recent studies show that the use of serum PSA as a diagnostic tool has led to a decrease in overall prostate cancer grade and a relative increase of moderate differentiated tumors[5-7]. On the other hand, Epstein et al. reported that a considerably high frequency of low volume, high grade cancer can be found in early detection programs, which suggests that prostate cancer sometimes has the potential to dedifferentiate early in its biological course[10].

We compared a series of screen detected radical prostatectomies with a historical series that was performed at the same hospital and reviewed by the same pathologist. We tried to minimize possible biases that could have been introduced by differences in patient age at operation and differences in the selection criteria for surgery. Still a number of limitations

to our study exist, including a possible bias introduced by having incomplete access to all radical prostatectomy specimens performed in the screened group and the use of a historical reference series. However, the observed differences in lymph node status, pathologic stage (Fig 1A) and grade (Fig. 1B) between the two series were substantial enough to strongly suggest that serum PSA measurement and systematic screening are responsible for changes in prostate cancer characteristics in surgically treated patients, which probably will result in an improved clinical outcome.

A comparison with other reports in the literature revealed that the observed volumes in our screen detected radical prostatectomies (median 0.6 mL, range 0.002 - 13.48) were relatively small. Our tumor volumes were similar to those in screen detected series reported by Humphrey et al.(median 1.0 mL, range 0.01 - 10.7)[11], but smaller than those in a generally referred population reported by Ohori et al. (median 2.23 mL, range 0.03 - 16.9)[12]. Although systematic differences caused by different methods for volume measurement cannot be ruled out as a possible cause of the observed differences, active screening for prostate cancer seems to lead to the discovery of generally smaller tumors. Long-term epidemiologic studies should reveal whether all of these tumors are clinically important. A shift towards moderately differentiated tumors is confirmed by our results, as in our screen detected radical prostatectomy series, as the frequency of Gleason score 8 to 10 tumors was low in the screened compared to the historical series of radical prostatectomies (Fig 1B). In most of the Gleason 7 tumors in the screened series high grade cancer comprised relatively small areas, which most often seemed to be located in the center of otherwise well differentiated tumor foci (figure 3). Our results also showed a clear correlation between tumor size and Gleason score and relative proportion of high grade cancer in separate tumor foci (figure 4). The same correlation was found regarding the total amount of tumor in each radical prostatectomy specimen.

The relation between tumor volume and the amount of high grade cancer has been reported previously[10,13]. It supports the theory that tumor progression starts with a small focus of dedifferentiation which, by having a growth advantage over the surrounding well differentiated areas, will grow relatively faster, giving rise to relatively larger proportions of high grade cancer. Further supporting this theory is the fact that only 2 out of 259 (0.8%) separate tumor foci in our series consisted entirely of high grade cancer. Despite a highly significant correlation between tumor volume and high grade cancer, a low

correlation coefficient between volume and relative proportion of high grade cancer was found, confirming the results of a similar study by Epstein et al.[10]. A possible explanation for this low correlation coefficient could be that dedifferentiation does not occur at a given tumor volume. It is possible that some well differentiated tumors could grow to considerable sizes until dedifferentiation occurs, while other tumors show focal dedifferentiation even at a very small volume.

The observed relation between tumor volume and amount of high grade cancer could also explain the observed shift towards moderately differentiated tumors in early detected series. Early detection of prostate cancer would lead to the discovery of generally smaller tumor foci with lower relative amounts of high grade cancer, resulting in the shift from Gleason scores 8 to 10 towards the Gleason score 7 category. The observed shift is not so much the result of a change in the actual Gleason patterns, but rather the effect of a shift in their relative proportions. Supporting this theory is the fact that, despite early detection, 73 (60%) of the 121 radical prostatectomies in our screened series contained high grade cancer areas. As small areas of high grade cancer probably represent early signs of prostate cancer progression, it seems that a large proportion of tumors detected after systematic screening are clinically important and, depending on age and comorbidity of the patient, could provide a serious threat when treatment is postponed.

As the frequency of Gleason score 7 tumors seems to increase with increased efforts for early detection of prostate cancer, Gleason score 7 is more often regarded as a separate category of tumors with a progression risk that lies intermediate between that of Gleason 5 and 6 tumors, and Gleason 8 to 10 tumors[14]. However, the heterogeneity within the Gleason score 7 category is considerable. Percentages of high grade cancer in the Gleason score 7 category in our series ranged from 5% to more than 80% (Fig 2). The accumulation of tumors in the Gleason 7 category brought about by early detection might lead to a decrease in the prognostic value of the Gleason score system. Indeed, a few recent studies are indicating that the relative amount of high grade cancer has a high prognostic value that is probably superior to that of the Gleason score system[15,16]. Like most grading systems currently used for grading prostate cancer, the Gleason score method was developed long before the introduction of serum PSA measurements as an effective tool for earlier detection of prostate cancer. The changing characteristics of prostate cancer caused by early detection might lead to the need to provide extra

information, such as the relative amount of high grade cancer, besides overall grade. It might even lead to reconsideration and perhaps revision the current grading systems.

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Chapter 6

DOES A SMALL FOCUS OF WELL DIFFERENTIATED CANCER AT NEEDLE BIOPSY INDICATE MINIMAL CANCER?

Robert F. Hoedemaeker
Theodorus H. Van der Kwast
Fritz H. Schröder

Translated from:
De klinische betekenis van een kleine haard goed gedifferentieerd carcinoom in het prostaatbiopt
[The clinical significance of a small focus of well-differentiated carcinoma at prostate biopsy].

Ned Tijdschr Urol 2001;9:3 - 9.

Summary

The clinical significance of a small focus of well-differentiated prostate cancer on biopsy is still unclear.

We compared a series of 121 sextant needle biopsy sets with their corresponding radical prostatectomy specimens in screened participants in the European Randomized study of Screening for Prostate Cancer (ERSPC), a study that investigates the impact of screening for prostate cancer on disease-specific mortality and quality of life. The expected clinical significance of the discovered tumors was estimated using an arbitrary model combining volume, grade, and stage characteristics.

Of 34 patients, that had a small focus (less than 3 mm on a single biopsy core) of well differentiated carcinoma on biopsy, only 18 (53%) were found to have minimal carcinoma (a small focus of well differentiated carcinoma) at radical prostatectomy, while 16 (47%) had moderately advanced or advanced carcinoma at radical prostatectomy. Preoperative prediction of minimal carcinoma improved when the amount of cancer in the sextant biopsy set was combined with the preoperative serum prostate specific antigen (PSA)-level. Of 12 patients with a small focus of well-differentiated carcinoma on biopsy and a serum-PSA lower than 2.5 ng/mL, 11 (92%) proved to have minimal carcinoma at radical prostatectomy, while minimal carcinoma was found in only 7 out of 22 (32%) patients with a small focus of well differentiated carcinoma on biopsy and a serum-PSA above 4 ng/mL.

The predictive value of a small focus of well differentiated cancer on systematic sextant biopsy for a small well differentiated tumor in the prostate is limited. The predictive value improves when serum PSA-levels are considered concurrently, but is still thought to be insufficient to support a base for therapy-choice for the individual patient.

2. Introduction

Prostate biopsies are essential for the establishment of a definite diagnosis of prostate cancer. Currently, it is generally agreed that obtaining systematic sextant biopsies, obtained during ultrasonographic scanning of the prostate is the most effective method for detecting prostate cancer[1-3]. Besides the establishment of the diagnosis of prostate cancer, the examination of prostate biopsies can reveal certain tumor characteristics such as grade and extent. It is clear, that when tumor tissue is extensively present in every single one of the obtained biopsy cores, the patient is likely to harbor a large tumor.

Screening for prostate cancer entails a risk of detecting increased numbers of clinically unapparent and biologically indolent tumors that will not lead to morbidity or mortality. Several studies have shown, that the frequency of prostate cancer as a chance finding in prostate specimens removed for bladder cancer or at autopsy far exceeds the clinical incidence[4-6]. Apparently, the chances of dying with prostate cancer are much higher than the chances of dying of prostate cancer. The literature contains many reports on the clinical importance of prostate cancer. Overall it is believed, that the chance for prostate cancer progression is directly proportional to tumor volume. Several studies have laid down arbitrary volume thresholds for clinical significance. Stamey et al concluded that tumors that are smaller than 0.5 mL are probably clinically insignificant[7]. After finding small tumors (between 0.2 and 0.5 mL) with extraprostatic extension (a feature, that is obviously inconsistent with biologic indolence), Epstein et al. proposed a threshold for the clinical significance of prostate cancer at 0.2 mL[8].

The finding of a small amount of well differentiated prostate cancer at needle biopsy could possibly indicate a clinically unimportant tumor. To avoid unnecessary treatment, a propensity towards deferred treatment or conservative management could result in cases with such clinical findings. Some studies have already shown that small foci of prostate cancer at biopsy are associated with the detection of insignificant, low volume tumors[2]. To examine the clinical importance of a single small focus of well differentiated prostate cancer in sextant needle biopsy sets obtained by population-based screening, we compared a series of systematic sextant prostate biopsies with corresponding radical prostatectomy specimens obtained from participants of the Rotterdam section of the European Randomized study of Screening for Prostate Cancer (ERSPC). We examined the

predictive value of a small amount of well differentiated cancer at biopsy for the amount and the characteristics of tumor present at radical prostatectomy.

3. Methods

3.1. Patients and protocol

Between June 1994 and March 1997, a total of 8763 participants in the Rotterdam section of the ERSPC aged 55-75 years old underwent first-time systematic screening for prostate cancer. None of the screened participants had a previous diagnosis of prostate cancer. Written informed consent was obtained from every participant before randomization and the local medical ethics committee approved of the study. Participants in the screening arm underwent a PSA determination (Hybritech Tandem E assay, Hybritech Beckman-Coulter Corp., San Diego, California, USA), digital rectal examination, and transrectal ultrasonography. Biopsy was recommended for each participant who had either an elevated serum PSA level (≥ 4.0 ng/mL), an abnormal digital rectal examination (DRE) or abnormal findings on transrectal ultrasonography (TRUS). Systematic sextant biopsies were obtained during longitudinal ultrasonographic scanning of the prostate. Biopsies were directed cranially at an angle of approximately 45° from the transversal plane and outward at approximately 30° from the sagittal plane. A separate, seventh biopsy was performed in every case when a hypoechogenic lesion was visible at TRUS. In these cases, the seventh biopsy was directed at that hypoechogenic lesion. Each biopsy core was inked at its capsular end, numbered according to its site of origin, and sent in a separate container to the pathology department.

3.2. Histologic examination of biopsies and radical prostatectomy specimens

All biopsy cores were processed for routine histopathologic examination as described previously in Chapter 2. In brief, after fixation in a 4% saline-buffered formalin solution, every core was embedded separately in paraffin, sectioned longitudinally into 5-μm sections, and stained with hematoxylin-eosin. At least three histologic sections of different

cutting levels of each biopsy core were examined.

In each case of prostate cancer, the reference pathologist for urologic pathology (Th.vd K.) recorded the number of positive biopsy cores in each sextant set. The length (in millimeters) of cancer involvement was measured in each core and calculated for the sextant biopsy set as a whole. All adenocarcinomas were graded according to the Gleason scoring system[9].

Focal carcinoma in biopsy sets was defined as a single positive biopsy core with a small focus of adenocarcinoma (3mm or less) without high grade cancer (Gleason pattern 4 or 5) components. This definition is essentially the same as the one used in an earlier study by Weldon et al. [10].

Radical prostatectomy specimens were sent to the Pathology department immediately after surgery. The protocol for the processing of radical prostatectomy specimens is discussed in Chapter 2. Briefly, radical prostatectomy specimens were fixed for 24 hours in a 4% saline buffered formalin solution. After fixation the specimens were inked and cut at 4mm intervals in the transversal plane perpendicular to the rectal surface. Each transversal slice was divided into two dorsal and two ventral quadrants. To enhance the accuracy of the determination of tumor extension in the apical surgical margins, the apical part of the prostate was cut parasagittally at 4mm intervals. Additional representative slices of the base of the seminal vesicles were prepared and each slice was totally embedded in paraffin. From each paraffin block, hematoxylin-eosin stained histological slides were prepared for routine pathologic examination. For each radical prostatectomy specimen, pathologic stage (TNM'92 classification)[11] and Gleason score[9] were evaluated by a single pathologist (Th.vd K.). Extracapsular extension was determined when tumor was present in the fatty periprostatic tissue. Seminal vesicle invasion required tumor invading the muscular wall of the seminal vesicles and bladder neck invasion was called when tumor tissue was present between the smooth muscle bundles of the bladder wall. Digital morphometric analysis (Kontron Imaging System (KS400), Kontron Elektronik GmbH, Eching, Germany) was performed to measure each tumor area using computer software for morphometry. Tumor volume in each radical prostatectomy specimen was determined by totaling all measured tumor areas and total slide areas (in square millimeters) and their multiplication by 4 (the thickness in mm of the original slices).

3.3. Categorization of tumors

Categorization of radical prostatectomy series based on tumor characteristics is the only way to assess different subsets of radical prostatectomies for their clinical significance. The categorization model we used for this study is the same as the one used in Chapter 4. It was based on proposed categorization models for prostate cancer characteristics reported in two recent studies[8,12]. Our constructed arbitrary model for categorization is shown in Table 1.

Table 1. Categorization of tumors

Category	Tumorvolume	Gleason	Tumor extent
Minimal	< 0.5 mL	No pattern 4 or 5	Confined
Moderate	Any	Any	Confined
	Any	No pattern 4 or 5	Extracapsular extension
Advanced	Any	Pattern 4 or 5	Extracapsular extension
	Any	Any	Seminal vesicle invasion
	Any	Any	Bladder neck invasion
	Any	Any	Positive Lymph nodes

3.4. Statistical analysis

Tumor characteristics in radical prostatectomy specimens obtained from participants with focal carcinoma at biopsy were compared with those of participants with more than focal carcinoma at biopsy. The additive predictive value of preoperative PSA levels was assessed by dividing participants with focal carcinoma at biopsy into a group with PSA levels below 4 ng/mL and a group with PSA levels of 4 ng/mL or above.
Statistical analyses of comparisons between subsets of distributions based on ordinal variables, such as pathologic stage or the categorization model for radical prostatectomy specimens were performed with a two-sided Pearson chi-squared test. The null hypothesis (statistical independence of the tested variables in subsets of participants) was rejected for P values under 0.05. Statistical analyses of comparisons of characteristics based on continuous variables with a skewed distribution, such as tumor volume, were performed

with a two-tailed Mann-Whitney *U* test. The null hypothesis (a similar rank distribution of the tested variable in subsets of participants) was rejected for *P* values under 0.05.

4. Results

4.1. Prostate cancer characteristics

Prostate biopsies were obtained in 1824 men (25%) and prostate cancer was discovered in 399 (22%) of the biopsy sets. All patients were referred to their general physicians who in turn referred to an urologist of their choice. After treatment options were thoroughly discussed with all patients, 194 elected radical prostatectomy, of which 121 (62%) were performed at our hospital. The mean age of the 121 patients who underwent radical prostatectomy at our hospital was 63.7 years (standard deviation 4.7). Preoperative serum PSA ranged from 0.8 to 29.5 ng/mL (mean 6.1, median 5.2). None of the participants had positive lymph nodes at surgery.

The tumor characteristics in the radical prostatectomy specimens are shown in Table 2. The total tumor volume of the 121 radical prostatectomy specimens ranged from 0.002 to 13.84 mL (mean 1.09, median 0.63). Areas with high grade cancer (Gleason pattern 4 or 5) were present in 73 of the 121 radical prostatectomies (60%).

The overall distribution of pathologic stage showed 74 (61%) organ confined tumors. A total of 31 cases (26%) showed extraprostatic extension (stage pT3ab), 4 tumors (3%) invaded one or both seminal vesicles (stage pT3c) and bladder neck invasion (stage pT4a) was found in 12 cases (10%). Positive surgical margins were present in 37 cases (31%). The arbitrary categorization model showed minimal tumor in 26 cases (21%), moderate tumor in 52 cases (43%), and advanced tumor in 43 cases (36%)(Table 2).

4.2. Patients with focal carcinoma at biopsy

In 34 of the 121 participants in this study (28%), the tumor characteristics in the diagnostic sextant biopsy set met the criteria for focal carcinoma (a single positive biopsy core with a small focus of adenocarcinoma [3mm or less] without high grade cancer components [Gleason pattern 4 or 5]). In one of these 34 participants (3%), the positive

biopsy core was a seventh biopsy directed at a small hypoechogenic area.

A comparison of the tumor characteristics at radical prostatectomy of patients with focal carcinoma at biopsy with those of patients with more than focal carcinoma at biopsy is shown in Table 2. The table shows a statistically significant difference between the two groups with regard to tumor volume (Mann Whitney *U* test, two-tailed $P < 0.001$), pathologic stage (Pearson chi-squared test, two-tailed $P < 0.001$), the frequency of high grade cancer areas (Pearson chi-squared test, two-tailed $P < 0.001$) and the distribution in the three arbitrary tumor categories (Pearson chi-squared test, two-tailed $P < 0.001$). Of 26 patients with minimal tumor at radical prostatectomy, 18 (69%) had focal carcinoma at biopsy.

Table 2. Tumor characteristics at radical prostatectomy and biopsy features.

	All patients (n=121)	Patients with focal carcinoma at biopsy (n=34)	Patients with more than focal carcinoma at biopsy (n=87)	Statistical analysis *P*-value (Test)
Tumorvolume, mL Mean / median (range)	1.10 / 0.63 (0.002 – 13.5)	0.5 / 0.26 (0.002 - 4.7)	1.33 / 0.85 (0.02 – 13.5)	$P < 0.001$ (Mann-Whitney *U* test, two-tailed)
Pathologic stage No. (%)				
pT2	74 (61)	31 (91)	43 (49)	
pT3a	31 (26)	2 (6)	29 (33)	$P < 0.001$ (Pearson chi-squared test, two-tailed)
pT3b	4 (3)	0 (0)	4 (5)	
pT4	12 (10)	1 (3)	11 (13)	
Frequency of high grade cancer areas, No. (%)	73 (60)	12 (35)	61 (70)	$P < 0.001$ (Pearson chi-squared test, two-tailed)
Clinical importance No (%)				
Minimal tumor	26 (21)	18 (53)	8 (9)	
Moderate tumor	52 (43)	14 (41)	38 (44)	$P < 0.001$ (Pearson chi-squared test, two-tailed)
Advanced tumor	43 (36)	2 (6)	41 (47)	

Despite the clear relation between focal carcinoma at biopsy and smaller, better

differentiated carcinoma at radical prostatectomy, 21 (62%) of the 34 participants with focal carcinoma at biopsy had a tumor volume above 0.2 mL. In 12 cases (36%), tumor volume was higher than 0.5mL. Extraprostatic extension was present in 3 cases (9%) and 5 cases (15%) had positive surgical margins. Finally, in 12 cases (36%), areas with high grade cancer (Gleason pattern 4 or 5) were present at radical prostatectomy. A single focus of well differentiated prostate cancer at biopsy correctly predicted minimal tumor at radical prostatectomy in only 53% of cases.

The PSA level at biopsy proved to be an important additional parameter with a predictive value for the amount and the grade of tumor at radical prostatectomy. Table 3 shows the 34 participants with focal carcinoma stratified for PSA level at biopsy. There was a statistically significant difference between the group with focal carcinoma at biopsy and a PSA below 4 ng/mL and the group with focal carcinoma at biopsy and a PSA level of 4ng/mL or above with regard to tumor volume (Mann Whitney *U* test, two-tailed $P = 0.002$) and frequency of high grade cancer areas at radical prostatectomy (Pearson chi-squared test, two-tailed $P = 0.01$). Also the distribution in our arbitrary model for clinical significance was statistically significantly different in these two groups (Pearson chi-squared test, two-tailed $P = 0.02$) (Table 3).

The two participants with advanced carcinoma at radical prostatectomy and focal carcinoma at biopsy as well as 13 of 14 participants with moderate carcinoma at radical prostatectomy and focal carcinoma at biopsy had PSA levels of 4 ng/mL or above. Associated with a serum PSA level below 4 ng/mL, the predictive value of a single focus of well differentiated carcinoma at biopsy increased dramatically, as it correctly predicted minimal tumor at radical prostatectomy in 92% of the cases. Of 22 participants with PSA levels of 4 ng/mL or above and focal carcinoma at biopsy, 15 (68%) had moderate or advanced carcinoma at radical prostatectomy. In 16 (73%) of these 22 cases, tumor volume was 0.2 mL or higher and tumor volume was 0.5 mL or higher in 11 (50%).

Table 3. Tumor characteristics at radical prostatectomy of patients with focal carcinoma stratified for PSA levels at biopsy.

	All patients with focal carcinoma at biopsy (n=34)	PSA < 4ng/mL (0.9 - 2.5 ng/mL) (n = 12)	PSA ≥ 4 (4.0 - 12.6 ng/mL (n=22)	Statistical analysis *P*-value (Test)
Tumorvolume, mL Mean / median (range)	0.5 / 0.26 (0.002 – 4.7)	0.13 / 0.08 (0.002 – 0.4)	0.7 / 0.5 (0.004 - 4.7)	*P* = 0.002 (Mann-Whitney *U* test, two-tailed)
Pathologic stage No. (%)				
pT2	31 (91)	12 (100)	19 (86)	
pT3a	2 (6)	0 (0)	2 (9)	*P* = 0.4 (not significant) (Pearson chi-squared test, two-tailed)
pT3b	0 (0)	0 (0)	0 (0)	
pT4	1 (3)	0 (0)	1 (5)	
Frequency of high grade cancer areas, No. (%)	12 (35)	1 (8)	11 (50)	*P* = 0.01 (Pearson chi-squared test, two-tailed)
Clinical importance No. (%)				
Minimal tumor	18 (53)	11 (92)	7 (32)	
Moderate tumor	14 (41)	1 (8)	13 (59)	*P* = 0.02 (Pearson chi-squared test, two-tailed)
Advanced tumor	2 (6)	0 (0)	2 (9)	

5. Discussion

Our results show that the predictive value of a single small focus well differentiated carcinoma at prostate biopsy for a small well differentiated tumor at radical prostatectomy by itself is limited. In nearly half of the participants in our study who had a single small focus of well differentiated carcinoma at biopsy, moderate or even advanced tumor was found at radical prostatectomy (Table 2). Especially in combination with a serum PSA level of 4 ng/mL or above, the amount of tumor in the prostate should not be

underestimated when only a small focus of well differentiated carcinoma is found at biopsy. These results are consistent with those of a number of recent reports in the literature[8,10,13]. Sampling error, caused by the diffuse spread, the anterior location, or the multifocal localization of prostatic tumors is the most probable reason for the limited predictability of a single small focus of well differentiated tumor at needle biopsy for minimal cancer at radical prostatectomy. This is reflected by a number of recent studies that show that in approximately 30% of patients with confirmed carcinoma at initial sextant biopsy, cancer is not redetected at repeated biopsies [14,15].

The combination with serum PSA levels at biopsy greatly enhances the predictive value of a single focus of well differentiated carcinoma at prostate biopsy for a small well differentiated tumor at radical prostatectomy. In our series, the combination of focal cancer at biopsy with serum PSA levels below 4 ng/mL correctly predicted 92% of minimal tumors at radical prostatectomy (Table 3). Several studies confirm that the combination of biopsy features and serum PSA currently are the best predictors for prostate cancer characteristics[8,16,17].

Although our results strongly suggest that it is possible to predict minimal tumor in the prostate by combining tumor features at sextant biopsy with serum PSA level, it is still questionable whether the accuracy of the prediction is sufficient for use on an individual patient basis. Our results, however, do stress that, especially in combination with a serum PSA level of 4 ng/mL or above, the amount of tumor in the prostate should not be underestimated in patients a small focus of well differentiated carcinoma at biopsy. Furthermore, our findings do not by themselves warrant a more expectant attitude toward tumors with these clinical features. In our study, we used an arbitrary model for the determination of the clinical relevance of tumors found at radical prostatectomy (Table 1). The model, which was also used in Chapter 4, was based on two earlier reports in the literature[8,12]. The capacity of these kinds of models to predict PSA relapse after radical prostatectomy was confirmed by several studies[12,18]. However, they thereby do not necessarily prove the clinical significance of the different categories of tumors. Although the category of minimal tumors in our model is the most likely category to harbor clinically insignificant tumors, we have no knowledge of their biological behavior when they would not have been surgically treated. There is a possibility that some of these minimal tumors have the capacity to become life-threatening by accelerated growth rates

and dedifferentiation. In addition, the age and life-expectancy of the individual patient will play an important role in the clinical outcome.

The ability to decide which tumors should be treated and which can be managed with a more expectant clinical approach, therefore, will probably require additional large randomized studies with sufficient follow-up periods.

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Chapter 7

PROSTATE CANCER IN THE SECOND SCREENING ROUND

AFTER A FOUR-YEAR INTERVAL

Robert F. Hoedemaeker
Theodorus H. van der Kwast
Rob Boer
Harry J. de Koning
Monique Roobol
André N. Vis
Fritz H. Schröder

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1. Summary

The currently recommended frequency for prostate specific antigen (PSA) screening tests for prostate cancer is 1 year, but the optimal screening interval is not known. Our goal is to determine if a longer interval would compromise the detection of curable prostate cancer.

A cohort of 4491 men aged 55-75 years, all participants in the Rotterdam section of the European Randomized Study of (population-based) Screening for Prostate Cancer (ERSPC), were invited to participate in an initial PSA screening. Men who received that screening were invited for a second screen 4 years later. Pathology findings from needle biopsy cores were compared for men in both rounds. Statistical tests were two-sided.

A total of 4133 men were screened in the first round (the prevalence screen) and 2385 were screened in the second round. The median amount of cancer in needle biopsy sets was 7.0 mm (95% Confidence Interval [CI] 5.4 mmm to 8.6 mm) in the first round and 4.1 mm (95% CI = 2.6 mm to 5.6 mm) in the second round ($P = .001$). Thirty-six percent of the adenocarcinomas detected in the first round but only 16% of those detected in the second round had a Gleason score of 7 or higher (mean difference = 20% [95% CI = 10% to 30%]; $P < 0.001$). Whereas 25% of the adenocarcinomas detected in the first round had adverse prognostic features, only 6% of those detected in the second round did (mean difference = 19% [95% CI = 11% to 26%]; $P < 0.001$). Baseline PSA values were predictive for the amount of tumor in biopsies in men with cancer in the first round, but not in the second round.

Most large prostate cancers with high serum PSA levels were effectively detected in the prevalence screen. In this population, a screening interval of 4 years appears to be short enough to constrain the development of large tumors, although it is inconclusive whether this will result in a survival benefit.

2. Introduction

Prostate cancer is rapidly becoming a major health problem in Western countries. Epidemiologic studies show that it is now the second most commonly diagnosed malignancy in men after nonmelanotic skin cancer. In the United States, prostate cancer mortality is second only to mortality caused by lung cancer[1]. The clinical incidence of prostate cancer has risen substantially during the last decade since the introduction of serum prostate specific antigen (PSA) measurement as a tool for identifying men at risk for prostate cancer. The introduction and widespread use of this relatively cheap and simple test have resulted in mass screening of clinically asymptomatic men, especially in Western countries. Since 1993, the American Cancer Society has recommended annual serum PSA tests in asymptomatic men 50 years of age or older[2].

A potential and undesirable side effect caused by increased efforts for early detection of prostate cancer is an increased chance of detecting carcinomas that, had they remained undetected, would never have led to morbidity or mortality. At autopsy, the presence of clinically undiagnosed tumors in men 50 years of age or older is estimated to be at least five times higher than the lifetime risk for tumors that lead to morbidity or mortality [3,4]. As of yet, the effects of PSA screening on overall morbidity, mortality, and quality of life in the screened population are not known. Several randomized trials on screening for prostate cancer are underway to investigate these questions[5]. Variations in the screening protocol, including the interval between different rounds of screening for prostate cancer, are likely to have a considerable influence on the costs of prostate cancer screening and on the morbidity, mortality and the quality of life of the screened population.

The results of some recent studies[6-8] indicate that biannual screening would not compromise the detection of curable prostate cancers in some or possibly all of the men at risk for the disease and would lead to a substantial reduction in health-care costs. These studies, however, are based not on clinical experience but rather on models predicting the probability of prostate cancer in the population at risk using retrospective data.

To determine whether a longer interval between screening rounds would compromise the detection of curable prostate cancer, we studied prostate cancer characteristics in a cohort of men during two rounds of population-based screening for prostate cancer that were performed in the Rotterdam University Hospital, The Netherlands. The two rounds were

separated by an interval of 4 years. Histopathologically assessed tumor characteristics of screen-detected cancer on needle biopsy specimens were compared between the two rounds of screening.

3. Methods

The European Randomized Study of Screening for Prostate Cancer (ERSPC) is a multicenter, randomized, population-based trial that investigates the impact of systematic PSA screening for prostate cancer on prostate cancer mortality and quality of life. The study was approved by a government commission supervising the compliance with the Dutch law on population screening, and written informed consent was obtained from every participant before randomization. This report concerns a cohort of 4491 men aged 55-75 years, all of whom had been randomly assigned to the screening group in the Rotterdam section of ERSPC from June 1994 to March 1996. None of the participants had a previous diagnosis of prostate cancer. During the study period, screening was discontinued in all participants who reached the age of 75 years. Men who did not respond to the invitation for screening were excluded from further evaluation in this report. Information on various reasons for not visiting (e.g. because men died of other causes or moved out of the area) was obtained from the local government.

3.1. Screening protocols

3.1.1. First round of screening (prevalence and interim screen)

The first round of screening (the prevalence screen) took place from June 1994 to March 1996. The 4133 men who accepted the invitation to the first screen underwent serum PSA measurement, digital rectal examination (DRE), and transrectal ultrasound investigation (TRUS). Biopsies were recommended for men whose serum PSA level was 4 ng/mL or greater or whose DRE or TRUS was abnormal. Men who were recommended for biopsy but who either refused a biopsy or could not undergo a biopsy for medical reasons (e.g., because they were receiving anticoagulant therapy or had a comorbid condition) were excluded from further evaluation. For men with a benign biopsy outcome, an interim round of screening was conducted after 1 year. A small number of men (seven) with

benign biopsies in the first interim round were reinvited for a second interim round which took place 1 year after the first interim round.

3.1.2. Second round of screening

The second round of screening took place from June 1998 to March 2000. All 2385 participants in the second round of screening had been screened 4 years earlier, and 645 (27%) of them had undergone an interim screen 3 years earlier after being recommended for biopsy in the first round. By the time the second round of screening began, the screening protocol had changed[9]. In brief, because of the low positive predictive value and sensitivity of DRE and TRUS, biopsies were now recommended to all participants with a serum PSA of 3 ng/mL or higher, regardless of the outcome of DRE or TRUS. In addition, the 1-year interval rescreen after a benign biopsy outcome was omitted.

3.2. Biopsy technique

In participants who complied with the recommendation for biopsy, systematic sextant biopsies were obtained during longitudinal ultrasonographic scanning of the prostate. All biopsies were performed with Bard 18-gauge biopsy needles (Bard Inc. Murray Hill, NJ) driven by a pro-mag spring-loaded biopsy gun (Manan, Northbrook, IL). The needles were directed cranially at an angle of approximately 45° from the transversal plane and outward at approximately 30° from the sagittal plane. Each biopsy core was inked at its capsular end, numbered according to its site of origin, and sent in a separate container to the pathology department.

3.3. Histopathologic examination

3.3.1. Processing and examination of biopsy cores

All biopsy cores were processed for routine histopathologic examination as described previously in Chapter 2. In brief, after fixation in a 4% saline-buffered formalin solution, every core was embedded separately in paraffin, sectioned longitudinally into 5-μm sections, and stained with hematoxylin-eosin. At least three histologic sections of different cutting levels of each biopsy core were examined.

In each case of prostate cancer, the reference pathologist for urologic pathology (Th.vd K.) recorded the number of positive biopsy cores in each sextant set. The length (in millimeters) of cancer involvement was measured in each core and calculated for the sextant biopsy set as a whole. All adenocarcinomas were graded according to the Gleason scoring system[10]. In addition, the length (in mm) and the percentage of high-grade tumor (i.e., Gleason growth pattern 4 or 5) were calculated for each sextant biopsy set.

Table 1. Categories for amount and grade of adenocarcinoma on sextant prostate biopsies and comparison with progression after radical prostatectomy in 79 participants

Category	Criteria		Outcome after radical prostatectomy (n=79)		
	Tumor extent	Grade	No. of cases (%)	Extraprostatic tumor growth, i.e., stage higher than pT2, at surgery (%)[a]	Biochemical progression within 4 y after surgery (%)[b]
A	Only one positive biopsy core, with 30% or less of the core involved	Only Gleason growth pattern 1-3	22 (28)	3 (14)	1 (5)
B	Only one positive biopsy core, with more than 30% of the core involved, or more than one positive biopsy core, with a total percentage of cancer involvement 30% or less	Gleason score 7 or less	45 (57)	21 (47)	4 (9)
C	All others	Any	12 (15)	7 (58)	3 (25)
Total (%)			79 (100)	31 (39)	8 (10)

[a] The association between biopsy category and the frequency of extraprostatic tumor growth at radical prostatectomy is statistically significant (Pearson Chi-Square test 2-tailed p=.01).
[b] Although an association between biopsy category and biochemical progression is also visible, this association is not statistically significant (Pearson Chi-Square test 2-tailed p=.06).

3.3.2. Categorization of cancer involvement and grade in biopsy sets

Both the amount of tumor present in biopsy sets and the prostate cancer grade are prognostic features for biochemical relapse after treatment with curative intent[11]. To account for the fact that both large well-differentiated tumors and small poorly differentiated tumors could have a poor prognosis, we constructed an arbitrary categorization model that combines these tumor features (Table 1). Category A contains

biopsy sets with only a single small focus of well-differentiated adenocarcinoma. In addition to small but potentially dangerous tumors, this category is also likely to contain clinically insignificant tumors. Category B includes biopsy sets with larger amounts of adenocarcinoma, which sometimes contain high-grade cancer (Gleason growth pattern 4 or 5). This category is likely to contain prostate cancers that pose a threat to their host if left untreated. Biopsy sets in category C contain either large amounts of adenocarcinoma or carcinomas that consist largely of poorly differentiated tumor (Gleason growth pattern 4 or 5). Men whose tumors fall in this category would have a considerable risk of therapy failure.

To validate our categorization model for sextant biopsy sets, the categorization in the model for sextant biopsy sets of 79 men in the first round of screening who underwent radical prostatectomy was compared with clinical follow-up data, i.e., biochemical failure during a 4-year follow-up period (defined as three consecutive postoperative PSA levels > 0.1 ng/mL). Table 1 shows that biopsy categories of the 79 men were associated with the chance for extraprostatic tumor growth (Pearson chi-squared test, two-tailed $P = 0.01$). Biopsy categories were also associated with the chance for biochemical progression after surgery, although this association was not statistically significant (Pearson chi-squared test, two-tailed $P = 0.06$).

3.4. Statistical analysis

The characteristics (i.e., amount and grade) of the adenocarcinomas that were detected in the first round of screening (the prevalence and interim screens combined) were compared to those of the adenocarcinomas that were detected during the second round of screening. To investigate whether characteristics of second- round adenocarcinomas were different in men who had undergone previous biopsies, we also compared the characteristics of the adenocarcinomas of participants with adenocarcinomas detected in the second round screen who had and who had not undergone biopsy during the first round of screening. Statistical analyses of comparisons between subsets of distributions based on ordinal variables, such as Gleason Score or the arbitrary biopsy categories, were performed with a two-sided Pearson chi-squared test. The null hypothesis (statistical independence of the tested variables in subsets of participants) was rejected for P values under 0.05. Statistical

analyses of comparisons of characteristics based on continuous variables with a skewed distribution, such as PSA values or the amount of tumor or high-grade cancer in biopsy sets, were performed with a two-tailed Mann-Whitney *U* test. The null hypothesis (a similar rank distribution of the tested variable in subsets of participants) was rejected for *P* values under 0.05.

Table 2. Prostate cancer detection rates at the different rounds of screening

	No. invited	Screened No. (% of Invited)	Biopsy recommendations No.(% of Screened)	Performed Biopsies No.(% of Screened)	Prostate Cancer		
					No.	% of Performed Biopsies	% of Screened[a]
Round 1:	4491	4,133 (92.0)	1,129 (27.3)	1,027 (24.8)	177	17.2	4.3 [a]
Round 1: men aged 59–75y[b]	-	3,032	881 (29.1)	839 (27.7)	149	17.8	4.9 [a]
Interim Screens	823	662 (80.4)	301 (45.5)	284 (42.9)	33[c]	11.6	5.0
Total Round 1	-	-	-	-	210		5.1 [a]
Round 2	3023	2,385 (78.9)	481 (20.2)	440 (18.4)	94	21.4	3.9 [a]

[a]Statistical tests on prostate cancer detection rates (Pearson chi-squared test, two-tailed): round 1 versus round 2 $P = 0.51$; Total round 1 versus round 2 $P = 0.36$); round 1 (ages 59–75 years) versus round 2 $P = 0.09$
[b]To correct for age differences between the two rounds of screening, a separate calculation was done for men aged 59 to 75 in round 1.
[c]One additional case of prostate cancer was detected at a second interim screen that was performed in seven participants 1 year after the first interim screen.

4. Results

4.1. Participation rates

Of the 4491 men invited for PSA screening (after randomization) in the first round, 4133 (92%) accepted (Table 2). Of 1129 men with biopsy recommendations, 102 (9%) did not undergo biopsy because of refusal (49 men, 48%) or medical reasons (53 men, 52%). Of the 850 men with a benign biopsy outcome in the first round, 823 (97%) were invited for an interim rescreen (27 men were not invited, because they had reached the age of 76 years). Of the 823 invited men, 662 (80%) accepted (Table 2). Of the 161 men who did not visit, two (1%) had moved out of the area and 16 (10%) had died of causes other than

prostate cancer. The reason for the failure to visit was unknown for 143 men (89%). Of the 301 men who were recommended for biopsy during the interim round, 17 men (6%) did not undergo biopsy because of refusal (15 men, 88%) or medical reasons (2 men, 12%).

After the various exclusions, 3616 men were left at the beginning of the second screening round. Of these, 593 (16%) were not invited because they had reached the age of 76 years. Of the 3023 men who were ultimately invited for the second screen, 2385 (79%) accepted (Table 2). Of the 638 men who did not visit, 128 (20%) had moved out of the area and 155 (24%) had died of causes other than prostate cancer. In 12 men (2%), prostate cancer had been detected outside the screening study. The reason for not attending the second screen was unknown for 343 men (54%). Of 481 biopsy recommendations, 41 men (9%) did not undergo biopsy because of refusal (31 men, 76%) or medical reasons (10 men, 24%).

4.2. Prostate cancer detection rates

We compared the prostate cancer detection rates during the first screening round (prevalence screen), the interim screens, and the second screening round to determine whether the rate of detecting prostate cancer would differ between subsequent screening rounds. Table 2 shows that prostate cancer detection rates were similar in all rounds. During the prevalence screen, the detection rate was 4.3% (5.1% if the interim round is included). The detection rate of 3.9% in the second round did not differ statistically significantly from the rates in the first round (Pearson chi-squared test, two-tailed $P = 0.51$ for the first round versus the second round and $P = 0.36$ for the total first round [including the interim rounds] versus the second round).

To correct for any possible bias caused by age difference (ages in the first round ranged from 55 to 75 years, while ages in the second round ranged from 59 to 75 years), we examined the prostate cancer detection rate specifically in those men who were aged 59 to 75 years in the first round (Table 2). We found that the detection rate was slightly higher in this group of men during the first round. However, this rate still did not differ statistically significantly from that in the second round (Pearson chi-squared test, two-tailed $P = 0.09$).

4.3. Interval cancers

The number of interval cancers (i.e., prostate cancers detected in a screened population outside regular screening) gives an indication on the efficacy of the screening protocol. In the cohort studied, prostate cancer was diagnosed outside the regular screening rounds in only 12 men. Prostate cancer in this group was mostly clinically unapparent and found coincidentally at transurethral resection for prostatism or cystoprostatectomy for bladder cancer.

4.4. Age, serum PSA levels, and tumor characteristics

To evaluate differences in cancer characteristics (such as grade and size) between the subsequent rounds of screening and their relationship with patient's age and serum PSA level, we compared these parameters. In all rounds, the age of participants with prostate cancer did not differ substantially from the age of the participants who had undergone a biopsy.

Although biopsies were not performed at serum PSA levels below 3 ng/mL in the second round, the median serum PSA levels of participants with prostate cancer was lower in the second round than in the first round (Table 3). In addition, PSA levels at biopsy after the second round screen did not predict the presence of adenocarcinoma. That is, at the prevalence (the first round) screen, serum PSA levels at biopsy were statistically significantly higher in participants with adenocarcinoma (median PSA level = 6.1 ng/mL) than in participants with a benign biopsy outcome (median PSA level = 2.7 ng/mL) (Mann Whitney U test two-tailed $P < 0.001$). In the second round, however, serum PSA levels at biopsy did not differ between men with a benign biopsy outcome (median PSA level = 4.5 ng/mL) and those with adenocarcinoma (median PSA level = 4.3 ng/mL) (Mann Whitney U test two-tailed $P = 0.57$). The amount of adenocarcinoma in sextant biopsy sets was statistically significantly lower in tumors detected at the second round of screening than in tumors detected at the first round (Mann Whitney U test two-tailed $P = 0.001$; Table 3). The median amount of cancer in needle biopsy sets was 7.0 mm (95% confidence interval [CI] = 5.4 mm to 8.6 mm) in the first round and 4.1 mm (95% CI = 2.6 mm to 5.6 mm)

in the second round (Mann Whitney *U* test two-tailed $P = 0.001$; Table 3). Nevertheless, the average number of positive biopsy cores in men with adenocarcinoma decreased only

Table 3. Age, serum PSA levels, and tumor characteristics of participants at biopsy and participants with adenocarcinoma in the different rounds of screening

	Round 1 prevalence screen		Round 1 interim screen	
	Benign biopsies	Cancer at biopsy	Benign biopsies	Cancer at biopsy
No. of participants	850	177	251	33
Mean age, y (standard deviation)	65.4 (5.8)	65.7 (5.6)	66.9 (5.1)	66.3 (6.0)
Serum PSA level, ng/mL median (range)	2.7 (0.1 – 49.4)	6.1 (0.3 – 304.0)	5.1 (0.1-26.2)	5.4 (1.0-24.8)
Tumor length at biopsy, mm, median (range)		8.4 (0.8 – 72.5)		3.2 (0.7-10.6)
High-grade tumor length on biopsy, mm mean (standard deviation) /median (range)		4.4 (10.3) /0.0 (0.0–72.5) available for 175 cases		0.7 (1.7) /0.0 (0.0–8.4) available for 32 cases
Gleason score No. (%)				
4		6 (3)		1 (3)
5		12 (7)		2 (6)
6		91 (51)		22 (67)
7		42 (24)		7 (21)
8		22 (12)		1 (3)
9		3 (2)		0
10		1 (1)		0

	Total round 1	Round 2 screen		Statistical tests on difference between total round 1 and round 2
	Cancer at biopsy	Benign biopsies	Cancer at biopsy	
No. of participants	210	346	94	
Mean age, y (standard deviation)	65.8 (5.7)	67.4 (4.5)	66.8 (4.6)	
Serum PSA level, ng/mL median (range)	5.8 (0.3-304.0)	4.5 (3.0-36.0)	4.3 (3.0-15.1)	
Tumor length at biopsy, mm, median (range)	7.0 (0.7-72.5)		4.1 (1.1-56.1)	Mann Whitney *U* test, two tailed $P = 0.001$
High-grade tumor length on biopsy, mm mean (standard deviation) /median (range)	3.8 (9.6) /0.0 (0.0–72.5) available for 208 cases		0.6 (1.7) /0.0 (0.0–10.6) available for 93 cases	Mann Whitney *U* test, two tailed $P < 0.001$
Gleason score No. (%)				
4	7 (3)		1 (1)	
5	14 (7)		3 (3)	
6	113 (54)		75 (80)	Pearson chi-squared test, two-tailed $P = 0.001$
7	49 (23)		14 (15)	
8	23 (11)		1 (1)	
9	3 (1)		0	
10	1 (1)		0	

slightly, from 2.5 in the first round to 2.2 in the second round (Pearson chi-squared test, $P = 0.13$; data not shown).

In addition to the smaller amount of cancer, prostate cancers detected at the second round were better differentiated than the ones detected during the combined first rounds (i.e., the prevalence and interim screens). The median amount of high-grade cancer (expressed in millimeters of cancer with Gleason growth pattern 4 or 5) was statistically significantly lower in prostate cancers detected at the second round than in the ones detected during the first rounds (Mann Whitney *U* test two-tailed $P < 0.001$; Table 3). Gleason score was

statistically significantly lower in adenocarcinomas detected at the second round (Pearson chi-squared test two-tailed $P = 0.001$; Table 3). Thirty-six percent of the adenocarcinomas detected in the first round, but only 16% of those detected in the second round had a Gleason score of 7 or higher (mean difference = 20% [95% CI = 10% to 30%]; P < 0.001).

To investigate whether the observed differences in tumor characteristics were reflected by serum PSA levels, we stratified the frequency of biopsies, the frequency of prostate cancer at biopsy, and the median amount of tumor in biopsy specimens to range of serum PSA levels (Table 4). Both prostate cancer detection frequencies and the amount of prostate cancer in biopsy specimens at the prevalence screen were clearly associated with serum PSA levels at screening (Table 4). Despite overall higher serum PSA levels at the interim screen, both detection frequency and the amount of tumor in biopsy specimens were lower than during the prevalence screen, especially at high PSA levels (≥ 10 ng/mL; Table 4). The same trend was seen in the second round. That is, cancer detection rates in the second-round screen and the prevalence screen were similar at serum PSA levels of 3.0 ng/mL to 10.0 ng/mL, but the frequency of prostate cancer in biopsies performed at serum PSA levels of 10.0 ng/mL or above in the second-round screen was only half of the frequency that was observed in the prevalence screen.

In addition, the association between the range of serum PSA levels and the median length of tumor at biopsy that was clearly present in the first round, was lost in the second round. Whereas in the first round a serum PSA level of 10 ng/mL or above was associated with a high amount of cancer in biopsies, the amount of cancer that was present in biopsies performed at serum PSA levels of 10 ng/mL or above was comparatively low in the second round (Table 4).

4.5. The categorization model

To examine whether the 4-year interval between PSA screenings in our study resulted in an increase in advanced-stage tumors at the second round, we compared the biopsy-determined categories of screen-detected prostate cancers in the first and second rounds. We found a substantial difference in the distribution of cancers in the three categories that we defined. There was a moderate increase in the number and the frequency of tumors in

both categories A and B, from 39 (19%) and 119 (56%), respectively, in the first round to 28 (30%) and 60 (64%), respectively in the second round. The number and the frequency of category C tumors at biopsy, however, dropped dramatically, from 52 (25%) in the first round to six (6%) in the second round (mean difference = 19% [95% CI = 11% to 26%]; $P < 0.001$). The category distribution of adenocarcinomas detected in the second round was statistically significantly lower than the distribution of adenocarcinomas detected in the first round (Pearson chi-squared test, two-tailed $P < 0.001$). These results suggest that the frequency of prostate cancer with adverse prognostic features did decrease after the interval of 4 years between the two screening rounds in this study.

Table 4. Cancer detection and tumor length at biopsy of participants in different PSA ranges during screening

Serum PSA level range, ng/mL	No.of biopsies (%)	Cancer at biopsy (%/% of biopsies)	Cancer length at biopsy, mm median (range)
Round 1 Prevalence screen			
0–2.9	469 (46)	27 (15 / 6)	4.4 (1.1 – 31.8)
3.0–3.9	42 (4)	10 (6 / 24)	5.4 (2.0 – 15.8)
4.0–9.9	437 (42)	95 (54 / 22)	9.2 (0.8 – 52.3)
≥10.0	79 (8)	45 (25 / 58)	14.6 (0.8 – 72.5)
Totals	1,027 (100)	177 (100 / 17.3)	8.4 (0.8 – 72.5)
Round 1 Interim screen			
0–2.9	66 (23)	6 (18 / 9)	1.9 (1.0 – 6.0)
3.0–3.9	13 (5)	3 (9 / 23)	4.4 (3.4 – 5.2)
4.0–9.9	178 (63)	20 (61 / 11)	3.0 (1.5 – 8.0)
≥10.0	27 (9)	4 (12 / 15)	2.6 (0.7 – 10.6)
Totals	284 (100)	33 (100 / 11.4)	3.2 (0.7 – 10.6)
Round 2			
0–2.9	0 (0)	0 (0)	-
3.0–3.9	157 (36)	35 (37 / 23)	3.3 (1.2 – 27.2)
4.0–9.9	252 (57)	52 (56 / 21)	5.2 (1.2 – 56.1)
≥10.0	31 (7)	7 (7 / 23)	4.2 (1.1 – 21.0)
Totals	440 (100)	94 (100 / 21.6)	4.1 (1.1 – 56.1)

4.6. Baseline PSA of biopsied men in the second round

Of the 440 participants who underwent a biopsy in the second round, the baseline serum PSA level (i.e., the PSA level found at the first round of the study) did not differ statistically significantly between men who turned out to have prostate cancer and those who had a benign biopsy outcome (Mann-Whitney U test two-tailed $P = 0.13$). Baseline serum PSA levels were even slightly lower in men with prostate cancer detected in the second round (median 3.2 ng/mL; range 0.7 – 9.3 ng/mL) than in men with a benign biopsy outcome in the second round (median 3.7 ng/mL; range 0.5 – 35.7 ng/mL). Thus, PSA values obtained during the first round of the study (baseline PSA) did not predict prostate cancer in subsequent screening rounds.

5. Discussion

Although annual PSA screening for prostate cancer has been recommended by the American Cancer Society since 1993[2], to our knowledge, no study has yet demonstrated that this is the optimum interval for prostate cancer screening programs. Nevertheless, performing PSA tests at an annual interval is now the most commonly used method to screen for prostate cancer in the United States. A few reports [6-8], however, have postulated that biannual screening would be more cost-efficient because, although it is not likely to miss curable prostate cancers, it does lead to substantial savings in health-care costs. These reports are based on models constructed by use of historical data on prostate cancer incidence rates and associated PSA levels; to our knowledge, they have not yet been confirmed in clinical practice.

Our study shows a substantial decrease in both the amount and the grade of screen-detected prostate cancers 4 years after an initial prevalence screen (Tables 3 and 4). Relatively few advanced (category C) tumors were found after the 4-year interval. In addition, the frequency of prostate cancer in needle biopsies dropped at high PSA ranges (Table 4). These observations suggest that large prostate cancers with high PSA values are effectively detected during a prevalence screen and that even an interval of 4 years is not long enough for most large tumors to develop.

The findings our study are in striking contrast to those in breast cancer screening: A pooled analysis of breast cancer screening programs with a 1.5- to 3-year screening interval shows that, despite a clear reduction in breast cancer-related mortality associated with screening, the stage of the detected tumors does not change statistically significantly during subsequent rounds of screening[12].

It is important to note that the changes in prostate cancer characteristics that we observed in the current study took place after a prevalence screen. In a previous report (see Chapter 5), a comparison of characteristics of prostate cancer detected at the prevalence screen with a series of not-screen-detected prostate cancers showed a statistically significant drop in stage and grade in the series detected during the prevalence screen. The changes between cancer detected at the first round and cancer detected at the second round of screening that were observed in the current study suggest that periodic screens will have an even greater beneficial effect on the grade and stage at which prostate cancer is detected.

Only very few reports have addressed the question whether different screening intervals would be applicable for men with different clinical profiles (e.g., age, comorbidity, or baseline serum PSA level at the beginning of the screening program). Carter et al.[6] used PSA conversion rates to conclude that biannual screening for prostate cancer can be safely recommended in men with a baseline serum PSA level below 2.0 ng/mL. Annual testing would be required only for men with baseline serum PSA levels of 2.0 ng/mL or above. This approach contends that baseline PSA levels can be used to determine the length of the interval by which screening should occur. Our findings do not confirm this assumption, because the baseline PSA levels (observed at the prevalence screen) did not predict the occurrence of prostate cancer in the second round.

Despite the substantial reduction in both the amount and the grade of screen-detected prostate cancer over the 4-year interval between the first and second rounds, our findings do not prove that screening for prostate cancer has a beneficial effect on prostate cancer mortality. Moreover, screening for prostate cancer potentially has the undesirable effect of leading to overtreatment for clinically unimportant tumors. However, we saw little indication of this in our study because the fraction of category A tumors showed only a moderate increase in the second round. Category A tumors largely represent small well-differentiated adenocarcinomas with an uncertain clinical significance. Apart from potentially dangerous tumors at an early stage, this category is likely to harbor cancers

that will not pose a threat to their hosts during their lifetime. Therefore, a substantial increase in category A tumors would have been more alarming than reassuring.

In screening for malignant diseases, the interval between subsequent screens is very important. When the interval between screens is too long, the chance increases for the development of large incurable tumors between rounds of screening. In the studied cohort of this report, the number of interval cancers was, however, limited. A total of 304 cancers were detected during the regular screening rounds, and only 12 (3.8% of all 316 cancers) were detected between screening rounds.

Our study has several limitations. One limitation, which applies to all studies that rely on sextant prostate biopsy outcome as an endpoint, is that tumor features observed on sextant prostate biopsies are not necessarily representative of adenocarcinoma in the prostate gland. However, Table 1 shows that the frequency of extraprostatic tumor growth is statistically significantly higher for higher biopsy categories. The model we used is also associated with biochemical failure after surgery (although this association is not statistically significant). The observed drop in category C tumors between the two rounds, therefore, seems to indicate a more favorable outcome for men in whom cancer is detected at periodical rounds of screening.

Another limitation is the decreased attendance rate during the second round of screening. Although an attendance rate of 79% after a four-year interval could be considered reasonable, it might have led to a bias in our results if men who forgo further regular screens have clinical characteristics that might favor the presence or absence of prostate cancer.

Finally, our study may have been compromised by the use of different screening protocols during the first and second rounds of screening. In the second round, biopsy recommendations no longer relied on the outcome of DRE and TRUS, and the threshold of serum PSA levels as a sole tool for biopsy indication was lowered from 4 ng/mL to 3 ng/mL. Previous investigations of the participants in ERSPC[13] have shown that the number of aggressive tumors detected at low PSA levels is small (see also Chapter 4). In addition, Table 4 clearly shows that differences in characteristics between tumors detected in the first round and tumors detected in the second round were most pronounced in the high PSA ranges (≥ 10 ng/mL), where the protocols of both rounds were the same. It is likely that the fraction of men with a high PSA level caused by diseases other than prostate cancer (e.g., chronic prostatitis or benign prostate hyperplasia) increased during

the second round of screening, thereby accounting for the lower detection rate at high serum PSA levels and for the loss of the predictive value of serum PSA levels for both the presence and the amount of prostate cancer during the second round (Table 4).

Aside from these limitations, our results strongly suggest that, even over an interval of 4 years between screening rounds, there was no evidence of unfavorable changes in the characteristics of detected carcinomas in the subsequent rounds of prostate cancer screening. It appears that, during the prevalence screen, large prostate cancers manifested by high PSA levels are effectively detected. A screening interval of 4 years seems short enough to constrain the development of most large tumors. Moreover, baseline PSA levels found during a prevalence screen do not predict the chance of prostate cancer detection in subsequent screening rounds.

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SUMMARY AND CONCLUDING REMARKS

1. Introduction

Prostate cancer is an increasingly important health problem. In the USA, prostate cancer mortality is now second only to that of lung cancer[1]. As lung cancer mortality is declining and the age-expectancy of humans is expected to rise, prostate cancer mortality seems destined to become the leading cause of male cancer death in the near future. The relatively high relapse rate after initial treatment with curative intent[2,3] and the difficulties that are encountered with the clinical management of advanced prostate cancer are major incentives for attempts to detect prostate cancer at an early stage. Therefore, since 1993, annual screening by PSA measurements is recommended to all men over 50 in the USA[4]. The changes in the incidence and mortality rates that have since then been witnessed in the population-based registry data of the Surveillance, Epidemiology and End Results (SEER) program[5-7] seem to indicate that prostate cancer screening reduces prostate cancer mortality rates. However, the results of mass screening for prostate cancer may be influenced by two important biases. Because tumors are detected later without screening, the "life span" from the moment of tumor detection is seemingly prolonged in screened and treated participants (lead time bias) Apart from this bias, mass screening of the general population could result in the detection and subsequent treatment of tumors that would not have been found without screening but would not have posed a threat to the life-expectancy of their host. An increased detection of these kinds of tumors also has a seemingly beneficial effect on a screened group (length time bias). Especially length time bias may considerably influence the outcome of screening for prostate cancer, as the frequency of latent cancers, which are detected at autopsy studies and seem to be mostly of limited or no clinical significance has shown to be very high (ranging from 30% to 50% in males older than 50 years)[8-10].

Because of the above biases, the question whether population-based screening for prostate cancer would benefit the population at risk has been the matter of much debate[11-13]. The only way to prove a beneficial effect of systematic screening for prostate cancer in the general population is to perform a randomized trial[14]. Randomized trials on screening for prostate cancer, which evaluate the effects of systematic screening for prostate cancer on mortality and quality of life, are underway but final results are not expected until 2008[15,16].

The studies outlined in this thesis describe the characteristics of prostate cancer and its

premalignant lesions detected in the general population by systematical periodical screening. They were intended to address the following questions:

- Are the frequencies of performed biopsies and repeat biopsies during screening for prostate cancer acceptable?
- What are the characteristics of the detected tumors at screening for prostate cancer? Is there a tendency towards better treatable tumors and thereby towards a better prognosis of screened participants?
- What about the clinical significance of tumors detected by screening? Are clinically insignificant tumors more frequently diagnosed?
- What happens at subsequent screening rounds? Is there an indication that a four-year interval between subsequent screens is too long? Is there an indication that more clinically unimportant tumors are detected during the second round?

2. Prostate biopsies in the general male population

For a definite diagnosis of prostate cancer obtaining and examining prostatic biopsies is required. A previously reported study performed by Rietbergen et al. within ERSPC[17] showed that taking sextant biopsies of the prostate constitutes a relatively safe procedure. Although there are often minor complications, such as transient hematuria and hematospermia (in 24% and 45% of the cases respectively), major complications are infrequent (about 0.4% of biopsied men will require hospitalization because of biopsy complications).

Chapter 3 of this thesis shows that during the initial screen for prostate cancer, about one in every five men has an indication for biopsy, and that a definite diagnosis of prostate cancer is made in about one of every five biopsied men.

Systematic sextant biopsies are not necessarily directed towards palpable or echographically visible lesions within the prostate. Obviously, a blind biopsy procedure is always the case when biopsies are prompted by an increased serum PSA level only (i.e. in the absence of a palpable or echographically invisible lesion). When one compares the detection rate of prostate cancer in the general population (about 5%) with the reported high rate of latent prostate cancer (30- 50%), it is clear that not every prostate cancer is detected at screening. Since previous studies have shown that latent (and probably

clinically insignificant) prostatic carcinomas are mostly very small[9], they will probably be more frequently missed by sextant biopsy, than clinically important tumors, which are likely to be larger. Therefore, the sensitivity of sextant prostate biopsies for determining the presence of prostate cancer *per se* seems limited, but the sensitivity of prostate biopsies for detecting clinically important prostate cancer is much higher.

2.1. Repeat biopsy indications

Certain lesions encountered in biopsy cores require repeat biopsies. High grade PIN is considered the most likely precursor of prostate cancer, and warrants repeat biopsies to exclude concurrently existing or consecutively developing prostate cancer.
Sometimes, lesions occur that lack criteria for a definite diagnosis. Although these lesions might consist of prostate cancer, sufficient evidence for their malignant or benign nature is lacking, mostly because of the small amount of tissue (see Chapter 1, paragraph 2.5.3 *The histologic diagnosis of prostate cancer*). These lesions require repeat biopsies to obtain additional tissue for more information concerning their nature.
Bostwick et al. originally described these lesions as "suspicious for, but not diagnostic of prostate cancer"[18]. Later, his group proposed the term "Atypical Small Acinar Proliferations (ASAP)"[19,20]. The latter can be considered a catching acronym, because it signifies that repeat biopsies should be performed "As Soon As Possible". Other than representing small amounts of what is in fact prostate cancer, lesions that are diagnostically difficult to interpret include a wide variety of well known mimics of prostate cancer, such as atrophy, postatrophic hyperplasia[21], atypical adenomatous hyperplasia[22], atypical basal cell hyperplasia[23] and paraganglia[24].
The application of terms such as ASAP for these lesions is confusing, because it tends to indicate that they form a separate morphologic entity, while in fact they are a highly heterogeneous group of lesions. Therefore, in Chapter 3 of this thesis, the more general term "borderline lesions" is introduced to indicate these lesions.
All in all, both the presence of high grade PIN and borderline lesions warrant the performance of repeat biopsies to exclude prostate cancer. Because the reasons why repeat biopsies should be obtained differ for these two groups of lesions, repeat biopsy strategies are different as well. In the case of high grade PIN lesions, repeat sextant biopsy is indicated because of the chance of concurrent prostate cancer occurring either at the site

of the lesion or elsewhere in the prostate as the result of a carcinogenic field effect[25-27]. In the case of a borderline lesion, however, the need exists to clarify the nature of the lesion itself. Looking for additional cancer foci elsewhere in the prostate is not the purpose of repeat biopsies for borderline lesions and therefore, repeated biopsies should be aimed at the site of the initial lesion.

2.2 Repeat biopsy frequency and diagnosis

The reported frequencies of prostate cancer in repeat biopsies taken because of the occurrence of a high grade PIN lesion or a borderline lesion in the initial biopsy vary considerably in the literature. The data of Chapter 3 show that isolated high grade PIN (i.e. without concurrent prostate cancer) is diagnosed in about 0.7% of prostate needle biopsies performed in the general population, while the frequency in the literature ranges from 1% to 15%. Upon a prostate needle biopsy review by a pathologist with expertise in urologic pathology, an additional 1% of isolated high grade PIN lesions was found. Doubling frequencies of high grade PIN in prostate needle biopsies upon review were previously reported in the literature [28]. Apparently, about half of the high grade PIN lesions is missed by general pathologists. Therefore, besides the use of different study populations, differences in diagnostic expertise might explain the wide variation of the frequency of high grade PIN in the literature. An increased awareness of the diagnostic features of high grade PIN (by better training, low consultation thresholds or reference images) is needed to enhance a more accurate diagnosis of this putative cancer precursor lesion.

In the study presented in Chapter 3, high grade PIN lesions coincided with a focus of prostate cancer in the same biopsy set in 75% of the cases. Repeat biopsies for the remaining 25% of high grade PIN lesions did not lead to the discovery of additional prostate cancer. Later studies performed in the ERSPC report a limited prostate cancer detection rate in 10% (3 out of 30) men with isolated high grade PIN at initial biopsy, a detection rate that is similar to that at repeat biopsy after an initial benign biopsy[29]. The frequency of prostate cancer detected after repeat biopsies for high grade PIN is strikingly low compared to frequencies reported in the literature (ranging from 28% to 100%)[26,27,30-34]. A possible explanation is that most concurrent prostate cancers were already detected at the initial biopsy.

Borderline lesions were found in 2.4% of all screened participants. A definite diagnosis of prostate cancer was made in 39% of repeat biopsies. The frequency of a final diagnosis of prostate cancer in repeat biopsies for borderline lesions apparently far exceeds that in repeat biopsies for high grade PIN, something that was confirmed by later studies from the ERSPC[29].

Repeat biopsy indications, such as high grade PIN and borderline lesions on needle biopsy sets of screened participants proved not to represent major diagnostic subsets in population-based screening. This is of great importance, since a too high rate of repeat biopsy indications would lead to high health costs and a large emotional burden on screened participants. The absolute number of additional prostate cancers that are detected by pursuing high grade PIN and borderline lesions at screening is limited. Long term follow-up is needed to get more insight into their clinical significance.

3. The clinical significance of the detected and treated tumors

3.1. Tumor categorization

The clinical significance of prostate cancer depends on a combination of tumor characteristics. In addition, age and life expectancy of the individual patient will strongly influence the clinical outcome. Prostate cancer stage and grade have shown to be independent prognostic parameters for biochemical relapse (i.e. rising serum PSA levels) after treatment with curative intent[35]. Because of this, both large well differentiated tumors and small poorly differentiated tumors are associated with poor prognosis. To estimate the clinical significance of the characteristics of the screen-detected tumors in the ERSPC, we constructed an arbitrary model for tumors found at radical prostatectomy (Chapter 4). This model is based on combinations of tumor extent and grade and was partially based on models proposed in two earlier reports[36,37]. The model globally divides tumors into categories of minimal, moderate, and advanced tumor. At the time of construction of our model, we lacked sufficient follow-up data to confirm its predictive capacity for clinical outcome. Meanwhile, however, the capacity of our model to predict PSA relapse after radical prostatectomy has been confirmed by Vis et al. in a later study[38].

However, it must be realized that a correct prediction of clinical outcome after treatment does not necessarily correctly reflect the biological behavior of prostate cancer. In Chapter 4, we stated that patients with moderate tumors are the ones most likely to have an optimal benefit from treatment by radical prostatectomy. We also stated that patients with advanced tumors are the ones most likely to experience recurrence of disease after treatment. Patients with minimal tumors are expected to have an excellent prognosis, although this group is most likely to harbor tumors that would not have posed a health threat if they would have been left untreated. These statements, however, do not exclude that a significant proportion of men with advanced tumors may be cured by radical prostatectomy. They do not exclude either, that a significant proportion of minimal tumors may demonstrate an aggressive behavior, if left untreated. Our model of clinical significance, therefore, should be regarded with these considerations in mind.

3.2 Pathologic features of detected and treated tumors

The data presented in Chapter 4 show that around 80% of the prostate cancers that are detected by screening and treated by radical prostatectomy, fit the criteria of moderate or advanced tumors in our categorization model. The remaining 20% fit the criteria for minimal tumors. These frequencies are confirmed by the findings in Chapter 6, in which a larger number of radical prostatectomies was studied. Therefore, the majority of the detected and treated tumors seems to have pathological features that indicate clinical significance.

3.2.1. The relation between pathologic features and detection methods

The study outlined in Chapter 4 describes tumor features of screen-detected tumors in ERSPC participants. Pathological characteristics are compared to the methods by which the tumors were detected (i.e. an abnormal finding at DRE or TRUS or a serum PSA level of 4ng/mL or above).

A special emphasis is placed on the characteristics of prostate cancers that were detected with an elevated PSA level as only criterion for biopsy (i.e. a serum PSA of 4ng/mL or above, without clinical evidence of palpable or echographically visible abnormalities). These tumors have raised some concern in the literature, since their clinical significance was hitherto unclear. The data presented in Chapter 4 show that the fraction of non-

palpable and echographically invisible (T1c-) tumors detected in the screened general population is considerable. No less than 33% of all radical prostatectomies and 46% of radical prostatectomies performed for tumors detected on the basis of an elevated PSA level were performed in patients with T1c-tumors. In our arbitrary model, almost 90% of T1c-tumors fit the criteria for moderate or advanced tumor. However, they are generally smaller and have a lower pathologic stage compared to tumors that were detected with an elevated PSA level in combination with palpable or visible abnormalities. Considering the independent prognostic value of pathologic stage[2,39], it would be expected that the long-term outcome after radical prostatectomy would be more favorable for men with T1c tumors as compared to men with non-T1c tumors and elevated serum PSA levels. Evidence for this hypothesis was obtained in a recent study with limited follow-up, which showed that men with T1c-tumors seem to have a more favorable outcome than men with non-T1c tumors detected within a similar range of preoperative serum PSA concentrations[40]. The detection of impalpable and echographically invisible tumors by performing biopsies on the basis of an elevated serum PSA level, therefore, is of great importance in reducing prostate-cancer-related mortality in population-based screening. The characteristics of tumors detected by DRE and TRUS in patients with PSA levels below 4 ng/mL raise some concern. This group contains the smallest tumors with the lowest pathologic stages, and 43% fit the criteria of minimal tumor in our categorization model. The overall small size of these tumors implicates that many are in fact detected by chance (meaning that the outcomes of DRE and TRUS are actually false). The performance of DRE for the detection of prostate cancer in men with low serum PSA levels has been the subject of several studies performed within the screened population of the ERSPC. Without exception, the performance within low serum PSA ranges of DRE in particular was concluded to be poor[41-43]. Because of the results of these studies, the screening procedure was adapted by the discontinuation of biopsies at serum PSA levels below 3 ng/mL[42-44]. In the new protocol, serum PSA level is the single parameter for the determination of biopsy recommendations. Early evaluations of the new screening protocol show that the implemented changes have led to an improvement of screening test's positive predictive value for prostate cancer, while prostate cancer detection rates and prostate cancer characteristics remain virtually unchanged[45].

3.2.2. Changes in tumor stage of early detected and treated prostate cancer

Several reports in the literature have shown a dramatic increase in performing radical prostatectomies since the introduction of PSA as a tool for prostate cancer detection[46-48]. As the results of Chapter 4 indicate, the increased frequency of treatment with curative intent is most likely due to the detection of non-palpable prostate cancer, which seems to result in a higher number of clinically prostate-confined tumors. Whether changes have occurred in volume, stage, and grade of tumors that are treated by radical prostatectomy is much less clear, as different reports show conflicting results[47,49].

The study presented in Chapter 5 was performed to see whether the characteristics of early detected and treated prostate cancer in screened ERSPC participants showed favorable changes compared to non-screen-detected prostate cancer. Currently, the number of radical prostatectomies performed in participants in the control group of the ERSPC is still limited. Therefore, the characteristics of treated prostate cancer in screened participants were compared to a historic series of radical prostatectomy specimens obtained from prostate cancer patients in the period before the introduction of serum PSA measurements and systematic screening. A disadvantage of such a comparison of course is that differences in preoperative patient selection criteria cannot be controlled.

The results of Chapter 5 show that early detection of prostate cancer by systematic screening seems to have reduced the pathologic stage and grade at the moment of surgery and that more relatively small tumors have been treated. The most striking result was the complete absence of pelvic lymph node metastases in the studied screened series, while positive pelvic lymph nodes were the reason for discontinuing radical surgery in 18% of the historic surgery. This observation is in line with the results of an earlier study, where a comparison of ERSPC screen-detected tumors with a series of incidentally detected cases in the Amsterdam area between 1989 and 1994 showed a dramatic decrease in the fraction of metastasized disease in the former[50].

3.2.3. Prostate cancer grade: heterogeneity and multifocality

The results of Chapter 5 show, that the observed shift towards a lower grade of screen-detected prostate cancer is mainly due to a decreased number of high Gleason score tumors (Gleason score 8 to 10). High grade cancer areas (Gleason pattern 4 or 5), however, are found in 60% of the early detected tumors, which is still a considerably high figure. A detailed mapping study of radical prostatectomy specimens obtained from

screened participants of ERSPC shows that most of these (67%) contained more than one tumor. Unfortunately, data on tumor multifocality were not available for the historic reference series. The relatively high frequency of multifocal tumor in the screened series is consistent with the idea that prostate cancer arises simultaneously at different sites, possibly as a result of a carcinogenic "field effect". Moreover, the majority of histologically demarcated tumor areas contains areas with different grades (*intra-tumor* grade heterogeneity). Some of the tumor foci with intra-tumor grade heterogeneity might arise when separate tumor foci with different growth patterns collide (collision tumors). However, the fact that areas of high grade cancer are most frequently found at the center of a larger well-differentiated tumors indicates that most of them arise as the result of dedifferentiation within a single tumor focus. The observed generally lower grade in early detected tumors does not seem to be the result of a decreased frequency of these areas of dedifferentiation, but seems to be the result of a decrease of the relative proportion of high grade cancer areas in heterogeneous and multifocal tumors. In other words, high grade cancer areas occur at an equal frequency, but tend to be a lot smaller in screen-detected prostate cancer. In line with the hypothesis of dedifferentiation is the direct correlation between the relative amount of high grade cancer in each tumor with tumor volume. This supports the theory that tumor progression starts with a small focus of dedifferentiation which, by having a growth advantage over the surrounding well differentiated areas, will grow relatively faster, giving rise to relatively larger proportions of high grade cancer. In the future, detailed studies that compare DNA aberrations between histologically different areas within single tumor foci should be able to prove or reject this theory of dedifferentiation.

The high frequency of focal dedifferentiation in early detected prostate cancer could easily interfere with the prognostic value of current grading systems. Most of the current grading systems fail to account for focal dedifferentiation. In the Gleason score system for instance, secondary tumor growth patterns are included in the Gleason score only when they make up more than 5% of the total tumor. When two major growth patterns of well differentiated tumor are present, there is no clear rule on the inclusion of small amounts of poorly differentiated prostate cancer. As a result, focally dedifferentiated early detected tumors would end up having the same overall grade as well-differentiated tumors. The changing characteristics of prostate cancer caused by early detection might some day force us to reconsider and perhaps revise current grading systems. Recent studies have

advocated to mention the relative proportion of high grade cancer, since it has shown to have a high prognostic value, which possibly even exceeds that of the Gleason score system[51,52].

3.3 The clinical significance and the preoperative prediction of minimal tumor

As is outlined in Chapter 1, systematic screening for prostate cancer entails a risk of detecting a large number of clinically insignificant tumors (i.e. tumors that will not pose a threat to a patient's health). The purpose of an early detection program for malignant tumors is to detect and treat cancer at an early stage, thereby improving prognosis and life-expectancy of the screened population. However, the frequency of mostly small and well differentiated prostate cancers that are found incidentally (e.g. at autopsy or surgery for bladder cancer) is very high[8-10]. Increased detection of clinically insignificant tumors may lead to high rates of unnecessary treatment and thereby the risk of iatrogenic injury and complications.

In recent years, a major scientific effort has been put into use to try to distinguish clinically significant tumors from the clinically insignificant ones, or as they are sometimes referred to, the "tigers" from the "pussycats"[53]. Important characteristics for the determination of the clinical significance of prostate cancer that have been proposed are tumor volume[54] and tumor doubling times[55]. It is, however, likely that a clear distinction between tigers and pussycats, which is solely based on tumor characteristics, is impossible, since tigers and pussycats are likely to represent two extremes of a continuous spectrum. Besides this, patient-related features such as age, life-expectancy, and co-morbidity play a crucial role in determining the clinical significance of prostate cancer[56]. The arbitrary model that was presented in Chapter 4 divides the early detected tumors into categories of minimal, moderate and advanced tumors. The results of the studies presented in Chapters 4 and 6 show, that the proportion of minimal tumors (small, well differentiated tumor at radical prostatectomy) in treated participants in the screening arm of ERSPC lies around 20%. Men with a minimal tumor at radical prostatectomy seem to have an excellent prognosis[38]. However, this finding does not by itself warrant a more expectant attitude towards patients with tumors with these clinical features. Although the category of minimal tumors in our model is the most likely category to harbor clinically insignificant tumors, there is a possibility that some of these minimal tumors have the

capacity to become life threatening by accelerated growth rates and dedifferentiation. In other words, we have no knowledge of their biologic behavior and therefore do not know how they would have developed without surgical treatment.

Histologically, prostate cancers with features consistent with those of minimal tumors in our model form a relatively homogeneous group with constant features. By definition, they consist of a single small focus of well differentiated (mostly Gleason growth pattern 3) tumor. A recent study on DNA aberrations of tumors detected in the Rotterdam section of the ERSPC, however, shows that a significant proportion of the minimal tumors have genetic characteristics that are consistent with tumors that show an aggressive clinical behavior [57].

A sound decision to determine which tumors should be treated and which should be managed with a more expectant clinical approach, will require additional large randomized studies that compare treatment with expectant management or "deferred treatment" in patients with minimal tumors. Such studies, however, require a reliable method for the preoperative prediction of minimal cancer.

Chapter 6 discusses whether minimal tumors can be reliably predicted with combinations of clinical parameters. The results show that the predictive value of a small amount of well differentiated cancer at biopsy is limited, as nearly half of such patients proved to have moderate or even advanced tumor at radical prostatectomy. Adding serum PSA level to the equation considerably enhances the ability to predict prostate cancer characteristics at radical prostatectomy, as over 90% of patients with a small amount of well differentiated cancer at biopsy and a PSA level below 4 ng/mL prove to have minimal tumor, whereas almost 70% of patients with similar biopsy features and a PSA level of 4 ng/mL or above have moderate or advanced tumors. Although these results strongly suggest that it is possible to predict for the presence of minimal tumor in the prostate by combining tumor features at sextant biopsy with serum PSA levels, it is still questionable whether the accuracy of the prediction is sufficient for use on an individual patient basis or for a randomized study of treatment versus deferred treatment. On the other hand, the results of Chapter 6 strongly indicate that, the presence of a small focus of well-differentiated adenocarcinoma at biopsy by itself should not be underestimated.

4. Periodic screening for prostate cancer: the screening interval

The studies reported in Chapters 3 to 6 were performed on tissue specimens from screened participants in the initial screening round (prevalence screen) of the ERSPC. After the prevalence screen, screened participants are rescreened at four-year intervals. In Chapter 7, a comparison of cancer characteristics on needle biopsies in the two first screening rounds is presented. The results show a considerable decrease in both the amount and the grade of prostate cancer detected in the second screening round, while the number of coincidentally detected prostate cancers outside regular screening and in between the two rounds is small. Therefore, even after the long interval of four years between screening rounds, there is no evidence of unfavorable changes in the characteristics of detected carcinomas in the subsequent rounds of prostate cancer screening. Also, the detection rate of minimal prostate cancer seems to remain constant. The diminished value of serum PSA to predict both the frequency and the amount of cancer in biopsies of the second screening round bears witness to the tremendous effect on the composition of the screened population exerted by the prevalence screen four years earlier. It appears that, during the prevalence screen, large prostate cancers manifested by high PSA levels are effectively detected. Prostate cancer generally seems to have a low growth rate and therefore, a screening interval of four years seems short enough to constrain the development of most large and potentially dangerous tumors. The results of Chapter 7 stand out against the guidelines of the National Cancer Society in the United States of America, which, since 1993, has recommended annual screening for prostate cancer in men of 50 years and older[4]. Annual screening for prostate cancer may increase prostate cancer detection rates, but the chance of detecting more clinically insignificant tumors thereby also increases, unavoidably accompanied by increased rates of unnecessary treatment. Besides avoiding this, screening for prostate cancer at longer intervals would save a substantial amount of health care costs.

5. Concluding remarks and future perspectives: questions, answers and more questions

The studies in this thesis were aimed at the histopathologic characteristics of prostate cancer detected at screening of the general male population between 55 and 75 years of age. They were intended to answer a number of questions, which were posed earlier in this chapter. I come back to these questions now, and will try to answer them briefly:

- *Are the frequencies of performed biopsies and repeat biopsies during screening for prostate cancer acceptable?*
  The studies in this thesis show that during screening for prostate cancer, the biopsy procedure seems efficient for the detection of clinically important prostate cancer and does not pose too high a burden for the screened participants. The frequency of repeat biopsy indications is relatively low compared to that in generally referred urologic patients.

- *What are the characteristics of the detected tumors at screening for prostate cancer? Is there a tendency towards better treatable tumors and thereby towards a better prognosis of screened participants?*
  While most tumors during the prevalence (first) screen for prostate cancer have characteristics of clinically important tumors that require treatment, they do have relatively favorable prognostic features in comparison to conventionally detected prostate cancer. Therefore, the prognosis after treatment seems more favorable in screen-detected tumors.

- *What about the clinical significance of tumors detected by screening? Are clinically insignificant tumors more frequently diagnosed?*
  The group of very small and well differentiated prostate cancer, defined as minimal tumor in this thesis, is the one most likely to harbor clinically insignificant prostate cancer. Judged by the low frequency of these tumors during the first screen, screening for prostate cancer does not seem to lead to an alarming increase of the detection of these minimal tumors and thereby a possible increase in treatment for clinically

insignificant prostate cancer. The clinical significance of these minimal tumors is, however, unclear and will also depend on patient characteristics, such as age and comorbidity.

- *What happens at subsequent screening rounds? Is there an indication that a four-year interval between subsequent screens is too long? Is there an indication that more clinically unimportant tumors are detected during the second round?*
  In combination with the limited number of prostate cancers that were coincidentally detected outside regular screening, the decrease in size and grade of the detected tumors in the second round indicates, that the four-year interval between the different screening rounds is short enough to constrain the development of most large, and possibly harmful tumors. There is no indication that clinically unimportant tumors are more frequently detected in the second round.

Although the studies in this thesis have provided answers to some questions, other questions that require future research remain. For instance:

- *How will we be able to determine the clinical significance of minimal prostate cancers?*
  This is probably going to be one of the key problems in prostate cancer screening. The high prevalence rates of – mostly minimal - prostate cancer at autopsy studies and the much lower detection rate of prostate cancer at screening indicate that most of these small tumors are not detected by screening. The ones that are detected are most probably detected by chance.
  To determine the clinical significance of minimal prostate cancers that are eventually detected, we need to set up randomized trials that compare deferred treatment with curative treatment for these kinds of tumors. Given the fact that the prognosis of minimal prostate cancers after for instance, radical prostatectomy, is most probably excellent, such trials would also have to have an emphasis on the quality of life of treated and followed patients. Before we start with such a randomized trial, however, we have to be able to accurately and individually predict prostate cancer characteristics before treatment. At the moment we are not capable to predict tumor characteristics accurately enough, and the development of new and highly sensitive

imaging techniques or serum markers would be necessary to enhance the detection and the pretreatment characterization of prostate cancer in a way that would suit these purposes. New revolutionary methods for prostate cancer treatment with a minimum of adverse side-effects may catch up with these efforts and render them less important. Until such diagnostic or therapeutic improvements are developed, however, we have to keep trying to detect and treat prostate cancer at a stage where it is curable.

- *Is a screening interval of four years the optimal interval for prostate cancer screening?*
  Although the studies in this thesis suggest that screening for prostate cancer with a four-year interval does not lead to an increase of prostate cancer with adverse prognostic features, this does not by itself prove that a four year interval is optimal for prostate cancer screening. The fact that serum PSA levels in the second round do no longer predict for the frequency and the amount of prostate cancer at biopsy is slightly worrisome. It even poses questions as to whether the use of a threshold value for serum PSA levels during the second screening round is recommendable and whether even longer intervals would be more cost-effective. Questions about the optimal interval length of prostate cancer screening can probably only be answered by comparing prostate cancer characteristics of second-round tumors with tumors detected at subsequent screening rounds.

- *Do the studies in this thesis provide evidence for a benefit of systematic screening for prostate cancer?*
  No. It is important to note that, while the studies in this thesis without exception indicate favorable changes in the characteristics of early detected prostate cancer, they provide no conclusive evidence for an overall beneficial effect of screening for prostate cancer in the screened participants of the ERSPC. Some of the participants may benefit from screening, but others may suffer from it. Conclusive evidence will depend on comparisons of the screened and control populations in the ERSPC, not only on prostate cancer related and overall mortality, but also on quality of life. These overall results of the ERSPC study are not expected until 2008. While it remains unclear what kind of care we should offer a man of 55 years or older, it seems

sensible and ethically sound to continue to respectively screen or follow-up the men in both arms of the ERSPC.

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SAMENVATTING EN CONCLUSIES

1. Inleiding

Prostaatcarcinoom vormt een steeds belangrijker probleem in de volksgezondheid. In de Verenigde Staten is prostaatcarcinoom na longkanker de tweede oncologische doodsoorzaak[1]. Aangezien de sterfte aan longkanker begint af te nemen en de gemiddelde levensverwachting stijgt, lijkt het onvermijdelijk dat prostaatcarcinoom in de nabije toekomst de voornaamste oncologische doodsoorzaak bij mannen gaat worden. De belangrijkste aanleidingen voor pogingen om prostaatcarcinoom in een vroeg stadium op te sporen worden gevormd door de relatief hoge frequentie van recidief carcinoom na behandeling met een initieel curatieve opzet[2,3] en de problemen rond het klinische beleid bij verder gevorderd prostaatcarcinoom. Daarom wordt in de Verenigde Staten sinds 1993 aan alle mannen boven de 50 jaar een jaarlijkse screening met serum PSA metingen aanbevolen[4].

De veranderingen in de incidentie en mortaliteit van prostaatcarcinoom, die recent volgens de gegevens van het "Surveillance, Epidemiology and End Results (SEER)" programma werden waargenomen[5-7], lijken aan te geven, dat bevolkingsonderzoek tot een lagere mortaliteit ten gevolge van prostaatcarcinoom leidt. Toch kunnen deze resultaten vertekend worden door twee belangrijke factoren. Omdat het zich laat aanzien dat prostaatcarcinoom zonder screening in een later stadium zou worden gevonden, lijkt de levensverwachting bij gescreende mannen met prostaatcarcinoom toe te nemen, terwijl dit in werkelijkheid niet zo is (lead time bias). Verder ligt het in de verwachting, dat bevolkingsonderzoek op prostaatcarcinoom zou kunnen leiden tot de detectie van tumoren die zonder screening niet gevonden zouden worden, en die geen bedreiging vormen voor de gezondheid van de patiënt. Een toegenomen detectie van dergelijke tumoren zou kunnen leiden tot een betere prognose voor gescreende prostaatcarcinoompatiënten, terwijl de prognose in werkelijkheid niet verbeterd is (length time bias). Omdat de prevalentie van "latent" prostaatcarcinoom, dat incidenteel gevonden wordt bij obductie en waarvan de klinische relevantie zeer beperkt lijkt, volgens studies zeer hoog is (in de orde van 30% tot 50% bij mannen boven de 50 jaar oud)[8-10], lijkt vooral deze *length time bias* de resultaten van screening voor prostaatcarcinoom te vertekenen. Daarom is de vraag of bevolkingsonderzoek op prostaatcarcinoom gunstig is voor de mannelijke bevolking *at risk*, het onderwerp van veel discussie[11-13]. De enige manier om een

eventueel gunstig effect van bevolkingsonderzoek op prostaatcarcinoom aan te tonen, is het verrichten van een gerandomiseerd onderzoek waarbij mannen worden verdeeld in groepen met en zonder systematische screening[14]. Gerandomiseerde onderzoeken naar de effecten van systematische screening op prostaatcarcinoom op mortaliteit en kwaliteit van leven worden thans verricht, maar de eerste resultaten zullen niet voor 2008 bekend zijn[15,16].

De studies in dit proefschrift beschrijven de histologische karakteristieken van prostaatcarcinoom en premaligne laesies, welke werden gevonden in de algemene mannelijke bevolking bij systematische periodieke screening. De studies werden verricht om de volgende vragen te beantwoorden:

- Zijn de aantallen biopten en herhalingsbiopten verricht bij bevolkingsonderzoek op prostaatcarcinoom acceptabel?
- Wat zijn de karakteristieken van de tumoren die werden gevonden bij bevolkingsonderzoek op prostaatcarcinoom? Is er een tendens naar een betere prognose na behandeling bij gescreende mannen met prostaatcarcinoom?
- Hoe zit het met het klinisch belang van de bij screening gevonden tumoren? Is er een toename van klinisch onbelangrijke tumoren?
- Wat gebeurt er bij opeenvolgende screeningsronden? Zijn er aanwijzingen dat een interval van vier jaar tussen opeenvolgende screeningsronden te lang is? Zijn er aanwijzingen dat in de tweede ronde meer klinisch onbelangrijke tumoren worden gevonden?

2. Prostaatbiopten in de algemene mannelijke bevolking

Bij de definitieve diagnose van prostaatcarcinoom is het verkrijgen en het onderzoeken van prostaatbiopten noodzakelijk. Een eerdere studie in de European Randomized Study of Screening for Prostate Cancer (ERSPC) door Rietbergen et al. [17] toonde aan, dat het afnemen van sextant naaldbiopten uit de prostaat een relatief veilige procedure is. Ofschoon kleine complicaties, zoals kortdurende hematurie en hematospermie vrij vaak voorkomen (respectievelijk in 24% en 45% van de gebiopteerde mannen), zijn belangrijke

complicaties zoals sepsis met ziekenhuisopname infrequent (ongeveer in 0.4% van de gebiopteerde mannen). Hoofdstuk 3 van dit proefschrift laat zien, dat ongeveer één op de vijf gescreende mannen een bioptindicatie heeft, en dat bij ongeveer één op de vijf gebiopteerde mannen de diagnose prostaatcarcinoom wordt gesteld.
Systematische sextantbiopten zijn niet specifiek gericht op palpabele of echografisch zichtbare afwijkingen in de prostaat. In het geval van een verhoogd serum PSA gehalte als enige indicatie voor biopsie (d.w.z. wanneer rectaal toucher en echografisch onderzoek niet afwijkend zijn), worden biopten uit de prostaat per definitie blind afgenomen. Het moge duidelijk zijn, dat niet elk prostaatcarcinoom wordt gevonden bij screening, aangezien de detectiefrequentie van prostaatcarcinoom in de algemene populatie (ongeveer 5%) in vergelijking tot de hoge prevalentie van latent prostaatcarcinoom (30% tot 50%), laag is. Eerdere studies toonden reeds aan, dat latente - en waarschijnlijk vaak klinisch irrelevante - prostaatcarcinomen meestal zeer klein zijn[9] en dat dergelijke tumoren bij bevolkingsonderzoek vaker gemist zullen worden dan klinisch relevante tumoren, die meestal groter zijn. De sensitiviteit van blinde sextant naaldbiopten voor het bepalen van de aanwezigheid van prostaatcarcinoom is daarom laag, terwijl de sensitiviteit voor de detectie van klinisch relevant prostaatcarcinoom veel hoger is.

2.1. Indicaties voor herhalingsbiopten

Sommige afwijkingen in prostaatbiopten vormen een indicatie voor herhalingsbiopten. Hooggradige Prostaat Intraepitheliale Neoplasie (PIN) wordt beschouwd als de meest waarschijnlijke premaligne variant van prostaatcarcinoom en de detectie van hooggradige PIN vormt een indicatie voor herhalingsbiopten om prostaatcarcinoom uit te sluiten. De aanwezigheid van hooggradige PIN kan duiden op latere ontwikkeling van prostaatcarcinoom op de plaats van de laesie of op een prostaatcarcinoom, dat elders in de prostaat aanwezig is.
In prostaatnaaldbiopten zijn bij sommige afwijkingen onvoldoende criteria voor een definitieve diagnose aanwezig. In dergelijke gevallen zou eventueel sprake kunnen zijn van prostaatcarcinoom, maar er is - veelal door het ontbreken van voldoende tumorweefsel in het biopt - onvoldoende bewijs om de laesie definitief als benigne of maligne te duiden (zie Hoofdstuk 1, paragraaf 2.5.3 *The histologic diagnosis of prostate cancer*). Bij dergelijke laesies zijn herhalingsbiopten geïndiceerd om meer weefsel te

verkrijgen, teneinde een definitieve uitspraak over de al dan niet maligne achtergrond mogelijk te maken. Bostwick et al. beschreven dergelijke laesies oorspronkelijk als "suspicious for, but not diagnostic of prostate cancer"[18]. Later stelde zijn groep de term "Atypical Small Acinar Proliferations (ASAP)"voor[19,20]. Laatstgenoemde term kan worden beschouwd als een pakkend acroniem, omdat de afkorting in de Verenigde Staten eveneens bekend staat als "zo snel mogelijk" ("As Soon As Possible") en omdat dit de voorgestelde snelheid zou zijn waarmee biopten zouden dienen te worden herhaald. Een grote variëteit van soms moeilijk te classificeren afwijkingen, zoals atrofie, post-atrofische hyperplasie[21], atypische adenomateuze hyperplasie[22], atypische basaalcelhyperplasie[23] en paraganglia[24], kan in het prostaatnaaldbiopt verdacht zijn voor prostaatcarcinoom. Het gebruik van de term ASAP is verwarrend, omdat de suggestie gewekt wordt, dat afwijkingen verdacht voor prostaatcarcinoom een morfologische entiteit zouden vormen, terwijl zij juist een zeer heterogene groep van verschillende laesies zijn. Daarom hebben wij in hoofdstuk 3 van dit proefschrift de term "borderline laesies" geïntroduceerd om dergelijke laesies aan te duiden.

Al met al zijn de aanwezigheid van hooggradige PIN of borderline laesies thans indicaties voor het verrichten van herhalingsbiopten om de aanwezigheid van prostaatcarcinoom uit te sluiten. Omdat de reden van de herhalingsbiopten bij deze twee groepen van laesies verschilt, verschilt ook de manier van het nemen van herhalingsbiopten. Bij de aanwezigheid van hooggradige PIN in het naaldbiopt zijn herhalingssextantbiopten geïndiceerd, omdat er een kans is op een tegelijkertijd aanwezig zijn van prostaatcarcinoom op de plaats van de hooggradige PIN of elders in de prostaat, als het gevolg van een carcinogeen "veld-effect" [25-27]. Bij borderline laesies op het prostaatbiopt bestaat er de noodzaak om de aard van de laesie zelf duidelijk te maken. Het verkrijgen van meer weefsel van de plaats van de afwijking is bij dergelijke laesies van belang en daarom dienen in dit geval herhalingsbiopten op de plaats van de initiële laesie gericht te zijn.

2.2 Herhalingsbiopten: frequentie en diagnoses

De in de literatuur vermelde frequenties van prostaatcarcinoom bij herhalingsbiopten voor hooggradige PIN en borderline laesies variëren aanzienlijk. Hoofdstuk 3 van dit proefschrift laat zien, dat geïsoleerde hooggradige PIN (in afwezigheid van

prostaatcarcinoom) gediagnosticeerd wordt in 0.7% van de prostaat naaldbiopten van de algemene gescreende populatie, terwijl de frequentie in de literatuur varieert van 1% tot 15%. Bij het reviseren van prostaatnaaldbiopten door een in de urologische pathologie gespecialiseerde patholoog werd een additionele 1% geïsoleerde hooggradige PIN gevonden. Een verdubbelde frequentie van hooggradige PIN na revisie werd eerder in de literatuur gerapporteerd[28]. Blijkbaar wordt ongeveer de helft van alle hooggradige PIN-laesies gemist door algemene pathologen. Behalve een verschil in de bestudeerde populatie, kan derhalve ook een verschil in diagnostische expertise het grote verschil in de gerapporteerde frequenties van hooggradige PIN in de literatuur verklaren. Het zich beter bewust zijn van de diagnostische criteria van hooggradige PIN (bijvoorbeeld door beter onderwijs, een lage drempel voor consultatie van experts of meer en betere referentieplaatjes) is nodig om deze vermeende voorloper van prostaatcarcinoom accurater te herkennen en te diagnosticeren.

Hoofdstuk 3 laat zien, dat in 75% van de gevallen hooggradige PIN tegelijkertijd voorkomt met prostaatcarcinoom elders in de sextantbiopten. In de studie in hoofdstuk 3 leidden herhalingsbiopten voor de overige 25% niet tot de ontdekking van prostaatcarcinoom. Latere studies in de ERSPC hebben inmiddels echter aangetoond, dat prostaatcarcinoom wordt gevonden in 10% van de herhalingsbiopten (3 van 30 mannen) voor hooggradige PIN, een getal dat min of meer gelijk is aan de frequentie van prostaatcarcinoom in herhalingsbiopten bij een initieel benigne biopt[29]. De frequentie van prostaatcarcinoom in herhalingsbiopten na hooggradige PIN is opvallende laag vergeleken met de in de literatuur vermelde frequenties (variërend van 28% tot 100%)[26,27,30-34]. Een mogelijke verklaring voor dit gegeven is dat de meeste prostaatcarcinomen reeds werden gevonden bij het initiële naaldbiopt.

Bij 2.4% van de gebiopteerde deelnemers werden borderline laesies gevonden. Bij 39% van de herhalingsbiopten voor deze laesies werd de definitieve diagnose prostaatcarcinoom gesteld. Blijkbaar is de frequentie van prostaatcarcinoom bij herhalingsbiopten voor borderline laesies veel hoger dan bij herhalingsbiopten voor hooggradige PIN, een bevinding die werd bevestigd door latere studies in de ERSPC[29]. Indicaties voor herhalingsbiopten, zoals hooggradige PIN en borderline laesies bij naaldbiopten van gescreende mannen, vormen slechts een zeer klein percentage van de gestelde diagnoses bij bevolkingsonderzoek. Dit is van groot belang, omdat een te hoge frequentie van herhalingsbiopten zou leiden tot te hoge kosten en een te hoge belasting

van mannen die gescreend worden voor prostaatcarcinoom. Het absolute aantal additionele prostaatcarcinomen dat bij bevolkingsonderzoek gedetecteerd wordt door herhalingsbiopten te verrichten voor hooggradige PIN en borderline laesies is beperkt. Om het klinisch belang van deze additioneel gevonden tumoren te bepalen is langdurige follow-up nodig.

3. Het klinisch belang van gedetecteerde en behandelde carcinomen

3.1. De categorisatie van tumoren

Het klinisch belang van prostaatcarcinoom hangt af van een combinatie van tumorkarakteristieken, de leeftijd en de levensverwachting van de patiënt. Voor de biochemische terugval (een stijgend PSA gehalte in het serum) na initieel curatieve behandeling hebben het stadium en de graad van prostaatcarcinoom een onafhankelijke voorspellende waarde[35]. Daarom hebben zowel grote goed gedifferentieerde als kleine slecht gedifferentieerde prostaatcarcinomen een slechte prognose. Om het klinisch belang van de gedetecteerde tumoren in de ERSPC in te schatten, maakten wij een arbitrair model voor tumoren gevonden bij radicale prostatectomie (Hoofdstuk 4). Dit model is gebaseerd op combinaties van de uitgebreidheid en de graad van de tumor en is deels afgeleid van modellen uit eerdere studies[36,37].
In ons model maken wij globaal onderscheid tussen minimaal, matig uitgebreid en geavanceerd carcinoom. Op het moment dat wij het model opstelden, bestond onvoldoende follow-up om de voorspellende waarde voor het klinisch beloop te toetsen. Een latere studie uitgevoerd door Vis et al. heeft inmiddels echter de prognostische waarde van ons model voor biochemische (PSA) terugval bevestigd[38]. Het correct voorspellen van het klinische beloop van prostaatcarcinoom na curatieve behandeling is echter niet noodzakelijkerwijs representatief voor het biologisch gedrag van de behandelde tumoren. In hoofdstuk 4 stelden wij dat patiënten met tumoren die voldoen aan onze definitie van matig uitgebreid carcinoom waarschijnlijk de meeste baat hebben bij behandeling door radicale prostatectomie. Wij stelden ook, dat patiënten met geavanceerd carcinoom de grootste kans hebben op terugkeer van prostaatcarcinoom na therapie met curatieve intentie. De patiënten met minimaal carcinoom worden verwacht

de meest gunstige prognose te hebben, ofschoon deze groep ook de grootste kans heeft een prostaatcarcinoom te hebben gehad, dat nooit tot ziekte of dood zou hebben geleid als behandeling niet had plaatsgevonden. Deze veronderstellingen sluiten echter niet uit, dat een groot deel van de patiënten met tumoren met kenmerken van geavanceerd prostaatcarcinoom genezen zal blijken te zijn. Zij sluiten ook niet uit, dat een niet onaanzienlijk deel van de minimale tumoren een agressief gedrag zou hebben vertoond bij uitblijven van behandeling. Ons categorisatiemodel voor het klinisch belang van prostaatcarcinoom dient daarom met deze overwegingen in gedachte te worden beschouwd.

3.2 De pathologische karakteristieken van gedetecteerde en behandelde tumoren

De gegevens van hoofdstuk 4 tonen aan, dat ongeveer 80% van de prostaatcarcinomen gevonden bij screening en behandeld door radicale prostatectomie voldoet aan de criteria voor matig uitgebreid of geavanceerd carcinoom in ons categorisatiemodel. De overige 20% voldoet aan de criteria van minimaal carcinoom. Deze getallen worden bevestigd door de latere studie in hoofdstuk 6, waarin een groter aantal radicale prostatectomiepreparaten werd bestudeerd. De meerderheid van de behandelde prostaatcarcinomen gevonden bij screening lijkt dus pathologische karakteristieken te hebben, die wijzen op klinische relevantie.

3.2.1. De relatie tussen pathologische karakteristieken en detectiemethoden

De studie in hoofdstuk 4 beschrijft de karakteristieken van door screening gedetecteerde tumoren in deelnemers aan de ERSPC. De pathologische karakteristieken werden vergeleken met de detectiemethoden (een abnormale bevinding bij rectaal toucher of echografisch onderzoek, of een serum PSA gehalte van 4ng/mL of hoger). De nadruk werd gelegd op prostaatcarcinomen die werden gevonden met een verhoogd serum PSA gehalte als enig criterium voor biopsie. De detectie van dergelijke tumoren heeft in het verleden tot bezorgdheid geleid, omdat hun klinische relevantie onduidelijk was. De gegevens in hoofdstuk 4 tonen aan dat de fractie niet-palpabele en echografisch onzichtbare (T1c-) tumoren gevonden in de gescreende populatie aanzienlijk is. Niet minder dan 33% van alle radicale prostatectomieën en 46% van radicale prostatectomieën voor tumoren met een verhoogd PSA gehalte wordt verricht in patiënten met T1c

tumoren. In ons arbitraire model voldoet bijna 90% van de T1c-tumoren aan de criteria voor matig uitgebreid of geavanceerd carcinoom. Toch zijn zij gemiddeld kleiner en hebben een lager stadium dan tumoren, die worden gevonden bij een verhoogd serum PSA gehalte in combinatie met een afwijkend rectaal toucher of echografisch onderzoek. Gezien de onafhankelijke prognostische waarde van het pathologisch stadium[2,39], zou men verwachten dat de klinische uitkomsten op lange termijn voor mannen met T1c tumoren gunstig zijn vergeleken met mannen met niet-T1c tumoren en een verhoogd serum PSA gehalte. Een recent onderzoek met beperkte follow-up, waarin mannen met T1c tumoren een betere prognose lijken te hebben dan mannen met niet-T1c-tumoren met vergelijkbare serum PSA gehaltes, lijkt deze hypothese te bevestigen[40]. Voor het reduceren van prostaatcarcinoom-gerelateerde sterfte bij bevolkingsonderzoek lijkt het detecteren van niet-palpabele en echografisch onzichtbare prostaatcarcinomen bij een verhoogd serum PSA gehalte derhalve van groot belang.

De karakteristieken van tumoren die gedetecteerd worden naar aanleiding van een afwijkend rectaal toucher of echografisch onderzoek in patiënten met een serum PSA lager dan 4 ng/mL leiden tot enige bezorgdheid. In deze groep worden de kleinste tumoren met de laagste pathologische stadia gevonden, en 43% voldoet aan de criteria van minimaal carcinoom in ons categorisatiemodel. De vaak kleine afmetingen van deze tumoren doet vermoeden dat velen bij toeval werden ontdekt (en dus dat de uitkomsten van het echografisch onderzoek en het rectaal toucher in feite niet klopten). De waarde van het rectaal toucher bij de detectie van prostaatcarcinoom in mannen met lage PSA waarden is het onderwerp geweest van verschillende studies in de gescreende populatie van de ERSPC. Zonder uitzondering bleek de waarde van rectaal toucher bij lage PSA-waarden beperkt[41-43]. Gezien de resultaten van deze studies werd de screeningsprocedure aangepast door geen biopsie meer te verrichten bij PSA-waarden lager dan 3 ng/mL[42-44]. In het nieuwe protocol is serum PSA-gehalte de enige parameter voor het stellen van een biopsie-indicatie. Voorlopige evaluaties van het nieuwe screeningsprotocol tonen aan dat deze veranderingen hebben geleid tot een verbetering in de positieve voorspellende waarde voor de aanwezigheid van prostaatcarcinoom, terwijl de detectiefrequentie en de tumor karakteristieken vrijwel onveranderd blijven[45].

3.2.2. Veranderingen in het tumor stadium van vroeg gedetecteerd en behandeld prostaatcarcinoom

Verschillende studies in de literatuur hebben een aanzienlijke toename van het aantal verrichte prostatectomieën aangetoond sinds de introductie van PSA voor de detectie van prostaatcarcinoom[46-48].

Zoals de resultaten van hoofdstuk 4 aangeven, is de toegenomen frequentie van behandeling met curatieve intentie hoogstwaarschijnlijk het gevolg van de detectie van niet-palpabele tumoren, hetgeen lijkt te leiden tot een hoger aantal tumoren die klinisch tot de prostaat beperkt lijken. Of er veranderingen zijn opgetreden in volume, stadium en graad van tumoren die behandeld werden met radicale prostatectomie is minder duidelijk omdat de literatuur hierover tegenstrijdige resultaten toont[47,49].

De studie in hoofdstuk 5 werd verricht om te zien of de karakteristieken van vroeg gedetecteerde en behandelde prostaatcarcinomen in gescreende deelnemers van de ERSPC gunstiger waren vergeleken met carcinomen bij niet-gescreende mannen. Op dit moment is het aantal radicale prostatectomieën verricht in deelnemers in de controle-arm van de ERSPC nog gering. Daarom werden de karakteristieken van de behandelde prostaatcarcinomen in gescreende deelnemers vergeleken met een historische serie van radicale prostatectomiepreparaten verkregen in de periode voor de introductie van serum PSA metingen en screening. Een nadeel van een dergelijke vergelijking is dat niet gecorrigeerd kan worden voor verschillen in preoperatieve selectiecriteria.

De resultaten van hoofdstuk 5 laten zien dat vroege opsporing van prostaatcarcinoom door systematische screening aanleiding lijkt te hebben gegeven tot een daling in pathologisch stadium en graad op het moment van operatie, en dat relatief meer kleine tumoren worden behandeld. Het meest opvallende resultaat was het ontbreken van positieve pelviene lymfklieren in de gescreende groep, terwijl lymfkliermetastasen een reden waren geen radicale prostatectomie te verrichten in 18% van patiënten uit de historische groep. Deze bevindingen komen overeen met de resultaten van een eerdere studie waaruit bleek dat metastasen bij vroeg gedetecteerde carcinomen in de ERSPC aanzienlijk minder vaak voorkwamen dan in een serie van incidenteel gedetecteerde prostaatcarcinomen in de regio Amsterdam tussen 1989 en 1994[50].

3.2.3. Histologische graad: heterogeniteit en multifocaliteit

De resultaten van hoofdstuk 5 laten zien dat de lagere histologische graad van vroeg

gedetecteerde prostaatcarcinomen voornamelijk het gevolg is van een afgenomen aantal tumoren met hoge Gleason scores (Gleason score 8 t/m 10). Gebieden met hooggradig carcinoom (Gleason patroon 4 of 5) worden echter gevonden in 60% van de vroeg gedetecteerde carcinomen, hetgeen een hoog percentage is. Een gedetailleerde studie van radicale prostatectomiepreparaten van gescreende deelnemers uit de ERSPC laat zien dat het merendeel (67%) meer dan één tumor bevat. Helaas waren gegevens over tumormultifocaliteit in de historische serie niet beschikbaar. Het relatief hoge aantal multifocale tumoren in de gescreende groep doet vermoeden dat prostaatcarcinoom op verschillende plaatsen tegelijkertijd ontstaat als gevolg van een carcinogeen "veldeffect". Bovendien bestond een meerderheid van de histologisch circumscripte tumorgebieden uit velden met verschillen in histologische graad (*intra-tumor* heterogeniteit). Een deel van de tumorgebieden met intra-tumor heterogeniteit is mogelijk ontstaan door het botsen van afzonderlijke tumoren met verschillende histologische graad (zogenaamde "collision tumors"). Het feit dat gebieden met hooggradig carcinoom meestal worden gevonden in het centrum van grotere gebieden met goed gedifferentieerd carcinoom impliceert dat het grootste deel van de gebieden met hooggradig carcinoom ontstaat door dedifferentiatie. De lagere histologische graad die gezien wordt bij carcinomen gevonden bij bevolkingsonderzoek lijkt niet het resultaat te zijn van een lagere frequentie van gebieden met dedifferentiatie, maar lijkt eerder het gevolg van een afname van het relatieve volume hooggradig carcinoom in heterogene en multifocale tumoren. Met andere woorden: de frequentie van hooggradig carcinoom is niet afgenomen in vroeg gedetecteerd prostaatcarcinoom, maar de relatieve afmetingen van de gebieden met hooggradig carcinoom wel. De directe correlatie tussen de relatieve hoeveelheid hooggradig carcinoom in een tumor met het volume van die tumor ondersteunt de dedifferentiatie-hypothese. Waarschijnlijk wordt tumorprogressie geïnitieerd door een klein focus met dedifferentiatie dat, doordat het een groeivoordeel heeft ten opzichte van de omgevende gebieden, relatief sneller zal groeien en aanleiding zal geven tot relatief grotere proporties hooggradig carcinoom. In de toekomst zal onderzoek dat DNA aberraties tussen histologisch verschillende gebieden in één tumor vergelijkt, moeten uitwijzen of de dedifferentiatietheorie juist is.

De hoge frequentie van focale dedifferentiatie in vroeg gedetecteerde prostaatcarcinomen kan leiden tot vermindering van de prognostische waarde van de huidige graderingssystemen. Het merendeel van de huidige graderingssystemen is niet sensitief

genoeg om focale dedifferentiatie aan te geven. In het Gleason scoringssysteem worden secundaire groeipatronen slechts geïncludeerd indien zij meer dan 5% van de totale tumor uitmaken. Wanneer twee verschillende groeipatronen van goed gedifferentieerd prostaatcarcinoom reeds aanwezig zijn, is het niet duidelijk hoe een kleine hoeveelheid slecht gedifferentieerd carcinoom in het scoringssysteem kan worden aangegeven. Dit zou betekenen dat tumoren die focaal dedifferentiatie tonen in dezelfde categorie eindigen als geheel goed gedifferentieerde carcinomen. De verandering in de karakteristieken van prostaatcarcinoom door vroege detectie zou uiteindelijk kunnen leiden tot heroverweging en mogelijke revisie van de huidige graderingssytemen. Recente studies hebben gepleit voor het aangeven van de relatieve hoeveelheid hooggradig carcinoom omdat dit gegeven een goede prognostische waarde blijkt te hebben, mogelijk zelfs beter dan die van het Gleason scoringssysteem[51,52].

3.3 Het klinisch belang en de preoperatieve voorspelling van minimaal carcinoom

Zoals reeds werd beschreven in hoofdstuk 1, brengt systematische screening voor prostaatcarcinoom het risico van het vinden van een groot aantal klinisch onbelangrijke tumoren (tumoren die geen gevaar zullen gaan vormen voor de gezondheid van de patiënt) met zich mee. Het doel van een bevolkingsonderzoek is tumoren in een vroeg stadium op te sporen en te behandelen om zo de prognose en de levensverwachting van de gescreende bevolkingsgroep te verbeteren. De frequentie waarmee veelal kleine en goed gedifferentieerde prostaatcarcinomen incidenteel (bij obductie of na operatie voor blaascarcinoom) worden aangetroffen, is echter zeer hoog[8-10]. Een toegenomen detectie van klinisch onbelangrijke tumoren zou kunnen leiden tot een verhoogde frequentie van eigenlijk onnodige behandelingen met de daaraan gekoppelde iatrogene schade en complicaties. De laatste tijd is veel wetenschappelijk onderzoek verricht om te proberen de klinisch belangrijke tumoren te onderscheiden van de klinisch onbelangrijke tumoren, of, zoals zij in de literatuur wel worden aangeduid, de "tijgers" van de "poezen" [53]. De belangrijkste kenmerken die zijn voorgesteld voor het inschatten van het klinisch belang van prostaatcarcinoom zijn tumorvolume[54] en tumorverdubbelingstijden[55]. Het is echter waarschijnlijk, dat een onderscheid dat alleen gebaseerd is op tumorkenmerken, te beperkt is, omdat tijgers en de poezen hoogstwaarschijnlijk de uitersten vormen van een breed en continu spectrum van tumoren. Bovendien spelen kenmerken van de patiënt zelf, zoals

levensverwachting en co-morbiditeit, een cruciale rol in het bepalen van het klinisch belang van zijn prostaatcarcinoom[56].

Het arbitraire model, dat werd voorgesteld in hoofdstuk 4, verdeelt vroeg gedetecteerde tumoren in categorieën van minimaal, matig uitgebreid en geavanceerd carcinoom. De resultaten van de studies in hoofdstuk 4 en 6 laten zien, dat het percentage minimaal carcinoom (een kleine haard goed gedifferentieerd carcinoom bij radicale prostatectomie) in behandelde deelnemers uit de screeningsarm van de ERSPC rond de 20% ligt. Mannen met minmaal carcinoom bij radicale prostatectomie blijken een uitstekende prognose te hebben[38]. Toch is deze bevinding niet voldoende om een meer afwachtende houding tegenover patiënten met dergelijke tumoren te rechtvaardigen. Hoewel de categorie minimaal carcinoom in ons model waarschijnlijk klinisch onbelangrijke tumoren herbergt, bestaat de mogelijkheid dat sommige tumoren uit deze categorie de capaciteit hebben levensbedreigend te worden door een toegenomen groeisnelheid en dedifferentiatie. Met andere woorden, onze kennis over het biologisch gedrag van tumoren in de categorie van minimaal carcinoom is onvoldoende voor een voorspelling hoe deze tumoren zich zouden hebben gedragen zonder chirurgische behandeling.

Histologisch gezien vormen prostaatcarcinomen met de kenmerken van minimaal carcinoom in ons model een relatief homogene groep. Per definitie bestaan zij uit een enkel klein focus goed gedifferentieerd carcinoom (meestal Gleason groeipatroon 3). Een recente studie naar DNA-afwijkingen in tumoren die werden gevonden in de screeningsarm van de Rotterdamse sectie van de ERSPC toont echter aan, dat een niet onaanzienlijk deel van de minimale carcinomen DNA-afwijkingen heeft, die passen bij tumoren met een agressief klinisch beloop[57].

Een goede besluitvorming over welke tumoren behandeling behoeven en welke met een meer afwachtende houding kunnen worden benaderd, vergt additionele gerandomiseerde studies, die een directe behandeling met uitgestelde behandeling in patiënten met minimaal prostaatcarcinoom vergelijkt. Het uitvoeren van dergelijke studies hangt echter af van een betrouwbare methode voor de preoperatieve voorspelling van de aanwezigheid van minimaal prostaatcarcinoom.

In hoofdstuk 6 wordt onderzocht of de aanwezigheid van minimaal carcinoom betrouwbaar kan worden voorspeld met een combinatie van klinische parameters. De resultaten laten zien, dat de voorspellende waarde van de aanwezigheid van een kleine hoeveelheid goed gedifferentieerd carcinoom in het naaldbiopt beperkt is, omdat bijna de

helft van patiënten met een kleine hoeveelheid goed gedifferentieerd carcinoom in het naaldbiopt matig uitgebreid of zelfs geavanceerd carcinoom blijkt te hebben bij radicale prostatectomie. Het meewegen van het preoperatieve serum PSA gehalte verbetert de voorspellende waarde voor de karakteristieken van carcinoom in de prostaat, aangezien meer dan 90% van de mannen met een kleine haard goed gedifferentieerd carcinoom in het naaldbiopt en een serum PSA gehalte onder de 4 ng/mL minimaal carcinoom blijkt te hebben, terwijl bijna 70% van de mannen met gelijksoortige biopten en een PSA gehalte boven de 4 ng/mL matig uitgebreid of geavanceerd carcinoom hebben. Hoewel deze resultaten suggereren dat het mogelijk is de aanwezigheid van minimaal carcinoom in de prostaat te voorspellen met een combinatie van naaldbioptkarakteristieken en serum PSA gehalte, is het zeer de vraag of deze voorspellende waarde voldoende is om toe te passen op een individuele basis of voor het verrichten van gerandomiseerd onderzoek naar behandeling versus uitgestelde behandeling. Aan de andere kant laten de resultaten van hoofdstuk 6 namelijk zien, dat een kleine haard goed gedifferentieerd carcinoom in het naaldbiopt niet dient te worden onderschat.

4. Periodiek bevolkingsonderzoek op prostaatcarcinoom: het screeningsinterval

De studies in hoofdstuk 3 tot en met 6 werden verricht op prostaatweefsel van gescreende deelnemers uit de eerste ronde (prevalentiescreen) van de ERSPC. Na een prevalentiescreen worden gescreende deelnemers iedere vier jaar opnieuw gescreend. In hoofdstuk 7 worden de tumorkarakteristieken in naaldbiopten uit de eerste twee screeningsronden vergeleken. De resultaten laten een aanzienlijke afname zien van zowel de hoeveelheid als de graad van de gevonden tumoren in de tweede screeningsronde, terwijl het aantal carcinomen dat incidenteel tussen beide screeningsronden werd gevonden, klein is. Er is derhalve geen bewijs, dat zelfs een relatief lang screeningsinterval van vier jaar leidt tot ongunstige veranderingen in de karakteristieken van de tumoren gevonden in volgende screeningsronden. Verder lijkt de detectiefrequentie van minimale tumoren constant te zijn. Het ten opzichte van de eerste ronde sterk gedaalde vermogen van het serum PSA om in de tweede screeningsronde de frequentie en de hoeveelheid carcinoom in naaldbiopten te voorspellen, getuigt van de

sterke invloed van de vier jaar eerder verrichte prevalentiescreen op de samenstelling van de populatie in de screeningsgroep. Het lijkt er sterk op dat, tijdens de prevalentiescreen, grote kankers die zich manifesteren met hoge serum PSA waarden effectief worden gedetecteerd. De groeisnelheid van prostaatcarcinoom lijkt in het algemeen laag te zijn, waardoor een screeningsinterval van vier jaar kort genoeg lijkt om de ontwikkeling van de meeste grote en gevaarlijke tumoren te beteugelen. De resultaten van hoofdstuk 7 staan in scherp contrast met de richtlijnen van de National Cancer Association in de Verenigde Staten, die sinds 1993 jaarlijkse screening voor prostaatcarcinoom adviseert aan mannen van 50 jaar en ouder[4]. Jaarlijkse screening voor prostaatcarcinoom zou de detectiefrequentie van prostaatcarcinoom kunnen verhogen, maar dit zou gepaard kunnen gaan met een verhoogd risico voor een toegenomen detectie van klinisch onbelangrijke tumoren, hetgeen onvermijdelijk leidt tot een toename van onnodige behandelingen. Behalve dat deze risico's beperkt zijn bij bevolkingsonderzoek op prostaatcarcinoom met langere screeningsintervallen, zou minder frequent screenen tot aanzienlijke kostenbesparingen in de gezondheidszorg leiden.

5. Conclusies and toekomstperspectieven: vragen, antwoorden en meer vragen

De studies in dit proefschrift onderzochten de histopathologische karakteristieken van prostaatcarcinoom gevonden bij bevolkingsonderzoek op mannen tussen de 55 en 75 jaar oud. Met de studies werd beoogd een aantal vragen, die eerder in dit hoofdstuk werden gesteld, te beantwoorden. Ik zal thans terugkomen op deze vragen en trachten ze kort te beantwoorden:

- *Zijn de aantallen biopten en herhalingsbiopten verricht bij bevolkingsonderzoek op prostaatcarcinoom acceptabel?*
  De studies in dit proefschrift tonen aan dat het protocol voor het nemen van biopten bij bevolkingsonderzoek op prostaatcarcinoom leidt tot een efficiënte detectie van klinisch relevante tumoren en dat de fysieke belasting voor gescreende deelnemers

niet te hoog is. Het aantal indicaties voor herhalingsbiopten is relatief laag vergeleken met verwezen en niet gescreende patiënten.

- *Wat zijn de karakteristieken van de tumoren die werden gevonden bij bevolkingsonderzoek op prostaatcarcinoom? Is er een tendens naar een betere prognose na behandeling bij gescreende mannen met prostaatcarcinoom?*
  De meeste tumoren die gevonden worden tijdens de eerste ronde (prevalentiescreen) hebben de karakteristieken van klinisch relevante tumoren die behandeling behoeven. Toch zijn de karakteristieken ten opzichte van conventioneel gedetecteerd prostaatcarcinoom gunstig. Daarom lijkt de prognose voor behandelde prostaatcarcinomen die door screening worden gevonden relatief gunstig.

- *Wat is het klinisch belang van de bij screening gevonden tumoren? Is er een toename van klinisch onbelangrijke tumoren?*
  De kleine en goed gedifferentieerde prostaatcarcinomen, die in dit proefschrift ook wel als minimaal carcinoom worden aangeduid, vormen de meest waarschijnlijke groep voor het bevatten van klinisch onbelangrijke tumoren. Gezien het relatief lage aantal minimale carcinomen dat werd gevonden in de eerste screeningsronde, lijkt bevolkingsonderzoek op prostaatcarcinoom niet te leiden tot een verontrustende toename van dergelijke minimale tumoren en daarmee tot een toename van vermoedelijk onnodige behandelingen voor klinisch onbelangrijke tumoren. Het klinisch belang van minimaal carcinoom is onduidelijk en hangt mede af van andere karakteristieken van de patiënt, zoals levensverwachting en co-morbiditeit.

- *Wat gebeurt er bij opeenvolgende screeningsronden? Zijn er aanwijzingen dat een interval van vier jaar tussen opeenvolgende screeningsronden te lang is? Zijn er aanwijzingen dat in de tweede ronde meer klinisch onbelangrijke tumoren worden gevonden?*
  De sterke afname van de hoeveelheid carcinoom en de graad van carcinoom in naaldbiopten uit de tweede screeningsronde duidt er samen met het lage aantal tumoren dat incidenteel buiten de screeningsronden wordt gevonden op, dat een interval van vier jaar kort genoeg is om de ontwikkeling van de meeste grote en

mogelijk gevaarlijke tumoren te beteugelen. Er is geen aanwijzing voor een toename van detectie van minimaal carcinoom in de tweede ronde.

Hoewel met de studies in dit proefschrift een aantal vragen kan worden beantwoord, blijven vragen bestaan, die alleen na verder onderzoek beantwoord kunnen worden. Bijvoorbeeld:

- *Hoe kunnen wij het klinisch belang van minimaal prostaatcarcinoom bepalen?*
  Dit wordt waarschijnlijk een belangrijk probleem bij het bevolkingsonderzoek op prostaatcarcinoom. De hoge prevalentie van – voornamelijk minimaal – prostaatcarcinoom in obductiestudies en de veel lagere detectiefrequentie van prostaatcarcinoom bij bevolkingsonderzoek duiden er op, dat het merendeel van deze kleine prostaatcarcinomen bij bevolkingsonderzoek niet wordt gevonden. De tumoren die wel ontdekt worden, worden waarschijnlijk min of meer bij toeval ontdekt. Om het klinisch belang van de wel gedetecteerde minimale prostaatcarcinomen te kunnen inschatten, zijn gerandomiseerde studies die een meer afwachtende houding bij deze tumoren vergelijken met de uitkomsten van curatieve behandeling nodig. Gegeven het feit, dat minimale carcinomen hoogstwaarschijnlijk een vrijwel vlekkeloze prognose hebben na curatieve therapie zoals radicale prostatectomie, zou bij dergelijke onderzoeken in het bijzonder gelet dienen te worden op de levenskwaliteit bij behandelde en niet behandelde patiënten. Voordat een dergelijk onderzoek plaats zou kunnen vinden, moeten wij in staat zijn om voordat behandeling plaatsvindt de tumorkarakteristieken prostaatcarcinoom accuraat en op individuele basis te voorspellen. Op dit moment zijn wij niet in staat om de karakteristieken van prostaatcarcinoom op een individuele basis te voorspellen, en de ontwikkeling van nieuwe sensitievere beeldvormdende technieken of serummarkers is waarschijnlijk nodig om de detectie en de klinische voorspelling van de karakteristieken van prostaatcarcinoom op het peil te kunnen brengen, waarmee dergelijke studies mogelijk zouden worden. De eventuele ontdekking van revolutionair nieuwe therapieën die het mogelijk maken om prostaatcarcinoom met minimale neveneffecten te behandelen zouden bovengenoemde ontwikkelingen overigens kunnen achterhalen, waardoor zij minder belangrijk worden. Totdat dergelijke nieuwe diagnostische of therapeutische ontwikkelingen ons verder kunnen helpen bij deze

problematiek rond minimaal prostaatcarcinoom, moeten wij blijven proberen om prostaatcarcinoom te behandelen in een stadium waarin het nog curabel is.

- *Is een screeningsinterval van vier jaar het optimale interval voor bevolkingsonderzoek op prostaatcarcinoom?*
  Hoewel de studies in dit proefschrift suggereren dat bevolkingsonderzoek met een screeningsinterval van vier jaar niet leidt tot een toename van prostaatcarcinomen met nadelige prognostische kenmerken, bewijst dit op zich niet dat vier jaar het optimale screeningsinterval is voor bevolkingsonderzoek op prostaatcarcinoom. Het feit dat serum PSA gehaltes in de tweede ronde geen voorspellende waarde meer hebben voor zowel de hoeveelheid als de frequentie van prostaatcarcinoom bij biopsie baart enige zorgen. Men zou zich bij een dergelijke bevinding af kunnen vragen of het gebruik van een drempelwaarde voor serum PSA nog wel verantwoord is, en of nog langere intervallen niet nog effectiever zouden kunnen zijn. Vragen over de optimale lengte van het screeningsinterval bij bevolkingsonderzoek op prostaatcarcinoom kunnen waarschijnlijk alleen worden beantwoord na het vergelijken van de karakteristieken van prostaatcarcinoom in de tweede ronde met die uit navolgende screeningsronden.

- *Leveren de studies in dit proefschrift bewijs voor het bestaan van een voordelig effect van bevolkingsonderzoek op prostaatcarcinoom?*
  Nee. Het is belangrijk om te realiseren dat, terwijl de studies in dit proefschrift duiden op gunstige veranderingen in de karakteristieken van prostaatcarcinoom na systematisch bevolkingsonderzoek, dit nog geen bewijs is voor een algemeen gunstig effect op de gescreende deelnemers van de ERSPC. Een deel van de deelnemers zou van screening kunnen profiteren, een ander deel zou er nadelige gevolgen van kunnen overhouden. Sluitend bewijs voor het bestaan van een algemeen gunstig effect van bevolkingsonderzoek op mortaliteit maar ook op kwaliteit van leven kan alleen worden geleverd door de gescreende populatie van de ERSPC te vergelijken met de controle-populatie. De eerste algemene resultaten van de ERSPC worden niet voor 2008 verwacht.

Nu het nog onduidelijk is welke zorg wij een man van 55 jaar of ouder zouden moeten bieden, lijkt het verstandig en ethisch verantwoord om door te gaan met het respectievelijk screenen of vervolgen van mannen in beide armen van de ERSPC.

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Curriculum vitae

Ik ben geboren op 26 november 1964 te Groningen. In 1983 behaalde ik het Gymnasium ß diploma aan het Praedinius Gymnasium te Groningen. Wegens uitloten voor de studie Geneeskunde startte ik in 1983 met de studie Informatica aan de Universiteit Groningen en in 1984 met de studie Geneeskunde aan de Rijksuniversiteit Gent in België. In 1986 heb ik de studie Geneeskunde voortgezet aan de Universiteit Leiden, waar ik in 1990 het doctoraalexamen haalde. Hierna liep ik stage obductie- en klinische pathologie bij de afdeling Pathologie van de Universiteit Leiden. Na het behalen van het artsexamen in 1992 verrichtte ik onderzoek naar de immunocytochemische fenotypering van mammacarcinoom en ovariumcarcinoom bij de afdeling Pathologie van de Universiteit Leiden. Van 1993 tot 1994 was ik werkzaam als AGNIO op de afdeling Gynaecologie in het Bronovo Ziekenhuis te 's-Gravenhage. Hierna werkte ik mee aan de ontwikkeling van een digitaal Beeld Informatie en Presentatie Systeem (BIPS), dat gerealiseerd werd vanuit een samenwerkingsverband tussen de afdelingen Pathologie, Gynaecologie en Informatica van de Universiteit Leiden.

In 1995 begon ik bij de afdeling Pathologie van de Erasmus Universiteit Rotterdam met het onderzoek dat de basis vormt voor dit proefschrift. Dit onderzoek vormt een onderdeel van een internationale studie naar de voor- en nadelen van bevolkingsonderzoek op prostaatkanker, de European Randomized study of Screening for Prostate Cancer (ERSPC). Mijn deelonderzoek werd begeleid door mijn promotoren Prof. Dr. Th.H. van der Kwast van de afdeling Pathologie en Prof. Dr. F.H. Schröder van de afdeling Urologie. Prof. Dr. Schröder is tevens de internationale coördinator van de ERSPC studie. Sinds 1998 ben ik in opleiding tot patholoog bij de afdeling Pathologie aan de Erasmus Universiteit Rotterdam; mijn opleiders zijn Prof. Dr. W.J. Mooi en Prof. Dr. Th.H. van der Kwast.

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