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PROSTATE CANCER.

CLINICAL IMPLICATIONS OF OBESITY

Joep Gerardus Henricus van Roermund
PROSTATE CANCER.

CLINICAL IMPLICATIONS OF OBESITY

Joep Gerardus Henricus van Roermund
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PROSTATE CANCER.

CLINICAL IMPLICATIONS OF OBESITY

Een wetenschappelijke proeve op het gebied van de Medische Wetenschappen

PROEFSCHRIFT

Ter verkrijging van de graad van doctor aan de Radboud Universiteit Nijmegen op gezag van de Rector Magnificus, prof. mr. S.C.J.J. Kortmann volgens besluit van het College van Decanen in het openbaar te verdedigen op vrijdag 25 juni 2010 om 13.00 uur precies

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26 juli 1979 21 februari 2010

Rosanne tijdens de verdediging op 15 januari 2009 van haar proefschrift getiteld "Between pathogenesis and treatment of psoriasis: a search for discriminating markers and therapeutic applications".

Aan mijn ouders
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Abbreviations

ADT androgen deprivation therapy
ASA American Society of Anaesthesiologists
ASTRO American Society for Therapeutic Radiology and Oncology
BCR biochemical recurrence
BPH benign prostatic hyperplasia
CaPSURE Cancer of the Prostate Strategic Urological Research Endeavor
CCCE Comprehensive Cancer Centre East
CI confidence interval
CSS cancer-specific survival
CT computed tomography
DES diethylstilbestrol
DRE digital rectal examination
EBRT external beam radiotherapy
HR hazard ratio
HRQOL health-related quality of life
HU Hounsfield Units
IGF insulin-like growth factor
IL-6 interleukin 6
IMRT intensity-modulated three-dimensional conformal radiotherapy
IQR Interquartile range
JNK c-Jun NH2-terminal kinase
OR odds ratio
OS overall survival
P13-K phosphatidylinositol 3-kinase
PC prostate cancer
PFD periprostatic fat density
PPB permanent prostate brachytherapy
PSA prostate-specific antigen
RP radical prostatectomy
RRP radical retropubic prostatectomy
SEARCH Shared Equal Access Regional Cancer Hospital
SHBG sex-hormone-binding globulin
TNF-α tumour necrosis factor α
TPF total periprostatic fat area
TRUS transrectal ultrasonography
VEGF vascular endothelial growth factor
VUS vesico-urethral strictures
<table>
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<tr>
<td>WC</td>
<td>waist circumference</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WHR</td>
<td>waist-to-hip ratio</td>
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General Introduction and Outline of the thesis
1.1 General Introduction

During the last decades prostate cancer has attracted an enormous attention in the field of scientific research as well as the non-professional press. The discovery of prostate-specific antigen (PSA), public prostate awareness and shifting population age distributions towards the elderly in many populations has prioritized prostate cancer research.

Prostate cancer is the most common human visceral malignancy and the second or third major cause of cancer death among men in the European Union. In 2007 more than 9,500 men were diagnosed with prostate cancer and more than 2,400 died of prostate cancer in the Netherlands. (www.ikcnet.nl, Association of Comprehensive Cancer Centers, the Netherlands) In many ways, prostate cancer is a natural part of the aging male. Autopsy studies show that men in the fourth decade of life have a one-third risk of harbouring small carcinomas. By the age of 60, this risk reaches approximately 60%. Numerous countries worldwide have shown similar rates of microscopical prostate cancer at autopsies. However, wide variations in clinically significant prostate cancer and prostate cancer death rates among these populations are seen. The lifetime risk of being diagnosed with prostate cancer now approaches 1 in 10 in the Netherlands.

Currently, the only established risk factors for prostate cancer are age, family history, race and a few dozens of low-penetrance genetic variants. Large geographic variation in prostate cancer incidence (with by far the highest rates in the USA and Canada) suggest that lifestyle factors related to westernization, are likely to be involved in the aetiology of prostate cancer. One particular lifestyle factor related to westernization is obesity.

Obesity is one of the most challenging and growing health problems in industrialized countries. It is now so widespread within the world’s population that it is beginning to replace malnutrition and infectious diseases as the most significant contributor to ill health. In the United States, over the last 20 years the prevalence of obesity among adults has doubled to 30%. Although obesity is less common in Europe, the prevalence has also more than doubled during the last two decades. See figure 1 for the prevalence of obesity in adults in Europe. According to Netherlands Statistics (Centraal Bureau voor de Statistiek, CBS, available at: http://statline.cbs.nl), in 2008 less than half of the Dutch adult men had a normal weight, 42% had overweight and 10% was obese. (figure 2)

What is obesity?

Obesity can be defined as a condition in which excess body fat has accumulated to such an extent that health may be adversely affected. There is a disbalance
between caloric intake and expenditure. Although genetic differences are important (as illustrated by the extremely high occurrence of obesity among Pima Indians in the USA), the marked rise in prevalence of obesity is best explained by behavioural and environmental changes. Body weight is determined by an interaction between genetic, environmental and psychosocial factors (figure 3). The transition from an active lifestyle during the teens and twenties to a more sedentary lifestyle thereafter is also associated with weight gain in many men. The distribution of body fat (visceral and nonvisceral, i.e. subcutaneous) is clinically important. Visceral central adiposity is associated with a greater risk of metabolic and cardiovascular disorders including insulin resistance, type 2 diabetes mellitus, hypertension and coronary heart disease, a combination of phenotypes known as the ‘metabolic syndrome’. Obesity is not a single disorder but a heterogeneous group of conditions with multiple causes.

How to measure obesity?
Currently there is no universally accepted method of measuring obesity. In clinical practice, body fat is most commonly and simply estimated by using a formula that standardizes weight by height. The underlying assumption is that most variation in

Figure 1 Prevalence of adult obesity in males. International Obesity Task Force.
(available at: http://www.iotf.org/media/europeadults.pdf)
Figure 2 Percentage of Dutch adult men who have overweight or are obese according to the Netherlands Statistics (CBS). (available at: http://statline.cbs.nl)

Figure 3 Factors influencing the development of obesity.
weight for persons of the same height is due to fat mass. By far the most widely used weight-for-height measure is the body mass index (BMI, also called Quetelet’s Index), which is defined as weight (in kilograms) divided by height (in metres squared).9 The World Health Organization (WHO) expert committee has proposed a classification of overweight and obesity.10 (table 1)

The main limitation of BMI is that it does not distinguish fat mass from lean mass. For example, BMI may overestimate the degree of obesity in individuals who are overweight but very muscular (professional athletes or bodybuilders). Another limitation is that the relationship between percent body fat and BMI is different among different ethnic groups. In some populations, the level of risk in terms of percent body fat is reached at a lower BMI (South Asians), and in others, at a higher BMI (blacks), compared to whites. However, population-specific cut-offs are not currently available, and therefore the WHO definition has been widely adopted. Despite these shortcomings, there is a close relationship between BMI and the incidence of several chronic conditions caused by excess fat.8

Other anthropometric measures commonly used in epidemiological studies to quantify obesity are the waist-to-hip ratio (WHR) and, more recently, waist circumference (WC). WHR and WC try to capture abdominal adipose tissue (or circumference) and fat distribution. The waist is defined as the abdominal circumference midway between the costal margin and the crest of the iliac. The largest circumference just below the iliac crest is defined as the hip. For men a WHR > 0.90 or WC ≥ 94 cm is a fairly accurate determination of an increased risk for obesity-related events.11 In patients with a BMI ≥ 35 kg/m2, measurement of waist circumference is less helpful since it adds little to the predictive power of the disease risk classification of BMI; almost all individuals with this BMI also have an abnormal waist circumference.

As mentioned before, obesity is associated with numerous conditions that include hypertension, high glucose levels, dyslipidemia, and central adiposity. This cluster of conditions refers to the metabolic syndrome.12 This metabolic syndrome is

<table>
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<th>Classification</th>
<th>BMI (kg/m²)</th>
<th>Risk of comorbidities</th>
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<tr>
<td>Normal</td>
<td>18.5-24.9</td>
<td>average</td>
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<tr>
<td>Overweight</td>
<td>25-29.9</td>
<td>increased</td>
</tr>
<tr>
<td>Obesity</td>
<td>≥ 30</td>
<td></td>
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<tr>
<td>Grade I</td>
<td>30-34.9</td>
<td>moderate</td>
</tr>
<tr>
<td>Grade II</td>
<td>35-39.9</td>
<td>severe</td>
</tr>
<tr>
<td>Grade III</td>
<td>≥ 40</td>
<td>very severe</td>
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Table 1 Classification of body mass index (BMI) proposed by a WHO expert committee and risk of comorbidity.
accompanied by numerous chronic diseases, including hypertension, coronary artery disease, asthma, diabetes and arthritis. In addition to its link to several chronic medical conditions, obesity has also been identified as a risk factor for cancer-related death for several cancers, like some colon cancers, postmenopausal breast cancer, endometrial cancers, kidney cancers, and adenocarcinomas of the oesophagus. In Europe obesity accounts for up to 6% of direct health costs and more than 12% of indirect health costs like, a reduced life span, reduced productivity, and lower incomes. Besides the ongoing obesity epidemic, the incidence and prevalence of prostate cancer have risen substantially, starting to be a major health problem too. This increase in incidence and prevalence began with the introduction of PSA, growing prostate awareness and increasing accessibility to public health care. Any association between obesity and prostate cancer might have important clinical and public health implications. This possible association has gained popularity in the field of scientific research. In the past five years the number of published scientific papers about this topic has risen spectacularly. 

Although a relation between obesity and increased risk of several types of cancer is described in epidemiological studies, the exact pathophysiology underlying this association is not well understood. Alteration in sex hormones, growth factors and cytokines have been postulated. The link between having prostate cancer in specific and obesity is inconsistent. There is, however, evidence that there is an association between the role of obesity and the increased risk of having an aggressive prostate cancer. With the increased incidence of both obesity and prostate cancer, it is plausible that physicians will be confronted with an obese patient suffering from prostate cancer more often. Studies have also suggested that obesity increased the
risk of biochemical recurrence after prostate cancer therapy.\textsuperscript{24-29} All these studies are performed in the USA. Compared to Europe, the population of the USA is not only more obese but the composition of the population is also different. In these studies obesity is measured using BMI. It may be questioned whether obese patients (measured using BMI) from Europe have a similar risk of developing biochemical recurrence. Furthermore, are other measurements for obesity more appropriate to use when studying the association between obesity and the risk of advanced prostate cancer or biochemical recurrence?

Besides active surveillance, patients with localized prostate cancer can be treated with different treatment modalities like surgery (open or laparoscopic/robotic assisted) and radiotherapy (external or permanent brachytherapy). The exact role of obesity in terms of functional outcomes when treated with one of the treatment options is not well known and few data about this topic are published. However, knowledge of the role of obesity in this respect is of great importance when informing an obese patient suffering from prostate cancer about the different treatment options.

1.2 Outline of the thesis

Growing interest in the potential association between obesity and prostate cancer is seen, which is reflected in the rising number of articles published in recent years. This thesis describes and discusses the clinical implications of obesity on prostate cancer in a Dutch population. To shed light over the functional and oncological outcomes of prostate cancer patients in relation to obesity, several studies have been performed. To obtain more knowledge on how obesity is related to prostate cancer, the literature is thoroughly reviewed in chapter 2. As a sequel to obesity, different hormonal changes occur. Besides these changes other biological mechanisms potentially affecting the prostate take place. The potential link between obesity and the development and detection of prostate cancer is also discussed. Finally the impact of obesity on surgical outcomes and biochemical recurrence following prostate surgery and radiotherapy are summarized in this section.

Urinary incontinence is a well-known complication after a radical prostatectomy and feared by both the patient and the urologist. Very few studies are available about the impact of obesity on surgical outcomes. The results of a single centre historical cohort of 252 men who underwent an open radical prostatectomy are described in chapter 3. This chapter provides information whether obesity is a complicating factor in terms of incontinence, vesico-urethral strictures and postoperative morbidity when performing an open radical prostatectomy.
Different studies carried out in The United States of America revealed a higher risk of biochemical recurrence in obese patients suffering from localized prostate cancer undergoing a radical prostatectomy. In chapter 4, a multicenter analysis was performed to identify if obesity is also a prognostic marker for biochemical recurrence in a Dutch cohort of men who underwent a radical prostatectomy.

Permanent prostate brachytherapy is another treatment modality used for patients having clinically localized prostate cancer. Chapter 5 deals with another important clinical issue: does obesity influence treatment outcomes in patients who underwent permanent brachytherapy? In this section we describe the effect of obesity on biochemical recurrence and cancer specific survival in a large cohort of Dutch men who underwent brachytherapy.

Abdominal, especially visceral fat, is the most active endocrine organ. Almost all studies, which studied the effect of obesity on prostate cancer outcome, have used BMI to measure obesity. In chapter 6, we conducted a study to assess if the distribution of body fat contributes to the prediction of aggressive prostate cancer. To test this hypothesis we compared periprostatic fat and subcutaneous fat measured on computed tomography with body mass index to identify if periprostatic fat is a better marker for aggressive disease in men who underwent brachytherapy. Because this study population consisted mostly of patients with low and intermediate risk disease we also conducted a similar study in chapter 7, where we also included patients who underwent external radiotherapy. By doing so, we created a more mixed group consisting of both low/intermediate and high-risk prostate cancer.

It has been hypothesized that blood lipid profiles are associated with prostate cancer risk; however, results are fairly inconsistent and underlying mechanisms are not fully understood. The aim of the study presented in chapter 8 was to address the association between serum total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides and prostate cancer risk in a Dutch, prospective cohort study. Finally, chapter 9, provides a general discussion and the conclusions of these thesis and chapter 10 gives a summary of the thesis.
Reference List

The impact of obesity on prostate cancer

Based on a review article:

The impact of obesity on prostate cancer


JGH van Roermund
JA Witjes

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PROSTATE CANCER: CLINICAL IMPLICATIONS OF OBESITY
This chapter reviews the most relevant hormonal and adipokines alterations caused by obesity and the possible effect of these changes on prostate cancer (PC) development and progression. In relation to PC treatment, the impact of obesity and its influence on functional and oncological outcomes of the different treatment modalities for PC are discussed.

2.1 Potential biochemical mechanisms affecting the prostate

Adipose tissue constitutes a large, active endocrine and metabolic organ. Adipocytes contain the cytochrome P450 aromatase enzymes, which are encoded by the CYP19 gene. These enzymes are responsible for catalyzing the conversion of androgens to estrone and estradiol. Adipocytes can also secrete a myriad of peptides (adipokines) that intervene in the framework of a complex network of endocrine, autocrine and paracrine signals.1 Although the exact biochemical processes underlying the association between PC and obesity are unknown, several potential mechanisms have been proposed and will be discussed in this paragraph.

2.1.2 Androgen pathway

PC is a sex steroid (estrogens, androgens and progesterone) sensitive disease. Thus, steroid hormone alterations associated with obesity may play some role. Obesity has an important impact on the synthesis and bioavailability of endogenous sex steroids and is associated with increased serum estradiol and decreased serum concentrations of free testosterone. Increased levels of estradiol are caused by peripheral conversion of testosterone to estradiol by increased aromatase activity secondary to the accumulation of adipose tissue. Obesity also reduces the concentrations of sex-hormone-binding globulin (SHBG). Both phenomena increase the fraction of bioavailable estradiol and lead to a reduction in total testicular testosterone production.2,3 Although estrogens have been proven to be an effective therapy for metastatic PC treatment, it is not used anymore due to its higher mortality rate, caused by cardiovascular complications. It is well known that most prostatic carcinomas are hormone dependent and that approximately 70-80% of men with metastatic PC respond to various forms of androgen deprivation therapy by lowering testosterone levels to castration levels. Nowadays this is the first choice for patients with metastatic PC. At first sight obesity (increased levels of estrogens and lower levels of testosterone) might seem protective for PC. However, reports have shown a lower preoperative total testosterone correlated with a poorer pathological stage at the time of surgery.4,6 Also, a large prospective case-control study nested in cohorts in Finland, Norway and Sweden, found a modest, but significant decrease in PC risk for increasing levels of total testosterone.7 Although estrogen was used as an anti-
Chapter 2

androgen in the treatment of PC, the role of estrogen in PC aetiology is unclear. Several lines of evidence suggest that estrogens may enhance prostate carcinogenesis. First, through the actions of SHBG, estrogen has direct and indirect effects on epithelial cell differentiation and proliferation. Second, estrogens may interact with the SHBG receptor in the stroma of the prostate gland to activate insulin-like growth factor (IGF) synthesis and direct stromal proliferation (through IGFs), to mediate the response to epithelial cells to androgens. Third, experimental studies addressed that induction of prostate tumours by administration of testosterone in laboratory rats was considerably enhanced by the addition of estradiol, suggesting that estrogens in conjunction with androgens may stimulate the development of PC. Finally, prenatal exposure to an extremely low dose of diethylstilbestrol (DES) and other estrogenic compounds significantly affected mouse prostate development in vivo and in vitro in the presence of androgens and increased the risk of PC in offspring of DES-exposed mothers. Together, although estrogen has been used as an anti-androgen in the treatment of advanced PC, these data suggest that estrogens may enhance the risk of PC earlier in life.

2.1.3 Adipokines

Beyond alterations in sex steroid hormones, obesity is also associated with increased levels of several adipokines, such as leptin, insulin-like growth factor-1 (IGF-1), tumour necrosis factor α (TNF-α), interleukin 6 (IL-6), vascular endothelial growth factor (VEGF), and decreased level of adiponectin.

**Leptin**

Leptin, first described by Zhang et al. in 1994, is a 16-kD adipokine produced by adipocytes in white adipose tissue and plays a major role in controlling body weight homeostasis. Circulating leptin concentrations exhibit a positive correlation with the degree of obesity and leptin receptors have been identified in the prostate gland, suggesting a plausible biological role in this gland. Recently, leptin has been shown to stimulate the in vitro growth of hormone refractory PC cell lines. In both reports leptin caused a significant proliferation in both the PC-3 and DU145 cell lines when compared with untreated control cells. The proliferative response of PC cells to leptin has been shown to involve intracellular signalling molecules such as phosphatidylinositol 3-kinase (p13-K) and c-Jun NH₂-terminal kinase (JNK). Alterations in these signalling pathways are not only critical in processes of prostate carcinogenesis and malignant transformation, but also important in obesity, diabetes, and insulin resistance.

Results of clinical studies addressing the relation between leptin and PC are not consistent. A Chinese case-control study reported an increased risk of PC, but the trends were not statistically significant. After adjustment for age, men in the highest
tertile of leptin levels had an approximately twofold risk of PC (Odds ratio, OR=1.78, 95% confidence interval (CI)=1.07-2.95). However, a Norwegian case-control study found no support for this hypothesis (OR=0.9, 95% CI=0.6-1.6).²¹ Although the risk for PC in individuals with higher levels of leptin is not clearly proven, some studies showed that higher levels of leptin were linked to tumour progression and advanced disease. Saglam et al.²² noticed in a cross-sectional study that elevated leptin was significantly associated with poorly differentiated cancer and a greater frequency of extraprostatic cancer. Chang et al.²³ reported men with elevated plasma leptin concentrations had an increased risk of being diagnosed with high-volume PC that was attenuated after adjustment for body mass index (BMI) (OR=2.41, 95% CI=0.93-4.58). One study, a cohort of 225 men, did not find a relation between serum leptin and advanced pathological stage (pT3a, extraprostatic extension; OR=1.14, 95% CI=0.76-1.71). However this study was done in predominantly white men with mainly low risk disease (28% of the patients had a pT3a).²⁴ In all, these observations suggest that leptin may play no role in initiation of PC but may rather play some part in the progression of PC.

**Insulin-like growth factor-1**

The metabolic (or insulin resistance) syndrome is characterized by a cluster of biochemical abnormalities and associated clinical conditions, not all of which are necessarily present in a given case, but which include disturbed glucose metabolism and insulin bioactivity resulting in hyperglycaemia and hyperinsulinemia, dyslipidemia (hyper-triglyceridemia and low levels of HDL cholesterol), hypertension and type 2 diabetes.²⁵ Central obesity is often present, but the syndrome does occur in its absence. In obesity, different endocrine and metabolic signals lead to insulin resistance, resulting in a chronic compensatory hyperinsulinaemia and increased levels of bioavailable IGF-1. In their turn, insulin and IGF-1 promote cellular proliferation and inhibit apoptosis in many tissue types.² These effects may be responsible for tumorigenesis of PC in obese patients. In an *in vitro* study a significantly lower proliferation rate of androgen-independent PC-3 prostate cells was seen in IGF-1 deficient hosts in comparison to IGF-1 expressing hosts.¹³ Recently, Cox et al. discovered the presence of insulin receptors on human prostate cancers. The findings are relevant because this may explain the hypothesis that obesity associated hyperinsulinemia mediates the adverse effect of obesity on PC prognosis.²⁶ In addition several prospective cohort and case-control studies have shown positive associations between PC risk and circulating IGF-1 level in men.²⁷-²⁸

**Tumour necrosis factor α**

Human TNF-α is a 17 kDa pleiotropic cytokine produced by a variety of cells including macrophages, monocytes, T cells and nonhematopoietic cells. It can regulate a wide
variety of cellular responses including proliferation, differentiation, inflammation and cell death. In obese men higher levels of TNF-α were seen in those with a higher BMI. Although several studies have documented the ability of TNF-α to promote development of neoplasia, studies that investigated the effect on PC are sparse. No study investigated the direct effect of obesity on TNF-α and the development of PC. Few studies have examined associations between TNF polymorphisms and PC risk. Results have been mixed, with one observing significant associations with PC risk while three others did not.

**Interleukin 6**

IL-6 circulates in multiple glycosylated forms ranging from 22 to 27 kDa and is involved in regulation of multiple cellular functions like proliferation, apoptosis, angiogenesis, and differentiation. Many different cell types, including adipocytes, immune cells, fibroblasts, endothelial cells, monocytes and a variety of endocrine cells, produce it. Adipocytes only produce 10% of the total tissue production and it circulates at high levels in the peripheral blood. Interestingly, studies have shown a positive correlation between circulating levels of IL-6 and obesity. Adler et al. reported that IL-6 is also produced by human prostate cancer cells and is elevated in patients with PC. In vitro studies using androgen-independent prostate cancer cell lines show they secrete high levels of IL-6 into the culture medium, suggesting a function of IL-6 as an autocrine or paracrine regulator of PC growth. More importantly, results of several reports demonstrate that higher levels of IL-6 in patients with advanced PC were associated with poor prognosis compared to the patients with lower IL-6 levels. Obesity-related increases in IL-6 levels could thus potentially interfere and enhance this mechanism and further promote prostate carcinogenesis.

**Vascular endothelial growth factor**

Angiogenesis is a process by which new blood vessels are formed from pre-existing vasculature. VEGF is the most prominent cytokine responsible for endothelial cell differentiation, migration, proliferation, tube formation, and vessel assembly. VEGF regulates physiological angiogenesis, but also plays a crucial role in pathological angiogenesis associated with PC and facilitates local invasion of malignant cells and the development of distant metastases. Studies have shown a correlation between obesity and the level of VEGF. In their turn, plasma VEGF levels have shown positive correlation with tumour stage, grade and clinical outcome. Although no studies have reported the direct correlation between obesity, VEGF plasma levels and PC risk, it is attractive to speculate that PC cells may also be influenced by increased VEGF plasma levels secreted by adipocytes in obese patients.
Adiponectin

Adiponectin, a 30 kDa collagen-like protein, is exclusively synthesized in adipocytes and circulated in the peripheral blood at a concentration which amounts to 0.05% of the total serum proteins. It plays an important role in regulating energy metabolism and inflammation. In contrast to other adipokines, plasma levels are negatively correlated with obesity and especially visceral fat accumulation. The regulation of adiponectin secretion is complex and poorly understood. Multiple hormones appear to have a role, including TNF-α, IGF-1, glucocorticoids and β-adrenergic agonists. It is secreted with a diurnal variation, attaining a nadir in the early morning. The two putative adiponectin receptors (AdipoR1 and AdipoR2) have not only been expressed in metabolically active organs but also in the LNCaP-FGC, DU145 and PC-3 prostate cancer cell lines. Thus, in addition to its insulin-sensitizing role, adiponectin may also regulate cell proliferation and specific signalling pathways in cancer cells. Recently an oligomer of adiponectin inhibited proliferation of an androgen-dependent (LNCaP-FGC) as well as two androgen-independent (DU 145 and PC-3) prostate cancer cell lines. It should be noted that this study was performed under serum-free conditions, which may favour a decrease in cell proliferation and/or inhibit cell growth. A small case-control study of PC patients, patients with benign prostatic hyperplasia (BPH), and healthy subjects found significantly reduced adiponectin concentrations in men with PC relative to BPH and healthy controls. Another case-control study found a marked reduction in PC risk in patients with higher serum adiponectin levels. The relationship between serum adiponectin and PC aggressiveness was investigated by two studies. Both studies found an inverse relation between serum adiponectin and high grade PC. However, the direction of the association may depend on the extent of obesity.

In summary, possible mechanisms by which obesity may impact upon PC include altered serum steroid hormones, leptin, insulin, IGF-1, TNF-α, IL-6, VEGF levels and decreased levels of adiponectin. (figure 1, gives an overview of the possible mechanisms for obesity-related PC progression) Most studies of hormone levels and PC risk have evaluated each hormone individually. Difficulties comparing these studies are caused by complex interrelationships between hormones, binding proteins and their receptors and the moment of exposure. In addition, most studies on adiposity usually reflect a single evaluation in time, while cumulative effect of fat content (all-life exposure) may be of greater importance in prostatic disease development.
2.2 The risk of obesity on the development of prostate cancer

Large studies have addressed the association of obesity and the risk of PC. However, inconsistent results are reported. Two large historical cohort studies, one among 135,000 Swedish construction workers and a large Norwegian cohort of 950,000 men, reported a positive relation between BMI and PC,\textsuperscript{62,63} while another prospective population-based cohort study found no association.\textsuperscript{64} In contrast, in two recent studies an inverse relation between BMI and PC risk was found.\textsuperscript{55,66} It should be noted that non-biological explanations may contribute to the apparent disparate results.
among epidemiological studies. For example, some studies were done before the prostate-specific antigen (PSA) era and different BMI categorizations were used. One of the limitations is that most of these studies have been focused on recent BMI, which mainly means obesity late in life. This is important, because obesity in preadolescent years might be more critical for the development of PC later in life. An Australian population-based, case-control study reported no association between BMI measured at the age of 21 and the risk of developing PC later in life.67 However, Robson et al. and the Health Professionals Follow-up Study, who addressed the effect of obesity before the age of 30, found an inverse relation of preadolescent and early-adult obesity with a diagnosis of advanced PC later in life.68,69

Another difficulty comparing the epidemiologic studies is that most of the epidemiologic studies accept all PCs as one biological entity when it is probable that PC is biologically heterogeneous, not only in terms of grade and stage but also with respect to its clinical behaviour.70

In summary, obesity is associated with endocrine changes and hormonal factors have been implicated in the cause of PC. A link between BMI and the risk of developing PC may be expected. However, the results of the large studies were inconsistent and do not permit definite conclusions. It demonstrates the difficulty to interpret epidemiologic data when it comes to obesity and PC risk.

### 2.3 Obesity and prostate cancer aggressiveness

The relation between obesity and PC risk is complex. Although it has been studied extensively, it remains inconclusive. Studies that have linked obesity with PC mortality, advanced stage disease, and high grade Gleason score, however, have produced more consistent results.

In the Physicians’ Health Study, which has a prospective design, 2,546 men developed PC and 281 (11%) died from PC during the 24-year follow-up. Compared with normal weight men, obese men had a 2.66 (95% CI 1.62-4.39) higher risk to die from their disease.71 Unfortunately, data on different choices of treatment for the PC patients were not available. In another prospective study of obesity in relation to PC mortality, obesity was not related to PC incidence, but a 2.12 (95% CI 0.92-2.33) higher risk of PC mortality was seen in the highest BMI category.72 The correlation between obesity and fatal PC is also confirmed by other authors.62,72-74 In line with PC mortality, studies have been published about the increased risk of advanced PC in obese patients.74-77 The Cancer Prevention Study II Nutrition Cohort is a very large prospective study that enrolled 86,404 males and investigated the link between aggressive PC and obesity.74 During the 12 years of follow-up 5,252 incident primary PC cases were diagnosed.
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The results of the study suggested that obese patients were at increased risk to develop more aggressive PC compared to the normal weight men. These observations suggest that the relationship between obesity and PC is the result of its biological effects in promoting an aggressive phenotype rather than the transformation of the prostatic epithelium per se.

2.4 The effect of obesity on screening and detection of prostate cancer

Transrectal ultrasonography (TRUS) guided prostate needle biopsy has become the cornerstone in the detection of PC. A biopsy is performed when patients have an abnormal digital rectal examination (DRE) and/ or elevated PSA level and/ or abnormal TRUS. Factors that alter PSA, DRE or influence TRUS guided biopsies can have an impact on the detectability of PC, unrelated to cancer biology. When considering the likelihood of detecting PC in glands of various sizes, several factors must be considered, e.g. the prevalence of cancer in prostates of different sizes, tumour volume, distribution of the lesion or lesions, and the overall size of the biopsy specimen in relation to that of the gland. Several authors have studied the impact of prostate volume. In a study by Eskicorapci et al., 503 men with an abnormal DRE and, or elevated PSA level (>2.5 ng/ml) were included. The cancer detection rates decreased significantly from 50% to 28% for patients with a prostate volume between 14.9 to 35.0 cc and 35.1 to 50.0 cc, respectively. Uzzo et al. stated that patients with a prostate volume of 50 cc or lower had significantly higher cancer detection rates than patients with a prostate volume of higher than 50 cc (38% vs 23%). Karakiewicz et al. confirmed these findings. With this in mind, studies have shown variations in prostate size with increasing degrees of obesity. An American case-control study of black men found that BMI was directly associated with the prostate volume. Additionally, in two other studies, the prospective Veterans Affairs Normative Aging study and a second one carried out in a population of men with lower urinary tract symptoms, obesity was also directly associated with prostate volume. Recently, a prospective cohort study composed of community volunteers found that obesity and abnormal glucose homeostasis potentially influence prostate growth through mechanisms other than testosterone. DRE, is harder to perform in obese men, so palpable nodules can be missed. The difficulties in performing the DRE, however, have been challenging to quantify. Furthermore, nowadays, most PC’s are detected on biopsy following an abnormal PSA. Multiple studies have shown an inverse relationship between serum PSA levels and BMI. A recent population-based study examined the association between BMI and PSA levels in nearly 3,000 men without PC. The authors found that the mean
PSA level decreased with increasing BMI, such that the mean PSA level in men with a normal BMI was 1.01 ng/ml and the mean PSA level in morbidly obese men (BMI ≥ 40 kg/m²) was 0.69 ng/ml. In the multivariate model, age and race did not attenuate the association between PSA levels and BMI. The authors hypothesized that PSA production is androgen-dependent and that obesity is associated with lower levels of circulating androgens. Recent studies found the same association between BMI and PSA. In the study of Bañez et al., patients underwent a radical prostatectomy (RP). After controlling for clinicopathological characteristics, higher BMI was also associated with higher plasma volume. They concluded that hemodilution might be responsible for the lower PSA levels among obese men with PC.

Taken together, lower PSA levels result in possible delayed biopsies because it takes longer for PSA levels to rise above a given threshold. The combination of this delay and larger prostates seen in obese patients may affect PC detection and may result in a postponed diagnosis and poor outcome. To examine this hypothesis Freedland et al. conducted a historical cohort study of 1,375 and 2,014 men treated by RP between 1988 and 2007 using the Shared Equal Access Regional Cancer Hospital and Duke Prostate Center database, respectively. Obese men with PSA-detected cancers (cT1c) and treated with RP since 2000, were at significantly greater risk of biochemical recurrence (BCR), while obese men treated before 2000 or diagnosed with an abnormal DRE were not at significantly greater risk of progression. These findings support the hypothesis that current PSA-based screening is less effective at finding cancers in obese patients.

In a study of a referral-based biopsy population in the United States, Presti et al. clearly explored the relation between BMI and PC detection. On the one hand a normal BMI correlated with a higher cancer detection rate and larger cancers in men referred for prostate biopsy. On the other hand, a referral-based biopsy population in Asia found no significant differences among the BMI groups in the PC detection rate. Different racial distributions, population selections and study sizes could explain this disparity. Interestingly, two studies found that overweight and obese men living in the United States are more likely to receive a PSA test than their counterparts in the healthy weight range. Fontaine et al. found that among men aged 50 years and older, overweight and obese men were significantly more likely to have had a PSA test in the past year, possibly due to more health seeking behaviour of obese men.

In summary, lower PSA levels, a more difficult DRE and larger prostates seen in obese patients may negatively influence the detection rate of PC in obese patients. Although some authors suggest that the PSA cut-points used to recommend biopsy need to be adjusted for the degree of obesity, further investigations are needed to determine the exact role of obesity in the detection of PC.
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2.5 Influence of obesity on treatment outcomes

It is generally held that obesity makes many urological procedures technically more challenging. Not surprisingly, obesity makes anatomical dissection of the apex difficult and has a higher likelihood of postoperative complications such as postoperative incontinence or stricture of the anastomosis. Besides technical difficulties during an intervention in achieving good mucosa-to-mucosa apposition, obesity itself may poorly influence healing at the vesicourethral anastomosis. However, few data are available on the exact impact of obesity on the different surgical techniques. Of the existing studies many comprise small numbers of patients.

A retropubic RP can be more technically challenging in obese patients. Eastham et al. reported that weight was a significant risk factor for urinary incontinence on univariable analysis. Multivariable analysis, however, was not performed due to the large number of missing values.94 Few reports investigated the impact of obesity and postoperative incontinence. Three retrospective studies found no association between obesity and incontinence and used questionnaires to evaluate the incontinence with a response rate varying from 55% to 70%, which may have biased the results.95-97 Another difficulty in comparing studies on incontinence is the different definitions used in the studies.

Elliott et al. examined the incidence of stricture after multiple forms of PC therapy (RP, permanent prostate brachytherapy (PPB), external beam radiotherapy (EBRT) and cryotherapy) in more than 6,500 men, using the Cancer of the Prostate Strategic Urological Research Endeavor (CaPSURE) database.98 The overall stricture treatment rate was 5.2% and in the multivariate model primary treatment type, age at PC treatment and BMI were significant predictors of stricture treatment.

Perineal RP has gained renewed interest in obese patients. Anatomically this makes sense because the surgeon can excise the prostate without traversing the abdominal fat and to avoid the dorsal venous complex. Three studies addressed the feasibility of perineal RP in obese patients. Retrospective series by Dahm et al.99 and Bockzo et al.100 have suggested that perineal RP is both safe and feasible, not only in obese, but also in morbidly obese patients. Dahm et al. reviewed a cohort of 18 morbidly obese men and Bockzo et al. analysed 7 obese patients. The numbers of obese patients in both reports were too small to draw firm conclusions. However, a recent control study of 71 severely obese and 71 non-obese patients, who were matched by age, addressed an increased risk of both surgical and anesthesia-related perioperative complications in obese men. Transient neuropraxia in the lower extremities was the most common complication in obese men.101 The study did not provide information about late complications and functional outcomes.

Laparoscopic prostatectomy is gaining popularity. The magnification of a laparoscope makes an apical dissection and sparing of the striated sphincter easier when
Impact of obesity on prostate cancer compared to conventional open prostatectomy. In a prospective study by Singh et al., no significant differences were seen between operative and perioperative morbidity in obese patients who underwent a laparoscopic prostatectomy compared to non-obese men. Although prostatectomy in an obese patient was found more technically challenging due to the significant amount of intra-abdominal tissue, the continence rate did not have any correlation with BMI or prostate size. Except for a longer mean operative time in obese patients, same conclusions were reported by three other reports. Brown et al. used both the transperitoneal and extraperitoneal technique in 151 patients and reported a 16-minute longer operative time in obese men compared to non-obese men. No differences were seen in continence rate and erectile function. However, patients travelled a distance to undergo surgery and consistent follow-up data (erectile function, continence rate) were not available. Likewise Eden et al. reported a 15-minute longer operation time in 532 patients who underwent both transperitoneal (first 111 cases) and extraperitoneal laparoscopic RP. Although there was no statistically significant difference in outcome between the non-obese and obese patients, erection rates were lower in obese compared with the non-obese patients. In line, a recent study by Liatsikos et al. who used the extraperitoneal approach in 500 patients, found also a 20-minute significantly longer operative time. In contrast with the other studies they used validated questionnaires for urinary and sexual function. An analysis of the functional data before and after surgery showed a similar baseline status regardless of the BMI. The comparison among the groups showed no statistical significance, but there was a trend to a slower recovery in the obese patients. Data on erectile function showed comparable results. Although the erectile function rates were lower in the obese group there were too few patients who had potency-preserving procedures and thus the influence was difficult to assess. All obese men required the use of phosphodiesterase-5 inhibitors to achieve an erection sufficient for sexual intercourse.

A novel approach of laparoscopic surgery is robotic assisted laparoscopic prostatectomy (RALP). Besides magnification, it provides the surgeon a three-dimension image and a more ergonomic position during the operation. In a prospective study reported by Mikhail et al. obesity did not increase perioperative and postoperative morbidity, except for operative time and estimated blood loss. After one year of follow-up, 74% of the obese patients returned to baseline continence. However the response rate of the validated questionnaires was only 22% after 12 months. Ahlering et al. reported on their results for 100 RALP’s in the presence and absence of obesity. They noted that blood loss during RALP was greater and the operative duration longer in 19 obese patients than in 81 who were not obese. Among the obese group there was also a significantly higher incidence of complications (26% vs 5%) and they required more time to return to baseline urinary function compared
with their non-obese counterparts. At 6 months only 47% of obese patients had achieved urinary continence. Maybe the different length of follow-up, definition of urinary incontinence and very low response rate can explain the discrepancy of the continence rate between both studies.

A prospective study by Khaira et al. collected duration for different steps during the robotic procedure of 285 patients. The study population consisted of 49 patients who had a BMI > 30 kg/m². The authors also found that blood loss, transfusion rate and complications during RALP did not differ between the non-obese and obese group. However the time of urethral dissection, anastomosis and port closure was significantly longer in the obese patients. It was harder to perform a urethral anastomosis in obese patients due to intra-abdominal fat and omental tissue falling into the visual field, unfortunately functional data were not available. In two reports, obesity was a risk factor for positive surgical margins. The positive surgical margin rate varied between 21% and 27% in the obese men, and 11% and 13% in the non-obese men treated with RALP.

Although the primary goal of cancer treatment is to cure the patient from his disease, not less important is the influence on quality of life by different treatment options. Several studies have addressed the role of BMI in health-related quality of life (HRQOL) before and after RP. Comparing obese men with their normal or overweight counterparts, lower postoperative HRQOL measures might be partially attributed to lower baseline HRQOL scores and might not be completely attribute to more severe postoperative morbidity. Anast et al. retrospectively evaluated 672 men in the CaPSURE database and found that increased BMI did not predict worse HRQOL outcomes after RP, with the exception of very obese men (BMI ≥ 35 kg/m²) who had worse urinary bother and functional scores at 24 months compared with men who had a BMI < 35 kg/m². In line, Freedland et al. reported, after adjusting for age, baseline HRQOL and nerve-sparing status, that obese men did not have significant differences in HRQOL compared with non-obese men. Overweight men however, had significantly lower urinary function scores than men with normal BMI at 24 months. In contrast, Montgomery et al. evaluated in a prospective study 376 men who underwent RP. They reported that obesity adversely affect HRQOL before and after the RP. The use of different questionnaires and regional variation in practitioner expertise and patients factors may affect these outcomes. One study by Sanda et al. measured HRQOL outcomes reported by 1,201 patients who underwent different treatment modalities (RP, PPB, EBRT) for PC. The factor that was associated with worse patient-reported outcomes was obesity. Symptoms related to vitality and hormonal function were adversely affected by obesity in patients who underwent EBRT or PPB.
Davies et al. evaluated the effect of BMI on PC treatment choice for patients with clinically localized PC using a large, prospective community-based database (CaPSURE).\textsuperscript{115} After adjusting for clinical status, age, race, number of comorbidities, and level of education in the multivariable analysis, BMI continued to be significantly associated with type of treatment. Compared with normal BMI, very obese patients (BMI > 35 kg/m\textsuperscript{2}) were more likely to receive primary androgen therapy only (OR 1.77, 95% CI 1.12-2.81), PPB (OR 1.59, 95% CI 1.01-2.52), and EBRT (OR 1.29 95% CI 0.73-2.26) rather than RP. Physician perception of obesity has been found to influence patterns of medical care.\textsuperscript{116,117} In addition, health professionals tend to perceive obese persons more negatively than those who are not obese, viewing obese individuals as unattractive, unmotivated and noncompliant.\textsuperscript{118,119} If such perceptions and attitudes exist in the urologic community, it may help to explain some of the trends.

In summary, obesity makes a radical RP procedure technically more challenging. However, few data are available on the exact role of obesity on the different treatment options for localized PC. Since treatments other than open RP are available for clinically localized PC, possible postoperative complications can affect the decision of choosing a therapy. To date, only small study samples with low response rates have investigated the effect of obesity on operative outcomes in patients who underwent an open or perineal RP. More studies in the field of obesity and its effects on laparoscopic RP’s are performed. Although it was more technically challenging to perform an RP in an obese patient, only one report showed a higher incidence of complications. Future comparative prospective studies are necessary to delineate the cancer-related and functional outcomes of obese patients undergoing the different treatment options.

2.6 Biochemical recurrence after surgery and radiotherapy in obese patients

Although the majority of men newly diagnosed with PC will have early-stage disease, little is known about the impact of obesity on oncological outcomes of primary therapy for clinically localized disease. Compared to non-obese men, two recent large American multi-institutional studies observed a significant higher biochemical failure rate among obese men treated with RP.\textsuperscript{120,121} In the study by Amling et al. several interesting racial observations were made. In comparison with whites, Afro-Americans were significantly more likely to be obese, had significantly higher PSA levels, and had significantly higher-grade cancers. They were also more likely to have positive surgical margins at the time of RP. In a multivariate analysis including all pathologic tumour factors (stage, grade, surgical margin, and seminal vesicle status),
black race remained among these as a significant independent predictor of cancer recurrence, whereas BMI did not. In the study of Freedland et al., obesity was also significantly related to race. BMI, whether categorical or continuous, was a significant predictor of BCR and was associated with higher-grade tumours. Although previous studies found a relation between obesity and BCR, Mallah and co-workers found weak associations with disease progression for BMI, which was of negligible prognostic value in men who received surgery. However, the definition of disease progression used, as well as the statistical approach, makes their results hard to compare with the reports mentioned before. The discrepancies between these studies also suggest that obesity may affect BCR but is not the only prognostic factor when determining whether PC will recur after surgery.

In a retrospective analysis of 436 patients, obese men were likely to lose significantly more blood during a retropubic RP, compared to non-obese men. Taking this into account, Oefelein et al. found intraoperative blood loss as a risk factor for PC recurrence. Perioperative transfusion with allogeneic blood may impair immune response and has proved to have a detrimental effect on the recurrence of curable colorectal cancers. This may play a role in the higher BCR rates seen in obese patients with PC. A reduction of peroperative bloodloss in obese patients with PC may have a positive impact on cancer recurrence. It is possible that the pneumoperitoneum and magnification of the scope during laparoscopy in obese patients may allow better hemostasis compared to the open surgical approaches. Despite the possible clinical relevance, no comparative data are available.

Additionally, compared to non-obese patients, more positive surgical margins were seen in obese men who underwent an RP. Studies showed that a positive surgical margin after RP is associated with an increased risk of PC recurrence. Positive surgical margins may be due to bad surgical technique and/or from extension of tumour beyond the planned limits of resection. Jayachandran et al. addressed the risk of positive surgical margins by anatomic location after RP in 1,434 men, using the Shared Equal Access Regional Cancer Hospital (SEARCH) database. Obesity was associated with an increased risk of positive margins at all anatomical locations. It was suggested that extreme obesity (BMI ≥ 35 kg/m²) was more strongly associated with positive apical and bladder neck margins (OR 3.11 and 3.74, respectively). Of note, the 95% CI’s overlapped with the estimates for the other site-specific positive margins.

To hypothesize if similar technical difficulties were seen in open RP and perineal RP Fitzsimons et al. retrospectively analysed 1,006 patients treated with open RP or perineal RP. They found that obese men, after adjusting for clinicopathologic characteristics, were likely to have positive margins as normal-weight men more than twice, regardless of prostatectomy type. The data did not provide evidence that open RP should be preferred to perineal RP in mildly obese men.
Elevated BMI has been associated with BCR after RP. Whether this is due to aggressive disease biology or to technical limitations is not fully clear, Freedland et al. attempted to determine whether the increased rate of BCR in obese patients was due to technically inferior surgery. 130 Using capsular incision on the pathological specimen as a proxy for a technically worse operation, they found that mildly obese patients had a 30% increased chance of capsular incision and moderately to severely obese men had a 57% increased risk. Several other studies have further noted a trend towards increased positive surgical margins in the overweight and obese patients. Interestingly, however, in a study of RP patients with negative surgical margins, the SEARCH database study group still found an increased risk of BCR in patients with elevated BMI. This observation led to the conclusion that a technically inferior operation cannot fully account for the differences in outcome, but more aggressive PC seen in obese patients also plays a role in BCR.

Morbidly obese men (BMI >40 kg/m²) with PC are frequently not good candidates for general anaesthesia and surgical procedures such as RP. Radiotherapy, which is also challenging in this kind of patients, may be the first choice of treatment. Unfortunately, little is known about the oncological results in obese patients with PC who underwent radiotherapy. Radiotherapy is also used in the treatment of localized PC. In obese patients delivery of precision high-dose EBRT is more difficult because of a greater chance of daily setup errors and excessive intra-abdominal adipose tissue, which may increase organ motion.131 Three reports also found a higher risk of BCR in obese patients who underwent EBRT compared to non-obese patients.132-134 The problem comparing these studies is the different definition used for BCR. In 1996 the American Society for Therapeutic Radiology and Oncology (ASTRO) defined BCR as three consecutive PSA rises after a nadir with the date of failure as the point halfway between the nadir and the first rise of PSA. In 2005 the ASTRO definition was revised by the Radiation Therapy Oncology Group in Phoenix. The panel recommended a rise by 2 ng/mL or more above nadir PSA as BCR.135-136 Two studies used the Phoenix definition132,134 while the other one133 used the ASTRO definition. Palma et al. found that obese patients had a higher risk of PC specific death after EBRT. In the EBRT studies, intraprostatic gold markers, which may improve the targeting of the prostate gland and minimize daily setup errors due to organ motion especially in obese patients, were not used.

PPB is considered an established treatment option for low-risk PC.137-139 PPB maybe less affected by obesity and is technically feasible in obese patients with postoperative dosimetry and quality of life outcomes comparable to those of non-obese patients.140-141 Two recent studies addressed the link between BCR and obesity.142,143 In both studies BMI was not associated with PSA failure. Merrick et al.143 reported the cancer specific survival as well and found that BMI was not associated with higher risk to die from PC.
In summary, various studies suggested that obesity may result in higher recurrence rates after RP. The question remains, are the differences in outcome predominantly driven by biologically worse features or technical difficulties during the surgical or radiotherapy procedure? The possibility that PPB is a preferred management option for obese patients is intriguing and warrants further investigation. Possible explanations why obese patients are at higher risk for BCR are summarized in figure 2.

2.7 Conclusion

Obesity, related to multiple chronic diseases, is a growing problem in Western countries. Autopsy studies from numerous countries worldwide, however, have shown similar rates of latent or clinically insignificant PC, despite markedly different PC death rates among these populations. These findings suggest that although clinically insignificant PC may be common to all races and ethnic groups, some as yet unknown factor or factors may promote progression of these latent tumours into clinically significant cancers. Recent international trends show that PC incidence is
increasing in low-incidence countries such as China and Japan. At the same time these countries are adopting westernized lifestyles associated with higher rates of obesity. These observations suggest that obesity may be a risk factor for PC. However, by adopting a westernised lifestyle, it is also possible that more Asian men tested their PSA, resulting in a higher detection rate. In any case, epidemiological studies are showing conflicting results between obesity and the development of prostate diseases. In contrast, more consistent findings have linked obesity with PC mortality, advanced stage and higher Gleason score.
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Impact of obesity on surgical outcomes following open radical prostatectomy

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Abstract

Objective: The increasing incidence of both obesity and prostate cancer detection will confront the urologist more often with obese men having prostate cancer. It is unknown whether obesity affects the surgical and oncological outcomes following open radical retropubic prostatectomy (RRP). Knowledge concerning this issue is relevant when counselling obese patients with prostate cancer for RRP.

Patients and methods: A single institution cohort study was performed including 252 men who underwent a RRP between 1992 and 2003. The surgical complications (perioperative complications, post-RRP urinary incontinence, vesico-urethral strictures (VUS)) were compared between obese (BMI > 30 kg/m²) and non-obese (BMI ≤ 30 kg/m²) men.

Results: Compared to non-obese (N=221), obese men (N=31) developed more frequently wound infections (16.1% vs. 4.5%; p<0.05), urinary incontinence (25.8% vs. 8.7%; p<0.05) as well as VUS (45.2% vs. 12.3%; p<0.05). The pathology results and the 5-year cumulative risk of PSA recurrence were comparable between both groups.

Conclusion: Compared to non-obese, obese men suffered more frequently from post-RRP urinary incontinence and VUS following open RRP.
Impact of obesity on surgical outcomes

Introduction

The reported incidence of prostate cancer is highly variable throughout the world owing to multiple factors. In The Netherlands, like most countries in Western Europe, prostate cancer is the most common cancer and second leading cause of death among men. On the one hand, the increased public prostate cancer awareness and rising use of prostate-specific antigen (PSA) testing, resulted in a higher amount of clinically localized prostate cancer, amenable to curative surgery.

On the other hand, obesity, a rapidly growing worldwide epidemic, is beginning to replace malnutrition and infectious diseases as the most significant contributor to ill health. In Europe, the prevalence of obesity - according to the World Health Organization (WHO), obesity is defined as the body mass index (BMI; weight in kilograms divided by height in meters squared) over 30 kg/m² - has more than doubled during the last two decades. At present, more than half of all adults are categorized as having overweight (according to the WHO, BMI, between 25 and 30 kg/m²), and in some European areas up to 30% are obese. In summary, it is expected that urologists will increasingly be confronted with obese men having a localized prostate cancer.

Generally, radical retropubic prostatectomy (RRP) is one of the treatment options for localized prostate cancer. Obesity, however, may be a complicating factor when performing an RRP resulting in higher complication rates, and worse functional results. It is unknown whether obesity affects the surgical outcomes following RRP. Knowledge concerning this issue is relevant when counselling obese prostate cancer patients for RRP.

In order to be informed about the possible impact of obesity on surgical outcomes following RRP, a historical cohort study was conducted including a single centre consecutive series of men who underwent an open RRP.

Patients and methods

The records were reviewed of a consecutive series of 252 men treated by a RRP between 1992 and 2003 at the Canisius-Wilhelmina Hospital in Nijmegen, The Netherlands.

The pre-biopsy serum PSA concentrations and transrectal ultrasonography prostate volume measurements were recorded. The perioperative complications, length of hospital admission, vesico-urethral strictures (VUS), urinary stress incontinence, as well as postoperative PSA-levels were evaluated. During follow-up visits patients were asked about their urinary continence status. We defined continence if no pads were required.
|                          | Non-obese (N=221) | Obese (N=31) | p-value  
|--------------------------|-------------------|--------------|----------
| **Age** (± IQR) (yr)     | 65.0 ± 9          | 63.0 ± 10    | 0.128^a  
| **BMI** (± IQR) (kg/m²) | 25.4 ± 3.6        | 31.4 ± 2.9   |          
| **Preoperative PSA** (± IQR) (ng/mL) | 8.7 ± 6.8       | 9.4 ± 6.9    | 0.402^a  
| **Prostate volume** (± IQR) (mL) | 37.5 ± 21        | 38.0 ± 20    | 0.365^a  
| **Clinical stage (%)**    |                   |              |          
| T1                       | 145 (65.6)        | 26 (83.9)    | 0.042^b  
| T2                       | 76 (34.4)         | 5 (16.1)     |          
| **ASA-classification (%)** |                  |              |          
| I                        | 152 (68.8)        | 15 (48.4)    | 0.053^c  
| II                       | 0 (27.6)          | 13 (41.9)    |          
| III                      | 8 (3.6)           | 3 (9.7)      |          
| **Comorbidities (%)**     |                   |              |          
| None                     | 137 (62.0)        | 14 (45.2)    | 0.024^c  
| Preoperative TUR-P       | 16 (7.2)          | 3 (9.7)      | 0.71^c   
| Diabetes                 | 4 (1.8)           | 3 (9.7)      | 0.042^c  
| Cardiopulmonary history  | 64 (29.0)         | 16 (51.6)    | 0.014^c  
| **Follow-up** (± IQR) (months) | 54.7 ± 39.4   | 42.6 ± 35.6  | 0.254^a  
| **Gleason score** (± IQR) |                   |              |          
| ≤ 6 (%)                  | 6.0 ± 1           | 6.0 ± 1      | 0.347^c  
| 7 (%)                    | 161 (72.9)        | 22 (71.0)    |          
| 8-10 (%)                 | 41 (18.5)         | 4 (12.9)     |          
| **Pathological stage**    |                   |              |          
| pT2 (%)                  | 147 (66.5)        | 20 (64.5)    | 0.841^b  
| pT3 (%)                  | 74 (33.5)         | 11 (35.5)    | 0.841^b  
| pN+ (%)                  | 5 (2.3)           | 0 (0)        | 1.00^b   
| **Positive surgical margins (%)** | 64 (29.0)       | 11 (35.5)    | 0.530^b  

Table 1 Demographic, clinical and pathologic characteristics.

Data presented as median, with interquartile ranges, or number with percentages in parentheses. IQR= Interquartile range (=P25-P75); ASA= American Society of Anaesthesiologists.

a = Mann-Whitney U test  
b = Two-sided Fisher’s exact test  
c = Chi-square test

The patients’ American Society of Anaesthesiologists (ASA) classification, height, weight, estimated blood loss, and operative time were retrieved from anesthesiology reports. Gleason score, the pathological stage and surgical margin status were obtained from the pathology records.

The frequency of follow-up visits was every 3 months in the first year, every 6 months until the 5th year and annually thereafter. During these visits, serum PSA levels were determined and patients were asked about urinary continence. An urethrocystoscopy was performed if a VUS was suspected.
Patients were stratified into two groups: obese (BMI > 30 kg/m²) and non-obese (BMI ≤ 30 kg/m²) for data analysis.

**Statistical analysis**

Because of non-normal distributions, all variable distributions are summarized using the median values with the interquartile range (IQR, i.e., the range between the 25th and the 75th percentile of the distribution). In the univariable analysis of categorical variables (e.g., perioperative and long-term complications as well as Gleason score, pathological stage, tumour grade and surgical margin status) differences between obese and non-obese subjects were tested by a Chi-square test (in cases of more than two categories) or Fisher’s exact test (in case of two categories). Differences in continuous characteristics were tested by the Mann-Whitney U test. Kaplan-Meier survival analysis (with a log-rank test) was used to calculate the cumulative risk of PSA recurrence between both groups. Differences were considered to be statistically significant if p < 0.05.

### Table 2

Surgical characteristics and complications.

<table>
<thead>
<tr>
<th></th>
<th>Non-obese (N=221)</th>
<th>Obese (N=31)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Operation time</strong> (± IQR) (hours)</td>
<td>3.5 ± 1.00</td>
<td>4.0 ± 1.00</td>
<td>0.144*</td>
</tr>
<tr>
<td><strong>Estimated blood loss</strong> (± IQR) (mL)</td>
<td>1700 ± 1100</td>
<td>2000 ± 1750</td>
<td>0.146*</td>
</tr>
<tr>
<td><strong>Hospital stay</strong> (± IQR) (days)</td>
<td>8.0 ± 5</td>
<td>9.0 ± 8</td>
<td>0.061*</td>
</tr>
<tr>
<td><strong>Perioperative complications</strong> (%)</td>
<td>28 (12.7)</td>
<td>8 (25.8)</td>
<td>0.059b</td>
</tr>
<tr>
<td>Major: Died</td>
<td>2 (0.9)</td>
<td>0</td>
<td>1.000b</td>
</tr>
<tr>
<td>Minor: Lymfocele</td>
<td>5 (2.3)</td>
<td>1 (3.2)</td>
<td>0.549b</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1 (0.5)</td>
<td>0</td>
<td>1.000b</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2 (0.9)</td>
<td>1 (3.2)</td>
<td>0.327b</td>
</tr>
<tr>
<td>Wound infection</td>
<td>10 (4.5)</td>
<td>5 (16.1)</td>
<td>0.025b</td>
</tr>
<tr>
<td>Epididymitis</td>
<td>2 (0.9)</td>
<td>0</td>
<td>1.000b</td>
</tr>
<tr>
<td>Gross haematomas</td>
<td>2 (0.9)</td>
<td>0</td>
<td>1.000b</td>
</tr>
<tr>
<td>Fever of unknown origin</td>
<td>3 (1.4)</td>
<td>0</td>
<td>1.000b</td>
</tr>
<tr>
<td>Prolonged ileus</td>
<td>1 (0.5)</td>
<td>0</td>
<td>1.000b</td>
</tr>
<tr>
<td><strong>Post-RRP urinary incontinence</strong> (%)</td>
<td>19 (8.7)</td>
<td>8 (25.8)</td>
<td>0.009b</td>
</tr>
<tr>
<td><strong>Vesico-urethral strictures</strong> (%)</td>
<td>27 (12.3)</td>
<td>14 (45.2)</td>
<td>0.000b</td>
</tr>
</tbody>
</table>

* = Mann-Whitney U test
b = Two-sided Fisher’s exact test
c = Only 219 patients were suitable for measuring the long term complications, because 2 patients died shortly after surgery.
Results

Out of 252 patients, 221 (88%) were categorized as non-obese, and 31 (12%) as obese. For demographic, clinical and pathologic characteristics see table 1. Gleason score, pathological stage, and prevalence of positive surgical margins were not different among obese and non-obese men.

For surgical characteristics and complications see table 2. Two non-obese patients died immediately postoperatively; 1 patient, classified as ASA 3, died from heart failure, while another ASA 3 patient died from a pulmonary embolism. Twenty-seven non-obese men developed a VUS. Five patients were managed conservatively by urethral dilatation, whereas 22 needed an urethrotomia. In 4 non-obese patients the stricture recurred. Of the 14 obese men who developed a VUS, 3 patients were managed conservatively by urethral dilatation, whereas 11 needed an urethrotomia. In this group, no strictures recurred.

During a median follow-up of 54.7 months, 2 non-obese patients died from prostate cancer and 12 died from non-prostate cancer related causes. None of the obese men died from prostate cancer, whereas one patient died from a non-prostate cancer related cause. The follow-up in this group was 42.6 months. In both groups, the 5-year progression-free survival was 64%. (figure 1) Patients who required additional therapy are listed in table 3.

<table>
<thead>
<tr>
<th>Non-obese (N=219)</th>
<th>Obese (N=31)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First PSA (ng/mL) postoperatively (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 0.1</td>
<td>192 (87.7)</td>
<td>27 (87.1)</td>
</tr>
<tr>
<td>&gt; 0.1</td>
<td>27 (12.3)</td>
<td>4 (12.9)</td>
</tr>
<tr>
<td><strong>Patients with PSA recurrence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>88 (40.2)</td>
<td>12 (38.7)</td>
</tr>
<tr>
<td><strong>Last PSA (ng/mL) postoperatively (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 0.1</td>
<td>161 (73.5)</td>
<td>21 (67.7)</td>
</tr>
<tr>
<td>&gt; 0.1</td>
<td>58 (26.5)</td>
<td>10 (32.3)</td>
</tr>
<tr>
<td><strong>Primary additional radiotherapy (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>47 (21.5)</td>
<td>7 (22.6)</td>
</tr>
<tr>
<td><strong>Primary additional hormonal therapy (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19 (8.7)</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td><strong>Hormonal therapy after radiotherapy (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 (3.2)</td>
<td>1 (3.2)</td>
</tr>
</tbody>
</table>

Table 3 Postoperative PSA levels and additional therapy.
Numbers in parentheses denote percentages. Only 219 patients were suitable for measuring the PSA levels postoperatively, because 2 patients died shortly after surgery.

a = Irrespective of any additional therapy. Median follow-up; non-obese 54.7 months, and obese 42.6 months.
b = Two-sided Fisher’s exact test
c = Kaplan-Meier log-rank test (figure 1)
Impact of obesity on surgical outcomes

Figure 1 PSA recurrence-free survival.
Blue line: non-obese. Green line: obese
The 5-year risk developing a PSA recurrence is 36% (95% CI 28%-44%) for the non-obese and 36% (95% CI 14%-58%) for the obese (Kaplan-Meier log-rank p value is 0.53).

Discussion

Obesity is one of the fastest growing health problems in industrialized countries. According to Dutch Statistics (www.cbs.nl) 10% of Dutch adult men are obese. With the introduction of PSA testing in the 1980s, the detection rate of localized prostate cancer has increased enormously. The increasing incidence of both obesity and prostate cancer suggests that urologists will be confronted frequently with obese patients having a potentially curable prostate cancer.
In the present study, the incidence of perioperative complications (14.3%) is comparable to the incidence reported in the literature (6.3%-28.6%). A larger number of complications (predominantly wound infections) was observed in obese compared to non-obese men. Obese patients had significantly more comorbidities such as diabetes mellitus and cardiopulmonary diseases. This could be an explanation why obese patients suffered more frequently from wound infections.

Urinary incontinence is a particularly vexing problem after RRP with social as well as personal implications. Reported rates range between 2.5% and 87%, and differ considerably according to its definition, follow-up, and surgical technique.
Although this complication is feared by both the patient and the urologist, less is known about the impact of obesity on the development of urinary incontinence postoperatively. In the present study, obese men suffered more frequently from post-RRP urinary incontinence in comparison to non-obese men (25.8% vs. 8.7%, p=0.009). Only four reports investigated the impact of obesity and postoperative incontinence (table 4). In contrast with the present study, most of these studies reported no association between obesity and incontinence. Of note, all studies used self-administered and not validated questionnaires concerning urinary symptoms to evaluate the incontinence.

A second well known complication of RRP is the development of a VUS. Rates of VUS after RRP are 5% to 25.7% and they vary with the definition of stricture and practice setting (university vs community). In the present study, obese men developed significantly more VUS (45.2% vs. 12.3%, p=<0.005) in comparison to non-obese men. Only one other study also examined the influence of obesity and the development of a VUS after primary treatment for prostate cancer. In accordance with the present study, in the RRP-treated group, obesity was a predictor of the development of a VUS.

One of the reasons for the higher incidence of incontinence and VUS in obese men can be explained from a surgical viewpoint. Obese men have a relatively deep pelvis, making a proper preparation of the striated sphincter, a fine apical dissection, as well as the construction of urethrovessical anastomosis, more difficult. The combination of sphincter damage and increased intra-abdominal pressure, in obese men, can make obese patients prone to develop postoperative urinary stress incontinence. Another reason can be the experience of the surgeon. In this study 252 patients were treated over 12 years by 3 surgeons. The majority, 72% of all patients and 84% of all obese patients, however, have been operated in the last 6 years of the present study. In this time frame an average of 10 RRPs a year per surgeon was performed. In theory, the low-volume of prostatectomies per surgeon may be associated with higher prevalence of complications in obese men. To the best of our knowledge, no minimum volume threshold regarding the performed number of RRPs a year per surgeon has been determined and related to any RRP outcome. Interestingly, in a self-reported study of Denberg et al., a considerable number (37%) of the urologist in the US performed ≤ 10 RRPs a year. Although no threshold has been determined, it is an evolving topic that has major health policy implications. Nowadays, all RRPs in our hospital are performed by a single surgeon.

A comparison of complication rates of different surgical modalities used in obese patients with prostate cancer should be done to make an informed treatment selection for those patients. However, data are lacking. An alternative approach
Impact of obesity on surgical outcomes

<table>
<thead>
<tr>
<th>References</th>
<th>Eastham et al.⁹</th>
<th>HSU et al.¹⁰</th>
<th>Wille et al.¹¹</th>
<th>Mulholland et al.¹²</th>
<th>Present study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>581</td>
<td>1024</td>
<td>742</td>
<td>268</td>
<td>252</td>
</tr>
<tr>
<td>No of surgeons</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>Continence rate, %</td>
<td>91</td>
<td>91</td>
<td>70</td>
<td>68</td>
<td>89</td>
</tr>
<tr>
<td>Definition of continence</td>
<td>0 to 1 pad</td>
<td>0 to 1 pad</td>
<td>0 to 1 pad</td>
<td>Never or occasional incontinence, no more than once weekly</td>
<td>No pad</td>
</tr>
<tr>
<td>Data assessment</td>
<td>MR/SAQ</td>
<td>MR/SAQ</td>
<td>SAQ</td>
<td>SQA</td>
<td>MR</td>
</tr>
<tr>
<td>RR, %</td>
<td>NA</td>
<td>NA</td>
<td>76</td>
<td>68</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Patient weight (continuous) significant risk factor (univariable analysis)</td>
<td>Patient weight (categorical) was not a risk factor*</td>
<td>BMI ≤ 30 vs. BMI &gt; 30, CR 76% vs. 75% (NS)</td>
<td>No relationship between BMI (continuous) and incontinence</td>
<td>BMI ≤ 30 vs. BMI &gt; 30, CR 74% vs. 91% (p&lt;0.05)</td>
</tr>
</tbody>
</table>

Table 4 Obesity as a risk-factor for postoperative incontinence after radical prostatectomy of several series.
MR= medical record; SAQ= self-administered questionnaire; No= number; RR= response rate; NA= not available; NS= not significant; CR= continence rate.
* = continence status was evaluated for 422 men.

for RRP could be the perineal one. Three studies addressed the feasibility of radical perineal prostatectomy in obese patients. Small case series by Bockzo¹⁸ and Dahm et al.¹⁹ retrospectively reviewed the surgical results of 7 and 18 (morbid) obese patients, respectively. In the study reported by Bockzo et al. 4 patients were continent after one year of follow-up. Dahm and associates evaluated morbid obese men (BMI > 40 kg/m²). Long-term follow-up data were only available for 10 patients, and 9 were urinary continent. Although both studies were too small to draw firm conclusions, both authors have suggested that radical perineal prostatectomy is both safe and feasible, not only in obese but even in morbidly obese patients. The most recent matched-controlled study of 71 severely obese (BMI > 35 kg/m²) and 71 non-obese patients, however, did find an increased risk of both surgical and anesthesia-related perioperative complications, e.g. laryngospasm requiring reintubation, myocardial infarction, rectal injury and pulmonary oedema.²⁰ This study did not provide information about late complications and functional outcomes.

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The most recent surgical approach is laparoscopy. Since the laparoscopic approach is obviously less hindered by obesity, it is not surprising that in a prospective study no significant relation was established between operative and peroperative morbidity (including incontinence) in obese patients who underwent a laparoscopic prostatectomy compared to non-obese men. These data are confirmed by others. Another form of laparoscopy is robotic-assisted surgery. In contrast, Ahlering et al. reported significantly more complications in obese men who underwent robotic-assisted laparoscopy and they required more time to return to baseline urinary function. At 6 months, 47% of 19 obese patients had achieved urinary continence. Theoretically, with the magnification of a laparoscope, the apical dissection and the preservation of the striated sphincter may be more appropriate in a deep pelvis, compared to the conventional open RRP. In all, few data are available about the impact of obesity on the different surgical techniques and randomised studies are lacking.

Recently, obesity was identified as a risk factor for cancer-related death for several cancers. For prostate cancer different studies suggested a positive association between BMI and grade, stage, positive surgical margins and PSA recurrence after RRP. The exact link between obesity and increased risk of developing aggressive prostate cancer, is not well understood. Development and progression of cancer in obese men may be elicited by alterations in sex hormones (testosterone, estradiol), and elevated levels of adipokines like insulin-like growth factors, leptin, and interleukin-6. Although obese men suffered more from a worse Gleason score (>7) and an increased number of positive surgical margins compared to non-obese, the present study could not demonstrate a significant association between BMI and the pathological characteristics, as well as the progression-free survival. However, the overall number of obese patients was too small for a firm interpretation of the aforementioned association.

Several limitations of the present study need to be mentioned. First, the numbers of obese patients were small as far as statistical power was concerned. Particularly, a multivariable analysis to adjust for potentially significant co-variables could not be performed in a meaningful way. Second, information was collected retrospectively and functional outcomes were not obtained by self-reported validated questionnaires. Third, other treatment modalities like brachytherapy and external beam radiotherapy are becoming more popular in the last few years. It is possible that more obese patients were shunted into these treatment options. This would bias the obese men in this study towards incontinence. Fourth, compared with the literature, the current study showed a high proportion of ASA 1 patients. Possibly ASA classifications were not well documented or a selection bias may have been occurred by referring ASA 2 patients with prostate cancer easier to a radiotherapist.
Conclusion

This study suggests that obese patients are at higher risk for developing urinary incontinence and VUS following RRP. These present findings can help when counselling obese patients who are prepared to undergo a radical prostatectomy.
Chapter 3

Reference List


Body mass index as a prognostic marker for biochemical recurrence in Dutch men treated with radical prostatectomy

BJU Int. 2009 Aug; 104:321-5

JGH van Roermund
DEG Kok
MF Wildhagen
LALM Kiemeney
F Struijk
S Sloot
IM van Oort
CA Hulsbergen- van de Kaa
GJLH van Leenders
CH Bangma
JA Witjes

PROSTATE CANCER. CLINICAL IMPLICATIONS OF OBESITY
Chapter 4

Abstract

Objective: To investigate whether body mass index (BMI) is a prognostic factor for biochemical recurrence (BCR) in Dutch men after radical prostatectomy (RP). Although epidemiological studies of obesity in relation to prostate cancer have provided conflicting results, recent studies from The United States of America suggest that a higher BMI as a risk factor for progression of prostate cancer.

Patients and methods: Of the 1,417 patients with prostate cancer who had RP at two university hospitals, 1,302 patients were included in the study. BMI (kg/m²) classes were defined as normal (<25), overweight (25-30) and obese (≥30). The median follow-up was 59 months and clinical data were obtained retrospectively from charts. BCR was defined as two consecutive prostate-specific antigen (PSA) levels of >0.10 ng/ml.

Results: In all, 600 patients were classified as having normal weight (43.9%), 665 as overweight (48.6%), and 103 as obese (7.5%). Overall, 297 patients developed BCR after RP; the 10-year risk (95% confidence interval) of BCR was 31.9% (26.6-37.2), 30.5% (25.8-35.2) and 23.9% (14.9-32.9) for patients in the three categories, respectively (p=0.836). Multivariable proportional hazard regression analyses of BMI and established prognostic factors for BCR did not change these results.

Conclusion: BMI appeared to have no prognostic value for BCR in Dutch patients with clinically localized prostate cancer treated with RP.
Introduction

Prostate cancer and obesity are among the most common health problems currently affecting European men. Obesity is now so common among the world's population that it is beginning to replace under-nutrition as the most significant contributor to ill health. Moreover, obesity has enormous public health consequences because it not only increases the risk of several chronic diseases like diabetes, hypertension, coronary heart diseases, and certain cancers, but it also imposes a large burden on healthcare use and costs.

The relationship between obesity and prostate cancer is debatable, with some studies indicating that obesity is associated with a decreased risk of prostate cancer and other studies suggesting an increased risk. However, recently two large American multi-institutional studies addressed a significantly higher biochemical recurrence (BCR) rate among obese men treated with radical prostatectomy (RP). Nearly all studies on obesity and the risk of death from prostate cancer or BCR are conducted in The United States of America (USA); this might be important, because not only is the incidence of obesity much higher in the USA than in Europe, but the mean body mass index (BMI) of obese patients is also higher. In addition, the USA population partly consists of African-Americans, who are more prone to be obese and have higher-grade prostate cancers. Therefore, the USA population has a distinct composition and characteristics compared to the European population. Thus we analysed men who had RP for clinically localized prostate cancer at two university hospitals (Radboud University Medical Centre, Nijmegen and Erasmus MC, University Medical Center, Rotterdam) in the Netherlands to evaluate the relationship between obesity and risk of BCR.

Patients and methods

Patients

The study population consisted of patients who had RP and for whom the medical records were reviewed retrospectively; 542 patients were treated at the Radboud University Medical Centre between 1992 and 2005, and 875 at the Erasmus University Medical Center between 1988 and 2007. Excluded were patients who had preoperative androgen deprivation or radiotherapy, and those with missing data for height or weight; in all, 49 patients were excluded. For an analysis of risk of BCR, patients with incomplete follow-up data, positive lymph nodes or PSA values that did not reach a nadir of < 0.1 ng/mL were also excluded (N=66). This resulted in a study population of 1,302 patients. Preoperative height and weight data were collected retrospectively by reviewing anaesthesia records. The BMI was calculated
as usual (kg/m²), and according to the World Health Organization categories⁹, patients were stratified into three groups, i.e. normal weight (<25), overweight (25-30) and obese (≥ 30).

Follow-up
In general, patients were seen every 3 months during the first year, every 6 months during the second and third year, and yearly thereafter unless there was evidence of cancer recurrence, in which case more frequent follow-up visits were necessary. The serum PSA level was obtained before surgery and at every follow-up visit. BCR was defined as two subsequent PSA levels of >0.10 ng/mL or if a second treatment after RP was needed. The time to BCR was measured from the date of RP until the date of first PSA level of >0.10 ng/mL.

Pathologic evaluation
All RP specimens were fixed overnight, inked, embedded and processed according to well-established protocols.¹⁰ Pathological staging and examination (seminal vesicle invasion, extracapsular extension, margin status and Gleason scores) were done by two specialised genitourinary pathologists (CAHK, GJL). The presence of tumour cells in the inked resection margin was considered a positive surgical margin. All stages were converted to the TNM staging criteria, using the 2002 American Joint Committee on Cancer classification.

Statistical analysis
Associations between the predefined BMI subgroups and clinical or pathological characteristics were examined using Chi-square tests in case of categorical characteristics and Mann-Whitney U tests or Kruskal-Wallis tests in case of continuous characteristics. The risk of BCR was assessed with the Kaplan-Meier method, using the log rank-test to compare subgroups. Cox proportional hazard model was used for multivariable analyses. Differences were considered to be statistically significant if p<0.05. Data were analysed using SPSS for Windows (version 15.0)

Results
Table 1 summarizes the clinical and pathologic characteristics of the study population stratified by preoperative BMI groups. The median (range) age of the patients at the time of RP was 63.1 (42.4-75.0) years, and the median BMI was 25.5 kg/m². In all, 600 patients were classified as having normal weight (43.9%), 665 as overweight (48.6%), and 103 as obese (7.5%). The median follow-up was 59.3 months and the median Gleason score was 6.
Overall, 297 patients developed BCR after RP. The 10-year Kaplan-Meier risk (95% CI) of BRC was 30.5% (27.2-33.8). Patients in the obese group had slightly lower recurrence rates than those in the normal weight group, but this was not statistically significant. The 10-year risk (95% CI) of BCR was 31.9% (26.6-37.2), 30.5% (25.8-35.2) and 23.9% (14.9-32.9) for patients in the normal, overweight and obese groups, respectively (p=0.836; figure 1).

Using Cox proportional hazards regression models, prognostic factors for the risk of BCR were evaluated by using univariable and multivariable analyses (table 2). Univariable regression analysis showed no significant association between the risk of BCR and obesity in obese (HR=0.94; 95% CI 0.59-1.48, p=0.78), and overweight patients (HR=1.05; 95%CI 0.83-1.34, p=0.67) compared with normal weight patients. Likewise, in multivariable regression analysis for risk of BCR, BMI did not appear to have an independent prognostic value.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal Weight N=600 (43.9%)</th>
<th>Overweight N=665 (48.6%)</th>
<th>Obese N=103 (7.5%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>63.0 (59.0-67.1)</td>
<td>63.3 (58.6-67.1)</td>
<td>62.1 (58.3-65.0)</td>
<td>0.127</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.5 (22.5-24.3)</td>
<td>26.9 (25.8-27.8)</td>
<td>31.4 (30.5-32.3)</td>
<td></td>
</tr>
<tr>
<td>Pre-operative PSA level, ng/ml</td>
<td>7.1 (4.8-11.1)</td>
<td>7.1 (4.6-11.8)</td>
<td>7.2 (4.6-10.2)</td>
<td>0.815</td>
</tr>
<tr>
<td>Follow-up, months</td>
<td>58.9 (23.7-100.4)</td>
<td>52.9 (18.0-98.2)</td>
<td>54.8 (21.5-102.8)</td>
<td>0.191</td>
</tr>
<tr>
<td>Pathological stage, T2</td>
<td>404 (67.4)</td>
<td>419 (63.3)</td>
<td>68 (66.0)</td>
<td>0.402</td>
</tr>
<tr>
<td>Pathological stage, T3</td>
<td>167 (27.9)</td>
<td>213 (32.3)</td>
<td>28 (27.2)</td>
<td></td>
</tr>
<tr>
<td>Pathological stage, T4</td>
<td>28 (4.7)</td>
<td>30 (4.5)</td>
<td>7 (6.8)</td>
<td></td>
</tr>
<tr>
<td>Gleason Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-6</td>
<td>278 (56.2)</td>
<td>299 (52.7)</td>
<td>39 (47.6)</td>
<td>0.310</td>
</tr>
<tr>
<td>7</td>
<td>170 (34.3)</td>
<td>221 (39.0)</td>
<td>37 (45.1)</td>
<td></td>
</tr>
<tr>
<td>8-10</td>
<td>47 (9.5)</td>
<td>47 (8.3)</td>
<td>6 (7.3)</td>
<td></td>
</tr>
<tr>
<td>Positive margins</td>
<td>208 (34.9)</td>
<td>256 (38.7)</td>
<td>42 (40.8)</td>
<td>0.276</td>
</tr>
<tr>
<td>Seminal vesicle involvement</td>
<td>67 (11.2)</td>
<td>55 (8.3)</td>
<td>10 (9.8)</td>
<td>0.776</td>
</tr>
<tr>
<td>Extracapsular extension</td>
<td>174 (29.5)</td>
<td>217 (33.3)</td>
<td>32 (31.7)</td>
<td>0.347</td>
</tr>
<tr>
<td>Lymph node involvement</td>
<td>18 (3.0)</td>
<td>11 (1.7)</td>
<td>2 (2.0)</td>
<td>0.277</td>
</tr>
</tbody>
</table>

Table 1 Patients and pathological characteristics.
IQR= Interquartile range
Discussion

Obesity is a growing problem in Western countries; in Europe, the prevalence of obesity has more than doubled during the last two decades. Obesity accounts for up to 6% of direct health costs and more than 12% of indirect health costs of shortened lives, reduced productivity, and lowered incomes in Europe. Simultaneously, since the introduction of PSA and the growing awareness of prostate cancer in men, the incidence and prevalence of localized prostate cancer is substantially increased and has become a major health problem. Several biological mechanisms have been proposed to explain the relation between adiposity and the risk of prostate cancer. Adipose tissue is an active endocrine and metabolic organ. Beyond alterations in sex steroid hormones (increased serum concentrations of oestradiol and decreased serum concentrations of testosterone) it produces adipokines like leptin, insulin-like growth factor-1, interleukin 6 and vascular endothelial growth factor. Alterations in sex steroid hormones and adipokines might contribute to the molecular basis of the association between obesity and prostate cancer. However, the exact role of obesity as related to the development of prostate cancer is not yet clear, although recent evidence does suggest a particular role for obesity in prostate cancer progression.
Mechanisms and the effect of obesity on prostate cancer have been reviewed in more detail elsewhere. Two large European historical cohort studies reported a positive relation between BMI and risk of prostate cancer, while others found a protective influence of obesity on the development of prostate cancer. Most studies examined incident prostate cancer cases regardless of stage or grade. However, prostate cancer has a highly variable natural history, which can range from fast disease progression in months to a more indolent tumour in which survival can be measured in decades.

Although the relation between obesity and prostate cancer risk has been indistinct, recently more consistent results were published on the positive association between obesity and prostate cancer mortality. Recent reports, all from the USA, showed poorer cancer control after RP, with a significantly greater propensity for higher grade disease, positive margins, and nodal and seminal involvement than in non-obese patients; the results of these studies are summarized in table 3. This suggests that obesity has a more prominent role in aggressiveness and progression rather than in the development of prostate cancer. These five studies from the USA,
**Table 3** A comparison of American studies reporting a relationship between BCR and obesity.

<table>
<thead>
<tr>
<th>Abbreviations: No= number; FU= follow-up; BMI= body mass index; SV= seminal vesicles; BCR= Biochemical recurrence; NA= not available; CI= Confidence interval; cont= continuous.</th>
</tr>
</thead>
<tbody>
<tr>
<td>* = Not significant</td>
</tr>
<tr>
<td>a = Patients in the normal weight and overweight cohorts were matched 1:1 to the cohort of obese patients on the basis of propensity scores</td>
</tr>
<tr>
<td>b = Pathologic Gleason score ≥7</td>
</tr>
<tr>
<td>c = Normal and overweight groups are combined</td>
</tr>
<tr>
<td>d = Univariable hazard ratio</td>
</tr>
<tr>
<td>e = Multivariable hazard ratio</td>
</tr>
</tbody>
</table>

reported a higher risk of BCR in obese than in non-obese patients within the first 5 years. Combining these studies, the risk of BCR within 5 years was, 23.1% for the non-obese and 31.8% for the obese patients. The present study could not confirm this relationship, as the 5-year risk of BCR was 23.9% for obese patients vs. 20.7% in the normal-weight patients. There are several explanations for this difference. First, all five previous studies mentioned were done in the USA; by contrast with these studies, in which 20 to 25% of men were obese, the present study had only 7% of obese patients in the study population. This is not surprising, when assessing the
National Health and Nutrition Examination Survey; in 2004 the prevalence of obesity among American men was around 32%. According to the Netherlands Health Interview Survey the prevalence of obesity in Dutch adult men was only 9%. The present study population had not only fewer obese patients, but more importantly, the obese patients in the study weighted less than those in the American studies listed in table 3. The higher degree and frequency of obesity might translate into more ‘fatter’ fat cells, which might produce a greater quantity of adipokines. This in their turn might result in a higher risk of BCR. Secondly, by contrast with the Dutch population, the population of the USA included African-American men. As an ethnic group, African-American men, who are also more obese, have significantly higher incidence of prostate cancer and of mortality rates than white men. For example, in the study of Amling et al. black race and BMI were associated with higher BCR in the univariable analysis, but in multivariable only black race remained significant. It is tempting to speculate that increased rates of African-American men might in part explain the differences in BCR after RP, especially because African-Americans are on average more obese and are more prone to have aggressive tumours.

In the present study, obese men more often had (although not significant) positive margins (40.8%) and T4 tumours (6.8%) than men had with normal weight (34.9% and 4.7%, respectively). Nevertheless, the risk of BCR was no higher in the obese men. This might be related to the rather few obese patients in the present study than in others. Interestingly, if there was BCR, the mean time to develop BCR was much shorter in the obese men, at 19.9 months, than in normal weight men, at 37.7 months.

The limitations of the present study are, first, the use of BCR as a surrogate of cancer-specific survival. This is important because it was previously reported that BCR can occur late in the postoperative course, and that the presence of BCR is not always a good predictor of prostate-cancer-specific death. A 10-year cohort study by Siddiqui et al., reported that despite worse pathologic features at the time of RP in obese patients, the long-term cancer-specific survival remained the same regardless of BMI. Second, additional quantitative measures of obesity, such as waist-to-hip ratio (calculated as the ratio of waist circumference, at the level midway between the lower rib margin and iliac crest, over the hip circumference at the maximum circumference over the buttocks) and waist circumference were not available. In clinical practice and epidemiological studies, body fat is most commonly estimated using BMI. Abdominal fatness, which is more metabolic active, is best measured by waist-to-hip ratio or waist circumference. This is particularly true in patients older than 75 years. In the present study most patients were much younger. Third, the height and weight data used were recorded from the anesthesia records, as reported by the patients at the time of surgery and introduced the possibility of a bias.
Chapter 4

Conclusion

Obese patients undergoing RP in two Dutch academic hospitals, had no worse pathological characteristics, and had no significantly greater risk of developing BCR.
Reference List

Chapter 4


Body mass index is not a prognostic marker for prostate-specific antigen failure and survival in Dutch men treated with brachytherapy

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JGH van Roermund
KA Hinnen
JJ Bateman
JA Witjes
JLHR Bosch
LALM Kiemeney
M van Vulpen

PROSTATE CANCER. CLINICAL IMPLICATIONS OF OBESITY
Abstract

Objective: Given the limited information regarding the impact of obesity on treatment outcomes for prostate cancer, we sought to examine the relation between body mass index (BMI) and biochemical recurrence (BCR), cancer-specific (CSS) and overall survival (OS) in men treated with brachytherapy.

Patients and Methods: In all, 1,530 patients with clinically localized prostate cancer who underwent brachytherapy were studied. Clinical and pathological data were retrospectively obtained from medical records. The BMI was classified as normal (<25 kg/m²), overweight (25-30 kg/m²) and obese (≥30 kg/m²). BCR was defined as a rise in PSA of ≥2 ng/mL after the nadir had been reached. The cause of death was determined for each deceased patient. Patients with metastatic prostate cancer who died of any cause were classified as prostate cancer deaths.

Results: 617 (40.3%) patients were classified as having a normal weight, 754 (49.3%) overweight and 159 (10.4%) were obese. The Kaplan-Meier 8-year risk of BCR (95% CI) was 33.3% (27.2-39.4), 29.2% (23.5-34.9) and 29.3% (12.4-46.2) for patients with a BMI of <25 kg/m², 25-30 kg/m² and ≥30 kg/m², respectively. The 8-year CSS was 88.2% (83.1-93.3), 88.6% (83.7-93.5) and 90.6% (79.9-100.0) and the 8-year OS was 70.1% (63.6-76.6), 72.9% (66.6-79.2) and 81.8% (69.3-94.3) for these 3 groups, respectively. Multivariable proportional hazard regression analyses of BMI and established prognostic factors for BCR confirmed the absence of any prognostic value of BMI on BCR, CSS and OS.

Conclusion: BMI did not appear to have any prognostic value for BCR, CCS or OS in with patients with clinically localized prostate cancer treated with brachytherapy.
### Introduction

Obesity and prostate cancer are two major health concerns in Western communities. In The Netherlands, like most countries in Western Europe, prostate cancer is one of the top three causes of cancer-related death among men. The increased public awareness of prostate cancer and increased prostate-specific antigen (PSA) testing has resulted in a higher incidence of clinically localized prostate cancer. Obesity is a fast growing epidemic worldwide. With the increasing prevalence of obesity and prostate cancer, the urologist and radiation oncologist will be confronted more frequently with obese patients having a potentially curable disease. However, the exact impact of obesity on treatment outcome of different treatment options for patients with prostate cancer is not well understood. Interestingly, in a study by Davies et al. obese patients were more likely to receive permanent prostate brachytherapy (PPB) compared with patients who were not obese.

Obesity, usually measured by body mass index (BMI, weight in kilograms divided by height in meters squared) has been linked to several chronic conditions such as cardiovascular disease, diabetes mellitus and hypertension. Obesity has also been identified as a risk factor for certain types of cancers, e.g. colorectal cancer, postmenopausal breast cancer, kidney cancer and endometrial cancer. More consistent data exist on the association between increased BMI and ‘aggressive’ prostate cancer, i.e. higher grade tumours, higher rate of positive surgical margins and a greater risk of biochemical recurrence (BCR) after radical prostatectomy (RP) or external beam radiation therapy (EBRT).

Obesity and prostate cancer are being increasingly addressed reflected by the increasing number of articles published on this topic in the recent years. However, to date, few data have been reported on the treatment of obese patients with prostate cancer, especially on PPB. Besides, most of these studies are conducted in the USA; this might be important because the USA population differs from the European population. Therefore, we investigated the relationship between BMI and biochemical recurrence (BCR), cancer-specific survival (CSS) and overall survival (OS) in a historical cohort of Dutch patients treated with PPB for clinically localized prostate cancer. To the best of our knowledge, this is the largest European study investigating the relation between BMI and prostate cancer outcome after PPB.
Patients and methods

Patients

Between 1991 and 2008, 1,730 patients with low-stage prostate cancer (stage cT1 or cT2) were treated with PPB at the department of Radiotherapy, University Medical Center Utrecht. Patients with no data on height or weight (N=154), missing follow-up data (N=13) or patients who received salvage PPB after EBRT (N=33) were excluded. This resulted in a study population of 1,530 patients. Height and weight data were collected retrospectively by reviewing anaesthesia records. According to the World Health Organization, patients were stratified into three groups, normal weight (<25 kg/m²), overweight (BMI 25-30 kg/m²) and obese (BMI ≥ 30 kg/m²). Patients underwent clinical staging by medical history, digital rectal examination and serum PSA measurement. Bone scans, pelvic lymph node dissection and computed tomography (CT) of the pelvis were obtained as clinically indicated.

Because Gleason grading was performed by different pathologists, Gleason scores were divided into three groups to minimize possible inconsistencies: low grade (Gleason score ≤ 6), intermediate grade (Gleason score 7), and high grade (Gleason score ≥ 8). Patients were also classified into three risk groups according to Ash et al.: low-risk disease (cT1b-cT2a [2002 American Joint Committee on Cancer system], low grade, and PSA level of ≤10 ng/mL), intermediate-risk disease (cT2b-cT2c or intermediate grade or PSA level between 10-20 ng/mL) and high-risk disease (>cT3 or high grade or PSA level of ≥ 20 or ≥ two intermediate risk factors).

Treatment

Patients underwent prostate implantation using I-125 seeds by three brachytherapists. Different treatment techniques were used throughout the study period (1989-2008), as previously described. Initially I-125 brachytherapy treatment consisted of transperineal implantation using single seeds, the latter being replaced by stranded seeds by July 1996. From 1998 onwards, routine volume study and pre-planning were performed in all patients. After that, in December 2000, a real-time intraoperative-planned approach was introduced, namely the Sonographic Planning of Oncology Treatment (SPOT) system and from 2002 the Fully Integrated Real-time Seed Treatment (FIRST) system (Nucletron B.V., Veenendaal, The Netherlands) was used. According to the Radiation Therapy Committee Task Group No. 43 of American Association of Physicists in Medicine, the planned dosage consisted of 144 Gy. Specific dose constraints, like D90 (minimal dose received by 90% of the prostate gland) and V100 (percentage of prostate volume receiving 100% of prescribed minimal peripheral dose) were not available for the early years of I-125 treatment. Since 2004, a post-planning CT and magnetic resonance imaging, on which these values were determined, are routinely performed. Because of the large amount of missing values before 2004, they were not used in the analysis.
### Table 1 Patients and pathological characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Normal Weight</th>
<th>Overweight</th>
<th>obese</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=617 (40.3%)</td>
<td>N=754 (49.3%)</td>
<td>N=159 (10.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>Median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>67.0 (62.0-71.0)</td>
<td>66.0 (61.0-70.0)</td>
<td>64.0 (60.0-70.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Body Mass Index, kg/m²</strong></td>
<td>23.5 (22.4-24.3)</td>
<td>26.7 (25.8-27.8)</td>
<td>31.3 (30.4-33.1)</td>
<td>0.62</td>
</tr>
<tr>
<td><strong>Pretreatment PSA, ng/mL</strong></td>
<td>9.1 (6.3-13.0)</td>
<td>8.8 (6.2-13.0)</td>
<td>8.8 (6.1-12.4)</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Follow-up, months</strong></td>
<td>47.0 (23.0-78.0)</td>
<td>47.0 (23.0-74.0)</td>
<td>37.5 (18.1-64.8)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Prostate volume, cm³</strong></td>
<td>33.1 (27.0-41.0)</td>
<td>35.0 (28.0-43.0)</td>
<td>35.0 (30.1-42.0)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Number of seeds</strong></td>
<td>70 (58-81)</td>
<td>73 (61-83)</td>
<td>73 (66-82)</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>N (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment period</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I 1989- June 1996</td>
<td>50 (8.1)</td>
<td>44 (5.8)</td>
<td>4 (2.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>II July 1996-2001</td>
<td>168 (27.2)</td>
<td>187 (24.8)</td>
<td>35 (22.0)</td>
<td></td>
</tr>
<tr>
<td>III 2002- present</td>
<td>397 (64.3)</td>
<td>519 (68.8)</td>
<td>118 (74.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>378 (61.3)</td>
<td>483 (64.1)</td>
<td>113 (71.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>T2</td>
<td>238 (38.6)</td>
<td>271 (35.9)</td>
<td>45 (28.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Pathological Grading</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>326 (52.8)</td>
<td>397 (52.7)</td>
<td>95 (59.7)</td>
<td>0.09</td>
</tr>
<tr>
<td>2</td>
<td>277 (44.9)</td>
<td>349 (46.3)</td>
<td>60 (37.7)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>9 (1.5)</td>
<td>3 (0.4)</td>
<td>1 (0.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Ash Risk group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>189 (30.6)</td>
<td>224 (29.7)</td>
<td>50 (31.4)</td>
<td>0.19</td>
</tr>
<tr>
<td>Intermediate</td>
<td>234 (37.9)</td>
<td>321 (42.6)</td>
<td>71 (44.7)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>191 (31.0)</td>
<td>206 (27.3)</td>
<td>36 (22.6)</td>
<td></td>
</tr>
<tr>
<td><strong>PLND</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>35 (5.7)</td>
<td>30 (4.0)</td>
<td>5 (3.1)</td>
<td>0.22</td>
</tr>
<tr>
<td>No</td>
<td>582 (94.3)</td>
<td>724 (96.0)</td>
<td>154 (96.9)</td>
<td></td>
</tr>
<tr>
<td><strong>ADT</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>82 (13.3)</td>
<td>165 (21.9)</td>
<td>34 (21.2)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>532 (86.2)</td>
<td>588 (78.0)</td>
<td>124 (78.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Preoperative TURP</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.13</td>
</tr>
<tr>
<td>Yes</td>
<td>49 (7.9)</td>
<td>40 (5.3)</td>
<td>9 (5.7)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>568 (92.1)</td>
<td>714 (94.7)</td>
<td>150 (94.3)</td>
<td></td>
</tr>
</tbody>
</table>

In all, 281 patients (18.4%) received androgen deprivation therapy (ADT) for 6 months before their PPB. ADT was initiated if patients had a large prostate (>50 cm³) to achieve prostate volume reduction before the planned PPB. The ADT consisted of a luteinizing hormone-releasing hormone agonist. No patients received supplemental EBRT.
Follow-up

Generally, patients were seen every 3 months during the first year, every 6 months during the second and third year and yearly thereafter unless there was evidence of cancer recurrence, in which case more frequent follow-up visits were deemed necessary. The serum PSA level was obtained before PPB and at every follow-up visit. According to the Phoenix Consensus Conference BCR was defined as a rise in PSA of $\geq 2$ ng/mL after the nadir had been reached. Time to BCR was measured from date of PPB until date of a PSA level of nadir plus $\geq 2$ ng/mL was reached. The cause of death was determined for each deceased patient. Patients with metastatic prostate cancer who died of any cause were classified as prostate cancer deaths.

Statistical analysis

Associations between predefined BMI subgroups and clinical or pathological characteristics were examined by Chi-square tests in case of categorical characteristics and Kruskal-Wallis tests in case of continuous characteristics. The risk of BCR, cause specific and overall survival was assessed with the Kaplan-Meier method using the
Table 2 8-year risk of biochemical recurrence, cancer-specific and overall survival (95% confidence interval).

<table>
<thead>
<tr>
<th></th>
<th>Normal weight</th>
<th>Overweight</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemical recurrence, (%)</td>
<td>33.3 (27.2-39.4)</td>
<td>29.2 (23.5-34.9)</td>
<td>29.3 (12.4-46.2)</td>
</tr>
<tr>
<td>Cancer-specific survival, (%)</td>
<td>88.2 (83.1-93.3)</td>
<td>88.6 (83.7-93.5)</td>
<td>90.6 (79.9-100.0)</td>
</tr>
<tr>
<td>Overall survival, (%)</td>
<td>70.1 (63.6-76.6)</td>
<td>72.9 (66.6-79.2)</td>
<td>81.8 (69.3-94.3)</td>
</tr>
</tbody>
</table>

log rank-test for the comparison between subgroups. Univariable and multivariable Cox's proportional hazard models were used to determine if any of the clinical or treatment variables predicts BCR, CSS and OS. The PSA level before PPB, pathologic stage and grading were not included in the multivariable analyses, because the variable risk group is based on these parameters. Differences were considered to be statistically significant if p < 0.05. Data were analysed using SPSS for Windows (version 15.0).

Results

Table 1 summarizes the clinical and pathological characteristics of the study population stratified by preoperative BMI. At time of PPB, the study population had a median age of 67.0 years and a median BMI of 25.7 kg/m². In all, 617 (40.3%) patients were classified as having a normal weight, 754 (49.3%) were overweight, and 159 (10.4%) were obese. The median PSA level before PPB was 8.9 ng/mL and the median Gleason score was 6. Compared to patients that were not obese, obese patients were significantly younger and received PPB more frequently during the most recent treatment period (2002-present). Obesity was significantly associated with prostate volume, adjuvant ADT and number of seeds needed during PPB. Over time there was a significant increase in BMI, each year the BMI increased with 0.09 kg/m².

As expected, patients whose prostate cancer progressed were more likely to have more advanced disease (highest risk group) than those who did not progress (data not shown). After a median follow-up of 47.0 months 249 patients (16.3%) developed BCR and 193 (12.6%) died after the PPB, of which 61 died of prostate cancer. The overall 8-year Kaplan-Meier risk (95% CI) of BCR, CSS and OS was 32.2% (28.1-36.3), 88.6% (85.3-91.9), 72.3% (68.0-76.6), respectively. The 8-year risk of BCR, CSS and OS did not differ significantly within the three BMI groups. (figure 1; table 2)
Table 3a Univariable and multivariable Cox proportional hazard analyses of Biochemical Recurrence-free Survival.
Abbrevations: PSA= prostate-specific antigen; Preop = preoperative; PLND= pelvic lymph node dissection; ADT= androgen deprivation therapy; BMI= Body Mass Index; NS=non significant.

Using univariable proportional hazards regression analysis, there was no significant association between the risk of BCR, CSS or OS and obesity. (table 3) Likewise in multivariable regression analysis for risk of BCR, CSS and OS, BMI did not appear to have an independent prognostic value.

As listed in table 3, in univariable analyses, age, preoperative PSA level, pathological stage and grade, risk group, treatment in the first period and number of seeds were significantly associated with increased risk of BCR, CSS and OS. In multivariable analyses only patients in the highest risk group were significantly associated with increased risk of BCR, CSS and OS. In multivariable analysis, age was a strong prognostic factor for OS.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Biochemical Progression-free survival</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariable HR (95% CI)</td>
<td>p-value</td>
<td>Multivariable HR (95% CI)</td>
<td>p-value</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.03 (1.01-1.05)</td>
<td>0.001</td>
<td>1.00 (0.98-1.02)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Preoperative PSA</td>
<td>1.05 (1.04-1.06)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathological stage (T1 vs. T2)</td>
<td>1.98 (1.55-2.55)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathological grade Good</td>
<td>1.42 (1.09-1.84)</td>
<td>0.009</td>
<td>4.58 (2.21-9.50)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Pathological grade Intermediate (vs. good)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathological grade Poor (vs. good)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk group</td>
<td>2.08 (1.28-3.39)</td>
<td>0.003</td>
<td>2.30 (1.41-3.75)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Treatment period</td>
<td>7.83 (5.02-12.24)</td>
<td>&lt;0.001</td>
<td>7.45 (4.69-11.82)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Prostate volume (cm³)</td>
<td>0.99 (0.98-1.00)</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop PLND (yes vs. no)</td>
<td>2.35 (1.60-3.43)</td>
<td>&lt;0.001</td>
<td>1.14 (0.76-1.71)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>ADT (yes vs. no)</td>
<td>0.88 (0.62-1.26)</td>
<td>NS</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>BMI &lt; 25 kg/m²</td>
<td>0.91 (0.70-1.19)</td>
<td>NS</td>
<td>1.00 (0.77-1.31)</td>
<td>NS</td>
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</tr>
<tr>
<td>BMI 25-30 kg/m²</td>
<td>0.93 (0.59-1.46)</td>
<td>NS</td>
<td>1.15 (0.72-1.85)</td>
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<td>BMI ≥ 30 kg/m²</td>
<td>0.98 (0.94-1.02)</td>
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<tr>
<td>Treatment period</td>
<td>1989-June 1996</td>
<td>0.83 (0.97-1.00)</td>
<td>&lt;0.001</td>
<td>0.83 (0.97-1.00)</td>
<td>NS</td>
</tr>
<tr>
<td>Number of seeds</td>
<td>0.99 (0.98-0.99)</td>
<td>&lt;0.001</td>
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### Table 3b Univariable and multivariable Cox proportional hazard analyses of Cause-specific Survival.

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<tr>
<th>Variable</th>
<th>Univariable HR (95% CI)</th>
<th>p-value</th>
<th>Multivariable HR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
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<td>0.007</td>
<td>1.02 (0.98-1.06)</td>
<td>NS</td>
</tr>
<tr>
<td>Preoperative PSA</td>
<td>1.04 (1.03-1.06)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Pathological stage (T1 vs. T2)</td>
<td>2.97 (1.72-5.14)</td>
<td>&lt;0.001</td>
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</tr>
<tr>
<td>Pathological grade</td>
<td></td>
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<tr>
<td>Good</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate (vs. good)</td>
<td>3.20 (1.81-5.65)</td>
<td>&lt;0.001</td>
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<tr>
<td>Poor (vs. good)</td>
<td>6.30 (1.39-28.67)</td>
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<td></td>
</tr>
<tr>
<td>Risk group</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate (vs. low)</td>
<td>1.78 (0.46-6.90)</td>
<td>NS</td>
<td>1.80 (0.46-7.00)</td>
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</tr>
<tr>
<td>High (vs. low)</td>
<td>11.5 (3.59-37.0)</td>
<td>&lt;0.001</td>
<td>8.81 (2.65-29.2)</td>
<td>&lt;0.001</td>
</tr>
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<td>Prostate volume (cm³)</td>
<td>1.00 (0.97-1.02)</td>
<td>NS</td>
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<td></td>
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<tr>
<td>Preop PLND (yes vs. no)</td>
<td>2.20 (1.11-4.39)</td>
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<td></td>
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</tr>
<tr>
<td>ADT (yes vs. no)</td>
<td>0.56 (0.20-1.54)</td>
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<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt; 25 kg/m²</td>
<td></td>
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<tr>
<td>25-30 kg/m²</td>
<td>0.94 (0.56-1.60)</td>
<td>NS</td>
<td>1.07 (0.60-1.88)</td>
<td>NS</td>
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<td>≥ 30 kg/m²</td>
<td>0.80 (0.28-2.28)</td>
<td>NS</td>
<td>1.46 (0.50-4.28)</td>
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<td>BMI (continuous)</td>
<td>0.96 (0.88-1.04)</td>
<td>NS</td>
<td></td>
<td></td>
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<tr>
<td>Treatment period</td>
<td></td>
<td></td>
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<td>1989-June 1996</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>July 1996-2001</td>
<td>0.35 (0.20-0.61)</td>
<td>&lt;0.001</td>
<td>1.05 (0.41-2.71)</td>
<td>NS</td>
</tr>
<tr>
<td>2002-present</td>
<td>0.13 (0.04-0.40)</td>
<td>&lt;0.001</td>
<td>0.53 (0.14-2.08)</td>
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</tr>
<tr>
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<td>0.001</td>
<td>0.98 (0.95-1.00)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Discussion

The exact role of obesity in the development and progression of prostate cancer is not well understood. Several biological mechanisms have been proposed. Adipose tissue, especially abdominal visceral fat, is an active endocrine and metabolic organ. Besides alterations in sex steroid hormones (increased serum concentrations of estradiol and decreased serum concentrations of testosterone) it produces adipokines, e.g. insulin-like growth factor-1, interleukin-6, vascular endothelial growth factor and leptin. Two large European historical cohort studies reported a positive correlation between BMI and prostate cancer risk, while others found a protective effect of obesity on
<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable HR (95% CI)</th>
<th>p-value</th>
<th>Multivariable HR (95% CI)</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>1.09 (1.06-1.11)</td>
<td>&lt;0.001</td>
<td>1.07 (1.04-1.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preoperative PSA</td>
<td>1.02 (1.01-1.04)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathological stage (T1 vs. T2)</td>
<td>1.56 (1.16-2.08)</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathological grade Good</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate (vs. good)</td>
<td>1.63 (1.21-2.20)</td>
<td>0.01</td>
<td></td>
<td></td>
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<tr>
<td>Poor (vs. good)</td>
<td>4.75 (2.05-11.00)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
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<tr>
<td>Risk group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate (vs. low)</td>
<td>1.03 (0.66-1.61)</td>
<td>NS</td>
<td>0.94 (0.60-1.49)</td>
<td>NS</td>
</tr>
<tr>
<td>High (vs. low)</td>
<td>2.38 (1.61-3.53)</td>
<td>&lt;0.001</td>
<td>1.59 (1.04-2.44)</td>
<td>0.03</td>
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<tr>
<td>Prostate volume (cm³)</td>
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<tr>
<td></td>
<td>0.99 (0.98-1.00)</td>
<td>NS</td>
<td></td>
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</tr>
<tr>
<td>Preop PLND (yes vs. no)</td>
<td>1.41 (0.88-2.28)</td>
<td>NS</td>
<td></td>
<td></td>
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<tr>
<td>ADT (yes vs. no)</td>
<td>0.59 (0.35-1.01)</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
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<td>&lt; 25 kg/m²</td>
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<tr>
<td>25-30 kg/m²</td>
<td>0.89 (0.66-1.19)</td>
<td>NS</td>
<td>0.98 (0.72-1.33)</td>
<td>NS</td>
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<tr>
<td>≥ 30 kg/m²</td>
<td>0.77 (0.43-1.39)</td>
<td>NS</td>
<td>1.09 (0.59-2.01)</td>
<td>NS</td>
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<tr>
<td>BMI (continuous)</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td>0.95 (0.91-1.00)</td>
<td>NS</td>
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<tr>
<td>Treatment period</td>
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<tr>
<td>1989-June 1996</td>
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<tr>
<td>July 1996-2001</td>
<td>0.45 (0.32-0.62)</td>
<td>&lt;0.001</td>
<td>0.96 (0.57-1.61)</td>
<td>NS</td>
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<tr>
<td>2002-present</td>
<td>0.30 (0.19-0.48)</td>
<td>&lt;0.001</td>
<td>0.78 (0.42-1.45)</td>
<td>NS</td>
</tr>
<tr>
<td>Number of seeds</td>
<td>0.98 (0.97-0.99)</td>
<td>&lt;0.001</td>
<td>0.98 (0.96-0.99)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Table 3c: Univariable and multivariable Cox proportional hazard analyses of Overall Survival.
Abbrevations: PSA= prostate-specific antigen; Preop = preoperative; PLND= pelvic lymph node dissection; ADT= androgen deprivation therapy; BMI= Body Mass Index; NS=non significant.

prostate cancer. Although the relation between obesity and prostate cancer risk is indistinct, there is more consistency in published papers about a positive association between obesity and prostate cancer mortality. This suggests that obesity might play a more prominent role in the progression than in the development of prostate cancer.

Recently, reports have shown a higher risk of BCR in obese patients who underwent RP or EBRT compared those who were not obese. The hazard ratio (HR) varied between 1.04 (95% CI, 1.02-1.07) to as high as 1.99 (95% CI, 1.21-3.27) when comparing obese patients with normal weight patients. This may be explained by technical difficulties during dissection of the prostate in obese patients resulting...
BMI as a marker for biochemical recurrence

in more positive margins. Also, in obese patients receiving EBRT, daily treatment is often compromised by set up errors because of the increased organ motion by excessive intra-abdominal adipose tissue. However, in the present study there was no significant association between the risk of BCR and obesity. The 8-year risk of BCR was 29.3% for obese patients compared with 33.3% in the normal weight patients. The present findings are consistent with three other published reports evaluating the relationship between obesity and BCR after PPB. Notably, 13% to 54% of the patients received adjuvant EBRT in these studies.24-26

By contrast with the RP and EBRT studies, several explanations can be given as to why BMI did not influence BCR in the present study. First, compared with patients who were not obese, in the present study obese patients were more frequently treated in the most recent treatment period (2002-present). Patients treated in this period had a significantly smaller risk of BCR after PPB (HR=0.27, 95% CI 0.18-0.39) in the univariable analysis. However, in the multivariable analysis treatment period did not have an independent prognostic value. Second, there has been less enthusiasm for the use of PPB in men with high-risk disease. On the one hand, the present PPB patient group might very well be a selected and more homogeneous group of patients with a better prognostics profile. It is attractive to speculate that obese patients with high-risk prostate cancer are more often treated with RP or EBRT. As a result, patients who are treated with other methods might be more at risk of developing BCR. On the other hand, in the present study a smaller percentage (although not statistically significant) of obese men had high-risk disease compared with normal weight men. Third, the studies that evaluated the risk of BCR after RP consisted of many more Afro-Americans (average 21%) compared with the PPB studies (<5%). Afro-Americans are more prone to be obese and more frequently have aggressive tumours compared with white men. In the study of Amling et al.7 black race and BMI were associated with higher BCR after RP in the univariable analysis; however, in multivariable only black race remained significant. Differences in BCR risk in obese patients, treated by RP or PPB, may be partly explained by the differences in the distribution of race seen in the aforementioned studies.

Fourth, obese patients significantly more often received ADT in the present study (Table 1); this may have improved prognosis in patients with a higher BMI. Fifth, older age correlates with worse disease. In the present study, the obese patients were significantly younger and the follow-up among the obese patients was tending toward significance. Although these differences are small, it should be considered whether these factors in concert could mask an effect.

It is important to notice that BCR is a surrogate of CSS. BCR can occur late in the postoperative course and the presence of BCR is not always a good predictor of CSS. A 10-year cohort study by Siddiqui et al.27 reported that despite worse pathological
features at time of RP in obese patients, long-term CSS remained the same regardless of BMI. In the present study BMI was not related with CSS. Only one other study by Merrick et al.\textsuperscript{26} examined the relation between BMI and CSS in patients who underwent PPB, and same conclusions were drawn.

To determine if obesity was an independent predictor for BCR, Freedland et al.\textsuperscript{28} investigated patients who underwent RP and had organ confined disease and negative surgical margins. After controlling for the higher pathological Gleason grades among obese men, BMI remained a significant predictor of BCR with moderately and severely obese men (BMI $\geq$ 35 kg/m$^2$) having nearly a four-fold increased risk for BCR. In that study, surgical technique (margin status) could not fully explain the worse outcomes among obese patients, suggesting that obesity may be associated with a biologically more aggressive prostate cancer.

Limitations of the present study are the following. First, the retrospective nature of this study. Second, additional quantitative measures of obesity, such as waist-to-hip ratio and waist circumference were not available. Abdominal fat is the most metabolic and endocrine active fat in the human body and best measured by waist-to-hip ratio or waist circumference. Third, specific dose constraints, like D90 and V100 were not available for the whole study population. Fourth, the cohort of obese men was only 10%. It is possible that some of the associations that were tending towards significance might reached significance with a few more men in the obese group. However, according to the Netherlands Health interview Survey the prevalence of obesity in Dutch men is only 9%.\textsuperscript{29}

Urologists and radiation oncologists will be confronted more often with obese men with clinically localized prostate cancer. However, to date there is no consensus about what the best treatment option (RP, EBRT, PPB) should be for an obese patient with localized prostate cancer. Although accrual might be difficult, randomised prospective studies are needed to clarify this problem.

**Conclusion**

The present study is the largest single institution series to describe the possible impact of BMI on BCR, CSS and OS in patients who underwent PPB for clinically localized prostate cancer. BMI was not a prognostic marker for BCR, CSS or OS.
Reference List


Periprostatic fat measured on computed tomography as a marker for prostate cancer aggressiveness

World J Urol. 2009 Dec 22
[Epub ahead of print]

JGH van Roermund
GH Bol
JA Witjes
JLHR Bosch
LALM Kiemeney
M van Vulpen

PROSTATE CANCER. CLINICAL IMPLICATIONS OF OBESITY
Abstract

Objective: Several reports found that obesity was associated with prostate cancer aggressiveness among men treated with radical prostatectomy or radiotherapy. Studies concerning this issue have basically relied on body mass index (BMI), as a marker for general obesity. Because visceral fat is the most metabolic active fat, we sought to evaluate if periprostatic fat measured on a computed tomography (CT) is a better marker than BMI to predict prostate cancer aggressiveness in a Dutch population who underwent brachytherapy for localized prostate cancer.

Patients and methods: Of the 902 patients who underwent brachytherapy, 725 CT scans were available. Subcutaneous fat thickness, periprostatic fat area (cm²) and periprostatic fat density (%) were determined on the CT scan. Patients were stratified into 3 groups: <25, 25-75 and > 75 percentile of the fat-density. Associations between the three fat-density subgroups and BMI and prostate cancer aggressiveness were examined.

Results: 237 patients were classified as having normal weight (37.2%), 320 as overweight (50.2%) and 80 as obese (12.6%). There was a strong significant association between BMI and periprostatic fat density and subcutaneous fat thickness. The strongest correlation was seen between BMI and subcutaneous fat thickness (Pearson r coefficient=0.71). Logistic regression analysis revealed no statistically significant association between the different fat measurements and the risk of having a high-risk disease.

Conclusion: Periprostatic fat and periprostatic fat density as measured with CT were not correlated with prostate cancer aggressiveness in patients receiving brachytherapy. However, 31% of the patients with a normal BMI had a periprostatic fat density of >75 percentile of the periprostatic fat density.
Introduction

Obesity and prostate cancer are two major health concerns. On the one hand, obesity is a rapidly growing worldwide epidemic and it increases the risk of several chronic diseases and certain cancers. On the other hand, prostate cancer is diagnosed more often in the prostate-specific antigen (PSA) era and the disease is often diagnosed in a localized stage suitable for curative treatment. The relationship between obesity and prostate cancer is debated, with studies finding an inverse, a linear correlation with prostate cancer, or no relation at all. However, several studies found a link between obesity and disease aggressiveness. Recently, the classical perception of adipose tissue as a storage place of fatty acids has been replaced by the notion that adipose tissue produces a large number of hormones and cytokines, e.g., tumour necrosis factor-α, interleukin-6, leptin and adiponectin. The exact role of these cytokines in prostate carcinogenesis, however, is not known. Most of the studies that investigated the role of obesity on prostate cancer used body mass index (BMI, the weight in kilograms divided by the squared height in meters) as a marker of general obesity. Although there is a strong correlation between BMI and waist-circumference, the most metabolic active fat is the abdominal visceral fat and a better way to measure this is by waist-hip ratio or waist-circumference. Therefore, waist-circumference as an indicator of abdominal fat may be a better predictor for prostate cancer risk than BMI alone, especially in men with a low BMI. Computed tomography (CT) is another technique which measures visceral fat even more accurately.

The aim of this study was to investigate whether periprostatic fat, measured on a CT scan, is a better marker for prostate cancer aggressiveness in patients who underwent brachytherapy for localized prostate cancer compared to BMI. We also evaluated the relation between BMI and different fat measurements. To the best of our knowledge such a study has never been performed.

Patients and methods

Patients

Between April 2004 and August 2008, 902 patients with biopsy-proven localized prostate cancer (stage cT1 or cT2) were treated with transrectal ultrasonography guided transperineal permanent mono brachytherapy at the department of Radiotherapy, University Medical Center Utrecht, The Netherlands. Due to the very short follow-up of this cohort of men we only focused on prostate cancer baseline characteristics. Patients underwent clinical staging by medical history, digital rectal examination and serum PSA measurement. Bone scans were obtained and pelvic lymph node dissection
A CT was performed when clinically indicated. A CT was performed to determine specific dose constraints 4 weeks after brachytherapy. A CT was performed one day after the brachytherapy to determine specific dose constraints. The CT was not performed in 153 patients and in 24 patients the quality of the CT was poor due to hip prostheses. This resulted in a study population of 725 men. Because different risk classifications are used in the literature we decided to use two different risk classifications, one according to Ash et al.13 and the other according to D’Amico et al.14 Tumour stage was described according to the 2002, TNM, American Joint Committee on Cancer system.

**Fat measurement**

Preoperative height and weight data were collected retrospectively by reviewing anaesthesia records. The BMI (kg/m²) was calculated and stratified into three groups according to the WHO, i.e. normal weight (<25), overweight (25-30) and obese (≥30). Only one patient had a BMI value of < 18.5 kg/m², this patient was included in the normal weight group. The CT scans were acquired on a single slice CT (Aura, Philips Medical Systems, Best, The Netherlands), and had an in-plane slice resolution of 0.49 X 0.49 mm with a slice thickness of 3 mm. We used an in-house developed software tool for delineation of the pelvic fat region and the measurement of the subcutaneous fat thickness (figure 1).15

Because there are no comparable studies available we chose to delineate along established lines (figure 1). The fat contained within the delineated contours of the CT, is segmented by thresholding on the Hounsfield Units (HU). We differentiated between fat (-190 to -30 HU), air (< -500 HU) and other soft tissue types.16 Since the delineated contours did not contain bony structures, we did not include a threshold for segmenting the bones separately. The total contour area (cm²) was calculated by the total number of voxels within the contour minus the number of air voxels and the periprostatic fat area (cm²) by counting ‘fat’ voxels within the total contour area. The periprostatic fat density (%) was calculated by dividing periprostatic fat by the total contour area.

Patients were stratified into 3 groups: <25 percentile (group 1), between 25 and 75 percentile (group 2) and >75 percentile (group 3) of the fat-density.

**Statistical analysis**

Associations between the predefined three fat-density subgroups and clinical or pathological characteristics were examined by Chi-square tests in case of categorical characteristics and Kruskal-Wallis tests in case of continuous characteristics. The Pearson correlation coefficient was used to quantify correlations between BMI and the different fat measurements. Binary logistic regression analyses were performed to
Periprostatic fat measured on CT

Figure 1 Images demonstrate our method for determining visceral fat distribution and subcutaneous fat thickness on a CT scan.

A: Tranverse section is made at the level of the femoral head and the greater trochantor of the femur. The red line outlines the total contour area (cm²), in which attenuation is measured. The line is drawn at the back side of the pubic bone, following the border of the internal obturatorius muscle, anterior side of the gluteus maximus muscle and coccyx bone. Within the region of interest the periprostatic fat area (cm²) and the periprostatic fat density (%) dividing periprostatic fat by the total area within the red countour) was calculated.

B: Transverse section is made at the level of superior pubic ramus. The red line outlines the subcutaneous fat thickness by which the distance between the skin and pubic bone is measured (cm).

evaluate the independent effect of each variable on the risk of having high-risk disease versus low- or intermediate-risk (according to Ash et al.\textsuperscript{13} and D’Amico et al.\textsuperscript{14}). Differences were considered to be statistically significant if p<0.05. Data were analysed using SPSS for Windows (version 15.0).

Results

The median age (range), BMI and periprostatic fat density at the time of brachytherapy was 66 years (45-81), 25.8 kg/m² (17.6-56.8) and 31.8% (10.0-52.2), respectively. In 88 (12%) patients the BMI was not available. In all, 237 patients were classified as having normal weight (37.2%), 320 as overweight (50.2%) and 80 as obese (12.6%). Table 1 summarizes the clinical and pathological characteristics of the study population stratified by periprostatic fat density. Patients in group 3 were significantly older. The median prostate volume was statistically different between the 3 groups but the differences were not clinically relevant. A clear significant association was seen between the periprostatic fat density groups and BMI, subcutaneous fat thickness and periprostatic fat. Figure 2 shows
Table 1 Baseline characteristics.
Patients were stratified by fat density. IQR= interquartile range; a = Kruskal-Wallis-test; b = \( \chi^2 \)-test.

the correlation between BMI and the different fat measurements. The strongest correlation was seen between BMI and subcutaneous fat thickness (Pearson \( r \) coefficient=0.71, \( p<0.001 \)).

Logistic regression analysis revealed no statistically significant association between the different fat measurements and the risk of having high-risk disease (table 2). Only age was significantly associated with increased risk of having a high-risk disease, however in the multivariable analysis (data not shown) this significance disappeared.
Figure 2 Correlation between body mass index and different fat measurements. The linear regressive line is shown with 95% CI. The vertical line represents the median.

Discussion

The urologist and radiation oncologist will be confronted more frequently with obese patients having a localized prostate cancer. Although the association between obesity and the risk of prostate cancer risk is controversial, a stronger link between obesity and increased risk for higher pathologic grade and higher rates of biochemical recurrence compared with normal weight patients was seen in several studies. Of note, all these studies were done in the USA. We conducted a study in The Netherlands where we evaluated 1,302 patients who underwent a radical prostatectomy. In that study BMI did not appear to have any prognostic value for biochemical recurrence or worse pathologic features. Same conclusions were drawn by Pfitzenmaier et al. In contrast with the USA, where 30% of the population is obese, only 9% to 14% of the European population was obese. Thereby, obese patients are less obese than the obese men in the USA and a relatively large proportion of the USA population consists of Afro-Americans who are more prone to be obese and more frequently have aggressive tumours compared with white men.

A question may present itself: are we measuring obesity in the right way? In most studies investigating obesity in relation to prostate aggressiveness and biochemical recurrence, BMI is used as a criterion for general obesity. The most metabolic active
<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.07 (1.03-1.11)</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Prostate volume, cm³</strong></td>
<td>1.00 (0.98-1.02)</td>
<td>0.68</td>
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<td>BMI (continuous)</td>
<td>0.97 (0.92-1.03)</td>
<td>0.37</td>
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<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
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<tr>
<td>&lt;25 kg/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-30 kg/m²</td>
<td>0.80 (0.53-1.21)</td>
<td>0.29</td>
</tr>
<tr>
<td>≥30 kg/m²</td>
<td>0.51 (0.24-1.06)</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Periprostatic fat density (continuous)</strong></td>
<td>1.00 (0.97-1.03)</td>
<td>0.94</td>
</tr>
<tr>
<td><strong>Periprostatic fat density</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>0.89 (0.56-1.40)</td>
<td>0.61</td>
</tr>
<tr>
<td>Group 3</td>
<td>1.05 (0.63-1.76)</td>
<td>0.85</td>
</tr>
<tr>
<td><strong>Subcutaneous fat thickness</strong></td>
<td>0.96 (0.85-1.10)</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>Periprostatic fat area</strong></td>
<td>1.00 (0.976-1.02)</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Table 2a Univariable logistic regression analysis of factors predicting high-risk disease according to Ash.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.06 (1.00-1.13)</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Prostate volume, cm³</strong></td>
<td>1.01 (0.97-1.05)</td>
<td>0.57</td>
</tr>
<tr>
<td>BMI (continuous)</td>
<td>0.89 (0.79-1.01)</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 kg/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-30 kg/m²</td>
<td>0.63 (0.29-1.34)</td>
<td>0.23</td>
</tr>
<tr>
<td>≥30 kg/m²</td>
<td>0.40 (0.86-1.73)</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>Periprostatic fat density (continuous)</strong></td>
<td>1.00 (0.95-1.06)</td>
<td>0.94</td>
</tr>
<tr>
<td><strong>Periprostatic fat density</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>0.69 (0.30-1.59)</td>
<td>0.39</td>
</tr>
<tr>
<td>Group 3</td>
<td>1.24 (0.52-2.96)</td>
<td>0.62</td>
</tr>
<tr>
<td><strong>Subcutaneous fat thickness</strong></td>
<td>0.80 (0.95-1.05)</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Periprostatic fat area</strong></td>
<td>1.00 (0.96-1.05)</td>
<td>0.93</td>
</tr>
</tbody>
</table>

Table 2b Univariable logistic regression analysis of factors predicting high-risk disease according to D’Amico.

Fat however, is the abdominal visceral fat. Waist-circumference, as an indicator of abdominal obesity may be a better predictor of risk of more aggressive prostate cancer than BMI, especially in individuals with a lower BMI. Visceral fat is the most metabolic active fat and produces adipokines. Obesity is associated with increased levels of several adipokines and studies reported a link between the level of adipokines and aggressive prostate cancer.25-27
A large study by the European Prospective Investigation into Cancer and Nutrition (EPIC) group concluded that once general obesity was adjusted for abdominal fat distribution it was positively associated with the risk of death. This association tended to be stronger among participants with a lower BMI.\textsuperscript{28} In a large prospective cohort of 148,372 men, Pischon et al. found that higher waist-circumference was associated with increased risk of advanced prostate cancer and high-grade prostate cancer among individuals with lower BMI. The relative risk of advanced prostate cancer was 1.06 (95% CI 1.01-1.10) per 5-cm-larger waist circumference.\textsuperscript{29} Same conclusions were drawn in a prospective Swedish study.\textsuperscript{30} These data suggest that especially abdominal adiposity may be associated with an increased risk of advanced prostate cancer and waist-circumference is a better way to measure obesity.

Visceral fat can affect both the lean and obese and is more metabolically active than subcutaneous fat. By measuring the waist-circumference the discrepancy between thin outside (subcutaneous fat) and thick inside (visceral fat) cannot be made. A CT scan can distinguish between these two “layers”. In our study we measured the visceral and subcutaneous fat on a CT to identify if one of these parameters is a better marker for tumour characteristics compared with BMI. Possible explanations for the lack of this correlation can be: first, there has been less enthusiasm for the use of brachytherapy in men with high-risk disease. These patients might be very well selected which can be an explanation for these negative findings. Second, the fat measurement was performed on one cross-sectional scan. Theoretically the accuracy of the fat measurement could be improved by measuring the fat content on more cross-sectional scans (volume measurement). However, in this study the selection bias of the brachytherapy patients is probably more important than the technique of fat measurement. Third, it is possible that the fat around the intra-abdominal organs are more metabolic active than the periprostatic fat. It would be interesting to measure the fat around the intra-abdominal organs, however, this scans were not available and it was not possible to measure the intra-abdominal fat distribution and body circumference at the level of the umbilicus. Fourth, it would be very interesting to correlate the BMI and periprostatic fat density with clinical outcome like biochemical recurrence or disease specific survival instead of pretreatment Gleason score, because these are better prognostic markers for prostate cancer aggressiveness. However, in this study the follow-up was too short to evaluate these outcomes.

Our analysis showed a correlation between BMI and subcutaneous fat thickness and periprostatic fat density. The correlation between BMI and subcutaneous fat thickness was much stronger (Pearson r coefficient=0.71 vs r=0.35). Interestingly, 31% of the patients with a normal BMI had a fat-density > 75 percentile, compared with only 10% of the obese patients who had a fat-density < 25 percentile of the fat-density. Thus, what you measure on the outside is definitely not always representative for the
fat distribution on the inside. It is attractive to speculate that when this study was performed in a group of patients with more high-grade tumours, e.g. a group treated with external radiotherapy, these parameters could be a better prognostic marker for tumour characteristics than BMI, especially in patients with a low BMI. However, further studies are needed to identify the real value of these fat measurements on CT as correlates with prostate cancer aggressiveness.

Conclusion

Periprostatic fat and fat-density were not of any value to predict prostate cancer aggressiveness in patients receiving brachytherapy. However, 31% of the patients with a normal BMI had a fat-density of >75 percentile of the periprostatic fat-density. More studies, including patients who have more aggressive prostate cancer, are needed to identify the true value of fat measurement on a CT as a correlate of prostate cancer aggressiveness and/or predictor of treatment failure.
Reference List


Periprostatic fat correlates with tumour aggressiveness in prostate cancer patients

Submitted

JGH van Roermund
KA Hinnen
CJ Tolman
GH Bol
JA Witjes
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LALM Kiemeney
M van Vulpen

PROSTATE CANCER. CLINICAL IMPLICATIONS OF OBESITY
Abstract

Purpose: To examine if the periprostatic fat measured on computed tomography (CT) correlates with advanced disease we examined patients who received radiotherapy for localized prostate cancer. Several USA reports found a positive association between obesity and prostate cancer aggressiveness. However, in recent European studies these conclusions were not confirmed. Studies concerning this issue have basically relied on body mass index (BMI), as a marker of general obesity. Visceral fat, however, is the most metabolically active and best measured on CT.

Patients and methods: In 932 patients, with T1-3N0M0 prostate cancer, different fat measurements (periprostatic fat, subcutaneous fat thickness) were performed on a CT. Associations between the different fat measurements and risk of having high-risk disease was measured.

Results: Logistic regression analyses revealed a significant association between periprostatic fat density (PFD) and high-risk disease.

Conclusion: Patients with a higher PFD had more often aggressive prostate cancer.
Introduction

In the USA and most countries of Western Europe, prostate cancer is the most common cancer among men and the second leading cause of death. Although the prevalence of prostate cancer at autopsy studies is more or less the same worldwide, the reported incidence is highly variable. On the one hand these differences can be explained by variation in PSA testing. On the other hand diet has been implicated in the aetiology of prostate cancer. Obesity, a major and increasing health problem, has been correlated with advanced stage at diagnosis and increased risk of biochemical recurrence (BCR). Adipose tissue is not only a storage place of fatty acids but it also produces a large number of hormones and cytokines, e.g. tumour necrosis factor-α, interleukin-6, leptin and adiponectin. The exact role of these cytokines in prostate carcinogenesis, however, is not known. All the studies that found an association of obesity with prostate cancer aggressiveness were performed in the USA. We conducted two studies in The Netherlands and could not confirm this relation. Neither could another European study by Gallina et al. It may be wondered however, whether obesity has been measured in the right way, especially in a population that is less obese compared to that of the USA. In all studies body mass index (BMI, the weight in kilograms divided by the squared height in meters) was used as a marker for general obesity. However, the most metabolic active fat is the visceral fat. Computed tomography (CT) is a technique which can measure fat at different levels in the human body very accurately and can distinguish the contribution of central and peripheral fat. In a small Portuguese case-control study body fat was assessed by CT in 63 prostate cancer cases and 63 age-matched healthy community controls. Although both groups had the same BMI (26 kg/m²), the prostate cancer group had a significantly higher mean visceral fat area compared to the control group. These data suggest a role of visceral fat as a risk factor for prostate cancer. We investigated whether different fat measurements (periprostatic fat and subcutaneous fat), on CT correlate with advanced stage in a group of patients who underwent external radiotherapy or brachytherapy for localized prostate cancer. Both treatment modalities were used to get a good compilation of patients having both low- and high-risk disease.

Patients and methods

Patients

In our database a CT was available from 363 patients who received five-field intensity-modulated three-dimensional conformal radiotherapy (IMRT) and for 725 patients who received brachytherapy at the Department of Radiotherapy, University Medical Center Utrecht, The Netherlands. All patients had stage T1-T3N0M0 prostate cancer and
Chapter 7

Figure 1 Images demonstrate our method for determining different fat measurements. Transverse section made at the level of the femoral head and greater trochanter of the femur. The green contour outlines the area, in which attenuation is measured. The line was drawn at the backside of the pubic bone, following the obturatorius internus muscle, the gluteus maximus muscle and coccyx bone. Within the region of interest the total periprostatic fat area (cm²) and periprostatic fat density (%, dividing periprostatic fat by the total contour area within the green line) were measured. The blue line measures the subcutaneous fat thickness.

were treated between January 2003 and August 2008. Patients who had undergone IMRT received 76 Gy in 35 fractions and prostate position was determined daily by using three gold markers. Patients, who received brachytherapy, underwent prostate implantation by using 125I seeds (144 Gy). Both treatment techniques used have been previously described. Bone scans were obtained and pelvic lymph node dissection was performed when clinically indicated. Six months of neo-adjuvant hormonal therapy with a LHRH-agonist was given to 120 (19%) brachytherapy patients presenting with a prostate volume >50 cm³ to achieve volume reduction. 101 (32.5%) high-risk IMRT patients received adjuvant hormonal therapy with a LHRH-agonist for 3 years. The patients were classified into 3 risk groups according to Ash. Tumour stage was described according to the 2002, TNM, American Joint Committee on Cancer system.

Fat measurement
BMI was calculated and stratified into three groups according to the WHO, i.e. normal weight (<25), overweight (25-30) and obese (≥30). A preplanning CT was performed in patients who received IMRT and one day after treatment in patients who received brachytherapy. In total, 156 patients (N=52 IMRT and N=104 brachytherapy), were
Table 1 Patients' pathological characteristics and fat measurement characteristics.

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Group 1 Low Risk N=260</th>
<th>Group 2 Intermediate Risk N=293</th>
<th>Group 3 High Risk N=379</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>65.0 (59.6-68.0)</td>
<td>66.5 (62.0-71.0)</td>
<td>69.0 (64.1-73.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prostate volume, cm³</td>
<td>36.0 (29.0-43.0)</td>
<td>35.0 (30.0-42.5)</td>
<td>35.0 (27.0-44.8)</td>
<td>0.96</td>
</tr>
<tr>
<td>Initial PSA, ng/ml</td>
<td>7.2 (5.3-8.5)</td>
<td>9.8 (6.8-13.0)</td>
<td>14.0 (10.0-22.8)</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.7 (24.2-28.0)</td>
<td>26.0 (24.3-28.4)</td>
<td>25.7 (24.0-28.4)</td>
<td>0.38</td>
</tr>
<tr>
<td>Total periprostatic fat, cm²</td>
<td>31.9 (26.8-36.8)</td>
<td>32.0 (25.9-37.2)</td>
<td>35.3 (28.6-41.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Periprostatic fat density, %</td>
<td>32.2 (27.5-36.3)</td>
<td>32.4 (27.1-36.6)</td>
<td>35.6 (29.9-41.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Subcutaneous fat thickness, cm</td>
<td>4.5 (3.8-5.3)</td>
<td>4.7 (3.7-5.7)</td>
<td>4.7 (3.9-5.6)</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>N (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>235 (90.4)</td>
<td>265 (90.4)</td>
<td>121 (31.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IMRT</td>
<td>25 (9.6)</td>
<td>28 (9.6)</td>
<td>258 (68.1)</td>
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</tr>
<tr>
<td>WHO-classification</td>
<td></td>
<td></td>
<td></td>
<td>0.22</td>
</tr>
<tr>
<td>Normal weight</td>
<td>94 (38.5)</td>
<td>93 (33.6)</td>
<td>89 (38.7)</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>123 (50.4)</td>
<td>139 (50.2)</td>
<td>102 (44.3)</td>
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<tr>
<td>Obesity</td>
<td>27 (11.1)</td>
<td>45 (16.2)</td>
<td>39 (17.0)</td>
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</tr>
<tr>
<td>Missing BMI</td>
<td>16 (6.1)</td>
<td>16 (5.5)</td>
<td>149 (39.3)</td>
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</tr>
<tr>
<td>Clinical stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>194 (74.6)</td>
<td>197 (67.2)</td>
<td>70 (18.5)</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>66 (25.4)</td>
<td>96 (32.8)</td>
<td>83 (21.9)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>0</td>
<td>0</td>
<td>226 (59.6)</td>
<td></td>
</tr>
<tr>
<td>Gleason Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 6</td>
<td>241 (93.4)</td>
<td>139 (47.6)</td>
<td>50 (13.3)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>17 (6.6)</td>
<td>153 (52.4)</td>
<td>250 (66.5)</td>
<td></td>
</tr>
<tr>
<td>≥ 8</td>
<td>0</td>
<td>0</td>
<td>76 (20.2)</td>
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<tr>
<td>Hormonal therapy</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>40 (15.5)</td>
<td>60 (20.7)</td>
<td>257 (68.0)</td>
<td></td>
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<tr>
<td>No</td>
<td>218 (84.5)</td>
<td>230 (79.3)</td>
<td>121 (32.0)</td>
<td></td>
</tr>
</tbody>
</table>

Table 1 Patients' pathological characteristics and fat measurement characteristics.

IQR= interquartile range; BMI= body mass index; BCR= biochemical recurrence.

excluded because the CT was of poor quality. This resulted in a study population of 932 men. Preoperative height and weight data were collected retrospectively by reviewing medical records. The CT scans were made with a single slice CT (Aura, Philips Medical Systems, Best, The Netherlands) and had an in-plane slice resolution of 0.49x0.49 mm² with a slice thickness of 3 mm. We used an in-house developed software tool for delineating different regions of the human body.14 Fat measurements were performed on a transverse section at the level of the femoral head and greater trochanter of the femur. Figure 1 shows the method used for determining the different fat measurements. Because there are no comparable studies available we chose to delineate along established lines. The fat contained within the delineated contours of the CT, was segmented by thresholding...
on the Hounsfield Units (HU). We differentiated between fat (-190 to -30 HU), air (< -500 HU) and other soft tissue types. Since the delineated contours did not contain bony structures, we did not include a threshold for segmenting the bones separately.

**Statistical analysis**

Associations between the predefined risk groups and clinical and pathological characteristics or fat measurements were examined by Chi-square tests in case of categorical characteristics and Kruskal-Wallis tests in case of continuous characteristics. Logistic regression analyses were performed with adjustment for age to evaluate the effect of each variable on the risk of having high-risk disease versus low- or intermediate-risk. The PSA level before treatment, pathological stage and grading were not included in the logistic regression analyses and Cox’s proportional hazard models, because the risk group (according to Ash) was based on these parameters. Differences were considered to be statistically significant if p<0.05. Data were analysed using SPSS for Windows (version 15.0).

**Results**

Table 1 summarizes the clinical, pathological and different fat measurements of the study population stratified by Ash risk group. The median age (IQR) was 67.0 years (62.0-71.0) and the median BMI (IQR) was 25.8 (24.2-28.3). BMI was missing in 19.4% (181) of the cases. Patients in the highest risk group were significantly older. 83.0% of the patients who received IMRT had high-risk disease and 80.5% of the patients who underwent brachytherapy had low/intermediate-risk disease. Patients in the highest risk group had a significantly larger total periprostatic fat area (TPF, cm²) and PFD (%) compared with the low and intermediate risk group. Logistic regression analyses (table 2), adjusted for age, revealed a statistically association between TPF and PFD and increased odds of having high-risk disease.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio(95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (continuous)</td>
<td>1.02 (0.98-1.06)</td>
<td>0.41</td>
</tr>
<tr>
<td>BMI</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&lt; 25 kg/m²</td>
<td>0.84 (0.60-1.19)</td>
<td>0.34</td>
</tr>
<tr>
<td>25-30 kg/m²</td>
<td>1.22 (0.76-1.97)</td>
<td>0.41</td>
</tr>
<tr>
<td>≥ 30 kg/m²</td>
<td>1.06 (0.96-1.17)</td>
<td>0.29</td>
</tr>
<tr>
<td>Subcutaneous fat thickness, (cm)</td>
<td>1.04 (1.03-1.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total periprostatic fat, (cm²)</td>
<td>1.06 (1.04-1.08)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 2 Logistic regression analysis of factors predicting high risk disease according to Ash. BMI = body mass index; * = after adjustment for age.
Discussion

This is the first paper which shows that periprostatic fat measured on CT is directly correlated with prostate cancer aggressiveness and is more important than BMI, as a measurement of general obesity. Although the specific biologic processes linking obesity to prostate cancer remain to be elucidated completely, previous studies consistently suggested that obesity is associated with advanced stage at diagnosis and increased risk of BCR after therapy. These findings might be important and may indicate that obese patients require different treatment considerations. However, these findings could not be confirmed in recent European studies.

Several explanations can be given for this discrepancy. First, North America has a different population composition than Europe. Second, compared to Europe the prevalence and severity of obesity is much higher in North America. In Europe only 9 to 14% is obese while in the USA obesity prevalence is as high as 30%. Although obesity is less common in Europe, the trend is progressing rapidly. In all aforementioned studies BMI has been used as a marker for general obesity. In a large cohort study among 129,502 men (the European Prospective Investigation into Cancer and Nutrition) waist circumference and waist-to-hip ratio (as a measure of abdominal obesity) were positively associated with risk of advanced disease. The relative risk (95% CI) was 1.06 (1.01-1.1) per 5-cm-higher waist circumference and 1.21 (1.04-1.39) per 0.1-unit higher waist-to-hip ratio. Waist circumference and waist-to-hip ratio were positively associated with advanced disease among men with a lower but not among men with a higher BMI. These data suggest that an increased risk of advanced prostate cancer is more strongly associated with abdominal adiposity than with BMI, especially in a population that is less obese. A CT scan is an excellent technique to distinguish and quantify subcutaneous and visceral fat.

Contrary to BMI and subcutaneous fat thickness, the TPF and PFD significantly increased the odds of having high-risk disease in the present study. One percent increases of PFD increased the risk of having high-risk disease with 6%. With this in mind, one should expect that the patients with the highest PFD are at a greater risk of BCR.

Our study has some limitations. As this was a retrospective study, an abdominal cross-sectional CT-scan was not available. It would be interesting to have a scan at the level of the umbilicus to measure the intra-abdominal fat. It is possible that the intra-abdominal fat is more metabolic active than the fat around the prostate. Second, in order to be able to evaluate a study population that consists of both low/intermediate (brachytherapy) and high-risk disease (IMRT) we had to use patients (of whom a CT-scan was on hand) who were treated with the two treatment modalities. It would have been more ideal if all patients were treated by only one treatment modality.
Another essential issue that must be considered is the metabolic activity of individual fat cells. ‘Fat’ fat cells, which are more common in obese patients, produce larger quantities of cytokines than ‘thin’ fat cells. A CT scan can not distinguish between these two different types of fat cells. A future step would be to measure the activity of fat by collecting fat from different parts of the body (e.g. during a radical prostatectomy) and to determine the cytokine production of the fat cells collected from different locations. By linking these data with anthropometric data of the patient and its prostate cancer characteristics, a better insight may be gained in the exact role of obesity on prostate cancer. A first step is made by Finley et al. They recently investigated the periprostatic fat quality by analyzing the periprostatic fat quality and found that high levels of IL-6 correlated with tumour grade.

**Conclusion**

In contrast with a higher BMI, patients with a higher PFD had an increased risk of having a more aggressive prostate cancer.
Reference List

7. van Roermund JG, Hinnen KA, Battersmann JJ, Witjes JA, Bosch JL, Klemenc LA et al. Body mass index is not a prognostic marker for prostate-specific antigen failure and survival in Dutch men treated with brachytherapy. BJU.Int. 2009; Epub.


Cholesterol, triglycerides and prostate cancer risk; a cohort study

Submitted

DEG Kok
JGH van Roermund
KK Aben
M den Heijer
DW Swinkels
E Kampman
LALM Kiemeney
Abstract

Objective: It has been hypothesized that blood lipid profiles are associated with prostate cancer risk. However, results are scarce and inconsistent and underlying mechanisms are not fully understood. The aim of the present study was to address the association between serum total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides and prostate cancer risk in a Dutch, population-based cohort study.

Subjects and methods: The association between blood lipid profiles and prostate cancer risk was assessed in a population-based study among 2,862 men. Serum total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides were evaluated as potential risk factors for prostate cancer using age-adjusted proportional hazards regression models.

Results: In total, 38 new cases of prostate cancer were identified during a median follow-up of 56.4 (IQR: 50.9-59.4) months. Increased risks per mmol/L were observed for total cholesterol (HR 1.22, 95% CI: 0.91-1.66), HDL cholesterol (HR 1.83, 95% CI: 0.71-4.69) and LDL cholesterol (HR 1.36, 95% CI: 0.97-1.91). Triglycerides were associated with decreased prostate cancer risk (HR 0.77 per mmol/L, 95% CI: 0.54-1.09). However, no statistically significant associations were observed.

Conclusion: The results of this study did not provide strong evidence that blood lipid levels are associated with risk of prostate cancer in this cohort. However, statistical power is limited due to the relatively small number of prostate cancer cases. Further studies are needed to provide additional data.
Lipid profile and prostate cancer risk

Introduction

Epidemiological studies suggest that lipid profiles in blood are associated with risk of prostate cancer. Although some studies indicated that high serum triglycerides, low serum HDL cholesterol, and high total or LDL cholesterol might contribute to the development or progression of prostate cancer, results are scarce and inconsistent.

So far, few studies have assessed the relation between serum triglycerides and prostate cancer risk. A case-control study among 504 cases with prostate cancer and 565 controls with benign prostatic hyperplasia (BPH) found a positive association between serum triglycerides and prostate cancer risk (OR 1.15, 95% CI: 1.00-1.32). A recent, prospective study based on 29,364 Norwegian men (687 incident cases), however, did not confirm an association between serum triglycerides and risk of incident or fatal prostate cancer.

Cholesterol has been regarded as a potential risk factor for prostate cancer. Although, two case-control studies have shown that hypercholesterolemia increases the risk of prostate cancer, most prospective studies only reported a positive association for high-grade disease. Other prospective studies did not find any association or suggested that risk of prostate cancer decreased with increasing cholesterol levels.

Supportive evidence for the potential role of cholesterol in prostate cancer development has been provided by observations that cholesterol-lowering drugs (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, commonly known as statins) might be inversely associated with risk of (advanced) prostate cancer. A recent meta-analysis by Bonovas et al., confirmed that statin use lowers the risk of advanced prostate cancer (RR 0.77, 95% CI: 0.64-0.93); however, no effect for total prostate cancer risk was found (RR 0.95, 95% CI: 0.73-1.23). Others addressed that the cholesterol-lowering effects of statins might not be the only reason why these drugs are associated with reduced risk of advanced prostate cancer. Direct pro-apoptotic and anti-inflammatory effects of statins are suggested to inhibit development or progression of prostate cancer independent of cholesterol. Furthermore, differences in PSA screening patterns between statin users and nonusers might be responsible for the observed associations as well. Since results are conflicting and underlying mechanisms have to be elucidated, further research is needed to evaluate the effects of cholesterol-lowering drugs on prostate cancer prevention, whereas robust studies on serum cholesterol and other blood lipids should confirm whether these blood lipids itself are potential risk factors for prostate cancer.
As described above, the relation between blood lipid profiles and prostate cancer risk has been previously investigated, but only a few recent and population-based prospective studies have been reported. The aim of the present study was to address the association between serum cholesterol, triglycerides and prostate cancer risk in a Dutch, population-based cohort study.

Subjects and methods

The Nijmegen Biomedical Study is a survey of the general population in which a random, age- and sex-stratified sample was recruited among adult inhabitants of Nijmegen, Lent and Oosterhout (eastern part of the Netherlands) between 2001 and 2003. In total, 21,756 inhabitants received an invitation to participate in this study. Of these, 9,350 (43%) subjects agreed to participate and filled out a postal questionnaire on lifestyle and medical history at baseline. The majority of the participants (90%) in this region were Caucasian. Furthermore, 6,468 (69%) participants donated two non-fasting blood samples, which were collected in tubes containing heparin (8.5 ml) or EDTA (8.5 ml). Blood samples were processed within two hours after withdrawal and aliquots of serum were stored at -40°C. All analyses of blood lipid profiles were performed between October 2004 and April 2005. Levels of serum total cholesterol, HDL cholesterol and triglycerides were analysed enzymatically using an Abbott Aeroset autoanalyser. Levels of LDL cholesterol were estimated using the Friedewald formula. Since the Friedewald formula only appeared to be accurate up to triglyceride levels of 8 mmol/L, we did not calculate LDL levels for participants with triglyceride levels above 8 mmol/L (N=8). Criteria of the National Cholesterol Education Program were used to define hypercholesterolemia (≥ 5.17 mmol/L), low HDL cholesterol (<1.03 mmol/L), high LDL cholesterol (≥ 3.36 mmol/L) and high triglycerides (≥ 1.69 mmol/L). This study was approved by the Institutional Review Board and all participants provided written informed consent.

All 3,050 male participants of the Nijmegen Biomedical Study who provided blood samples were initially included in our analyses. Of these, 162 participants were excluded since no blood lipid measurements were available and 13 participants were excluded because of incomplete follow-up data. Incident cases of prostate cancer (N=51) diagnosed between 2002 and 2007 were identified through record linkage with the population-based cancer registry of the Comprehensive Cancer Centre East (CCCE). The CCCE has a catchment area of 1.3 million inhabitants living in the Eastern part of the Netherlands, including Nijmegen and surroundings. Subjects with a diagnosis of prostate cancer before blood withdrawal were excluded from the analyses (N=13), leaving 38 cases and 2,862 cohort members for final analyses. The
Lipid profile and prostate cancer risk

<table>
<thead>
<tr>
<th>Median (IQR) or numbers (%)</th>
<th>Total cohort</th>
<th>Prostate cancer cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>62.1 (47.3-73.3)</td>
<td>71.7 (68.1-76.3)</td>
</tr>
<tr>
<td>Follow-up, months</td>
<td>56.4 (50.9-59.4)</td>
<td>26.6 (16.0-45.0)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>178 (173-183)</td>
<td>175 (170-178)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>80 (73-88)</td>
<td>79 (71-85)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.2 (23.4-27.5)</td>
<td>26.2 (23.7-27.8)</td>
</tr>
<tr>
<td>Smoking, ever, %*</td>
<td>2231 (78)</td>
<td>33 (87)</td>
</tr>
<tr>
<td>Diabetes, yes, %*</td>
<td>193 (8)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Hypertension, yes, %&quot;</td>
<td>673 (26)</td>
<td>14 (39)</td>
</tr>
<tr>
<td>Use of cholesterol-lowering drugs, ever, %*</td>
<td>422 (17)</td>
<td>7 (21)</td>
</tr>
<tr>
<td>Serum total cholesterol, mmol/L</td>
<td>5.6 (4.9-6.3)</td>
<td>5.8 (5.1-6.8)</td>
</tr>
<tr>
<td>Serum HDL cholesterol, mmol/L</td>
<td>1.2 (1.0-1.4)</td>
<td>1.2 (1.0-1.5)</td>
</tr>
<tr>
<td>Serum LDL cholesterol, mmol/L</td>
<td>3.5 (2.8-4.1)</td>
<td>3.8 (3.1-4.3)</td>
</tr>
<tr>
<td>Serum triglycerides, mmol/L</td>
<td>2.0 (1.4-2.7)</td>
<td>1.7 (1.3-2.3)</td>
</tr>
</tbody>
</table>

Table 1 Baseline characteristics of all cohort members and members with incident prostate cancer in this population-based study. * = Percentages are based on the number of cohort members and cases without missing values for these variables.

Follow-up of all participants was defined as the day of blood withdrawal until date of death, emigration, prostate cancer diagnosis or the end of follow-up (December 31st, 2007), whichever came first.

Information on age, height, weight, smoking status (current, former, never), history of hypertension (yes, no), history of diabetes mellitus (yes, no), use of cholesterol-lowering drugs (current, former, never) and use of other drugs (drug names) were obtained from the self-reported questionnaires. For the prostate cancer cases, date of diagnosis, clinical or pathological tumour stage (TNM based on the 2002 American Joint Committee on Cancer guidelines24), Gleason score and PSA levels were obtained through the cancer registry, whenever available.

We used age-adjusted proportional hazards regression models to calculate hazard ratios (HR) and 95% confidence intervals (95% CI) for prostate cancer incidence. Blood lipid levels were all evaluated individually both as categorical variables (high versus low) and as continuous measures (per mmol/L) in these age-adjusted models. Analyses were repeated after exclusion of participants who ever used cholesterol-lowering drugs to evaluate whether use of these drugs might have an effect on the risk estimates. The Statistical Package of Social Sciences (SPSS, version 16.0, Chicago, Illinois) was used for all statistical analyses.
Table 2 Age-adjusted models for prostate cancer incidence associated with blood lipid levels.

<table>
<thead>
<tr>
<th></th>
<th>No of cases</th>
<th>HR *</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum total cholesterol, per mmol/L</td>
<td>38</td>
<td>1.22</td>
<td>0.91-1.66</td>
</tr>
<tr>
<td>&lt;5.17</td>
<td>10</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td>≥5.17</td>
<td>28</td>
<td>1.38</td>
<td>0.67-2.86</td>
</tr>
<tr>
<td>Serum HDL cholesterol, per mmol/L</td>
<td>38</td>
<td>1.83</td>
<td>0.71-4.69</td>
</tr>
<tr>
<td>&lt;1.03</td>
<td>7</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td>≥1.03</td>
<td>31</td>
<td>1.64</td>
<td>0.72-3.72</td>
</tr>
<tr>
<td>Serum LDL cholesterol, per mmol/L</td>
<td>38</td>
<td>1.36</td>
<td>0.97-1.91</td>
</tr>
<tr>
<td>&lt;3.36</td>
<td>15</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td>≥3.36</td>
<td>23</td>
<td>1.29</td>
<td>0.67-2.47</td>
</tr>
<tr>
<td>Serum triglycerides, per mmol/L</td>
<td>38</td>
<td>0.77</td>
<td>0.54-1.09</td>
</tr>
<tr>
<td>&lt;1.69</td>
<td>18</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td>≥1.69</td>
<td>20</td>
<td>0.71</td>
<td>0.38-1.35</td>
</tr>
<tr>
<td>Use of cholesterol-lowering drugs, ever vs never</td>
<td>7 vs 27</td>
<td>0.89</td>
<td>0.39-2.04</td>
</tr>
</tbody>
</table>

* = Adjusted for age

Results

Baseline characteristics of the participants are presented in Table 1. Among 2,862 participants, 38 incident prostate cancer cases were identified during a median follow-up of 56.4 (IQR: 50.9-59.4) months. Of these, 21 patients were diagnosed with low-grade prostate cancer (Gleason <7 at biopsy), while 14 patients had high-grade tumours (Gleason ≥7 at biopsy), and for 3 patients Gleason scores were unknown. The median time between blood withdrawal and diagnosis of prostate cancer was 26.6 (IQR: 16.0-45.0) months. Median age was 62.1 (IQR: 47.3-73.3) years for all cohort members and 71.7 (IQR: 68.1-76.3) years for cases. Seventeen percent of all men in the cohort reported former or current use of cholesterol-lowering drugs (N=422). Median serum levels of total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides appear to be fairly similar between the cohort members and prostate cancer cases.

As shown in Table 2, none of the serum lipid levels (i.e. total cholesterol, HDL cholesterol, LDL cholesterol or triglycerides) were significantly associated with prostate cancer risk in age-adjusted proportional hazards regression models. For LDL cholesterol (continuous) a modest association was found for prostate cancer incidence, although this effect was not statistically significant (HR 1.36 per mmol/L, 95% CI: 0.97-1.91). Exclusion of subjects who reported ever use of cholesterol-lowering drugs did not change these results (for LDL cholesterol, HR 1.47 per mmol/L, 95% CI: 0.96-2.23).
Discussion

Overall, our study did not provide strong evidence that blood lipid levels are associated with prostate cancer risk in this Dutch cohort. We found a positive association with prostate cancer risk for high levels of total cholesterol and HDL cholesterol; however, these associations did not reach statistical significance. These findings were partially consistent with those of Martin and colleagues who assessed blood lipid profiles and other components of the metabolic syndrome in a large, population-based cohort study among 29,364 Norwegian men. They neither did observe a significant association between total or HDL cholesterol and triglycerides with prostate cancer incidence or mortality.

Triglyceride levels in our study were inversely related to prostate cancer risk, although this association was not statistically significant. Similar results were observed by Martin and colleagues who observed triglyceride levels inversely related with advanced prostate cancer (HR 0.89 per 1.3 mmol/L, 95% CI: 0.72-1.10). As in our study, this finding was based on relatively few cases (N=135) and was not statistically significant, therefore raising the possibility of a chance finding.

Findings from our study suggested that increased levels of serum LDL cholesterol might be associated with prostate cancer risk, although these results were not statistically significant. Our results with respect to LDL cholesterol need to be interpreted with some caution, since non-fasting blood samples were used. The Friedewald formula for calculating levels of LDL cholesterol is based on the assumption that total cholesterol minus HDL cholesterol minus VLDL cholesterol equals LDL cholesterol. This method requires measurements of total cholesterol, HDL cholesterol and triglycerides (as a proxy for VLDL cholesterol) levels. Using non-fasting samples might result in abundant triglycerides, a subsequent overestimation of VLDL cholesterol and therefore might underestimate levels of LDL cholesterol. Nevertheless, in our population-based cohort we had only eight cohort members with non-fasting triglyceride levels above 8 mmol/L, which is suggested as the upper level for accurate Friedewald calculations. Since we did not calculate LDL cholesterol levels for these eight patients, we do not expect that an underestimation of LDL cholesterol strongly affected our results.

The mechanisms underlying the possible association between blood lipid profiles and prostate cancer risk are poorly understood and are most likely related to signaling functions of cholesterol. Cholesterol is incorporated into moving platforms in the fluid bilayer of cellular membranes, which are referred to as lipid rafts. As reviewed by others, these lipid rafts might play an important role in cell signalling (such as the EGFR/Akt or IL6/STAT pathways) and could thereby act on growth and...
survival of prostate cancer cells.\textsuperscript{30,31} Future experiments focusing on lipid rafts should elucidate these and other signaling networks and its effects with respect to prostate cancer development or progression. Another hypothesis is based on the theory of steroidogenesis, which postulates that prostate cancer cells itself might be able to produce androgens which can bind to the androgen receptor and stimulate growth and survival.\textsuperscript{32} It has recently been shown that prostate cancer cells in advanced stages could synthesize androgens directly from cholesterol.\textsuperscript{33} These findings might explain the suggested association between serum cholesterol levels and risk of local and advanced prostate cancer; however, future studies are needed to confirm the exact role of cholesterol and other blood lipids in the development and progression of prostate cancer.

It has been previously suggested that associations between blood lipid profiles and prostate cancer risk are more pronounced in aggressive or advanced prostate cancer.\textsuperscript{2,5} Hammersten et al. evaluated several features of the metabolic syndrome among 299 patients with recently diagnosed prostate cancer. Subjects with poorly differentiated prostate cancer had lower HDL cholesterol levels and higher triglyceride levels compared to those with well differentiated disease.\textsuperscript{2} Furthermore, Platz et al., had previously demonstrated that use of statin drugs lowers the risk of advanced prostate cancer (RR 0.51, 0.30-0.86), whereas no association for total prostate cancer risk was found.\textsuperscript{14} Recently, they have evaluated the association between plasma cholesterol and prostate cancer risk in a nested case-control study to address whether cholesterol-lowering properties might explain the effects of statins on prostate cancer risk.\textsuperscript{5} Low cholesterol levels were not associated with total prostate cancer risk (OR 0.93; 0.72-1.20), however an inverse association was found for high-grade disease (OR 0.61; 0.39-0.98).\textsuperscript{5}

Unfortunately, we were not able to distinguish between localized and advanced or aggressive disease due to the relatively small number of cases in our study. Therefore, it was not possible to perform subgroup analyses for prostate cancer grade or stage. Despite this small number of cases in our study, a-posteriori power calculations demonstrated that we would have been able to detect a difference in serum cholesterol levels of 0.5 mmol/L between cases and members of the cohort (power of 80\%). Since median cholesterol levels in our population were 5.6 mmol/L, a difference of 0.5 mmol/L could have made the distinction between desirable (<5.17 mmol/L) and borderline high (≥5.17 mmol/L) cholesterol levels.

Potential limitations of the present study were the non-fasting blood samples, the relatively short follow-up (median 56 months) and the incapability to stratify for localized and advanced disease. Strengths of this study are the prospective design
and the analyses of total cholesterol, HDL cholesterol and triglycerides in blood samples from a population-based cohort.

**Conclusion**

This study did not provide strong evidence that blood lipid levels are associated with prostate cancer risk in a Dutch cohort. Larger, prospective, population-based studies are needed to verify whether blood lipids might have more pronounced effects on advanced or aggressive prostate cancer risk or mortality. Knowledge of these and other specific metabolic factors associated with prostate cancer risk might be relevant with respect to preventive strategies or even therapeutic options.
Chapter 8

Reference List

General Discussion & Future Perspectives
General Discussion

Globally, prostate cancer is highly prevalent. It is the most common non-cutaneous cancer in men. An estimated 782,600 new cases and 254,000 deaths caused by the disease occurred in 2007 worldwide.\(^1\) Interestingly, autopsy studies worldwide show that approximately 60% of men in their sixth and seventh decade of life have prostate cancer.\(^2\)\(^3\) Although the prevalence of prostate cancer is similar across different populations, enormous differences in prostate cancer incidence and mortality between the United States and Asia are seen. Age-adjusted incidence rates in China are 3 per 100,000 men as compared with 108 for white and even 184 per 100,000 for African-American men.\(^4\) The incidence of prostate cancer in Chinese men, however, increases substantially after migration to the United States.\(^5\) This epidemiological relationship between incidence and geography supports a major contribution of environmental factors to the progression of prostate cancer. One of these environmental factors related to westernization is obesity, which is a common and rapidly growing epidemic in the United States and in Western European countries.\(^6\) With the aging male, increased use of PSA, and increasing trend of obesity the physician will be confronted more and more with obese patients having prostate cancer. Although the relation of obesity and prostate cancer has gained popularity in the field of scientific research most of these studies are performed in the United States. This thesis focused on the clinical implications of obesity on prostate cancer in the Dutch population.

Localized prostate cancer can be treated with surgery (open or laparoscopic) or radiotherapy (external or brachytherapy). Thus, when an obese patient with localized prostate cancer visits the outpatient clinic, the urologist and/or radiation oncologist can offer this patient different treatment options. But which of those fit the obese patient best in terms of cure and, not less important, morbidity? Obesity makes many urological procedures technically more difficult. A proper preparation of the striated sphincter and a good apical dissection as well as the reconstruction in a deep pelvis is challenging. Besides technical difficulties during an operation, obesity itself may have a negative impact on healing, especially at the vesico-urethral anastomosis. However, data are lacking on the exact role of obesity on the different surgical techniques and the existing studies consist of a small number of patients.

The incidence of postoperative urinary incontinence, differs between 2.5% and 87%.\(^7\)\(^8\) Three studies, all using self-administered and non-validated questionnaires, investigated the impact of obesity on postoperative incontinence after open radical prostatectomy and found no association between obesity and postoperative incontinence.\(^9\)\(^10\)\(^11\) In our series \((\text{chapter 3})\) however, the postoperative incontinence rate of obesity was much higher in the obese men compared to the non-obese men (25.8% vs. 8.7%, \(p=0.009\)) in patients who underwent an open radical prostatectomy.
Different operation techniques and various definitions of incontinence as well as the retrospective nature of the studies, make comparisons between these series not easy. In the same chapter we also described that obese men were at higher risk of developing vesico-urethral strictures postoperatively compared with non-obese men (45.2% vs. 12.3%, p<0.005). Only one other study drew the same conclusion. These days the robotic assisted/laparoscopic radical prostatectomy is becoming more popular in the urological field. Theoretically, the magnification of a laparoscope and better vision in the deep pelvis may help the urologist performing a prostatectomy more precisely compared to the open approach. Despite the different and improving surgical techniques, it is particularly the co-morbidity of the patient that determines the recovery and healing process of an obese patient. Limitations of the study presented in chapter 3 was that the absolute number of obese patients was small, making multivariable analysis to adjust for potentially significant co-variables impossible in any meaningful way. Besides, the functional outcomes were not obtained by validated questionnaires.

The risk of obesity in developing prostate cancer is controversial. However, more agreement exists on the increased risk of biochemical recurrence in obese men who underwent a radical prostatectomy. Of note, all studies were done in the United States. Compared to The Netherlands not only the prevalence of obesity is different, but also the composition of the population. We conducted a study in which we retrospectively analysed 1,302 men with clinically localized prostate cancer who underwent a radical prostatectomy in one of two Dutch academic hospitals (Nijmegen and Rotterdam). In this study BMI did not appear to have any prognostic value for biochemical recurrence. One of the explanations for this discrepancy may be that American men are more obese and have more ‘fatter’ fat cells which produce larger quantities of adipokines. These adipokines may be responsible for more aggressive prostate cancer and higher biochemical recurrence rates. In chapter 4, although not significant, obese men had more often positive margins (40.8% vs. 34.9%) compared with normal-weight men. However, this resulted not in a higher risk of biochemical recurrence in the obese men. A question that may present: are these positive surgical margins a consequence of the technical difficulty during dissection of the prostate or is this due to adverse pathological features seen in obese men? In chapter 4, obese patients were not at risk of having more aggressive prostate cancer compared with non-obese men. It is tempting to speculate that the higher rate of positive margins seen in the obese group was caused by surgical difficulties. Interestingly, to determine whether the higher biochemical recurrence rates seen in an American study were due solely to the higher positive margin rate, Freedland et al. examined whether obesity was an independent predictor for biochemical recurrence among men with negative surgical margins. After controlling for preoperative characteristics, moderately and severely obese men (BMI >35 kg/m²) had a nearly a 4-fold increased risk of biochemical
recurrence. Thus, in that study the surgical technique did not fully explain the worse outcomes among obese men, suggesting that obesity was associated with a more aggressive form of prostate cancer. A limitation of the study presented in chapter 4 was that biochemical recurrence was used as an end-point. It would be more ideal to use cancer-specific survival.

To date, only a few studies reported the risk of biochemical recurrence in obese patients who underwent brachytherapy.\textsuperscript{27-29} In all studies obesity was not shown to be a risk factor for biochemical recurrence compared with non-obese patients. In chapter 5, 1,530 Dutch patients who had localized prostate cancer were treated with brachytherapy and were retrospectively evaluated. To the best of our knowledge this was the first and the largest European study investigating the relation between BMI and prostate cancer outcome. BMI was not a risk factor for biochemical recurrence after brachytherapy. Because biochemical recurrence is a surrogate for prostate cancer progression, we also examined the relation between BMI and cancer specific survival. BMI did not appear to have any prognostic value also for cancer specific survival. Compared with external radiotherapy\textsuperscript{27,30,31} where obese patients are at risk to develop biochemical recurrence, none of the brachytherapy studies found a correlation between obesity and worse treatment outcome. The following question arises: is this the result of a better technique or is this due to selection bias?

It is conceivable that a greater chance of daily setup uncertainties and excessive intra-abdominal adipose tissue, which may increase organ motion, may lead to external beam treatment uncertainties and in their turn lead to increased failure rate seen in obese patients. In a study by Wong et al.\textsuperscript{32} severe obese patients who underwent external radiotherapy tended to have a greater magnitude of left-right prostate shifts compared to their non-obese counterparts. The technical aspects of brachytherapy, where radioactive seeds are brought into the prostate with real-time ultrasound imaging, may bypass the daily setup errors seen in external radiotherapy. However, there has been less enthusiasm for brachytherapy in patients with high-risk disease which may result in a more homogeneous group of patients with a better prognostic profile. Theoretically, obese patients with high-risk disease might be treated by other treatment modalities like surgery or external radiotherapy and thereby the differences seen in treatment failure in obese patients is not a matter of technique but due to selection bias. More studies are needed to clarify this.

In most studies investigating obesity in relation to prostate aggressiveness and biochemical recurrence, BMI is used as a criterion for general obesity. Although scientists have used BMI as a reliable indicator of overweight, new insights are now rapidly undermining this consensus. Terms such as ‘fat’ and ‘thin’ tell us much less about health than we assumed.\textsuperscript{33} The most metabolic active fat is the abdominal visceral fat. Although the specific biologic processes linking obesity to prostate
cancer remain to be elucidated completely, several studies (as mentioned before), consistently suggest that obesity is associated with the advanced stage at diagnosis and the increased risk of biochemical recurrence in patients who undergo surgery or external radiotherapy. These findings, however, were not observed in recent European studies. (chapter 4 & 5)

One of the reasons of this discrepancy may be clarified by the fact that we do not measure obesity (read: visceral fat) in the right way by using only BMI as a marker for general obesity. Especially in a population where obesity is less prevalent and less severe as compared with the USA. Pischon et al. found in a large European prospective cohort that greater waist circumference, as a measure of abdominal fat distribution, was associated with increased risk of advanced disease among individuals with lower BMI. One disadvantage of using waist circumference is that it cannot distinguish between a thin subcutaneous and a thick visceral fat layer or a thick subcutaneous and a thin visceral fat layer. A computed tomography (CT) scan is a very accurate technique, which can distinguish between these two “layers”. A possible clarification of discrepancies seen between the European and North American studies on the risk of BCR may be resolved by measuring fat distribution more precisely on a CT. In chapter 6 we used a CT scan to measure the visceral fat and subcutaneous fat of 725 men who underwent brachytherapy for localized prostate cancer in relation to pathologic baseline characteristics. No association between periprostatic fat density (% , dividing periprostatic fat area by the total contour area measured around the prostate) and prostate aggressiveness was found. This is probably caused by the fact that patients with aggressive prostate cancer were not treated with this modality resulting in selection. Interestingly we found that 31% of the patients with a normal BMI had a >75 percentile of the periprostatic fat density. Thus, what one measures on the outside is definitely not representative for the fat distribution on the inside. The patient population in chapter 6 consisted mainly of patients with low and intermediate risk prostate cancer. To get a greater insight into the true value of fat measurement on a CT scan in relation to prostate aggressiveness and to overcome the problem that the study population mainly consisted of low/intermediate risk prostate cancers, we performed a similar study in a more heterogeneous group of patients. In chapter 7 we evaluated 932 patients who had undergone brachytherapy (mainly low/intermediate-risk patients) or external radiotherapy (mainly high-risk patients) for localized prostate cancer. In this chapter the periprostatic fat density was strongly associated with the risk of having a high-risk disease. One percent increase of the periprostatic fat density increases the risk of having high-risk disease with 6% (HR 1.06 95% CI 1.04-1.08, p<0.001). Unfortunately the follow-up was too short to determine the risk of biochemical recurrence in this population. It would be more ideal if all patients were treated by only one treatment modality. Studies with a longer follow-up and patients who are treated with only one treatment modality are
warranted to evaluate if patients with a higher periprostatic fat density are at greater risk to die from their prostate cancer.

Although results are still inconsistent and biochemical mechanisms have to be elucidated, lipid profiles in blood have been associated with prostate cancer risk.\textsuperscript{40-45} It is very plausible that the signalling function of cholesterol plays an important role in prostate cancer aggressiveness. The cholesterol is packed and moved into moving platforms in the fluid bilayer of cellular membranes, which are called lipid rafts.\textsuperscript{46} These rafts might play a central role in cell signalling (such as the EGFR/Akt\textsuperscript{47} or IL6/STAT3\textsuperscript{48} pathways) and could thereby act on growth and survival of prostate cancer cells. Another hypothesis is based on the theory of steroidogenesis, which postulates that prostate cancer cells themselves might be able to form androgens directly from cholesterol. The aforementioned hypothesis could explain the association between serum cholesterol levels and risk of (advanced) prostate cancer. Two case-control\textsuperscript{40,42} studies demonstrated that hypercholesterolemia increased the risk of prostate cancer and one prospective study\textsuperscript{44} reported a positive association for high-grade disease, while others found no\textsuperscript{43,49,50} or even a decreased\textsuperscript{51} association. Supplementary evidence of the role of cholesterol in prostate cancer has been provided by cholesterol-lowering-drugs (statins) studies. A recent meta-analysis by Bonnovas et al.\textsuperscript{52} addressed that statins were associated with an increased risk of having advanced prostate cancer. Besides the direct cholesterol-lowering effect of statins by statin-users, it is assumable that differences in PSA screening patterns between statin users and non-users also have contributed to the increased risk of having advanced prostate cancer. The other component in blood serum which is associated with prostate cancer is triglyceride.\textsuperscript{41,45}

Although the relation between blood lipid profiles and prostate cancer risk has been investigated, only a few recent and population-based prospective studies have been reported. In chapter 8 we studied the association between serum cholesterol, triglycerides and prostate cancer risk in a Dutch, prospective population-based cohort among 2,862 men. After a median follow-up (IQR) of 56.4 (50.9-59.4) months, 38 new cases of prostate cancer were identified. In this study, no strong evidence regarding blood lipid levels and risk of having prostate cancer was found. In contrast with other studies triglyceride levels, although not significant, were inversely related to prostate cancer risk. Our study, however, was based on relatively few cases, raising the possibility of a chance finding. Because of this we were not able to distinguish between localized and advanced or aggressive prostate cancer. Larger, prospective, population-based studies are needed to verify whether blood lipids might have more pronounced effects on advanced/ aggressive prostate cancer risk or mortality.
Future Perspectives

Due to the ongoing obesity epidemic and increasing incidence of prostate cancer, a relatively new topic ‘obesity and prostate cancer’ has gained more and more popularity among urologists and radiation oncologists in recent years. Although this thesis has shed light on this subject, there are still various issues that have to be resolved in the future. In this paragraph several of these issues will be addressed briefly.

Most of the issues concerning this subject have been focused on epidemiological studies, tumour characteristics and oncological outcome. However, to date there is no consensus which of the different treatment modalities (surgery, external radiotherapy or brachytherapy) gives the obese patient suffering from prostate cancer the best oncological and functional outcome and quality of life. Although randomised controlled trials would be ideal to study outcome of therapy in obese and non-obese patients, this will be impossible to do. Therefore, data of patients who are treated for prostate cancer patients must be collected prospectively and validated questionnaires and uro-dynamic investigations are needed in order to achieve this goal. Without these trials making an assumption on which technique is the best for the obese patient suffering from prostate cancer cannot be made.

Obese men undergoing external radiotherapy for localized prostate cancer may be at a greater risk of biochemical recurrence compared with their thinner counterparts. Besides tumour characteristics, technical issues may also contribute to this discrepancy. In obese patients who undergo external radiotherapy daily setup errors can occur due to excessive intra-abdominal adipose tissue. These prostate shifts may result in not receiving the intended dose and leads to increased treatment failures if not corrected. Gold seeds and real time image-guided radiation therapy may be useful to improve the prostate targeting during radiotherapy, especially in obese patients. Comparative trials are needed to investigate whether gold seeds or image-guided radiation therapy can improve the oncological and functional outcome of obese patients suffering from prostate cancer.

Besides BMI to determine obesity we also used CT to measure different fat entities in patients having prostate cancer. One of the disadvantages of using a CT is that it can only measure fat quantity. In addition to its lipid-storage capacity, adipose tissue is a highly active endocrine and metabolic organ. A very important question that must be answered is how metabolically active is that fat at the different locations of the human body? ‘Fat’ fat cells, those common in obese patients, produce larger quantities of cytokines (messengers to the rest of the body) than their ‘thin’ counterparts. However, a CT cannot distinguish between those two different types of fat cells. It may be assumed that some ‘fat compartments’ of the body produce more quantities of cytokines than other ‘fat compartments’. So far we do not know...
if the abdominal fat which is wrapped around the intestines produces more or less cytokines than the fat which is located around the prostate. The fat around the prostate may act in a paracrine way by releasing the cytokines near the prostate while the abdominal fat releases the cytokines into the blood. To measure the fat activity it would be very interesting to collect fat at the different anatomical parts of the body during e.g. a radical prostatectomy. After the fat of different anatomical locations is collected, the fat cells can be brought into a medium where they are stimulated. The amount of cytokines produced by each of the fat cells at different parts of the body may represent its metabolic activity. By linking these data with the different anthropometric data of the patients and its prostate cancer characteristics and oncological outcome, a better insight may be gained in the exact role of obesity on prostate cancer. In contrast with the USA, different European studies did not find a higher rate of biochemical recurrence in obese patients who were treated for their prostate cancer compared with their thinner counterparts. Therefore, it would be very interesting to perform this study in Europe and America to determine if there are differences between the two continents that can explain this discrepancy.

Most of the studies concerning the risk of obesity on developing prostate cancer, high-risk disease and biochemical recurrence after treatment were based on just one BMI measurement in adulthood. However, the following questions may arise: can an obese patient in whom prostate cancer is diagnosed improve his prognosis by losing weight? Is childhood obesity of greater risk of developing aggressive prostate cancer than adulthood gained obesity? Besides better definitions of obesity, where mostly BMI is just a marker for general obesity, further research should investigate the role of not just obesity at one point but rather lifelong obesity. Analogous to smoking where pack-years (i.e. number of cigarette packages smoked per year multiplied by the number of years of smoking) is used we should use the “obesity years duration” in oncological research to get a better insight in the real effect of obesity on cancer.

Finally, although better understanding of the link between obesity and prostate cancer and their molecular pathways might provide therapeutic targets, preventing overweight and obesity still remains number one priority. It is a bitter irony that as developing countries continue their efforts to reduce hunger, some are also facing the opposing problem of obesity. Besides the fact that obesity is related with a higher incidence of chronic illness including diabetes, heart disease and cancer, it could place significant financial burdens on the health care systems all over the world. In the European Union it is estimated that 113 million adult males and 98 million adult females have either overweight or are obese, while the prevalence is still increasing. Important measures to slow down the increasing prevalence among adults and children might be e.g. good education about healthy behaviour, lifestyle modifications, stimulation of exercise and removing television advertising of high-fat and/or high-sugar food and beverages or fast-food commercials at the children's peak viewing times.
Closing Remarks

Obesity is a growing health problem that is increasingly affecting numerous aspects of medical care. This thesis focused on the effect of obesity on prostate cancer among Dutch patients. However, we need to realize that there are still many unresolved issues and more data regarding the effect of obesity on prostate cancer outcomes with the various treatment modalities are emerging. Based on the data presented in this thesis, I conclude the following: In a Dutch cohort of men who underwent a radical prostatectomy for prostate cancer, obese men were at risk for developing vesicourethral strictures and incontinence compared to their non-obese counterparts. Obese patients who underwent brachytherapy or surgery were not at higher risk for developing biochemical recurrence compared with the non-obese patients. In this thesis we measured the periprostatic fat density by CT. 31% of the patients with a normal BMI who received brachytherapy for their prostate cancer had a periprostatic fat density of > 75 percentile. In a group of patients with low and high-grade localized prostate cancer an increase of the periprostatic fat density was significantly correlated with the odds of having a high-risk disease. In a Dutch, prospective population-based cohort study among 2,862 men, no strong evidence of a relation regarding blood lipid levels and risk of having prostate cancer was found. I would suggest that future research on the topic of obesity and prostate cancer must not simply focus on BMI, as a marker for general obesity but rather on correlating visceral obesity and adipocyte dysfunction. People with a healthy weight and even people with a very low BMI can still be too ‘fat’. Although BMI does correlate with many health factors, it is not the amount of fat, but its location that matters for health. Therefore, a better definition of adiposity may expose clearer and perhaps new associations with prostate cancer and other diseases as well. Future research needs to evaluate the role of central versus peripheral obesity in epidemiologic studies.

Finally, the clinician must approach a prostate cancer patient in a holistic manner and educate the patient about the relation between the early all-cause morbidity and mortality associated with obesity.

“To prevent is better than to cure!”


Chapter 10

Summary/ Samenvatting

PROSTATE CANCER. CLINICAL IMPLICATIONS OF OBESITY
Summary

The aim of this thesis was to investigate the clinical implications of obesity on disease aggressiveness and treatment outcome in prostate cancer patients.

Chapter 1 presents a general introduction and outline of the thesis. The general introduction provides a short overview of the epidemiology and aetiology of prostate cancer. It sheds light over the definition of obesity, the different clinical aspects and the epidemiology of both obesity and prostate cancer. In this chapter the relation between obesity and prostate cancer and its clinical implications are described briefly. The chapter ends with an outline of the thesis.

Chapter 2 is a review of the literature about the possible impact of obesity on prostate cancer development, its clinical implications and effect on treatment outcome. The chapter starts with potential biochemical mechanisms related to obesity, which may act on prostate cancer development or progression. Alteration of hormone profiles and different adipokines are described. Obesity is associated with increased levels of estradiol and decreased serum concentrations of free testosterone and sex-hormone-binding globulin. At first sight this might seem protective for prostate cancer, however, several reports have shown a correlation between higher pathological disease stage at the time of surgery and lower levels of serum testosterone. Besides hormonal changes, obesity is associated with increased levels of several adipokines, like leptin, insulin-like growth factor-1, tumour necrosis factor α, interleukin 6, vascular endothelial growth factor and decreased levels of adiponectin. The available literature about each adipokine in relation with prostate cancer is discussed separately. The relation between different adipokines and prostate cancer progression is more consistent than the relation between different adipokines and prostate cancer development. However, most studies evaluated the adipokines individually, while a cumulative effect of all adipokines together may be of greater importance in prostate cancer progression.

The chapter continues with an overview of the literature about the influence of obesity on the risk of developing prostate cancer. Also, the relation between obesity and the prevalence of aggressive vs. non-aggressive prostate cancer is discussed. Although the relation between obesity and the risk of having prostate cancer is inconsistent, the existing evidence suggest that obesity is associated with a higher risk of having a more aggressive prostate cancer at the time of diagnosis. The detection rate of prostate cancer in an obese patient may be influenced because obesity lowers the PSA level, enlarges the prostate and makes a digital rectal examination more difficult to perform. In this section, possible explanations why obese patients are at higher risk for biochemical recurrence are given. It is
undisputed that obesity influences outcome, both functionally and oncologically. However, it is questionable whether higher recurrence rates seen after surgery and external beam radiotherapy are driven by worse biological features or caused by technical difficulties during the therapy or a combination of both. A short summary of the available literature that describes the relation between obesity and different treatment outcome is given.

Chapter 3 reports on a historical cohort study including 252 men who underwent a radical retropubic prostatectomy at the Canisius-Wilhelmina Hospital, Nijmegen to gain more knowledge about the effects of obesity on treatment outcome. Compared to non-obese men (N=221, 88%), obese men (N=31, 12%) were at a significantly higher risk of developing wound infections (16.1% vs. 4.5%), urinary incontinence (25.8% vs. 8.7%) and vesico-urethral strictures (45.2% vs. 12.3%). Obese patients were not at increased risk of having worse pathological features or biochemical recurrence after surgery.

Chapter 4 compares obese and non-obese patients with localized prostate cancer who have been operated in one of the following Dutch university hospitals: Radboud University Medical Centre, Nijmegen or Erasmus University Medical Center, Rotterdam. Although epidemiological studies of obesity in relation to prostate cancer development have provided conflicting results, recent studies from the USA suggested that a higher body mass index (BMI) is associated with an increased risk of biochemical recurrence after a radical prostatectomy. A total of 1,368 patients, of whom 600 (43.9%) were classified as having normal weight, 665 (48.6%) as overweight and 103 (7.5%) as obese, were included. To determine the risk of biochemical recurrence, 1,302 patients were analyzed. After a median follow-up of 59 months, 297 patients developed biochemical recurrence. The 10-year risk (95% confidence interval) of biochemical recurrence was 31.9% (26.6%-37.2%), 30.5% (25.8%-35.2%) and 23.9% (14.9%-32.9%) for patients in the normal, overweight and obese group, respectively (p=0.84). In this study, BMI appeared to have no significant prognostic value for biochemical recurrence in Dutch patients with clinically localized prostate cancer treated with radical prostatectomy.

Chapter 5 reports a study on the impact of obesity on treatment outcome in patients who underwent brachytherapy at the University Medical Center Utrecht. In total, 1,530 patients with clinically localized prostate cancer were evaluated retrospectively. The study included 617 (40.3%) normal-weight patients, 754 (49.3%) over-weight patients and 159 (10.4%) obese patients. The focus of this study was on biochemical recurrence, cancer-specific survival and overall survival. After a median follow-up of 47.0 months, 249 (16.3%) patients developed biochemical recurrence and 193
(12.6%) patients died. The Kaplan-Meier 8-year risk of biochemical recurrence (95% confidence interval) was 33.3% (27.2%-39.4%), 29.2% (23.5%-34.9%) and 29.3% (12.4%-46.2%) for patients in the normal, overweight and obese group, respectively. The Kaplan-Meier 8-year cancer-specific survival (95% CI) was 88.2% (83.1%-93.3%), 88.6% (83.7%-93.5%) and 90.6% (79.9%-100.0%) for patients in the normal, overweight and obese group, respectively. Multivariable proportional hazard regression analyses of BMI and established prognostic factors for biochemical recurrence confirmed the absence of any prognostic value of BMI on biochemical recurrence, cancer-specific survival and overall survival.

From the three previous chapters we can conclude that BMI seems to be related to functional outcome of a radical prostatectomy, but BMI has no prognostic value when oncological outcome is analysed after local therapy with curative intent. However, in these chapters BMI is used as a general marker of obesity. Computed tomography (CT) can measure the fat distribution very accurately and can distinguish the contribution of central and peripheral fat. In chapter 6 a CT was used to measure the subcutaneous fat distribution and the fat around the prostate, the so-called periprostatic fat. To investigate whether the amount of periprostatic fat correlates with prostate cancer aggressiveness, 725 CT scans of patients who were treated with brachytherapy were evaluated. 237 (37.2%) of the patients were classified as having normal weight, 320 (50.2%) as overweight and 80 (12.6%) as obese (from 88 patients the BMI was not available). The patients were stratified into 3 groups: <25, 25-75 and >75 percentile of the periprostatic fat density. There was a significant association between BMI and periprostatic fat density and subcutaneous fat thickness. The strongest correlation was seen between BMI and subcutaneous fat thickness (Pearson coefficient=0.71). Logistic regression analysis revealed no statistically significant association between periprostatic fat density and prostate cancer aggressiveness. However, the study population consisted exclusively of low and intermediate grade and T1 to T2 prostate cancers. Interestingly, 31% of the patients with a normal BMI were above the 75th percentile of the periprostatic fat density. Thus, what is measured on the outside is definitely not always representative of the fat distribution around the prostate.

Chapter 7 describes 932 patients with T1-T3N0M0 prostate cancer who underwent radiotherapy (brachytherapy (N=621) and external beam radiotherapy (N=311)) for their localized prostate cancer. Their CT scans were evaluated and the periprostatic fat and subcutaneous fat thickness was measured. A possible association between these fat measurements and the risk of having high-risk disease was examined. Logistic regression analyses revealed a significant association between periprostatic fat density and the risk of having high-risk disease.
Chapter 8 represents a population-based cohort study among 2,862 men. It has been hypothesized that blood lipid profiles are associated with prostate cancer risk. In this chapter we addressed serum total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides as potential risk factors for prostate cancer using age-adjusted proportional hazards regression models. During a median follow-up of 56.4 months, 38 new cases of prostate cancer were identified. Non-significantly increased risks (95% CI) per mmol/L were observed for total cholesterol (HR 1.22, 0.91-1.66), HDL cholesterol (HR 1.83, 0.71-4.69) and LDL cholesterol (HR 1.36, 0.97-1.91). Triglycerides were associated with decreased prostate cancer risk (HR 0.77, 0.54-1.09). Unfortunately, the follow-up was too short and the population size too small to reach sufficient statistical power for any definitive conclusion.

Chapter 9 provides a general discussion of the various investigations of the present thesis in light of the relevant literature. Future perspectives for further research are outlined and the closing remarks bring this thesis to an end.
Samenvatting

Het doel van dit proefschrift is om een aantal verschillende klinische aspecten van obesitas te onderzoeken in relatie tot de agressiviteit van de ziekte en de behandelingsresultaten van patiënten met prostaatkanker.

Hoofdstuk 1 bestaat uit een algemene introductie en uiteenzetting van het proefschrift. De algemene introductie geeft een kort overzicht over de epidemiologie en etiologie van prostaatkanker. Tevens behandelt het de definitie van obesitas en de verschillende klinische en epidemiologische aspecten. Ook komen de relatie tussen obesitas en prostaatkanker en in het kort de klinische implicaties daarvan aan de orde. Tot slot wordt een uiteenzetting van dit proefschrift gegeven.

Hoofdstuk 2 is een literatuuroverzicht waarin de mogelijke invloed van obesitas op de ontwikkeling van prostaatkanker, klinische implicaties en behandelingsresultaten worden beschreven. Het hoofdstuk begint met de potentiële biochemische mechanismen die worden gezien bij obesitas, welke op haar beurt invloed kunnen uitoefenen op zowel de ontwikkeling van prostaatkanker als ook op de progressie. Daarna volgt een beschrijving van hormonale veranderingen en verschillende adipokines. Obesitas is geassocieerd met verhoogde oestraadiol spiegels en verlaagde serumconcentraties van het vrije testosteron en sex-hormoon-bindend globuline. Op het eerste gezicht lijkt deze verandering juist beschermend tegen prostaatkanker. Verschillende studies bevestigen een correlatie tussen een slechter pathologisch stadium en een lage testosteronspiegel ten tijde van de operatie. Naast hormonale veranderingen is vetzucht ook geassocieerd met verhoogde concentraties van verschillende adipokines zoals leptine, insulin-like growth factor-1, tumor necrose factor α, interleukine 6, vascular endothelial growth factor en verlaagde concentraties van adiponectine. De beschikbare literatuur over elk adipokine in relatie tot prostaatkanker worden separaat besproken. De relatie tussen de verschillende adipokines en progressie van prostaatkanker is minder inconsistent dan de relatie tussen de verschillende adipokines en het risico op het krijgen van prostaatkanker. Echter, de meeste studies bestuderen de adipokines individueel terwijl een cumulatief effect van alle adipokines bij elkaar mogelijk een grotere invloed zouden hebben op prostaatkanker progressie.

Het hoofdstuk gaat verder met een literatuuroverzicht over het risico van obesitas op de ontwikkeling van prostaatkanker. De relatie tussen obesitas en een verhoogde kans op het hebben van een agressieve vorm van prostaatkanker vergeleken bij een niet obese man wordt ook besproken. Hoewel de relatie tussen obesitas en het risico op het krijgen van prostaatkanker niet duidelijk is, bestaat er meer bewijs over de rol van obesitas ten tijde van behandeling en het hebben van een meer agressieve vorm van prostaatkanker.
De detectiegraad van prostaatkanker bij patiënten met obesitas kan worden beïnvloed omdat obesitas de PSA waarde verlaagt, de prostaat vergroot en rectaal onderzoek bemoeilijkt. Mogelijke verklaringen waarom obes patiënten een hoger risico lopen op het krijgen van een biochemisch recidief komen ook in het hoofdstuk aan bod. Het is onomstreden dat obesitas invloed heeft op de behandelingsresultaten in functionele en oncologische zin. Het is echter niet duidelijk of de hogere recidiefkans, die valt waar te nemen na chirurgie en uitwendige bestraling, wordt veroorzaakt door slechtere biologische tumorkenmerken, technische problemen tijdens de behandeling of een combinatie van beiden. Het hoofdstuk eindigt met een korte samenvatting van de beschikbare literatuur die de relatie beschrijft tussen obesitas en verschillende behandelingsresultaten.

Hoofdstuk 3 rapporteert een historisch cohortstudie bestaande uit 252 mannen die een radicale prostatectomie hebben ondergaan in het Canisius-Wilhelmina Ziekenhuis in Nijmegen. Om meer kennis te krijgen over het effect van obesitas op de behandelingsresultaten, werden de patiënten retrospectief geanalyseerd. vergeleken met niet-obese mannen (N=221, 88%), hadden mannen met obesitas (N=31, 12%) een significant hoger risico op het ontwikkelen van wondinfecties (16.1% vs. 4.5%), urine incontinentie (25.8% vs. 8.7%) en vesico-urethrale stricuturen (45.2% vs. 12.3%). Obese patiënten hadden geen verhoogd risico met betrekking tot slechtere pathologische kenmerken of biochemisch recidief.

Hoofdstuk 4 vergelijkt obese en niet obese patiënten met gelokaliseerde prostaatkanker, die zijn geopereerd in het Radboud Universitair Medisch Centrum Nijmegen, danwel het Erasmus Universitair Medisch Centrum Rotterdam. Alhoewel epidemiologische studies over obesitas in relatie tot de ontwikkeling van prostaatkanker tegenstrijdige uitkomsten laten zien, tonen recente Amerikaanse onderzoeken aan dat een hogere body mass index (BMI) is geassocieerd met een hoger risico op een biochemisch recidief bij patiënten die een radicale prostatectomie hebben ondergaan. In totaal werden er 1368 patiënten geïncludeerd van wie er 600 (43.9%) een normaal gewicht hadden, 665 (48.6%) hadden overgewicht en 103 (7.5%) waren obees. Om het risico op biochemisch recidief vast te stellen werden 1302 patiënten geanalyseerd. Na een mediane follow-up van 59 maanden ontwikkelden 297 patiënten een biochemisch recidief. Het 10-jaar risico (95% betrouwbaarheidsinterval) op de ontwikkeling van biochemisch recidief was 31.9% (26.6%-37.2%), 30.5% (25.8%-35.2%) en 23.9% (14.9%-32.9%) voor patiënten met respectievelijk een normaal gewicht, overgewicht en obesitas (p=0.84). In dit proefschrift blijkt de BMI, bij Nederlandse patiënten met een klinisch gelokaliseerde prostaatkanker en die behandeld zijn met een radicale prostatectomie, niet van prognostische waarde te zijn voor het krijgen van een biochemisch recidief.
Hoofdstuk 5 betreft een studie over de invloed van obesitas op de behandelingsuitkomsten van patiënten die brachytherapie hebben ondergaan in het Universitair Medisch Centrum Utrecht. In totaal werden 1530 patiënten met klinisch gelokaliseerde prostaatkanker retrospectief geanalyseerd. De studie bestond uit respectievelijk 617 (40.3%) patiënten met een normaal gewicht, 754 (49.3%) met overgewicht en 159 (10.4%) met obesitas. In deze studie werd de relatie tussen obesitas enerzijds en biochemisch recidief, kanker specifieke overleving en totale overleving anderzijds bekeken. Na een mediane follow-up van 47.0 maanden ontwikkelden 249 (16.3%) patiënten een biochemisch recidief en overleden 193 (12.6%) patiënten. Het Kaplan-Meier 8-jaarsrisico op biochemisch recidief (95% CI) was 33.3% (27.2%-39.4%), 29.2% (23.5%-34.9%) en 29.3% (12.4%-46.2%) voor patiënten met respectievelijk een normaal gewicht, overgewicht en obesitas. In dezelfde volgorde bedroeg de Kaplan-Meier 8-jaar kankerspecifieke overleving (95% CI) respectievelijk 88.2% (83.1%-93.3%), 88.6% (83.7%-93.5%) en 90.6% (79.9%-100.0%). De multivariabele proportionele hazard regressie-analyse tussen BMI en de bekende prognostische factoren voor biochemisch recidief bevestigde de afwezigheid van enige prognostische waarde van de BMI op het voorspellen van biochemisch recidief, kankerspecifieke overleving en totale overleving.

De conclusie uit de vorige drie hoofdstukken is dat BMI wel is gerelateerd aan de functionele uitkomsten na een radicale prostatectomie, maar de BMI heeft geen voorspellende waarde met betrekking tot de oncologische resultaten na lokale, in opzet curatieve therapie. Echter, in de vorige drie hoofdstukken is BMI als generale maat voor vetzucht gebruikt. Computed tomography (CT) kan de distributie van vet erg nauwkeurig bepalen en een onderscheid maken tussen centraal en perifeer vet. In hoofdstuk 6 wordt met behulp van een CT de subcutane vetdikte en het vet rond de prostaat, verder genoemd het periprostatisch vet, berekend. Om te onderzoeken of de hoeveelheid periprostatisch vet correleert met prostaatkankeragressiviteit werden 725 CT’s geëvalueerd van patiënten die waren behandeld met brachytherapie voor gelokaliseerd prostaatkanker. Geclassificeerd zijn er onder deze 725 patiënten, 237 (37.2%) met normaal gewicht, 320 (50.2%) met overgewicht en 80 (12.6%) met obesitas (bij 88 patiënten kon de BMI niet worden bepaald). De patiënten werden in 3 groepen ingedeeld, te weten: <25, 25-75 en >75 percentiel van de periprostatische vetdichtheid. Er was een significante associatie tussen BMI en periprostatische vetdichtheid en subcutane vetdikte. De sterkste correlatie werd gevonden tussen BMI en subcutane vetdichtheid (Pearson-coëfficiënt= 0.71). Logistieke regressie-analyse leverde geen statistisch significante associatie op tussen periprostatische vetdichtheid en prostaatkankeragressiviteit. Echter, de studiepopulatie bestond hoofdzakelijk uit patiënten met een tumor van een lage en intermediaire graad van agressiviteit, met een klinisch stadium T1 of T2. Interessant genoeg hadden 31% van
de patiënten met een normale BMI een periprostatische vetdichtheid van hoger dan de 75ste percentiel. Concluderend is wat je aan de buitenkant meet niet automatisch representatief voor de vetverdeling rond de prostaat.

Hoofdstuk 7 beschrijft 932 patiënten met T1-3N0M0 prostaatkanker die radiotherapie (brachytherapie (N=621) en externe radiotherapie (N=311)) voor gelokaliseerde prostaatkanker hebben ondergaan. De CT’s van deze mannen zijn geëvalueerd en het periprostatisch vet en de subcutane vetdichtheid gemeten. Een mogelijke associatie tussen deze verschillende vetbepalingen en het risico op het hebben van een hoog risico prostaatkanker werden bestudeerd. Logistische regresstie-analyse laat een significante associatie zien tussen de periprostatische vetdichtheid en het risico op het hebben van een agressieve vorm van prostaatkanker.

Hoofdstuk 8 gaat over een populatie-gebaseerde cohortstudie van 2862 mannen. Er wordt verondersteld dat vetprofielen die meetbaar zijn in het bloed geassocieerd zijn met het risico op het krijgen van prostaatkanker. In dit hoofdstuk behandelen we het totale serum cholesterol, HDL cholesterol, LDL cholesterol en triglyceriden als potentiële risicofactoren voor prostaatkanker. Hierbij hebben we gebruik gemaakt van een voor leeftijd gecorrigeerde proportionele hazard analyse. Gedurende een mediane follow-up van 56.4 maanden werd bij 38 mannen prostaatkanker vastgesteld. Een niet significant toegenomen risico (95% CI) per mmol/L werd gevonden voor totaal cholesterol (HR 1.22, 0.91-1.66), HDL cholesterol (HR 1.83, 0.71-4.69) en LDL cholesterol (HR 1.36, 0.97-1.91). Triglyceriden (HR 0.77, 0.54-1.09) werden geassocieerd met een verminderde kans op het diagnosticeren van prostaatkanker. Ongelukkigerwijs was de follow-up te kort en het aantal patiënten met prostaatkanker te laag om voldoende statistische power te verkrijgen om tot een definitieve conclusie te komen.

Hoofdstuk 9 bediscussieert de resultaten van de bovenstaande studies in het licht van relevante literatuur. Verder worden enkele slotopmerkingen gemaakt en suggesties gedaan voor verder onderzoek.
Appendix

List of Publications
Dankwoord
Curriculum Vitae
List of Publications

The value of 3-dimensional greyscale transrectal ultrasonography in the detection of prostate cancer
JP Sedelaar, JG van Roermund, GJ Leenders, CA Hulsbergen-van de Kaa, FM Debruyne.
*Urology.* 2001 May;57(5):914-920.

Laserfragmentatie van ureterstenen – Hoe kunnen de behandelingsresultaten verbeterd worden?
AJ Hendrikx, JG van Roermund, DL Floratos, B Arends.

Medische vignetten – Diagnose in beeld: Een lintworm in een dunnendarmstoma
JG van Roermund, JM Klaase.

Medische vignetten – Diagnose in beeld: Een man met een acuut scrotum
JG van Roermund, HF Karthaus.

The impact of obesity on prostate cancer
JG van Roermund, JA Witjes.

Body mass index as a prognostic marker for biochemical recurrence in Dutch men treated with radical prostatectomy
JG van Roermund, DE Kok, MF Wildhagen, LA Kiemeneij, F Struik, S Sloot, IM van Oort, CA Hulsbergen-van de Kaa, GJ Leenders, CH Bangma, JA Witjes.
*BJU Int.* 2009 Feb; Epub ahead of print.

Impact of obesity on surgical outcomes following open radical prostatectomy
JG van Roermund, JP van Basten, LA Kiemeneij, HF Karthaus, JA Witjes.
*Urol Int.* 2009 May;82(3): 256-261.

Body mass index is not a prognostic marker for prostate-specific antigen failure and survival in Dutch men treated with brachytherapy
JG van Roermund, KA Hinnen, JJ Battersmann, JA Witjes, JL Bosch, LA Kiemeneij, M van Vulpen.
Periprostatic fat measured on computed tomography as a marker for prostate cancer aggressiveness
JG van Roermund, GH Bol, JA Witjes, JL Bosch, LA Kiemeny, M van Vulpen.

Long term biochemical and survival outcome of 921 patients treated with I-125 permanent prostate brachytherapy
KA Hinnen, JJ Battermann, JG van Roermund, MA Moerland, IM Jürgenliemk-Schulz, SJ Frank, M van Vulpen.

Health-related quality of life up to six years after I-125 brachytherapy for localized prostate cancer
EM Roeloffzen, IM Lips, MP van Gellekom, JG van Roermund, SJ Frank, JJ Battermann, M van Vulpen.
Int J Radiat Oncol Biol Phys. 2009; accepted.

The impact of acute urinary retention after I-125 prostate brachytherapy on health-related quality of life
EM Roeloffzen, KA Hinnen, JJ Battermann, EM Monninkhof, JG van Roermund, MP van Gellekom, SJ Frank, M van Vulpen.

Acute urinary retention after I-125 prostate brachytherapy in relation to dose in different regions of the prostate
EM Roeloffzen, EM Monninkhof, JJ Battermann, JG van Roermund, MA Moerland, M van Vulpen.
Int J Radiat Oncol Biol Phys. 2010; accepted.

Langetermijnresultaten van 921 patiënten behandeld met I-125 brachytherapie voor prostaatkanker
KA Hinnen, JJ Battermann, JL Bosch, M van Vulpen, JG van Roermund.

Loose seeds versus stranded seeds in I-125 prostate brachytherapy: Differences in clinical outcome
KA Hinnen, MA Moerland, JJ Battermann, JG van Roermund, Monninkhof EM, IM Jürgenliemk-Schulz, M van Vulpen.
Radiother Oncol. 2010 Mar 8; Epub ahead of print.
Dankwoord

‘Jullie waren de motor voor dit succes!!’

Een aantal jaar geleden had ik niet kunnen voorspellen dat, na een avondje tv kijken en wederom de nodige dikke, snackende mensen te hebben gezien, mijn onschuldige nieuwsgierigheid zou uitgroeien tot het proefschrift wat nu voor u ligt. Ik vroeg me daadwerkelijk af wat de gevolgen van de steeds dikker wordende mens zouden zijn op mijn vakgebied. Ook al ben ik de inspirator en initiator van de onderzoeken in dit proefschrift, zonder de steun, zonder gebruik te mogen maken van verschillende databasen, zonder patiënten en zonder morele ondersteuning was het me absoluut niet gelukt. Iedereen die op welke manier dan ook een bijdrage heeft geleverd die geleid heeft tot dit proefschrift ben ik dan ook zeer veel dank verschuldigd. Een aantal mensen wil ik nog persoonlijk bedanken:

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Prof. dr. J.A. Witjes, beste Fred, in de eerste weken van mijn academische opleiding vroeg ik je of het mogelijk was om onder jouw vleugels te mogen promoveren. Je antwoordde redelijk resoluut: “Veel assistenten willen graag bij me promoveren, maar hun verzoek blijft vaak onaangeroerd in de la liggen.” Gelukkig ben ik niet één van de velen en heb ik de daad bij het woord gevoegd. Spoedig kreeg ik mijn eigen mapje. Zie hier het resultaat. Ik wil je enorm bedanken voor jouw enthousiasme en betrokkenheid gedurende het onderzoekstraject. Stukken die ik naar je opstuurde ter correctie waren in mum van tijd weer bij me terug. Daarnaast ben ik je veel dank verschuldigd voor de vele leermomenten tijdens mijn opleiding. Het was altijd een groot genoegen om met jou aan de operatietafel te staan. Je nam altijd de tijd om dingen uit te leggen. Je hebt de gave om je assistent het gevoel te geven dat hij of zij de operatie geheel zelfstandig heeft uitgevoerd. Als assistenten noemden we dat “knippen over de stippellijn”. Als jonge klare zelfstandig aan tafel is het soms wel eens zoeken naar die stippellijn!
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Dankwoord

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CURRICULUM VITAE


Ter gelegenheid van het 100-jarig bestaan van de Nederlandse Vereniging voor Urologie, nam hij deel aan het ludieke lustrum cabaret.

In 2009, enkele weken na haar eigen promotie, werd bij zijn vrouw Acute Myeloïde Leukemie vastgesteld. Een jaar later overleed ze aan de gevolgen van deze ziekte.