Aspects of health related quality of life in prostate cancer
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Chapter 1

Introduction and outline of the thesis
**Introduction**

To date, prostate cancer is one of the most diagnosed malignancies in men worldwide. Despite enormous efforts in time and money, many questions concerning several aspects of prostate cancer remain unanswered. For example, it is unclear whether all patients need treatment at all, the effect of screening is still being discussed. There is worldwide no consensus about the best treatment in different stages of the disease. There are several treatment options for the same stage of disease with more or less comparable objective outcome measures. The optimal therapy in case of progressive disease after primary hormonal manipulation is still being sought for. To date, no effective second-line treatment is available. As soon as we realised that knowledge about the impact on the health related quality of life (HRQOL) plays an important role in answering these questions, the interest in the research on HRQOL in prostate cancer was born. Finally, this interest resulted in the current thesis. In this chapter the clinical background of prostate cancer is briefly discussed and at the end the aim of the thesis is outlined.

**Clinical background**

Prostate cancer is, after lung cancer, the second most commonly diagnosed malignancy in men worldwide. It is estimated that 38.7 million men in North-America, Europe and Japan have prostate cancer. In the European Union an estimated 85.000 and in the Netherlands 7000 new cases are diagnosed each year. Nowadays, prostate cancer is recognized as one of the principal medical problems facing the male population [1,2].

**Etiology**

The exact cause or causes of prostate cancer are unknown. Predetermining factors for the development of prostate cancer are age, a family history of prostate cancer, and racial characteristics. Prostate cancer is rarely found in men under the age of 50, but is increasingly common with rising age [3]. Case-control analyses showed familial patterns of prostate cancer. A man with one first-degree relative with prostate cancer is estimated to have a 2.1 fold to 2.8 fold greater risk of being diagnosed with prostate cancer than a man of the same age without a positive family history. If two or more first degree relatives are affected, the risk increases to 5 till 11 fold [4-6]. Approximately 10% of all diagnosed prostate cancers are believed to be due to familial genetics. Concerning racial characteristics, the highest incidence of clinical disease is in Afro-Americans and the lowest in Japanese living in Japan [7-9]. However, several studies have demonstrated that migration from low risk areas to high risk areas is associated with an increased risk of developing clinical prostate cancer in migrants compared with men living in the low risk country of origin. This observation, combined with the fact that the incidence of clinical prostate cancer is increasing in Japan and China with their concurrent increased westernization, as well as the fact that the frequency of autopsy-detected cancers is roughly the same in different parts of the world, suggest that environmental factors such as diet play an important role in prostate cancer etiology [7,10-12].

The identification of these exogenous factors is very complicated and still under debate. But an increased risk of developing prostate cancer may be related to a high content of animal fat in the diet and, among others, increased levels of Cadmium [13-15]. Decreased risk on the other hand, might be associated with intakes of Vitamin A and E, Selenium, lignans and iso-flavonoids [16-19]. Although sometimes suggested otherwise, there is no sound evidence that smoking, socioeconomic factors, vasectomy, occupation, sexual behaviour and infections, and benign prostatic hyperplasia are associated with a higher risk of developing prostate cancer [20-25].

**Clinical symptoms and signs of prostate cancer**

In its early stages prostate cancer may remain clinically obscure for prolonged periods of time. In most cases prostate cancer is diagnosed in men older than 50 who are evaluated because of micturition problems. A suspicious digital rectal examination or an elevated prostate-specific antigen (PSA) is the reason to perform further diagnostics in order to discover the possible presence of prostate cancer. There is no sound relationship between bladder outlet obstruction (voiding dysfunction, micturition problems, 'prostatism') and the presence of localised prostate cancer. Just as the American Urological Association symptom severity index is non-specific for BPH, none of the symptoms of bladder outlet
obstruction is unique to prostate carcinoma [26]. However, extensive local disease can cause several symptoms, like micturition problems, priapism, ureteral obstruction, rectal involvement with symptoms quite similar to that of rectosigmoid carcinoma such as constipation, abdominal pain, rectal bleeding and intermittent diarrhea [27-29]. Often, patients first show symptoms of metastatic disease [30,31]. Persistent, often severe bone pain in the back or the hip is one of the common presenting symptoms. The lymphnodes are a common, usually clinically silent site of metastatic spread for prostate cancer [32]. Involvement of other organs other than the bone and lymphatics is rare and most often associated with widely disseminated disease. The clinical signs of metastatic, systemic disease are non-specific. No sign of dissemination is unique to prostate cancer.

Clinical diagnosis

Adequate diagnostic tools for the detection of prostate cancer include digital rectal examination, prostate-specific antigen and transrectal ultrasonography. The final diagnosis demands the presence of malignant cells (mostly adenocarcinoma) in the prostate biopsy cores or aspiration needle cytology. Once the diagnosis is made, dissemination investigations are performed by means of a bone scan supplemented with computed tomography/magnetic resonance imaging and chest X ray in specific situations.

- Digital rectal examination (DRE): the overall detection rate for an abnormal DRE varies from 15%-40% [33-35]. So DRE is an imprecise and in fact rather disappointing tool in detecting prostate cancer. If DRE is used for screening of prostate cancer it will identify carcinoma in 0.1-4.0 % of those who are examined [36,37].

- Prostate-specific antigen (PSA): PSA has, during the 1980s and 1990s, revolutionized the management of prostate cancer patients at every level: from improved early detection, more accurate staging, more reliable monitoring of disease progression, to response of therapy [38]. PSA is a kallikrein-like serine protease produced almost exclusively by the epithelial cells of the prostate. Because PSA may be elevated also in patients suffering from BPH, prostatitis or other non-malignant conditions, PSA is organ-specific but not cancer-specific. Nevertheless, it is argued that PSA is probably the most valuable tumor marker in all oncology [39]. PSA level as an independent variable is a better predictor of cancer than suspicious findings on DRE or TRUS [33]. The positive predictive value of PSA for the detection of prostate cancer is approximately 25%-35% for levels between 4 ng/ml and 10 ng/ml and 50%-80% for those above 10 ng/ml, depending on the findings at DRE [40].

In order to enhance the specificity of PSA, several methods have been developed. These methods are PSA density [33,41-43], PSA density of the transition zone [44], age-specific reference ranges [45-47], PSA molecular forms [48,49], PSA velocity [50] and PSA doubling time [51]. The precise value of these methods is still debatable and no consensus has been reached yet.

- Transrectal ultrasonography (TRUS): the appearance of prostate cancer differs from the classic hypoechoic area to hyperechoic areas. However, many cancers are isoechoic and therefore only detectable from systemic biopsies. The potential role of TRUS includes the identification of suspected lesions and the improvement of the accuracy of prostate biopsies. The value of TRUS for the detection of prostate cancer in case of a normal DRE and normal level of PSA is very limited [34,52].

The positive predictive value of the various combinations of diagnostic procedures used in a screening population, ranges from 20%-80%. If a result obtained by any of the three modalities is abnormal, the positive biopsy rate is 6%-25%; with two abnormalities it is 18%-60%, and if all three modalities are positive it is 56%-72% [33,53].

- Bone scan: Bone scintigraphy remains the most sensitive method of assessing bone metastases, as it is superior to clinical evaluation, bone radiographs, serum alkaline measurements, and prostatic acid phosphatase (PAP) determination [54,55].

- Computed tomography (CT)scan: although of high technical standard, the sensitivity and specificity are to low to play a role in the local staging (T staging) of prostate cancer [56]. The same is true for
the detection of pathological lymphnodes. The sensitivity varies from 0%-70% [57]. CT scan, on the other hand, is an appropriate method to investigate if symptoms suggest the possibility of soft tissue metastases, for example in liver, lungs or brain.

- Magnetic resonance imaging (MRI): with respect to its role in prostate cancer MRI is comparable with CT scan, which means that the sensitivity and specificity are to low for adequate local staging or detection of lymphadenopathy. It is adequate to identify soft tissue metastases [57,58].

Pathological diagnosis
Adenocarcinoma of the prostate accounts for at least 98% of all prostate cancers [59]. For the grading of prostate adenocarcinoma a few systems are available. The most widely used and generally accepted system is that proposed by Gleason [60]. Gleason distinguishes five different grades or patterns on a scale of 1 to 5, from well differentiated to poorly differentiated. Because prostate cancer is usually very heterogeneous, with two or more grades in a given cancer, Gleason incorporates both a primary (most prevalent) and a secondary (next most prevalent) grade into his system. The final score is the sum of the primary and the secondary grade, ranging from 2 (1+1) to 10 (5+5). Other grading systems are the Anderson and the Mostofi grading [61,62]. Malignant tumors other than adenocarcinoma occurring in the prostate are, among others, small cell carcinoma’s, squamous and adenosquamous carcinoma’s, carcinosarcoma’s and transitional cell carcinoma’s.

Staging systems of prostate cancer
Definition of the extent of a patient’s cancer is a prerequisite for designing a plan for successful therapy. Practitioners rely on clinical staging to allow a selection of therapy, comparison of results of different treatments, and assignment of prognosis for an individual or a group of patients. Staging systems of prostatic carcinoma have been discussed intensively during the last few decades. In the 1950s staging concepts began to include a TNM (tumor, node, metastasis) classification. Within each reference of T, N or M there are categories based on tumor size or extent, number of regional nodes containing metastasis and distant metastasis. The last generally accepted TNM classification of prostate cancer was presented in 1997 [63] (see table 1, page 12).

Treatment
Generally, the choice of treatment is based on considerations about disease stage, prognosis, therapy results and complications, and patient’s and practitioner’s preferences. The best compromise between these considerations will finally decide which therapy is executed. However, in case of prostate cancer the facts about the mentioned factors playing a role in therapy decision making are not always that clear. Moreover, there are several treatment modalities for the same stage of the disease with more or less comparable objective response rates. It is for these reasons that there are no worldwide accepted strict guidelines for the treatment of prostate cancer. The European Association of Urology recently published her guidelines for the treatment of cancer of the prostate (see table 2, page 13). The indications and considerations of the several therapeutic options are listed in this table. Generally, it is stated that for clinically localised prostate cancer in men in good condition with a life expectancy of 10 years or more the goal of treatment should be eradication of the disease [64]. This can be achieved by radical surgery or radiation therapy (external or interstitial). In locally advanced disease there is evidence that the combination of radiation and hormonal therapy is the best choice [65]. Patients with lymph node or distant metastasis can’t be cured anymore. Hormonal treatment is effective in most of these patients, but this effect is only temporary. The question whether hormonal treatment must be initiated immediately at the time of diagnosis or deferred to the time of the appearance of objective progression or symptoms is still under debate [66,67]. Once the disease is progressive under hormonal therapy, so called hormone resistant prostate cancer, there is no second-line treatment available demonstrating a consistent increase in overall survival.
### Table 1: Tumour Node Metastasis (TNM) classification of cancer of the prostate [63]

<table>
<thead>
<tr>
<th>T</th>
<th>Primary tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx</td>
<td>Primary Tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>T1</td>
<td>Clinically inapparent tumour not palpable or visible by imaging</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumour incidental histological finding in 5% or less of tissue resected</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumour incidental histological finding in more than 5% of tissue resected</td>
</tr>
<tr>
<td>T1c</td>
<td>Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen level)</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour confined within the prostate</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumour involves one lobe</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumour involves both lobes</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour extends through the prostatic capsule</td>
</tr>
<tr>
<td>T3a</td>
<td>Tumour extracapsular extension (unilateral or bilateral)</td>
</tr>
<tr>
<td>T3b</td>
<td>Tumour invades seminal vesicle(s)</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator ani and/or pelvic wall.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N</th>
<th>Regional lymph nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nx</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M</th>
<th>Distant metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mx</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>M1a</td>
<td>Non regional lymph node (s)</td>
</tr>
<tr>
<td>M1b</td>
<td>Bone (s)</td>
</tr>
<tr>
<td>M1c</td>
<td>Other site (s)</td>
</tr>
</tbody>
</table>

Tumour found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c. Invasion into the prostatic apex or into (but not beyond) the prostate capsule, is not classified as T3, but as T2. The regional lymph nodes are the nodes of the true pelvis, which essentially are the pelvic nodes below the bifurcation of the common iliac arteries. Laterality does not affect the N classification. When more than one site of metastasis is present, the most advanced category should be used.
### Table 2: Treatment options for the different stages of prostate cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>Watchful waiting</td>
<td>Standard treatment for well and moderately differentiated tumours and a &lt;10 year life expectancy. In patients with &gt;10 year life expectancy a staging with transrectal ultrasonography and biopsy is advised.</td>
</tr>
<tr>
<td></td>
<td>Radical prostatectomy</td>
<td>Optional in young patients with a long life expectancy, especially for poorly differentiated tumours.</td>
</tr>
<tr>
<td></td>
<td>Radiotherapy</td>
<td>Optional in younger patients with a long life expectancy, especially for poorly differentiated tumours. Higher complication risks after transurethral resection of the prostate, especially with interstitial radiation.</td>
</tr>
<tr>
<td></td>
<td>Hormonal</td>
<td>Not an option.</td>
</tr>
<tr>
<td></td>
<td>Combination</td>
<td>Not an option.</td>
</tr>
<tr>
<td>T1b-T2b</td>
<td>Watchful waiting</td>
<td>Asymptomatic patients with well and moderately differentiated tumours and a life expectancy &lt;10 years. Patients who do not accept treatment-related complications.</td>
</tr>
<tr>
<td></td>
<td>Radical prostatectomy</td>
<td>Patients with a life expectancy &gt;10 years who accept treatment-related complications.</td>
</tr>
<tr>
<td></td>
<td>Radiotherapy</td>
<td>Patients with a life expectancy &gt;10 years who prefer radiation treatment and accept treatment-related complications. Patients with contraindications for surgery. Unfit patients with a 5-10 year life expectancy and poorly differentiated tumours.</td>
</tr>
<tr>
<td></td>
<td>Hormonal</td>
<td>Symptomatic patients unfit for curative treatment.</td>
</tr>
<tr>
<td></td>
<td>Combination</td>
<td>Neoadjuvant hormonal therapy + radical prostatectomy: no better. Neoadjuvant hormonal therapy + radiotherapy: better local control. No proven survival benefit. Hormonal (3 years) + radiotherapy: better than radiotherapy in poorly differentiated tumours.</td>
</tr>
<tr>
<td>T3-T4</td>
<td>Watchful waiting</td>
<td>Option in asymptomatic patients with T3, well and moderately differentiated tumours and a life expectancy &lt;10 years.</td>
</tr>
<tr>
<td></td>
<td>Radical prostatectomy</td>
<td>Optional for selected patients with 'small T3', prostate specific antigen &lt;20 ng/ml, Gleason score &lt;8 and a life expectancy &gt;10 years.</td>
</tr>
<tr>
<td></td>
<td>Radiotherapy</td>
<td>T3: NO with &gt;5-10 years of life expectancy. Dose escalation &gt; 70 Gy seems to be of some benefit.</td>
</tr>
<tr>
<td></td>
<td>Hormonal</td>
<td>Symptomatic patients, extensive T3-T4, high prostate-specific antigen level (&gt;25 mg/ml), unfit patients.</td>
</tr>
<tr>
<td></td>
<td>Combination</td>
<td>Radiotherapy + hormonal seems better than radiotherapy alone. Neoadjuvant hormonal therapy + radical prostatectomy: no prove benefit.</td>
</tr>
<tr>
<td>N+, M0</td>
<td>Watchful waiting</td>
<td>Symptomatic patients. Driven by the patient.</td>
</tr>
<tr>
<td></td>
<td>Radical prostatectomy</td>
<td>No standard option.</td>
</tr>
<tr>
<td></td>
<td>Radiotherapy</td>
<td>No standard option.</td>
</tr>
<tr>
<td></td>
<td>Hormonal</td>
<td>Standard therapy.</td>
</tr>
<tr>
<td></td>
<td>Combination</td>
<td>No standard option. Patient driven.</td>
</tr>
<tr>
<td>M+</td>
<td>Watchful waiting</td>
<td>No standard option (requires asymptomatic, informed patient, good compliance and good access to health care).</td>
</tr>
<tr>
<td></td>
<td>Radical prostatectomy</td>
<td>Not an option.</td>
</tr>
<tr>
<td></td>
<td>Radiotherapy</td>
<td>Not an option (given for cure).</td>
</tr>
<tr>
<td></td>
<td>Hormonal</td>
<td>Standard therapy. Symptomatic patients should not be denied treatment.</td>
</tr>
<tr>
<td></td>
<td>Combination</td>
<td>Not an option.</td>
</tr>
</tbody>
</table>

Hormonal = all forms of hormonal therapy; combination = hormonal therapy given prior to and/or after radical prostatectomy or radiotherapy; TURP = transurethral resection on the prostate.

Because it is beyond the scope of this chapter to discuss the role of all therapeutic modalities in prostate cancer in detail, we hereafter give only a brief clarification of the most common applied treatment options.

Watchfull waiting: no active treatment is executed. This approach does not imply patient neglect, but rather involves periodic reassessment of clinically important data. In fact, watchfull waiting is an option in every stage of the disease.

Radical prostatectomy: the surgical treatment of prostate cancer consists of radical prostatectomy, meaning removal of the entire prostate gland and the seminal vesicles. This approach can be performed retropubically, perineally or laparoscopically. The advantage of the retropubic and laparoscopic way is that in the same procedure a pelvic lymphadenectomy can be performed. Principally, surgical treatment is only offered to patients with localized disease. Side effects include among others erectile dysfunction (29%-100%), slight stress incontinence (4%-50%), severe stress incontinence (0%-15%), bladder neck obstruction (0,5%-15%), urine leak/fistula (0,3%-15%) and major bleeding (1%-12%) [68-70].

External-beam radiation therapy: the prostate and the vesicle seminals are irradiated using high-energy photons produced by a linear accelerator. With conventionally planned techniques, doses in the 68Gy - 70Gy range are routinely used. Dose-escalation studies are currently underway. Indication for external beam radiation therapy with curative intent is localized prostate cancer. The most frequently reported side effects are erectile dysfunction (55%-67%), rectal bleeding (3%-15%), diarrhea (1%-8%), hematuria (3%-11%), and genitourinary strictures (3%-11%) [71].

Interstitial radiation therapy (brachytherapy): the most commonly used method is treatment with low dose rate (LDR) radiation sources (palladium 103 or iodine 125 isotopes) which are permanently placed within the prostate under ultrasound guidance. This therapy should be recommended only to patients with localized disease. Side effects are urinary retention (7%-30%), erectile dysfunction (6%-50%), bladder neck obstruction (1%-3%), and proctitis (1%-2%) [72,73].

Hormonal therapy: objective of hormonal therapy is to reduce the level of testosterone, either in the serum or at the prostate level. There are several ways to reach this objective including surgical castration (orchitectomy), oestrogens, Luteinizing Hormone Releasing Hormone analogues (LHRHa) and antiandrogens [74-77]. Essential is the fact that hormone based therapy is not able to cure prostate cancer. It can diminish the size of the tumour and its metastasis as well as its growth, but in time most prostate cancers become resistant to hormonal treatment. It is a standard therapy in patients suffering from metastatic disease (N+,M+). It can be offered as monotherapy in symptomatic patients with advanced disease (T3,T4) or in locally confined disease (T1b,T2) in symptomatic patients unfit for curative therapy. Moreover, it is an option as therapy in combination with radiation in patients with advanced disease. The major side effects are loss of libido and impotence occurring in almost all patients, while hot flushes, altered and diminished body-hair as well as tenderness in the breast are reported in varying degrees [78].

Second line therapy: there are different terms to describe cancers that relapse after initial hormonal therapy, including hormone resistant, hormone refractory, androgen independent and hormone independent prostate cancer [79]. Although it remains controversial, it seems that a reasonable criterion to describe this state involves serial PSA tests carried out at least 2 weeks apart, resulting in two 50% increases over the nadir value [80]. A wide range of treatment modalities has been investigated as so called second line therapy in patients suffering from hormone resistant prostate cancer. Among these are agents like secondary hormonal therapy, mitoxantrone, corticosteroids, estramustine, vinblastine, cyclophosphamide, medroxyprogesteron acetate, paclitaxel, suramin, bisphosphonates and all kinds of combination therapies [81-85]. Some of these agents show temporary biochemical and clinical responses. However, to date none of these second-line treatment options demonstrate a consistent increase in overall survival.

Prognosis
The prognosis as finally indicated by the overall and disease specific survival depends on several factors like tumour stage, tumour grade, age at diagnosis, competing medical hazards, social environment and treatment. Compiled 10 years disease specific survival rates for clinically localized prostate cancer, not differentiated according to tumour grade, are 83%-93% for radical prostatectomy, 66%-86% for external radiation therapy, and 80%-85% for watchfull waiting [86-88].
These rates are for locally advanced disease, 51%-67% for radical prostatectomy, 36%-42% for radiation therapy, 32%-45% for primary hormonal therapy while for combined hormonal and radiation therapy only 5 years survival (85%) rates are available [89-92]. In metastatic disease patients show progression to hormone resistant disease in 18 to 24 months after the start of hormonal therapy [93]. Finally, the median duration of survival of hormone resistant disease is 5 to 18 months [94].

**Aim of this thesis**

In the treatment of oncological patients, clinicians traditionally focused mainly on objective outcome parameters, like survival, time until progression, and control of symptoms. They paid little or no attention to the impact of the disease and its treatment on the patient's health related quality of life (HRQOL). This attitude has changed over the last decades. Not only physicians, but patients also take more and more interest in the impact the disease and its treatment have on the HRQOL. This applies to patients with prostate cancer as well. Moreover, knowledge about the HRQOL, among others, plays an increasingly essential role in final therapeutic decision making.

This dissertation aims to examine various aspects of the general and disease specific health related quality of life in patients suffering from and treated for prostate cancer.

In chapter 2 a number of methodological issues are considered. First, the question as to what quality of life actually means and how one can measure it will be examined. Second, the way to develop optimal questionnaires for measuring quality of life is discussed. The existing instruments are shown in tables. Furthermore, the question is considered under which circumstances and in which studies measuring HRQOL is useful. Finally, the question how to interpret the results of HRQOL studies and when they can be regarded as clinically significant, is briefly addressed.

In chapter 3 a substantial review is given of the existing literature on prostate cancer and general and disease specific health related quality of life. The discussion at the end of this chapter is about the question: What have we learned so far from the HRQOL research in patients with prostate cancer? To this end, the results and the clinical relevance of the various studies are critically assessed. Chapter 3, finally, discusses the direction in which HRQOL research should develop to achieve a situation in which the results of such research can be regarded as a reliable endpoint of clinical trials.

In 1997, consensus has achieved in an international consensus conference that the outcome of HRQOL studies as an endpoint in prostate clinical trials is as important as survival [95]. It is clear that HRQOL can only act as a serious endpoint when the outcome is based on qualitatively high standard studies. Therefore HRQOL research has to meet stringent requirements. In chapter 4 a systematic review is presented, evaluating the quality of the HRQOL studies executed in randomized clinical trials.

There is evidence in other areas than prostate cancer that the experienced HRQOL is influenced by psychosocial factors like stress, social support, (non)-expression of emotions and coping strategies. [96-103]. If the assessed HRQOL is correlated with psychosocial factors in prostate cancer patients also, this might have implications for the assessment of HRQOL in the way it is executed today, as well as for the interpretation of the results of the HRQOL research in prostate cancer patients until now. In chapter 5 we examined the relation between psychosocial factors and the assessed HRQOL.

Patients suffering from localized prostate cancer who are otherwise healthy and have a survival of over 10 years, basically receive a curative treatment. This means they either undergo a radical prostatectomy, or are treated with external or internal radiotherapy. The results of the various treatments are, in relation to the survival, more or less the same. The treatment’s impact on the HRQOL therefore, is essential. As shown in chapter 3, hardly any reliable comparative study on this subject is known of. However, there have been conducted many cross-sectional, non randomized, studies of patients treated with radical prostatectomy on the one hand, and with radiotherapy on the other. The results of such studies are only valuable if the HRQOL of the patients in both treatment groups is the same on the outset of the treatment. Moreover, it is shown in chapter 5 that also in
prostate cancer patients HRQOL is associated with several psychosocial factors. In chapter 6 will be examined if the baseline HRQOL and psychosocial profile of a group of patients who are scheduled for treatment with radical prostatectomy, corresponds to the baseline profile of a group of patients who will be treated with external radiotherapy.

As pointed out above, there have been published only a few methodologically sound comparative studies that describe the impact of a radical prostatectomy on HRQOL as compared to radiotherapy. In the daily practice, consistent results of such studies are essential to reach a well-considered decision in consultation with the patient when a curative treatment of localized prostate carcinoma is indicated. In chapter 7 the real impact of a radical prostatectomy and of external radiotherapy on the HRQOL is examined. It concerns a prospective, longitudinal study including pre-treatment assessments, in which validated questionnaires have been used. Moreover the role of other factors influencing the HRQOL, like age, socioeconomical status, stress, (non)-expression of emotions, coping style and social support, are evaluated. Finally, it is explored which factors, and to what extent, contribute to the assessed changes in HRQOL.

Patients with lymph node metastasis of prostate carcinoma can’t be cured. The primary palliative treatment is hormonal therapy. The best time to start this hormonal treatment is as yet unknown. Should it be done immediately after the disease is diagnosed, or should it be deferred until objective progression is observed? Studies concerning this question are not concluded yet. If a treatment has no effect on the survival, the treatment’s impact on the HRQOL is all the more important. In chapter 8 the impact of hormonal treatment on HRQOL of asymptomatic patients with lymph node positive prostate cancer is examined.

Patients who show progression during hormonal treatment have a restricted survival. So far, there aren’t any treatments known that influence the survival positively. The aim, therefore, of each therapy for patients suffering from a hormone resistant form of prostate cancer is stabilization or improvement of the HRQOL. Moreover, assessment of the HRQOL of these patients has proved to be difficult. The compliance often is low, which could be connected with the bad condition these patients generally are in. The research considered in chapter 9 aims at two goals. First, it explores whether it is possible at all to examine the HRQOL in this category of patients satisfactorily. Second, it examines whether Medroxyprogesterone Acetate combined with Epirubicin has a better effect on HRQOL than Epirubicin alone.

In chapter 10 is examined in the same patients group whether treatment with Epirubicin in a 4-weekly regimen is comparable with a weekly regimen with regard to the effect on HRQOL.

In chapter 11 the potential prognostic value of HRQOL factors in patients suffering from progressive metastatic hormone resistant prostate cancer (HRPC) is explored. Prognostic factors are useful instruments to assess the chance of survival and/or the likelihood of response to a specific therapy (predictive factors), to help in choosing the most appropriate therapy, and to help in the comparison of results from several clinical trials. They can also serve as a guideline for the stratification of various groups of patients in clinical studies. The identified factors in metastatic HRPC patients are limited and the value of HRQOL factors has rarely been studied before. The data from 391 patients randomized in three EORTC trials (30903, 30921, 30944) were used. Objective of the study was twofold. First, to explore whether it was possible to identify HRQOL domains with independent prognostic value for the survival. Second, to perform a prognostic factor analysis in order to develop risk groups that could distinguish patients with a relatively good prognosis from patients with a particularly bad or particularly favourable prognosis.

Finally, chapter 12 consists of the summary and discussion section of this thesis.
References


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