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EXPERIENCES OF SIGNS AND SYMPTOMS AMONG MEN WITH ADVANCED PROSTATE CANCER

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EXPERIENCES OF SIGNS AND SYMPTOMS AMONG MEN WITH ADVANCED PROSTATE CANCER

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By

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To my family

POPULAR SCIENCE SUMMARY OF THE THESIS

Prostate cancer is the form of cancer that is most common among new cancers each year in Sweden and in 2020 just over 9000 men were diagnosed. Men with a prostate cancer that cannot be cured can live longer nowadays compared to 10 years ago, thanks to many new treatments. A blood test called prostate-specific antigen (PSA) is used to detect and measure the progress of the disease. Other than the PSA value, the men's quality of life (QoL) and how they are affected by their symptoms is also taken into consideration in treatment decisions in late phases of the disease.

Symptoms from prostate cancer often increase over time and men with an incurable cancer can have many symptoms. For people with a life-limiting disease, symptom management is crucial in making sure their QoL is as good as possible.

The overall aim was to study signs, such as PSA, and symptoms in patients with prostate cancer who were receiving life-prolonging treatments as the disease progressed.

In order to investigate this, four studies were conducted. In three of the studies men with prostate cancer answered questionnaires, and in one of these three, the questionnaire was answered repeatedly every third month for a period of one year. In the fourth study, a selection of men were interviewed repeatedly over a two-year period. During this period, the interviews were repeated at time points when the disease progressed.

The overall results from these four studies showed that the PSA values are interpreted by the men as a way to understand how the disease progresses. This is especially true for the men who do not have any symptoms at all. Over time, as some men experienced more and more distressing symptoms, the importance of the PSA values decreased, and the symptoms and consequences from the symptoms became more important for the men.

Some men had a lot of symptoms already when starting treatment, and most were physical symptoms. Sexual problems were the symptoms reported by most, but pain and lack of energy were also common. Psychological symptoms were not so common. Apart from distress when their PSA values increased, many men did not describe feelings such as worry and fear, even if most of them knew that they had a limited time left to live.

These findings may help health care personnel to understand the disease from the men's perspective. It also highlights the need to discuss the changing interpretation of signs such as the PSA and to follow and manage the various symptoms arising during the life-prolonging treatment, to improve the men's QoL.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Prostatacancer är den cancerform flest människor får i Sverige per år. Strax över 9000 män fick diagnosen 2020. Män med obotlig prostatacancer lever längre nu jämfört med för 10 år sedan, tack vare nya behandlingar. Ett blodprov kallat PSA används för att upptäcka och mäta hur sjukdomens utvecklar sig. Utöver PSA-värdet tas även männens livskvalitet och hur påverkade de blir av symtomen i beaktande vid till exempel behandlingsbeslut i sena skeden av sjukdomen.

Symtomen av prostatacancer ökar ofta över tid, och män med obotlig cancer kan ha många symtom. Symtomhantering är väldigt viktigt när man har en livsbegränsande sjukdom och vill ha en så god livskvalitet som möjligt.

Det övergripande syftet var att studera tecken såsom PSA och symtom bland patienter med fortskridande prostatacancer vilka fick livsförlängande behandling

För att utforska detta genomfördes fyra studier. I tre av studierna svarade män med prostatacancer på formulär, i en av dessa tre besvarade formuläret var tredje månad under en ettårsperiod. I fjärde studien intervjuades ett urval av männen upprepade gånger under en tvåårsperiod. Under den perioden upprepades intervjuerna allteftersom sjukdomen försämrades

Resultatet av dessa fyra studier visade att PSA-värdena tolkades av männen för att förstå hur sjukdomen utvecklas. Detta gällde framför allt männen som inte hade några symtom. Över tid, då vissa män upplevde fler och mer besvärande symtom, minskade vikten av PSA-värdena och symtomen och dess konsekvenser blev viktigare för männen.

Vissa män har många symtom när de påbörjar behandling och de flesta var fysiska. Sexuella problem var de som rapporterades oftast, men också smärta och bristande energi var vanligt förekommande. Psykiska symtom var inte lika vanliga. Förutom att när PSA-värdena ökade så blev flera män stressade, men många av dem nämnde inte känslor som oro och rädsla trots att de flesta uppgav att de visste att de hade begränsad tid kvar i livet.

Studien hjälper oss förstå sjukdomen från männens perspektiv. Det belyser också behovet av att diskutera den förändrade tolkningen av tecken så som PSA, samt att följa och hantera de olika symtom som uppstår under den livsförlängande behandlingen för att kunna förbättra dessa mäns livskvalitet.

ABSTRACT

Background: In the past decade, thanks to improved treatment options, many men with metastatic prostate cancer now survive longer than they would have before. The PSA value is often followed during the entire disease trajectory as a sign, but in late phases, symptom burden, quality of life (QoL), and/or psycho-social factors are assigned more importance in treatment decisions and evaluations. From the men's perspective the change of the clinical importance of the PSA value in assessment of treatment effect and as a sign of disease progression may not be obvious and they may therefore experience distress about values with little clinical relevance. When having a life-limiting disease, symptom management also plays a vital role in the balance between prolonging life and QoL but there are few studies describing symptom burden in a real-world situation in these men.

In order to support these men, it is important to gain an understanding from the men's perspective of their experiences and interpretations of signs and symptoms.

Aim: The overall aim of this thesis project was to study signs and symptoms in relation to progression of the disease in men with advanced prostate cancer.

The underlying hypothesis was that signs and symptoms may be experienced as distressing as markers of potential progression influencing QoL in advanced prostate cancer.

Methods: Both quantitative and qualitative research approaches were used. The thesis is based on data from two different overall projects: a survey sent to all members of the Swedish Prostate Cancer Federation (SPCF) and the PROstate Cancer-Experiences and Expectations During treatment (PROCEED) project. In study **I** descriptive statistics and logistic regression analysis were used to analyze self-reported questionnaires regarding distress and PSA values. In study **II** content analysis was used to analyze longitudinal interview data. In study **III**, descriptive- and linear regression analysis were used to describe symptoms, symptom dimensions and symptom burden, and to investigate associations between QoL and symptom burden. In study **IV**, descriptive statistics regarding symptoms, symptom dimensions and symptom burden were described at five timepoints. To analyze changes over time for symptom burden, linear mixed modeling was applied.

Results: Men with advanced prostate cancer experience an uncertain illness situation when living with a life-limiting disease. They used signs and symptoms to make sense of their situation. Many of the men were preoccupied with the PSA values as the sign that they described as most important. Over time, as some men experienced more and more symptoms, the importance of the PSA values decreased, and the symptoms and consequences of the symptoms became more important to the men. Some men had a lot of symptoms when starting treatment, mostly physical and not so often psychological symptoms. Except for distress in relation to increased levels of PSA, many men did not report feelings such as worry or fear, even if most of them knew that they had a limited time to live. The different symptoms varied in dimensions of frequency, severity and distress, and sexual problems were

most reported, followed by pain and lack of energy. The physical symptoms worsened significantly over time while psychological symptoms and number of symptoms did not.

Conclusion: When living with progressing advanced prostate cancer, an uncertain illness situation was described. In this uncertainty, signs and symptoms were used to make sense of their situation. To understand the men's interpretations of signs and symptoms is important since misunderstandings or misinterpretations may cause unnecessary distress and reduced QoL in this late phase of the disease. The men experienced mostly physical symptoms, which also worsened over time. Sexual problems were common and may need to be acknowledged more, even if the underlying causes is difficult to resolve, support in handling the problem could be beneficial. Pain and fatigue were also common and were experienced as distressing, and some symptoms may have been insufficiently managed. These findings may help health care professionals to understand the disease from the men's perspective. Enhancing QoL is also the main goal for palliative care and a palliative approach early in the disease trajectory in the oncology outpatient setting could benefit these men.

LIST OF SCIENTIFIC PAPERS

- I. **Rönningås U**, Fransson P, Holm M, Wennman-Larsen A. Prostate-specific antigen (PSA) and distress: - a cross-sectional nationwide survey in men with prostate cancer in Sweden. *BMC Urology*. 2019;19:66
- II. **Rönningås U**, Holm M, Doveson S, Fransson P, Beckman L, Wennman-Larsen A. Signs and symptoms in relation to progression, experiences of an uncertain illness situation in men with metastatic castration-resistant prostate cancer- A qualitative study. *European Journal of Cancer Care*. 2022;31:e13592
- III. **Rönningås U**, Holm M, Fransson P, Beckman L, Wennman-Larsen A. Symptoms and quality of life among men starting treatment for metastatic castration-resistant prostate cancer. *In manuscript*. 2022.
- IV. **Rönningås U**, Fransson P, Holm M, Beckman L, Wennman-Larsen A. Symptom burden among men with castration-resistant prostate cancer during their first year of life prolonging treatment- a longitudinal study. *In manuscript*. 2022.

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LIST OF ABBREVIATIONS

ALP	alkaline phosphatase
ASCO	American Society of Clinical Oncology
BM-22	bone metastases module
CA125	cancer antigen 125
CI	Confidence Interval
CRPC	castration-resistant prostate cancer
CT	computed tomography
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire C30.
FACT	Functional Assessment of Cancer Therapy
FoP	Fear of Progression
FoR	Fear of Recurrence
HADS	Hospital Anxiety and Depression Scale
Hb	Hemoglobin
HRQoL	Health-related Quality of Life
IAHPC	International Association for Hospice and Palliative Care
LMM	Linear Mixed Model
mCRPC	metastatic castration-resistant prostate cancer
MID	minimal important difference
MRI	magnetic resonance imaging
MSAS	Memorial Symptom Assessment Scale
MSAS-PHYS	MSAS physical symptoms subscale
MSAS-PSYCH	MSAS psychological symptoms subscale
NCCN	National Comprehensive Cancer Network
OR	Odds Ratio
PARP	poly-(adenosine diphosphate-ribose) polymerase
PCSS	Prostate Cancer Symptom Scale
PROCEED	PROstate Cancer-Experiences and Expectations During treatment

PSA	Prostate-specific antigen
QoL	Quality of Life
SPCF	The Swedish Prostate Cancer Federation
STHLM-0	Region of Stockholm PSA and Biopsy Registry
TNM	Tumor, Node, Metastasis classification
WHO	World Health Organisation

1 INTRODUCTION

Before I started my PhD-studies (in March 2018), I worked for fourteen years as a clinical research nurse at the oncology department in Sundsvall. The oncology department has a small clinical trial unit with three nurses working with different studies, and also administering the study treatment to the patients. I mainly worked with colorectal cancer and prostate cancer studies, and I participated in some of the studies involving drugs that are now considered standard of care for men with a metastatic prostate cancer – treatments the men included in my research receive.

My interest in this research field stemmed from my clinical work with men with prostate cancer. Many of them were quite preoccupied by their prostate-specific antigen (PSA) values or imaging results. One of the men with metastatic prostate cancer who I had been giving treatment for quite a long time said that he couldn't hear anything the physician said until he was told the PSA value. He and some of his friends who also had prostate cancer talked about the value with each other and made diagrams of the development. He also told me that besides the rising PSA, he was worried about the feeling of pain when sitting, since he had experienced pain when sitting down when initially diagnosed. I became curious as to why the men were so preoccupied by the PSA and by the potential occurrence of symptoms they believed to be associated with progression, especially the men who were no longer curable but were being given life-prolonging treatments. I assumed that the quality of life (QoL) and symptom management would be more important to them.

In this thesis, my research interest is signs, such as PSA and imaging results, and symptoms in relation to progression of disease and how they influence QoL for these men living with a life-limiting disease.

2 BACKGROUND

This background begins with a description of the *Prostate cancer disease and its treatments* to give a brief overview. Thereafter, sections describe *Importance of quality of life in advanced disease* and *A palliative approach*. Then *Signs and symptoms* are described first with a brief overview and then both are described in relation to prostate cancer and to progression. Lastly, *Distress and fear of progression* are described in the context of prostate cancer.

2.1 PROSTATE CANCER – THE DISEASE AND ITS TREATMENTS

Globally, prostate cancer had the third highest incidence of all cancers in 2020 with 1.4 million new cases (1). In Sweden, this was the cancer form with highest incidence and just over 9000 men were diagnosed in 2020 (2). Prostate cancer is the older men's disease and in Sweden, men under the age of 50 were rarely diagnosed with prostate cancer (3). In the Region of Stockholm PSA and Biopsy Registry (STHLM-0), the median overall survival was 13.2 months from development of resistance to castration therapy for men with metastatic castration-resistant prostate cancer (mCRPC) who had metastases at diagnosis (4). This should be compared to 23.2 months for men with mCRPC who were without metastases at primary diagnosis.

The risk of dying of prostate cancer depends on e.g. the extent of the tumor and how aggressive it is. When prostate cancer is detected in a localized phase, treatment with a curative intent is given, and consists of radiotherapy or prostatectomy. Nevertheless, for one third of all men initially treated with prostatectomy or radiotherapy, the prostate cancer may recur. For low-risk prostate cancer, *active surveillance* is recommended for eventual later curative treatment. Active surveillance consists of systematic follow-ups including prostate palpation, PSA-testing and magnetic resonance imaging (MRI). Some men cannot be offered curative treatment, most often due to high age or comorbidities, and instead these men are followed-up through *watchful waiting*. This means that they are followed until PSA- or clinical progression, at which point antiandrogen treatment is initiated (3). Exacerbated pain and more use of analgesics and worsened QoL are factors used when assessing for clinical progression (5).

Some men already have metastases when diagnosed with prostate cancer; others have a recurrence of the disease and develop metastases. The men with metastases already at diagnosis are considered castration-sensitive, as most newly diagnosed men with metastases have not yet progressed to a castration-resistant phase. Once metastases have developed, the therapy is no longer curative but aims to prolong life and improve QoL (6). The predominant site for distant metastases is bone. At this metastatic stage, hormonal deprivation, i.e. medical or surgical castration, is the primary treatment option, and radiotherapy may be used to relieve bone pain (3). With time, during the hormonal deprivation therapy, all men will become resistant to the therapy and develop a CRPC (7).

Today, thanks to improved treatment options, the median survival time for men with metastases already at diagnosis and who are castration-sensitive, has further increased (8-20). Docetaxel was the first life-prolonging treatment in mCRPC and was approved in 2004 (21). In the last decade several other treatments such as cabazitaxel, abiraterone, enzalutamide, radium-223, and recently olaparib have also been approved (22-26). These drugs are sometimes used as first line treatment, but can be used even up to fifth line treatment after docetaxel failure.

The treatment options mentioned above can cause different side effects. Docetaxel and cabazitaxel are chemotherapies with side effects such as bone marrow suppression, fatigue and nausea. These treatments are given every second or third week intravenously, up to a maximum of six months. Second-generation antiandrogens such as abiraterone and enzalutamide have side effects such as hypertension, hot flashes and fatigue. These treatments are taken orally every day as long as there is no progression or serious side-effects. The side effects of the radiotherapeutic drug radium-223 include diarrhea, fatigue, nausea and increased bone pain for up to a week after treatment, this treatment is given every fourth week for six months. Olaparib, a poly-(adenosine diphosphate-ribose) polymerase (PARP) inhibitor, has side effects such as nausea, vomiting, diarrhea and fatigue among others and is taken orally continuously until progression or serious side-effects (21-26). For the individual patient, it may be difficult to distinguish between symptoms from the disease and side effects of a given treatment. Both may however, lead to mental or physical agony, depending of the patient's subjective responses to the symptoms or side effects (27).

With all these new treatment options for both castration-sensitive and castration-resistant prostate cancer, the men's lives can be prolonged, making the cancer more of a chronic disease (28) since many men may live with the disease for several years. However, this broader application of the concept of chronic disease is debated and the definitions differ (29). Irrespective of chronic disease or not, the QoL of these men is important as they live with a life-limiting disease.

2.2 IMPORTANCE OF QUALITY OF LIFE IN ADVANCED DISEASE

For patients living with a life-limiting disease, QoL is important and even though many patients want actions taken to prolong life, some may place higher priorities to other goals, including QoL (30). In a study of patients, receiving palliative care, most of whom had cancer (88%), the participants were asked about treatment goals:

In situations of serious illness with limited time to live difficult decisions may need to be made and some things may need to be prioritized over others [...] would it be more important to extend your life or to improve the quality of life for the time you had left or are both equally important? (31, p.273).

The option “[*improving*] the *quality of life for the time you have left*” (31) was chosen by 54% of the respondents, and 39% chose “*both are equally important*” (31), while only 3%

responded that extending their life was the most important goal. Men with mCRPC also express that QoL is an important factor when considering life-prolonging treatment (32).

The difference between QoL, health and health-related quality of life (HRQoL) has been discussed (33); the terms are sometimes used interchangeably and HRQoL overlaps with both the concepts of health and of QoL. The World Health Organisation (WHO) defines QoL as follows: “*an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.*” (34). When studying QoL in groups of patients with advanced cancer a high number of symptoms may be an important factor to take into consideration (35). When starting treatment, men with newly diagnosed metastatic prostate cancer have a QoL more strongly affected than those with localized disease whose QoL was similar to that of the general population (36). In this thesis the wider concept of QoL is applied, this since in these late phases of the disease concerns related to many aspects of the remainder of life may be of importance for the men.

In summary, patients with life-limiting disease perceive QoL as highly important even though balancing it with life-prolonging treatment approaches is also considered important by many.

2.3 A PALLIATIVE APPROACH

As mentioned above, severe symptoms and deteriorating functional status may affect patients QoL and hence a palliative approach may be relevant. In 2020, the International Association for Hospice and Palliative Care (IAHPC) presented a new definition of palliative care (37). According to the definition, palliative care “aims to improve the quality of life of patients, their families, and their caregivers” (37, p.761). Palliative care should be introduced early and concurrent with life-prolonging treatments such as for example chemotherapy. Further, it is important to integrate physical, psychological and spiritual aspects in patient care and provide relief from pain and other distressing symptoms (37). The American Society of Clinical Oncology (ASCO) suggests that early palliative care for patients with newly detected advanced cancer should start within eight weeks (38).

Touzel and Shadd (39) presents a model for a palliative approach to help health care professionals to understand the dimensions of care for patients in need of palliative care (Figure 1).



Figure 1. Proposed conceptual model of a palliative approach adapted from *Content Validity of a Conceptual Model of a Palliative approach*, (39, p.1628).

They suggest that a palliative approach is present when all three parts of the model are fulfilled. The approach can be applied by anyone, at any point in the illness trajectory, in different settings and for different diseases. The first part of the model consists of “*Whole-Person Care*”, and includes supporting, for example, existential, emotional and psychosocial needs. The second part is “*Mortality acknowledgement*”, which include areas concerning the acknowledgement of death and dying as well as living with a life-limiting disease, while the third part “*Focus on Quality of Life*” includes care that enhances the patients QoL (39). This approach is in line with IAHPCC’s definition which also mentions that palliative care has a place in all health service, which means that all health care professionals, regardless of workplace should be able to provide basic palliative care (37).

In Sweden, no specific time point is suggested for when palliative care should be initiated. However, the National Guidelines in Palliative Care state that palliative medicine and oncological treatment departments need to cooperate in new ways with the aim of integrating palliative care earlier in the disease trajectory (40). It has also been shown that when an approach that combines palliative and oncologic care is used, both QoL and symptom control are improved (41). Furthermore, patients perceive their health experience as more satisfactory when palliative care is given in conjunction with oncological treatments (42). It is the patient’s unique situation and needs that have to be taken into consideration. One example of a way of assessing needs is to make symptom screening a routine in oncological units (40).

One cornerstone in the palliative approach is the use of multidisciplinary teams which has been shown to have positive outcomes in palliative care (41). Nurses are a vital part of the multidisciplinary team and they must have excellent skills to assess and manage symptoms, as this can be rather complex to integrate in early palliative care (43). In symptom management it is important to understand the patients’ perceptions and the meanings they

attribute to a symptom (43). The specialist nurse's availability to the patients and ability to liaise between the patient and the medical system are two essential aspects of the specialist nurse's role in prostate cancer care (44), and the men also express a wish for more time with specialist nurses as well as more information (45).

A review by Wang et al. (46) shows that patients with advanced cancer have unmet psychological and physical needs (46). Further, unmet needs regarding symptoms and QoL have been shown in a Swedish context among men with metastatic prostate cancer (47). Men with advanced prostate cancer, have also described the need for integrated psychosocial support as a part of routine care, so that they do not have to raise these needs by themselves (48). Thus, this further stresses the important role of multidisciplinary teams as a link and supportive resource for men with prostate cancer.

2.4 SIGNS AND SYMPTOMS

To be able to monitor prostate cancer, continuous assessment of clinical manifestations, such as signs and symptoms is important. A *clinical sign* is a clinical finding about a patient (49). The sign can be observed by a physician or reported by another medical professional. It can also be any manifestation that the clinician judges to be of clinical significance. A *clinical symptom* is a finding about a patient that is reported by the patient or for example a family member (49). In the medical thesaurus MeSH, signs and symptoms are described as clinical manifestations that can be either objective when observed by a health care professional, or subjective when perceived by the patient. Several symptoms have been reported in prostate cancer patients. Signs such as PSA-values, or imaging results from computed tomography (CT) and bone scans, may be used during the prostate cancer disease trajectory for monitoring recurrence or disease progression (3).

2.4.1 Signs in the context of prostate cancer

One of the most central signs in the prostate cancer process is PSA. PSA is not a cancer-specific antigen, but its levels may increase when prostate cancer is present (50). The PSA-value is often followed during the entire disease trajectory but has different implications over time. During the diagnostic process it is used to identify prostate cancer and may also be used in screening. During the treatment decision process it is used to evaluate the level of risk posed by the tumor. After the initial treatment and in later stages, PSA is also used as a marker of recurrence or progression during follow-up and treatment (3).

After a diagnosis of metastatic non-curable prostate cancer, PSA is still used as a marker of treatment success or of progression, and it may sometimes reach very high levels (3). However, from a clinical perspective, the PSA value also may lose some of its relevance at these later stages, while other factors, such as symptom burden, QoL, and/or psycho-social factors are often assigned more importance in treatment decisions and evaluations by the treating physician. In clinical discussions with patients about treatment options, it is important to weight PSA levels against concerns about perceived symptom burden, age and treatment side effects together with the man's current life situation and wishes (3, 51).

Despite the clinical experience that the men are preoccupied with the PSA levels even at late stages of the disease, there are few studies about experiences around PSA from the men's perspective. For them, the change in the clinical importance of PSA in treatment decisions, assessment of treatment effect and as a sign of progression may be hard to follow and therefore cause distress. Further, patients state that they have limited knowledge of PSA and its significance, but also limited knowledge about the disease progression and its impact. However, they wish to know more about these factors (52). In a study of ovarian cancer (53), patients who have had their first line of chemotherapy could choose whether they wanted to test for CA125 (another serum antigen for evaluation of progression). Some chose not to take the test during the follow-up period; others took the test but did not wish to know the results; still others wanted both the test and the test results. The study showed that educating the patients about the test led to the majority refraining from routine testing. Another study that probed what patients with ovarian cancer (54) knew about CA125 and how much it preoccupied their thoughts showed an association between the number of metastases and CA125 preoccupation.

An increasing PSA value affect men with prostate cancer emotionally in early stages. Newly diagnosed men with mCRPC believed that the PSA-value was important for monitoring the disease. Some of them described the emotional distress the PSA values caused them, as they felt more worried when the values increased and more hopeful when the values decreased (55). Shen et al. (56) interviewed men with biochemical recurrence in the early stages of prostate cancer, concerning their experience and responses regarding increasing PSA values and treatment options. Most men experienced more worry and fear of death when they learned about the rising PSA than they did when their cancer was initially diagnosed. Furthermore, they were more worried before an appointment at which they should discuss PSA values with their physician. Notably, many of them kept track of their PSA values, checked the doubling time and identified their own PSA limits for when they thought new treatment would probably begin (56).

Roth and Passnik (57) have described a specific anxiety related to PSA, called "PSA-anxiety" among men with prostate cancer. Further, survivors of prostate cancer with high scores on FoR also reported higher levels of PSA-anxiety and lower HRQoL (58). Among men with metastatic prostate cancer, 77% reported PSA values as one of the ways they recognized if their cancer was progressing, versus 19% who reported pain/discomfort as a signal of progression (59).

In Sweden PSA testing is part of the plan for follow-up of men treated for localized prostate cancer (3). In a Swedish interview study (60) patients in this group described PSA as a value that shows the status of the man's body, a signal of potential progression, and said that waiting for the test results was distressing. This can be seen in light of the fact that prostate cancer may not cause many symptoms when progressing. The PSA tests were seen as offering "*The possibility of catching the cancer in good time*" (60). Although some studies

(57, 60-62) described the distress that PSA tests can cause, other studies report low levels of PSA-anxiety among long-time survivors (63, 64).

Men with CRPC may define changes in the disease through their PSA value rather than their physical and functional status, even at later stages when PSA may have lost some of its medical relevance. Around 25% of the men in the study by Loftler et al. (59) ranked a decreasing PSA value as a more important goal than a decrease in symptoms; for comparison, 46% ranked reductions of pain and other symptoms together with increasing PSA as more important (59).

To summarize, men with prostate cancer attach great importance to PSA values as a sign and often define changes in their disease by the values. They may feel worried and anxious about the testing and results, even if the PSA values lose some of their significance to health care professionals at late phases of the disease.

2.4.2 Perspectives on progression

Progression of the disease is usually shown by a PSA value that increases for several months even before symptoms occur. However, the course varies between patients and in some cases, a rapid progression takes place without any increase in PSA. After curative treatments, PSA is monitored to detect progression. However, when considering progression in patients with metastatic disease, the men's general condition, QoL and symptom burden have to be considered alongside signs such as PSA, other laboratory values and x-rays (5, 65). Here it is also important to keep in mind that PSA – although an objective sign for the health care professionals – is weighted down by the patients' subjective perception of his condition. Psychological distress in relation to PSA testing is more likely to be experienced after the diagnosis rather than during screening (62). In general it has been shown that men with prostate cancer have little knowledge about disease progression, different disease stages and different treatment options at each stage, although the average level of knowledge varies between countries (52).

The view of how a progression of the disease manifests itself has been shown to differ between patients and physicians: patients often report that it manifests through PSA values, whereas physicians consider a larger picture involving clinical progression and signs such as PSA values and bone scans. As mentioned earlier, many men interpret increasing PSA values as indicating that the disease is progressing. On the other hand, almost all physicians reported that a clinical progression, worsening pain, more use of analgesics, and worsening QoL, was also important when deciding on a therapy switch (5). When PSA increased during treatment for mCRPC, patients perceived the increase as a sign that the treatment was no longer having an effect. That in turn may lead to distress (66).

Patients' subjective interpretations of the severity of the disease and of signs such as PSA values can differ from the objective interpretations of these medical findings. Orom et al. (67) discuss that an important determinant for distress can be the patients' subjective beliefs about disease severity rather than objective medical findings (67). This is similar to when men who

experienced a rising PSA, set their own PSA cutoffs for when treatment should be started, cutoffs that were not always based on physicians' recommendations or even medically accurate (56).

2.4.3 Symptoms and symptom burden

Men diagnosed with prostate cancer can have a more or less long disease experience, hence they may have to deal with the symptoms of the disease and the side effects of treatment for a long time. The occurrence of symptoms after a prostate cancer diagnosis and its treatments have been extensively studied (68-72). The most common symptoms and/or side effects are urinary incontinence, bowel problems (69) and erectile dysfunction (71). Most studies do not distinguish between symptoms originating from the disease itself and side effects of treatment, and indeed, differentiating the cause of many symptoms may be difficult. Some of the described symptoms are however clearly related to hormonal treatment, such as loss of libido, breast changes and hot flashes (72). One way of looking at the relationships between symptoms is by clustering them. Symptoms such as pain, fatigue, anxiety and depression have been shown to form a cluster during treatment. This cluster of symptoms was associated with poor HRQoL (68).

The symptom experience has been described as multidimensional (73) and taking a multidimensional perspective is another strategy for looking at symptoms. The multidimensionality of symptoms has also been stressed by Gapstur (74) in a definition of symptom burden: "the subjective, quantifiable prevalence, frequency, and severity of symptoms that place a physiologic burden on patients and may produce multiple negative physical, psychological, and emotional patient responses" (p. 677). The definition of symptom burden has been further examined among patients with advanced cancer who were asked to define the term (75). Six themes were generated: "*Can't do usual activities*", "*Psychological suffering*", "*Specific severe symptoms*", "*Worry, anxiety about death and disease*", "*Old self*" and "*Drug issues*". The theme "*Can't do usual activities*" was the theme most often coded and was related to the negative impact of symptoms on their everyday functioning. "*Specific severe symptoms*" was symptoms or clusters of symptoms the patients experienced as especially distressing. Pain and fatigue were the symptoms most frequently mentioned.

In the metastatic phase of the disease, men with mCRPC may experience a substantial symptom burden, and in this phase certain symptoms may be related to potential metastases. In a previous study, over 40 symptoms were mentioned among patients. Symptoms such as urinary problems, pain and sexual problems were reported as the most salient (76). Sexual problems may affect the men's relationships, and thus, some men experienced distress (48). In an interview study (55), men frequently mentioned fatigue in addition to pain and sexual problems. They also clearly associated certain symptoms to metastases e.g pain in a specific location and increased blood in stool/urine (55)

Eton et al. (77) interviewed men with mCRPC and developed a conceptual framework for mCRPC outcomes. From the men’s self-reports, the authors identified four domains of concern: symptoms of disease, side effects of treatment, psychological issues, and QoL (Figure 2). The men rated PSA anxiety and fatigue highest among the symptoms and QoL issues that were perceived as severe (77).

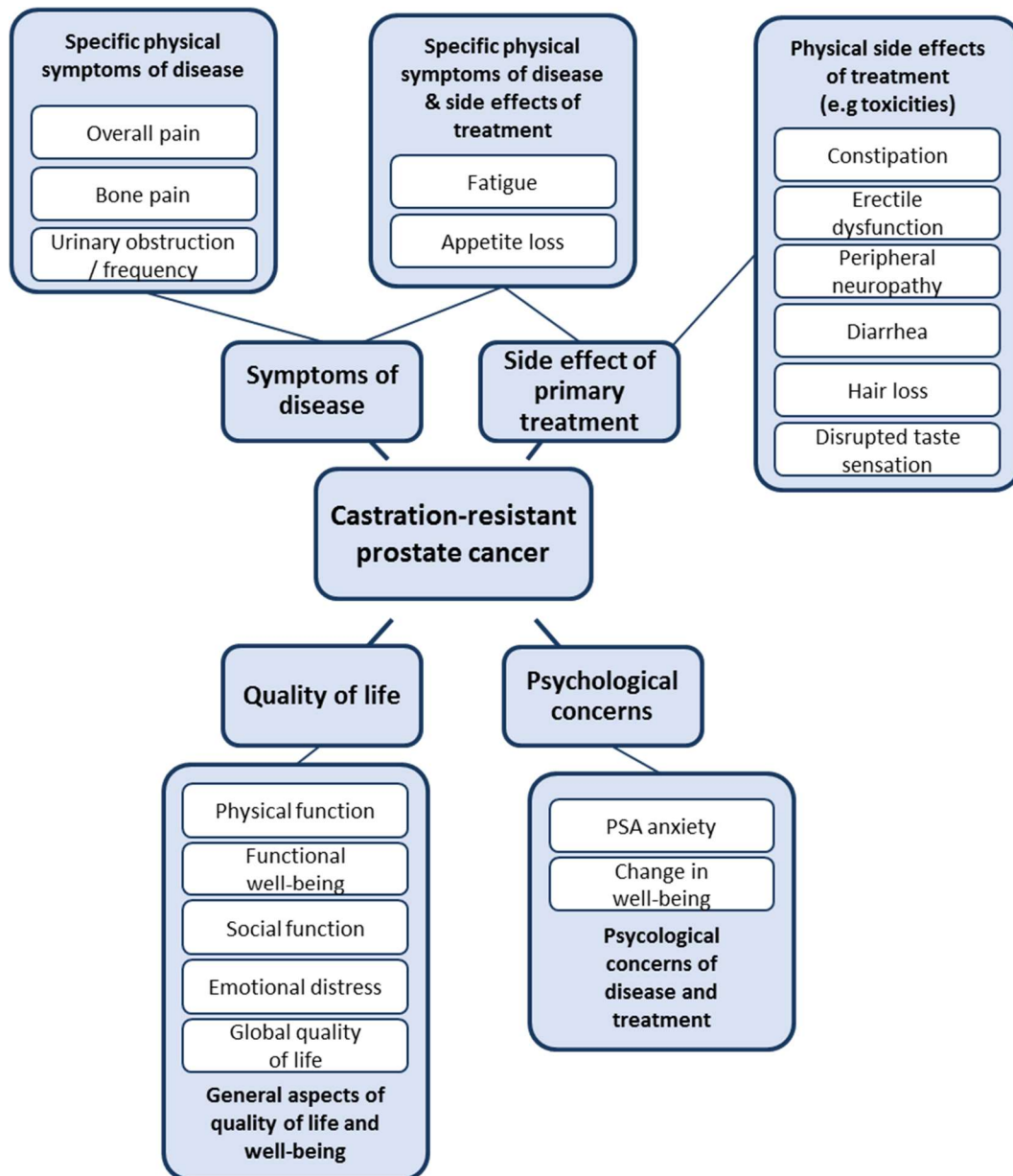


Figure 2. Conceptual framework of patient-reported outcomes for metastatic castration-resistant prostate cancer. Adapted from *Constructing a Conceptual Framework of Patient-Reported Outcomes for Metastatic Hormone-Refractory Prostate Cancer*, (77, p.622).

Over time the overall symptom burden in men with prostate cancer may increase. For example, the symptom burden increased, and QoL decreased, when the disease progressed from a metastatic non-castration-resistant phase to mCRPC. This was also associated with fatigue and pain, and affected physical activity (76, 78).

Clinical trials often use narrow inclusion criteria for the selection of patients. Consequently, there are few studies describing symptom burden in a real-world situation for men with mCRPC at the start of and during treatment. The impact of symptoms can also change over time; for instance, after three months of systemic therapy, most men in a study reported that fatigue was the worst symptom compared to reporting pain as worst at the start of treatment (61). Thus, it is important to have a broad study base and long follow-up time to determine the true impact of symptoms.

In an observational study, men with mCRPC were followed every third month regarding generic, cancer-specific and prostate-cancer-specific HRQoL and pain for up to two years. Prostate-cancer-specific symptoms were followed every sixth month. Changes over time were described with minimal important difference (MID) between subgroups of chemotherapy-naïve or post-chemotherapy patients. At inclusion the highest symptom burden was related to fatigue, pain, and insomnia. The highest proportion of patients reporting MID was for appetite loss and fatigue, where the median time to deterioration for fatigue was 8.2 months. Urinary symptoms and sexual activity were stable during the study period and did not change significantly. However, those with low pain scores at inclusion reported more pain during the follow-up period. In another study of men with mCRPC, Jenkins et al. (79) found that 47% of the men had clinically significant pain levels (moderate or severe) when starting life-prolonging treatment. After three months the pain levels had decreased for 43% of the men. On the other hand, more than 30% of the men without pain at baseline reported pain at three months.

For cancer patients in general, increasing symptoms usually give an understanding that the disease is progressing, and that death is coming closer. Patients with cancer have been reported to experience 11-13 symptoms simultaneously, and if the disease is advanced, the number of symptoms may increase (80). When symptoms occurred, some patients with cancer interpret them as a potential progression of disease. In such cases a referral to specialist palliative care, were often considered. Many of these patients were preparing for death both emotionally and practically, and most had concerns for their family. This should be compared with patients with heart or respiratory failure, who did not think of their condition in terms of coming closer to dying (81).

To summarize, the symptom experience is multidimensional and the presence and/or the frequency of symptoms does not provide enough information for a thorough assessment of symptom burden. In this thesis, symptom burden is viewed as multidimensional, but the number of symptoms experienced is also considered as symptom burden. Many symptoms are associated with having mCRPC, and pain and fatigue are two of the most common ones. Important is also the physical, psychological and emotional impact the symptoms have on the patient, and their effect on QoL.

2.5 DISTRESS AND FEAR OF PROGRESSION

Along with impaired QoL, men with metastatic prostate cancer may experience clinically relevant distress during the disease trajectory (82). Distress may interfere with their ability to cope with the illness. In the context of cancer disease one definition of distress suggested by the National Comprehensive Cancer Network (NCCN) is:

A multifactorial, unpleasant, emotional experience of a psychological (cognitive, behavioral, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness, and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and existential and spiritual crisis (83, p.450).

Several factors are involved in the concept of distress in relation to cancer. As stated in the definition above, factors such as psychological, social and spiritual may be experienced. Even if the above definition is commonly used, other concepts for defining the emotional experience have been described in the literature, for example emotional distress (84), psychological distress (85), symptom distress (86) and existential distress (87). Causes of distress have been shown to be, worry, fear about the future, thoughts of illness and death but also concerns about physical symptoms (83). Around 33% of the total amount of stress among cancer survivors is suggested to be due to somatic concerns and is related to FoR or FoP (88).

Anxiety has also been shown to be even more prominent at more advanced stages of prostate cancer (89). When the cancer progresses, the emotional distress may gradually worsen and clinical disorders such as anxiety and depression were observed in 30% and 25%, respectively of prostate cancer patients with metastases (90). Medical and sociodemographic factors have also been described to be associated with distress in prostate cancer. One demographic factor is age (67), overall distress and anxiety have been shown to decrease with age while depressive symptoms increase (91). Other sociodemographic factors are marital status (92) and support from a partner. Unpartnered men report higher levels of distress and men with low partner support report the same levels of distress as unpartnered men (93). An example of a medical factor influencing distress is ongoing hormonal treatment, which may increase the risk for anxiety and depression (94).

Anxiety and depression rates among men are higher if they report a high symptom burden and side effects of treatment. Men who report high scores for urinary, bowel and hormone-related symptoms as well as fatigue and dyspnea are at higher risk for anxiety (95). The risk of depression is also higher for men with more urinary, fatigue, insomnia and hormone related problems (95). According to men with mCRPC the most common emotional impacts of the disease were depression, frustration and anxiety (76). Similarly, Burbridge et al. (55) showed that one of the areas impacted most by a metastatic disease was emotional well-

being. The men mentioned feelings of worry, anxiety, depression and fear as well as frustration and anger.

In the literature, the concepts of FoR and FoP are often used regarding cancer survivors. For both concepts the same definition has been suggested (96):“Fear, worry, or concern relating to the possibility that cancer will come back or progress”(96). Patients who are cured, may experience FoR, and patients who have had a recurrence may experience FoP.

After radical prostatectomy, 36% of prostate cancer survivors experienced high FoR, and they also reported disease-related factors that triggered this, such as medical examinations (58). The authors also reported that high FoR was associated with lower QoL, higher distress and more physical problems (58). Furthermore, a study comparing FoR in different diagnoses (97) showed that prostate cancer survivors experienced the lowest FoR while breast cancer survivors experienced the highest FoR (97). Similar patterns are shown in another study where men with prostate cancer had lower FoR than men with other cancer diagnoses (98).

In men with advanced prostate cancer, fear/uncertainty about the future have also been shown while some men wanted to understand their disease progression in terms of knowing how much time was left, how their QoL would evolve and what would happen when all treatment options were exhausted (48). According to Mishel (99) uncertainty can occur when the patient is unable to find meaning in an illness event. Furthermore, uncertainty related to the illness negatively influences patients physical and mental well-being (100). In her uncertainty in illness theory, Mishel (99), describes that symptom pattern, event familiarity and event congruency influence uncertainty in illness. If symptoms form patterns, events are familiar and illness-related events are expected there is less uncertainty. These areas are also influenced by the patient’s cognitive capacity, educational level, social support and lastly by the health care professionals. If any of this is not present or malfunctioning the uncertainty may be greater (99). Higher PSA, more symptoms and lower support from others have been shown to be associated with greater illness uncertainty (101).

To summarize, men with mCRPC may experience distress. Sociodemographic and medical factors may affect the experience of distress. Furthermore, anxiety and depression are higher if there is a high symptom burden and if side effects are present. Illness uncertainty may affect both the physical and psychological well-being. Men with advanced prostate cancer may experience a FoP, which in turn may lower their QoL.

2.6 RATIONALE

In the past decade, thanks to improved treatment options aimed to prolong life, manage symptoms and improve QoL, many men with metastatic prostate cancer have a chance for an expanded life trajectory compared to men with metastatic prostate cancer just 10 years ago.

To be able to monitor prostate cancer, assessing clinical manifestations, such as signs and symptoms, is essential for clinicians. The PSA-value is often followed during the entire disease trajectory as a sign, but with different implications. From a clinical perspective the PSA-value may lose some relevance in the advanced stage of the disease. Other factors, such as symptom burden, QoL, and/or psycho-social factors are assigned more importance in treatment decisions and evaluations by the treating physician. However, from the men's perspective the change of the clinical importance of the PSA value in assessment of treatment effect and as a sign of disease progression may not be obvious and they may therefore experience distress about values with little clinical relevance.

The symptoms of metastatic prostate cancer often increase over time and the men can experience a substantial symptom burden. There are few studies describing symptom burden in a real-world situation for these men. Symptom management is always important but when having a life-limiting disease, symptom management plays a vital role in the balance between prolonging life and QoL. Some men associate new symptoms with progression and/or metastases. The views of patients and physicians may differ regarding progression. The patient's subjective interpretation of the severity of the disease, and signs such as PSA-values may differ from the objective interpretations of these medical findings.

So far, there is a lack of research regarding the experiences of signs and symptoms in men with mCRPC in a real-world situation. In order to support these men, it is important to gain an understanding from the men's perspective of their experiences and interpretations of signs and symptoms.

3 AIMS

3.1 OVERALL AIM

The overall aim of this thesis project was to study signs and symptoms in relation to progression of the disease in men with advanced prostate cancer.

The underlying hypothesis was that signs and symptoms may be experienced as distressing as markers of potential progression influencing quality of life in advanced prostate cancer.

3.2 SPECIFIC AIMS

The specific aims of the included studies are:

Study I. The aim was to investigate the association between PSA-value and distress among men with prostate cancer, adjusted for sociodemographic factors, ongoing hormonal treatment or surgical castration, and overall quality of life.

Study II. The aim was to illuminate the experience of signs and symptoms in relation to disease progression in men with mCRPC.

Study III. The aim was to describe different dimensions of symptoms in men with mCRPC, starting their first-line life-prolonging treatment, and to describe the association between symptom burden and QoL.

Study IV. The aim was to investigate changes in symptom burden during the first year from the start of life-prolonging treatment of mCRPC.

4 MATERIALS AND METHODS

This section first gives an overview of the four studies regarding design, sample, data collection and analyses, thereafter the specific studies are described.

4.1 STUDY DESIGNS

The thesis is based on data from two different overall projects: a survey sent to all members of the Swedish Prostate Cancer Federation (SPCF and the PROstate Cancer-Experiences and Expectations During treatment (PROCEED) project. An overview of the four studies is presented in Table 1.

Table 1. Overview of the included studies in the thesis

	Sample	Study Design	Data collection	Analyses
Study I	3165 men with prostate cancer who were members of the SPCF	Quantitative, cross-sectional	Questionnaires, the SPCF in cooperation with Umeå University	Descriptive statistics and logistic regression
Study II	A subgroup of 11 men from the PROCEED project	Qualitative longitudinal	Qualitative interviews Medical records	Qualitative content analysis
Study III	143 men from the PROCEED project who were starting treatment at four oncology departments	Quantitative, cross-sectional	Questionnaires Medical records	Statistics; proportions, Descriptive statistics and linear regression Mann-Whitney U-test, chi-squared test
Study IV	131 men from the PROCEED project who answered at least two questionnaires during their first year after starting treatment at one four oncology departments	Quantitative, longitudinal	Repeated questionnaires Medical records	Descriptive statistics and linear mixed model (LMM)

Both quantitative and qualitative approaches were applied to investigate the men's experiences of signs and symptoms during the course of their progressive disease. Three of the four studies had a quantitative approach and one of these quantitative studies had a longitudinal design allowing us to follow the men's trajectory over one year. Study I had a cross-sectional design and was believed to be the first investigation of how signs such as PSA affects men with prostate cancer. Studies II to IV were more focused on men with mCRPC and their experiences and outcomes in terms of signs, symptoms and QoL. Study III had a cross-sectional design where the focus was on different dimensions of symptoms and QoL at the start of life-prolonging treatment. Study IV had a longitudinal design, following the men during their first year after starting life-prolonging treatment and focusing on changes in symptom burden.

One study (Study II) had a qualitative longitudinal approach where interviews were conducted from the start of life-prolonging treatment with follow-up interviews in conjunction with any progression of the disease during a two-year period. This is a suitable design when the aim is to illuminate and give meaning to experiences of having a progressive disease (102). Study II's qualitative approach and longitudinal design gave the opportunity to illuminate the men's experiences about signs and symptoms during the progression of their disease.

4.2 PARTICIPANTS AND DATA COLLECTION

Participants in the four studies were from two different cohorts, one comprised of members from the SPCF and the other of participants from the PROCEED project as shown in the flow chart (Figure 3).

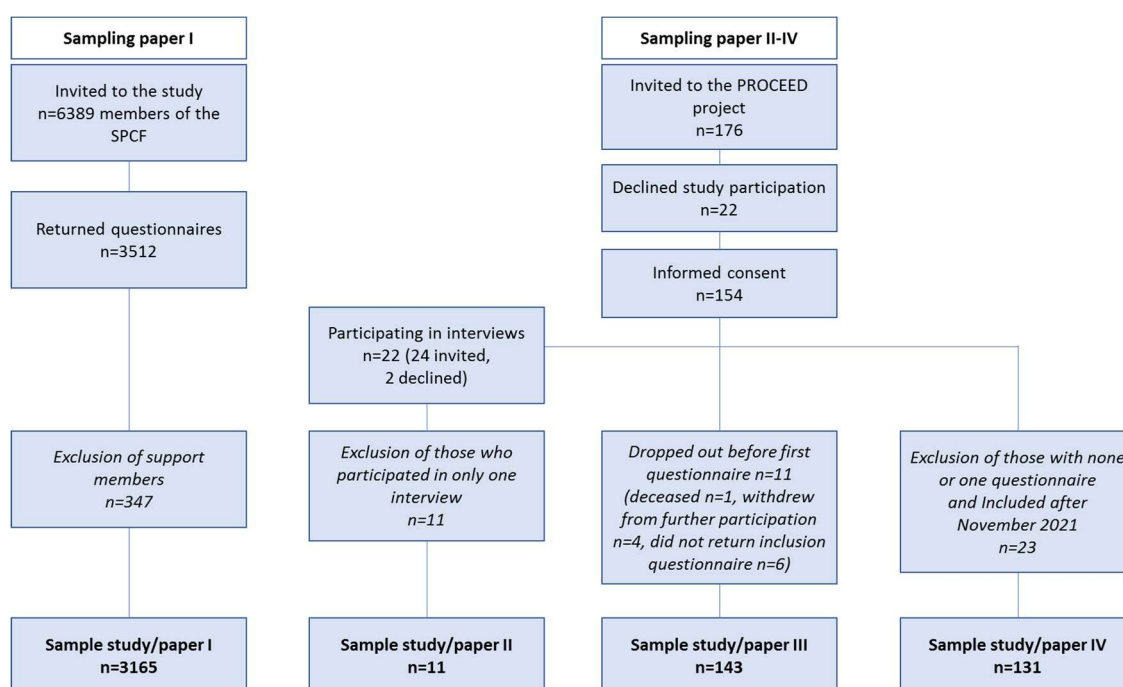


Figure 3. Flow-chart of the sampling in the four studies.

4.2.1 Overview study I

In 2012, on initiative from the SPCF and in collaboration with Umeå University, a questionnaire/survey was sent to members of SPCF. The aim of the project was to gain a better understanding of the members' experience of living with prostate cancer in everyday life. The survey also focused on how the members experience the care they receive. The SPCF consists of men with prostate cancer, their family members, and professionals, but also of individuals who join the federation in support of it. The SPCF sent the survey to all 6389 members in their register, at that time (2012) 6389. All local SPCF divisions in Sweden had been informed about the study through their national association board. The questionnaire, consisting of 45 questions, with information about the study, and a return envelope addressed to Umeå University was sent. The questionnaires were returned anonymously, so no reminder

could be sent to those who did not respond. The members were prompted to contact their local SPCF if having further questions.

The questionnaire consisted of study specific questions about sociodemographic and medical factors. Some of the questions about symptoms, health and QoL were taken from the Prostate Cancer Symptom Scale (PCSS) which is a validated questionnaire (103). Other questions were developed specifically for the project in close cooperation with the SPCF, such as questions about care and sources for information, as well as questions about the SPCF.

4.2.1.1 Sample and data used

For study I questions about overall QoL, distress, socio-demographic factors (age, marital status and educational level) and medical factors (time since primary diagnosis, types of treatments and latest PSA value) were used.

Distress was measured with the question “Do you have any problems with worry/anxiety/feelings of depression?” with the response options “Never”, “Sometimes”, “Often” and “Always”. Overall QoL was measured using the question “How would you estimate your QoL today?” with response options on a numeric rating scale from 0 “very bad” to 10, “Excellent”.

Time (year) of primary prostate cancer diagnosis was self-reported. Types of treatments were measured through a question about which treatment they had had just after diagnosis, later treatments, and which treatment they were receiving at the time of the survey. The options were no treatment, operation, radiotherapy, hormonal treatment, ablatio testis and chemotherapy. Latest PSA value was self-reported by the question “My latest PSA value was...”.

In total, the response rate was 55%. Of the returned questionnaires, 90% (3165) were returned from members who reported that they had been diagnosed with prostate cancer. These 3165 returned questionnaires were used for analysis.

4.2.2 Overview studies II, III and IV

Studies II, III, and IV are based on data from the PROCEED- project, which is a longitudinal, prospective multicenter project, following men with mCRPC from the start of life-prolonging treatment and over a period of two years. The men were recruited/included from four oncology departments in Sweden from April 2015 to March 2022. Due to a real-world approach and the intention to include unselected patients, there were few inclusion criteria: men who were about to start a first-line treatment for mCRPC and who could express themselves in Swedish. A physician and/or a research nurse, or study coordinator approached eligible men with oral and written information. Men who agreed to participate gave written informed consent and received a questionnaire and a pre-paid return envelope addressed to Sophiahemmet University.

After the inclusion questionnaire, the questionnaire was sent out by mail repeatedly every third month or in conjunction with a start of new treatment. In addition to sociodemographic data at inclusion, the questionnaire included several well-validated instruments such as the Memorial Symptom Assessment Scale (MSAS) (104, 105), Functional Assessment of Cancer Therapy (FACT) (106), Hospital Anxiety and Depression Scale (HADS) (107), and from the European Organization for Research and Treatment of Cancer (EORTC), the global QoL questions (108) and the bone metastases module (BM-22) (109). At inclusion, medical data was also collected from the medical record: primary diagnosis date, date of metastatic disease, tumor characteristics as well as PSA, hemoglobin (Hb), alkaline phosphatase (ALP) and prescribed analgesics. In conjunction with each follow-up questionnaire, latest blood sample results (PSA, ALP, Hb) change of treatment (end of treatment date, type and start date of new treatment) and prescribed analgesics were collected from the medical record. An a priori power analysis was performed based on clinically significant changes in the FACT instrument (110) (not used in these studies) which showed that a sufficient sample would be 120-150 men. The PROCEED project therefore included 154 men.

Twenty-four men were also approached by the research nurse/ coordinator about participating in an interview part of the project (Figure 3). Two men declined participation. The 22 men who agreed to participate, were contacted by one of the two interviewers for further information and booking of the first interview. For the interviews a purposeful sample with a maximum variation strategy (111) was the underlying goal in the sampling procedure, were differences in age, marital status, time since primary diagnosis, type of treatment and also place of residence (rural, urban) were considered. The men were then interviewed in conjunction with a progression, i.e., when a treatment was terminated ahead of plan or changed.

4.2.2.1 Sample and data collection study II

In order to illuminate experiences over time in relation to progression, the eleven men who had been interviewed more than once in the PROCEED project were included in the sample for study II (Figure 3). For research that aims to explore changes over time, longitudinal interviews are suitable. It is possible to build a relationship between the interviewer and the interviewee when follow-up interviews are conducted. To understand the trajectory being studied, the data collection period needs to be sufficiently long. In the present study, the men were interviewed in conjunction with a progression of disease during a two year-period. Progression was considered to have occurred when one treatment ended or a new treatment started with progression as the reason.

Between two and five interviews were conducted with each man. The average time between the interviews for each participant was 8 months and the follow-up interviews were conducted over a two-year period. Some of the men started a new line of treatment, while others terminated life-prolonging treatment. The interviews were conducted between late 2016 and 2021 and were between 27 min and 108 min long. The interviews were conducted

by me (UR) and another PhD student and the same person who did the initial interview did the follow-up interviews to establish a trustful relationship (112).

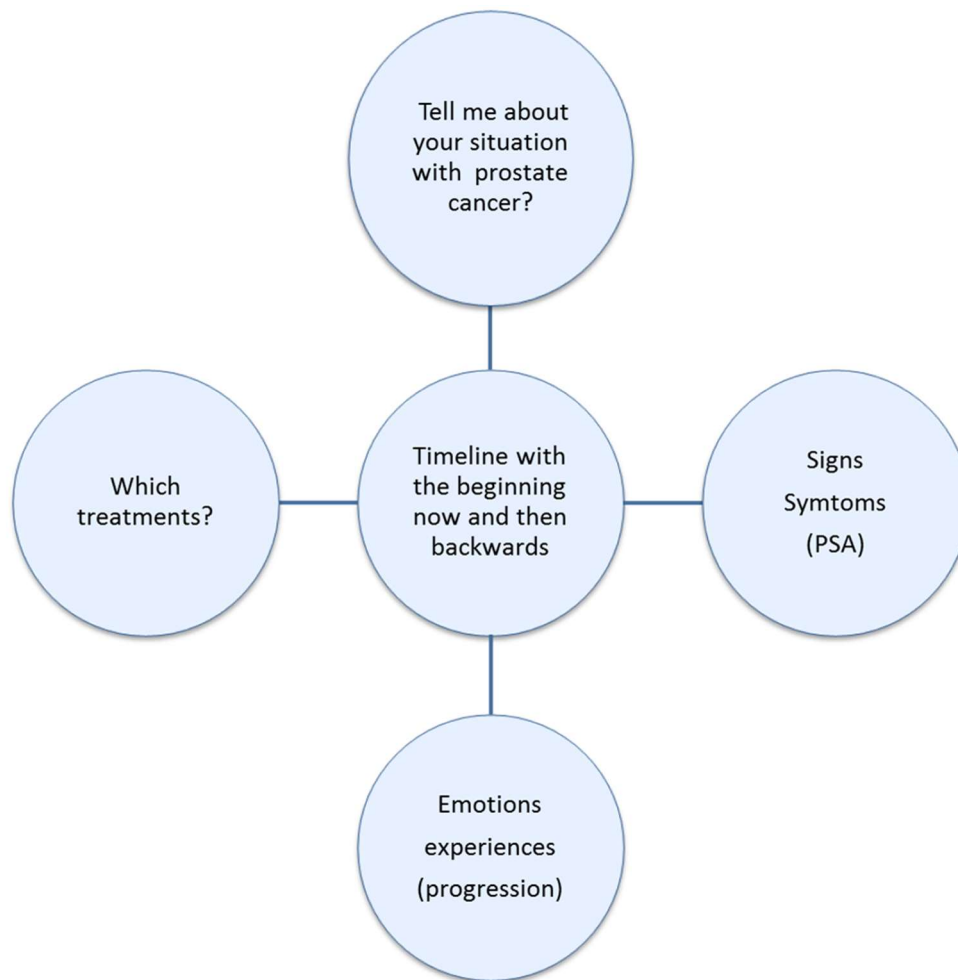


Figure 4. The interview guide with topics to cover.

The interviews took place at the participant's preferred location, usually a secluded room at the hospital, but sometimes in the patient's home. An interview guide with topic areas was used during the interviews (Figure 4). At the first interview, the men were asked "Can you please tell me about your situation with prostate cancer?" The interview then continued in a conversational manner with probing questions, about signs, symptoms and progression, as well as their earlier experience of prostate cancer, when necessary.

In the follow-up interviews they were asked "What has happened since the last time we met?" and then continued in a conversational matter. All interviews were recorded using a digital voice recorder and transcribed verbatim. After each interview, field notes were written and before each follow-up interview, the earlier interview transcripts and field notes were re-read. Medical variables were collected in order to describe the sample. During the follow-up time, two of the men declined further interviews after the first follow-up.

4.2.2.2 Measures study III and IV

In studies III and IV, data from the MSAS (105), and the European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire C30 (EORTC QLQ-C30) (108) questions about global health/QoL, together with sociodemographic and medical data were used.

Symptom and symptom burden were measured using the MSAS instrument (105). The MSAS was developed to provide multidimensional information about several symptoms. The original MSAS consists of 32 physical and psychological symptoms experienced in the last seven days. For the PROCEED project the question “problems with sexual activity and desire” was split into two questions. The question was split based on the fact that these men are all medically or surgically castrated and the activity or desire may be different from in a non-castrated population. In studies III and IV the MSAS consists of 33 symptoms. For 25 of these symptoms three dimensions (frequency, severity, distress) are measured. For the other eight symptoms the severity and distress dimensions are measured. The frequency and severity dimensions are measured on a four-point rating scale, while distress is measured on a five-point rating scale which is converted to a four-point scale prior to analysis. Higher scores indicate greater frequency, severity, and distress. The symptom scores were calculated for each symptom according to Portenoy et al. (105).

The MSAS consists of three subscales which are well used in the contexts of cancer and end-of-life research (113); the subscales are scored 0-4. The MSAS physical symptoms subscale (MSAS-PHYS) subscale contains 12 physical symptoms (lack of appetite, lack of energy, pain, feeling drowsy, constipation, dry mouth, nausea, vomiting, change in taste, weight loss, feeling bloated, dizziness). The MSAS psychological symptoms subscale (MSAS-PSYCH) subscale contains six symptoms (feeling sad, worrying, feeling irritable, feeling nervous, difficulty sleeping, and difficulty concentrating). The third subscale, MSAS-GDI, is a global distress index, and this subscale is not used in the two studies.

As a measure of symptom burden in studies III and IV, three measures from the MSAS were used. First, the number of symptoms, based on the occurrence of symptoms (*Did you have any of the following symptoms? No/yes* (0-33 symptoms)). Second and third, the two subscales MSAS-PHYS and MSAS-PSYCH were also used. The subscales are calculated according to Portenoy (105), briefly the dimension (frequency, severity, distress) scores are summed and then divided by the number of dimensions answered. Even if only 18 of the 33 symptoms from MSAS were used in the subscales, all symptoms were included in the count of number of symptoms. Cronbach’s alpha at inclusion, for MSAS-PHYS was 0.814 and for MSAS-PSYCH 0.803.

QoL was measured using the global QoL subscale from the EORTC QLQ-C30 questionnaire (108). The subscale is based on two questions: “How would you rate your overall health during the past week?” and “How would you rate your overall quality of life during the past week?” with response alternatives 1 = “poor” to 7 = “excellent”. The responses were

transformed to a 0-100 scale according to the scoring manual (114) where higher points indicate higher global QoL. Cronbach's alpha in the inclusion questionnaire was 0.940.

4.2.2.3 Sample and data used in study III

In study III, of the 154 men included in the PROCEED project, 143 men who had returned an inclusion questionnaire comprised the study sample (Figure 3). Of the 11 men not included, six had not returned a study questionnaire, four withdrew from further participation and one was deceased.

The MSAS instrument and the global QoL subscale from the EORTC QLQ-C30 from the inclusion questionnaire were used. Three measures of symptom burden from the MSAS were used: physical symptoms (MSAS-PHYS), psychological symptoms (MSAS-PSYCH) and number of symptoms. Self-reported sociodemographic data such as marital status and education were collected from the questionnaire while age was collected from the medical record. Other data collected from the medical record were: time since primary diagnosis, time since metastatic disease, tumor related characteristics (TNM, Gleason score), site of metastatic disease and treatment planned or just started. PSA at inclusion was also collected.

4.2.2.4 Sample and data used in study IV

In study IV, 131 men who were included in the PROCEED project before November 2021 participated. The total sample was by that time 147 men. Sixteen men had not returned two or more questionnaires and were excluded. The men who had returned two or more questionnaires independent of time point, were included. Each participant had returned two to five questionnaires (t1-t5), in total 557 questionnaires. The MSAS instrument and the global QoL subscale from the EORTC QLQ-C30 from all questionnaires returned the first year were used.

Self-reported sociodemographic data such as marital status and education were collected from the inclusion questionnaire, while age at inclusion was collected from the medical record. Other data collected from the medical record at time of inclusion were: time since primary diagnosis, time since metastatic disease, tumor related characteristics (TNM, Gleason score), site of metastatic disease. PSA, ALP and Hb values were also collected at inclusion. Treatments started and treatment changes were collected during the one-year period.

4.3 DATA ANALYSES

The four studies are presented in order. For the three quantitative analyses, the significance level was set at <0.05 and all statistical analyses were performed using IBM SPSS (Armonk, NY: IBM Corp).

4.3.1 Study I

In study I data were analyzed using descriptive statistics and multivariable logistic regression with odds ratios (OR) with 95% Confidence interval (CI).

Descriptive statistics were used regarding age, marital status, education, time since diagnosis, hormone therapy, and the latest known self-reported PSA-value.

The variables included in the regression were dichotomized by the median (QoL, age, years since prostate cancer diagnosis) or by categories (married/cohabiting/ in a relationship versus divorced/widowed/single; elementary school, high school, university; no hormone therapy versus hormone therapy; PSA: 0-19 ng/ml, 20-99 ng/ml 100-999 ng/ml, 1000 ng/ml and above). Hormone therapy was defined as surgical castration or ongoing medical therapy and the PSA categories were according to the suggestion of Koo et al. (115).

The logistic regression was performed in three models. The first model, Model 1, was performed as a bivariate analysis between distress and PSA values and for distress and respective covariates. Significant associations from Model 1 were marital status, education, PSA, hormone therapy and QoL. All significant associations from Model 1 were then included simultaneously in model 2, except for QoL. Since the concepts of distress and QoL are somewhat overlapping and there was a significant correlation between distress and QoL, in a third step a model was performed where QoL was included. In study I, missing data were handled in the analysis with listwise deletion. In the multivariable regression, 2970 men were included.

4.3.2 Study II

In study II, a conventional content analysis with an inductive approach inspired by Hsieh and Shannon (116) was performed for interview data. Inspiration for the longitudinal analysis was found in the approach presented by Murray et al. (112). To be able to delve deeper into topics of concern in the follow-up interview, analysis was initiated in conjunction with data collection. When no new perspectives or information emerged from the interviews, the inclusion of new participants ceased (117).

The interview transcripts were read and reread several times in accordance with the content analysis tradition (116). This was done to achieve a sense of the content. The transcripts were imported to the NVivo 12 software (QSR International Pte Ltd, Doncaster, Victoria, Australia) for further structuring and coding. All text was inclusively coded to avoid missing relevant content. Thereafter, codes that were relevant to the aim were conceived structurally. To enhance trustworthiness the codes were discussed and critically reviewed in the research group. The discussions about codes and content continued until consensus was achieved. Codes were then categorized into clusters according to how they related to each other. In the next step, through discussions regarding the content of the clusters, the sub themes emerged. To integrate the longitudinal aspects of the subthemes, matrices were used in the analysis to understand the experience over time, first for each participant, then for the trajectory for each theme (118). In the final step, the subthemes were synthesized into one overarching theme. In order to confirm the subthemes and overarching theme, they were further discussed within a multidisciplinary team with experience from oncology.

4.3.3 Study III

Data from the inclusion time-point in the PROCEED project were analyzed. For demographic and medical characteristics, frequencies and proportions are presented. Linear regression analyses were applied in two models, first a bivariate linear regression model with QoL as dependent variable and symptom burden and covariates considered important for QoL (Model 1). The variables with significant bivariate association were then included simultaneously in Model 2. All assumptions for linear regression were met (119).

A subgroup analysis was performed to investigate if there were any significant differences between those who were included in the analyses and those who were not (i.e. did not return the inclusion questionnaire, withdrew consent, or were deceased). Comparisons were made regarding medical data between the groups using Mann-Whitney U test and Chi2-test for continuous and categorical data respectively. A comparison was also made between those who had already started treatment when they answered the inclusion questionnaires and those who had not yet started treatment regarding the symptom burden variables (number of symptoms, physical and psychological symptoms) using Mann-Whitney U test.

Missing values in the MSAS questionnaire was managed according to Portenoy (105) as well as according to the guidelines for the EORTC QLQ-C30 (114).

4.3.4 Study IV

In study IV, data obtained during the first year from inclusion in the PROCEED project were used if two or more questionnaires were answered. Both data from the questionnaires and medical data collected in conjunction with the questionnaires were analyzed.

To analyze changes over time regarding the three measures of symptom burden, linear mixed modeling (LMM) was applied. Three separate LMM models were performed for the three symptom burden measures as outcomes. An unstructured covariance matrix was chosen since the time span between the data collection time points varied. The LMM was adjusted for covariates measured at inclusion (age, education, marital status, years since primary diagnosis, years since metastatic disease, analgesic use) as fixed effects.

Missing values in the MSAS questionnaire were managed according to Portenoy (105) as well as according to the guidelines for the EORTC QLQ C-30 (114). The LMM provides estimates using all available data.

5 ETHICAL CONSIDERATIONS

All studies in this thesis were granted ethical approval. Study I, was approved by the Ethical review board in Umeå, dnr 2012-150-31M. For studies II-IV ethical approval was from the Regional ethical review board in Stockholm dnr 2014/341-31/2, 2016/851-32, 2016-2230-32 and 2019-03675. The studies were performed in accordance with the Declaration of Helsinki (120).

Men with mCRPC have a cancer that is not curable and they have a relatively short expected survival even if some of them have lived with their cancer for several years. When conducting research on severely ill persons and collecting sensitive personal information such as data regarding health and sexual life, ethical concerns need to be addressed throughout the whole research process.

To ensure the men's' right to autonomy, which includes making rational decisions, informed consent is important (121). The informed consent procedure is applied to ensure that the participants have thoroughly been informed about the study aware that they have the right to decline participation as is emphasized in the Declaration of Helsinki (120). In study I, the questionnaire was returned anonymously. In studies II-IV, eligible men considered for inclusion in the study were given written and oral information about the study by their physician and/or research nurse/study coordinator. The research nurse/study coordinator also stressed that the men's care and treatment would not be affected by whether they chose to participate in the study or not. After a decision to participate, all men signed an informed consent form. The participants' freedom of choice whether to participate or not, and the freedom to withdraw from the study at any time, were also emphasized by the research nurse/study coordinator at several time points during the longitudinal follow-up.

The men have a life-limiting disease and are therefore considered to be a vulnerable group where the risk of physical or psychological harm may be increased (122). It is possible that the questionnaires used in studies I, III and IV, could evoke feelings of worry or anxiety for the men answering the questions, which could cause harm. In study I, the participants were encouraged to contact their local SPCF if needed, while in studies III and IV, the front page of each questionnaire contained information about how to reach the research group. The research group could then in turn contact the department treating the patient if wished by the patient. To eliminate the risk of sending questionnaires to the family of a newly deceased participant, the research nurse/study coordinator at each site verified that each patient was alive by checking the medical record before sending a questionnaire.

For men participating in study II, the interviews could have provided a chance for them to talk to someone outside the contexts of family and healthcare, which may be a benefit. It has been shown that participating in interviews has been beneficial for the person being interviewed, especially in studies where they talked about experiences and where a trustful relationship existed (123). Doing research on participants with a life-threatening disease such as prostate cancer is somewhat challenging. For example, during the interviews, sometimes in

the participants' home, one must be deferential and not raise anxiety while at the same time wanting knowledge about their experiences and feelings. Each interview ended with a question about how the man felt after the interview and if he had any further questions. Some of the interviews were conducted shortly before death but the overall impression is that most men were very willing to share their experience. To maintain neutrality and prevent a power imbalance and role conflict that might make the interviewee feel at disadvantage, the interviewer did not tell the interviewee that she was a nurse at the beginning of the interviews (122). It was occasionally hard to not step into the role of an oncology nurse, for example when some men expressed facts about treatments or side effects that I knew to be wrong. In such situations I encouraged them to speak to their contact nurse for further information.

In study I, the SPCF participated in the development of the questionnaire, the information about the study and the distribution of the questionnaires. There was no identification on the questionnaires or return envelopes, hence, the returned questionnaires were anonymous with no possibility to link the questionnaires to the participants. To protect the men's integrity, all data in studies II-IV were treated confidentially, which means that all data management and all analyses were performed on deidentified data where each man had a study number. The key to the study numbers was stored at the respective oncology departments. All data are stored and archived in locked storage units at Umeå University (Study I) and Sophiahemmet University (Study II-IV). The results are also presented in such a way that it is not possible to identify individuals.

6 RESULTS

This section presents first a brief description of sociodemographic data covering the four studies in the thesis, then the results from the four studies.

Altogether there were no large differences between the different studies regarding sociodemographic characteristics. The men in study I were slightly younger in average than the men in studies II-IV, 72.8 years versus 75.0-75.2 years. The men's ages covered a wide range in all studies, 40-95 (I), 60-89 (II), 50-88 (III), 50-88 (IV) respectively. The proportions of men that were married/cohabiting were similar in the four studies; however, the proportion of men who reported that they were single was lower in study I, 14.1% versus 23.8-27.3% in the other studies.

Regarding the reported educational level, the proportions correspond well within the quantitative studies I, III and IV, with 40.0-44.1% reporting elementary school, 26.6-29.0% reporting high school and 25.2-30.9% reporting university as highest educational level. In contrast, in study II, 27.3% reported elementary school, 54.5% high school and 18.2% reported university as highest educational level. The maximum variation sampling strategy and the small sample size in study II may be the reason for the discrepancy with the other studies.

6.1 STUDY I

In study I, 3165 men with prostate cancer participated. The men had a mean age of 72.8 years (SD 7.2) and most men (40.0%) had elementary school as highest educational level. Of the men, 80.0% were married/cohabiting and they had received their prostate cancer diagnosis on average 6.9 (4.4) years ago.

Most men (73.8%) had a PSA value below 20 ng/ml, while almost 15% of the men had PSA-values between 20-99 ng/ml and just above 8% had PSA values between 100-999 ng/ml. The group with values over 1000 ng/ml was just below 3%. Just above 53% of the men reported distress "sometimes", "often" or "always", and about 46% reported "never". Of the men, 64.3% ranked their QoL between 7-10 out of ten possible while 35.7% rated their QoL poorer, with values between 0-6.

The five variables that were significantly associated with distress in bivariate analyses (Model 1) were: marital status, education, PSA, hormonal therapy and QoL (Table 2). All variables except for QoL were included in Model 2.

The results show a significant association between higher PSA values and experiencing distress when adjusted for marital status, education and hormonal therapy (Model 2) (Table 2). There were also significant associations between distress and marital status and distress and hormonal therapy.

Table 2. Crude and adjusted odds ratios (OR) with 95% confidence interval (95%CI), for associations between distress and PSA, sociodemographic factors, hormonal therapy (surgical or medical) and overall QoL (n=3165) from *Prostate-specific antigen (PSA) and distress: - a cross-sectional nationwide survey in men with prostate cancer in Sweden* (124, p.4). CC BY 4.0

Variable	Model 1 ^(#)			Model 2 ^(§)			Model 3 ^(¶)		
	OR	(95 % CI)	p	OR	(95 % CI)	p	OR	(95 % CI)	P
Age n=3141	1			-			-		
41–73	0.90	(0.78–1.04)	0.14						
74–95									
Years since diagnosis n=3051	1			-			-		
0–6	1.10	(0.96–1.27)	0.18						
7–43									
Quality of life n=3118	1			-			1		
7–10	4.49	(3.81–5.29)	0.00				4.33	(3.62–5.17)	0.00
0–6									
Marital status n=2970									
Married/cohabiting/in relationship	1			1			1		
Single/widowed/divorced	1.50	(1.19–1.88)	0.00	1.40	(1.10–1.77)	0.01	1.16	(0.90–1.49)	0.25
Education n=3036									
Elementary school	1			1			1		
High school	1.04	(0.87–1.24)	0.83	1.06	(0.89–1.28)	0.50	1.21	(1.00–1.47)	0.05
University	0.83	(0.70–0.99)	0.02	0.85	(0.71–1.01)	0.07	1,00	(0,83–1,21)	0.98
PSA (ng/ml) n=3165									
0–19	1			1			1		
20–99	1.36	(1.11–1.66)	0.00	1.25	(1.01–1.55)	0.04	1.21	(0.96–1.51)	0.10
100–999	1.54	(1.19–2.01)	0.00	1.47	(1.12–1.94)	0.01	1.25	(0.93–1.68)	0.14
1000–	2.19	(1.38–3.47)	0.00	1.77	(1.11–2.85)	0.02	1.17	(0.70–1.94)	0.55
Hormonal therapy n=3165									
No	1			1			1		
Yes	1.42	(1.18–1.71)	0.00	1.35	(1.11–1.65)	0.00	1.12	(0.91–1.39)	0.28

p ≤ 0.05, significant values in bold

(#) Model 1: Bivariate association between all variables and distress

(§) Model 2: Association between PSA value and distress adjusted for all significant independent variables in Model 1 excluding QoL

(¶) Model 3: Association between PSA values and distress adjusted for all significant independent variables in Model 1 also including QoL

In Model 2, the association with marital status showed 40% higher odds for experiencing distress if living alone (single/widowed/divorced), and 35% higher odds for experiencing distress if having hormonal treatment, while the association with education did not remain significant. The model also showed that the odds for experiencing distress grew successively higher in each higher PSA group, and the highest PSA group had almost two times higher odds (OR 1.77) for experiencing distress compared to those with the lowest values. In Model 3, where QoL was included, there was a significant association between distress and QoL. No significant associations were found between distress and PSA values, distress and marital status, or distress and ongoing hormone therapy.

6.2 STUDY II

In total 11 men were interviewed, and 30 interviews were conducted (2 to 5 interviews with each man). The men had a median age of 75 and more than half of them (54.5%) had high school as the highest educational level. Eight of the men (72.7%) were married/cohabiting at the time of the first interview. Six of them lived in rural areas, while 5 lived in urban areas. They had received their prostate cancer diagnosis in median 2.75 years ago. Eight of the men had a performance status of 1 while the rest had 0 at baseline. The performance status worsened over time and at the last interview one man had 4, two men had 3, four had 2 and four had 1. In eight out of 11 men the first line of treatment was chemotherapy.

The overarching theme found in the men's stories was "The experience of an uncertain illness situation within the framework of progression" with four subthemes, as shown in Figure 5, together with representative quotes. No new information appeared in the last interviews. All men expressed aspects of all subthemes. The overarching theme and subthemes were related to the men's previous experiences. Experiences of symptoms, or the lack of them, when they were first diagnosed, and experiences from previous treatments, influence how the men interpret symptoms or lack of symptoms in this late phase when receiving life-prolonging treatments.

The experience of an uncertain illness situation within the framework of progression	Symptoms triggering thoughts about disease progression	"You get worried if you start to get pain somewhere else all of a sudden, in other words that it [the cancer] has spread in some way so it's not kept in place so to speak" (P8)
		"I don't know what it can be, if it's my hip joint, or if it's ... one feels uncertain if it's the cancer that has spread" (P7)
	Making sense of signs, also in the absence of symptoms	"... damn you have to be quite satisfied if it's [the PSA] just stable. It's [the cancer] not getting worse, huh" (P2)
		"You do not get any signals yourself, the information you get, that's from tests and the doctor's appointments. But you don't get any signals yourself from your body, that this is what is going on" (P4)
	Making sense of symptoms during treatment	"There have to be more effective [treatments]. I didn't feel anything of that treatment either" (P6)
		"... and then one feels suspicious and thinks, if I do not feel bad maybe the cancer does not feel bad either" (P2)
	Progression triggering thoughts about the remainder of life	"Then [if paralyzed] I will be so darned dependent ... I've been thinking about those things, I'm actually afraid of that" (P1)
		"...it's [the PSA] such a small part of everything, huh ... it is so very small ... it isn't like anything that could help me use my legs again ... " (P9)

Figure 5. The overarching theme with subthemes and representative quotes.

Signs, such as PSA and imaging results, and symptoms had different meanings in making sense of the men's situation with a progressive disease. If they experienced new symptoms that they interpreted as related to the prostate cancer, a feeling of uncertainty was described, and thoughts of a potential disease progression arose. Uncertainty about whether the prostate cancer was progressing or not was also described when no symptoms were experienced. PSA values were expressed as a more important sign than imaging results. Some of the men stated

that the only way to get information about the disease, both progression or effect of treatment, was through PSA values, imaging results, or from what the physician told them in the absence of symptoms.

Symptoms such as pain and fatigue, or a general decline in health, could trigger thoughts about the remainder of life. It was described in terms of fear for death or dying; it was also a fear of becoming dependent on others. During the follow-up period the men's thoughts about PSA values changed, from a decreasing PSA being very important, to being quite satisfied if it remained stable. In later follow-up interviews, the importance of symptoms that the men said they considered more serious superseded that of PSA values.

The men did not talk much about being worried or anxious but rather described it as they were pondering. Some of the men also expressed problems with sleep and sometimes their insomnia was related to them pondering at night (unpublished data). To handle this, they described ways to prepare for the future or strategies for not pondering so much. Examples were to walk in the forest with the dog or to do some gardening.

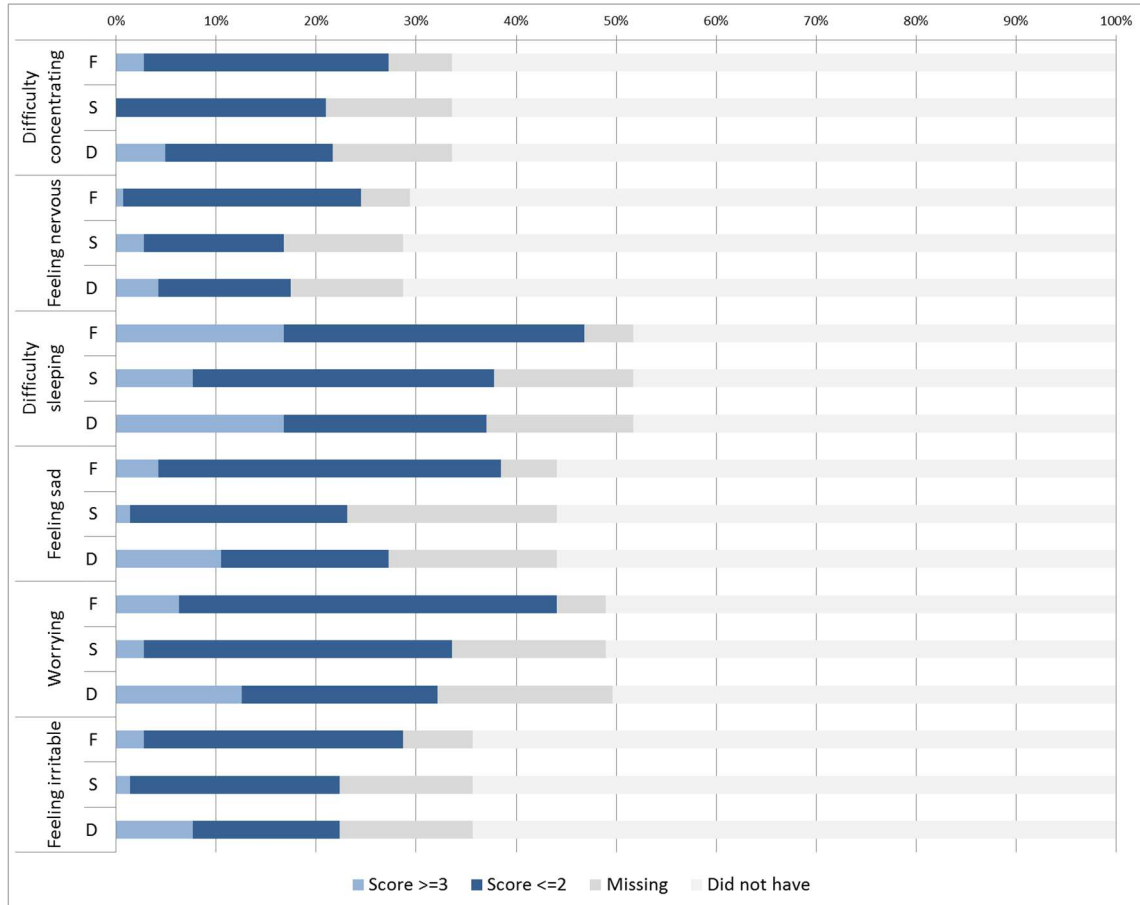
Although the men described that they experienced several symptoms, sexual problems were mostly mentioned in passing, both if they had them but also if they were bothered by them. Some said that they did not have a sex life due to the treatment; others said that they were so old that it did not matter. One man expressed the loss of sex life as a problem, he also said that it was a problem for his wife, as he saw it.

6.3 STUDY III

In study III, the 143 men who had returned an inclusion questionnaire participated. The men had a mean age of 75 years (SD 7.2) and 44.1% of them had elementary school as the highest educational level. Of the men, 74.8% were married/cohabiting. In average the men had received their prostate cancer diagnosis 4.6 (SD 4.7) years earlier, and had started or were about to start their first line of life-prolonging treatment. Most men started a second-generation antiandrogen (67.1%), while 30.1% started with chemotherapy and 2.8% with radium 223.

The span of symptoms reported was from 0 to 31 out of 33 possible symptoms, and the mean number of symptoms reported was 10.6 (SD 7.2). The most frequently reported symptoms were sweats (69%), lack of energy (59%), problems with sexual activity (52%) and sexual interest (51%) and pain (50%). These symptoms were reported by 50% or more. Of the 72 men who reported pain on the MSAS, 63.9% (n=46) were using analgesics while 36.1% (n=26) did not. Of the men using analgesics, 55.8 % reported that they had pain "frequently" or "almost constantly" and among the men who were not using analgesics 44% reported that they had pain "frequently" or "almost constantly". When reporting the severity of pain, among those using analgesics 27.5% reported severe or very severe pain while none of the men not using analgesics reported very severe pain, and 19% reported severe pain. In the distress dimension of pain, 51% of the men using analgesics reported quite a bit/very much distress in contrast to 38% of the men not using analgesics.

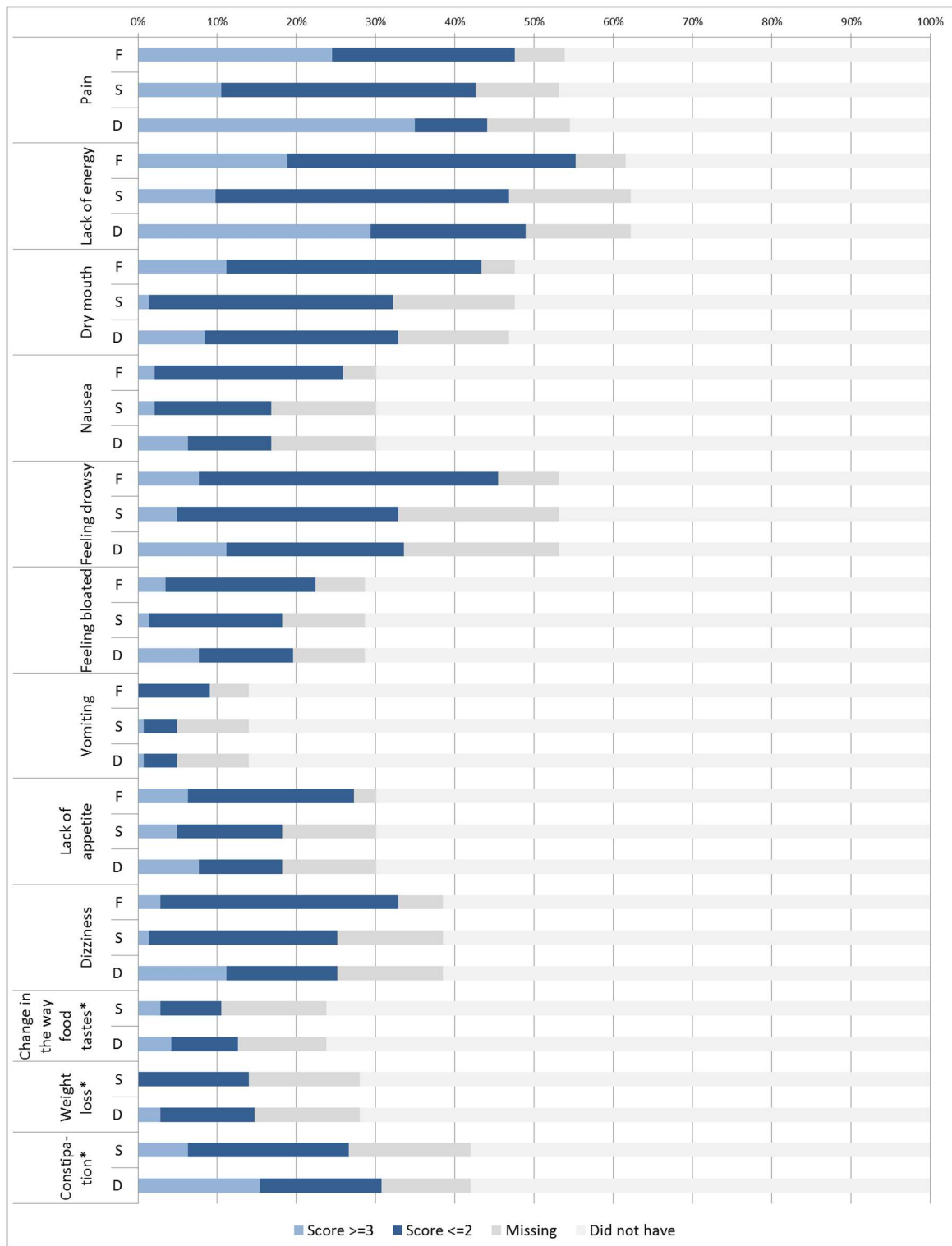
Figures 6 a-c show the proportions of men reporting high (≥ 3) or low (≤ 2) scores for frequency, severity and distress for each symptom reported in the MSAS. Sexual problems were the problems with highest proportion of ≥ 3 in all three dimensions (frequency, severity and distress). There were generally more missing values in the severity and distress dimensions than in the frequency dimension.



6 a. Proportions of men reporting high (≥ 3) or low (≤ 2) scores for frequency (F), severity (S) and distress (D) for each psychological symptom in the MSAS psychological subscale

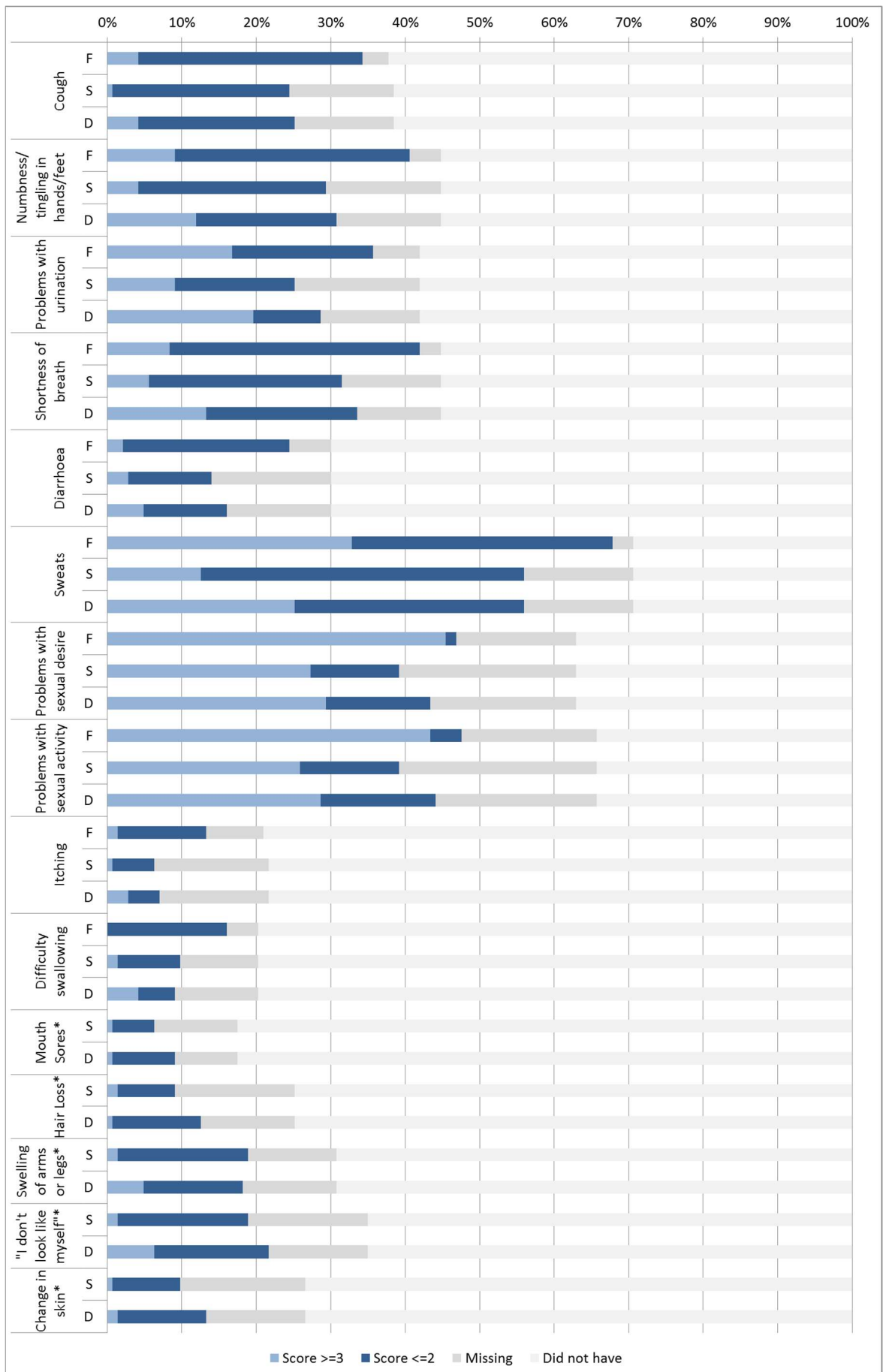
Difficulty sleeping was the psychological symptom with highest proportions in the frequency dimension (Figure 6 a). The severity was relatively low with most men scoring 2 or below. There were more men reporting higher levels of distress than severity, but still almost half of the men scored 2 or below. The second most reported psychological symptom was worrying; however, the frequency severity and distress dimensions were relatively low, with most men scoring below 2 in all dimensions. Quite a few, almost 40%, report feeling sad, but all three dimensions had scores that most often were below 2; just a few percent had high scores on severity, and slightly more, 10%, had high scores on the distress dimension.

More than 50% of the men reported having any frequency of lack of energy and lack of energy was the physical symptom with the most reported frequency, of the 50%, reporting lack of energy, almost 20% reported high levels (Figure 6 b).



6 b. Proportions of men reporting high (≥ 3) or low (≤ 2) scores for frequency (F), severity (S) and distress (D) for each physical symptom in the MSAS Physical subscale

Those reporting levels ≥ 3 in severity were fewer, 10%, while almost 30% reported high scores in the distress dimension of lack of energy. Over 40% of the men reported having any frequency of pain, lack of energy, dry mouth and feeling drowsy, while the most distressing symptoms were pain and lack of energy.



6 c. Proportions of men reporting high (≥ 3) or low (≤ 2) scores for frequency (F), severity (S) and distress (D) for each symptom not in the Physical or Psychological symptoms subscale

Figure 6 a-c. Percentages of men ($n=143$) scoring symptom frequency (F) as “frequently (3)/almost constantly (4)”= ≥ 3 or “rarely (1)/occasionally (2)”= ≤ 2 , symptom severity (S) as “severe (3)/very severe (4)”= ≥ 3 or “slightly (1)/moderate (2)”= ≤ 2 , and symptom distress (D) as “quite a bit (3)/very much (4)”= ≥ 3 or “not at all (0)/a little bit (1)/somewhat (2)”= ≤ 2 with MSAS. Percentages of men not answering the question as well as not having the symptoms are also shown. More than one symptom per man can be scored. Note: * = symptoms without frequency dimension.

Of the symptoms not included in either of the physical- or psychological subscales sweats were the most reported symptom. Almost 70% reported any frequency of sweats, and almost half of them reported high scores (≥ 3) (Figure 6c). This was the symptom, together with sexual problems, in where most men had the highest scores in all three dimensions. Over 30% also had any frequency of shortness of breath, numbness/tingling in hands/feet, problems with urination, and cough. However, the only of these symptoms where more men report higher levels of distress, almost 20%, were problems with urination. The corresponding numbers in the other symptoms was between approximately 5-14%.

In the analysis regarding the association between symptom burden and QoL, an association was found between having high physical symptom burden ($\beta = -0.287$, $p < 0.001$) and global QoL. There was also an association between the use of analgesics ($\beta = -0.153$, $p = 0.021$) and higher PSA values ($\beta = -0.143$, $p = 0.033$) and QoL respectively (Table 3). The multivariable linear regression model was statistically significant ($R^2_{adj} = 0.407$, $p = 0.001$).

Table 3. Adjusted regression coefficients with 95% confidence interval (95%CI) for associations between QoL and symptom burden adjusted for PSA and analgesic use.

Variable	Regression Model			
	B	95% CI	β	p
Global QoL [constant]	82.509	[76.76, 88.26]		
Number of symptoms	-.171	[-.675, .333]	-.055	.503
Physical symptoms	-24.363	[-32.175, -16.555]	-.287	<.001
Psychological symptoms	-.688	[2.650, 5.522]	.019	.820
PSA (ng/ml)	-.015	[-.028, -.001]	-.143	.033
Analgesic use	-6.767	[-12.486, -1.048]	-.153	.021

6.4 STUDY IV

In study IV, 131 men who had returned at least two questionnaires were included and in total the men returned 557 questionnaires that were included in the analyses. They had an average age of 75.2 (SD 7.0) and 42.7% of the men had elementary school as their highest educational level. Of the men, 73.2% were married/cohabiting and on average 4.7 (SD 4.8) years had passed since the prostate cancer diagnosis. When included in the study, 66.4% (n=87) of the men had bone metastases. As first line of treatment, 64% had a second-generation antiandrogen. Of the included 131 men, just above 60% continued their treatment or ended treatment as planned without progression (Figure 7a), while 38.9% had a progression during follow-up, and 31% of them changed treatment up to two times. Treatment changes are shown in Figure 7 b. Docetaxel was the drug most commonly used as a first line treatment and most changed to enzalutamide as a second-line treatment.

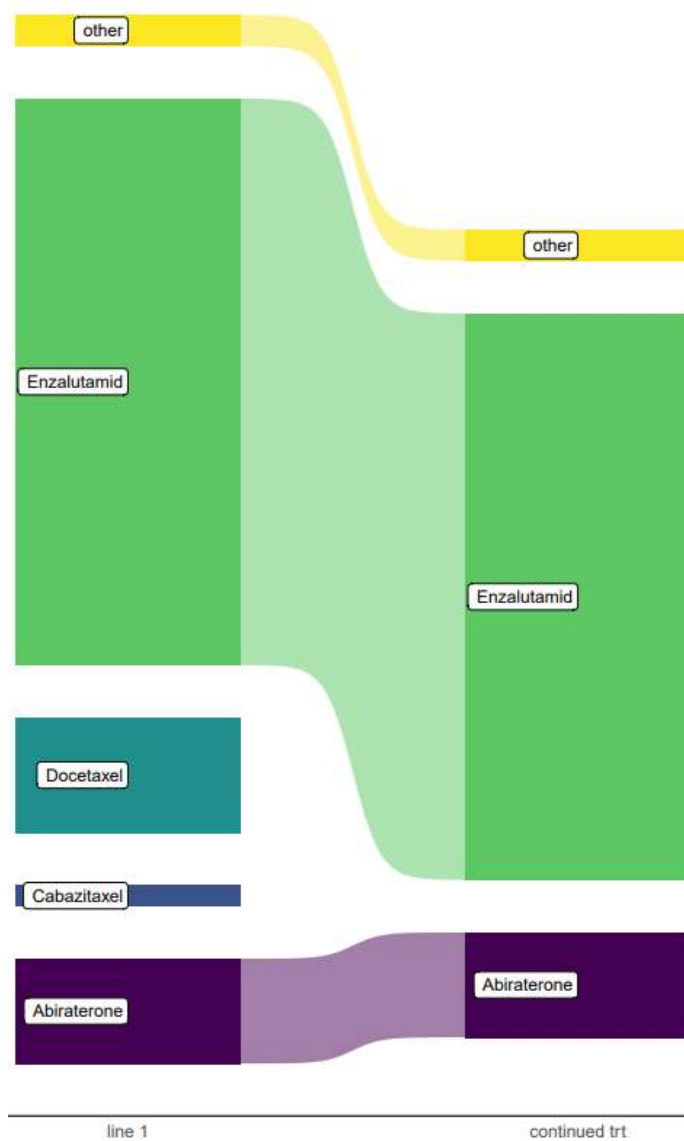


Figure 7 a. Treatment regimen the first year for the 80 men without progression, who continued or completed the planned treatment. Note: in “other” treatment is study treatments including enzalutamid and study drug/placebo.

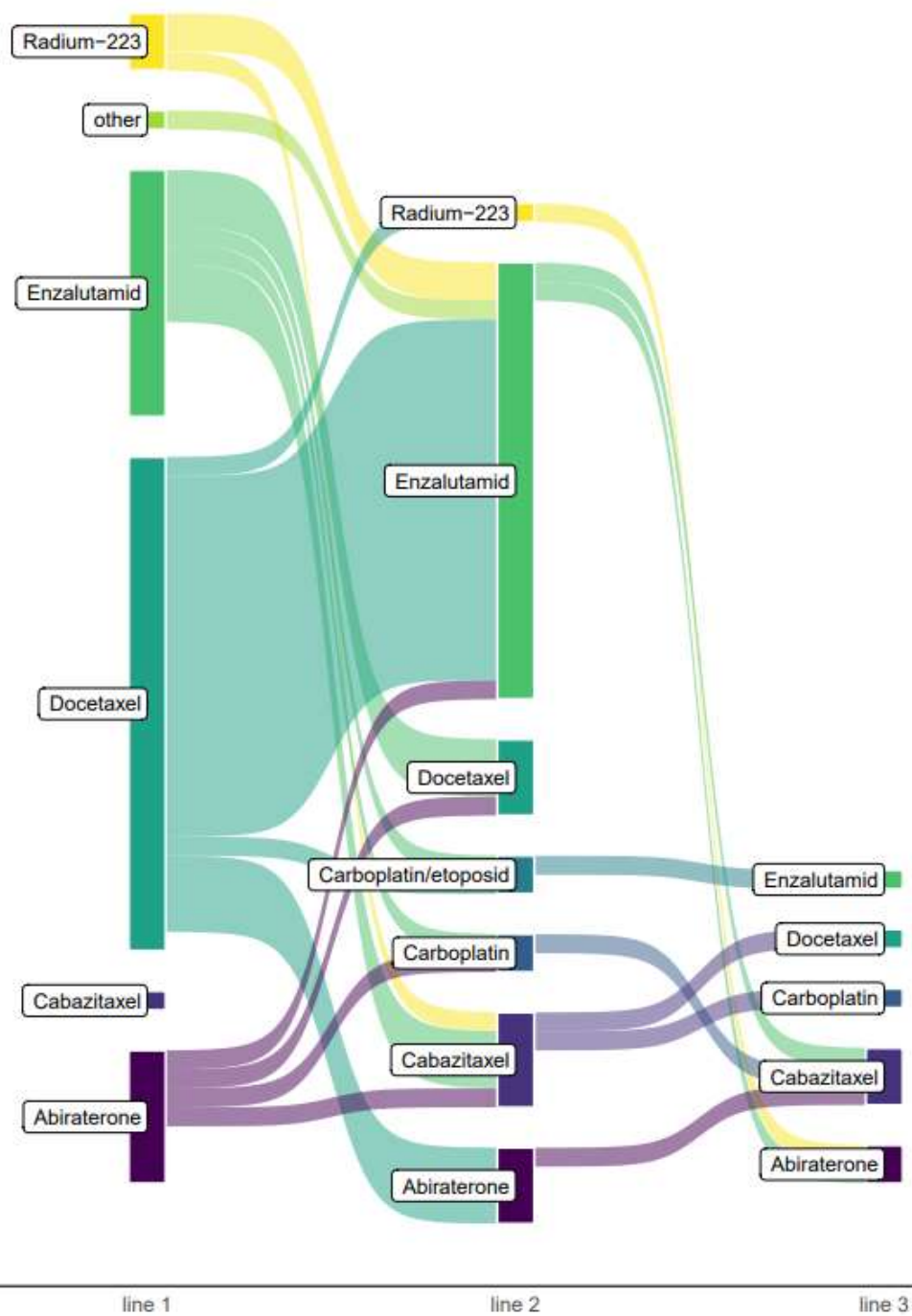


Figure 7 b. Treatment trajectories of the 41 men who switched treatment during the first year due to progression, and the ten men who terminated treatment after progression. Note: in “other” treatment is study treatments including enzalutamid and study drug/placebo.

The men had an average of 10.60 (SD 7.26) symptoms at inclusion and 12.40 (SD 7.94) symptoms at t5. The symptoms reported by 50% or more of the men at any time point are illustrated in Figure 8. Sexual problems were the problems with highest mean scores in all dimensions, and the frequency and severity scores were higher than the distress scores. For problems with sexual interest the mean scores for frequency and severity were 3.78 and 3.08 respectively at t1, and 3.43 and 3.17 at t5. The distress scores were lower with 2.80 at t1 and 2.5 at t5. For problems with sexual activity the mean scores for frequency and severity were 3.70 and 2.91 at t1, and 3.64 and 3.20 at t5. The distress scores were 2.70 at t1 and 2.54 at t5.

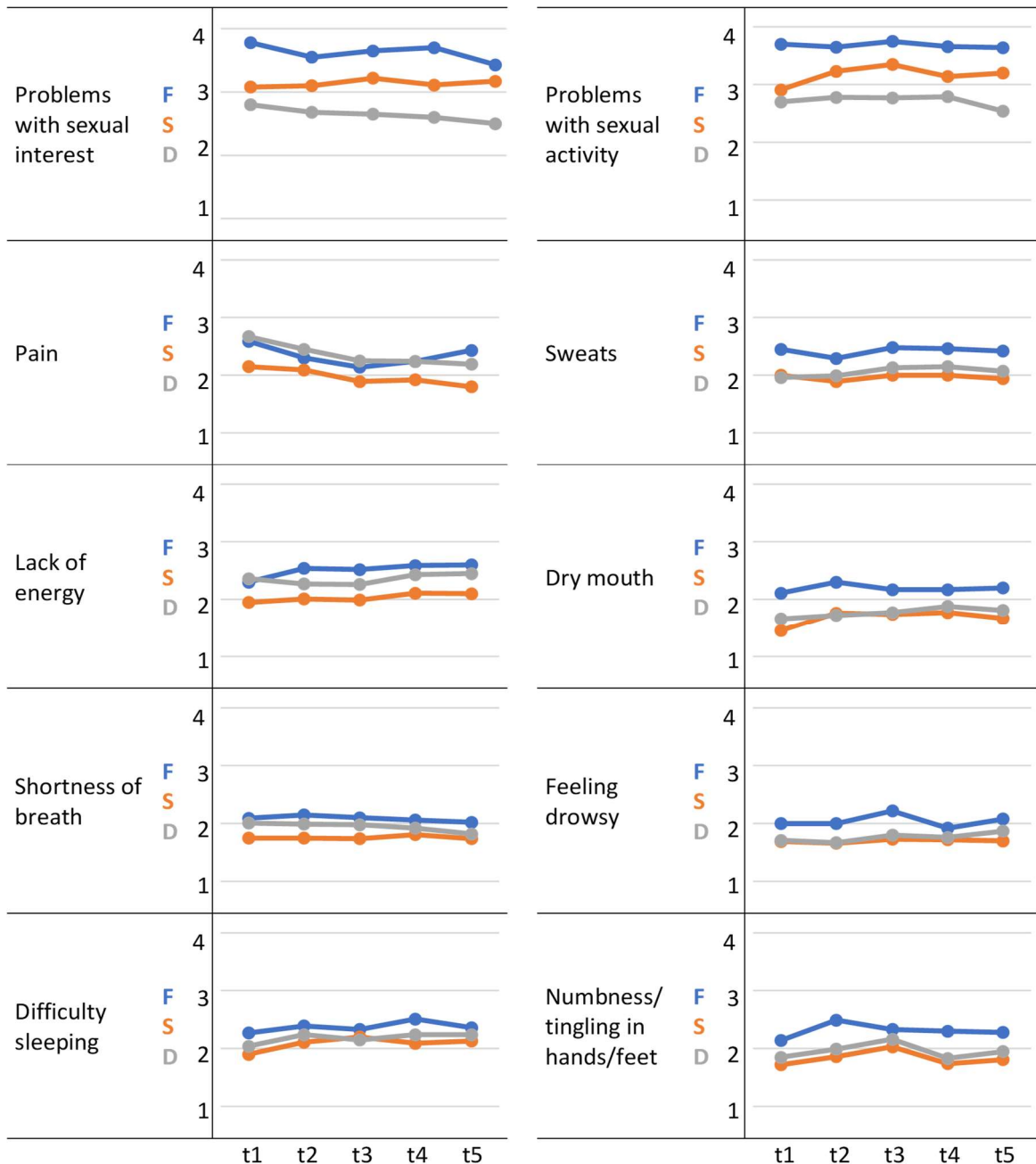


Figure 8. Frequency (F), severity (S) and distress (D) for symptoms reported by $\geq 50\%$ of the men at any of the time points t1-t5. Values 1-4 are the mean scores for each dimension (F, S, D), with higher scores showing higher symptom burden levels.

Nine of the ten symptoms were physical symptoms and only one symptom, difficulty sleeping, was a psychological symptom (Figure 8). Difficulty sleeping had a small increase in mean scores over time in all three dimensions. The mean score for frequency was 2.27 at t1 and 2.36 at t5. The severity score increased from 1.90 at t1 to 2.13 at t5, the distress scores increased from 2.04 at t1 to 2.24 at t5. Pain was the only symptom where the mean distress scores were higher than the frequency and severity at the first three time points. The severity and distress scores decrease over time: however, the frequency scores first decreased and then increased. Of the men, 47.3% reported pain at inclusion, and 69.4% of these used analgesics.

There was a significant change in physical symptom burden over time. The LMM test of fixed effects showed a significant increase from t1-t5 ($F=2.59$, $p=0.01$), in other words a worsening of the physical symptom burden was seen. Having elementary school as highest educational level was significantly associated with the change in physical symptom burden ($F=5.79$, $p<0.01$), as were having analgesics at t1 ($F=4.15$, $p=0.04$).

7 DISCUSSION

This thesis studied different aspects of signs and symptoms in relation to the progression of the disease in men with advanced prostate cancer. Below the results are discussed in sections starting with *The importance of signs*. Thereafter, *Symptoms and symptom burden*, and lastly *A palliative approach in progressive prostate cancer* will be discussed.

7.1 THE IMPORTANCE OF SIGNS

Signs such as the PSA value affect men with prostate cancer emotionally. The results in study I show that the odds of reporting distress were higher, the higher the PSA group. This has also been found as incidental findings in interview studies, where an increasing PSA value induced distress (55, 56). For example, men described that they experienced more worry and fear of death before an appointment with their physician when PSA would be discussed, than when their cancer was initially diagnosed (56). In study II the men described that signs, such as PSA, could generate worry and fear about progression if they were rising. But they could also ease worries that the disease had progressed, for example when symptoms had occurred or worsened, or in the absence of symptoms when the man was uncertain of whether the disease had progressed. This has also been described by Burbridge et al. (55) in that the men felt more worried when their PSA values were increasing and felt more hopeful when the values decreased. The PSA anxiety described by Roth and Passnik (57) may be considered similar to the distress, worry and fear that are shown in the results in study I and II. PSA anxiety was also one of the psychological concerns illuminated in the conceptual framework presented by Eton et al. (77). In the preparatory work for Eton's framework, PSA anxiety was also graded high by the interviewed men as an issue of importance for QoL, as was distress.

When men with mCRPC are receiving life-prolonging treatments, PSA tests are taken, but the value is only one of several parameters used in evaluating the treatment. In study II the results show that in the beginning of receiving life-prolonging treatments, increasing PSA values were the most important sign, one that the men followed carefully to know if a potential progression was approaching. However, from a clinical perspective the PSA value may lose some relevance in the advanced stage of the disease. Other factors, such as symptom burden, QoL, and/or psycho-social factors are assigned more importance in treatment decisions and evaluations by the treating physician (3, 5) but it may be difficult for the men to understand and adapt to this shift. It has been shown that some men have limited knowledge about how the disease progresses (52). Further, the results in study II showed that some men expressed that the only way to get information about a possible progression was by interpreting the PSA. They used the PSA-values as a way to make sense of their situation. This may indicate a need for improvement in information, both regarding the progression but also the markers of progression and that it is not only the PSA value that is of importance.

Many of the men were preoccupied by the PSA values irrespective of if they had terminated or changed treatment due to progression. PSA was shown to be the marker most men associate with progression, which has also been shown in previous studies (59, 60). For some

of the men in studies II-IV, the first line of treatment continued, while for others only a first line of treatment was given before a decision to terminate treatment. For others up to three lines were given during the first year. In other words, several of these men (38.9%) had a progression of the disease during this period. It was only 7.6% who terminated treatment for good during the first year. The men who changed treatment due to progression may still have a hope that the treatment could stabilize the disease and perhaps that there were more treatments available in case of progression. In women with advanced breast cancer receiving chemotherapy, hope was described as long as treatments were being given (125). It is possible that these men with advanced prostate cancer also experience hope as long as they are receiving treatment. It is also possible that a longer follow-up with more men having progressions for which no treatments are available would show changes in their perceptions in relation to PSA. However, even if the disease was considered stable the men were preoccupied with the PSA values, as shown in study II.

7.2 SYMPTOMS AND SYMPTOM BURDEN

For health care professionals to be able to manage symptoms, it is crucial that they have knowledge about which symptoms the men have, but also which symptom they experience as the worst. The men report more physical symptoms than psychological symptoms. This applies to start of treatment as well as during the follow-up period. The only psychological symptom that was reported by more than 50% of the men was difficulty sleeping.

The symptoms reported by most men both at start of treatment and during the follow-ups were problems with sexual activity, problems with sexual desire, lack of energy, sweats and pain. The high occurrence of sexual problems and sweats was expected since the men were castrated, either medically or surgically. What was more surprising from a clinical perspective was that the men scored so high on severity and distress for sexual problems, even if the distress scores were lower than the frequency and severity scores (study IV). At inclusion the frequency score for problems with sexual interest were 3.78 while the severity score was 3.08 and distress score 2.8. Earlier studies of men after radiotherapy show that the men's responses to sexual problems vary: some men took the problem in stride and expressed that it was nothing to worry about at their age, while others expressed a loss of manhood (126). In study II many men also described that they did not have a sex life due to the castration but that it was not a problem in their age. An interviewee in study II also expressed worry for the impact on the partner, and since over 70% of the men in all four studies had a partner, this may be another explanation for the severity and distress experiences. Chambers et al. (48) also found that the inability to have sex generated distress for some men, while other men focused more on expressing intimacy in other ways. It has also been shown that many men between 70-79 years old in the general population report reduced sexual functioning (127) which may be a reason to why the older men express that sexual problems may be expected, and are not seen as a major problem.

Together with sweats, lack of energy was the most reported symptom at every time point. This is also in line with a large survey on men with metastatic prostate cancer where fatigue

was the symptom most men reported (73%) (128). In the MSAS questionnaire the concept lack of energy is used, which could be considered equivalent to, or a part of, the fatigue concept (129). Fatigue has been defined as “a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning” (130, p.1014). Fatigue has also been described as one of the most common and distressing symptoms of cancer and cancer therapy (131). In study II the men described a fear that was related to fatigue and the interference with functioning in terms of being dependent on others. In study IV, the levels of the three dimensions of lack of energy were fairly stable over one year, although a small increase was seen. Fatigue together with pain has been reported to be a prioritized health problem for men with CRPC (132). The observation that men in a castration-sensitive phase rank other issues such as sexual problems higher, shows a change in the relative priority of the impact of symptoms between different stages of prostate cancer (132).

Pain was a symptom commonly reported by the men. At inclusion in study III, 50.3% of the men reported pain, and of these, 63.9% were using analgesics. In study IV, 47.3% of the men reported pain at inclusion and of them, 69.4% used analgesics. Pain was also the only symptom for which the men rated higher levels of distress than frequency and severity at most time points (study IV). However, there was a slight decline of the severity score over time although the frequency score increased at the two last time points (t4-t5). Pain is a well-recognized symptom in this group and may be related to bone metastases (133). The fact that around 50% of the men reported pain at inclusion, and that the frequency scores for pain increased may indicate that pain management was not sufficient. Drudge-Coates et al. (128) describes that some men have difficulties talking about pain with their health care professionals. Some men in their study also reported that they would fear a progression of their cancer if they recognized that they had pain. The theme *Symptoms triggering thoughts about disease progression* in study II similarly describes that more pain or pain at a new part of the body made the men worry about disease progression. Some of them related the pain to progression because they had experienced bone pain when the prostate cancer was diagnosed, and hence associated pain with progression. Guidelines also state that new pain should be investigated to clarify if there is a progression of the disease and if a change of treatment is needed (134).

It was surprising that psychological symptoms did not occur so frequently in study III and IV, while in study I, 53% reported having distress at least sometimes. The latter results are more in line with previous studies of metastatic prostate cancer, where it has been shown that distress, in terms of anxiety or depression, is frequently reported (55, 76, 89, 90). In study III and IV difficulty sleeping was the only psychological symptom among the top reported symptoms. Sleeping problems have also been reported in previous studies (132, 135). When men with mCRPC were asked to prioritize health problems, sleeping came in 6th place, after both pain and fatigue (132). In study IV the frequency, severity and distress dimension for sleeping difficulties had a slow increase in mean scores over time, indicating

a slow worsening. In the interviews in study II, the men did not talk explicitly about being worried, anxious or depressed but rather described that they were pondering and especially at night. This may of course be related to the sleeping problems and worrying, even if they did not explicitly mention feeling depressed or having anxiety. One can speculate that the reason for the slow increase in sleeping difficulties over time may be worry, and that it may be related to a progression of the disease. It is also possible that the men who had terminated treatment or changed treatment because of progression felt more distressed and therefore did not sleep as well. It would have been interesting to study the development of sleeping difficulties, as well as other psychological symptoms such as worry and sadness, over a longer time, when more of the men would probably have had a progression. Psychological symptoms have been shown to be more prominent in patients with a higher number of symptoms as measured with MSAS, than in patients with fewer symptoms (35). In study IV, it was shown that psychological symptom burden did not change significantly over time, probably because of the few psychological symptoms and the slow worsening in sleeping difficulties.

A large number of symptoms were reported over time. The actual numbers of symptoms (study IV) increased from 10.6 on average at start of treatment (study III, IV) to just under 12.4 at the last time point (t5) although the change over time was not significant. At t2-t5 there were men who experienced all 33 symptoms. This may in part be due to treatment side effects, especially for the around 30% of the men who started chemotherapy as a first line of treatment. For them the side effects may have risen by the first follow-up, at approximately 3 months after treatment start. As mentioned above, in study II, certain symptoms, especially pain, raised thoughts or fear that the prostate cancer was progressing (study II). This was often related to symptoms that the men experienced at the time of their diagnosis and that appeared again, but also if present symptoms worsened, or new symptoms appeared. Certain symptoms experienced during treatment were also interpreted by the men, both in relation to the effect of treatment but also to a potential progression. Gilbertson-White et al. (35) have shown that a high number of symptoms may be an important factor to take into consideration when studying QoL in groups of patients with advanced cancer. They describe that in the group with high number of symptoms (12 or more) more psychological symptoms appeared among the top 12 symptoms, specifically feeling nervous, feeling irritable, sad, and worrying. In the group with fewer symptoms (under 12) the only psychological symptom present was difficulties sleeping. One may speculate that among the men with a high number of symptoms, more thoughts about progression with subsequent FoP were present. Even if the results in the thesis did not show any significant changes over time regarding number of symptoms, a goal of reducing the number of symptoms experienced in a symptom management approach may be beneficial.

Physical symptom burden was associated with QoL in study III where worse symptom burden gave poorer QoL. It was also the only symptom burden measure with a significant change over time (study IV), since neither psychological symptoms, nor the number of symptoms changed over time (study IV). The MSAS-PHYS and MSAS-PSYCH subscale

means were relatively low in our study compared, for example, to those for patients with head and neck cancer undergoing radiotherapy (136), or with colorectal cancer undergoing chemotherapy (137). However, the range was relatively wide with MSAS-PHYS scores up to 2.06 and MSAS-PSYCH up to 3.20, out of a maximum of 4. Men with higher MSAS scores are probably more affected by their symptoms and may have a greater need of supportive care; for example, the study by Holm et al. (47) reports possible unmet needs regarding symptom management and QoL for men with metastatic prostate cancer.

7.3 A PALLIATIVE APPROACH IN PROGRESSIVE PROSTATE CANCER

The men interviewed in study II were all well aware of the fact that they had an incurable disease. Worsening of both symptoms and signs, mostly in the form of PSA, made the men think about progression. This included thoughts about the remainder of life and about the actual death and the process of dying.

The results in this thesis can be applied to the conceptual model of a palliative approach proposed by Touzel and Shadd (39). They suggest that a palliative approach can be provided in any setting, including – as in the context of this thesis – the oncology outpatient setting. The approach can be applied at any time in the disease trajectory, in any disease and by anyone with basic knowledge in palliative care. All three parts of the model; – Mortality acknowledgement, Focus on QoL, Whole person care – needs to be present for the care to qualify as a palliative approach according to the model.

A palliative approach should be implemented early in the cancer disease trajectory. ASCO guidelines suggests introduction within 8 weeks from diagnosis of an advanced disease (38). Swedish National guidelines for palliative care (40) also mention an early integration, although there is no predefined timeframe. This corresponds with the new palliative care definition where palliative care can be implemented in parallel with life-prolonging and symptom-relieving treatment (37). In Sweden men with an advanced prostate cancer undergoing life-prolonging treatment usually attend an outpatient oncology ward. These outpatient wards may seldom employ health care professionals specialized in palliative care but rather a multidisciplinary team with the ability to perform basic palliative care.

An adapted model as shown below (Figure 9) based on Touzel and Shadd's (39) model may help patients if applied early in the disease trajectory. The focus needs to be on the man's unique situation regarding cognitive ability, social support, experienced symptoms and also how well he understands or feels uncertain about his situation. In the middle of the adapted model are the three core concepts, Focus on QoL, Mortality Acknowledgement and Whole-person care.

In *focus on QoL*, the care aims to optimize the patient's well-being, functional status and comfort (39). The goal of palliative care is to enhance QoL, among other things by reducing distressing symptoms (37). The men report a symptom burden especially from physical symptoms (studies III-IV). An increasing number of symptoms may induce an uncertainty and the men in study II interpreted certain symptoms as related to a progression of the

disease. Having more symptoms has been found to be associated with greater uncertainty about the illness (101). Some men made interpretations of whether the treatments had effect or not depending on earlier experiences. If the interpretations were not accurate it may also cause uncertainty and unnecessary distress. Guan et al. (100) suggest that decreasing illness uncertainty may improve the QoL of men with prostate cancer.

In *mortality acknowledgement*, limited lifespan, death, and dying are addressed (39). The men with mCRPC have a limited lifespan and are already in a progressive phase when they start treatment, as in studies II-IV. The signs and symptoms may induce a FoP as the results in study II show. Higher PSA values were associated with higher distress (study I). The men probably associated higher PSA values with more advanced disease and/or to a progression of the prostate cancer. Higher PSA levels have been found to be associated with greater illness uncertainty (101).

In *whole-person care*, psychosocial, emotional, and spiritual domains, as well as social and/or existential issues are addressed (39). In study I, higher PSA was associated with higher likelihood of reporting distress. However, marital status was also associated with distress, in that men living without a partner had higher odds of experiencing distress. Psychological distress has been shown to be higher in unpartnered men than in married men, although married men with low partner support also experience distress (93). Guan et al. (101) describe that social support reduced the men's uncertainty over time. The results in study II showed that the men's experiences of signs and symptoms in relation to a FoP induced uncertainty.

The adapted model in Figure 9 also suggests that the three dimensions of a palliative approach are somewhat intertwined: symptoms and symptom burden may trigger a FoP, causing an uncertainty about what will happen, which in turn may generate distress. Thus, decreasing uncertainty may improve QoL. If basic palliative care at an oncology outpatient ward addresses uncertainty through symptom management, psychosocial support and by understanding the men's interpretation of signs and symptoms with regard to progression, it may improve their QoL and reduce their uncertainty. All domains of the conceptual framework of Eton et. al. (77) (Figure 2) are covered within the adapted model. It takes into account both *symptoms of disease* and *side effects of treatment*, which for the individual patient may be difficult to separate from each other (27). Further, *QoL* and *psychological concerns*, are addressed, where PSA anxiety lies within the psychological concerns domain and distress and global QoL are within the QoL domain.

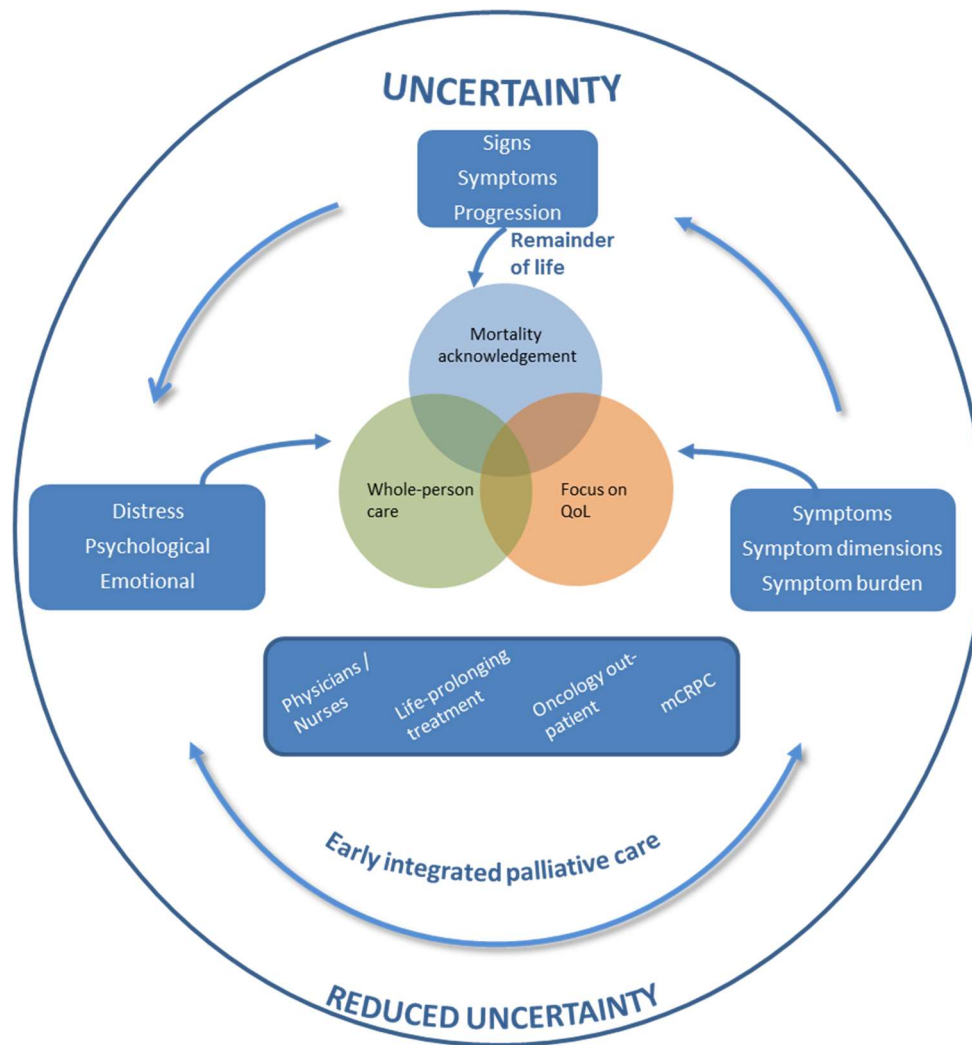


Figure 9. A modified model with the basic structure adapted from *Content Validity of a Conceptual Model of a Palliative approach*, (39), together with the results from this thesis reflected through Mishel's (99) *Uncertainty in illness theory*.

This adapted and modified model may be of use for the multidisciplinary team at oncology wards in meeting these men. Knowledge about the present symptoms and the change over time, as well as how the men interpret both signs and symptoms may also help the team to communicate with and support them.

7.4 METHODOLOGICAL CONSIDERATIONS

In order to reach the aim of this thesis four different approaches were used: a qualitative longitudinal study as well as cross-sectional and longitudinal quantitative studies. Using different study designs and methods should be considered a strength to reach the overall aim of this thesis. The included studies were based on two different cohorts. In study I, the survey of members of SPCF, there was no distinction between those who were and were not curable; however, the men with high and extremely high PSA most probably had advanced disease. Studies II-IV were from the PROCEED project and all men were in a mCRPC phase. The strengths and limitations of the different studies will be discussed below. First considerations regarding the quantitative studies, I, III and IV will be discussed and then considerations regarding the qualitative study II.

7.4.1 Quantitative methodological considerations

7.4.1.1 Sampling

Convenience samples were used in all three quantitative studies (I, III and IV). Using the members of a cancer association as basis for participant sampling, such as the members of the SPCF in study I, may be considered a risk for selection bias due to the potential selections of persons attending patient organizations. However, in previous studies, where data from prostate cancer associations have been used and in these studies disease status, symptoms and QoL have been shown to correspond well with the wider prostate cancer population (138-140). The large sample could also be considered a strength.

A power analysis was conducted for the overall PROCEED project (study III, IV) based on estimated values for clinically relevant changes in the FACT-G questionnaire (110), which is not used in any of the studies in this thesis. The decision to use the FACT questionnaire as basis for the power analysis was motivated by the existence of measures of clinically relevant changes over time, which was not available for the MSAS instrument. Based on this, 120 to 150 participants were estimated to be a sufficient sample to analyze clinically relevant changes over time.

In the overall project, 154 men were included. However, some (n=5) dropped out already before the first questionnaire. The reason for this is not known, but it can be speculated that the men felt that the questionnaire was overly extensive. Henoch et al. (141) mention in their discussion that when given an extensive questionnaire requesting assessment of symptoms in several dimensions, severely ill patients with a life-limiting disease may feel that they want to focus on other things. Over the study period in studies II-IV, some men also terminated their participation, some of them died, while others did not return the questionnaires without giving a reason. Attrition is common when performing studies on severely ill persons. For example, in a global study aimed at analyzing predictors for dropouts among patients with advanced cancer, the attrition rate was 33%. The strongest predictor was weak baseline performance status, but higher physical symptom burden, and shorter time from the cancer diagnosis were also predictors (142). A possibility is that the men who dropped out in studies I, III and IV had the worst health condition and thus also had a higher symptom burden in comparison to those who remained in the study. If this is the case the results regarding reported symptoms, symptom levels, and symptom burden are underestimated. Even if a sampling bias may be considered a limitation, it is important to offer persons with advanced disease an opportunity to participate in research.

Although there were relatively few inclusion and exclusion criteria in studies III and IV, to enhance the real-world approach, there are limitations to consider. First, the exclusion criterion of speaking Swedish meant that, there were few participants included that were born outside of Sweden which does not correspond with the prostate cancer population in Sweden.

Second, during the inclusion period from 2015 to 2022 the treatment options increased rapidly, and other studies, often treatment-related-, competed for inclusion of patients. This

resulted in the men in our sample being somewhat older than in the general prostate cancer population. Consequently, they were not candidates for all types of treatment and may have been excluded from some clinical trials. At the same time, a somewhat older sample may be considered a strength since this group of men have been sparsely represented in previous research and are for example often not included in clinical trials with narrower inclusion criteria. Further, the men were from different hospitals, both university and county hospitals, from rural and urban areas, and represented a wide range of age, education and marital status, which should be considered a strength.

7.4.1.2 Data collection

In study I the questions used for distress and QoL were not validated, which may be a limitation. The question measuring distress was “Do you have any problems with worry/anxiety/feelings of depression?” with the response options “Never”, “Sometimes”, “Often” and “Always”. The question used may however be seen as covering most distress related symptoms. Based on the results from study II, where the men were more likely to talk about “pondering” and not about anxiety or depression it is possible that it was easier to answer a broad question about problems with worry, anxiety or feelings of depression than a narrower, more specific question. One can discuss whether the questions regarding psychological symptoms were accurate enough, as mentioned above, but for study I the question probably captured the desired information. For studies III and IV, in the MSAS, the men were asked if they had any of six predefined psychological symptoms and to report the frequency, severity and distress of the symptoms that then were calculated into a subscale. It is a possibility that the men did not acknowledge that they for example felt worried or sad. In the qualitative interviews, many men expressed that they were pondering, and some said that they felt a bit worried – in many cases worried on the behalf of their families.

The MSAS instrument was used in both study III and IV. The instrument has been used in different cancer populations (104, 113, 137). It has also been used in longitudinal studies with newly diagnosed prostate cancer patients, but not in late phase of the disease (143). It may be a limitation that the instrument has not been used in a population of men with mCRPC such as in study III and IV. However, the MSAS has been used in later phases of other types of cancer and in end-of-life care (144). The validity and reliability of the Swedish version of MSAS, were tested in a group of women with breast cancer who were receiving adjuvant or palliative treatment (104). The MSAS has also been used longitudinally in a group of Swedish patients with colorectal cancer (137).

The MSAS is designed so that the different dimensions are answered in a row after each other. The highest number of missing values were in the severity and/or distress dimensions which are located last in the row. Therefore, these missing values might be attributed to some participants not knowing how to answer the questions. It is possible that these missing answers could affect the results. However, the missing values in the MSAS were managed according to the guidelines (105) which describe how to manage some of the problems with

missing data: symptoms for which at least two dimensions have answers are included in the calculation of subscales.

The questions regarding problems with sexual interest and sexual activity were the questions with most missing answers. This may be related to the fact that all the participating men were castrated, which may have led some to think that the questions were irrelevant. Many men had written comments to the questions, such as: *not relevant, does not work, do not have a sex life*. Another reason for missing responses may be the intimate nature of the questions. These were, however, the questions with the highest scores in all three dimensions. If more men had answered these questions, the scores would possibly have been lower, nevertheless, more than 50% of the men had problems with sexual interest and sexual activity, and were distressed by it.

In study I the medical data regarding the men's PSA values and treatments were self-reported and were not possible to confirm which may affect the data quality. In studies II-IV. the medical information was collected from the men's medical records and was monitored, and quality assured by an independent monitor. This procedure ensured high quality on the medical data collected.

7.4.2 Qualitative methodological considerations

Regarding the longitudinal qualitative study II, it is considered a strength to do longitudinal interview studies to cover experiences over time (102, 112). Several of the participants were not interviewed more than twice, which may be seen as a limitation. However, the disease trajectory of these severely ill men, was captured from the start of life-prolonging treatment until a decision to terminate treatment, for some of them with up to five interviews.

To achieve trustworthiness and clarify transferability, the methods have been thoroughly described. By interviewing the same man several times, a trustful relationship may be achieved in which the participants are more forthcoming in later interviews. This often generates more and better data and the sample need not be so large (122).

The sampling strategy in study II was purposeful, striving for maximum variation. In many aspects the variation strategy was successful, although a larger proportion of the men in this group started chemotherapy in comparison to the men in studies III and IV. In this aspect the sample may, on the other hand, be more comparable to the prostate cancer population overall, as the men in studies III and IV tended to be a bit older and not fit for chemotherapy. About half of the men lived in rural areas and the other half in urban areas. This may give insights into both the experiences when living close to the hospital, and when having a longer way to the hospital, and perhaps also not having neighbors close by. The experiences might probably have been more varied if men from outside Sweden had also been interviewed. In terms of transferability, the results may be transferable to the older group of men with advanced prostate cancer but the transferability of results in relation to a larger multicultural population may be done with caution.

To help ensure credibility, several actions have been taken. First, an interview guide was used to make sure that all topics were covered in the interviews. Second, all interviews were audio recorded and transcribed verbatim. Field notes were written after each interview to document the atmosphere and immediate thoughts that arose. In the analytical process the codes and interpretation of the data were discussed within the research group. This investigator triangulation (122) was done to avoid biased decisions based on the preconceptions of the first author. The first author is an oncology specialist nurse with long experience of caring for men with prostate cancer, which may affect the interpretation of the interview data. To avoid this, reflexive strategies – such as discussions regarding preconceptions – took place in parallel with data collection, coding, interpretation and in writing the results and discussion.

In order to confirm the results, the over arching theme and the subthemes were discussed within a multi-professional group consisting of an oncologist, a psychologist, contact nurses and research nurse at an oncology department.

8 CONCLUSIONS

The results presented in this thesis may contribute to a deeper knowledge and understanding regarding experiences of signs and symptoms among men with advanced prostate cancer. The studies are, to our knowledge, the first specifically aimed at studying signs and symptoms in this group.

To be able to support these men, who are living in an uncertain illness situation with progressing advanced prostate cancer, it is important to know that the men use signs and symptoms in different ways to make sense of their situation. It is also important to communicate about signs and symptoms, both within the team around the patient, but also with the men themselves. This, since they use signs and symptoms to understand what is going on with the disease in their bodies but also to evaluate how the treatment works. Misunderstandings or misinterpretations may cause unnecessary distress and reduced QoL.

Many of the men were preoccupied with the PSA values as the sign that they described as most important, and that was also causing distress. This may indicate a need for improvement in information, but also about the changed importance of signs as basis of decisions about starting, continuing or terminating of treatment, and that it is not only the PSA value that is of importance in this late phase of the disease.

The men also experience several symptoms, mostly physical, which were worsening over time. Sexual problems as well as pain and fatigue were common. Sexual problems may need to be acknowledged more, and even if the physical causes of the problems are difficult to resolve, there may be other ways to support the men and their partners to handle them.

Psychological symptoms were not so commonly reported in the questionnaires, even though the men in the qualitative study described an uncertain situation in relation to both signs and symptoms, and the men in Study I reported higher distress when the PSA values were higher. It is possible that different ways to measure psychological symptoms are important for finding men with psychological concerns. Even if they are difficult to catch with structured measures, it may be of value to raise these questions with the men, and also to have an understanding that they may express themselves in other words than in terms of for example depression, worry and fear. To be aware of the men's social situation may also be an area where added support could benefit men living alone.

Symptom management is important in order to attain the best possible QoL for these men. A structured symptom assessment may be of value. Enhancing QoL is also the main goal for palliative care, and a palliative approach early in the disease trajectory in the oncology outpatient setting could benefit these men.

9 FUTURE PERSPECTIVES

The results in this thesis have clarified some of the ways men with advanced prostate cancer perceive signs and symptoms. Nevertheless, the studies have also raised some questions for further research. First, the results regarding experienced symptoms in studies III and IV would be interesting to elaborate and deepen through in-depth interviews based on these findings. Additional qualitative findings regarding symptoms, symptom burden and the experiences in relation to the three –dimensions, frequency severity and distress – would enhance the value to the results from this thesis.

In the interviews the men described different strategies to cope with the disease and to prepare for further progression, hence it would be interesting to analyze the interview data from this angle.

It would also be interesting to study PSA anxiety using a more specific questionnaire and also view it in relation to PSA values measured at the time when PSA anxiety was reported.

Lastly, more than half of the men in study IV did not have a progression during the one-year follow-up. Thus, it would be interesting to follow the symptom burden, symptom occurrence and symptom dimensions over a longer time period.

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