







ORIGINAL ARTICLE

Signs and symptoms in relation to progression, experiences of an uncertain illness situation in men with metastatic castration-resistant prostate cancer—A qualitative study

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Abstract

Objective: Signs and symptoms are important in monitoring prostate cancer, but there is a lack of understanding about the men's interpretation of signs and symptoms in relation to disease progression in advanced phases of the disease. The aim was to illuminate the experience of signs and symptoms in relation to disease progression in men with metastatic castration-resistant prostate cancer (mCRPC).

Method: Thirty longitudinal interviews were conducted with 11 men undergoing life-prolonging treatment for mCRPC. Conventional content analysis was used.

Results: The results illuminate an uncertainty that the men experience when interpreting signs and symptoms. The overarching theme was *The experience of an uncertain illness situation within the framework of progression*, with four subthemes: *Symptoms triggering thoughts about disease progression; Making sense of signs, also in the absence of symptoms; Making sense of symptoms during treatment; Progression triggering thoughts about the remainder of life.*

Conclusion: In the uncertain illness situation, the men strive to make sense of signs and symptoms based on previous experiences and in relation to disease progression. Understanding the men's perspectives on signs and symptoms in this late phase may help health care professionals communicate about disease progression considering the balance between treatment outcome and quality of life.

KEYWORDS

metastatic castration-resistant prostate cancer, prostate-specific antigen, prostatic neoplasm, qualitative research, signs and symptoms, uncertainty

1 | INTRODUCTION

Globally, prostate cancer (PC) is the second most common cancer, in men (Bray et al., 2018). Bone is the predominant site for metastases (Gandaglia et al., 2015), and once metastases are diagnosed, the

treatment aims to prolong life and/or alleviate symptoms. Over time, the metastatic disease progresses and develops into metastatic castration-resistant PC (mCRPC) where chemotherapy or other life-prolonging treatments may be started. In this advanced phase of the disease, the balance between treatment outcome and quality of life

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(QoL) becomes more important (Chowdhury & Kirby, 2013). Life-prolonging treatment for mCRPC became available in 2004, and overall survival has been extended to over 30 months (Beer et al., 2014; Ryan et al., 2013, 2015; Tannock et al., 2004). Nonetheless, in this late disease phase, it has been recommended that symptom burden, QoL and psychosocial aspects should also be taken into consideration in treatment decisions and in treatment evaluations (Chowdhury & Kirby, 2013; Payne et al., 2012).

Signs and symptoms are important in the monitoring of PC. A clinical sign is an objectively measurable clinical finding (such as prostate-specific antigen-PSA-values and imaging), while a clinical symptom is a finding that is reported by the patient or by someone close to them (Cox et al., 2014) and that may originate from the cancer disease and/or treatment side effects (McClement et al., 1997).

Men with mCRPC experience a substantial symptom burden. Over 40 symptoms from PC or its treatment(s) were described in interviews with men with mCRPC, for example, categorised in groups such as urinary, cognitive and PC related (Holmstrom et al., 2019). When comparing men with mCRPC with men with non-metastatic PC, the men with mCRPC reported worse HRQoL, which was, in turn, related mostly to fatigue, pain and impaired physical activity (Fallowfield et al., 2016). Pain was reported to be the worst symptom by men with mCRPC (Catt et al., 2019).

Signs and symptoms are crucial in monitoring the progression of PC at all stages and PSA testing and PSA values may have an emotional impact on men with PC. It has also been shown that men with newly diagnosed mCRPC attribute great importance to the PSA values as a tool to monitor the disease (Burbridge et al., 2020; Hedestig et al., 2008; Roth, 1996; Torta & Munari, 2009). For some men, a decrease in PSA values was a more important treatment goal than a reduction of symptoms (Lofters et al., 2002). The association between distress and PSA values was also shown in one large cross-sectional study (Ronningas et al., 2019), although further studies are needed to understand the role of PSA values and also the role of symptoms in the late phase of PC.

Even if signs and symptoms are crucial in monitoring the progression of PC at all stages, in the late phases, enhancing HRQoL and managing symptoms may become more important. However, there is a lack of understanding about the interpretation of signs and symptoms in relation to progression of the disease in late phases of PC from the men's perspective. Therefore, this study aimed to illuminate the experience of signs and symptoms in relation to disease progression in men with mCRPC.

2 | METHODS

2.1 | Design

The present study had a qualitative longitudinal approach (Murray & Sheikh, 2006) with a subsample of 11 men from an overall longitudinal, multicentre project, PROCEED (Doveson et al., 2020). In the overall project, 150 men with mCRPC were included at four oncology

departments in Sweden. Inclusion criteria were men who were about to start their first-line treatment for mCRPC and who could understand and express themselves in Swedish.

Two to five recurring in-depth interviews were conducted with each man. There was no predetermined time interval, but all follow-up interviews were conducted in conjunction with a progression of the PC, where the men either started a new line of treatment or had terminated life-prolonging treatments. The average time between each participant's interviews was 8 months.

The authors followed the Guidance on Qualitative Research Reporting Standards (SRQR) to ensure accurate and complete reporting.

2.2 | Sample and procedure

The subsample for the present study was chosen to achieve maximum variation (Patton, 2015) in terms of age, marital status, time since diagnosis, type of treatment and place of residence (rural, urban).

A research nurse/study coordinator at the oncology departments informed the patients about the interview study and asked if they were interested in participating. The research nurse/study coordinator also emphasised that participation and contact with the researchers was voluntary. All participants gave written informed consent to participate. The interviews were conducted over a maximum period of 2 years. All interviews were performed by two of the authors (SD, UR), both interviewers with formal training, RN, PhD students and specialists in oncology or palliative care. The interviews were conducted in a secluded room at the hospital or in the patient's home, whichever they preferred. The follow-up interviews were conducted by the same person to establish a trustful relationship over time (Murray et al., 2009).

An interview guide was used as a foundation for the interviews that started with the question 'Can you please tell me about your situation with prostate cancer?' and then continued conversationally. When necessary, probing questions were used to gain more depth. Interviews were recorded using a digital voice recorder and transcribed verbatim. Field notes were written after each interview.

In total, 30 interviews were conducted, with 11 participants, between late 2016 and 2021 (Table 1). During the 2-year follow-up period, four men died and two declined further interviews after the first follow-up. The interviews lasted between 27 and 108 min (median 55 min, mean 60 min).

2.3 | Analysis

In this study, a conventional content analysis with an inductive approach, inspired by Hsieh and Shannon (2005), was used to analyse data. Due to the longitudinal design, inspiration for analysis was also found in Murray et al.'s (2009) approach, which provides a method to understand experiences over time. The analysis was initiated in conjunction with data collection, which provided an opportunity for

TABLE 1 Participants' performance status, number of interviews conducted and life-prolonging treatments received

Participant	ECOG ^a performance status at first interview	ECOG ^a at last interview	No of interviews	Life-prolonging treatments during follow-up period	Decision of no further life-prolonging treatment	Deceased during follow-up period
1	1	1	2	Docetaxel, enzalutamide		
2	0	1	5	Docetaxel, enzalutamide, cabazitaxel		
3	1	3	4	Docetaxel, enzalutamide, cabazitaxel	Yes	Yes
4	1	1	2	Cabazitaxel, abiraterone		
5 ^b	1	2	2	Docetaxel, abiraterone		
6	1	2	4	Docetaxel, enzalutamide, cabazitaxel		
7	1	2	2	Enzalutamide,	Yes	
8	1	2	2	Radium (Ra-223) diklorid, enzalutamide		
9	0	4	2	Docetaxel, enzalutamide		Yes
10	0	1	2	Docetaxel, abiraterone		
11	1	3	3	Enzalutamide, cabazitaxel	Yes	Yes

^aEastern Cooperative Oncology Group, ECOG (Oken et al., 1982).

^bDrop-out during study period.

follow-up topics of concern in the follow-up interviews. The procedure of working in parallel with inclusion, analysis and follow-up interviews was also used to ensure that saturation was met. When no new information was obtained and no new perspectives occurred when revisiting previous interview topics in the follow-up interviews, the inclusion of new participants ceased (Morse, 2000).

In accordance with the content analysis tradition (Hsieh & Shannon, 2005), interview transcripts were read several times by the first author (UR) to achieve a sense of the content in its entirety. The transcripts were then imported to the NVivo 12 software (QSR International Pte Ltd, Doncaster, Victoria, Australia) for structuring and subsequent coding (UR). All interview text was inclusively segmented based on its content, and each segment received a code that described the core of its content. The entire interviews were coded at this early stage to avoid missing relevant content. In the next step, codes relevant to the aim were conceived in a structured way.

Subsequently, to enhance trustworthiness, the codes were discussed and critically reviewed among the co-authors (the other interviewer [SD] and two researchers in the research group experienced in qualitative analysis [AWL, MH]). These continuous discussions about codes and contents continued until consensus was reached. Then, codes were categorised into clusters dependent on how they were related to each other (UR). Thereafter, depending on the content of the clustered codes, the content and defining features of the sub-themes emerged through discussions between all authors.

First, the transcripts were analysed separately for each participant as a longitudinal single unit (Murray et al., 2009). In the analysis, matrices were used to integrate the longitudinal aspects of the study into the themes, to understand the experience over time for each participant but also the trajectory for each theme (Grossoehme & Lipstein, 2016).

TABLE 2 Socio-demographic factors, times since primary diagnosis and PSA value at time of first interview for 11 men

Age	
Median	75 years
Range	60–89 years
Marital status	
Married	8
Single	3
Residency	
Urban	5
Rural	6
Education	
Elementary school	3
High school	6
University	2
Time since primary diagnosis	
Range	10–122 months
Median	33 months
PSA value	
Range	8.2–425 ng/ml
Median	90 ng/ml

In the final step of the analysis, the subthemes were synthesised into one overarching theme. The themes were further discussed within a clinically active multi-professional group consisting of a medical oncologist, a psychologist, contact nurses in oncology and oncology research nurses.

TABLE 3 Overarching theme with subthemes

The experience of an uncertain illness situation within the framework of progression			
Symptoms triggering thoughts about disease progression	Making sense of signs, also in the absence of symptoms	Making sense of symptoms during treatment	Progression triggering thoughts about the remainder of life

3 | RESULTS

Saturation of data was met, all themes were discussed by every participant and no new information emerged in the final set of interviews.

3.1 | Sample characteristics

The men were 60–89 years old with a median age of 75 years (Table 2). They had an Eastern Cooperative Oncology Group (ECOG) (Oken et al., 1982) performance status of 0–1 by the first interview (Table 1). However, most of them deteriorated to a worse ECOG score by the last follow-up interview. For some men ($n = 7$), only a baseline interview with one follow-up was done, while others were interviewed up to five times, depending on the number of treatments given and whether patients choose to participate in follow-up interviews. Most participants started chemotherapy as their first-line treatment. A few men only received one line of treatment before termination of life-prolonging treatments.

3.2 | Overarching theme: ‘The experience of an uncertain illness situation within the framework of progression’

All men expressed that they were aware of the fact that they had an incurable disease, and the overarching theme in the results was *The experience of an uncertain illness situation within the framework of progression*, with four subthemes (Table 3). The experience of an uncertain illness situation within the framework of progression permeates the men's narratives. Signs and symptoms were described to have different meanings in making sense of this situation, and the meaning of signs and symptoms was interdependent and sometimes changed during the illness trajectory. The theme was related to the men's previous experiences of either the presence of or lack of symptoms and to previous experiences of treatments and their side effects, as well as to progression and the importance and consequences of signs and symptoms of progression. Aspects of the four subthemes were expressed by all men.

3.2.1 | Symptoms triggering thoughts about disease progression

New symptoms, if interpreted by the men as PC-related, induced an uncertainty and triggered thoughts of a potential disease progression. For example, some men expressed that if, or when, new or increased

pain was experienced, they related this to bone metastases. This raised a concern for a potential disease progression of either existent or new bone metastases. One man said:

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).

For some men, the PC had debuted with bone pain and was already metastasised at diagnosis. Pain was therefore recognised as related to PC by these men, even if the symptoms had not been verified as cancer-related. Other symptoms that were also similarly experienced were, for example, urinary problems. One man described that he had problems urinating when the PC was diagnosed. These symptoms decreased when hormonal therapy started so he was worried about a potential disease progression, if symptoms such as pain or urinary problems should occur again:

... [if getting] pain in the back or if one suddenly begins to urinate badly ... (P11).

Another man described that there were no more life-prolonging treatment options available for him and that he knew that there were no more chances at slowing the disease down. Now when experiencing increased pain, he expressed an uncertainty about whether the symptoms were related to disease progression:

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).

This man was not alone in interpreting and trying to explain pain as related to something other than metastases. Even if the men expressed an awareness of the disease progression, they also expressed an uncertainty about how to interpret the symptoms they were experiencing regardless of where in the disease trajectory they were. Their concerns were more commonly expressed in the follow-up interviews, which may be related to an increase in both symptom frequency and intensity the longer they were in the disease.

3.2.2 | Making sense of signs, also in the absence of symptoms

When the men talked about signs, PSA values were expressed as more significant than other signs, such as imaging results; that is, if

an imaging result was good but the PSA was increasing, the imaging results did not relieve their worries. This was also expressed in that they did not understand why an imaging was necessary when the PSA value already had provided an answer, as one man described it:

... and then one can wonder, what is the point in doing a ... a computer tomography, when, when in terms of [PSA] value, it [the treatment] was a complete success (P1).

During the disease trajectory, there was a change in how the men expressed their thoughts about PSA values. In the initial interviews, the goal of achieving a decrease in PSA values was most prominent, while in later interviews, the goal of keeping a stable PSA was expressed. Here, they also sometimes referred to a stable value where previously they had experienced feeling well. One man stated:

... damn you have to be quite satisfied if it's [the PSA] just stable. It's [the cancer] not getting worse, huh (P2).

Some men described not having had any symptoms of the PC during their disease trajectory. The absence of symptoms created an uncertainty of whether the disease was progressing, or not, which increased the importance of the results of signs, such as PSA values. The men expressed that the only way to get information about the disease was through PSA values and other signs, such as imaging results or from the physicians' appraisal. One man said:

... but I really do not know how sick I am actually ... I don't know how it [the cancer] looks, but when receiving a message like this, that the PSA-values ... have gone from 14 to 1, then I assume that the cancer progression has slowed down (P4).

Having to rely on the PSA values in lack of feeling anything from the PC induced a sense of uncertainty of how the disease was progressing, which, in turn, was described as generating distress. The same man also said:

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).

3.2.3 | Making sense of symptoms during treatment

The men mostly talked about symptoms; however, it was clear that what they sometimes meant was side effects. They made their own

interpretations and appraisal about treatment effects based on previous symptom experiences during treatment for PC. Some men expressed that they had symptoms that they perceived as a confirmation that the treatment had the desired effect, and thus, they were not surprised when this was also confirmed by the physician. Consequently, the experienced symptoms could also lead to surprise and disappointment if the treatment did not have the expected effect. Some men also expressed that they did not have any symptoms during treatment, which generated an uncertainty about whether the treatment had an effect or if the disease was progressing. In these cases, the men sometimes expressed surprise if the treatment was shown to have good effect. It was difficult for the men to understand the absence of symptoms in relation to the treatment, as one man stated:

There have to be more effective [treatments]. I didn't feel anything of that treatment either (P6).

During the mCRPC treatment trajectory, the men related their experience of symptoms to previous experiences of treatments and their effect; sometimes this was related to a specific kind of treatment. One example is a man who received chemotherapy (docetaxel) as his first-line treatment of mCRPC with good effect but with a lot of symptoms. When he started another type of chemotherapy, he did not have any symptoms and hence assumed that the treatment did not have any effect. Another man expected to feel sick during his third-line treatment with chemotherapy since he had felt sick during previous lines of chemotherapy:

... and then one feels suspicious and thinks, if I do not feel bad maybe the cancer does not feel bad either (P2).

In the follow-up interviews, some men expressed that well-being and QoL were more important than having any treatment, with its potential symptoms, even if it meant that the treatment would decrease the PSA values.

3.2.4 | Progression triggering thoughts about the remainder of life

The men described that certain symptoms triggered thoughts about the remainder of life, which related to fear, both about their actual death/dying, of becoming dependent on others, and the impact it might have on their close family. Fear was expressed mostly in relation to fatigue, pain or a general health or functional decline, but also to being paralysed, as described by one man:

Then [if paralyzed] I will be so darned dependent ... I've been thinking about those things, I'm actually afraid of that (P1).

During the disease trajectory, thoughts of being dependent on others were more prominently expressed by the men in the follow-up interviews, often triggered by an experience of progression of the disease or by new symptoms or worsening of symptoms. Starting a new treatment after a verified disease progression also triggered these thoughts of possibly becoming more dependent. Thoughts regarding the remaining lifespan was also expressed, both regarding potential symptoms, and how the end of life and dying would be like. The men had these thoughts at varying degrees at the time of the first interview, but for most men, the thoughts increased as the disease progressed. After a progression during the first line of chemotherapy, one man said:

... now when the chemotherapy did not work, it [the cancer] became slightly worse. You became a little worse, you get somewhat different thoughts (P5).

The men expressed fear of how a potential progression might impact their relationship with close family, for example, grandchildren, but also a fear of how others would be able to manage life without them. Examples were what would happen to dogs and whether the partner could remain living in the house or manage financially.

... then I become sad [sobs] ... that we have to move away from here ... if I don't make it how will she manage (P10).

As the disease was progressing, in the follow-up interviews, symptoms that were viewed as more serious by the men, for example, being paralysed, were expressed as more paramount than signs such as the PSA value. One man described that even if the PSA values were decreasing with the new treatment, he was still not able to walk, and he was not so interested in the PSA value in this situation.

... 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).

4 | DISCUSSION

This study set out to illuminate the experience of signs and symptoms in relation to disease progression in men with mCRPC. All men were aware that their disease was not curable, and some men received several lines of life-prolonging treatments, and during their disease trajectory, most of them declined in performance status. In this progressive situation, signs and symptoms were described to have different meanings in making sense of the men's situation. The men described an uncertainty where the experience of signs and symptoms was interdependent but also dependent on previous experiences.

The men described their experiences of signs and symptoms in relation to fear of progression as an uncertainty concerning whether the cancer was progressing and which potential consequences this may have for the remainder of life. The experience of living with

coherent uncertainty changes the view on life over time as suggested by Mishel's (1990) reconceptualised uncertainty in illness theory. For example, it has previously been described that illness uncertainty may influence both physical and mental well-being among patients with PC (Guan, Santacroce, et al., 2020) and that higher PSA levels and more symptoms give greater illness uncertainty; however, in their study, no changes in uncertainty were found over time (Guan et al., 2020). In the present study, we did not look at these associations specifically but found that signs and symptoms may be used in trying to make sense in this uncertain illness situation.

The uncertainty related to signs and symptoms in relation to progression that the men described here may have existential dimensions. Existential uncertainty has been shown in patients undergoing treatment for advanced gastrointestinal cancer (Karlsson et al., 2014). The men described that their interpretation of signs and symptoms was related to progression (verified or suspected) and triggered thoughts about the remainder of life, about death and dying and about the risk of becoming dependent on others. This worry about being dependent on families and friends when coming closer to death has also been found in patients with metastatic bowel cancer (Carduff et al., 2018).

The results also show that the men try to make sense of their illness situation and manage the uncertainty by applying their own subjective interpretation of signs and symptoms in relation to the potential disease progression. Often these interpretations were made based on previous experiences of the disease or treatment. Mishel's (1988, 1990) theory suggests that previous symptom patterns, familiarity and congruency in previous experiences may serve as stimuli frame for the experience of uncertainty. Patients using their own parameters, for example, symptoms such as pain, or signs such as weight for monitoring the progress of their disease, have also been described in patients with metastatic bowel cancer (Carduff et al., 2018). Men's own interpretation of signs and symptoms might be a way of gaining control over the illness situation, giving hope and less uncertainty.

However, sometimes these interpretations may also lead to unnecessary uncertainty or distress. One example in this study is how some men used previously experienced symptoms or absence of symptoms during treatment to interpret whether the present treatment was having an effect or not. This sometimes caused unnecessary distress in cases where these interpretations were not relevant to the current treatment. The importance of feeling in control and having information about what lies ahead as the disease progresses is crucial for men with advanced PC, as described by Chambers et al. (2018). In this situation, the treating staff have an important role, both in providing information and in relating this information to previous experiences.

If the men in this study did not experience symptoms, they instead, in the absence of symptoms, tried to make sense of signs such as PSA values as the only marker of disease progression. This may be a way to gain a certain degree of control over their situation. The perception that PSA is the only sign to measure a change in disease is in line with previous research (Farrington et al.,

2020) where men with localised and advanced PC regard PSA as the only indicator at their disposal and attach great importance to testing their PSA.

In the present study, some men interpreted a decreasing PSA as positive, a phenomenon Mishel (1988) would possibly describe as *opportunity*, where the men appraise the uncertainty positively, as a way to cope. The impact of similar signs, such as CA-15, CA 125 and CEA in other cancer diagnoses, has to our knowledge not been studied from the patients' perspective. One exception is a study in ovarian cancer about how the women were preoccupied with their CA-125 levels (Parker et al., 2006). When symptoms were experienced as serious by the men, the importance of the PSA values changed as the disease progressed, and their focus instead turned to enhancing well-being and QoL. This was also the case when they realised that there were no more treatment options available.

4.1 | Strengths and limitations

The prospective interview design is a strength in the present study, as experiences over time are recorded, something that is particularly important in a progressive disease such as PC. An additional strength is that this study gives a rich, contextualised account of the experiences of men with advanced PC. Eleven men were interviewed in the study, and only a few men were interviewed more than twice. However, the longitudinal design and the parallel procedure of inclusion, analysis and follow-ups ensured that rich data were obtained from the 30 interviews. This procedure also guided the sample size. Since three of the men had terminated further life-prolonging treatment, and three died during follow-up period, their experiences covered the entire trajectory of life-prolonging treatments. Although the study included a reasonably varied sample, to include men born outside of Sweden and younger men might have given a broader perspective on the experiences.

The methods have been thoroughly described in order to achieve trustworthiness and to clarify transferability. Even if these results are based on a sample of mostly older men, which is representative to the larger group of men with PC, the results concerning uncertainty may also be transferable to other PC contexts, including younger men with PC. The results may also be useful in other cancer contexts where treatment is given for advanced disease and signs of disease progression are used. To enhance credibility in the analysis, the research group collaborated in the analysis, in coding and in forming themes and subthemes. Quotes from different men were also used to reflect the participant's voices.

5 | CONCLUSION

Men with mCRPC strive to make sense of signs and symptoms during their disease trajectory based on previous experiences and in relation to progression. From being of great importance to the men in the absence of symptoms, the importance of signs, such as PSA values,

changes if severe symptoms develop and becomes less important while thoughts of QoL prevail.

An understanding of the men's perspectives on how signs and symptoms are perceived and interpreted in relation to disease progression during the trajectory for treatment of mCRPC may help health care professionals in communicating with patients in late phases of PC where the balance between treatment outcome and QoL is important. Hence, unnecessary uncertainty and distress may be avoided.

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CONFLICT OF INTEREST

None of the authors (UR, MH, SD, PF, LB, AWL) have any conflict of interest to declare. The authors ensure that all co-authors have confirmed agreement with the final statement.

DATA AVAILABILITY STATEMENT

Data are not publicly available due to privacy/ethical restrictions. For data that support the findings of this study, contact Agneta Wennman-Larsen.

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