Shared decision-making

Achieving well-balanced treatment decisions for patients with prostate disease

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Je moet er niet op wachten
‘t Komt hoe het komt

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Chapter 1

General Introduction

Shared decision-making

In the process of Medical Decision-Making there are three essential components: clinical expertise, clinical research, and patient preferences (1). By including patient preferences, shared decision-making (SDM) has become an important concept in daily clinical practice (2). SDM is an approach whereby clinicians and patients jointly decide on the 'best' treatment decision. This decision is made after deliberation on the risks and benefits of treatment options, in light of the patient's goals and preferences (3). An important benefit of this approach is that patients are more often likely to consider conservative treatments after participating in the decision-making process, which contributes to the reduction in over-treatment and possibly in the reduction of health care costs (4).

To support SDM in clinical practice, different patient decision aids (PDAs) have been developed and investigated in past decades (4). PDAs are instruments to assist patients and clinicians by explaining the treatment decision to be made and by providing evidence-based information about treatment options, their advantages and disadvantages and their associated outcomes compared to their alternatives (4, 5). Frequently, patients' treatment preferences are based on misconceptions rather than on accurate information (6-9). According to a Cochrane review, PDA use makes patients more knowledgeable and could correct for these misconceptions. Furthermore, PDAs help to decrease levels of *decisional conflict* (defined as a state of uncertainty around the decision to be made) and cause less decisional regret on the longer term (defined as patients' reflection on the effect of a decision) (4, 10, 11).

According to the International Patient Decision Aid Standards (IPDAS) criteria, PDAs should include values clarification methods (VCMs) (5). These VCMs help to elicit patients' values and preferences by guiding them in making tradeoffs between different treatment characteristics (e.g. side effects) (5). Methods used for values clarification are often classified as being either implicit or explicit (12, 13). With implicit techniques patients are expected to weigh up the desirability of different treatment options on their own by using, for instance, a balance sheet with the pros and cons of the available options. Explicit VCMs are designed to actively engage patients in tasks to compare the relative importance of characteristics relevant to a decision (12). Examples of explicit VCMs are rating and ranking tasks, discrete choice experiments and multi-criteria decision analysis (MCDA) methods which allow patients for better structuring the decision problem (14). There is no consensus on which method is best in clarifying patients' values. However, according to a Cochrane review, PDAs including explicit

VCMs result in higher proportions of patients choosing an option congruent with their values compared to a simple decision aid without explicit VCM or usual care (4).

Unfortunately, multiple barriers can complicate the SDM process, such as time constraints, the organization of health systems, as well as patient and clinician characteristics (15). These factors may lead to a suboptimal SDM process. Also, the subsequent implementation of PDAs in clinical practice following randomized controlled trials remains disappointing, with only 44% of PDAs reported to be used after publication of the trial (16). Most commonly reported barriers are lack of funding to support dissemination, outdated PDAs, and clinicians disagreement with PDA use (16).

Shared decision-making in urology

One of the specialties in which SDM has come to play a more important role over the course of recent years, is the field of urology. In particular, SDM is of importance within the context of treatment selection for patients with localized prostate cancer. This treatment decision is highly preference sensitive, as patients need to choose between surgery, external beam radiotherapy, brachytherapy or active surveillance, which all have equivalent survival outcomes (17). However, these treatments differ in side effects that mainly concern the domains of urinary, bowel, and sexual function (18-20). Additionally, for patients that opt for active surveillance treatment-related toxicity is minimized without compromising survival, but on the other hand more cancer-related anxiety and distress may be experienced (17).

To facilitate this treatment selection, different PDAs are available nowadays, both paper-based and web-based. Even though PDAs have proven to be effective on several decisional outcomes, systematic reviews focusing on PDAs for patients with localized prostate cancer have shown variability in the effects of PDAs on these decisional outcomes, e.g. *decisional conflict*, knowledge, regret and treatment choice (21-24).

One general explanation for the inconsistent effects of PDAs on these outcomes may be that some of the used outcome measures are not appropriate to assess the effectiveness of PDAs. For instance, *decisional conflict* and regret can be highly time-sensitive (25). Patients can be poor decision makers, making irrational choices, but may – at the same time - experience less decisional conflict and regret (25, 26). Furthermore, after absorbing all available information, patients might become more

aware of the difficulty of the decision. Consequently, this might lead to high *decisional conflict* scores, although these scores may not be undesirable (25). Also, it has been argued that knowledge improvement alone should not be the primary aim of PDA use, as knowledge is not always used effectively and does not guarantee a good decision (27). Therefore, some researchers suggest *decision quality* as an important outcome measure to evaluate the impact of the implementation of PDAs (28). *Decision quality* is defined as the extent to which treatment decisions reflect the considered preferences of well-informed patients, as measured by the combination of knowledge scores and *value congruence*. *Value congruence* can be measured by matching responses on value statements to the chosen or received treatment or by matching the preferred treatment option to the chosen or received treatment (28).

Another explanation for the variability in outcomes in the effects of PDAs, especially in treatment choice, may be that the treatment characteristics used in VCMs to elicit patients' preferences may not always be relevant to the individual patient. Contextual factors, including lived experiences as well as cultural and spiritual beliefs are evidently also of influence on patients' comprehension and uptake of information. These contextual factors, also referred to as alternative knowledge, might subsequently influence the treatment decision-making process, especially in patients with lower numeracy levels (29). And, possibly due to time constraints in clinical practice, these contextual factors are all too often not discussed in the decision-making process.

Lastly, a recent systematic review showed that all PDAs for patients with localized prostate cancer presented rather general information applying to patient groups instead of personalized information, particularly in terms of outcome probabilities (22). However, it is suggested that personalized information is more likely to be considered as personally relevant compared to general information and may lead to increased patient involvement in the SDM process (30).

Although much research has been done in the field of SDM for localized prostate cancer patients, several challenges remain. The available literature highlights the fact that efforts are still needed to optimize PDAs and improve implementation of SDM and PDAs into routine care for prostate cancer patients. Therefore, this thesis will focus on the optimization of an existing PDA for prostate cancer and aims to expand the relevant knowledge to other prostate diseases, including benign prostate enlargement and metastatic castration-resistant prostate cancer.

Benign prostate enlargement

One common form of prostate diseases is non-cancerous enlargement of the prostate due to histologic benign prostatic hyperplasia, which leads to lower urinary tract symptoms (abbreviated as LUTS/BPH). These LUTS may include weak urinary stream, interrupted stream, hesitancy, leaking, and irritative symptoms i.e. increased frequency and urgency of urination, and nycturia. These symptoms can have a major impact on men's quality of life (QoL) (31-33). The burden of this disease is increasing worldwide, due to the growth and ageing of the population (34). In the Netherlands 20 to 30% of men older than 50 years' experience LUTS increasing to 76% in men older than 70 years (35).

Treatment of LUTS/BPH is focused on symptom improvement and increase of QoL, as well as prevention of risks and complications, such as acute urinary retention, urinary tract infections and renal insufficiency due to postrenal obstruction with hydronephrosis (31). Treatment options for patients with LUTS/BPH include watchful waiting, pharmacological and surgical treatment. Watchful waiting can be offered to men who experience limited symptoms or wish to postpone treatment. To patients with moderate-to-severe LUTS, α1-blockers and/or 5α-reductase inhibitors can be offered to reduce urinary symptoms and increase the peak urinary flow rate. In addition, 5α-reductase inhibitors can prevent disease progression by decreasing the prostate volume in three to six months. Muscarinic receptor antagonists or beta-3 agonists can be offered to patients whose main problem are bladder storage symptoms (e.g. urgency). These different pharmacological options can of course also be combined (31). When conservative or pharmacological treatment does not result in adequate symptom relief, surgery is an option. Surgical treatments for moderate-to-severe LUTS have notably evolved in the past few years. However, transurethral resection of the prostate (TURP) remains the gold standard. Additionally, for men with a prostate size larger than approximately 80 mL, open prostatectomy is most often offered. These days, next to TURP and open prostatectomy, laser enucleation, laser vaporization, prostatic urethral lift, transurethral microwave therapy and transurethral ablation are alternative surgical treatment options (31).

Altogether, these treatment options have their own specific indications, benefits and risks, and therefore tradeoffs between treatment effects and impact on QoL have to be considered. With the increasing treatment options for LUTS/BPH it may be beneficial for clinicians as well as for patients to optimize SDM. Compared to evidence on treatment PDAs for prostate cancer, evidence on PDAs for men with LUTS/BPH is

limited and outdated (36-39). In addition, consensus is lacking on the best outcome measure to evaluate the effectiveness of PDAs. Therefore, in this thesis, *decision quality* was used as primary outcome to evaluate the impact of the implementation of a previously developed PDA for patients who face treatment decisions for LUTS/BPH.

Metastatic castration-resistant prostate cancer

The majority of prostate cancer will be detected while it is still localized but first presentation can also be with metastases (17). When biochemical recurrence (i.e. increasing serum PSA level) occurs after curative treatment options, patients can consider salvage treatment. After some time patients can progress to metastatic hormone-sensitive prostate cancer that can be treated with androgen deprivation. The median survival of these patients is approximately 42 months (40). After a median of 20 months, these patients will become unresponsive to androgen blockade and thereby develop metastatic castration-resistant prostate cancer (mCRPC) (40). Compared to the available evidence on SDM and PDAs for localized prostate cancer, attention for the development and evaluation of both these concepts for patients with mCRPC is lacking. This might be explained by the complex multidisciplinary setting of treatment for these patients and the ongoing development of new treatment options and research on combinations of available treatment options (41).

In past decades, clinical practice with regard to treatment options for mCRPC has changed significantly due to the availability of novel treatment options. Next to chemotherapy, clinicians may opt for hormone targeted drugs, such as abiraterone acetate combined with prednisone, enzalutamide, apalutamide, as well as radioactive therapy (40, 42-48). Some of these treatment options are now even available for patients in the hormone-sensitive setting, allowing for more effective therapy in an earlier disease stage (42, 49). In all stages of the disease, best supportive care can be applied to minimize treatment-related toxicity, especially to patients with a life expectancy <10 years (40).

The constant development of new treatment options for mCRPC patients and their introduction in an earlier disease stage, as well as the absence of clear recommendations for a preferred treatment sequence, increasingly complicates treatment decision-making. An additional challenge within this particular group of patients is the fact that the majority of mCRPC patients is older than 70 years and suffers from additional comorbidities. Due to the combination of these comorbidities, tumor activity and

previous treatments, patients' condition may be limited which can make them vulnerable or frail. The concept of frailty is increasingly used to characterize patients' limited functional condition. Frailty not only affects survival; it can also affect patients' ability to tolerate treatment-related side-effects (50). Therefore, the International Society of Geriatric Oncology Prostate Cancer Working Group (SIOG) recommends a systematic evaluation of health status, using the Geriatric 8 (G8) screening tool (51), in the treatment decision-making process for elderly patients with prostate cancer. This means that for frail patients (G8 score ≤14) with reversible impairment after resolution of their geriatric problems the same treatments as younger patients should be discussed (52, 53). On the other hand, frail patients with irreversible impairment should be spared from toxic treatments.

The ongoing shift in treatment options, the importance of a multidisciplinary treatment approach and the introduction of the G8 screening tool clearly emphasizes the importance of SDM for this patient group. Treatment choice should be made after all eligible treatments have been discussed in a multidisciplinary team and after the balance of benefits and side-effects has been considered together with the patient (40). Also in this stage of prostate cancer clinicians as well as patients may benefit from a PDA, including G8, in the treatment decision-making process.

Thesis aims

This thesis aims to provide insight into the effectiveness of patient decision aids to support shared decision-making in various prostate diseases and to optimize the shared decision-making process by focusing on the introduction of various innovative decision-making tools.

To achieve these goals, several research questions will be addressed using existing decision aids for localized prostate cancer and lower urinary tracts symptoms due to benign prostatic hyperplasia (LUTS/BPH) and a newly developed decision aid for patients with metastatic castration-resistant prostate cancer:

- What is the effectiveness of the use of a decision aid for patients with LUTS/BPH on *decision quality* and other relevant decision process outcomes? **(Chapter 2 and 3)**
- Does the addition of an extra values clarification method to an existing decision aid for patients with localized prostate cancer improve decision process outcomes

and *decision quality*, as compared to the decision aid alone? (**Chapter 4 and 5)**
- Is the implementation of a decision aid, including a screening tool for frailty, for patients with metastatic castration-resistant prostate cancer effective in improving the treatment decision-making process, as compared to usual care? **(Chapter 6 and 7)**
- How can patients' contextual factors that influence their information comprehension and uptake be elicited during the shared decision-making process? (**Chapter 8)**

Outline

In Part I of this thesis, a patient decision aid for patients with lower urinary tract symptoms due to benign prostatic hyperplasia is evaluated.

Outcome measures, such as *decisional conflict* and regret, that are often used in decision aid effectiveness trails are being criticized in current literature, in **Chapter 2** the effectiveness of a decision aids for patients with LUTS/BPH (54) is evaluated with *decision quality* as primary outcome measure, and compared to usual care. Furthermore, **Chapter 3** focuses on decision aid users to evaluate their treatment preferences before and after the use of the web-based decision aid.

In Part II of this thesis, the development and evaluation of an additional decision-making tool for patients with localized prostate cancer is addressed.

Elaborating on the results of a previous cluster randomized trial that evaluated the impact of a decision aid for patients with localized prostate cancer on decision process outcomes, **Chapter 4** describes the development and usability testing of an additional multi-criteria values clarification method to the existing decision aid (55). This method allows patients to quantitatively assess and observe which treatment aligns with their value statements. In **Chapter 5**, this tool is evaluated and results are compared with patients who used the existing decision aid from the previous trial.

In Part III of this thesis, shared decision-making and a patient decision aid for patients with metastatic castration-resistant prostate cancer are evaluated.

To investigate the perspectives of the multidisciplinary team on shared decision-making in treatment decisions for older patients with metastatic castration-resistant

prostate cancer, a questionnaire study was done which is described in **Chapter 6.** In **Chapter 7,** a decision aid for these patients is evaluated using a national stepped wedge randomized controlled implementation trial. The novelty of this decision aid, is the addition of geriatric screening tools and goalsetting questions.

In Part IV of this thesis, suggestions for improvement of shared decision-making are addressed.

Several factors that are of influence to the decision-making process are addressed in the narrative review in **Chapter 8**. It highlights the importance of including context (29) (i.e. patients' lived experiences) into the decision-making process and introduces a conceptual framework to elicit these experiences that may positively influence the uptake of information.

Ideally, a patient decision aid contains or is combined with a prognostic model to guide and support clinicians in appropriate treatment selection for individual patients. For metastatic castration-resistant prostate cancer patients receiving first-line chemotherapy (docetaxel), prognostic models and nomograms have been developed, which identified parameters such as performance status, time since diagnosis, presence of pain, duration of androgen deprivation therapy and laboratory results to predict survival (56, 57). In **Chapter 9,** it was aimed to develop a model to predict mortality in these patients treated in first-line with either abiraterone, enzalutamide, docetaxel, watchful waiting or radium-223, with the goal to use the model for decision-making and to incorporate it into the decision aid, by using data from a retrospective observational registry. Due to insufficient data to develop this specific prognostic model, the exemplary dataset was used to guide clinicians through pitfalls and steps of developing such models.

In **Chapter 10** the findings of this thesis will be discussed with implications for daily practice and future research.

References

1. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. Bmj. 1996;312(7023):71-2.
2. Krumholz HM. Informed consent to promote patient-centered care. Jama. 2010;303(12):1190-1.
3. Charles C, Gafni A, Whelan T. Shared decision-making in the medical encounter: what does it mean? (or it takes at least two to tango). Soc Sci Med. 1997;44(5):681-92.
4. Stacey D, Legare F, Lewis K, Barry MJ, Bennett CL, Eden KB, et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev. 2017;4:CD001431.
5. Elwyn G, O'Connor AM, Bennett C, Newcombe RG, Politi M, Durand MA, et al. Assessing the quality of decision support technologies using the International Patient Decision Aid Standards instrument (IPDASi). PLoS One. 2009;4(3):e4705.
6. Kendel F, Helbig L, Neumann K, Herden J, Stephan C, Schrader M, et al. Patients' perceptions of mortality risk for localized prostate cancer vary markedly depending on their treatment strategy. Int J Cancer. 2016;139(4):749-53.
7. Wittmann D, He C, Coelho M, Hollenbeck B, Montie JE, Wood DP, Jr. Patient preoperative expectations of urinary, bowel, hormonal and sexual functioning do not match actual outcomes 1 year after radical prostatectomy. J Urol. 2011;186(2):494-9.
8. Emberton M. Medical treatment of benign prostatic hyperplasia: physician and patient preferences and satisfaction. Int J Clin Pract. 2010;64(10):1425-35.
9. Kim SI, Kang JY, Lee HW, Seong do H, Cho JS. A survey conducted on patients' and urologists' perceptions of benign prostatic hyperplasia. Urol Int. 2011;86(3):278-83.
10. Brehaut JC, O'Connor AM, Wood TJ, Hack TF, Siminoff L, Gordon E, et al. Validation of a decision regret scale. Med Decis Making. 2003;23(4):281-92.
11. O'Connor AM. Validation of a decisional conflict scale. Med Decis Making. 1995;15(1):25-30.
12. Baptista S, Heleno B, Teixeira A, Taylor KL, Martins C. Comparison of explicit values clarification method (VCM), implicit VCM and no VCM decision aids for men considering prostate cancer screening: protocol of a randomized trial. BMC Med Inform Decis Mak. 2020;20(1):78.
13. Abhyankar P, Bekker HL, Summers BA, Velikova G. Why values elicitation techniques enable people to make informed decisions about cancer trial participation. Health Expect. 2011;14 Suppl 1:20-32.
14. Dolan JG. Shared decision-making--transferring research into practice: the Analytic Hierarchy Process (AHP). Patient Educ Couns. 2008;73(3):418-25.

15. Legare F, Witteman HO. Shared decision making: examining key elements and barriers to adoption into routine clinical practice. Health Aff (Millwood). 2013;32(2):276-84.
16. Stacey D, Suwalska V, Boland L, Lewis KB, Presseau J, Thomson R. Are Patient Decision Aids Used in Clinical Practice after Rigorous Evaluation? A Survey of Trial Authors. Med Decis Making. 2019;39(7):805-15.
17. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol. 2017;71(4):618-29.
18. Wilt TJ, Jones KM, Barry MJ, Andriole GL, Culkin D, Wheeler T, et al. Follow-up of Prostatectomy versus Observation for Early Prostate Cancer. N Engl J Med. 2017;377(2):132-42.
19. Wilt TJ, Vo TN, Langsetmo L, Dahm P, Wheeler T, Aronson WJ, et al. Radical Prostatectomy or Observation for Clinically Localized Prostate Cancer: Extended Follow-up of the Prostate Cancer Intervention Versus Observation Trial (PIVOT). Eur Urol. 2020.
20. Lardas M, Liew M, van den Bergh RC, De Santis M, Bellmunt J, Van den Broeck T, et al. Quality of Life Outcomes after Primary Treatment for Clinically Localised Prostate Cancer: A Systematic Review. Eur Urol. 2017;72(6):869-85.
21. Lin GA, Aaronson DS, Knight SJ, Carroll PR, Dudley RA. Patient decision aids for prostate cancer treatment: a systematic review of the literature. CA Cancer J Clin. 2009;59(6):379-90.
22. Vromans RD, van Eenbergen MC, Pauws SC, Geleijnse G, van der Poel HG, van de Poll-Franse LV, et al. Communicative aspects of decision aids for localized prostate cancer treatment - A systematic review. Urol Oncol. 2019;37(7):409-29.
23. Violette PD, Agoritsas T, Alexander P, Riikonen J, Santti H, Agarwal A, et al. Decision aids for localized prostate cancer treatment choice: Systematic review and meta-analysis. CA Cancer J Clin. 2015;65(3):239-51.
24. Zhong W, Smith B, Haghighi K, Mancuso P. Systematic Review of Decision Aids for the Management of Men With Localized Prostate Cancer. Urology. 2018;114:1-7.
25. Vickers AJ. Decisional Conflict, Regret, and the Burden of Rational Decision Making. Med Decis Making. 2017;37(1):3-5.
26. Nelson WL, Han PK, Fagerlin A, Stefanek M, Ubel PA. Rethinking the objectives of decision aids: a call for conceptual clarity. Med Decis Making. 2007;27(5):609-18.
27. Kennedy AD. On what basis should the effectiveness of decision aids be judged? Health Expect. 2003;6(3):255-68.
28. Sepucha K, Ozanne EM. How to define and measure concordance between patients' preferences and medical treatments: A systematic review of approaches and recommendations for

standardization. Patient Educ Couns. 2010;78(1):12-23.

29. Hajizadeh N, Basile MJ, Kozikowski A, Akerman M, Liberman T, McGinn T, et al. Other Ways of Knowing. Med Decis Making. 2017;37(3):216-29.
30. Ritterband LM, Thorndike FP, Cox DJ, Kovatchev BP, Gonder-Frederick LA. A behavior change model for internet interventions. Ann Behav Med. 2009;38(1):18-27.
31. Gratzke C, Bachmann A, Descazeaud A, Drake MJ, Madersbacher S, Mamoulakis C, et al. EAU Guidelines on the Assessment of Non-neurogenic Male Lower Urinary Tract Symptoms including Benign Prostatic Obstruction. Eur Urol. 2015;67(6):1099-109.
32. Martin SA, Haren MT, Marshall VR, Lange K, Wittert GA, Members of the Florey Adelaide Male Ageing S. Prevalence and factors associated with uncomplicated storage and voiding lower urinary tract symptoms in community-dwelling Australian men. World J Urol. 2011;29(2):179-84.
33. Kupelian V, Wei JT, O'Leary MP, Norgaard JP, Rosen RC, McKinlay JB. Nocturia and quality of life: results from the Boston area community health survey. Eur Urol. 2012;61(1):78-84.
34. Egan KB. The Epidemiology of Benign Prostatic Hyperplasia Associated with Lower Urinary Tract Symptoms: Prevalence and Incident Rates. Urol Clin North Am. 2016;43(3):289-97.
35. Urology DAo. Richtlijn Mannelijke niet-neurogene LUTS 2017 [Available from: https://www.nvu.nl/en-us/kwaliteit/richtlijnen/actuelerichtlijnen.aspx.
36. Murray E, Davis H, Tai SS, Coulter A, Gray A, Haines A. Randomised controlled trial of an interactive multimedia decision aid on benign prostatic hypertrophy in primary care. BMJ. 2001;323(7311):493-6.
37. Barry MJ, Fowler FJ, Jr., O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J Urol. 1992;148(5):1549-57; discussion 64.
38. Wills CE, Holmes-Rovner M, Rovner D, Lillie J, Kelly-Blake K, Bonham V, et al. Treatment preference patterns during a videotape decision aid for benign prostatic hyperplasia (BPH). Patient Educ Couns. 2006;61(1):16-22.
39. Perestelo-Perez L, Perez-Ramos J, Gonzalez-Lorenzo M, Rivero-Santana A, Serrano-Aguilar P. Decision aids for patients facing health treatment decisions in Spain: preliminary results. Patient Educ Couns. 2010;80(3):364-71.
40. Cornford P, Bellmunt J, Bolla M, Briers E, De Santis M, Gross T, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer. Eur Urol. 2017;71(4):630-42.
41. Sternberg CN. Improving Survival for Metastatic Castrate-resistant Pros-

tate Cancer: Will Combination Therapy Help Us To Move Forward? Eur Urol. 2016;70(5):722-3.

42. James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet. 2016;387(10024):1163-77.
43. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004;351(15):1502-12.
44. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010;376(9747):1147-54.
45. Ryan CJ, Smith MR, Fizazi K, Saad F, Mulders PF, Sternberg CN, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2015;16(2):152-60.
46. Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fossa SD, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369(3):213-23.
47. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012;367(13):1187-97.
48. Smith MR, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Graff JN, et al. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. N Engl J Med. 2018;378(15):1408-18.
49. Rydzewska LHM, Burdett S, Vale CL, Clarke NW, Fizazi K, Kheoh T, et al. Adding abiraterone to androgen deprivation therapy in men with metastatic hormone-sensitive prostate cancer: A systematic review and meta-analysis. Eur J Cancer. 2017;84:88-101.
50. Droz JP, Aapro M, Balducci L, Boyle H, Van den Broeck T, Cathcart P, et al. Management of prostate cancer in older patients: updated recommendations of a working group of the International Society of Geriatric Oncology. Lancet Oncol. 2014;15(9):e404-14.
51. Bellera CA, Rainfray M, Mathoulin-Pélissier S, Mertens C, Delva F, Fonck M, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. Annals of oncology : official journal of the European Society for Medical Oncology. 2012;23(8):2166-72.
52. Droz JP, Albrand G, Gillessen S, Hughes S, Mottet N, Oudard S, et al. Management of Prostate Cancer in Elderly Patients: Recommendations of a

Task Force of the International Society of Geriatric Oncology. Eur Urol. 2017;72(4):521-31.

53. Climent MA, Torregrosa MD, Vazquez S, Girones R, Arranz JA. Aged patients with metastatic castration resistant prostate cancer: Should we treat with chemotherapy? Cancer Treat Rev. 2017;55:173-80.
54. Lamers RED, Cuypers M, Garvelink MM, de Vries M, Bosch J, Kil PJM. Development of a decision aid for the treatment of benign prostatic hyperplasia: A four stage method using a Delphi consensus study. Patient Educ Couns. 2016;99(7):1249-56.
55. Lamers RE, Cuypers M, de Vries M, van de Poll-Franse LV, Ruud Bosch JL, Kil PJ. How do patients choose between active surveillance, radical prostatectomy, and radiotherapy? The effect of a preference-sensitive decision aid on treatment decision making for localized prostate cancer. Urol Oncol. 2017;35(2):37 e9- e17.
56. Halabi S, Lin CY, Kelly WK, Fizazi KS, Moul JW, Kaplan EB, et al. Updated prognostic model for predicting overall survival in first-line chemotherapy for patients with metastatic castration-resistant prostate cancer. J Clin Oncol. 2014;32(7):671-7.
57. Armstrong AJ, Garrett-Mayer E, de Wit R, Tannock I, Eisenberger M. Prediction of survival following first-line chemotherapy in men with castration-resistant metastatic prostate cancer. Clin Cancer Res. 2010;16(1):203-11.

Part I

Shared decision-making in patients with benign prostatic hyperplasia

Chapter 2

Effectiveness of a web-based treatment decision aid for men with lower urinary tract symptoms due to benign prostatic hyperplasia

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Abstract

Objectives

To evaluate the effectiveness of a web-based decision aid (DA) with values clarification exercises (VCEs) compared with usual care for men with lower urinary tract symptoms due to benign prostatic hyperplasia (LUTS/BPH).

Patients and Methods

Between July 2016 and January 2017, all new patients with LUTS/BPH who consulted the urologist were invited to use the DA and participate in this prospective questionnaire study. Patients who consulted the urologist between December 2015 and February 2016 served as controls. The DA was designed to support patients in making a well-informed treatment decision, corresponding with their personal preferences and values. Well-informed decision was measured by using a knowledge questionnaire. Value congruent decision was measured by the correspondence between responses on nine value statements and chosen treatment. The primary outcome, *decision quality*, was defined as the combination of well-informed decision and value congruent decision. Secondary outcomes were decisional conflict, involvement and received role in shared decision-making, decisional regret, and treatment choice.

Results

A total of 109 DA-users and 108 controls were included. DA-users were younger (68.4 vs 71.5 years; $P = 0.003$) and their education level was higher ($P = 0.047$) compared with the controls. Patients who used the DA made a well-informed and value congruent decision more often than the control group (43% vs 21%; $P = 0.028$). DA-users had less decisional conflict (score 33.2 vs 46.6; $P = 0.003$), experienced a less passive role in decision-making (22% vs 41%; $P = 0.038$), and reported less process regret (score 2.4 vs 2.8; $P = 0.034$). Furthermore, DA-users who had not used prior medication chose lifestyle advices more often than the control group (43% vs 11%; $P = 0.002$). Outcomes were adjusted for significantly different baseline characteristics.

Conclusion

The LUTS/BPH DA seems to improve the *decision quality* by supporting patients in making more well-informed and value congruent treatment decisions. Therefore, further implementation of this DA into routine care is suggested.

Keywords

Benign Prostatic Hyperplasia, Decision Aid, Shared Decision-making, Patient-Centered Care

Introduction

Worldwide, LUTS due to BPH (LUTS/BPH) are common in ageing men. Prevalence ranges from 50% to 75% amongst men aged >50 years and increases with age [1]. Symptoms can have a major impact on quality of life (QoL) and, therefore, LUTS/BPH represents a substantial disease burden [2, 3].

For men with LUTS/BPH with mild symptoms lifestyle advices are usually offered first, prior to medication or surgery [4]. When conservative or pharmacological treatments do not result in adequate symptom relief, surgery is indicated. According to international guidelines, only a minority of patients with severe BPH complications are eligible for surgery [4, 5]. The treatment decision should not solely depend on the combination of diagnostic findings and the ability of treatments to reduce symptoms [4], but also on treatment preferences and expectations of individual patients. Therefore, trade-offs between treatment effects and impact on QoL have to be considered. Given the preference-sensitive elements of this treatment decision and common misconceptions about preferences and expectations about LUTS/BPH treatment [6, 7], integrating patient preferences may improve and support shared decision-making (SDM).

To overcome barriers experienced with implementation of SDM in clinical practice, decision aids (DAs) are developed to provide standardised information about available treatment options, to make decisions explicit, to support patients in exploring their preferences and values, and to engage patients and their clinicians into SDM [8]. Previous studies showed positive effects of DA use on different outcome measures for decision-making [9, 10]. Some studies even showed that DA use lowered elective surgical rates, although these results showed to be inconsistent regarding the effect of LUTS/BPH DAs [9-13]. Compared to evidence on treatment DAs for prostate cancer, evidence on treatment DAs for men with LUTS/BPH is limited and outdated [11, 14-21]. In addition, consensus is lacking on the best outcome measure to evaluate the effectiveness of DA implementation [22-24]. In many randomised controlled trials (RCTs) reduction of decisional conflict was considered as positive outcome because it captures the uncertainty involved in the decision-making process. Contrarily, Vickers *et al.* argued that high decisional conflict scores could indicate that patients become aware of the difficulty of the decision after involvement in the decision-making process and after absorbing all available information [22]. Furthermore, Kennedy *et al.* argued that knowledge improvement alone should not be the primary aim of DA use, as knowledge is not always used effectively and does not guarantee a good decision [24].

Therefore, in the present study, we chose *decision quality* as the primary outcome measure to evaluate the impact of the implementation of a previously developed DA for patients who face treatment decisions for LUTS/BPH [25]. *Decision quality* is one of the most important aspects of patient-centered care and is defined as the extent to which treatments reflect the considered preferences of well-informed patients, measured by knowledge scores combined with scores on value statements [26]. We hypothesised that DA use would improve *decision quality* by supporting patients in making more well informed treatment decisions that reflect their personal preferences (value congruence), as compared to control patients who received usual care. Furthermore, we hypothesised that patients using the DA would experience less decisional conflict and regret, would be more involved in decision-making, and patients would choose conservative treatments more often.

Patients and methods

Study population

A prospective observational questionnaire study was conducted in five Dutch hospitals (one academic and four non-academic) between July 2016 and January 2017. New patients who consulted the urologist in the outpatient clinic of all hospitals because of LUTS suggestive of BPH were invited by their treating urologist to use the DA and to participate in this study. Results were compared with control patients who had consulted the urologist between December 2015 and February 2016. Control patients were identified from 'diagnosis-treatment-combination'-register databases from all hospitals and were invited by their urologist by letter. Patients who were eligible for two treatments (lifestyle advices, medication, and/or surgery) were included. Furthermore, patients had to have access to Internet. Patients with an absolute medical indication for surgery [4], prior prostate surgery, prostate cancer, cognitive impairment or insufficient Dutch language comprehension were excluded. For both patients and physicians, study participation was voluntary without remuneration.

The intervention

The web-based DA was previously developed according to the International Patient Decision Aids Standards (IPDAS) [8, 25]. The DA contains the following two decisions for patients with LUTS/BPH: the decision between lifestyle advices or medication *(decision A)* and to continue medication or undergo surgery *(decision B)*. Based on clinical factors urologists need to indicate on a handout which treatment decision applies to the patients' individual situation. Subsequently, patients can log in and access the DA

at https://bph.keuzehulp.nl. The DA contains general information about LUTS/BPH based on current guidelines [4] and values clarification exercises (VCEs) to gain insight in patients' preferences [25].

In order to fit clinical practice, the pragmatic approach of this study allowed hospitals to integrate the introduction of the DA with their own standard information provision routines. Therefore, the time points of offering the DA differed between hospitals. To enable comparison with controls, patients were only included for analyses when the DA was offered before or after first or second consultation, and when patients had not visited an urologist in the past year for LUTS.

Outcome measures

The primary outcome measure was *decision quality*, defined as the combination of well-informed decision and value congruent decision. A disease-specific knowledge questionnaire, adapted from previous studies, was used to assess well-informed decision [21, 27]. Value congruent decision was measured by matching responses on nine value statements to chosen treatment. The nine value statements were based on the VCEs in the DA. Patients were asked to rate to what extent each statement was important for their decision, ranging from zero to 10. Each statement differentiates between one particular treatment and two alternative treatments (Table S1).

The decision-making process and decisional outcomes were secondary outcome measures in this study. The Decisional Conflict Scale (DCS) was used to measure patients' perceptions at time of treatment decision [28]. Scores were converted to an equivalent 0-100 scale, with higher scores indicating more conflict. To evaluate level of patient involvement in decision-making process the Shared Decision Making Questionnaire (SDM-Q-9) was used. All items were scored on a 6-point Likert scale and a mean score between zero and 5 was calculated, with higher mean scores indicating higher levels of involvement in SDM [29]. Patients' perceived role in decision-making was measured by the Control Preference Scale (CPS) [30]. Scores were summarised into provider-led, shared, and patient-led. One item was added to assess satisfaction with participation in decision-making. Decision regret was measured using the Brehaut Regret Scale and a new regret scale, which measures three different aspects of decisional regret: process, option, and outcome regret [31, 32].

Furthermore, to evaluate effectiveness of the DA on decisional outcomes, data on received treatment after the first visit to the urologist and performed diagnostics were collected from patient records. To investigate if DA use influenced surgical

rate, decision for surgery within three months after the first visit to the urologist was reported. Clinical characteristics were also assessed. To standardise co-morbidity the Charlson Co-morbidity Index (CCI) was used. International Prostate Symptom Score (IPSS) was used to report patients' urinary symptoms [33].

Patients completed the first (online or paper) questionnaire directly after written informed consent was obtained (T1). Three months later, after treatment was chosen and received, patients completed the second questionnaire (T2). Data from the questionnaires were linked to patients' DA data. A complete overview of outcome measures including instruments and time points is presented in Table 1. Patients of whom informed consent was not obtained were still able to use the DA without study participation.

Statistical analysis

The study was designed to enroll 99 patients per group to provide 80% power to detect effect sizes of 0.4 with an α of 0.05. Expecting high attrition rate and non-responders in both groups, we aimed to invite 200 patients for the DA group and 300 patients for the control group.

To compare baseline patient and clinical characteristics between groups, Chi-squared tests for categorical variables and *t*-tests for continuous variables were used.

First, unadjusted regression models (linear, logistic, and multinominal) were used to compare all outcome measures between groups. Secondly, multivariable multilevel regression models were used in order to adjust for group differences, including all baseline characteristics with $P < 0.05$ as fixed factors and a random effect for hospital to account for between-hospital heterogeneity. Intention-to-treat analysis was performed. Questionnaire responses were included if <25% of the data were missing. For calculating informed and value congruent decision no missing data were allowed. Detailed information on primary outcome analyses can be found in Appendix S1.

All analyses were conducted using the IBM Statistical Package for the Social Sciences (SPSS®), version 24.0 (SPSS Inc., Chicago, IL, USA), with a $P < 0.05$ considered statistically significant.

Table 1. Overview of all outcome measures including instruments used with time points

	Instrument / measures	# items	T1	T2	Medical record	Decision aid
Patient characteristics	Age	-	-	-	X	-
	Sociodemographic items	-	*	X	-	-
	Duration of urinary symptoms	-	-	X	-	-
	CCI and LUTS related variables	-	-	-	X	X
DA usability items[+]	SCIP-B	7	X	-	-	-
	Preparation for decision making scale	10	X	-	-	-
Decision quality	Knowledge questions	7	-	X	-	-
	Value statements	9	-	X	-	-
Decision process						
	Decisional conflict scale (DCS) Informed subscale Values clarity subscale Support subscale Uncertainty subscale Effective decision subscale	16	-	X	-	-
	SDM-Q-9	9	-	X	-	-
	Control preference scale (CPS)	1	-	X	-	-
	Satisfaction with perceived role in decision-making (study-specific)	1	-	X	-	-
Decision outcomes						
	First treatment choice after consultation	-	-	-	X	-
	Surgical rate	-	-	-	X	-
	New regret scales Process regret Option regret Outcome regret	18	-	X	-	-
	Brehaut regret	5	-	X	-	-

T1 directly after written informed consent was obtained and after DA use (DA group only). T2 three months after first questionnaire was sent: after treatment was chosen and received (for control group: three to six months after the first consultation with the urologist). *Sociodemographic data of DA-users were obtained from questionnaires at T1. [+] DA usability items were not described in this study.

Results

A flow chart of the study, with enrolment numbers, is shown in Figure 1. In total, 109 DA patients and 108 control patients were included for analyses based on eligibility criteria. In all, 11 of those 109 DA patients (10%) appeared not to have used the DA, resulting in a viewing rate of 90%. Nonetheless, these patients were included for analyses according to the intention-to-treat principle. Response rate on questionnaires was 60% (100/165) in DA group and 36% (108/303) in control group.

Marital status, work status, co-morbidity, and LUTS/BPH-related characteristics were comparable between groups. DA-users were younger (mean age 68.4 vs 71.5; *P* = 0.003) and their education level was higher (42% vs 26%; *P* = 0.047) compared with the controls. Furthermore, there was less time between the first consultation with the urologist and questionnaire completion amongst DA-users, at a mean (SD) of 5.3 (1.7) vs 7.0 (1.4) months (P < 0.001; Table 2).

Figure 1. Flow chart and enrolment numbers in the DA and the control groups.

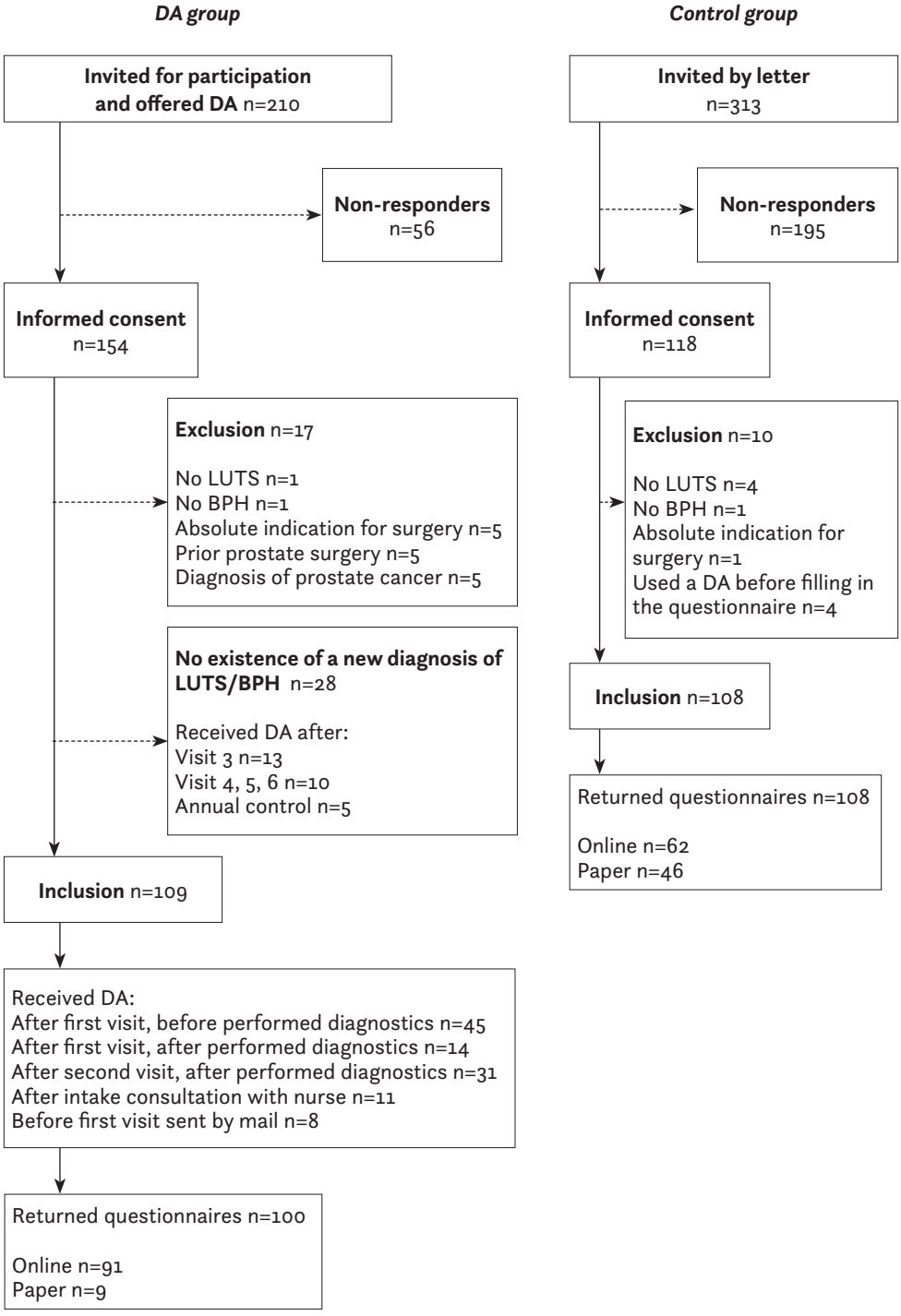

Table 2. Baseline characteristics of DA-users and controls (*n* = 217)

Variables	Categories/range	DA-users (*n* = 109)	Controls (*n* = 108)	*P*-value
Age, years, mean (SD)		68.4 (7.0)	71.5 (8.4)	0.003
Inclusion per hospital, % (*n*)	A B C D E	41 (45) 28 (31) 17 (18) 10 (11) 4 (4)	24 (26) 17 (18) 32 (35) 12 (13) 15 (16)	<0.001
Education, % (*n*)[x]	Low Medium High	32 (35) 24 (24) 42 (43)	41 (44) 33 (35) 26 (28)	0.047
Work status, % (*n*)	Employed/ volunteer job Not employed/retirement	32 (33) 68 (69)	33 (35) 67 (72)	0.956
Marital Status, % (*n*)	Married/living with partner Not married/living alone	85 (88) 15 (15)	80 (86) 20 (21)	0.330
CCI, % (*n*)	0 1-2 ≥3	57 (62) 37 (40) 6 (7)	50 (54) 44 (48) 6 (6)	0.509
Duration of urinary symptoms, months, % (*n*)	<6 6 – 12 12 – 60 >60	3 (3) 18 (18) 51 (51) 28 (28)	5 (5) 25 (27) 50 (54) 20 (21)	0.369
Use of medication before consultation, % (*n*)	No Yes	43 (47) 57 (62)	51 (55) 49 (53)	0.249
IPSS, % (*n*)	Mild (0-7) Moderate (8-19) Severe (20-35)	8 (5) 55% (35) 37 (24)	9 (6) 49 (35) 42 (30)	0.821
QoL score, mean (SD); *n*	Range 0 (delighted) – 6 (terrible)	3.2 (1.2); 64	3.4 (1.3); 70	0.264
Prostate volume, % (*n*)°	Small <30 mL Medium 31-50 mL Large >50 mL	17 (17) 46 (47) 37 (38)	21 (21) 48 (49) 31 (32)	0.614
PSA level, ng/mL, mean (SD); *n*		4.2 (3.3); 90	3.9 (3.9); 85	0.576
Q_{max} mL/s, mean (SD); *n*[+]		12.3 (5.1); 61	11.3 (4.6); 55	0.286
Post-void residual urine, % (*n*)	0-50 mL 51-100 mL 101-150 mL 151-200 mL >200 mL	34 (21) 28 (17) 15 (9) 7 (4) 16 (10)	49 (26) 19(10) 10 (5) 11 (6) 11 (6)	0.361
Time to completion of questionnaire, months, mean (SD)		5.3 (1.7)	7.0 (1.4)	<0.001

Q_{max}, maximum urinary flow rate. Percentages do not include missing data. QoL: Quality of Life measured by a single item. [x]Education: low (no primary school, lower general secondary education or lower vocational training), medium (higher general secondary education, vocational training), high (high vocational training and university). °Prostate volume is measured by rectal examination or trans rectal prostate ultrasound. [+]Voided volume was at least 150 mL.

DA-users had higher knowledge scores than the controls (mean score 3.1 vs 2.1; *P* = 0.009; Table S2). The proportion of patients who made a well-informed decision was higher in DA-users than in controls (62% vs 36%; *P* = 0.040). Overall, value statements discriminated well between treatments, better amongst DA-users than controls (Table 3). Value congruence scores (congruence between value statements and chosen treatment) were higher in DA-users than in controls for patients who chose medication after consulting the urologist (mean score 5.6 vs 4.8; *P* = 0.012; Table 4). There were no differences in value congruence scores between groups for patients who chose surgery or lifestyle advices. There were no differences in value congruent decision between groups (64% vs 55%; *P* = 0.165). To investigate *decision quality*, scores of well-informed decision and value congruent decision were combined, resulting in a higher proportion of *decision quality* in patients in the DA group than in the control group (43% vs 21%; *P* = 0.028; Table 4).

Overall decisional conflict was lower in the DA patients than in controls (mean score 33.2 vs 46.6; *P* = 0.003), in particular in the informed (mean score 37.3 vs 57.9; *P* < 0.001) and value clarity (mean score 36.9 vs 58.2; *P* = 0.001) subscales. DA-users experienced marginally more involvement in the SDM process (SDM-Q-9 mean score 3.3 vs 2.9; *P* = 0.049) and perceived a less passive role (CPS) than controls (22% vs 41%; *P* = 0.038). Satisfaction with perceived role in decision-making was similar between groups (Table 4).

DA-users who had not used prior medication at the time of consulting their urologist, chose lifestyle advices more often than the controls who had not used prior medication (43% vs 11%; *P* = 0.002). However, no differences in treatment choices were found in patients who had used prior medication. The surgical rate did not differ between groups. DA-users had significantly less process regret than controls (mean score 2.4 vs 2.8; *P* = 0.034). Option, outcome, and overall regret (Brehaut Scale) did not differ between groups (Table 4).

Discussion

Implementation of the web-based DA in clinical practice improved *decision quality* for patients deciding on treatments for LUTS/BPH. Furthermore, overall decision conflict was lower in DA-users. More specifically, they felt more informed and were clearer about their values. Involvement in the SDM process was slightly higher in the DA group than in the control group and DA-users experienced a less passive role. DA-users who had not used prior medication before consulting their urologist chose lifestyle advices

more often than controls. Although DA-users had less process regret, the other aspects of regret did not differ between the groups. Additionally, the impact on surgical rate did not differ between DA-users and controls.

To the best of our knowledge, this is the first study to have investigated the effectiveness of a LUTS/BPH DA on improving *decision quality* by comparing DA patients with control patients. Investigating *decision quality* is challenging, as standardised quantification methods are lacking. In the present study, we attempted to quantify it by combining the two key elements of *decision quality*: well-informed decision and value congruent decision. Well-informed decision was assessed by using a disease-specific knowledge questionnaire. Similar to previous studies that measured LUTS/BPH knowledge amongst patients in SDM programmes, DA-users had higher mean knowledge scores than patients who received usual care (3.1 vs 2.1; $P = 0.012$) [17, 21]. Evaluation of value congruent decision is relatively new. Only one study has investigated the association between ratings of possible health outcomes and actual treatment decisions amongst patients with LUTS/BPH before [20]. A systematic review by Munro *et al*. showed the supportive value of DAs in making value congruent decisions in different clinical settings [34]. Although not significant, we did find relatively higher proportions of patients who made a value congruent decision, with higher proportions in the DA than in the control group (64% vs 55%). Moreover, the proportion of patients who made both a well-informed and congruent decision was significantly higher in the DA than in the control group.

Table 3. Importance of individual value statements by chosen treatment

Value statements, score	Lifestyle advices	Medication	Surgery	η^2	*P*-value
DA-users, *n*	**24**	**64**	**10**		
My urinary symptoms bothered me so much, that I wanted active treatment	4.3	6.6	7.7	0.158	<0.001
I wanted to avoid taking medication daily	5.3	3.2	7.1	0.160	<0.001
I wanted to avoid taking medication because of side effects	5.5	3.1	5.8	0.131	0.001
I wanted to postpone surgery as long as possible	7.3	7.5	4.7	0.078	0.021
I wanted to postpone surgery because of the risks	7.3	7.6	4.4	0.120	0.002
I wanted a one-time treatment for my urinary symptoms	5.0	3.9	8.1	0.158	<0.001
I wanted a treatment with the highest chance of permanent effect	7.5	7.0	8.5	0.031	0.227
I wanted a treatment with the highest chance of significant improvement of my urinary stream force	7.3	6.7	8.5	0.047	0.102
I wanted a treatment with the highest chance of significant improvement of my urinary symptoms	7.4	7.6	8.7	0.028	0.257
Controls, *n*	**17**	**77**	**13**		
My urinary symptoms bothered me so much, that I wanted active treatment	4.0	6.8	8.3	0.177	<0.001
I wanted to avoid taking medication daily	3.9	4.0	7.3	0.102	0.005
I wanted to avoid taking medication because of side effects	5.0	3.2	6.1	0.098	0.006
I wanted to postpone surgery as long as possible	5.3	6.6	4.8	0.041	0.121
I wanted to postpone surgery because of the risks	5.8	6.2	4.4	0.030	0.221
I wanted a one-time treatment for my urinary symptoms	4.4	5.7	7.2	0.038	0.143
I wanted a treatment with the highest chance of permanent effect	7.3	8.0	9.5	0.055	0.061
I wanted a treatment with the highest chance of significant improvement of my urinary stream force	6.2	7.3	8.3	0.036	0.161
I wanted a treatment with the highest chance of significant improvement of my urinary symptoms	7.3	8.4	8.7	0.029	0.232

Cell entry is the mean on value statement (0 = not important to me, 10 = very important to me) computed for those choosing a specific treatment. Eta squared (η^2) and *P*-value from one-way analysis of explained variance.

Table 4. Differences in all outcome measures between DA-users and controls (*n* = 217)

Variables	Categories / range	DA users (*n* = 109)	Controls (*n* = 108)	Unadjusted		Adjusted[+]	
				β estimate/ OR (95% CI)	*P*-value	*β* estimate/ OR (95% CI)	*P*-value
Decision quality							
Informed choice	Total correctly answered questions, mean (SD); *n*	3.1 (1.8); 98	2.1 (1.7); 105	1.1 (0.6;1.6)	<0.001	0.6 (0.2;1.2)	0.009[I]
	Knowledge score >3/7, % (*n*/*N*)	62 (61/98)	36 (38/105)	2.9 (1.6;5.1)[¶]	<0.001	2.1 (1.0;4.1) [¶]	0.040[I]
Value congruent choice	Lifestyle advices, mean (SD); n Medication, mean (SD); n	4.9 (1.5); 24 5.6 (1.2); 63	4.5 (1.6); 16 4.8 (1.3); 72	0.3 (-0.7;1.3) 0.8 (0.4;1.2)	0.514 <0.001	0.4 (-0.7;1.4) 0.6 (0.1;1.1)	0.483 0.012[I]
	Surgery, mean (SD); n	7.3 (1.2); 10	7.3 (1.0);12	0.0 (-1.0;1.0)	0.948	-0.5 (-1.5;0.5)	0.336
	Mean value congruent score >5, % (*n*/*N*)	64 (62/97)	55 (55/100)	1.4 (0.8;2.5)[¶]	0.203	1.6 (0.8;3.2)[¶]	0.165
Informed and value congruent choice	Knowledge score >3/7 and mean value score >5, % (*n*/*N*)	43 (42/97)	21 (21/99)	2.8 (1.5;5.3)[¶]	0.001	2.3 (1.1;4.7)[¶]	0.028[I]
Decision process							
DCS	Total, mean (SD); n	33.2 (18.7); 95	46.6 (21.2); 92	-13.4 (-19.2;-7.6)	<0.001	-9.8 (-16.4;-3.3)	0.003[I]
	Informed subscale, mean (SD); n	37.3 (25.8); 96	57.9 (27.8); 106	-20.6 (-28.1;-13.2)	<0.001	-16.3 (-25.0;-7.7)	<0.001[I]
	Values clarity subscale, mean (SD); n	39.6 (25.1); 97	58.2 (28.1); 106	-18.6 (-26.0;-11.2)	<0.001	-14.6 (-23.2; -5.9)	0.001[I]
	Support subscale, mean (SD); n	28.7 (20.2); 97	42.3 (23.7); 105	-13.6 (-19.7;-7.5)	<0.001	-9.1 (-16.2;-2.0)	0.012[I]
	Uncertainty subscale, mean (SD); n	32.2 (23.2); 97	43.9 (29.8); 106	-11.7 (-19.1;-4.2)	0.002	-6.8 (-15.5;1.9)	0.124
	Effective decision subscale, mean (SD); n	30.3 (20.2); 97	37.6 (24.2); 105	-7.3 (-13.5;-1.1)	0.022	-4.8 (-12.1;2.4)	0.189
SDM-Q-9	mean (SD); n	3.3 (1.1); 96	2.9 (1.2); 96	0.5 (0.2;0.8)	0.004	0.4 (-0.0;0.7)	0.049[I]
Perceived role in decision-making	Provider-led, % (*n*)	22 (21)	41 (40)	2.2 (1.1;4.5)[¶]	0.029	2.5 (1.0;5.8)[¶]	.038[I]
	Shared, % (*n*)[*]	38 (36)	31 (31)				
	Patient-led, % (*n*)	40 (38)	28 (27)	0.8 (0.4;1.6)[¶]	0.584	0.9 (0.4;2.1)[¶]	0.884
	Satisfied with participation, % (*n*)	89 (85)	79 (79)				
	Would rather have a more active role, % (*n*)	11 (10)	21 (21)	0.4 (0.2;1.0)[¶]	0.049	0.5 (0.2;1.4)[¶]	0.161

table continues

Variables	Categories / range	DA users (*n* = 109)	Controls (*n* = 108)	Unadjusted		Adjusted[+]	
				β estimate/ OR (95% CI)	*P*-value	*β* estimate/ OR (95% CI)	*P*-value
	Would rather have a more passive role, % (*n*)	-	-		-		-
Decision outcomes							
First treatment choice after consultation the urologist	*Patients who did not use medication before:*						
	Lifestyle advices, % (*n*)	43 (20)	11 (6)	0.2 (0.1;0.4)¶	<0.001	0.2 (0.0;0.6)¶	0.002[†]
	Medication, % (*n*)**	51 (24)	87 (48)	-	-	-	-
	Surgery, % (*n*)	6 (3)	2 (1)	0.2 (0.0;1.7)¶	0.129	0.2 (0.0;2.4)¶	0.206
	Patients who used medication before:						
	Lifestyle advices, % (*n*)	3 (2)	2 (1)	0.5 (0.0;6.2)¶	0.623	0.9 (0.1;13.5)¶	0.945
	Medication, % (*n*)**	81 (50)	87 (46)	-	-	-	-
	Surgery, % (*n*)	16 (10)	11 (6)	0.7 (0.2;1.9)¶	0.441	0.6 (0.2;1.8)¶	0.393
Surgical rate	Decision for surgical treatment < 3 months, % (*n*)	12 (13)	11 (12)	0.8 (0.3;2.0)¶	0.851	0.8 (0.3;2.2)¶	0.945
New regret scales	Process regret, mean (SD); n	2.4 (0.7); 96	2.8 (0.7); 96	-0.3 (-0.6;-0.2)	<0.001	-0.3 (-0.5;0.2)	0.034[†]
	Option regret, mean (SD); n	2.1 (0.8); 96	2.3 (0.7); 96	-0.2 (-0.4;0.0)	0.116	0.0 (-0.3;0.2)	0.727
	Outcome regret, mean (SD); n	2.1 (0.8); 95	2.3 (0.7); 96	-0.1 (-0.4;0.1)	0.181	0.0 (-0.3;0.2)	0.904
Brehaut regret	mean (SD); n	2.1 (0.8); 95	30.3 (17.7); 96	-0.1 (-0.4;0.1)	0.117	-0.6 (-5.1;6.3)	0.844

Adjusted *P*-value is adjusted for age, level of education, time between first consultation and completion of questionnaire, and accounted for between-hospital heterogeneity with multivariable multilevel regression analyses. For linear regression analyses, the adjusted and unadjusted β coefficient with 95% CI are presented. For logistic and multinomial regression, the adjusted and unadjusted odds ratios (ORs) with 95% CIs are presented. The risk association with treatment arm is presented with the control group as reference. Percentages do not include missing cases. [†] Significant (P < 0.05). [‡] The reference category is 'shared'. ** The reference category is 'medication'. ¶ OR.

Together with the reduction of decisional conflict, less passive role in decision-making, and less process regret our findings suggest that the LUTS/BPH DA facilitates an improvement of *decision quality* and the decision-making process.

We also hypothesised that by providing patients with the DA, patients would choose conservative treatments more often. Consistent with this hypothesis, previous studies already demonstrated increased preferences for more conservative LUTS/BPH treatments after DA use [18, 19]. Some studies even showed that DA use may lower elective surgical rates [9-11]. Our present results only support less use of medication in the subgroup of DA-users who had not used prior medication before consultation, without an effect on surgical interventions. Thus, by improving patient knowledge, they were not only more empowered to choose the treatment that reflected their own values, but they also choose more conservative treatments if they had not used prior medication.

In contrast to a systematic review of RCTs for DAs [9], our study was not a randomised comparison of the DA and control groups. Nonetheless, we reason that the present study's pragmatic approach is a strength. In order to fit clinical practice, we allowed participating hospitals to integrate DA introduction with their own standard information provision routines, resulting in a viewing rate of 90%. This is a high percentage compared to the 25% [35] and 37% [36] described in the literature which may partly be explained by the mode of delivery [14]. In one study they used the automatic method of mailing the DA to men eligible for prostate cancer screening [35]. In the present study, most patients were directed to use the DA by either their urologist or the nurse. This approach may have promoted the viewing rate and successful DA implementation after the end of study. Furthermore, in order to respond to some barriers experienced by physicians with implementing DAs, such as lengthening consultation, patients were able to access the DA at home. The fact that the DA was developed using a Delphi study with urologists and patients with LUTS/BPH, and that five Dutch hospitals with different clinical practices participated in this study, suggests that our results are generalisable and further disseminating of the DA is feasible [25].

There are several limitations of the present study. First, to enable comparison with patients who received usual care, a 'historical' control group was used. Besides our goal to achieve successful implementation of the DA, we chose this design to avoid potential contamination of controls that might have occurred if urologists were required to use the DA for some patients and not others. However, historical controls come with their own bias, explaining the low response rate on questionnaires of 36%

amongst controls. The response rate might be extra low due to the benign nature of the disease. As urologists were aware that they participated in the present study, it is likely that they have encouraged patients more in decision-making than they usually would do. Furthermore, urologists could have applied their own selection criteria when offering the DA to patients resulting in selection bias. Significant differences in baseline characteristics between groups support this assumption. The mean age was lower in DA-users and education level was higher in the DA-users than in controls. In order to adjust for such group differences, we corrected outcomes for age, education level, and hospital. In addition, this non-randomised study design might have resulted in selection bias as variables, such as patient's personality, intelligence and mental health status, were not considered and adjusted for but which could have influenced the impact of the DA on the outcome measures.

A second limitation might be that results are influenced by the moment of completing the questionnaire. Although both groups were supposed to complete the questionnaire at the same time, there was significant difference in the time between first consultation with the urologist and completion of the questionnaire between groups (mean 5.3 vs 7.0 months). As preferences can change over time, this difference may have influenced the responses of controls on value statements [37]. Furthermore, it may be possible that disease-specific knowledge about LUTS/BPH diminishes after a few months. This may explain the overall low knowledge scores amongst patients in both groups, with significantly lower knowledge scores in the control group. Ideally, it would have been more appropriate to ask for patients' preferences before the treatment decision was made and to assess knowledge directly after the decision was made [26]. Furthermore, adverse clinical outcomes or side effects of treatments could have negatively influenced responses on decisional process measures. In order to adjust for group differences, we corrected outcomes for time between the first consultation with the urologist and questionnaire completion, next to age, education level, and hospital.

Lastly, we were not able to demonstrate an effect of the DA on prostatic surgical rates. Results of previous RCTs for LUTS/BPH DAs on this outcome varied between no difference to lower surgical rate amongst DA-users [13, 21]. The Cochrane review also describes that DA implementation does not result in a decrease in elective surgical rates in diseases where baseline surgical rates are already low (e.g., LUTS/BPH) [9]. Nevertheless, results on surgical rate in LUTS/BPH remain to be elucidated.

In conclusion, implementation of the web-based LUTS/BPH DA with standardised information based on current guidelines and assessment of personal preferences

seems to improve well-informed and value congruent treatment decisions, and thereby *decision quality*. Furthermore, results on treatment choice indicate that patients who are informed by the DA on the risks and benefits of treatments, choose lifestyle advices more often if they do not use prior medication. Our present findings are of importance in informing clinicians on how this LUTS/BPH DA can serve as guide to support the SDM process by helping well-informed patients choose treatments that reflect their individual preferences.

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References

1. Egan KB. The Epidemiology of Benign Prostatic Hyperplasia Associated with Lower Urinary Tract Symptoms: Prevalence and Incident Rates. Urol Clin North Am. 2016;43(3):289-97.
2. Martin SA, Haren MT, Marshall VR, Lange K, Wittert GA. Prevalence and factors associated with uncomplicated storage and voiding lower urinary tract symptoms in community-dwelling Australian men. World journal of urology. 2011;29(2):179-84.
3. Agarwal A, Eryuzlu LN, Cartwright R, et al. What is the most bothersome lower urinary tract symptom? Individual-and population-level perspectives for both men and women. European urology. 2014;65(6):1211-7.
4. Gratzke C, Bachmann A, Descazeaud A, et al. EAU guidelines on the assessment of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. European urology. 2015;67(6):1099-109.
5. Diagnostics and treatment of LUTS/BPH. Dutch association of Urology; 2006.
6. Emberton M. Medical treatment of benign prostatic hyperplasia: physician and patient preferences and satisfaction. International journal of clinical practice. 2010;64(10):1425-35.
7. Harkaway RC. What are the views of patients and urologists on benign prostatic hyperplasia and its management? european urology supplements. 2007;6(6):454-9.
8. Elwyn G, O'connor A, Stacey D, et al. Developing a quality criteria framework for patient decision aids: online international Delphi consensus process. Bmj. 2006;333(7565):417.
9. Stacey D, Légaré F, Lewis K, et al. Decision aids for people facing health treatment or screening decisions. The Cochrane Library. 2017.
10. Knops AM, Legemate DA, Goossens A, Bossuyt PM, Ubbink DT. Decision aids for patients facing a surgical treatment decision: a systematic review and meta-analysis. Annals of surgery. 2013;257(5):860-6.
11. Rovner DR, Wills CE, Bonham V, et al. Decision aids for benign prostatic hyperplasia: applicability across race and education. Med Decis Making. 2004;24(4):359-66.
12. Barry MJ CD, Chang Y, FJ JF, Skates S. A randomized trial of a multimedia shared decision-making program for men facing a treatment decision for benign prostatic hyperplasia. Disease Management and Clinical Outcomes. 1997;1(1):5-14.
13. Arterburn D, Wellman R, Westbrook EO, et al. Decision aids for benign prostatic hyperplasia and prostate cancer. The American journal of managed care. 2015;21(2):e130-40.
14. Elwyn G, Scholl I, Tietbohl C, et al. "Many miles to go …": a systematic review of the implementation of patient

decision support interventions into routine clinical practice. BMC Med Inform Decis Mak. 2013;13 Suppl 2:S14.

15. Murray E, Davis H, Tai SS, et al. Randomised controlled trial of an interactive multimedia decision aid on benign prostatic hypertrophy in primary care. Bmj. 2001;323(7311):493-6.
16. Piercy GB, Deber R, Trachtenberg J, et al. Impact of a shared decision-making program on patients with benign prostatic hyperplasia. Urology. 1999;53(5):913-20.
17. Holmes-Rovner M, Price C, Rovner DR, et al. Men's theories about benign prostatic hyperplasia and prostate cancer following a benign prostatic hyperplasia decision aid. Journal of general internal medicine. 2006;21(1):56-60.
18. Wills CE, Holmes-Rovner M, Rovner D, et al. Treatment preference patterns during a videotape decision aid for benign prostatic hyperplasia (BPH). Patient education and counseling. 2006;61(1):16-22.
19. Wagner EH, Barrett P, Barry MJ, Barlow W, Fowler Jr FJ. The Effect of a Shared Decisionmaking Program on Rates of Surgery for Benign Prostatic Hyperplasia Pilot Results. Medical care. 1995;33(8):765-70.
20. Barry MJ, Fowler Jr FJ, Mulley Jr AG, Henderson Jr JV, Wennberg JE. Patient reactions to a program designed to facilitate patient participation in treatment decisions for benign prostatic hyperplasia. Medical care. 1995;33(8):771-82.
21. Barry MJ, Cherkin DC, Chang Y, FJ JF, Skates S. A randomized trial of a multimedia shared decision-making program for men facing a treatment decision for benign prostatic hyperplasia. Disease Management and Clinical Outcomes. 1997;1(1):5-14.
22. Vickers AJ. Decisional Conflict, Regret, and the Burden of Rational Decision Making. Med Decis Making. 2017;37(1):3-5.
23. Nelson WL, Han PK, Fagerlin A, Stefanek M, Ubel PA. Rethinking the objectives of decision aids: a call for conceptual clarity. Med Decis Making. 2007;27(5):609-18.
24. Kennedy AD. On what basis should the effectiveness of decision aids be judged? Health Expect. 2003;6(3):255-68.
25. Lamers RE, Cuypers M, Garvelink MM, et al. Development of a decision aid for the treatment of benign prostatic hyperplasia: A four stage method using a Delphi consensus study. Patient education and counseling. 2016;99(7):1249-56.
26. Sepucha K, Ozanne EM. How to define and measure concordance between patients' preferences and medical treatments: A systematic review of approaches and recommendations for standardization. Patient education and counseling. 2010;78(1):12-23.
27. Sepucha K. Benign Prostatic Hyperplasia *Decision quality* Instrument v.1.0. 2010.
28. O'Connor AM. Validation of a decisional conflict scale. Medical decision making.

1995;15(1):25-30.

29. Rodenburg-Vandenbussche S, Pieterse AH, Kroonenberg PM, et al. Dutch translation and psychometric testing of the 9-item Shared Decision Making Questionnaire (SDM-Q-9) and Shared Decision Making Questionnaire-Physician version (SDM-Q-Doc) in primary and secondary care. PloS one. 2015;10(7):e0132158.
30. Degner LF, Sloan JA, Venkatesh P. The control preferences scale. Canadian Journal of Nursing Research Archive. 1997;29(3).
31. Tol-Geerdink JJ, Leer JWH, Wijburg CJ, et al. Does a decision aid for prostate cancer affect different aspects of decisional regret, assessed with new regret scales? A randomized, controlled trial. Health Expectations. 2016;19(2):459-70.
32. Brehaut JC, O'Connor AM, Wood TJ, et al. Validation of a decision regret scale. Med Decis Making. 2003;23(4):281-92.
33. Barry MJ, Fowler FJ, O'leary MP, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Journal of urology. 2017;197(2):S189-S97.
34. Munro S, Stacey D, Lewis KB, Bansback N. Choosing treatment and screening options congruent with values: Do decision aids help? Sub-analysis of a systematic review. Patient education and counseling. 2016;99(4):491-500.
35. Brackett C, Kearing S, Cochran N, Tosteson AN, Blair Brooks W. Strategies for distributing cancer screening decision aids in primary care. Patient Educ Couns. 2010;78(2):166-8.
36. Uy V, May SG, Tietbohl C, Frosch DL. Barriers and facilitators to routine distribution of patient decision support interventions: a preliminary study in community-based primary care settings. Health Expect. 2014;17(3):353-64.
37. Frosch DL, Kaplan RM, Felitti V. The evaluation of two methods to facilitate shared decision making for men considering the prostate-specific antigen test. J Gen Intern Med. 2001;16(6):391-8.

Supplementary Table 1. Relation of scores on value statements and chosen treatment

	Lifestyle advices	**Medication**	**Surgery**
Value statements			
My urinary symptoms bothered me so much, that I wanted active treatment	Low	High	High
I wanted to avoid taking medicine daily	High	Low	High
I wanted to avoid taking medicine because of side effects	High	Low	High
I wanted to postpone surgery as long as possible	High	High	Low
I wanted to postpone surgery because of the risks	High	High	Low
I wanted a one-time treatment for my urinary symptoms	Low	Low	High
I wanted a treatment with the highest chance of permanent effect	Low	Low	High
I wanted a treatment with the highest chance of a significant improvement of my urinary stream force	Low	Low	High
I wanted a treatment with the highest chance of significant improvement of my urinary symptoms	Low	Low	High

Cell entry demonstrate if 'high' or 'low' scores on value statements correspond with chosen treatment option at time of filling in the questionnaire.

Supplementary Table 2. Responses on knowledge items

Questions and statements	**DA-users** (*n*=109)	**Controls** (*n*=108)	***P*-value**
Benign enlargement of the prostate increases the risk of prostate cancer.	51% (50)	33 % (35)	0.008
What is NOT a treatment option for urinary symptoms due to benign enlargement of the prostate ?	26% (25)	16% (17)	0.088
What is NOT a complication of benign enlargement of the prostate?	26% (25)	14% (15)	0.038
All kinds of medication can prevent progress of urinary symptoms due to benign enlargement of the prostate.	64% (63)	52% (56)	0.083
Medication for the treatment of urinary symptoms due to benign enlargement of the prostate is usually necessary for the rest of life.	62% (61)	41% (44)	0.003
Which treatment option causes the greatest improvement on the urinary stream force?	62% (61)	31% (33)	0.000
Which long-term side-effect of surgery is most common?	29% (28)	17% (18)	0.004

Percentage correctly answered questions. Percentages do not include missing cases.

Appendix S1. Description of statistical analyses of primary outcome measure *decision quality,* defined as well-informed and value congruent decision.

Outcome analysis for our primary outcome *decision quality* was conducted as follows. First, to calculate well-informed decision a post-hoc threshold level (≥3/7) of correctly answered knowledge items was considered [1]. Second, to calculate value congruent decision, the match between value statements and chosen treatment (at moment of questionnaire completion) was calculated by first recoding the scores on the nine value statements. Then the association between the statements and treatments (lifestyle advices/medication/surgery) was calculated with one-way ANOVA and compared between groups. The explained variance (eta squared) was used as overall measure of association of value statements and chosen treatment. The magnitude of the explained variance was compared between both groups to test for differential levels per group [2]. Value congruent decision was defined as mean value agreement score above five. Finally, the proportion of patients who had made a well-informed and value congruent decision were combined to evaluate the *decision quality* outcome. The use of this matching calculation method has been described in previous studies [3-5].

References

1. Sepucha KR, Borkhoff CM, Lally J, et al. Establishing the effectiveness of patient decision aids: key constructs and measurement instruments. BMC medical informatics and decision making. 2013;13(2):S12.
2. Solberg LI, Asche SE, Sepucha K, et al. Informed choice assistance for women making uterine fibroid treatment decisions: a practical clinical trial. Medical Decision Making. 2010;30(4):444-52.
3. Sepucha K, Ozanne EM. How to define and measure concordance between patients' preferences and medical treatments: A systematic review of approaches and recommendations for standardization. Patient education and counseling. 2010;78(1):12-23.
4. Winn K, Ozanne E, Sepucha K. Measuring patient-centered care: an updated systematic review of how studies define and report concordance between patients' preferences and medical treatments. Patient education and counseling. 2015;98(7):811-21.
5. Schwalm J-D, Stacey D, Pericak D, Natarajan MK. Radial artery versus femoral artery access options in coronary angiogram procedures. Circulation: Cardiovascular Quality and Outcomes. 2012;5(3):260-6.

Chapter 3

Treatment preferences of patients with benign prostatic hyperplasia before and after using a web-based decision aid

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Abstract

Objective

To evaluate treatment preferences of patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH) before and after using a web-based decision aid (DA).

Patients and Methods

Between July 2016 and January 2017 patients were invited to use a web-based LUTS/BPH DA. Treatment preferences (for lifestyle advices, medication or surgery) before and after DA use and responses on values clarification exercises (VCEs) were extracted from the DA.

Results

In total, 126 patients were included in the analysis. Thirty-four percent (43/126) had not received any previous treatment and were eligible for (continuation of) lifestyle advices or to start medication, as initial treatment. The other 66% percent (83/126) did use medication and were eligible, either for continuing medication or to undergo surgery. Before being exposed to the DA, 67 patients (53%) were undecided and 59 patients (47%) indicated an initial treatment preference. Half of the patients who were initially undecided were able to indicate a preference after DA use (34/67, 51%). Of those with an initial preference, 80% (47/59) confirmed their initial preference after DA use. Five out of 7 values clarification exercises used in the DA were discriminative between final treatment preferences. In 79%, the treatment preferred after DA use matched the received treatment. Overall, healthcare providers were positive about DA feasibility.

Conclusion

Our findings suggest that a LUTS/BPH DA may help patients to confirm their initial treatment preference and support them in forming a treatment preference if they did not have an initial preference.

Keywords

Benign Prostatic Hyperplasia, Lower Urinary Tract Symptoms, decision aid, shared decision-making, treatment

Introduction

Prevalence rates of lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH) range from 50% to 75% among men over the age of 50 years and increase with age.[1] Symptoms can have substantial impact on quality of life.[2] Treatment options are watchful waiting, lifestyle advice, pharmacotherapy, or surgery. Indications for the various treatment options are not well defined in Dutch and European guidelines. Preferences and values of the individual patient are important factors in disease management, next to well-established factors like results of diagnostic tests, the estimation of disease progression and ability of treatments to reduce symptoms. Trade-offs must therefore be made between the expected benefits of treatment, the side effects, risks and burden of the treatments, and the disease burden itself.[3]

The majority of patients want to be involved in decision-making about their medical treatment; and once patients are well informed about their options, the need to be involved even increases.[4] However, observational research shows that a minority of healthcare providers consistently involve patients in the decision-making process.[5]

To support shared decision-making, decision aids (DAs) have been developed to assist patients and physicians in exploring patients' preferences, values and expectations. DAs provide standardized information in understandable language and help patients formulate a well-informed preference.[6] Previous research has shown that DA users feel more knowledgeable, are clearer about their values, take up a more active role in decision-making and have more accurate risk perceptions regarding treatment options compared to patients who were counseled without a DA. Furthermore, there is increasing evidence that DAs improve congruence between the chosen option and patients' values.[7-9]

Despite the high prevalence rate of LUTS/BPH, the development and evaluation of DAs in this area is far behind compared to other (oncological) conditions. Available LUTS/BPH DAs are outdated and conclusions are limited by variations in outcome measures.[10-17] We therefore developed a web-based DA with values clarification exercises (VCEs) to clarify patients' preferences and support shared decision-making in LUTS/BPH treatment counseling.[9, 18]

This study is a subanalysis of a prospective observational study on the effectiveness of the implementation of this DA in patients with LUTS/BPH, were the DA group was compared with a historical control group.[9] For this analysis, all patients who used the DA

were included. The aim of the current study was to zoom in on only DA users' treatment preference before and after exposure to the DA, as well as the match between their indicated values and preferred treatment, as well as subsequent congruence with received treatment.

Patients and methods

Study population

Between July 2016 and January 2017 patients from 5 hospitals in the Netherlands, who were diagnosed with LUTS/BPH by their urologist, were invited to use a web-based DA. Patients were eligible for inclusion if they had the choice between 2 treatment options; A: watchful waiting/lifestyle advices vs medication and B: (continuing) medication vs surgery. Patients had to have access to a desktop, laptop, or tablet with internet connection. Patients with prior prostate surgery, an absolute medical indication for surgery, prostate cancer, cognitive impairment, or insufficient knowledge of Dutch language were excluded.[9]

The intervention

The DA supports the following 2 treatment tradeoffs: treatment decision A (watchful waiting/lifestyle advices vs medication) and treatment decision B (continuing medication or surgery). Which tradeoffs apply to an individual patient/DA user is indicated by the urologist, based on current medication use.[9] Then, the DA guides the patient through the decision process step-by-step.

The DA contains general information about LUTS/BPH, diagnostics, and the various treatment options according to current guidelines.[3] Furthermore, patients are invited to respond to VCEs to obtain their individual preferences. The VCEs used in the DA are shown in Figure 1. With a pointer on a slider scale, patients could indicate the strength of their preference toward one of the treatment options. Finally, patients were asked to indicate their final treatment preference. The full DA development method has been described before.[18]

Procedure

After written informed consent, patients received online or paper questionnaires. Results from the questionnaires were linked to patients' DA data. Patients who did not return their informed consent form still had the opportunity to use the DA without participating in the study. The study was approved by the regional Medical Research Ethics Committee 'METC Brabant'.

Outcome measures

To assess the preferred role in decision-making, the Control Preference Scale was used prior to DA use and before treatment decision was made. Patients could respond on a 5-point Likert scale. Scores were summarized into 3 groups: active/active shared, collaborative, and passive/passive shared, to ease clinical interpretation.[19]

Patients had to indicate if they used medication for their urinary symptoms at time of this study. To quantify patients' LUTS, the validated International Prostate Symptom Score (IPSS) was used.[20] Level of education and age were obtained from completed questionnaires and patient records.

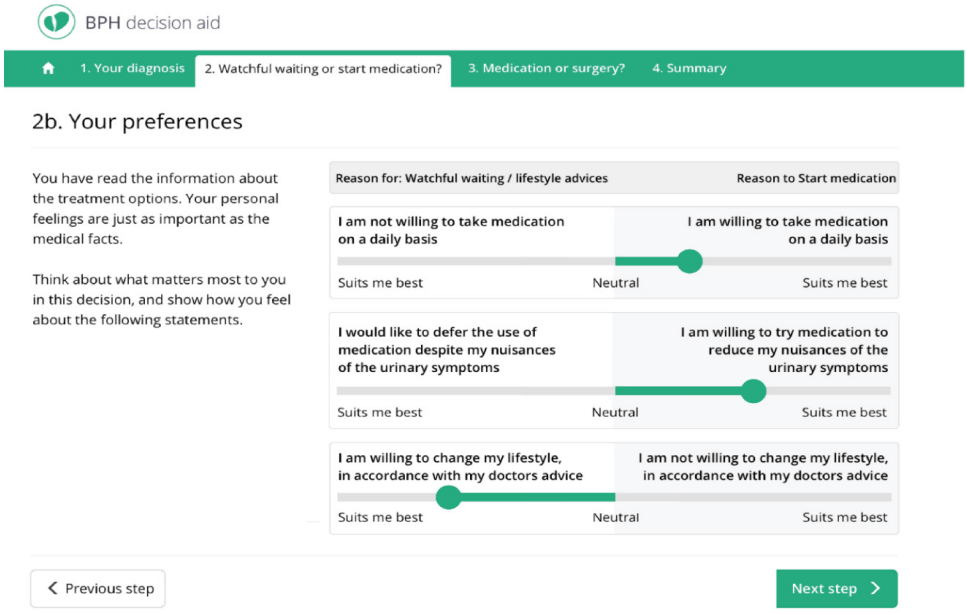
Treatment preferences and responses on VCEs were extracted from the DA. To assess the association between final preference in the DA and the received treatment, information about treatment decisions was collected from patient records.

Online questionnaires are used to evaluate healthcare professionals' satisfaction with the use of the DA. Questions were asked about attitude toward future use on which they could respond on a 5-point Likert scale, ranging from "mostly disagree" to "mostly agree". Finally, healthcare providers were asked to rate the overall quality of the DA on a scale from 1 to 10.

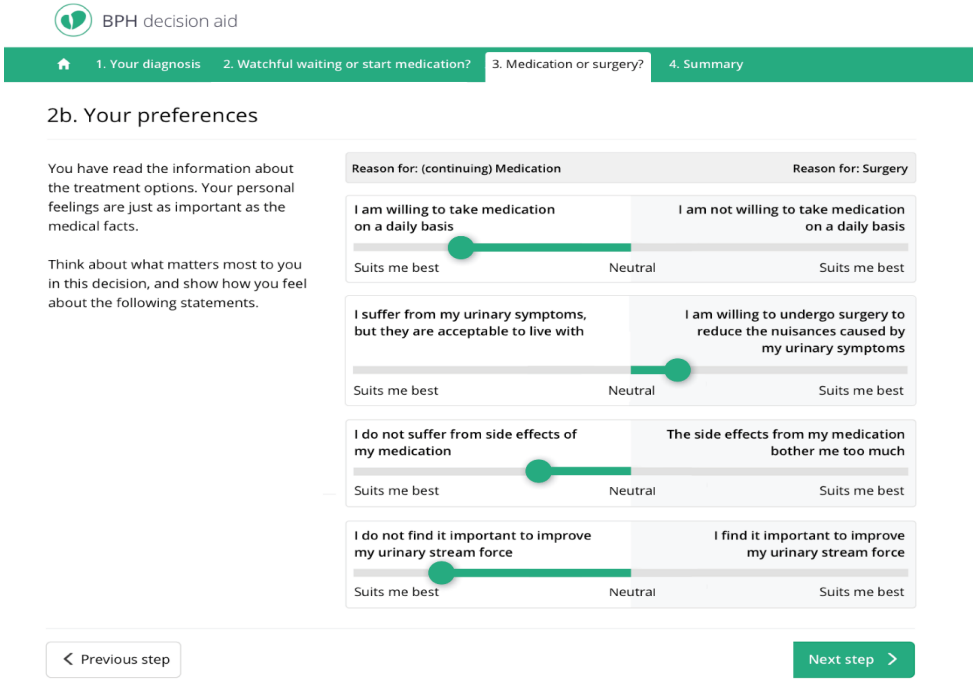
Statistical analysis

For continuous data, descriptive statistics were presented as means with standard deviations. Categorical data were presented as frequencies with percentages. Quantitative variables were examined with ANOVA and *t* tests when normality and homogeneity assumptions were satisfied. Non-normally distributed data were examined with a nonparametric test (Mann Whitney *U*). To compare proportions we used the Pearson chi-square test.

To analyze if individual VCE scores matched with final preferences at the end of the DA, responses were demonstrated in box-and-whisker plots. For both tradeoffs, a median VCE score of 0-39 indicated a preference for watchful waiting/lifestyle advices or (continuing) medication respectively, a median VCE score of 40-60 was not clearly pointing toward 1 particular treatment option and a score of 61-100 indicated a preference for starting medication or surgery (self-determined).To investigate the match between responses on VCEs and the received treatment, patients' mean VCE scores were calculated for decision A (3 VCEs) and B (4 VCEs).



Decision A



Decision B

Figure 1. Values clarification exercises used in the DA. Decision **A:** Watchful waiting/lifestyle advices vs medication, Decision **B:** Continuing medication vs surgery.

All analyses were conducted using the IBM Statistical Package for the Social Sciences (SPSS), version 24.0 (SPSS Inc., Chicago, IL, USA), with a $P < .05$ considered statistically significant.

Results

A total of 210 patients were invited for participation of whom 73% (154/210) returned the informed consent form. Eleven percent of these patients (17/154) were excluded based on exclusion criteria (no LUTS/BPH $N = 2$, absolute indication for surgery $N = 5$, prior prostate surgery $N = 5$, diagnosis of prostate cancer $N = 5$). After extraction of the DA user log data, 8% (11/137) of the patients appeared not to have used the DA and were excluded from analyses, 126 patients used the DA and were included for analyses (see supplemental file for flowchart).

Treatment preferences of 126 patients were obtained from DA log data both before and after DA use. Thirty-four percent (43/126) of these patients did not use medication for their LUTS and were eligible for decision A. Sixty-six percent (83/126) did use medication and were eligible for decision B. Response rate on questionnaires was 65% (126/193). Baseline characteristics are described in Table 1.

Treatment Preference Before and After DA use

Of all DA users, 53% (67/126) did not indicate an initial treatment preference. Fifty-one percent (34/67) of these patients were able to indicate a preference after DA use. Forty-nine percent (33/67) remained unable to decide after DA use.

In total, 47% (59/126) of patients indicated their initial preference before DA use. Of these patients 80% (47/59) stayed with their initial treatment preference and 19% (11/59) did not indicate a specific final treatment preference or were still undecided after DA use. Only 1 patient changed his initial treatment preference from medication to surgery after DA use (1/59).

Table 1. Patient-related characteristics of DA users (*N* = 126)

				***N* total (%)**	***P*-value**
Age (y), mean ± SD	67.8 ± 7.0				
Inclusion per hospital	A			50 (40)	
	B			34 (27)	
	C			21 (17)	
	D			12 (9)	
	E			9 (7)	
		No previous treatment (*Decision A*) *N* (%)	Prior medication use (*Decision B*) *N* (%)		
Education*	Low			42 (35)	
	Medium			29 (25)	
	High			48 (40)	
LUTS (IPSS score)	Mild (0-7)	7 (17)	5 (6)	12 (10)	.1
	Moderate (8-19)	24 (57)	43 (54)	67 (55)	
	Severe (20-35)	11 (26)	32 (40)	43 (35)	
Preferred role in decision-making	Active			55 (44)	
	Collaborative			63 (50)	
	Passive			8 (6)	

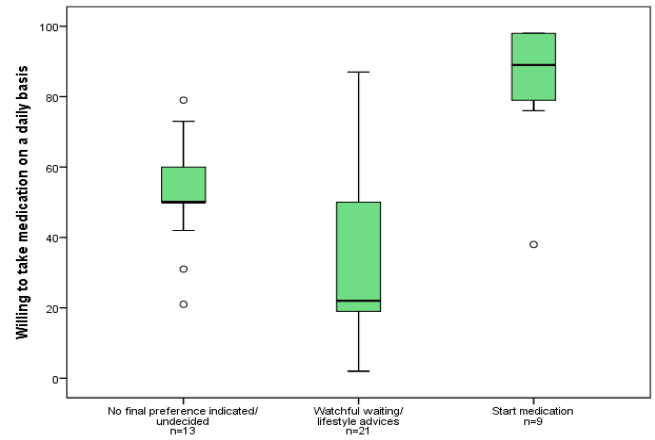
DA, decision aid. Percentages do not include missing values. * Education: low (no primary school, lower general secondary education or lower vocational training), medium (higher general secondary education, vocational training), high (high vocational training and university).

Responses on VCEs and Final Preference in DA

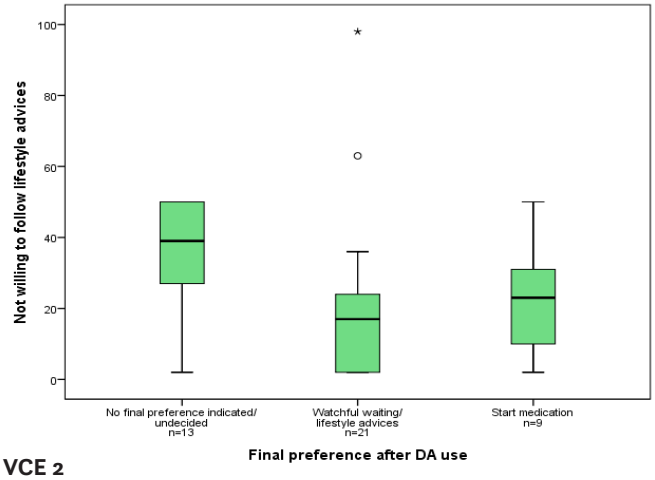
Used VCEs are demonstrated in Figure 1. For decision A, median scores of VCE 1 and 2 were congruent with final treatment preferences and were significantly different between preferences (P <.05). Median scores of VCE 3 were only congruent with final preference for 'watchful waiting/lifestyle advices' after DA use. Median scores of VCE 3 were not significantly different (P =.28) between final treatment preferences.

For decision B, median scores of VCE 4 and 5 were congruent with final treatment preferences and were significantly different between final treatment preferences (P <.05). Median score of VCE 6 was only congruent with final treatment preference for '(continuing) medication'. Median scores on this VCE were not significantly different between the final preferences (P =.35). Median score of VCE 7 was only congruent with final treatment preference 'surgery'. However, median scores of VCE 7 differed significantly between patients with final preference for '(continuing) medication' and 'surgery' (P <.05). Responses on all VCEs are illustrated in box-and-whisker plots (Figure 2).

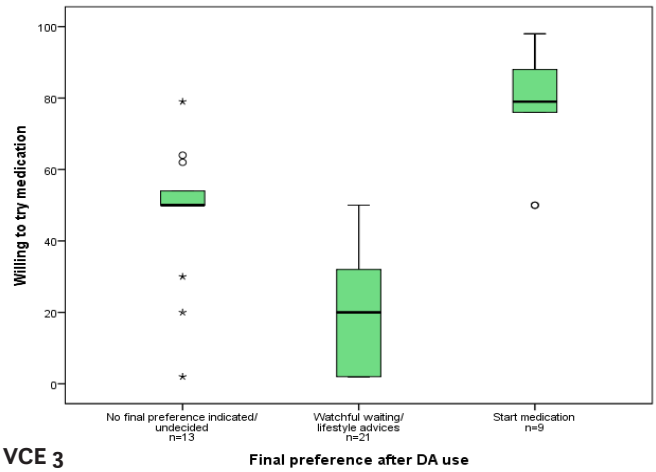
Decision A



VCE 1



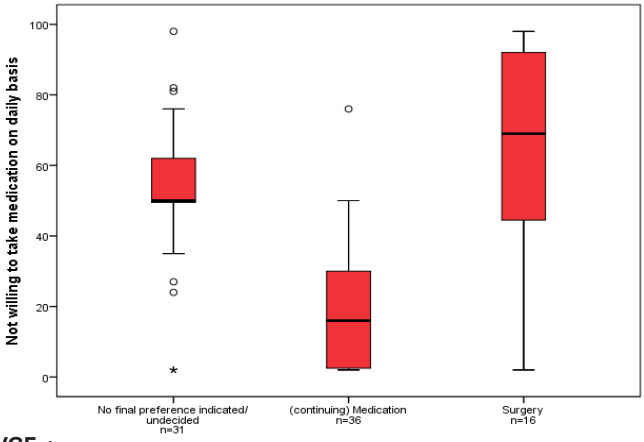
VCE 2



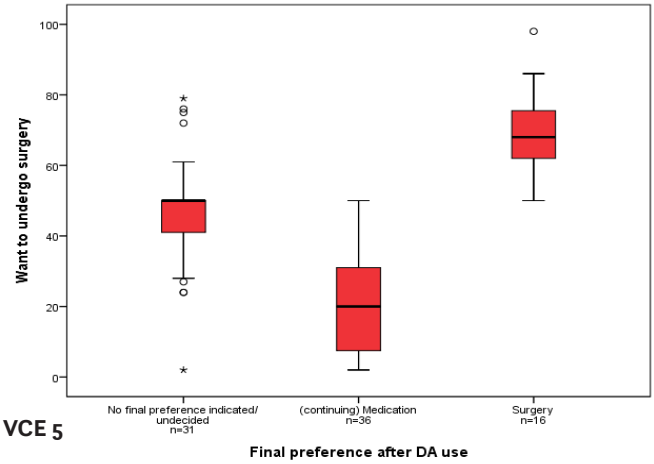
VCE 3

Figure 2. Patients' responses on VCEs. VCEs are named after the "active treatment" (*decision* **A**: toward medication and *decision* **B**: toward surgery). High scores correspond to concordance between statement and treatment option. Box represents 50% of the scores and the whiskers illustrate the minimum and maximum value. The horizontal line in the box represents the median. Dots(˚) are outliers and asterisks (*) are extremes.

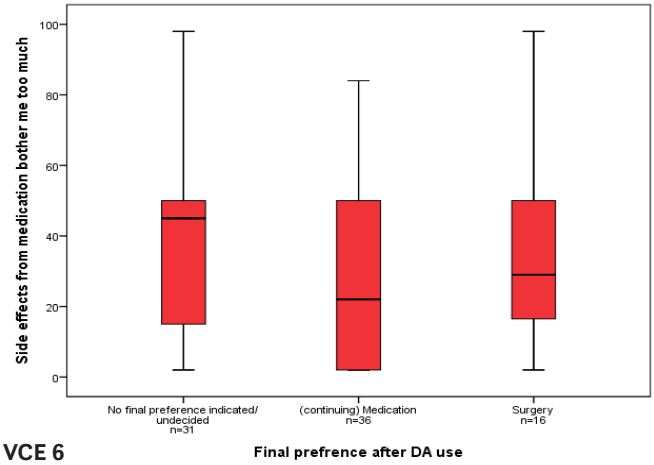
Decision B



VCE 4

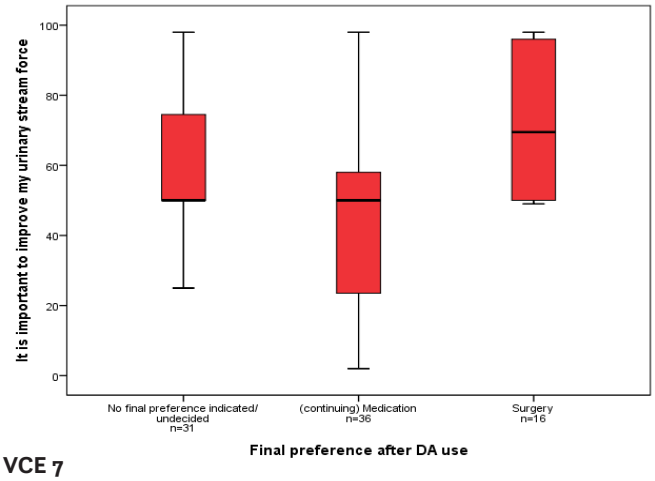


VCE 5



VCE 6

Figure 2 (continued). Patients' responses on VCEs. VCEs are named after the "active treatment" (*decision* **A**: toward medication and *decision* **B**: toward surgery). High scores correspond to concordance between statement and treatment option. Box represents 50% of the scores and the whiskers illustrate the minimum and maximum value. The horizontal line in the box represents the median. Dots(˚) are outliers and asterisks (*) are extremes.



VCE 7

Concordance Between Final Treatment Preference and Treatment Received

Sixty-five percent (82/126) of the patients were able to indicate a preferred treatment option after DA use (Table 2). At decision A, patients' final preferences for watchful waiting/lifestyle advices or starting medication, matched with their received treatment in 67% (14/21) and 100% (9/9), respectively. At decision B, 92% (33/36) of the final preference for (continuing) medication matched the received treatment.

From all study participants, their preferred treatment option after DA use matched with their received treatment in 79% (65/82) of the cases. Twenty-one percent (17/82) of the DA users received another treatment than indicated as final preference after DA use. Patients with a preference for surgery, underwent surgical treatment in 56% (9/16) and received medication in 44% (7/16) of the cases. Patients with a final preference for watchful waiting/ lifestyle advices were prescribed medication in 24% (5/21) of the patients and underwent surgery in 9% (2/21) of the patients. Three percent (1/36) received lifestyle advices and 5% (2/36) of the patients underwent surgery, in spite of their preference for (continuing) medication.

In only 29% (5/17) of these patients the mean calculated VCE score matched with their received treatment.

From all study participants, 35% (44/126) was not able to indicate a final preference after DA use. Of these patients 11% (5/44) received watchful waiting/lifestyle advices as treatment, 14% (6/44) received medication, and 5% (2/44) underwent surgery in decision A. In decision B, 2% (1/44) received watchful waiting/lifestyle advices as

treatment, 59% (26/44) continued medication, and 9% (4/44) underwent surgery. In these patients the calculated mean VCE score matched their received treatment in only 25% (11/44) or was not clearly associated with 1 treatment option in 57% (25/44).

Table 2. Treatment preferences before and after DA

Decision A: choice between watchful waiting/lifestyle advices vs medication			
	Initial treatment preferences		
Final treatment preferences	Watchful waiting/ lifestyle advices *N* = 15 *N*, (%)	Medication *N* = 11 *N*, (%)	No initial preference *N* = 17 *N*, (%)
Watchful waiting/lifestyle advices	12 (80)	-	9 (49)
Medication	-	9 (82)	-
Not indicated/ undecided	3 (20)	2 (18)	8 (47)
Decision B: choice (continuing) medication vs surgery			
	Initial treatment preferences		
Final treatment preferences	(continuing) Medication *N* = 20 *N* , (%)	Surgery *N* = 13 *N* , (%)	No initial preference *N* = 50 *N* , (%)
(continuing) Medication	17 (85)	-	19 (38)
Surgery	1 (5)	9 (69)	6 (12)
Not indicated/ undecided	2 (10)	4 (31)	25 (50)

Healthcare Professionals' Satisfaction with the DA

Healthcare professionals' response rate to online questionnaires was 40% (13 urologists, 11 residents, 2 nurses, 26/65). Seventy-seven percent (20/26) would recommend this DA to their colleagues and 69% (18/26) want to continue using this DA in the future. Mean number of overall satisfaction was 7.4 (standard deviations 1.0) (data not shown).

Discussion

The use of this LUTS/BPH DA in clinical practice demonstrates that it supports patients in forming and indicating a treatment preference after using the DA. In particular, when patients did not have an initial preference, they were able to indicate a preferred treatment after DA use (in 51%). Furthermore, 80% of patients with an initial preference found confirmation of this preference in the DA. Most VCEs used in this DA discriminated well between treatment options and matched with patients' final treatment preference. The percentage of patients with a clear treatment preference

increased from 47% before DA use to 65% after DA use. In the majority of the patients their preferred treatment matched their received treatment. Overall, healthcare providers were satisfied with the use of the DA in clinical practice, and most would recommend colleagues to use the DA.

Our results are in line with previous studies, showing that DAs are able to support patients in forming and indicating preferences about the treatment decision of LUTS/BPH.[15-17] Also, patients who indicated 1 specific preference before DA use, were in most cases (80%) confirmed in their initial treatment preference. Confirmation of the initially preferred treatment option is relevant, because patients gained more knowledge about possible risks, side effects, and alternative treatment options.[12, 15, 21-23] Perception of feeling more informed and being clearer about personal values was increased, which may result in lower decisional conflict.[7, 9] However, it might be possible that these patients read and interpreted the DA content in a selective way that confirmed their pre-existing preference, resulting in confirmation bias.

In agreement with our results, Piercy *et al*. demonstrated that a DA was not able to alter treatment preferences in most patients who had an initial preference for the treatment of LUTS/BPH.[15] However, few studies observed shifts in treatment preferences after DA use. One study showed that 38.8% of patients changed their preferences at least once while watching an educational DA videotape about LUTS/BPH.[22] These changes were equally balanced between watchful waiting and medication, with changes to surgery occurring only about 1/3 as frequently.[22]

After DA use one-third of the patients remained or became undecided. One could argue that these patients gained more knowledge about the different treatment options and risks which could have resulted in high decisional conflict scores indicating that they became more aware of the difficulty of the decision after DA use. However, it is not clear if these patients were truly undecided or just did not indicate a final preference (missing data).

In contrast to previously developed DAs for LUTS/BPH, this was the first DA to include VCEs to clarify patients' preferences.[18] Analysis of VCEs was done to indicate their discriminative power between treatment options.

Most VCEs in the DA were discriminative between final treatment preferences and congruent with final treatment preferences, which makes it easier for patients to relate their own preferences to the different treatment options. Since 2 VCEs (VCE 3 and VCE 6) did not discriminate between the treatment options, adjustments of these VCEs could be considered.

Most patients (79%) who indicated a preferred treatment after DA use also received that treatment. Previous studies showed comparable concordance rates (67- 93%).[24-28] Still, 1 in 5 patients (21%) in the present study did not receive the same treatment as preferred after DA use. Of this group, discrepancies between responses on VCEs, final treatment preference, and received treatment were observed, showing that some provided responses to VCEs that misaligned with their indicated post-DA treatment preference, but which did match their received treatment. Despite the fact that most of the VCEs discriminated well between treatment options, one can argue that the attributes (characteristics of treatment) of available treatments relevant to the individual patient were not included in the VCEs. Also, it could be possible that these patients may not have fully understood the use of the VCEs which resulted in discordance between their responses on VCEs and their final treatment preference. For other patients of whom their final preference did not match with their received treatment, their responses on VCEs neither matched with their received treatment nor with their final treatment preference. A possible explanation could be that their preferences were not discussed during consultation or that results of performed diagnostics changed their final treatment decision. Also, additional information provided by clinicians about side effects and complications of treatment options may have influenced patients' final treatment decision. Clinicians could affect the decision on unwarranted grounds as well, such as their personal preference and experience with different treatment options and bias in risk perception.

The participating hospitals were allowed to integrate the DA with their own standard information provision routines, with the aim to facilitate structural implementation of DA usage in routine clinical care. This may have resulted in the overall positive attitude of healthcare providers toward the usability of the DA in the decision-making process. They reported that procedural steps were clear and believed that DA use fitted in their daily practice. Thus, with this study (procedure) we demonstrated that some barriers for DA usage (e.g., lack of confidence in the DA, concerns of fitting in the workflow) were no longer an issue. Still, opinions are divided on the applicability of this DA to all LUTS/BPH patients due to concerns about patient's personality or health literacy levels.[29]

Some limitations should be addressed as well. First, 56 of the 210 invited DA users did not give informed consent and therefore we were not able to obtain DA data and questionnaires from all DA users. As all invited patients were given access to the DA, they could have decided not to participate in this study after evaluation of the DA. Second, when interpreting results, it has to be taken into account that the moment of DA use could be different between patients due to differences in standard information provision routines between participating hospitals. It may be possible that patients who received the DA before visiting the urologist were less satisfied with the usability of the DA due to lack of explanation. Furthermore, selection bias may have occurred since we were not able to track the number of patients that were eligible but who were not invited, it is therefore possible that healthcare professionals were selective in providing the DA to, for example, younger patients or patients with higher literacy levels or higher levels of education.

Conclusion

The percentage of patients with a clear treatment preference increased from 47% before DA use to 65% after DA use. Our findings suggest that this DA does not only help patients make decisions, which reflect their personal preferences, but also supports them in forming a treatment preference even if they did not have an initial preference. Healthcare providers were positive about its usefulness which may improve clinical implementation.

References

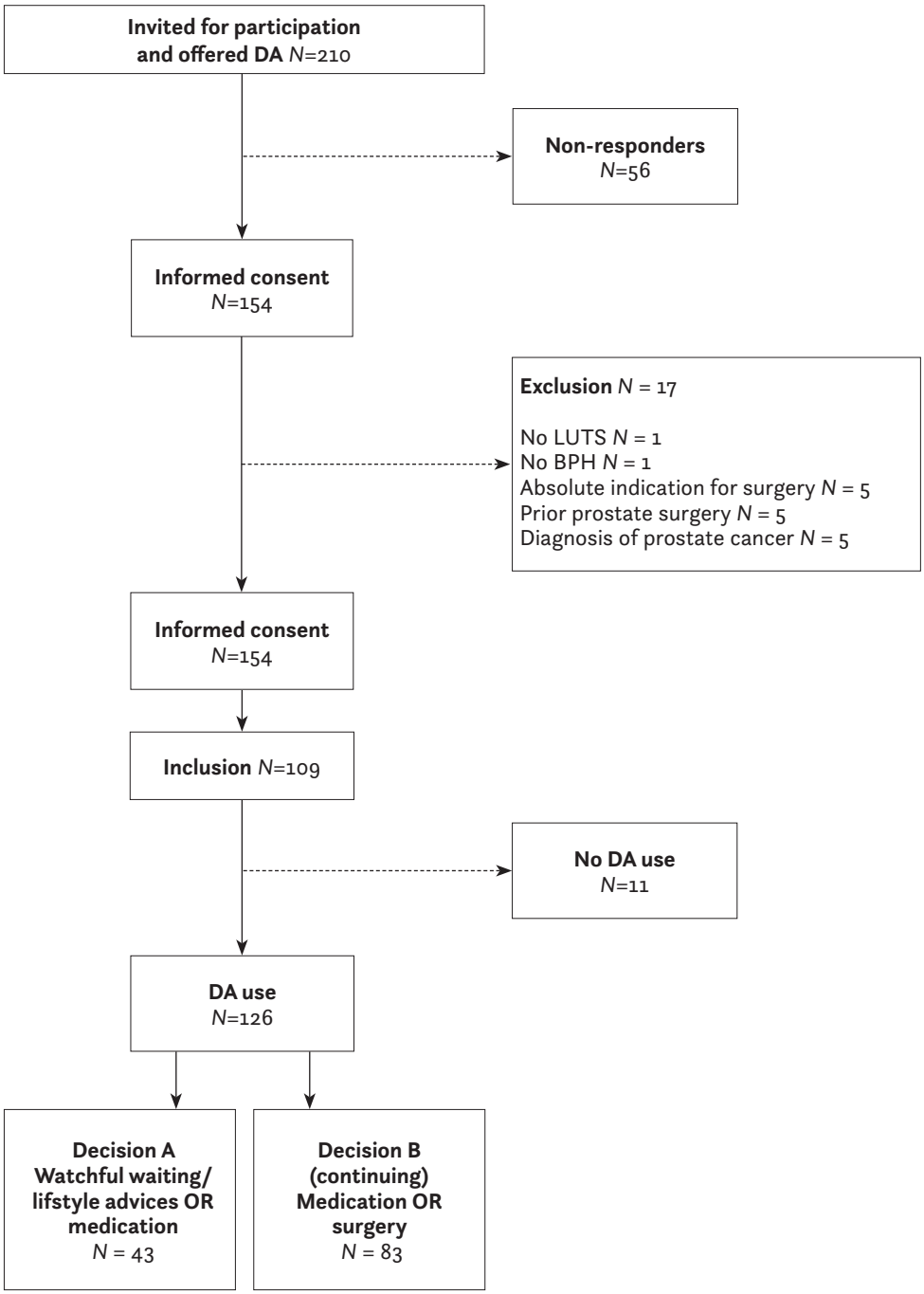
1. Egan KB: The Epidemiology of Benign Prostatic Hyperplasia Associated with Lower Urinary Tract Symptoms: Prevalence and Incident Rates. Urol Clin North Am 43: 289-297, 2016.
2. Kupelian V, Wei JT, O'Leary MP, et al: Nocturia and quality of life: results from the Boston area community health survey. Eur Urol 61: 78-84, 2012.
3. Gratzke C, Bachmann A, Descazeaud A, et al: EAU Guidelines on the Assessment of Non-neurogenic Male Lower Urinary Tract Symptoms including Benign Prostatic Obstruction. Eur Urol 67: 1099-1109, 2015.
4. van Tol-Geerdink JJ, Stalmeier PF, van Lin EN, et al: Do prostate cancer patients want to choose their own radiation treatment? Int J Radiat Oncol Biol Phys 66: 1105-1111, 2006.
5. Couet N, Desroches S, Robitaille H, et al: Assessments of the extent to which health-care providers involve patients in decision making: a systematic review of studies using the OPTION instrument. Health Expect 18: 542-561, 2015.
6. Elwyn G, O'Connor A, Stacey D, et al: Developing a quality criteria framework for patient decision aids: online international Delphi consensus process. Bmj 333: 417, 2006.
7. Stacey D, Legare F, Lewis K, et al: Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev 4: CD001431, 2017.
8. Knops AM, Legemate DA, Goossens A, et al: Decision aids for patients facing a surgical treatment decision: a systematic review and meta-analysis. Ann Surg 257: 860-866, 2013.
9. van der Wijden FC, de Angst IB, Lamers RED, et al: Effectiveness of a web-based treatment decision aid for men with lower urinary tract symptoms due to benign prostatic hyperplasia. BJU Int, 2018.
10. Barry MJ, Fowler Jr FJ, Mulley Jr AG, et al: Patient reactions to a program designed to facilitate patient participation in treatment decisions for benign prostatic hyperplasia. Med Care 33: 771-782, 1995.
11. Barry MJ, Cherkin DC, YuChiao C, et al: A randomized trial of a multimedia shared decision-making program for men facing a treatment decision for benign prostatic hyperplasia. Disease Management and Clinical Outcomes 1: 5-14, 1997.
12. Murray E, Davis H, Tai SS, et al: Randomised controlled trial of an interactive multimedia decision aid on benign prostatic hypertrophy in primary care. Bmj 323: 493-496, 2001.
13. Rovner DR, Wills CE, Bonham V, et al: Decision aids for benign prostatic hyperplasia: applicability across race and education. Med Decis Making 24: 359-366, 2004.
14. Wills CE, Holmes-Rovner M, Rovner D, et al: Treatment preference patterns during a videotape decision aid for be-

nign prostatic hyperplasia (BPH). Patient Educ Couns 61: 16-22, 2006.

15. Piercy GB, Deber R, Trachtenberg J, et al: Impact of a shared decision-making program on patients with benign prostatic hyperplasia. Urology 53: 913-920, 1999.
16. Wagner EH, Barrett P, Barry MJ, et al: The effect of a shared decisionmaking program on rates of surgery for benign prostatic hyperplasia. Pilot results. Med Care 33: 765-770, 1995.
17. Shepperd S, Coulter A, Farmer A: Using interactive videos in general practice to inform patients about treatment choices: a pilot study. Fam Pract 12: 443-447, 1995.
18. Lamers RED, Cuypers M, Garvelink MM, et al: Development of a decision aid for the treatment of benign prostatic hyperplasia: A four stage method using a Delphi consensus study. Patient Educ Couns 99: 1249-1256, 2016.
19. Degner LF, Sloan JA, Venkatesh P: The Control Preferences Scale. Can J Nurs Res 29: 21-43, 1997.
20. Barry MJ, Fowler FJ,Jr, O'Leary MP, et al: The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J Urol 148: 1549-57; discussion 1564, 1992.
21. Rovner DR, Wills CE, Bonham V, et al: Decision aids for benign prostatic hyperplasia: applicability across race and education. Med Decis Making 24: 359-366, 2004.
22. Wills CE, Holmes-Rovner M, Rovner D, et al: Treatment preference patterns during a videotape decision aid for benign prostatic hyperplasia (BPH). Patient Educ Couns 61: 16-22, 2006.
23. Holmes-Rovner M, Price C, Rovner DR, et al: Men's theories about benign prostatic hyperplasia and prostate cancer following a benign prostatic hyperplasia decision aid. J Gen Intern Med 21: 56-60, 2006.
24. Schwalm JD, Stacey D, Pericak D, et al: Radial artery versus femoral artery access options in coronary angiogram procedures: randomized controlled trial of a patient-decision aid. Circ Cardiovasc Qual Outcomes 5: 260-266, 2012.
25. Fraenkel L, Street RL,Jr, Towle V, et al: A pilot randomized controlled trial of a decision support tool to improve the quality of communication and decision-making in individuals with atrial fibrillation. J Am Geriatr Soc 60: 1434-1441, 2012.
26. Sawka AM, Straus S, Rotstein L, et al: Randomized controlled trial of a computerized decision aid on adjuvant radioactive iodine treatment for patients with early-stage papillary thyroid cancer. J Clin Oncol 30: 2906-2911, 2012.
27. Schroy PC,3rd, Emmons K, Peters E, et al: The impact of a novel computer-based decision aid on shared decision making for colorectal cancer screening: a randomized trial. Med Decis Making 31: 93-107, 2011.
28. Lamers RE, Cuypers M, de Vries M, et al: How do patients choose between

active surveillance, radical prostatectomy, and radiotherapy? The effect of a preference-sensitive decision aid on treatment decision making for localized prostate cancer. 35: 37. e9-37. e17, 2017.

29. Saab MM, Reidy M, Hegarty J, et al: Men's information-seeking behavior regarding cancer risk and screening: A meta-narrative systematic review. Psychooncology 27: 410-419, 2018.



Supplementary Figure 1. Flowchart

Part II

Shared decision-making in patients with localized prostate cancer

Chapter 4

Development and usability testing of a Multi-Criteria value clarification methods for patients with localized prostate cancer

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Abstract

Current guidelines for the development of decision aids recommend that they have to include a process for helping patients clarify their personal values, for example, by using values clarification methods. In this article, we extensively described the development process of the web-based values clarification method for patients with localized low- to intermediate-risk prostate cancer based on the analytic hierarchy process. With analytic hierarchy process, the relative importance of different attributes of available treatments can be determined through series of pairwise comparisons of potential outcomes. Furthermore, analytic hierarchy process is able to use this information to present respondents with a quantitative overall treatment score and can therefore give actual treatment advice upon patients' request. The addition of this values clarification method to an existing web-based treatment decision aid for patients with localized prostate cancer is thought to improve the support offered to patients in their decision-making process and their *decision quality*.

Keywords
analytic hierarchy process, clinical decision-making, decision aid, localized prostate cancer, shared decision-making, values clarification method, web-based

Introduction

For patients with localized low- to intermediate-risk prostate cancer, treatment options vary between active surveillance (AS) and curative treatments (radical prostatectomy (RP), brachytherapy (BT) or external beam radiation (EBRT)). As there is no clear benefit of one treatment over the others, shared decision making (SDM) is highly appropriate for this treatment decision.[1] In order to support patients and their clinicians in the decision-making process, a web-based treatment decision aid (DA) for localized prostate cancer was evaluated in a cluster randomized controlled trial (RCT) between August 2014 and July 2016 and subsequently implemented in hospitals across the Netherlands. This DA was developed based on the International Patient Decision Aid Standards (IPDAS) criteria and offers patients stepwise guidance through the decision process.[2] Moreover, it contains general information about prostate cancer, the available treatment options and a values clarification method (VCM). The VCM allows patients to indicate for a range of statements the strength of their preference towards one of the treatment options on a slider scale without giving a final treatment recommendation.[2, 3] Although the DA was positively evaluated, results illustrated that 34% (59/175) of the patients did not indicate a preferred treatment after using it.[4] It is unclear whether these patients were undecided or just did not indicate their final treatment preference. For these possible undecided patients, the DA may have been a suboptimal decision-support tool, and therefore, an alternative or additional decision-support may be more suitable for them. Also, 32% (60/186) of the DA users indicated that they preferred to receive an explicit treatment advice from the DA.[5]

Thus, comparable with other decision-support tools, the DA presents evidence and contains a VCM but does not combine these two aspects in a way that allows patients to see quantitatively which treatment aligns with their statements, that is, what having the desire to avoid erectile dysfunction would mean in terms of treatment choice. Therefore, some patients could benefit more from a VCM based on the analytic hierarchy process (AHP), where the relative importance of different attributes of available treatments can be determined through a series of trade-offs of the (un)desirability of possible outcomes (pairwise comparisons). AHP is one of the most frequently used multi-criteria decision analysis (MCDA) methods, which was originally developed by Saaty[6] in 1970s. AHP is a theory of measurement that derives ratio scales from these pairwise comparisons. With the use of AHP, we gain more insight into the individual's decision by identifying and visualizing the best treatment option based on the user's responses.[7] Literature has suggested that explicitly showing patients the implications of their stated values may be associated with positive outcomes.[8] Moreover, with this approach patients' are

more stimulated to deliberate on the pros and cons of the different treatments.

In addition, multiple VCM design features exist to elicit patients' well-informed values. Explicit guidelines and best practices for designing and developing VCMs are lacking. According to the systematic review by Witteman et al.,[8] the most common theory used was expected utility theory followed by conjoint analysis and AHP. However, Witteman et al. noted that the theory behind the design used is often not reported in studies. Previous studies, therefore, suggest that more research is needed regarding VCMs based on specific theories.[8, 9] Hence, in this study, we provide a detailed description of the development of an explicit VCM that is able to calculate the preferred treatment option of individual patients by using the AHP method. By involving patients and experts, we intended to develop a tool which patients can easily understand and use in the decision-making process, in addition to the existing DA. Recommendations from the literature are warranted, for example, description of the rationale for the design used and description of the stakeholder input.[9]

Methods

Patients' decision-making process requires several steps which are nearly identical to the basic steps in AHP[9-11] (Figure 1). AHP is a decompositional approach and starts with breaking down a complex decision problem into a hierarchical structure of objectives, alternatives (treatment options) and attributes (characteristics of treatment).[10, 11] Based on this information, the pairwise comparisons can be developed.

Figure 1. Required steps in the decision-making process according to the analytic hierarchy process

Aim of the VCM

The aim of the AHP-based online VCM is to support patients in deciding which treatment for localized low- to intermediate-risk prostate cancer best matches their personal values and preferences and to provide them with an explicit treatment advice based on their responses.

Determination of treatment options

To gain more insight into the decisional context and to identify alternative treatment options, current guidelines and the existing treatment DA with VCM were studied. AS, RP, EBRT and BT were considered as treatment options, as these are the most widely used treatment strategies for localized low- to intermediate-risk prostate cancer.[1]

Determination of most important attributes

After identification of the treatment options, the next step is to identify relevant attributes of these options, such as relevant outcome measures and process of care factors. Within a small working group, including two urologists, a PhD student from the Department of Urology, an epidemiologist and two researchers from the University of Twente, relevant literature[1, 3, 12-19] and the existing DA with VCM were critically discussed to determine the most important attributes. These include timing of treatment (immediate treatment/ postponed treatment), side effects (risk on erectile dysfunction/urinary incontinence/ bowel dysfunction), potentially unnecessary treatment, follow-up (e.g. frequency of prostate-specific antigen (PSA) testing), treatment aim (e.g. tumour is removed or not removed from the body), options at recurrence and procedure (e.g. major operation/ multiple radiation sessions/small operation). Subsequently, a focus group was used to explore, based on deductive reasoning, whether these attributes were also considered to be relevant by this selected group of patients. To initiate the discussion without influencing patients, a listing exercise from the study of Feldman-Stewart and colleagues was used, where patients were asked to individually rank the 10 most important attributes of a total of 32 attributes.[13] Patients were recruited by clinicians from the Elisabeth-TweeSteden Hospital and written informed consent was obtained. We attempted to approach a sample of patients who received different treatment options, and who varied in both age and time since diagnosis. The focus group was moderated by two experienced researchers and consisted of eight patients who had been treated for localized prostate cancer, one of whom was a member of the Dutch Prostate Cancer Foundation. Three patients underwent RP, one BT, one EBRT, two were on AS and one patient initially chose RP but received chemotherapy instead due to metastases. With permission of the participants the session was audio recorded. Two members of the working group (I.B.d.A. and M.G.M.W.) read the transcript independently and developed an outline of attributes with illustrative quotes using deductive techniques. This allowed us to explore whether the predetermined set of attributes was sufficient and appropriate. They shared their perspectives on all of the attributes and identified relevant illustrative quotes. After consensus was reached within the working group, a prototype of the VCM was developed. Subsequently, an iterative process of direct feedback from members of the working group was carried out, followed by usability testing between April and June 2017 among all participants of the

focus group.[20] For usability testing, all participants first had to complete the DA plus the additional VCM. Next, they had to complete a study-specific questionnaire with open- and closed-ended questions to elicit feedback about the content and design which allowed us to make improvements to the VCM. Descriptive statistics were used for analysis.

Developing the pairwise comparisons

After identification of the treatment options, and the most important attributes of the decision, two of the following main inputs are needed from patients to come up with a preferred treatment: attribute weights and performance scores.

Attribute weights reflect how important each attribute is and express how much each attribute influences a decision. AHP uses the method of pairwise comparisons, in which the patient needs to compare the attributes by considering all possible pairs. In a decision with *N* attributes, the patient needs to perform (*N**(*N*-1))/2 pairwise comparisons. Figure 2 displays an example of such a pairwise comparison. The response scale in AHP can be numerical, verbal or graphical, but the verbal mode is recommended when the AHP is used in a social or psychological context.[21] The patients' preference is initially expressed on a verbal scale and then converted into a numerical value to calculate priorities. The level of relative importance varies from equal, moderate, strong, very strong to extreme importance by 1, 3, 5, 7, and 9, respectively (Figure 2). Each comparison reflects the personal judgment of the patient on the importance of one attribute over another in the decision. For instance, an attribute which received the response "moderate importance" is assumed to have a 3 times higher importance than the non-preferred attribute which will receive the reciprocal of this value (1/3).[22] The intermediate values 2, 4, 6, and 8 may be used when it is difficult to choose between two adjacent importance levels, but these were omitted in the proposed VCM to facilitate the ease of application.

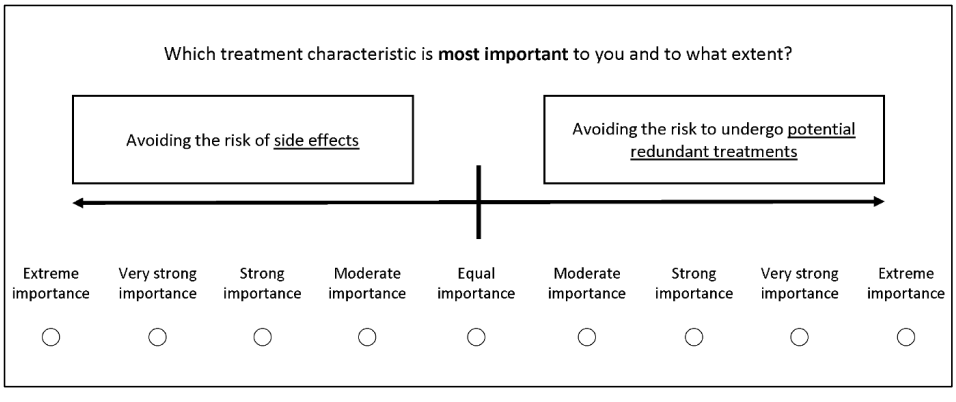

Figure 2. Example of a pairwise comparison to estimate the attribute weights

The reciprocal matrix can then be formed, which is the basis for identifying attribute weights by use of the geometric mean. For each individual patient, the normalized geometric mean is formed by taking the root of the product matrix of row elements divided by the column sum of row geometric means.[6] Results are summarized for each row and finally are normalized to obtain attribute weights. An example of the calculations for one patient can be found in Table 1.

Table 1. Reciprocal matrix and calculation of the normalized geometric mean

	Attribute A	**Attribute B**	**Attribute C**	**Attribute D**	**Geometric mean**	**Relative priority of the attribute**
Attribute A	1	3	5	9	$(1*3*5*9)^{(1/4)}$ 3.41	(3.41/5.80) 0.59
Attribute B	1/3 (0.33)	1	3	5	1.50	0.26
Attribute C	1/5 (0.2)	1/3 (0.33)	1	1	0.51	0.09
Attribute D	1/9 (0.11)	1/5 (0.2)	1	1	0.39	0.07
				Sum	5.80	

Performance scores are an assessment of how well the alternative treatment options perform on each attribute.[22] This can be done by using expert measurements but in case of preference-sensitive attributes, it is more sensible to ask the individual patient to provide performance scores. Performance scores can be assessed using various methods, such as point allocation, rating scales and pairwise comparisons. Introducing another method in the VCM may potentially lead to confusion and misunderstanding; therefore, it was chosen to let patients answer AHP pairwise comparisons to estimate performance scores for each alternative on each attribute (Figure 3). Similar to the first set of pairwise comparisons, the verbal responses of patients correspond to the underlying numerical performance scores.

The last step of the AHP is to aggregate the attribute weights and performance scores to come to an overall value of each treatment option. This overall value can then be used to select a most preferred treatment or to rank treatments from most to least appropriate according to the patients' preference (Table 2).

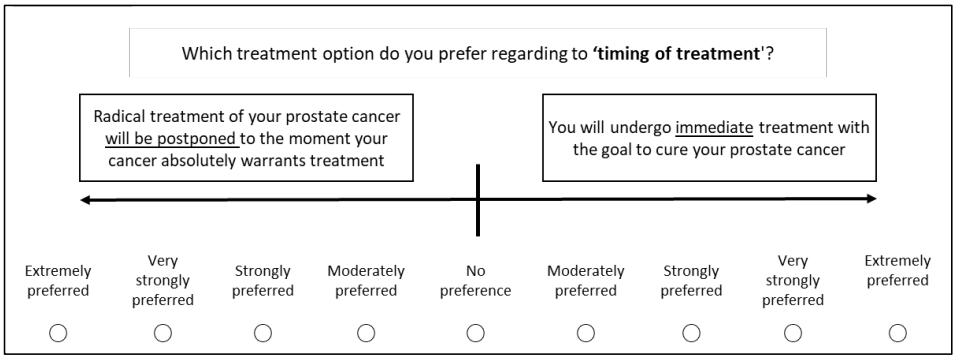

Figure 3. Example of a pairwise comparison to estimate performance scores for the attribute 'timing of treatment'

Table 2. Example of aggregation of attribute weights and performance scores to estimate the overall value of treatment options

	Performance scores		Attribute weights	Overall value	
	Treatment 1	**Treatment 2**		**Treatment 1**	**Treatment 2**
Attribute A	33	66	0.59	19.7	39.3
Attribute B	0	100	0.26	0	26
Attribute C	0	100	0.09	0	9
Attribute D	80	20	0.07	5.6	1.4
		Overall value:		25.3	75.7

Results

Treatment options

The existing treatment DA is designed for patients with localized low- to intermediate-risk prostate cancer. Therefore, a two-stepped approach was chosen. In the first step (VCM-1), patients have to consider AS or curative treatment. In the second step (VCM-2), patients have to make trade-offs between all curative treatment options. Based on patient characteristics, patients have to complete the first and second step or only the second step. For instance, some patients have intermediate-risk prostate cancer which makes them not eligible for AS. Furthermore, BT is only offered in patients without a medical history of transurethral resection of the prostate (TURP), with a

good International Prostate Symptom Score (IPSS), and a prostate volume <50 mL.[1] In case a patient is eligible for all treatment options and prefers AS in VCM-1, he does not have to complete VCM-2.

According to the previous cluster RCT, where the treatment DA for localized prostate cancer was compared with standard care, eight possible combinations of appropriate treatment options appeared to be most common, such as curative treatments only, AS versus RALP versus EBRT or AS versus EBRT versus BT. These specific treatment combinations are all integrated into the AHP-based VCM in order to make sure that patients only have to answer questions regarding the attributes which are relevant to their individual situation.

Treatment attributes

An outline of attributes with illustrative quotes are presented in Appendix 1. In the decision between AS and curative treatments (VCM-1), four attributes were selected, subsequently the patient needs to perform (4*(4-1)/2) six pairwise comparisons to estimate the attribute weights for VCM-1 (e.g. Figure 2). Performance scores of the attributes 'timing of treatment' and 'follow up' are subjective and need to be determined by the individual patient in two additional pairwise comparisons (e.g. Figure 3). For the two other attributes 'side effects' and 'potentially unnecessary treatment' there is an obvious preference for AS, because it has the best possible outcome on those attributes. Therefore, a score of 100 for AS and 0 for curative treatments was assigned by the working group.

For the decision between RP, EBRT, and brachytherapy (VCM-2), four attributes were selected and hence six pairwise comparisons need to be performed by patients to estimate attribute weights. Performance scores of all attributes in VCM-2 are subjective and need to be determined by patients. The attributes 'procedure' and 'side effects' both have three possible outcomes, resulting in three pairwise comparisons per attribute. In total, each patient has to answer 8 pairwise comparisons in VCM-1 and maximal 14 pairwise comparisons in VCM-2.

Attribute weighting

With the provided responses, the reciprocal matrix can be made and attribute weights can be calculated. Attribute weights will be displayed to patients in a simple vertical bar graph in addition to percentages (Figure 4). A vertical bar graph was chosen because they have been shown to be superior to horizontal bar graphs.[23] The combination of graphical information and numerical information allows communication of the bottom

line meaning and the exact size of the attribute weights.[23, 24] As well as information on attribute weights, patients receive a copy of the performance table with an additional column displaying patients' preference on each attribute based on provided performance scores (Figure 5). In theory, the VCM is able to give patients insight in the overall value of treatment options, by explicitly presenting a recommended option or scores that show how well or poorly each treatment option fits with the patients' responses (Figure 6).

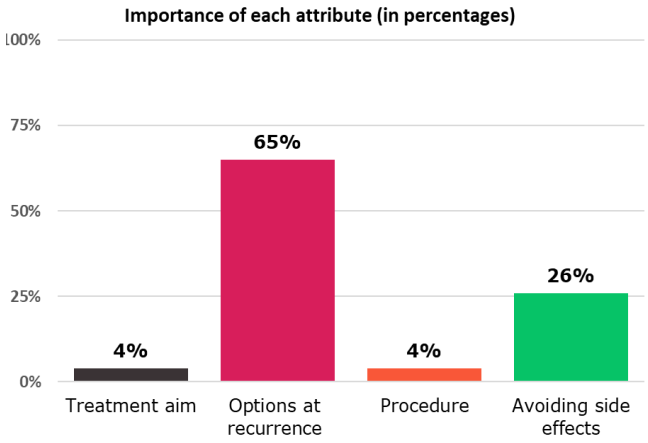

Figure 4. Patients' feedback: importance of each attribute

Usability testing

Only five participants of the focus group completed all steps and were included for analysis. These participants had a mean age of 63 years (range 57-71). Most of the participants (3 out of 5) had a high school education or less and 2 out of 5 participants were retired.

Both the existing DA and the additional VCM are web-based applications. Four out of 5 participants indicated that the online format was desired, and only one participant preferred a paper version of the VCM. For one participant, the questions in the VCM were too complicated. As mentioned previously, the calculated attribute weights are displayed to patients in a bar graph.

Attributes ↓	Treatment options			Your preference
	RP	BT	EBRT	
Treatment aim	The entire prostate will be removed.	The prostate will be preserved.	The prostate will be preserved.	The entire prostate will be removed.
Options at recurrence	After this treatment external beam radiation remains an option when the prostate cancer has recurred.	After this treatment an operation is seldom an option when the prostate cancer has recurred.	After this treatment an operation is seldom an option when the prostate cancer has recurred.	After this treatment external beam radiation remains an option when the prostate cancer has recurred.
Procedure	You have to undergo a major operation, which requires a 2 to 7 day stay in the hospital.	You have to undergo a small operation to place radioactive seeds directly into the prostate (day only admission and living rules)	This treatment will be delivered over 7 weeks, 5 days per week in the hospital (10 minutes per radiation session, without anesthesia)	You have to undergo a major operation, which requires a 2 to 7 day stay in the hospital.
Side effects	After this treatment you will have a higher chance on urinary incontinence and erectile dysfunction.	After this treatment you will have a chance on transient bowel dysfunction	After this treatment you will have a higher chance on long term bowel dysfunction	Avoiding side effects: transient bowel dysfunction are least bothersome to you

Figure 5. Example of performance table with on the left an additional column displaying the patients' preference on each attribute based on provided performance scores. RP: radical prostatectomy, BT: brachytherapy; EBRT: external beam radiation therapy

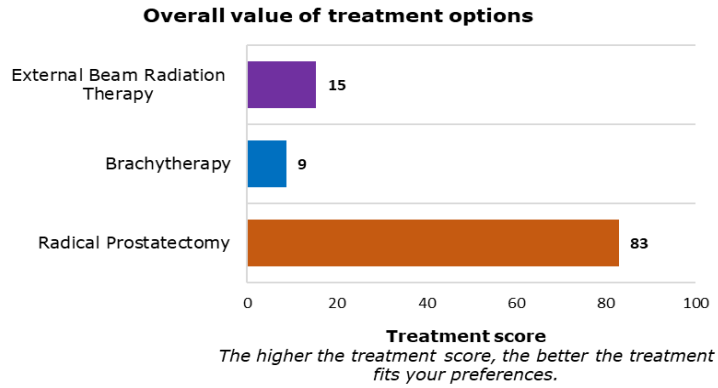

Figure 6. Overall value of treatment options

According to all participants, this bar graph was a clear and useful way of presenting their personal preferences. However, one participant found it hard to interpret the graph. Finally, 4 out of 5 would recommend this VCM to other patients, which gave us a sense of the overall opinion of participants on the use of the VCM. However, one participant stated the following: "*I cannot estimate whether all patients would correctly understand all questions of this VCM, some words might be too difficult to understand.*"

The feedback from this usability testing was used for the final review and revision of the VCM by the working group. Some questions had to be re-written at a grade 8 equivalent level to make sure that all questions can be understood by the majority of the target group.

Discussion and conclusion

Discussion

We described the development of an explicit AHP-based VCM, which is able to give prostate cancer patients insight in the overall value of treatment options, with the possibility of explicitly presenting a recommended treatment option. Based on the literature, the existing DA, and a single focus group, the content of the VCM was determined. Since the existing treatment DA is designed for patients with localized low- to intermediate-risk prostate cancer, meaning that not all patients are eligible for AS, a two-stepped approach for the VCM was chosen. This includes step (1) where patients first have to consider AS or curative treatment and step (2) where patients have to make trade-offs between all curative treatment options (RP, EBRT and BT). The feedback from usability testing was used for input for the final review and revision of the VCM by the working group.

According to previous research, the reporting of the development of VCMs is lacking. Therefore, recommendations have been made in the literature for future studies about VCMs to extensively report the rationale for the design of the VCM and report contribution of involved stakeholders.[9]

In this article, we have implemented these recommendations and described the AHP as a basis for the design of our VCM and for further guidance of the evaluation of the VCM.

Limitations. There are several limitations of this study and VCM. First, results of attribute weights will be displayed to patients in a bar graph, and one participant found it difficult to interpret the graph. Communicating risks to patients is challenging; the use of icon arrays, bar charts and pie charts are often employed to aid this risk communication. According to the literature, they have been found to be effective in improving perception, understanding and interpretation of quantitative information over both textual and numeric formats.[24, 25] Up to now, there is no consensus about which form of risk visualization is consistently more effective than the other. The type of visualization format might be dependent on the type of information needed for the particular medical decision.[26] Since the goal of this VCM is not to communicate actual risks, such as event rates, but to communicate patients' individual view on possible treatment outcomes, we have decided to use both a simple vertical bar graph in addition to percentages. We also present the performance table with an additional column displaying patients' preferences on each attribute based on the provided performance scores.

Second, for the development of the content of the VCM, a single focus group with prostate cancer patients was conducted. The number of focus groups often depends on data saturation.[27] In this study, the attributes and attribute levels chosen for this VCM were derived from the literature[1, 3, 12-19] and the existing treatment DA, which was developed using a Delphi study with patient and experts. Therefore, we chose to conduct a single focus group with patients to explore whether the predetermined set of attributes was still sufficient and appropriate, using deductive techniques. However, the limitation remains that the proposed VCM contains predetermined attributes, that may not all be relevant to the individual patient, or may omit attributes that are relevant to the patient. Furthermore, the algorithm used to calculate the importance score of attributes may not accurately reflect the way in which an individual patient would weigh importance of an attribute and its performance on the options.

Conclusion

Since extensively reporting the rationale for the design of the VCM is recommended, we described a structured method for the development of an AHP-based VCM well accepted by patients, to improve the existing treatment DA for patients with localized prostate cancer. By involving patients and urologists, we aim to facilitate future implementation into clinical practice.

Practice implications

The AHP method is a highly appropriate method to gain more insight into patients' values and treatment decisions, by structuring and breaking down the decision into smaller elements for analysis.[6] It encourages a process of pairwise comparisons of potential outcomes to determine the relative importance of different attributes of available treatment options.[7] Furthermore, this VCM is able to explicitly present the calculated treatment option based on the scores that show how well or poorly each treatment option fits with the patients' responses. This will be appropriate for patients who prefer actual treatment advice from the DA.

Currently, the effectiveness of this specific VCM, in addition to the existing DA, on the outcome *decision quality*, is being evaluated in a prospective cohort study. In that study, *decision quality* is defined as congruence between well-informed patients' values and the calculated and chosen treatment option. In addition, results on disease-specific knowledge and preparation for decision-making will be compared with a historical control group who only used the existing DA. Health literacy and numeracy will also be assessed to evaluate if the patients with low numeracy and/or low health literacy benefit from the VCM. Furthermore, the VCM will be further evaluated on its usage and

patients are able to include additional decision attributes that are not predetermined by the working group but are relevant to them.

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I.B.d.A and MGMW contributed equally to concept and design of the VCM. Furthermore, I.B.d.A and MGMW both moderated the focus group and read the transcript to determine whether the predetermined set of attributes was sufficient and appropriate. They also contributed equally to drafting the manuscript.

All authors were members of the working group and contributed to the review, critical revision and final approval of the manuscript. I.B.d.A and MGMW contributed equally to this work.

Ethics approval and consent to participate

The regional Medical Ethical Review Board of Brabant, The Netherlands, waived the need for formal ethical approval (reference number NW2017-26), and the study protocol was approved by the research board of the Elisabeth-TweeSteden Hospital in the Netherlands. Participants of the focus group were provided with study information and an informed consent form, which had to be understood and signed prior to any data collection.

Declaration of conflicting interests

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References

1. Urologie NVv. Prostaatcarcinoom. Richtlijnendatabase, 2014.
2. Cuypers M, Lamers RE, Kil PJ, et al. A global, incremental development method for a web-based prostate cancer treatment decision aid and usability testing in a Dutch clinical setting. *Health Informatics J*. 2017: 1460458217720393.
3. Cuypers M, Lamers RE, Kil PJ, van de Poll-Franse LV and de Vries M. Impact of a web-based treatment decision aid for early-stage prostate cancer on shared decision-making and health outcomes: study protocol for a randomized controlled trial. *Trials*. 2015; 16: 231.
4. Lamers RE, Cuypers M, de Vries M, van de Poll-Franse LV, Ruud Bosch JL and Kil PJ. How do patients choose between active surveillance, radical prostatectomy, and radiotherapy? The effect of a preference-sensitive decision aid on treatment decision making for localized prostate cancer. *Urol Oncol*. 2017; 35: 37 e9- e17.
5. Cuypers M, Lamers RED, Kil PJM, van de Poll-Franse LV and de Vries M. Impact of a web-based prostate cancer treatment decision aid on patient-reported decision process parameters: results from the Prostate Cancer Patient Centered Care trial. *Support Care Cancer*. 2018.
6. TL. S. What is the analytic hierarchy process? Mathematical models for decision support. *Springer*. 1988: 209-21.
7. Cunich M, Salkeld G, Dowie J, et al. Integrating evidence and individual preferences using a web-based multi-criteria decision analytic tool: an application to prostate cancer screening. *Patient*. 2011; 4: 153-62.
8. Witteman HO, Scherer LD, Gavaruzzi T, et al. Design Features of Explicit Values Clarification Methods: A Systematic Review. *Med Decis Making*. 2016; 36: 453-71.
9. Fagerlin A, Pignone M, Abhyankar P, et al. Clarifying values: an updated review. *BMC Med Inform Decis Mak*. 2013; 13 Suppl 2: S8.
10. Dolan JG. Multi-criteria clinical decision support: A primer on the use of multiple criteria decision making methods to promote evidence-based, patient-centered healthcare. *Patient*. 2010; 3: 229-48.
11. Dolan JG. Shared decision-making--transferring research into practice: the Analytic Hierarchy Process (AHP). *Patient Educ Couns*. 2008; 73: 418-25.
12. Korfage IJ, Essink-Bot ML, Borsboom GJ, et al. Five-year follow-up of health-related quality of life after primary treatment of localized prostate cancer. *Int J Cancer*. 2005; 116: 291-6.
13. Feldman-Stewart D, Tong C, Siemens R, et al. The impact of explicit values clarification exercises in a patient decision aid emerges after the decision is actually made: evidence from a randomized controlled trial. *Med Decis Making*. 2012; 32: 616-26.

14. Feldman-Stewart D, Capirci C, Brennenstuhl S, et al. Information for decision making by patients with early-stage prostate cancer: a comparison across 9 countries. *Med Decis Making*. 2011; 31: 754-66.
15. de Bekker-Grob EW, Bliemer MC, Donkers B, et al. Patients' and urologists' preferences for prostate cancer treatment: a discrete choice experiment. *Br J Cancer*. 2013; 109: 633-40.
16. Robinson JW, Moritz S and Fung T. Meta-analysis of rates of erectile function after treatment of localized prostate carcinoma. *Int J Radiat Oncol Biol Phys*. 2002; 54: 1063-8.
17. Stanford JL, Feng Z, Hamilton AS, et al. Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer: the Prostate Cancer Outcomes Study. *JAMA*. 2000; 283: 354-60.
18. van den Bergh RC, Essink-Bot ML, Roobol MJ, Schroder FH, Bangma CH and Steyerberg EW. Do anxiety and distress increase during active surveillance for low risk prostate cancer? *J Urol*. 2010; 183: 1786-91.
19. Fitch M, Pang K, Ouellet V, et al. Canadian Men's perspectives about active surveillance in prostate cancer: need for guidance and resources. *BMC Urol*. 2017; 17: 98.
20. Coulter A, Stilwell D, Kryworuchko J, Mullen PD, Ng CJ and van der Weijden T. A systematic development process for patient decision aids. *BMC Med Inform Decis Mak*. 2013; 13 Suppl 2: S2.
21. Saaty TL. *Decision Making for Leaders: The Analytic Hierarchy Process for Decisions in a Complex World*. RWS Publications, 1990.
22. Belton V, Stewart, Theo. *Multiple Criteria Decision Analysis: An Integrated Approach*. 2002.
23. Timmermans D, Molewijk B, Stiggelbout A and Kievit J. Different formats for communicating surgical risks to patients and the effect on choice of treatment. *Patient Educ Couns*. 2004; 54: 255-63.
24. Trevena LJ, Zikmund-Fisher BJ, Edwards A, et al. Presenting quantitative information about decision outcomes: a risk communication primer for patient decision aid developers. *BMC Med Inform Decis Mak*. 2013; 13 Suppl 2: S7.
25. Lipkus IM. Numeric, verbal, and visual formats of conveying health risks: suggested best practices and future recommendations. *Med Decis Making*. 2007; 27: 696-713.
26. Hawley ST, Zikmund-Fisher B, Ubel P, Jancovic A, Lucas T and Fagerlin A. The impact of the format of graphical presentation on health-related knowledge and treatment choices. *Patient Educ Couns*. 2008; 73: 448-55.
27. Krueger RA. Designing and Conducting Focus Group Interviews. 2002.

Supplementary Table 1. Selected attributes with representative quotes from the focus group

Attributes	Representative quote examples
Moment of treatment	• *"[The doctors] told me about all the side effects and other problems that could come from an operation, and that in my stage it's better to wait."* • *"If I can live to an old age with the cancer, I might as well wait with treatment for now."* • *"I had no problems [with the cancer itself], it wasn't a reason to think 'there's something wrong and it has to be removed'. After two or three consultations it was clear to me. I had the choice between nothing of internal or external radiation. And yeah, I thought 'I can also just do nothing'."* • *"We are going to wait with treatment for now, but I wonder what we're waiting for, I'd prefer like some other patients that the prostate is just removed because I want the cancer to be out of my body."* • *"...but when I heard what kind of problems you can have if there are metastases I keep thinking 'well just get that terrible thing [the cancer] out of me".*
Side effects	• *"I heard you can sometimes get an erectile dysfunction from the operation, but after talking it over with my wife I made the conscious choice to go through with the operation"* • *"Unfortunately they could not spare the nerves during my operation and they removed all of them. I will never be able to get an erection again. I knew this going into it, and thought it was more important that I would be alive, and I still feel that way."* • *"With my cancer stage, treatment could give me irritating side effects but removing the prostate wouldn't have many positive benefits."* • *"I told the doctors [who said I didn't need an operation] if they think the operation would give me more symptoms, such as cramping after the operation, removal of my bladder and other side effects, that I agree I wouldn't want to have the operation done."* • *"[I made the choice to wait with treatment] because there are a lot of side effects."* • *"I looked at the [treatment options] on the computer with my wife. We decided not to surgically remove my prostate because it will also have an effect on her [because of possible erection dysfunction]...If you read other stories you sometimes make the choice that you still want to live, so we went through with the treatment anyway."* • *"The doctor advised me that in principle I would have the least side effects and problems with brachytherapy."* • *"The operation has effect on the relationship. Of course you want to treat the disease and that's also nice for the partner. But on the other hand it will change the sexual relation between you."* • *"[When deciding for treatment using the ranking] I also considered the effect on my bladder"*
Unnecessary treatment	• *"The doctors have told me that in my stage I can better wait with treatment, because it's possible I become 80 years old without problems."* • *"I'd heard from other patients about someone who didn't die from the cancer [without an operation] but lived until he was 50 with it. He did not die from his prostate cancer but lived with his prostate cancer until he was old."* • *"Three or four doctors have told me that I don't necessarily have to be treated, so if I don't want to be treated I don't have to be."*

table continues

Attributes	Representative quote examples
Follow up scheme	• *"I do not have an aggressive form. Hopefully, I can stay on active surveillance for a while. Every three months I have my PSA measured. Recently, I had my PSA checked and it was the same as three months before. Yes, I feel reluctant to get my PSA checked every time, but I should not feel that way. You must not lose any sleep over it, otherwise you should get active treatment."* • *"Getting the results [of the tests] is stressful, I can't deny that even though I'm mentally prepared that you cannot change the result [if it is negative]."*
Aim of treatment	• *"He [other participant] made the choice [to undergo surgical treatment] to ensure the cancer was completely removed from his body"* • *"My father also had prostate cancer and died young to a metastasis, I didn't want to go through that myself to I thought 'it has to be removed'."* • *"I wanted the cancer removed and I thought the best way to do that would be with the Da Vinci robot, in this case in the Maasstad Hospital in Rotterdam."* • *"No matter what the cost, I knew I wanted [the cancer] removed from my body"*
Options at recurrence	• *..."Then we looked up more about treatment and it turns out if you do radiation and it doesn't work, you can't be operated anymore. But if you operate and it doesn't go well, you can still do radiation. That was the biggest eye-opener for me to switch to a surgical treatment"*
Procedure	• "[I first chose to get an operation] because I didn't want to be in the hospital for 2 days, I thought with radiation I just get there at 7 a.m. and can get back home quickly."

Chapter 5

Multi-Criteria Decision Analysis to optimize the decision aid for patients with localized prostate cancer: a prospective study with historical control group

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Submitted for publication

Part III

Shared decision-making in patients with advanced prostate cancer (mCRPC)

Chapter 6

Should we involve patients more actively? Perspectives of the multidisciplinary team on shared decision-making for Metastatic Castration-Resistant Prostate Cancer

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Abstract

Objective

To evaluate perspectives of the multidisciplinary team concerning shared decision-making (SDM) in treatment decisions for older patients with metastatic castration-resistant prostate cancer (mCRPC).

Materials and Methods

A survey among Dutch healthcare providers was conducted to assess healthcare providers' perspectives on patient involvement in decision-making and the value of a decision aid (DA) in the decision-making process. Treatment recommendations were assessed using hypothetical cases in which providers were asked to evaluate their likelihood of pursuing listed treatment options.

Results

In total, 170 Dutch healthcare providers, including 82 urologists, 31 oncologists, and 57 oncology nurses completed the survey. Sixty-two percent of urologists, 65% of oncologists, and 51% of oncology nurses found that mCRPC patients take a passive role in decision-making and delegate treatment decisions to doctors due to advanced age ($p = .45$). Yet, 70% of urologists, 71% of oncologists, and 63% of oncology nurses agreed that mCRPC patients should be always involved in decision-making ($p = .91$). Fifty-two percent of urologists and 55% of oncologists stated that they are inadequately trained to apply SDM in clinical practice. Conversely, only 20% of oncology nurses believed that oncology nurses are inadequately trained. Fifty-four percent of all providers considered a DA suitable to support these patients and their healthcare providers in the decision-making process. All hypothetical cases showed variation in treatment recommendations among providers, with each of the five treatments ranging from extremely likely to extremely unlikely.

Conclusions

The wide variation in treatment recommendations observed among the multidisciplinary team suggests that mCRPC patients and their healthcare providers may benefit from implementation of informed SDM. Given the perceived passive role of older patients with mCRPC in decision-making, interventions to engage them are needed. With slightly more than half of respondents finding DAs useful to facilitate the decision-making process, development and implementation of a DA would be an interesting field of research.

Keywords

Shared decision making (SDM), Castration-Resistant Prostate Cancer (CRPC), Decision Aid

Introduction

With the rapid increase of available treatment options for patients with metastatic castration-resistant prostate cancer (mCRPC), the preferred treatment sequence remains unclear due to limited high level evidence [1]. Current treatment options following androgen blockade therapy are either chemotherapy, abiraterone acetate, enzalutamide, or Radium-223 [2]. Given the advanced age and number of comorbidities in this heterogeneous patient population, it is important to consider the effects of treatment not only on potential life expectancy gains, but also its deleterious effects on quality of life. The complexity of these decisions are a potential reason for suboptimal tailoring of treatment.

The European Association of Urology-European Society for Radiotherapy and Oncology-International Society of Geriatric Oncology (EAU-ESTRO-SIOG) Guidelines recommend that treatment for older patients should be tailored based on individual health status by a multidisciplinary team of clinicians [1, 2]. EAU-ESTRO-SIOG Guidelines advocate for a treatment decision-making process that takes into consideration not only a patient's clinical characteristics and expected benefits, but also their preferences [2]. Patient-centered communication between healthcare providers (HCP) and their patients is crucial to understanding these preferences. Such open ended dialogue introduces shared decision making (SDM) into clinical practice. The use of decision aids (DA) that include values clarification excercises (VCEs) may further facilitate the SDM process. Indeed, previous studies have shown that DA use supports SDM by increasing patient disease-specific knowledge and thus improving health outcomes [3].

Although SDM has become a hallmark of patient-centered care, its implementation into routine care of patients with mCRPC is suboptimal [4]. This may be explained by either the multidisciplinary treatment of these patients or HCP's lack of familiarity with SDM practices.

Currently, there is little data about the multidisciplinary clinical team's attitudes towards mCRPC patient involvement in treatment decisions. Therefore, the aim of this study was to investigate perspectives of Dutch urologists, oncologists, and oncology nurses on patient involvement in the decision-making process, to explore their view on the added value of DAs, and to assess their treatment recommendations for different patients with mCRPC.

Material and methods

Study population

An anonymous self-administered paper version of the survey was distributed among Dutch urologists during the annual autumn meeting of the Dutch Association for Urology in November 2016. From then until October 2017, the survey was electronically distributed among urologists and oncology nurses by the Dutch Association for Urology and Dutch National Consultation Oncology Nurses. The link to the survey was also repeatedly posted in the Foundation Dutch Uro-Oncology Study group newsletter as a means to distribute it to oncologists for whom prostate cancer is a field of interest. Due to privacy regulations we were not allowed to receive actual mailings lists from the different associations, resulting in the inability to accurately report how many unique surveys were sent out and to provide a response report.

The perspectives of oncology nurses, nurse specialists, and nurse practitioners were also included in this study, because they play a crucial role in the care path for older patients with mCRPC in the Netherlands by providing patients emotional support, additional treatment information, and in the case of nurse practitioners, monitoring treatment responses.

The regional Medical Ethics Review Board 'METC Brabant' waived the need for formal ethical approval (reference:NW2018-47).

Survey

A validated survey to assess HCPs opinions concerning SDM in patients with mCRPC was not available. Therefore, we used a study-specific survey, divided into four parts. Formal pilot testing was not performed, because the survey was adapted from similar studies which investigated opinions of HCPs on SDM in other disease sites, e.g. lung cancer and aortic valve disease [5-7]. The translated survey is presented in Supplementary 1.

The first part consisted of four general questions: providers' age, specialty, hospital type, years of clinical experience.

The second part consisted of questions to assess opinions on involvement of older patients with mCRPC in decision-making and opinions on discussing all treatments with risks using a 1-5-Likert scale ranging from never to always [6] and the Control Preference Scale [8]. The capability of HCPs to weigh the importance of risk and benefits

of treatments for patients was also assessed using a 1-5-Likert scale ranging from completely disagree to completely agree. In daily practice, urologists and oncologists decide which treatments apply to individual patients, the question about whether or not to discuss all treatment options even if the patient does not have a choice was only asked to them. One question specifically asked HCPs if they think older patients with mCRPC take a more passive role in decision-making due to their advanced age than younger patients. Furthermore, opinions on being adequately trained to apply SDM in clinical practice were assessed. Respondents could explain their answers in free text.

The third part explored perspectives of HCPs on the additive value of a DA for patients with mCRPC in supporting the decision-making process using a 1-5-Likert scale ranging from completely disagree to completely agree. The most appropriate HCP for and most appropriate timing of presenting the DA was also assessed. One question explored HCP's familiarity with DAs for prostate cancer patients in general.

In the fourth part, HCP's recommendations for treatment was assessed using four hypothetical cases in which they rated the likelihood of recommending a particular treatment option (watchful waiting, Abiraterone, Enzalutamide, Docetaxel, and Radium-223) using a 1-5 Likert scale [6]. The hypothetical cases were adapted from real life patient cases presented to a uro-oncology research group during a meeting in May 2016.

Statistical analysis

Continuous variables are presented as mean with standard deviation and range or as medians with interquartile range (IQR). Counts or proportions are used to present categorical data. Responses regarding treatment recommendations of HCPs are presented as median, IQR, and total range. Comparison of group characteristics was done using one-way ANOVA. Differences between responses were tested by using the Kruskal-Wallis test or chi-square test with p-values representing differences between HCPs. Due to the anticipated small sample size of this study, we decided to describe the data rather than to stratify or adjust for significantly different characteristics. Complete-case analysis was performed to handle missing data.

All tests were two-sided, with a $p < .05$ considered significant. All analyses were conducted using IBM SPSS Statistics v24.0 (Chicago,IL,USA).

Results

In total, 170 Dutch HCPs, including 82 urologists, 31 oncologists, and 57 oncology nurses participated. Table 1 presents characteristics of the different HCPs. There were no differences in median age and median years in clinical experience between groups. All respondents indicated that they participated in weekly multidisciplinary team meetings.

Table 1. Demographics of the different healthcare providers (n = 170).

	Total	**Urologists**	**Oncologists**	**Oncology nurses***
Total, N (%)	170 (100)	82 (48)	31 (18)	57 (34)
Age in years, median (IQR)	47 (40–54)	46 (40–56)	46 (40–58)	47 (40–52)
Clinical experience in years, median (IQR)	9 (4–18)	10 (5–20)	11 (5–25)	6 (3–12.5)
Type of hospital, N (%)				
Academic	25 (15)	11 (13)	7 (23)	7 (12)
Community	140 (82)	67 (82)	23 (74)	50 (88)

* Oncology nurses, nurse specialists, and nurse practitioners are summarized into oncology nurses. IQR = interquartile range. Percentages of missings are not presented.

Patient involvement in decision-making

Figure 1 illustrates HCP's opinion on involvement of patients with mCRPC in treatment decision-making ($p = .91$), their opinion about trying to actively involve patients even if they do not want to be involved ($p = .29$), their beliefs of physician's capability to decide how risks and benefits should be weighed in patients' context ($p = .47$), and their opinion on discussing all potential risks ($p < .05$). Furthermore, 12% of urologists and 26% of oncologists indicated that all treatments have to be discussed with patients even if they do not have a choice ($p = .03$). Oncologists were more inclined to discuss all treatments. Sixty-two percent of urologists, 65% of oncologists, and 51% of oncology nurses agreed that mCRPC patients take a passive role in decision-making because of their advanced age ($p = 0.45$). Figure 2 illustrates HCP's preference for final treatment decision-making for mCRPC patients. Sixty-three percent of urologists, 74% of oncologists, and 65% of oncology nurses found that ideally physicians and patients should decide together ($p < .05$). Fifty-two percent of urologists and 55% of oncologists believed that physicians are inadequately trained to apply and implement SDM in clinical practice. In contrast to physicians, only 20% of oncology nurses believed that oncology nurses are inadequately trained. Additional comments regarding these questions are presented in Supplementary 2,Table 1. The proportion of missing values ranged from 7% to 13%.

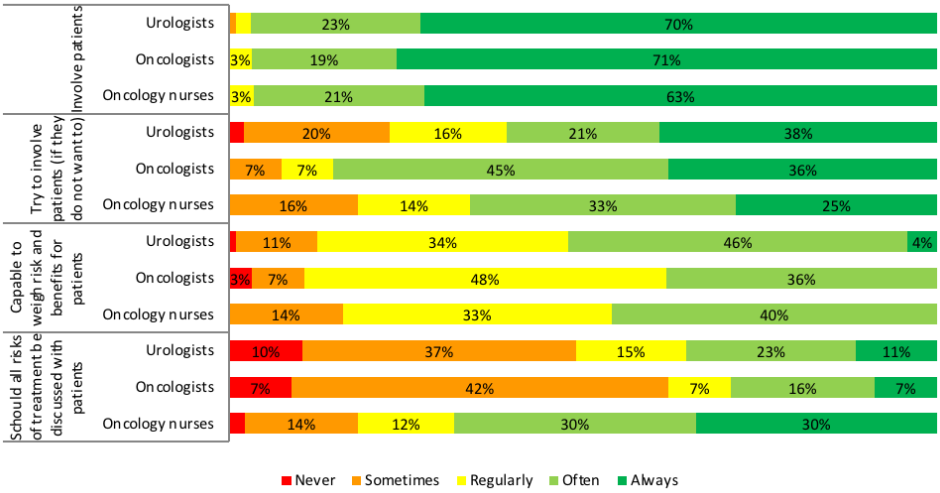


Figure 1. Opinion of healthcare providers on patient involvement and shared decision-making in mCRPC treatment decisions. The overflow of colors present the various responses of Dutch urologists, oncologists, and oncology nurses. Labels for percentages of ≤2% are not presented. Percentages of missings are not presented

Value of a decision aid

Forty-five percent of urologists, 32% of oncologists, and 56% of oncology nurses agreed that a DA is suitable to support mCRPC treatment decisions, with oncology nurses most in favor of a DA ($p = .01$). Eleven percent of urologists, 3% of oncologists, and 7% of oncology nurses thought that DA use would be stressful for their patients ($p = .35$). Sixty-six percent of urologists who were neutral or thought that a DA is not suitable to support mCRPC treatment decisions also thought that DA use would be stressful for their patients, this applied to 75% of oncologists and 35% of oncology nurses. Figure 3 presents the opinions on the effect of DA use on consultation time. Urologists more often thought that consultation time would not change with DA use than others ($p < .05$). Figure 4 illustrates that there is no consensus among HCPs on who the most appropriate HCP is to present the DA ($p < .05$). Forty-eight percent of oncologists think they should do it, but only 28% of oncology nurses and 18% of urologists think that their HCP type should do it. Among the nurses, 38% think that urologists should do it, while 28% of urologists think that the nurses should do it. Fifty percent of urologists, 52% of oncologists, and 67% of oncology nurses shared the opinion that presenting the DA to patients directly after the multidisciplinary meeting is the most appropriate timing ($p = .07$). The majority of all team members were familiar with a DA for localized prostate

cancer (urologists 87%, oncologists 65%, and oncology nurses 75% (p = .05)). Only for oncology nurses a correlation was found between their attitude towards the value of a DA for mCRPC and their familiarity with DAs (r_s = .429; p < .05). The proportion of missing values ranged from 11% to 15%.

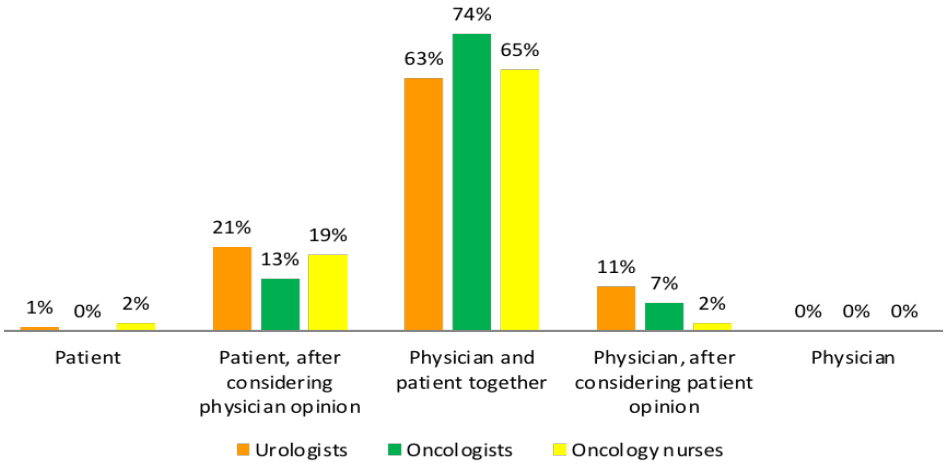


Figure 2. Preference for patient involvement in final decision for treatment of patients with mCRPC. Percentages of missings are not presented

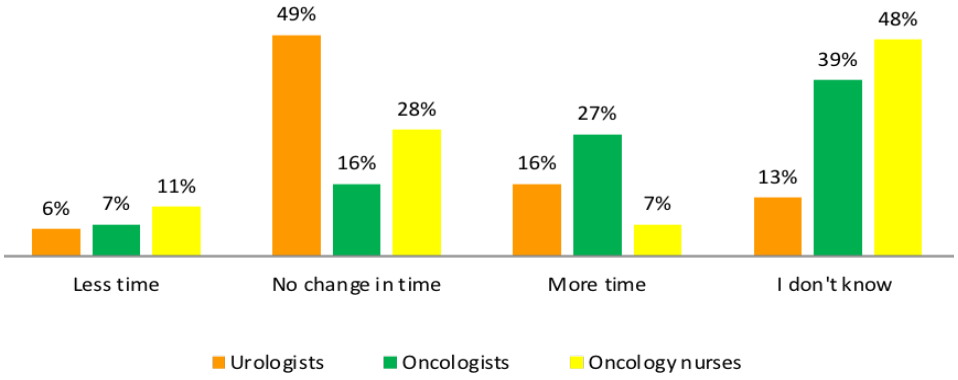


Figure 3. Healthcare provider's opinion on the effect of DA use on consultation time. Percentages of missings are not presented

Treatment preferences for patients with mCRPC

Responses to four hypothetical cases are summarized in box-and-whiskers plots in Figure 5. This figure illustrates how likely it was that a HCP would recommend a particular treatment for individual patients. In the first case watchful waiting was more likely to be recommended by oncologists compared to other HCPs ($p < .05$). As for the second case, oncologists were more likely to recommend enzalutamide than others ($p = .02$). In the third case, with a relatively young asymptomatic, non-progressive patient, oncologists were less likely to recommend docetaxel than other HCPs ($p = .03$).

In the last, more complicated case, no differences in likelihood of recommending a particular treatment was found between groups. However, 20 HCPs suggested an alternative treatment option with the combination of pain killers and local radiotherapy. Overall, the occurrence of symptoms, comorbidities, and patients' performance status were considered important attributes by HCPs when recommending a treatment option to patients. An overview of these attributes is presented in Supplementary 2, Table 2. The proportion of missing values range from 34% to 40%.

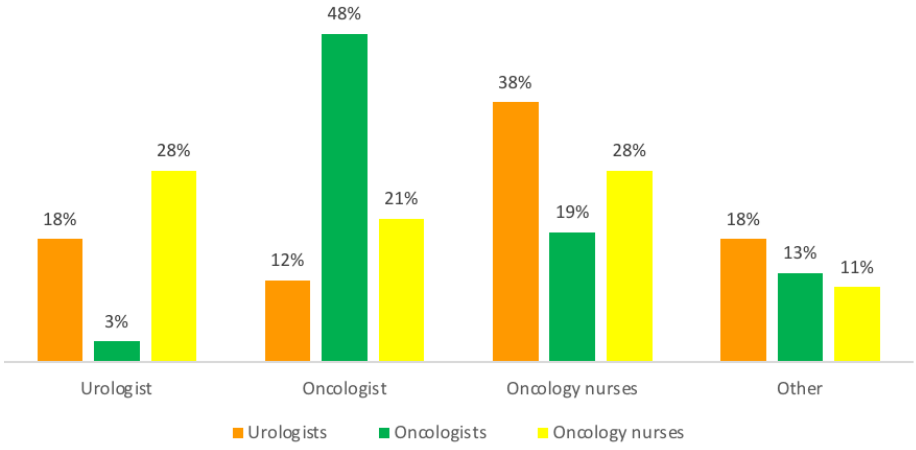


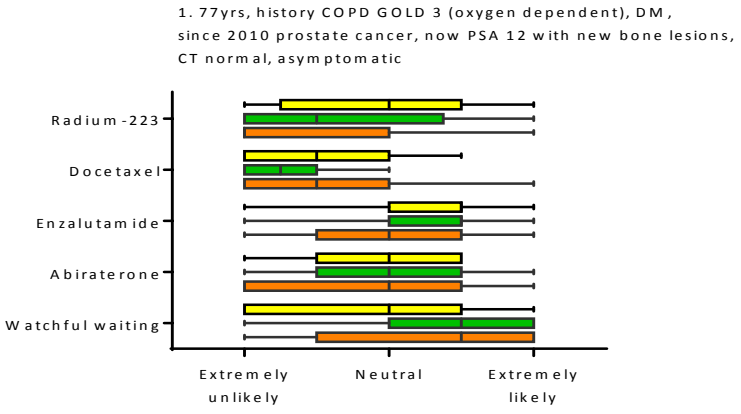
Figure 4. Healthcare provider's perspective on most appropriate person to provide patients with the DA. Percentages of missings are not presented

Discussion

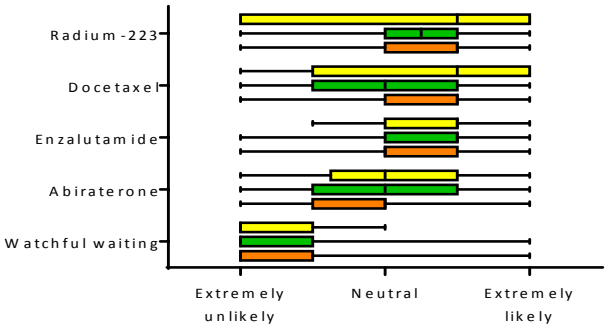
To the best of our knowledge, this is the first study that explores perspectives of the multidisciplinary team on SDM in older patients with mCRPC. Although most team members indicated that these patients should be involved in the decision-making

process, more than half of the physicians indicated that they are not adequately trained to apply SDM in clinical practice. Overall, half of respondents found a mCRPC treatment DA suitable to support the decision-making process. Furthermore, the wide variation observed in treatment recommendations in the hypothetical cases illustrates the preference sensitivity of these decisions.

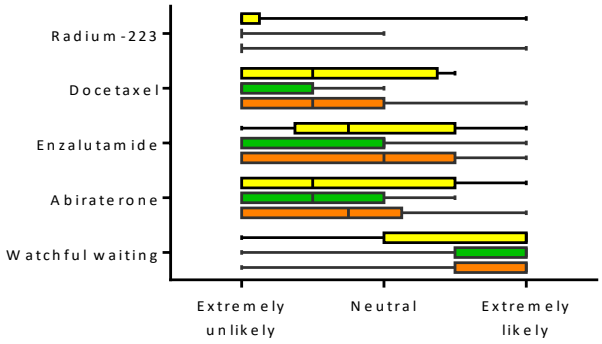
There seems to be consensus among members of the multidisciplinary team that patients with mCRPC should be involved in treatment decisions whenever possible. As Mokhles et al. previously explored among lung cancer clinicians, the motivation to involve patients in SDM could be that it potentially leads to better disease-specific knowledge and more realistic expectations of treatments [6]. However, most respondents thought that these older patients take a passive role in the decision-making due to advanced age. Some respondents argued that physicians have a more paternalistic role in decision-making with older cancer patients. This assumption is in line with previous studies that have shown that older adults tend to seek less information to make decisions [9, 10]. Moreover, older patients seem to prefer less choice options and seem to have greater difficulties in understanding information about treatments [10]. In addition, communication with older patients with cancer can be more complicated by age-related barriers [11, 12]. Despite these findings, previous studies also described the continuously unmet information and communication needs [11, 13] which influence quality of life more negatively in older than younger patients with cancer [11, 14]. This implicates a possibility for improvement. Importantly, older patients with cancer should be treated as a heterogeneous group with multiple health problems [15]. As such, treatment decision-making should be conducted by multidisciplinary teams that take into account patients' individual health statuses, as mandated by EAU-ESTRO-SIOG Guidelines [1, 2].



2. 74yrs, history mild congestive heart LVEF 42%, WHO 1-2, since 2014 prostate cancer, now biochemical and radiologic progression, symptomatic



3. 65yrs, no comorbidities, since 2008 prostate cancer, now PSA 9, T<1.7 nmol/L, GFR >60mL/min, no new bone lesions, CT normal, asymptomatic



4. 80yrs, history CVA (wheelchair dependent), DM, depression, corinary heart disease, since 2007prostate cancer, now PSA 0.62, T<1.7 nmol/L, GFR 50-60 mL/min, new bone lesions, symptomatic, patients' preferred treatment: chemotherapy

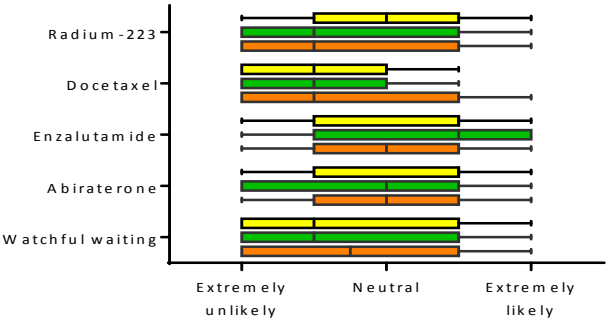


Figure 5. HCPs treatment preferences in 4 hypothetical cases. All patients were unresponsive to androgen blockade therapy. Yellow box = oncology nurses, green box = oncologists, and orange box = urologists. Box represents 50% of the treatment preference and the whiskers illustrate the minimum and maximum value.

A majority of respondents in this study indicated that they find themselves capable to decide how risks and benefits should be weighed in patients' context. However, previous studies showed a mismatch between physician's perception and actual patient preferences due to lack of communication skills needed to identify these individual preferences [6, 11, 16-18]. Our results, at the same time, showed that >50% of physicians found that they are inadequately trained to apply SDM in clinical practice. On the other hand, most of oncology nurses do find themselves adequately trained to apply SDM.

Some physicians indicated that resident training was more focused on honing practical skills rather than on learning skills to negotiate with patients regarding treatments. Moreover, literature suggests that due to time constraints, physicians often provide a one-sizefits-all approach by giving patients a fixed set of facts about treatments which they repeat from patient to patient [19]. This seems efficient to physicians, but this routine of giving information that some patients are not interested in or already understand, can lead to less time for physicians to engage in back-and-forth dialogue with patients [19]. According to the literature there is need for international consensus on ways to address SDM training programs [20]. Ubel et al. suggested that teaching communication techniques in the context of SDM should be continued after medical school by involving ethicists and emphasizing concrete examples of communication failures, rather than abstract theories about autonomy [19].

To elicit individual patient preferences, DAs can be beneficial to support SDM. Urologists and oncology nurses were more in favor of a DA for mCRPC patients than oncologists. This may be explained by the observation that oncology nurses were more familiar with DAs for localized prostate cancer. Furthermore, in most Dutch clinical practices, patients often visit oncology nurses for additional treatment information after their doctor's visit. Therefore, oncology nurses may find the use of a supportive tool, such as a DA, more suitable than other HCPs. A review by Weert et al. showed positive results on the effectiveness of DAs for older patients with e.g. atrial fibrillation, type II diabetes, breast cancer, prostate cancer, and advanced dementia [10]. Comparable to younger patients, DA use increases older patients' risk perception, improves disease-specific knowledge, and improves involvement in decision-making [10]. As most patients with mCRPC find themselves in an emotional situation affecting information uptake, an up-to-date DA can offer patients the opportunity to gain knowledge about their disease and values in their own time with their family, prior to their next visit. This might also save consultation time for physicians.

One important finding of this study is the observed variation within groups in recommending particular treatments for individual patients with mCRPC. In contrast to comparable studies that observed that physicians recommend treatments in line with their specialty [6, 21], we observed less variation between groups. Overlap of treatment recommendations in all cases confirms the ongoing discussion about 'best' timing and treatment sequence for patients with mCRPC. Furthermore, it confirms that this treatment decision needs to carefully weigh evidence on potential harms and benefits in light of decreasing life expectancy, making this decision 'preference sensitive' [10].

Currently, discussing patient preferences regarding treatments and older patients' individual health status are not systematically integrated into multidisciplinary meetings [22]. Addressing a patient's individualized health status using a validated geriatric screening instrument (for example G8) [23] prior to multidisciplinary meetings can improve effective communication between HCPs. Additionally, to guide physicians in appropriate patient selection for specific mCRPC treatments, integrating a clinical prediction model in multidisciplinary meetings can be helpful to optimize the decision-making process. Estimated outcomes of the prediction model can be simplified communicated to patients and their families in understandable language by HCPs, in combination with a DA to clarify patients' values. However, attention to patients' context (alternative knowledge), such as lived experiences, is also crucial when communicating risks [24]. It helps HCPs to identify and overcome patients' misconceptions about treatments and prognosis and will improve effective communication and SDM for patients with mCRPC.

This study has several limitations. Firstly, response bias is difficult to ascertain due to the inability to determine how many unique surveys were sent out.

Secondly, residents in training were not approached for participating this study. Residents in training belong to the new generation of physicians who have been more exposed to the concept of SDM in current practice than older generations. Additionally, perspectives of mCRPC patients were not included. However, with the amount of literature on unmet information needs of (advanced) prostate cancer survivors and their partners available [4, 11, 25-28], we decided to focus on the ongoing discussion about 'best' treatment sequence and the attitudes of the multidisciplinary team towards SDM that could support future decision-making.

Lastly, this study is conducted in the Dutch healthcare system setting among Dutch HCPs, including a minority of oncologists compared to urologists and oncology

nurses. Perspectives of oncology nurses, nurse specialists, and nurse practitioners were grouped together but they may have different roles and attitudes towards SDM and DAs. Results and suggestions may therefore not apply equally in other health care systems and require formal exploration. Also, there was a substantial amount of missing data for the responses to the hypothetical cases, probably due to the fact that these questions were asked at the end of the survey. Results should therefore be interpreted with caution.

In conclusion, this survey among Dutch multidisciplinary team members illustrates that there is consensus about the importance of patient involvement in mCRPC treatment decision-making. Lack of training in communication skills to apply and implement SDM is an important barrier. Although the majority of physicians believed that not all treatments with risks should be discussed with patients, the variation of treatment recommendations suggests that it might be useful to discuss all treatment options. Furthermore, the variation underlines the preference sensitive nature of this treatment decision. Training HCPs on effective patient communication skills remains an imperative. Facilitating these conversations by making DA usage common place may better inform patients about treatments, associated risks, and expected prognosis thus improving the decision-making process for both older patients and their HCPs.

Author contribution statements

I.A and J.T. conceived the presented idea. I.A., P.K, J.T., and C.B. developed the survey and P.K. and C.B. made it possible to distribute the survey on the annual autumn meeting of the Dutch Association for Urology in November 2016 and via the Dutch National Consultation Oncology Nurses and Dutch Uro-Oncology Studygroup Foundation. P.K., J.T., and C.B. supervised the findings of this work analyzed by I.A. I.A. was responsible for the preparation of the manuscript. All authors have read and approved the final version of the manuscript. There are no ethical problems or conflicts of interest of any of the authors related to this paper.

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References

1. Mottet N. Metastatic Castration-resistant Prostate Cancer: Major Progress Leading to Even More Questions. Eur Urol Focus. 2016;2(5):562-4.
2. Cornford P, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer. Eur Urol. 2017;71(4):630-42.
3. Stacey D, Legare F, Lewis K, et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev. 2017;4:CD001431.
4. Carter N, Bryant-Lukosius D, DiCenso A, Blythe J, Neville AJ. The supportive care needs of men with advanced prostate cancer. Oncol Nurs Forum. 2011;38(2):189-98.
5. Korteland NM, Kluin J, Klautz RJ, et al. Cardiologist and cardiac surgeon view on decision-making in prosthetic aortic valve selection: does profession matter? Neth Heart J. 2014;22(7-8):336-43.
6. Mokhles S, Maat A, Aerts J, et al. Opinions of lung cancer clinicians on shared decision making in early-stage non-small-cell lung cancer. Interact Cardiovasc Thorac Surg. 2017;25(2):278-84.
7. Pieterse AH, Baas-Thijssen MC, Marijnen CA, Stiggelbout AM. Clinician and cancer patient views on patient participation in treatment decision-making: a quantitative and qualitative exploration. Br J Cancer. 2008;99(6):875-82.
8. Degner LF, Sloan JA, Venkatesh P. The Control Preferences Scale. Can J Nurs Res. 1997;29(3):21-43.
9. Reed AE, Mikels JA, Simon KI. Older adults prefer less choice than young adults. Psychol Aging. 2008;23(3):671-5.
10. van Weert JC, van Munster BC, Sanders R, et al. Decision aids to help older people make health decisions: a systematic review and meta-analysis. BMC Med Inform Decis Mak. 2016;16:45.
11. van Weert JC, Bolle S, van Dulmen S, Jansen J. Older cancer patients' information and communication needs: what they want is what they get? Patient Educ Couns. 2013;92(3):388-97.
12. Stewart M, Meredith L, Brown JB, Galajda J. The influence of older patient-physician communication on health and health-related outcomes. Clin Geriatr Med. 2000;16(1):25-36, vii-viii.
13. Hack TF, Degner LF, Parker PA, Team SC. The communication goals and needs of cancer patients: a review. Psychooncology. 2005;14(10):831-45; discussion 46-7.
14. Maguire P. Improving communication with cancer patients. Eur J Cancer. 1999;35(10):1415-22.
15. Chouliara Z, Kearney N, Stott D, Molassiotis A, Miller M. Perceptions of older people with cancer of information, decision making and treatment: a systematic review of selected literature. Ann Oncol. 2004;15(11):1596-602.
16. Fallowfield L, Jenkins V. Current con-

cepts of communication skills training in oncology. Recent Results Cancer Res. 2006;168:105-12.

17. Rutten LJ, Arora NK, Bakos AD, Aziz N, Rowland J. Information needs and sources of information among cancer patients: a systematic review of research (1980-2003). Patient Educ Couns. 2005;57(3):250-61.
18. Hoffmann TC, Del Mar C. Patients' expectations of the benefits and harms of treatments, screening, and tests: a systematic review. JAMA Intern Med. 2015;175(2):274-86.
19. Ubel PA, Scherr KA, Fagerlin A. Empowerment Failure: How Shortcomings in Physician Communication Unwittingly Undermine Patient Autonomy. Am J Bioeth. 2017;17(11):31-9.
20. Diouf NT, Menear M, Robitaille H, Painchaud Guerard G, Legare F. Training health professionals in shared decision making: Update of an international environmental scan. Patient Educ Couns. 2016;99(11):1753-8.
21. Fowler FJ, Jr., McNaughton Collins M, Albertsen PC, et al. Comparison of recommendations by urologists and radiation oncologists for treatment of clinically localized prostate cancer. Jama. 2000;283(24):3217-22.
22. Pillay B, Wootten AC, Crowe H, et al. The impact of multidisciplinary team meetings on patient assessment, management and outcomes in oncology settings: A systematic review of the literature. Cancer Treat Rev. 2016;42:56-72.
23. Bellera CA, Rainfray M, Mathoulin-Pelissier S, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. Ann Oncol. 2012;23(8):2166-72.
24. Hajizadeh N, Basile MJ, Kozikowski A, et al. Other Ways of Knowing. Med Decis Making. 2017;37(3):216-29.
25. Carter N, Bryant-Lukosius D, DiCenso A, Blythe J, Neville AJ. The supportive care needs of family members of men with advanced prostate cancer. Can Oncol Nurs J. 2010;20(4):166-76.
26. Zhou ES, Bober SL, Nekhlyudov L, et al. Physical and emotional health information needs and preferences of long-term prostate cancer survivors. Patient Educ Couns. 2016;99(12):2049-54.
27. Bernat JK, Skolarus TA, Hawley ST, et al. Negative information-seeking experiences of long-term prostate cancer survivors. J Cancer Surviv. 2016;10(6):1089-95.
28. Eliasson L, de Freitas HM, Dearden L, Calimlim B, Lloyd AJ. Patients' Preferences for the Treatment of Metastatic Castrate-resistant Prostate Cancer: A Discrete Choice Experiment. Clin Ther. 2017;39(4):723-37.

Supplementary 1. Study-specific survey

What is your age?

.....

What is your specialty?
Urologist
Oncologist
(Oncology) nurse

Do you work in a community or academic hospital?
o Community hospital
o Academic hospital

How many years have you been working in your specialty?

.....

Do you think that patients with mCRPC should be involved in choosing a treatment?
Never Sometimes Regularly Often Always I don't know
Comments: .....

If a patient doesn't want to be involved in choosing a treatment, do you think that physicians should try to involve the patient in the decision?
Never Sometimes Regularly Often Always I don't know
Comments:.....

The final decision in treatment choice should be made by:
The patient
The patient, after considering physician's opinion
The patient and physician together
The physician, after considering patient's opinion
The physician
Comments:.....

To choose a treatment for mCRPC, the advantages and disadvantages of treatment options are taken into consideration. Do you think physicians can decide for patients how risks and benefits should be weighted?

Never Sometimes Regularly Often Always I don't know
Comments:.....

Do you believe that *physicians/oncology nurses* are adequately trained to implement shared decisions in clinical practice?
Yes, because.....
No, because.....

Do you think that patients with mCRPC take a more passive role in decision-making because of their advanced age?
Yes, because.....
No, because.....

Do you think that *all* disadvantages of treatment options should be discussed with patients (even if the risk is really small) ?
Never Sometimes Regularly Often Always I don't know
Comments:.....

Is there a weekly multidisciplinary team meeting in your hospital, including an urologist, a radiotherapist, a pathologist, and an oncologist?
Yes
No, because.....

Do you think that *all* treatment options (watchful waiting, abiraterone, enzalutamide, docetaxel, and radium-223) should be discussed with the patient (even if the patient does not have a choice)? *(physicians only)*
Never Sometimes Regularly Often Always I don't know
Comments:.....

To what extent are you familiar with decision aids for prostate cancer (e.g. for localized prostate cancer)?
o Not familiar
o I know the content of a decision aid for prostate cancer
o I know a decision aid, but I have not read it (yet)
o I know a decision aid and I briefly read it
o I know a decision aid and I reviewed it completely
o Other:.....

A decision aid is appropriate for patients with mCRPC to support the decision-making process, if they have a choice between two or more treatment options.

Completely disagree Disagree Neutral Agree Completely agree

Comments:.....

The use of a decision aid would be stressful for my patients.

Completely disagree Disagree Neutral Agree Completely agree

Comments:.....

The use of a decision aid will lead to:

- o Less consultation time
- o No change in consultation time
- o More consultation time
- o I don't know

Who is the most appropriate healthcare provider to present the decision aid to patients with mCRPC?

- o Urologist
- o Oncologist
- o (Oncology) nurse
- o Other:.....

What is the best timing to present the decision aid to patients with mCRPC?

- o Directly after the diagnosis of mCRPC
- o Directly after the multidisciplinary meeting by urologist
- o Directly after the multidisciplinary meeting by oncologist
- o Other:.....

Case 1

Man, 77 years. New patient with mCRPC with three new bone lesions, **asymptomatic**.

Additional information:

Comorbidities
COPD GOLD 3 (oxygen dependent), diabetes
Urologic history
2010 cT3NxMx, Gleason 3+4 =7 , iPSA 20 , PLND 3/8 + ADT (gosereline)
2014: PSA 0,6
2015: PSA 1,25
2016: PSA 12, Testosterone <0.1 nmol/L, GFR >60 mL/min
Additional diagnostic information
Bone scan (skeletal scintigraphy): 3 bone lesions (progressive); CT-scan: normal

	Extremely unlikely				Extremely likey
Watchful waiting	1	2	3	4	5
Abiraterone	1	2	3	4	5
Enzalutamide	1	2	3	4	5
Docetaxel	1	2	3	4	5
Radium-223	1	2	3	4	5

Comments:.....

Case 2

Man, 74 years. New patient with mCRPC with multiple bone metastases (progressive), **symptomatic**.

Additional information:

Comorbidities
Mild congestive heart failure, LVEF 42%
WHO: 1-2
Urologic history
2014 T3NxM+, Gleason 3+4 = 7, iPSA 250 for which treated with ADT.
Now PSA 166, Testosterone <1.7 nmol/L, GFR >60 mL/min.
Additional diagnostic information
Bone scan (skeletal scintigraphy): multiple bone lesions (progressive); CT-scan: normal

	Extremely unlikely				Extremely likey
Watchful waiting	1	2	3	4	5
Abiraterone	1	2	3	4	5
Enzalutamide	1	2	3	4	5
Docetaxel	1	2	3	4	5
Radium-223	1	2	3	4	5

Comments:.....

Case 3

Man, 65 years. New patient with mCRPC without radiologic progression, **asymptomatic**.

Additional information:

Comorbidities
None
Urologic history
8 years ago RALP for T2aN0M0, Gleason 4+4 = 8, iPSA 7. PSA nadir <0.1.
4 years ago PSA ↑ for which treated with salvage radiotherapy.
2 years ago PSA ↑ with bone metastases for which started with ADT.
Now PSA 9, Testosterone <1.7 nmol/L, GFR >60 mL/min.
Additional diagnostic information
Bone scan (skeletal scintigraphy): no progression; CT-scan: normal

	Extremely unlikely				Extremely likey
Watchful waiting	1	2	3	4	5
Abiraterone	1	2	3	4	5
Enzalutamide	1	2	3	4	5
Docetaxel	1	2	3	4	5
Radium-223	1	2	3	4	5

Comments:.....

Case 4

Man, 80 years. New patient with mCRPC with two new bone metastases, **symptomatic**.

Additional information:

Comorbidities
2011 CVA (stroke) with hemi paralysis for which wheelchair dependent.
Coronary artery disease for which treated with stents and CABG.
Diabetes Mellitus
Depression
Urologic history
2007 T3N1M0, Gleason 3+4 = 7, iPSA 8.99 for which treated with radical prostatectomy with PLND
2010 PSA ↑ for which treated with salvage radiotherapy
2013 PSA ↑ for which started with ADT
Now PSA 0.62, Testosterone <1.7 nmol/L, GFR 50-60 mL/min
Additional diagnostic information
Bone scan (skeletal scintigraphy): 2 bone lesions (progressive)
Patients' treatment preference
Patient considers chemotherapy

	Extremely unlikely				Extremely likey
Watchful waiting	1	2	3	4	5
Abiraterone	1	2	3	4	5
Enzalutamide	1	2	3	4	5
Docetaxel	1	2	3	4	5
Radium-223	1	2	3	4	5

Comments:.....

Supplementary 2

Supplementary Table 1. Additional comments of respondents regarding the questions about: discussing all potential risks, discussing all treatments, passive role of mCRPC patients, and adequacy of training to apply SDM.

	Total n	Urologists n	Oncologists n	Oncology nurses n
Discussing all risks				
Too much information is too stressful	16	9	2	5
Small risks do not need to be discussed *(only risks >10%)*	6	4	-	2
Patient dependent	7	3	-	4
Depending on severity of rare side effects	4	2	1	1
Open conversation (discuss everything)	7	-	1	6
Written information to discuss all risks needed	1	-	1	-
Discussing all treatments*				
Eligible treatment options only	18	15	3	-
Discuss all options to clarify why some options are not appropriate	10	9	1	-
Patient dependent	5	4	1	-
Role of oncologist	2	2	-	-
Region dependent	2	2	-	-
Passive role in SDM due to advanced age				
Paternalism (generation dependent)	33	19	4	10
Not age dependent, multi-factorial	26	11	2	13
"Life is completed"	3	2	-	1
Experience of daily practice	6	4	1	1
Region dependent	2	2	-	-
Adequacy of training to apply SDM				
Lack of training in curriculum	23	19	2	2
Learning by gaining experience	19	13	3	3
"That is what being a doctor is about"	10	10	-	-
Person dependent (empathy)	6	4	2	-
Time constraints	7	4	-	3
In-service training	6	1	-	5
Trained to be practical and to determine what is best for any given patient	2	1	1	-
Lack of good information provision	2	2	-	-
Depends also on adequate knowledge about risks and benefits of all options	8	-	-	8

*Physicians only.

Supplementary Table 2. Overview of attributes which were considered important by healthcare providers when recommending a treatment option presented as total and per case.

	Total n	**Case 1 n**	**Case 2 n**	**Case 3 n**	**Case 4 n**
Stated attributes by healthcare providers					
Symptoms yes/no	17	5	5	3	4
Age	5	1	-	1	3
Comorbidities	17	8	2	-	7
Depends on oncologist (+ radiotherapist)	7	3	2	1	1
Effect on survival	5	3	1	1	-
Visceral metastases yes/no	2	2	-	-	-
Initial ADT response	2	1	1	-	
Treatment costs	4	-	3	1	-
Level of testosterone	1	-	1	-	-
Medication to prevent skeletal events	2	-	-	2	-
Consult geriatrician	1	-	1	-	-
Performance status	10	-	5	1	4
PSA level	5	-	-	3	2
Decide together (patients' preference)	4	-	-	3	4
Alternative treatment suggested: pain killers combined with local radiotherapy	20	-	-	-	20

Chapter 7

Does the use of a patient decision aid improve decision-making in treatment selection for older patients with metastatic Castration-Resistant Prostate Cancer? A stepped wedge cluster randomized controlled trial

Isabel B. de Angst, Paul J.M. Kil, Huub A.A.M. Maas, Inge M. van Oort, Annet W. Coumou, Erik B. Cornel, Kevin M. Veen, Hans M. Westgeest, Ilze E.W. van Onna, Tineke J. Smilde, Romy E.D. Lamers, Franchette F. van den Berkmortel, Jorg R. Oddens, Menno A. van Leeuwen, Frederiek Terheggen, Irma M. Oving, Chris H. Bangma, Johanna J.M. Takkenberg

Submitted for publication

Part IV

Improvements for shared decision-making

Chapter 8

Setting the stage for effective patient-clinician communication: a review of factors relevant to decision-making and introducing the bidirectional Ask-Tell-Ask approach

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Submitted for publication

Chapter 9

A clinician's guide for developing a prediction model: A case study using real-world data of mCRPC patients

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Abstract

Purpose

With the increasing interest in treatment decision-making based on risk prediction models, it is essential for clinicians to understand the steps in developing and interpreting such models.

Methods

A retrospective registry of 20 Dutch hospitals with data on patients treated for castration-resistant prostate cancer was used to guide clinicians through the steps of developing a prediction model. The model of choice was the Cox proportional hazard model.

Results

Using the exemplary dataset several essential steps in prediction modelling are discussed including: coding of predictors, missing values, interaction, model specification and performance. An advanced method for appropriate selection of main effects, e.g. Least Absolute Shrinkage and Selection Operator (LASSO) regression, is described. Furthermore, the assumptions of Cox proportional hazard model are discussed, and how to handle violations of the proportional hazard assumption using time-varying coefficients.

Conclusion

This study provides a comprehensive detailed guide to bridge the gap between the statistician and clinician, based on a large dataset of real-world patients treated for castration-resistant prostate cancer.

Keywords

Decision-making · Prediction modeling · Castration-resistant prostate cancer · Cox proportional hazard model

Introduction

As an urologist or oncologist it is not rare to encounter a 77 year old prostate cancer patient treated with androgen deprivation therapy, whose PSA rises consecutively at castrate serum levels of testosterone and who develops new bone lesions on imaging studies. According to the European Association of Urology guidelines, this patient meets the criteria for metastatic Castration-Resistant Prostate Cancer (CRPC) (1). The patient has a medical history of chronic obstructive pulmonary disease (COPD) and diabetes mellitus. He has no prostate cancer related symptoms but due to his comorbidities he has a performance status of 1. We have previously shown that based on these factors Dutch clinicians are more likely to opt for watchful waiting or hormone targeted drugs, instead of docetaxel/prednisolone or radium-223 (2). In absence of clear recommendations for a preferred treatment option and sequence, clinicians may benefit from support of a clinical prediction model that is able to predict survival per treatment option based on patients' clinical baseline characteristics.

Recently, a significant amount of work has been published concerning risk prediction in prostate cancer (3). Risk prediction models evolved to indispensable tools to aid clinicians in making evidence-based decisions. In the urology field clinical risk prediction models for different disease states of prostate cancer exist, to predict for example the probability of biopsy-detectable aggressive prostate cancer, lymph node involvement, or overall survival (OS) in first-line chemotherapy. Nevertheless, despite existing general guidelines for reporting of a multivariable prediction model for individual prognosis or diagnosis (4), the process of developing and validating such models is still shrouded in mystery for most clinicians. The aim of this paper is to provide a comprehensive detailed guide to help clinicians understand the (sometimes complex) steps in developing a useful prediction model for CRPC patients, based on a real-life case, using a retrospective dataset of real-world patients treated for CRPC. We aim to both assist the clinician in understanding the development of a prediction model and to support the clinician in recognizing common shortcomings in existing prediction models. Of course, it is of highly importance to involve a statistician in the preparatory phase as well as constructing and validating the model.

Methodology

Research question and statistical model choice

First and foremost, one needs to formulate a clear research question. Additionally, before delving into the process of developing a prediction model it should first be checked if a similar model exists. In this case it may sometimes be more appropriate to update or adapt these previous models. In this study we aimed to develop a model to predict mortality in patients with CRPC treated in first-line with either abiraterone, enzalutamide, docetaxel, watchful waiting (defined as best supportive care using systemic treatment without proven life prolonging benefits, such as anti-androgens and ketoconazole) or radium-223, with the goal to use the model for treatment decision-making and to incorporate the model into a decision aid. Based on the type of outcome an appropriate model should be chosen, because different models should be used for different types of data (Supplementary Table 1). In our case we are dealing with survival data. Hence, a non-parametric Cox proportional hazard model was chosen. It should be noted that for very long-term predictions a parametric model (e.g. Weibull) may be preferred, since these provide more stable predictions at the end of follow up (5). A summary of all considerations in model development is presented in Table 1.

Data inspection

In our case we used a retrospective dataset called the CAstration-resistant Prostate cancer RegIstry (CAPRI), which is an investigator-initiated, observational multi-center registry in 20 hospitals in the Netherlands. In the subset of the data we used, with first line treatment only, 3588 patients and 2335 deaths were recorded (6). The patients were treated according to clinical practice with a variety of first-line treatments including abiraterone, enzalutamide, docetaxel, or watchful waiting. Radium-223 was excluded from analysis due to the fact that only ten patients received Radium-223 as first line treatment in this dataset. Baseline variables are presented in Table 2. Furthermore, this dataset contained sixteen potential predictors. In general, it is recommended to have at least ten events (deaths in our case) to investigate one predictor. If a predictor has multiple categories you need 10*(number of categories – 1) events for that predictor.

Missing values and coding of predictors

In an ideal world the predictors in a dataset are all clinically relevant [1], comprehensible [2], measured reliably [3], without missing data [4], and not correlated with each other [5]. Unfortunately, datasets fulfilling all these criteria are the exception rather than the rule. Regarding the first three criteria it is recommended that clinician's perspectives are taken into account. Several authors mentioned to perform systematic reviews in

order to find suitable candidate predictors (7). In the sections below we will address the latter two criteria (missing values and correlation between predictors). Additionally, we will give special attention on how to handle continuous predictors (e.g. age and hemoglobin).

Table 1. Summary of considering in prediction modelling. Adapted from original version of Steyerberg *et al.* (7).

Step	**Specific Issues**	**CAPRI-dataset**
General considerations		
Research question	Aim: predictors/prediction?	Prediction
Intended application	Clinical practice/research?	Clinical practice
Outcome	Clinically relevant?	Mortality
Predictors	Reliable measurement? Comprehensiveness	Oncological clinical work-up and literature; extensive set of candidate predictors
Study design	Retrospective/prospective? Cohort; case-control	Registry study: retrospective cohort
Statistical model	Appropriate for research question and outcome?	Non-parametric cox proportional hazard
Sample size	Sufficient for aim?	3588 patients; 2335 events
5 modelling steps		
Data inspection	Data distribution Missing values Correlation between predictors	Table 2 (baseline table) Multiple imputation Using Pearson's R or Spearman's rho
Coding of predictors	Continuous predictors	Extensive checks of transformations for continues predictors
	Combining categorical predictors	Comorbidity score was collapsed to 3 categories instead of 8
	Combining predictors with similar effects	Pain and opioid use
Model specification	Appropriate selection of main effects?	LASSO regression
	Assessment of assumptions	Additivity checked with interaction terms, interaction with treatment was checked, 3 interaction terms included Proportional hazard assumption checked -> relaxed by time varying coefficients
Model performance	Appropriate measures used?	Discrimination
Model validation	Internal validation? External validation?	Bootstrap and k-fold cross-validation No, external dataset was available

Missing values

Various approaches are described to handle missing data, each with its own limitations and benefits (8). In our case we used multiple imputation using the MICE statistical package of R (9). "Imputation" in the context of missing baseline variables basically means that missing values are predicted upon other baseline values and/or outcome. Alike almost every statistical manipulation, certain assumptions must be made about the missing data, especially the mechanism of missing data (missing completely at random, missing at random, missing not at random) should be addressed (8). Following the latest consensus we incorporated the outcome in the imputation model using the Nelson-Aalen estimator, a non-parametric estimator of the cumulative hazard rate function (10). Using multiple imputation one creates multiple datasets in which the missing values are imputed, resulting in multiple completed datasets. The formal rules state that the analyses need to be conducted on all datasets separately and the obtained estimated must be pooled thereafter (11). Nevertheless, in case of a few missing values some authors proposed to develop the model on one dataset and test the model on the other datasets (7). Controversy remains on the cut-off of how much missing values is "too much" missing (8).

Table 2. Baseline characteristics of patients with CRPC treated with abiraterone, enzalutamide, docetaxel or watchful waiting

Treatment	**Abiraterone** ***N = 249***	**Enzalutamide** ***N = 184***	**Docetaxel** ***N = 1006***	**Watchful waiting** ***N = 2149***
Antiandrogens before CRPC *N*, (%)	114 (46.0)	81 (44.0)	397 (39.5)	788 (36.8)
Comorbidity score *N*, (%)				
0	168 (67.5)	107 (58.2)	703 (70.0)	1227 (57.1)
1	43 (17.3)	38 (20.7)	185 (18.4)	496 (23.1)
2	24 (9.6)	23 (12.5)	80 (8.0)	252 (11.7)
3	6 (2.4)	6 (3.3)	22 (2.2)	86 (4.0)
4	5 (2.0)	4 (2.2)	8 (0.8)	46 (2.1)
5	0 (0.0)	2 (1.1)	3 (0.3)	13 (0.6)
6	3 (1.2)	2 (1.1)	4 (0.4)	17 (0.8)
7	0 (0.0)	1 (0.5)	0 (0.0)	5 (0.2)
8	0 (0.0)	1 (0.5)	0 (0.0)	5 (0.2)
Bone metastases *N*, (%)	142 (87.7)	103 (87.3)	703 (91.1)	929 (81.7)
Lymph node metastases *N*, (%)	66 (80.5)	41 (83.7)	373 (82.5)	507 (76.6)
Visceral metastases *N*, (%)	8 (16.7)	8 (24.2)	57 (21.7)	52 (16.1)

table continues

Treatment	Abiraterone *N = 249*	Enzalutamide *N = 184*	Docetaxel *N = 1006*	Watchful waiting *N = 2149*
WHO *N*, (%)				
1	37 (40.2)	26 (43.3)	222 (42.0)	360 (47.1)
2	41 (44.6)	21 (35.0)	245 (46.3)	317 (41.5)
3	14 (15.2)	13 (21.7)	62 (11.7)	87 (11.4)
Pain *N*, (%)	47 (42.0)	28 (37.8)	317 (49.2)	323 (31.0)
opioid use *N*, (%)	22 (32.8)	9 (24.3)	120 (29.3)	113 (22.7)
Gleason >7 *N*, (%)	143 (67.8)	105 (65.2)	591 (65.9)	998 (55.5)
Time to castration (median [range])	11.17 [1.4, 192]	13.34 [1, 196]	10.12 [0.2, 172.7]	20.47 [0.3, 248.4]
Age (median [range])	76.00 [46, 95]	77.00 [50, 94]	70.00 [46, 93]	78.00 [49, 99]
Weight (median [range])	83.00 [52, 120]	86.00 [60, 120]	84.50 [48, 150]	81.00 [44, 118]
Hemoglobulin (median [range])	8.00 [5.1, 9.6]	8.00 [4.7, 10.3]	8.00 [4.3, 10.2]	8.10 [3.9, 10.5]
Platelets (median [range])	234.00 [37, 569]	228.50 [54, 473]	243.00 [0.4, 749]	233.00 [0.3, 714]
Lactate dehydrogenase (median [range])	218.00 [72, 3179]	216.00 [98, 730]	232.00 [21, 4100]	218.00 [79, 4329]
Alkaline phosphatase(median [range])	122.00 [41, 1673]	109.00 [38, 1263]	136.00 [34.8, 3457]	93.00 [21, 4315]
PSA (median [range])	34.00 [0.1, 8730]	24.40 [0.1, 4150]	40.00 [0.0, 8700]	9.70 [0.1, 4034]

Correlation between predictors

In medicine many variables roughly describe the same phenomena and are therefore correlated with each other. One should avoid putting highly correlated variables in the same model. Firstly, the aim of a prediction model is to be as simple as possible, and incorporating similar variables is considered redundant. Secondly, in case of highly correlated variables a phenomena called "multicollinearity" can occur, characterized by extremely high/low estimates or standard errors (12). Therefore, it is advisable to investigate all the correlations between the predictors by means of Pearson's R or Spearman's rho, and high correlation should be addressed. This can either be done by excluding one of the two correlated variables or recoding the variables into one new variable. In our case the variables "pain" and "opioid use" were correlated (Spearman's rho: 0.36). Clinically this makes perfect sense, as opioids are prescribed when a patient is in pain. We recoded opioid use and pain in several variables and a combined variable consisting out of three categories proved to be the best predictor (Supplementary Table 2).

Continuous predictors

Continuous predictors are variables that can take an infinite number of values (e.g. age and lactate dehydrogenase), and contain a lot of information. Hence, simply dichotomizing continuous predictors is paired with significant information loss (13). Nevertheless, incorporating continuous predictors into a statistical model comes along with the assumption the continuous predictors is associated with the outcome in a linear way. While a linear association can also be applied for some non-linear associations, this may not always be the case (Figure 1). Thus, we recommend firstly to explore the association of the continuous predictor with the outcome in a univariable model. In order to explore the best fitting association with the outcome and a continuous predictor one can use: transformation (like logarithmic transformation), categorization, splines and fractional polynomials, as is explained in Table 3 and Figure 2 (7).

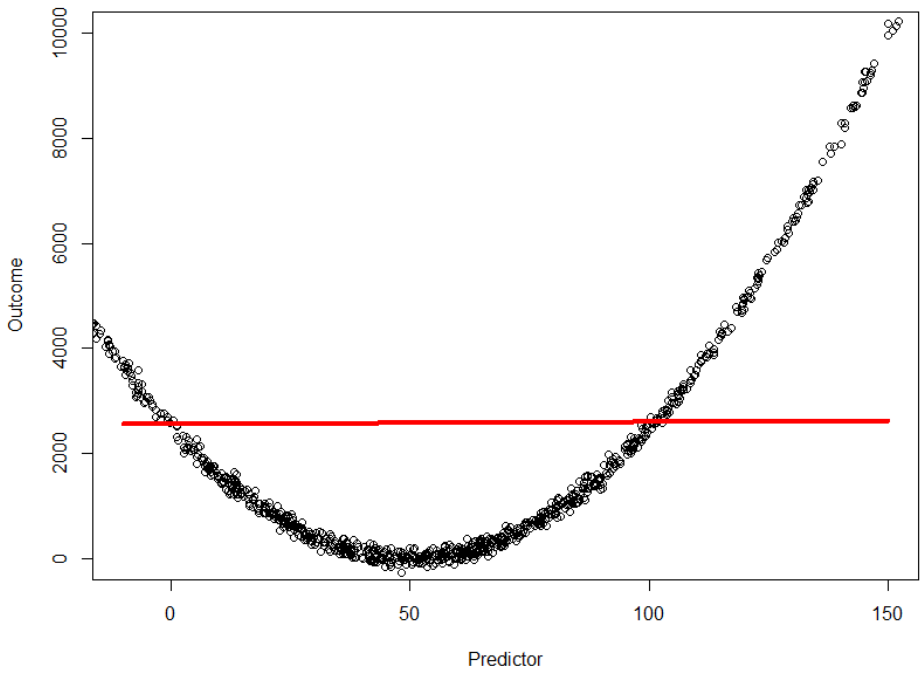


Figure 1. Example of a continuous outcome (y-axis) and continuous predictor (x-axis). As is shown: with the assumption the relation is linear the model (red line) does not fit the observed data well (black dots)

Interaction

Let us consider two predictors. Separately, they have no association with the outcome, however, when they are both present, a significant association with the outcome is observed (or vice versa). Such a phenomena is called "interaction" (7). For example these interactions are quite common in gene studies: Only when gene X *and* gene Y are turned on a certain chemical reaction will start. When either one of the genes is turned off, the reaction will not begin. Naturally, these interactions can also be present in epidemiology studies. However, especially when one considers many predictors, constructing interaction terms can be an overwhelming task. There are so many possibilities one cannot see the wood for the trees. In this case it is advisable to avert to the clinicians and a priori select a number of possible interactions, which make clinical sense. In our study, we tested the interaction term "watchful waiting" and "opioid use or pain", which turned out to be highly significant. This corresponds to the clinic; a patient with watchful waiting and opioid use or pain indicates a palliative setting, in which the patient is expected to die soon. Hence, watchful waiting and opioid use together have a stronger association with the outcome than watchful waiting and opioid use separately.

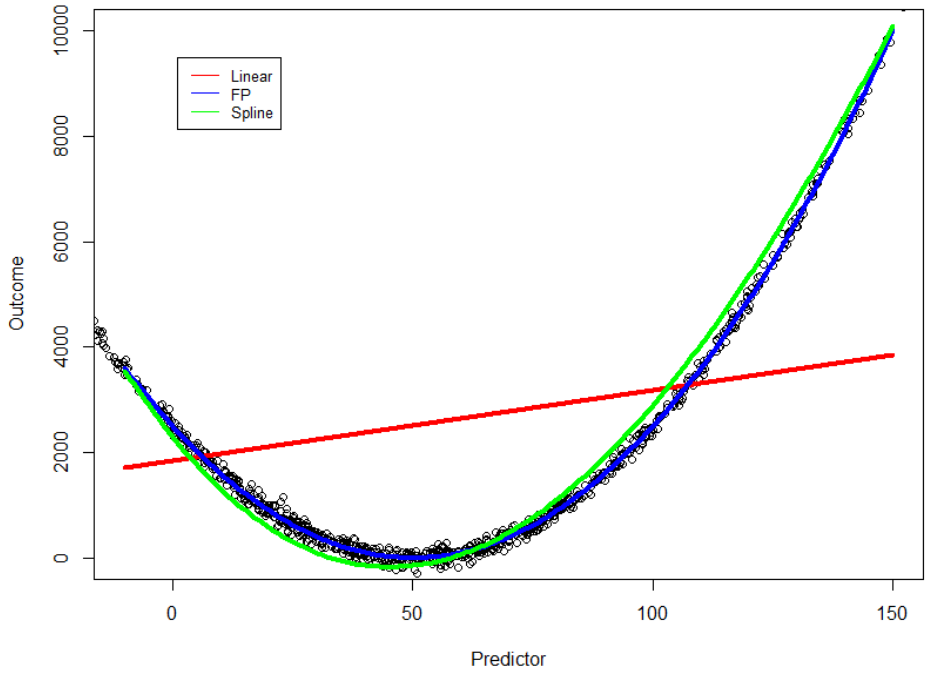


Figure 2. Example of relaxation of the linear assumed association (red line) of a continuous outcome and predictor. This can be done either with natural splines (green line) or fractional polynomials (FP) (blue line). Using splines the data is divided in separate sections, and each

section has its own estimate of the line. Using fractional polynomials the relationship is described as multiple polynomials, which can produce a very flexible line

Table 3. Performance of a linear model by adding flexibility to assume linear association with the outcome

Variable	***R*-squared***
Predictor linear	0.00938
Predictor with splines with 1 knot	0.9853
Predictor with fractional polynomial	0.9992

**R*-squared is measure of how close the model fits the data, 1 indicates the model explains all the variability of the data, whereas with 0 the model does not explain any variability. For other types of models similar measurements are available

Model specification

As mentioned earlier, the first step of predictor selection should be together with subject-specific experts. Predictor selection is arguably the hardest part of model building (14). Multiple methods exist to address the selection process of the *a priori* selected set of predictors. The most widely used methods include stepwise selection and best subset regression, and these are previously described (15, 16). In our case we had a lot of variables due to the interaction terms and non-linear continuous predictors. One always wants the most parsimonious model and does not want to exceed the one predictor per ten events rule of thumb. Therefore, it is reasonable to drop predictors that do not add much to the performance of the model. We employed a lesser known selection method using Least Absolute Shrinkage and Selection Operator (LASSO) regression (17). This is a penalized machine learning technique that shrinks the estimate of unimportant predictors to zero (Supplementary Figure 1). An estimate of zero equals no association with the outcome and, therefore a predictor is excluded. This method also can handle correlation within predictors to some extent, as the algorithm will "see" that in case of high correlation of predictor A and B, shrinking predictor B to zero will not influence performance of the model (17). Nevertheless, an algorithm cannot judge which predictor is more comprehensible or measured reliably. Therefore, one should never skip the step of looking for correlations between predictors. An excellent package to run LASSO regression in R is the "glmnet" package (18), with an elaborate vignette to code this in R (19). However, in our case we had multiple polynomials describing the relation of a continuous predictor with the outcome (see *Continuous predictors*). One wants either include all the polynomials in the model or none at all. Hence, we need to "tell" the LASSO algorithm they belong together as a group. The statistical R package

"grpreg" has implemented such a function (20).

We opted for a two-step approach. Firstly, we ran the LASSO regression and thereafter we incorporated all the non-zero predictors in a cox-model. The final model is shown in Table 4.

Assessment of assumptions

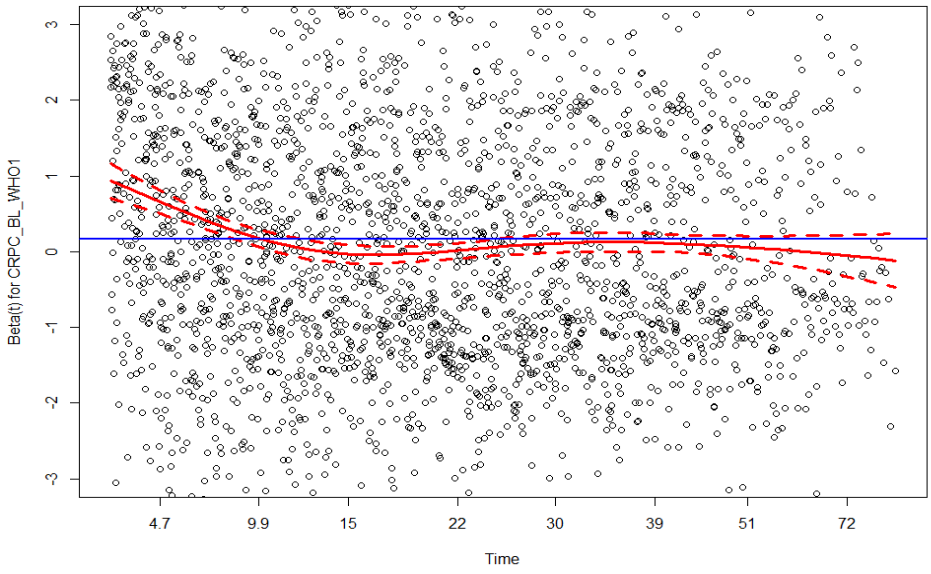
Every statistical model comes along with certain assumptions (21). If these assumptions are not met, the model is not or less valid (21). Each model family has its own specific assumptions. A key assumption in the cox model we used is the proportional hazard (PH) assumption. This basically means that ratio of hazards (the output of a cox model) is constant over time. Two approaches are commonly used to test whether this assumption is violated: plotting Kaplan Meier curves or plotting the residuals. Both methods are implemented in most statistical programs or packages. The Schoenfeld residuals should be used to test the PH assumption. Schoenfeld residuals represent the difference between the observed covariate and the expected given the risk set at that time. If one draws and average line through the residuals, this line should be straight (22). A formal test has also been developed (Schoenfeld F test) (23). In our model certain variables did not meet the PH assumption. Fortunately, this is not the end of the world. One can avert to parametric models, since some of these models do not rely on the PH assumption, however you need to start all over again. Another approach is to use an extension of the Cox model called time-varying *coefficients*, not to be confused with time-varying *covariates* (24, 25). Time-varying coefficients can be applied if the effect of a predictor is not constant over time, or in other words if the PH assumption is violated. In our case the effect predictor WHO performance status was not constant over time. As is shown in the Schoenfeld residual plot the effect of the performance status was higher in the first months compared to later in follow-up (Figure 3a). Therefore, we decided to use a stepwise time-varying coefficient function; we made a separate hazard ratio for the first ten months and for the following months thereafter. As presented in Figure 3b, the PH assumption was not violated anymore. A vignette to implement time-varying coefficients in R has been published previously (26).

Table 4. Final Cox model for predicting mortality in patients with CRPC

Characteristic	Hazard ratio (95% CI)	*P*-value
Age	1.07 (1.04 to 1.09)	<0.001
Antiandrogens before CRPC	0.87 (0.8 to 0.95)	0.001
Bone metastases	1.16 (1.03 to 1.32)	0.016
AF polynomial 1[1]	1.02 (0.9 to 1.16)	0.75
AF polynomial 2[2]	0.75 (0.57 to 0.99)	0.044
Enzalutamide vs abiraterone	1.17 (0.64 to 2.15)	0.60
Docetaxel vs abiraterone	1.85 (1.23 to 2.77)	0.003
Watchful waiting vs abiraterone	0.45 (0.31 to 0.67)	<0.001
Time to start castration spline $1_{\text{HR for <10 months}}$	0.2 (0.1 to 0.39)	<0.001
Time to start castration spline $2_{\text{HR for <10 months}}$	0.19 (0.13 to 0.26)	<0.001
Time to start castration spline $1_{\text{HR for >10 months}}$	1.45 (0.75 to 2.8)	0.27
Time to start castration spline $2_{\text{HR for >10 months}}$	0.71 (0.51 to 1)	0.048
$\text{WHO}_{\text{HR for <10 months}}$	1.64 (1.44 to 1.87)	<0.001
$\text{WHO}_{\text{HR for >10 months}}$	1.07 (0.99 to 1.15)	0.11
PSA polynomial $1^{3}_{\text{HR for <10 months}}$	1.34 (1.15 to 1.56)	<0.001
PSA polynomial $1^{3}_{\text{HR for >10 months}}$	1.02 (0.88 to 1.17)	0.82
PSA polynomial $2^{4}_{\text{HR for <10 months}}$	1.27 (1.16 to 1.4)	<0.001
PSA polynomial $2^{4}_{\text{HR for >10 months}}$	1.11 (1.01 to 1.21)	0.023
$\text{HB}_{\text{HR for <10 months}}$	0.82 (0.76 to 0.89)	<0.001
$\text{HB}_{\text{HR for >10 months}}$	0.92 (0.87 to 0.97)	0.003
Platelets polynomial $1^{5}_{\text{HR for <10 months}}$	0.97 (0.95 to 0.99)	0.001
Platelets polynomial $1^{5}_{\text{HR for >10 months}}$	1.01 (0.99 to 1.02)	0.42
Platelets polynomial $2^{6}_{\text{HR for <10 months}}$	1 (1 to 1.01)	0.001
Platelets polynomial $2^{6}_{\text{HR for <10 months}}$	1 (1 to 1)	0.46
$\text{LDH}_{\text{HR for <10 months}}$	1.66 (1.42 to 1.94)	<0.001
$\text{LDH}_{\text{HR for >10 months}}$	1.09 (0.96 to 1.23)	0.18
Opioid or pain vs none $_{\text{HR for <10 months}}$	1.09 (0.97 to 1.22)	0.16
Opioid or pain vs none $_{\text{HR for >10 months}}$	1.02 (0.94 to 1.09)	0.67
Age*Enzalutamide vs abiraterone[7]	0.94 (0.9 to 0.97)	0.001
Age*Docetaxel vs abiraterone[7]	0.96 (0.93 to 0.99)	0.003
Age*Watchful waiting vs abiraterone[7]	0.99 (0.96 to 1.01)	0.25
Log(PSA)*Enzalutamide vs abiraterone[7]	1.08 (0.92 to 1.26)	0.35
Log(PSA)*Docetaxel vs abiraterone[7]	0.91 (0.83 to 1)	0.057
Log(PSA)*Watchful waiting vs abiraterone[7]	1.23 (1.12 to 1.35)	<0.001

The model contains fractional polynomials and splines to address non-linear associations of a continues variable with the outcome and a stepwise time-varying coefcient function; e.g. some covariates have a hazard ratio for below ten months of follow-up and above ten months of follow-up 1:(AF/100)^–2), 2: (AF/100)^–1, 3: PSA^–1, 4: log(PSA), 5: Platelets*1, 6: Platelets * log(Platelets), 7: interaction term

a: Schoenfeld residual plot (WHO constant hazard)



b: Schoenfeld residual plot (WHO stepwise coefficient)

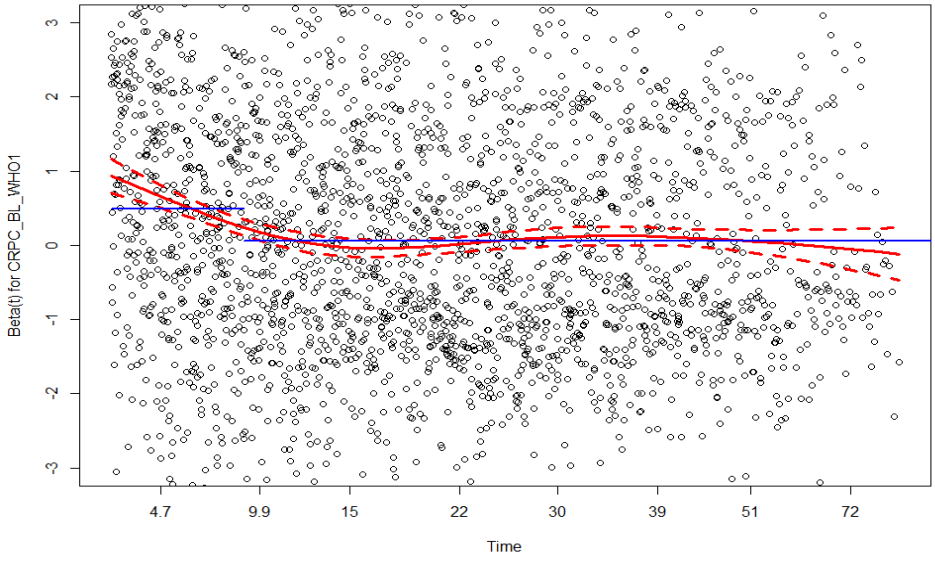


Figure 3. a Example of a Schoenfeld residuals plot in order to check the proportional hazard assumption. When the hazard of WHO is assumed constant over time (blue line in part a), the assumption is violated, especially in the frst ten months the blue line deviates from the red line. In part **b** we have two coefcients for WHO, one for the first ten months and one for more than ten months. Proportional hazards assumption is not violated anymore

Model performance

Two related terms are important in model performance: discrimination and calibration (27). Discrimination describes how well a model discriminates a high risk patient from a low risk patient or, in other words: Does the model estimate higher probabilities for patients that have an event compared to patients that do not have an event? Discrimination of binary outcomes is measured with the c-statistic or with ROC-curves (28). In our study the overall c-statistic of the model was 0.74, which indicates a good discrimination of the model. Calibration or goodness-of-fit conveys to which extent the predicted probability agrees with the observed probability. For example a high risk patient had a 7-fold higher probability of an event compared to a low risk patient and predicted risks are 7% vs 1%. The observed probabilities of a high risk patient and a low risk patient were 70% vs 10%. In this case discrimination is satisfactory, as the model discriminates well between a high and low risk patient. Nevertheless, calibration is extremely off; the observed risks are not even close to the predicted risks. Several methods exist to assess calibration and are described previously (29).

Model validation

Testing model performance on the dataset on which is developed is most of the time overly optimistic (30). After all, the model "learned" the estimates out of the correlations/associations derived from that specific dataset. To assess the possibly overly optimistic performance a statistical model should be validated. Preferably, this should be done internally and externally. During internal validation the model is validated with the original dataset. Historically, this is done by randomly splitting the original dataset into two datasets. One training dataset and one validation dataset. Nevertheless, we do not recommend this approach, because this inherently implies one cannot train the model on all the patients. In small datasets the amount of data is reduced, possibly leading to overfitting, and in very large datasets randomly splitting results in very comparable datasets. Therefore, we recommend to employ either bootstrapping techniques or *k*-fold cross validation. Using *k*-cross validation one splits the dataset in *k* groups (usually ten groups). One group is the validation set and the others are the training sets. This process is repeated *k* times with each a different group for the validation set (Supplementary Figure 2) (16). Using bootstrapping random samples are drawn from the original data. Herein a patient can be drawn multiple times and the drawn sample is usually of the same size of the original dataset. The model is run on the different randomly drawn datasets (Supplementary Figure 3) (31).

Notwithstanding, the ultimate test for a model is external validation. This means that the performance of the model is still satisfactory if it is tested on a different dataset. For example this dataset could be derived from another center, or geographical area. A model that calibrates poorly on external data can be recalibrated, whereas a model that discriminates poorly cannot. In this case a new model is required (32).

There is another highly important form of validity called "face validity". Yet, again the expert clinician comes into play here, as there are no formal ways to test face validity. Face validity says something about whether the test or model measures what it is supposed to measure. For instance face validity may be impaired when key predictors are not included in the model because they were not collected. Or when the dataset is old and does not represent clinical practice anymore. In our case, the patients in the CAPRI dataset were included from January 1, 2010 until December 31, 2017. Our aim was to develop a model to predict mortality in patients with CRPC treated with either abiraterone, enzalutamide, docetaxel, or watchful waiting in first line, in order to support adequate decision-making. However, due to the retrospective nature of this dataset, strong selection bias is present for treatment, especially since abiraterone and enzalutamide were not available as first-line treatment in the Netherlands from 2010 – 2013. So patients that were eligible for those treatments, received watchful waiting or docetaxel in this period. Of course, a multivariable model will adjust to some extend for this, and one can include intervention year as covariate to assess/and adjust for this phenomena. However, for future predictions, intervention year as covariate implies that a certain trend will continue in the future. This does not make (clinical) sense at all. Hence, this model failed the face validity.

Conclusion

Risk prediction is becoming increasingly more important in medical practice. In this article we discuss several steps in developing a prediction model including missing data, predictor encoding and selection using LASSO, testing model assumptions, performance and validation, using an example from uro-oncology. Prediction model development is not a futile task and both the input of the clinician and statistician are essential. This article may be used to bridge the gap between the two disciplines.

Compliance with ethical standards

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Ethical approval: This article does not contain any studies with human participants performed by any of the authors.

References

1. Cornford P, Bellmunt J, Bolla M, Briers E, De Santis M, Gross T, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer. Eur Urol. 2017;71(4):630-42.
2. de Angst IB, Kil PJM, Bangma CH, Takkenberg JJM. Should we involve patients more actively? Perspectives of the multidisciplinary team on shared decision-making for older patients with metastatic castration-resistant prostate cancer. J Geriatr Oncol. 2019;10(4):653-8.
3. Kearns JT, Lin DW. Prediction models for prostate cancer outcomes: what is the state of the art in 2017? Curr Opin Urol. 2017;27(5):469-74.
4. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. J Clin Epidemiol. 2015;68(2):134-43.
5. Carroll KJ. On the use and utility of the Weibull model in the analysis of survival data. Control Clin Trials. 2003;24(6):682-701.
6. Westgeest HM, Uyl-de Groot CA, van Moorselaar RJA, de Wit R, van den Bergh ACM, Coenen J, et al. Differences in Trial and Real-world Populations in the Dutch Castration-resistant Prostate Cancer Registry. Eur Urol Focus. 2018;4(5):694-701.
7. Steyerberg EW. Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating: Springer New York; 2008.
8. Papageorgiou G, Grant SW, Takkenberg JJM, Mokhles MM. Statistical primer: how to deal with missing data in scientific research? Interact Cardiovasc Thorac Surg. 2018;27(2):153-8.
9. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. 2011. 2011;45(3):67.
10. Moons KG, Donders RA, Stijnen T, Harrell FE, Jr. Using the outcome for imputation of missing predictor values was preferred. J Clin Epidemiol. 2006;59(10):1092-101.
11. Rubin DB. Multiple imputation for nonresponse in surveys: John Wiley & Sons; 2004.
12. Multicollinearity. Wiley International Encyclopedia of Marketing.
13. Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. Stat Med. 2006;25(1):127-41.
14. Ratner B. Variable selection methods in regression: Ignorable problem, outing notable solution. Journal of Targeting, Measurement and Analysis for Marketing. 2010;18(1):65-75.
15. Miller A. Subset selection in regression: Chapman and Hall/CRC; 2002.
16. Harrell Jr FE. Regression modeling strategies: with applications to linear

models, logistic and ordinal regression, and survival analysis: Springer; 2015.
17. Tibshirani R. Regression shrinkage and selection via the lasso. Journal of the Royal Statistical Society: Series B (Methodological). 1996;58(1):267-88.
18. Friedman JH, Hastie T, Tibshirani R. Regularization Paths for Generalized Linear Models via Coordinate Descent. 2010. 2010;33(1):22.
19. Hastie T, Qian J. Glmnet Vignette 2016 [Available from: https://web.stanford.edu/~hastie/Papers/Glmnet_Vignette.pdf.
20. Breheny P, Huang J. Group descent algorithms for nonconvex penalized linear and logistic regression models with grouped predictors. Statistics and computing. 2015;25(2):173-87.
21. Freedman DA. Statistical models: theory and practice: cambridge university press; 2009.
22. Schoenfeld D. Partial Residuals for The Proportional Hazards Regression Model. Biometrika. 1982;69(1):239-41.
23. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika. 1994;81(3):515-26.
24. Hastie T, Tibshirani R. Varying-coefficient models. Journal of the Royal Statistical Society: Series B (Methodological). 1993;55(4):757-79.
25. Fisher LD, Lin DY. Time-dependent covariates in the Cox proportional-hazards regression model. Annual review of public health. 1999;20(1):145-57.
26. Therneau T, Crowson C, Atkinson E. Using time dependent covariates and time dependent coefficients in the cox model. Red. 2013;2:1.
27. Alba AC, Agoritsas T, Walsh M, Hanna S, Iorio A, Devereaux PJ, et al. Discrimination and Calibration of Clinical Prediction Models: Users' Guides to the Medical Literature. JAMA. 2017;318(14):1377-84.
28. Pencina MJ, D'Agostino RB, Sr. Evaluating Discrimination of Risk Prediction Models: The C Statistic. JAMA. 2015;314(10):1063-4.
29. Van Calster B, Nieboer D, Vergouwe Y, De Cock B, Pencina MJ, Steyerberg EW. A calibration hierarchy for risk models was defined: from utopia to empirical data. J Clin Epidemiol. 2016;74:167-76.
30. Babyak MA. What you see may not be what you get: a brief, nontechnical introduction to overfitting in regression-type models. Psychosomatic medicine. 2004;66(3):411-21.
31. Efron B, Tibshirani RJ. An introduction to the bootstrap: CRC press; 1994.
32. Su T-L, Jaki T, Hickey GL, Buchan I, Sperrin M. A review of statistical updating methods for clinical prediction models. Statistical methods in medical research. 2018;27(1):185-97.

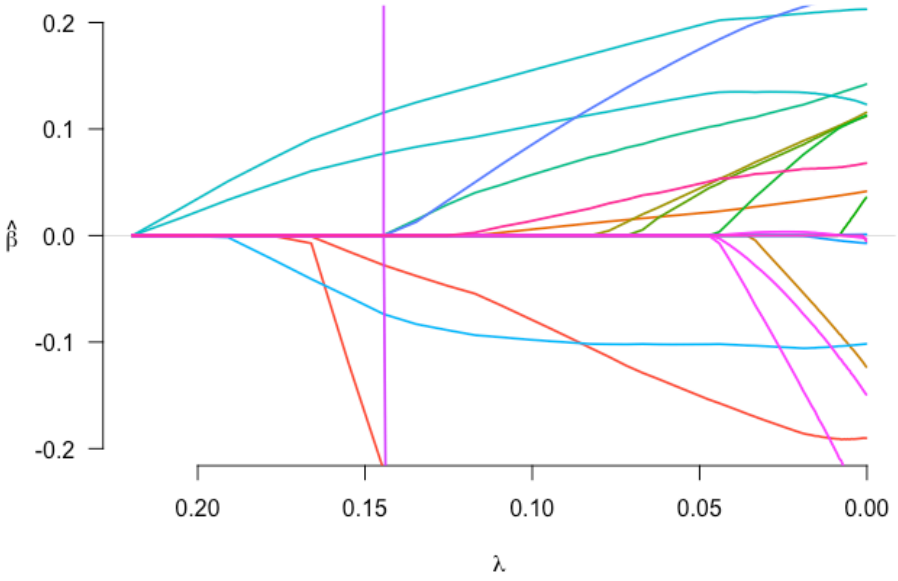
Supplementary Table 1. Types of data and their associated models

Type of data	Example	Regression model
Continuous	Blood pressure, age	Linear regression
Discrete	Yes/no variables	Logistic regression
Count data (special case of continuous data)	Hospital stay	Poisson regression Negative binomial regression
Ordinal data	WHO class	Ordinal regression
Survival data	Mortality	Cox regression (non-parametric) Accelerated time failure models (parametric)

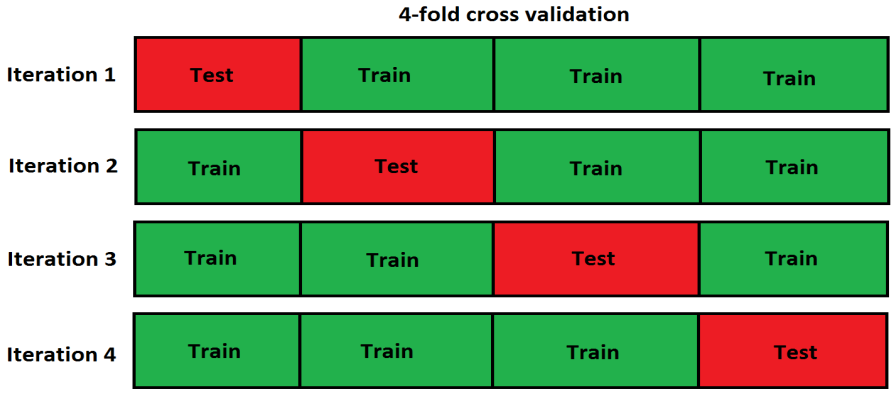
Supplementary Table 2. The variables opioid use and pain were correlated. Hence, these variables were combined into several ways and tested which variable had the best prediction. 1 is if the characteristics is present and 0 when not.

Name recoded variable	Recoding scheme	AIC	BIC
Opioid and pain	If opioid = 1 AND pain = 1 -> Opioid and pain = 1 Else: Opioid and pain = 0	35954.57	35960.37
Opioid or pain	If opioid=1 OR pain = 1 -> Opioid or pain = 1 Else: Opioid or pain = 0	35962.20	35968.00
Ordered opioid and pain_3 (3 levels)	If opioid =1 OR pain = 1 -> Ordered opioid and pain_3 = 1 If opioid =1 AND pain = 1 -> Ordered opioid and pain_3 = 2 Else: Ordered opioid and pain_3 = 0	35910.92	3596.72
Ordered opioid and pain_4 (4 levels)	If pain = 1 -> Ordered opioid and pain_4 = 1 If opioid = 1 -> Ordered opioid and pain_4 = 2 If opioid =1 AND pain = 1 -> Ordered opioid and pain_4 = 3 Else: Ordered opioid and pain_4 = 0	35911.34	35922.93

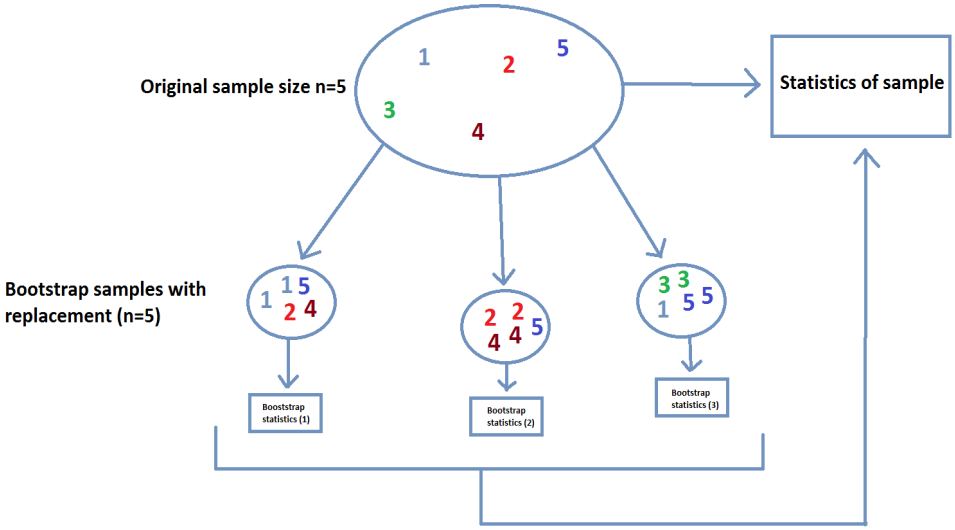
AIC =Akaike information criterion and BIC =Bayesian information criterion, both are comparative measurements of the fit of a model, penalized for the number of fitted covariates. A lower AIC and BIC indicate a better model.



Supplementary Figure 1. Shrinkage of predictors to zero using LASSO regression



Supplementary Figure 2. Schematic of k-fold cross validation in which k=4.



Supplementary Figure 3. Schematic of bootstrapping. The general idea behind bootstrapping is that of the original sample several bootstrap samples can be drawn with the same sample size as the original sample. In the bootstrap sample replacement is possible (e.g. the same subject can be drawn multiple times and at every step every subject has equal probability to be selected). Bootstrapping can be used to test model performance.

Part V

General discussion and summary

Chapter 10

General Discussion

In the medical literature and in clinical practice, shared decision-making (SDM) has become increasingly important. Considerable research has been done regarding the effectiveness of SDM in prostate disease, resulting in even more research questions to be answered. Most important to realize is that a "one-size-fits-all" approach is not optimal when pursuing informed and value congruent decision-making. In the ideal SDM process concerning prostate disease all of the following aspects are included:

1. Prognostic information based on individual patient characteristics that are communicated in understandable plain language with help of arrays/pictographs when needed (1)
2. A values clarification method (VCM) to help patients explore their own preferences (1)
3. Goalsetting questions to identify patients' ultimate treatment goals
4. Questions that elicitate patients' contextual factors to help clinicians discuss treatments in light of patients' context
5. For elderly patients a validated geriatric screening to help clinicians identify potentially frail patients and to select the appropriate treatment

Instruments, such as patient decision aids (PDAs), are developed to facilitate the SDM process and to achieve well-balanced treatment decisions. This thesis aimed to provide insight into the effectiveness of PDA use for various prostate diseases and to optimize the SDM process by integrating the above mentioned aspects. This was done by introducing novel supportive decision-making tools and to evaluate these tools in various prostate diseases. In this discussion, the key findings and implications for clinical practice and future research are discussed and illuminated from a diversity of perspectives, including the patient, clinician, organization, healthcare system, and researcher perspective.

Patient perspectives on SDM and PDA use

Literature shows that most patients want to be involved in treatment decision-making (2). Only a minority of patients with localized prostate cancer prefer a passive role; these patients are older and less educated than patients who report preference for a shared or active role (3). **Chapter 2, 5,** and **7** confirm these findings. Most patients with a benign prostate enlargement (LUTS/BPH), patients with localized prostate cancer, and even older patients with metastatic castration-resistant prostate cancer (mCRPC) indicated that they want to be involved in the decision-making process. However,

there were no differences in preferred or perceived role between patients who used the PDA and standard care, except for patients with LUTS/BPH who perceived a less passive role compared to control patients after using the PDA (**Chapter 2**). In addition, PDA use might have empowered patients with mCRPC to ensure their preferred role in the decision-making (**Chapter 7**). A sub-analysis of pre- and post-decision-making showed that control patients' role in decision-making shifted from active to more passive, implying that their clinicians more often made the final decision. Although not significant, PDA patients' role seemed to shift more to active role. However, it should be taken into account that response bias may have occurred in patients participating in our prospective studies because of their awareness of our study aims. Knowing that a PDA was evaluated may raise patients' and clinicians expectations and change behavior (4).

Most outcomes of SDM and PDA use have been considered on the individual patient level, often assessed shortly after treatment decision-making. However, the best way and timing to evaluate the effectiveness of SDM and PDA use is subject of ongoing debate (5). For instance, *decisional conflict* is one frequently used measure in PDA studies that focuses on patients' current state. This is measured by the *Decisional Conflict Scale (DCS)* that covers four topics, including: perceived level of information, values clarity, support from others, and certainty about what is best (6). The value of the answers to questions about the patient's state is limited by their perspective. For instance, the answers to questions about the perceived level of information depend on whether or not the patient has been informed in the first place. Thus, a patient may not be able to accurately report on feeling well-informed about the relevant pros and cons (7). The fact that patients can be poor decision makers, in spite of having good knowledge and understanding of their personal values, has led to an increasing interest in *decision quality* as short-term outcome measure (8). *Decision quality* is defined by two key domains: the extent to which patients are informed (knowledge score) and *value congruence* (9). *Value congruence* can be measured by matching responses on value statements (e.g. what having the desire to avoid erectile dysfunction would mean in terms of treatment choice) to the chosen or received treatment or by matching the preferred treatment option to the chosen or received treatment (10). When a patient makes an informed choice based on adequate knowledge, but the chosen treatment does not match his values, it will not be a high quality decision (8). Patients can struggle to make value congruent decisions, and therefore PDAs that include values clarification methods (VCMs) to elicit their values and preferences may help. There are not many PDA effectiveness trials that measured *decision quality* (8). In **Chapter 2** *decision quality* was the primary outcome measure to assess the effectiveness of a PDA for patients with LUTS/BPH. In **Chapter 5** *decision quality* was the secondary outcome

measure to assess the effectiveness of an additional VCM for patients with localized prostate cancer. This VCM was based on the analytic hierarchy process (referred to as AHP-VCM) and was offered to patients after completing an existing PDA; results were compared to results of patients who used the PDA alone. Only patients who used the LUTS/BPH PDA (**Chapter 2**) had higher scores of *decision quality*. Interestingly, all LUTS/BPH patients scored relatively low on knowledge items, suggesting that either the questionnaire or the PDA used might have been too difficult. However, in this study knowledge was assessed after a median of five months, which also may have had an impact, since it is to be expected that disease-specific knowledge about LUTS/BPH will diminish after a few months. Although in **Chapter 5** no difference was found in *decision quality*, the treatment decision for patients with localized prostate cancer was more congruent with their values (*value congruence*) after using the AHP-VCM directly after completing the PDA compared to PDA alone. In **Chapter 2** this could not be demonstrated because results were compared with a retrospective control group consisting of patients who had already made their treatment decision for LUTS/BPH which may have influenced their answers on value statements (confirmation bias).

Investigating *decision quality* remains challenging as standardized quantification methods are still lacking (10). Furthermore, a wide variety of VCMs exist these days without the theory behind the design used reported (11). In order to move this emerging field forward, we published the development of the AHP-VCM in **Chapter 4** with adequate descriptions of the design and the relevant theory behind it. It is important that the VCM supports an iterative discovery process of value clarification to reach stabilized preferences and that the VCM explicitly presents the implications of the patient's expressed values (11). In **Chapter 5** the additional AHP-VCM was able to do so by quantitatively showing to which extent each treatment option fits with patients' expressed values. Although assessed in a relatively small cohort of patients, results indicate that the addition of this AHP-VCM to the existing PDA (referred to as PDA-AHP) enables more patients to indicate a preferred treatment option after using both decision-making tools than patients who used only the PDA.

Chapter 5 showed that 58% of the PDA-AHP patients actually used the AHP-VCM, and these patients had higher numeracy levels than non-users. Furthermore, there was a significant positive correlation between patient numeracy levels and patient comprehension of the graphs that displayed patients' implications of their responses in the AHP-VCM. These findings highlight the fact that not all patients are suitable for the use of this specific decision supportive tool. In addition, **Chapter 7**, where results of an effectiveness trial of a PDA for older patients with mCRPC were presented,

showed that 44% of the PDA users preferred a paper-based over a web-based PDA, whereas results of a previous trial assessing the effectiveness of a PDA for patients with localized prostate cancer showed that only 16% preferred a paper-based PDA (12). This previous trial found that patients with localized prostate cancer favoring a web-based PDA were younger, which may explain the difference in format preference between both trials. Moreover, it showed that patients favoring a paper-based PDA had more often medium or severe scores of anxiety and depression (12). Despite these findings, with internet referred to as part of standard information these days and the increasing use of electronic patient records it may be expected that older patients will get more familiar with using web-based applications in the future. However, our results do suggest that some patients may require more guidance and support during PDA use and treatment counseling.

It has to be acknowledged that VCMs may not always include treatment characteristics (attributes) that are relevant for an individual patient (13). For instance, when a patient with prostate cancer babysits his grandchildren he may not consider brachytherapy as valid treatment option. Since direct physical contact with children and pregnant women is discouraged during the first two months. Thus, it is important to emphasize that PDAs are supportive tools to facilitate the SDM process, but do not directly help clinicians understand patients' individual/unique preferences within their distinct social contexts. In **Chapter 8** we elaborated on non-biomedical factors (also referred to as contextual factors or alternative knowledge), including lived experiences, cultural factors (i.e. religion, ethnicity, class, sex) and embodied knowledge (i.e. subjective knowledge derived from a patient's body, feelings) (14). These elements relate to a set of fundamental beliefs about one's self and life that are mostly stable over time despite changing circumstances (15). Contextual factors may influence the comprehension, uptake and application of prognostic information presented in PDAs and during the clinical encounter, especially in patients with low numeracy scores (14). This indicates that PDAs are merely supportive tools that are most effective when combined with high quality patient-clinician interaction during consultation, with personal tailoring of the PDA to the individual patients' context (16).

Clinician perspectives on SDM and PDA use

Individual effects of SDM and PDA use on clinicians must be considered as well when evaluating SDM and PDA effectiveness. The experience of supporting patients in achieving the 'best' informed decisions may be rewarding for clinicians (17). However,

many barriers for implementing SDM for clinicians are described, including time constraints, lack of applicability due to patient characteristics and the individual clinical situation (18). To accomplish effective implementation, many clinicians need to be willing to share information with patients about alternative treatment options to support comparisons and consider patient preferences (17). In order to do so, clinicians need knowledge, skills, and a shift in attitude.

In **Chapter 6** the perspectives of the multidisciplinary team concerning SDM in treatment decisions for older patients with mCRPC were evaluated. The study showed that most team members indicated that mCPRC patients should be actively involved in the SDM process. This suggests that clinicians' attitudes towards SDM have shifted from a more paternalistic role to a more collaborative role. The majority of respondents found themselves capable of deciding how risks and benefits should be weighted in patients' context. However, mismatches are often described between the clinicians' perception and the actual patients' preferences (19-21). Our results also illustrated that >50% of the clinicians found that they are inadequately trained to apply SDM in clinical practice. Training programs for communication skills and SDM vary widely in format and components, with lack of high-quality research to draw conclusions about effectiveness (4, 22-24). Common components of training are role play, discussion, education in small groups, printed materials, audit/feedback, and booster sessions to refresh training content (4). A recently published randomized controlled trial evaluated the effect of skills training for oncologists in combination with a PDA on SDM about palliative systemic treatment, and showed that SDM training effectively changed oncologists practice (4). They even showed that consultation time of trained oncologists took 5 minutes longer when they communicated with patients who did not receive the PDA (4). This indicates that this type of effective SDM training should be considered for implementation. Not only in clinical practice but also in educational programs for medical students and, subsequently, residents-in-training from different specialties.

Due to the previously described time constraints, clinicians often apply a 'one-size-fits-all' approach by giving patients a fixed set of facts about treatment options, and repeat the same content for every patient in roughly the same format (25). This routine of giving information about alternative treatments that some patients are not interested in or already understand, leads to less time for clinicians to engage in back-and-forth dialogue with their patients to correct potential misperceptions and discuss treatments in light of patients' context (25). Therefore, in **Chapter 8**, we introduced a conceptual framework for clinicians to help them and their patients with the elicitation of contextual factors during the clinical encounter. This framework was based on the

known ask-tell-ask approach wherein clinicians are taught to first 'ask' the patient what they already know about their disease state and possible treatments. Secondly, they 'tell' patients what they exactly need to know about it. And, finally, patients' are asked to 'teach back' what they learned, so that clinicians can ensure comprehension and clarify/correct as needed (26, 27). To enhance this, we proposed a bidirectionality to this approach wherein a patient hypothetically 'asks' the clinician whether he knows about the patient's contextual factors (also including preferences/fears/goals), then the patient 'tells' the clinicians his context relevant for the decision and 'asks' the clinician to teach back to them. In this way, the exchange of information and emphasis on comprehension is no longer unilateral (that of ensuring biomedical information comprehension) but rather bilateral (also including the clinician's comprehension of patients' concerns, views and context). Similar to elicitation of patients' values and preferences, it is unlikely that patients themselves bring up these contextual factors during the clinical encounter. Thus, to operationalize this concept both parties are targeted, including a PDA with exploratory questions helping patients to think about what is meaningful to them and what them helped to make the decision. Also, a pocket version of the same exploratory questions is available for clinicians to use during the clinical encounter. This approach, referred to as the *bidirectional Ask-Tell-Ask* approach, can be spread across one or multiple consultations, depending on the decision that needs to be made. It is an innovative concept, and reflects the type of bold thinking that is required in order for us to get to the heart of what really matters to patients. However, as previously discussed, lack of training is a barrier for clinicians to adapt such innovative concepts. Therefore, an effective mixed method training program, including training in small groups with instructions, modelling, and exercise with role play, is recommended to make healthcare providers familiar with this novel approach.

Other supportive decision-making tools for clinicians are presented and evaluated in **Chapter 7** and **9**. As the International Society of Geriatric Oncology (SIOG) has recommended that potentially frail patients should be managed according to their individual health status, international urology guidelines incorporated frailty screening for patients with prostate cancer (28). A full geriatric assessment is time-consuming and not always feasible in practice, therefore the Geriatric 8 (G8) screening tool was proposed as one of the most robust screening tools associated with improved survival (29, 30). In **Chapter 7** the additive value of the G8 in the decision-making process for older patients with mCRPC was evaluated. The G8 scores were compared to the judgement of the clinician, defined as patients' performance state (WHO PS). Exploratory analyses showed that the G8 in combination with WHO PS provided a better association with two QoL subscales (physical functioning and mobility) and Global QoL compared to the

WHO PS alone. However, these results should be interpreted with caution because of the small sample size. Nevertheless, the addition of the G8 to performance status as possible predictor for overall survival has been confirmed in the literature and might, therefore, still be useful to implement in the decision-making process for patients with mCRPC either in combination or without the PDA (31, 32).

Many PDAs for patients with localized prostate cancer present rather general information applying to patient groups instead of tailored information, particularly in terms of outcome probabilities (33). However, a better cancer risk perception is observed after presenting risk tailored information compared to standard information (34). To obtain valid and accurate risk prediction models to guide clinicians in treatment selection is not a straightforward task. It is essential for a clinician to have at least a basic understanding of the developmental process of such models in order to properly interpret its value and place it in the context of the individual patient. Therefore, in **Chapter 9**, we present a guide for clinicians, explaining common pitfalls and techniques. In this way, clinicians and statisticians can be more on the same page when discussing this concept.

Similar to patients, not all clinicians have developed skills that are necessary for independently evaluating and understanding complex statistics. Insufficient clinician numeracy can impede patients' informed decision-making (35). In addition, many clinicians are unaware of their misunderstanding (36) and lack the time and training of communicating prognostic information (14). To avoid misguided recommendations from clinicians, it is necessary to improve numeracy, risk literacy, statistical skills training and risk communication in medical curriculums and continuing education (35, 37). At the same time, well-designed PDAs that communicate tailored information in tabular format, accompanied by visual aids in the form of icon arrays can support risk communication (35).

In **Chapter 7** most of the mCRPC patients were discussed in the uro-oncology multidisciplinary team (MDT). The field of prostate cancer treatment is rapidly changing and many factors influence the decision-making process. This is particular true for patients with mCRPC in whom factors such as patients' condition, previous experiences with chemotherapy, and health care inaccessibility due to immobility may arise. It is important to discuss these patients in a MDT more often, preferably in the presence of a geriatrician. Patient satisfaction and outcomes can be improved when channeled through the MDT process (38). To engage mCRPC patients in the SDM process it is important for them to be aware of the different treatment options and that they must

weigh the pro and cons with or without the support of a PDA. However, the treatment recommendation from their treating clinician, often determined after discussing the patient in a MDT and by taking into account patients' personal preferences/context/frailty, is still one of the most important influencing factors for these particular patients in SDM (39, 40).

Organizational and healthcare system persepectives on SDM and PDA use

The healthcare organization is composed of multiple delivery teams or microsystems that needs management by higher order functions such as financial departments (17). For an organization to accomplish SDM consistently, supportive decision-making tools can be integrated into the workflow and electronic record systems (17). However, organizations might resist the investment required and decline to redesign workflow or refuse to redistribute work roles. This is one of the barriers described for the implementation of SDM and/or PDAs, resulting in low uptake of PDA use in daily routine, outside clinical trials (41). With regard to the uptake of PDA use, the absolute numbers of the PDAs distributed are often known, but their relative reach within the targeted population often remain unknown (41). In our studies the relative reach within the targeted population were for LUTS/BPH PDA 59% (98/165) vs. PDA-VCM 40% (69/174) vs. mCRPC PDA 58% (64/110). These usage rates are relatively high compared to other PDAs, ranging from 25% to 35% (42). This may be partly explained by the mode of delivery: distribution did not solely rely on clinicians but oncology nurses were often leaders in identifying eligible patients and to initiate access to these tools in our studies (42).

A scoping review on organizational- and system-level characteristics that influence implementation of SDM and strategies to address them showed that most proposed strategies focused on the organizational level, including leadership, culture, teamwork, resources and workflow (43). Only a few studies described strategies that address the healthcare system-level, for instance incentives, policies and guidelines, and education (43). As for LUTS/BPH and prostate cancer guidelines, giving weight to patients' preferences in treatment selection is already recommended (28, 44). The availability of resources (i.e., time, workforce and space) and workflow (i.e., standard patient information provision, scheduling routines and use of electronic patient records) are described as most influencing characteristics to implement SDM and thus PDA use (43).

When conducting the prospective studies (**Chapter 2, 5** and **7**) in this thesis, a

substantial hospital heterogeneity was noted, especially in workflow. Therefore, a strength of these studies was the pragmatic approach used that allowed hospitals to integrate the introduction of the PDA with their own standard information provision routines. Moreover, in all studies multivariable multilevel modelling statistics were used to correct for these hospital heterogeneity. In **Chapter 7** a stepped wedge cluster randomized controlled trial was conducted in ten Dutch hospitals. Each hospital started in the control period and switched to the use of the mCRPC PDA, based on randomization of the timing of introduction of the PDA. This pragmatic trial design took into account differences in standard decision-making between hospitals and time effects, and aimed to improve implementation after trials ending. This resulted in at least two hospitals who wanted to continue using the mCRPC PDA after being updated. SDM does lead to changes in resource utilization, as previous studies have shown that patients with different diseases who use a PDA more often choose conservative treatment options (2). So, in the long term, SDM may result in reductions of healthcare costs. Despite the shift towards value-based health care, some organizations, motivated by continued income derived from achieving high volumes of procedures, will see this as a disadvantage (17). Costs may also have influenced the inclusion rate in our studies. For example, Enzalutamide and Abirateron acetate were relatively new on the market at the start of the mCRPC PDA study, which made them more expensive for hospitals to prescribe than chemotherapy. Since these additional hormonal therapies were presented in the mCRPC PDA, it may have been a burden for clinicians to use the PDA because they were afraid patients would choose the expensive additional hormonal therapy more often instead of watchful waiting or chemotherapy (**Chapter 7**).

In the Netherlands, policy makers have strongly embraced value-based healthcare which is a health care delivery model that aims to improve outcomes for patients and populations while optimizing resource utilization (45, 46). It has the potential to promote SDM and PDA use, particularly, by using information based on patient-reported outcome measures (PROMs) during routine medical encounters (47). PROMs are standardized questionnaires for patients to measure their health-related quality of life (HRQoL). Aggregated PROMs scores can be useful to inform patients more completely about risk and benefits of the alternative treatment options, next to information about survival rates derived from clinical registries (48). Therefore, putting more emphasis on PROMs, within the context of SDM and PDA use, provides an opportunity for patients to appraise and deliberate about their treatment preferences.

Nevertheless, applying SDM with or without PDA use might, hypothetically, also have a negative impact on PROMs. Patients might have a greater sense of responsibility

with regard to their treatment decision and, subsequently, might blame themselves more when experiencing side effects or negative treatment consequences. Moreover, absorbing all information about alternative treatment options might lead to higher levels of *decisional conflict* and uncertainty which may in turn also lead to negative impact on HRQoL. However, evidence about the impact of PDA use on HRQoL remains inconclusive and, more importantly, evidence contradicting this hypothesis can be found in the literature (49, 50).

Researcher perspectives on SDM and PDA use

Since research on SDM is highly time-sensitive, this paragraph highlights the lessons learned from this PhD trajectory from the researcher's point of view.

Although there seems to be a shift from a paternalistic role to a more collaborative role in treatment decision-making (**Chapter 6**), in practice, still many clinicians are reluctant to apply SDM and use a PDA during the clinical encounter. During the recruitment process of the prospective studies (**Chapter 2, 5** and **7**) some clinicians stated that they themselves were the PDA, and others were assuming that they already applied SDM. However, this was often not the case when they explained their concept of SDM. Some clinicians were afraid that providing the PDA would lead to more questions elicited by patients, leading to more unwanted consultation time to discuss why some treatment options are not appropriate for that individual patient. On the other hand, it was stimulating to observe that (oncology) nurses were more often willing to systematically identify eligible patients and to initiate the PDA. As described in the literature, patients view nurses as "mediators" who explain information, provide support by listening to patients' preferences, and provide doctors with information about patients' preferences (51). This illustrates that a multiple-consultation model, which is often the case in the Netherlands, can support SDM. Furthermore, the MDT was often used as moment to identify eligible patients to provide PDAs and to recruit for prospective studies. In every participating center one or two leaders in SDM were present, who were able to motivate the team to participate in the study. They often assisted in introducing the PDA in the clinical routine and organizing kick-off presentations. To keep clinicians motivated for recruiting patients for prospective PDA studies, giving monthly updates of inclusion rates at hospital and individual level were necessary. Additionally, prior to start of the study goals were set, i.e., after 10 patient inclusion the whole team would be rewarded.

As previously described, selecting the most appropriate outcome measure for the evaluation of the effectiveness of PDAs was challenging. Eventually, we learned not to choose too many outcome measures to avoid ceiling effect which could affect the response rate. Low response rates resulted in smaller sample sizes which can explain the absence of statistically significant differences in outcome measures between PDA users and control patients.

In all prospective PDA studies in this thesis several biases may have occurred, including selection bias, response bias and recall bias. Clinicians could have applied their own criteria when offering the PDA to patients resulting in selection bias. Significant differences in baseline characteristics between LUTS/BPH PDA users and controls support this assumption (**Chapter 2**). The mean age was lower in PDA patients and education level was higher than in controls. In order to adjust for such group differences, we corrected outcomes for age, education level, and hospital. In addition, the nonrandomized study design in **Chapter 2** and **5** might have resulted in selection bias as variables, such as patient's personality, intelligence and mental health status, were not considered and adjusted for but which could have influenced the impact of the PDA on the outcome measures. However, in the stepped wedge cluster randomized controlled trial presented in **Chapter 7**, some baseline characteristics seemed to be imbalanced as well. This is explained by the fact that although randomization ensures that there is no systematic bias in allocation, the number of clusters may not be large enough to assume that there are imbalances due to chance (52). Alternatively, selection bias may have occurred as well because once switched to the intervention phase clinicians may have provided the PDA to patients based on their own criteria. However, balance between intervention and control group in stepped wedge designs often also depends of the presence of secular trends in the outcome (52). Therefore, we accounted for the potential bias from secular trends in the outcome by including time between patient inclusion and the study's start date as fixed effect in the multi-level models.

As both patients and clinicians were aware that they participated in SDM studies, it is likely that clinicians encouraged patients more in decision-making than they usually would do, the so called Hawthorne-effect (53). And patients could have given socially desirable answers to our questionnaires, resulting in response bias.

Conducting an implementation trial by using a stepped wedge cluster randomized controlled trial design was challenging (**Chapter 7**). One important disadvantage was that it took longer time to perform, due to the stepwise introduction of the mCRPC PDA.

Especially hospitals that started later had to wait longer depending on the duration of each step, which caused one hospital to drop out.

Conclusion and future perspectives

Bringing all perspectives together, it seems that shared decision-making in prostate disease has been welcomed by patients, clinicians and policy makers worldwide. In general, it does more good than harm. The following conclusions and lessons to be learned, drawn from this thesis, can be added:

- *Decision quality* is an appropriate short-term outcome measure for evaluating the effectiveness of supportive decision-making tools, although standardized quantification methods are still lacking (**Chapter 2** and **5**).
- The addition of an extra values clarification method, based on the analytic hierarchy process, to the existing patient decision aid for localized prostate cancer may help patients indicate a preferred treatment more often (**Chapter 5**).
- Not all patients are suitable for shared decision-making and web-based decision aids. Multiple influencing factors such as numeracy level, health literacy, age, educational level and patients' context should be taken into account (**Chapter 5, 7** and **8**). Future research should focus more on how best to determine and tailor information needs and preferences.
- It remains to be investigated if systematically screening older patients' health status with the Geriatric 8 (G8) in addition to patients' performance state (WHO PS) improves treatment decision-making in older patients with metastatic castration-resistant prostate cancer (**Chapter 7**).
- Tailored information can lead to better risk perception than general information. Therefore, prediction models providing expected survival rates should be incorporated in the shared decision-making process and patient decision aids. However, the process of developing, validating and sustainably implementing such models is still shrouded in mystery for most clinicians. A comprehensible guide can help them to understand the steps of developing a useful prediction model and to bridge the gap between statistician and clinician (**Chapter 9**).

Yet, in this extensive research field some gaps remain to be addressed:

- Implementation of shared decision-making in medical curriculums and continuing education of health care professionals is currently underway in the Netherlands

and should help (future) doctors to focus on strategies to elicit patients' context and to improve clinicians' risk communication and patients' risk perception.

- Despite some practical drawbacks, implementation trials with a stepped wedge design can be valuable in the setting of prostate cancer, for example to investigate shared decision-making training programs and the G8.
- Clinical practice for patients with lower urinary tract symptoms due to benign prostatic hyperplasia and for patients with prostate cancer change continuously due to the availability of novel diagnostics and treatment options which makes frequently updating of decision aids' content essential. To improve subsequent use of decision aids after trials, researchers should update decision aids with end users to ensure fit in clinical practice. Structural and active engagement of the Dutch Association for Urology and Oncology and patient representatives can enable the sustainability of decision aids.
- With healthcare likely to shift towards primary care in the Netherlands, family physicians become more important in the treatment decision-making process. Some patients have a long relationship with their family physician whom they trust. As an additional beneficial effect, family physicians often have knowledge of patients' values, preferences and context. After referral there is often a gap in communication between hospital clinicians and family physicians (54). Improving the communication between them can improve quality of care at every stage of the disease (54), and ideally decision aids should be made available in electronic patient records throughout the healthcare chain in order for patients, family physicians and hospital clinicians to consistently use the same tools. With the recent emphasis on value-based health care in health policy, new opportunities for improving the involvement of family physicians and the implementation of shared decision-making and decision aids in the medical encounter exist because teams of professionals are now more willing to redesign health care pathways (47).

References

1. Elwyn G, O'Connor A, Stacey D, Volk R, Edwards A, Coulter A, et al. Developing a quality criteria framework for patient decision aids: online international Delphi consensus process. Bmj. 2006;333(7565):417.
2. Stacey D, Légaré F, Lewis K, Barry MJ, Bennett CL, Eden KB, et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev. 2017;4(4):CD001431.
3. Cuypers M, Lamers RED, de Vries M, Husson O, Kil PJM, van de Poll-Franse LV. Prostate cancer survivors with a passive role preference in treatment decision-making are less satisfied with information received: Results from the PROFILES registry. Urol Oncol. 2016;34(11):482 e11- e18.
4. Henselmans I, van Laarhoven HWM, van Maarschalkerweerd P, de Haes H, Dijkgraaf MGW, Sommeijer DW, et al. Effect of a Skills Training for Oncologists and a Patient Communication Aid on Shared Decision Making About Palliative Systemic Treatment: A Randomized Clinical Trial. Oncologist. 2019.
5. Nelson WL, Han PK, Fagerlin A, Stefanek M, Ubel PA. Rethinking the objectives of decision aids: a call for conceptual clarity. Med Decis Making. 2007;27(5):609-18.
6. O'Connor AM. Validation of a decisional conflict scale. Med Decis Making. 1995;15(1):25-30.
7. Sepucha KR, Fowler FJ, Jr., Mulley AG, Jr. Policy support for patient-centered care: the need for measurable improvements in *decision quality*. Health Aff (Millwood). 2004;Suppl Variation:VAR54-62.
8. Munro S, Stacey D, Lewis KB, Bansback N. Choosing treatment and screening options congruent with values: Do decision aids help? Sub-analysis of a systematic review. Patient Educ Couns. 2016;99(4):491-500.
9. Sepucha KR, Borkhoff CM, Lally J, Levin CA, Matlock DD, Ng CJ, et al. Establishing the effectiveness of patient decision aids: key constructs and measurement instruments. BMC Med Inform Decis Mak. 2013;13 Suppl 2(Suppl 2):S12.
10. Sepucha K, Ozanne EM. How to define and measure concordance between patients' preferences and medical treatments: A systematic review of approaches and recommendations for standardization. Patient Educ Couns. 2010;78(1):12-23.
11. Witteman HO, Gavaruzzi T, Scherer LD, Pieterse AH, Fuhrel-Forbis A, Chipenda Dansokho S, et al. Effects of Design Features of Explicit Values Clarification Methods: A Systematic Review. Med Decis Making. 2016;36(6):760-76.
12. Cuypers M, Lamers RED, Kil PJM, van de Poll-Franse LV, de Vries M. Impact of a web-based prostate cancer treatment decision aid on patient-reported decision process parameters: results from the Prostate Cancer Patient Centered Care trial. Support Care Cancer. 2018;26(11):3739-48.
13. Prins A. EI, Schermer M. Een goed gesprek is de beste persoonsgerichte zorg. Medisch contact. 2018(24).

14. Hajizadeh N, Basile MJ, Kozikowski A, Akerman M, Liberman T, McGinn T, et al. Other Ways of Knowing. Med Decis Making. 2017;37(3):216-29.
15. Naik AD, Martin LA, Moye J, Karel MJ. Health Values and Treatment Goals of Older, Multimorbid Adults Facing Life-Threatening Illness. J Am Geriatr Soc. 2016;64(3):625-31.
16. van Weert JC, van Munster BC, Sanders R, Spijker R, Hooft L, Jansen J. Decision aids to help older people make health decisions: a systematic review and meta-analysis. BMC Med Inform Decis Mak. 2016;16:45.
17. Elwyn G, Frosch DL, Kobrin S. Implementing shared decision-making: consider all the consequences. Implement Sci. 2016;11:114.
18. Légaré F, Ratté S, Gravel K, Graham ID. Barriers and facilitators to implementing shared decision-making in clinical practice: update of a systematic review of health professionals' perceptions. Patient Educ Couns. 2008;73(3):526-35.
19. Kim SI, Kang JY, Lee HW, Seong do H, Cho JS. A survey conducted on patients' and urologists' perceptions of benign prostatic hyperplasia. Urol Int. 2011;86(3):278-83.
20. Stalmeier PF, van Tol-Geerdink JJ, van Lin EN, Schimmel E, Huizenga H, van Daal WA, et al. Doctors' and patients' preferences for participation and treatment in curative prostate cancer radiotherapy. J Clin Oncol. 2007;25(21):3096-100.
21. Stiggelbout AM, Van der Weijden T, De Wit MP, Frosch D, Légaré F, Montori VM, et al. Shared decision making: really putting patients at the centre of healthcare. Bmj. 2012;344:e256.
22. Epstein RM, Duberstein PR, Fenton JJ, Fiscella K, Hoerger M, Tancredi DJ, et al. Effect of a Patient-Centered Communication Intervention on Oncologist-Patient Communication, Quality of Life, and Health Care Utilization in Advanced Cancer: The VOICE Randomized Clinical Trial. JAMA Oncol. 2017;3(1):92-100.
23. Diouf NT, Menear M, Robitaille H, Painchaud Guérard G, Légaré F. Training health professionals in shared decision making: Update of an international environmental scan. Patient Educ Couns. 2016;99(11):1753-8.
24. Légaré F, Stacey D, Turcotte S, Cossi MJ, Kryworuchko J, Graham ID, et al. Interventions for improving the adoption of shared decision making by healthcare professionals. Cochrane Database Syst Rev. 2014(9):CD006732.
25. Ubel PA, Scherr KA, Fagerlin A. Empowerment Failure: How Shortcomings in Physician Communication Unwittingly Undermine Patient Autonomy. Am J Bioeth. 2017;17(11):31-9.
26. Back AL, Arnold RM, Baile WF, Tulsky JA, Fryer-Edwards K. Approaching difficult communication tasks in oncology. CA Cancer J Clin. 2005;55(3):164-77.
27. Gaster B, Edwards K, Trinidad SB, Gallagher TH, Braddock CH, 3rd. Patient-centered discussions about prostate cancer screening: a real-world approach. Ann Intern Med. 2010;153(10):661-5.
28. Cornford P, Bellmunt J, Bolla M, Briers E, De Santis M, Gross T, et al. EAU-ES-

TRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer. Eur Urol. 2017;71(4):630-42.

29. van Walree IC, Scheepers E, van Huis-Tanja L, Emmelot-Vonk MH, Bellera C, Soubeyran P, et al. A systematic review on the association of the G8 with geriatric assessment, prognosis and course of treatment in older patients with cancer. J Geriatr Oncol. 2019;10(6):847-58.
30. Momota M, Hatakeyama S, Soma O, Tanaka T, Hamano I, Fujita N, et al. Geriatric 8 screening of frailty in patients with prostate cancer. Int J Urol. 2020.
31. Shevach JW, Weiner AB, Kasimer RN, Miller CH, Morgans AK. Risk Assessment and Considerations for Proper Management of Elderly Men with Advanced Prostate Cancer: A Systematic Review. Eur Urol Oncol. 2020.
32. Beardo P, Osman I, San José B, Llarena R, Congregado B, Campá J, et al. Safety and outcomes of new generation hormone-therapy in elderly chemotherapy-naive metastatic castration-resistant prostate cancer patients in the real world. Archives of Gerontology and Geriatrics. 2019;82:179-85.
33. Vromans R, Tenfelde K, Pauws S, van Eenbergen M, Mares-Engelberts I, Velikova G, et al. Assessing the quality and communicative aspects of patient decision aids for early-stage breast cancer treatment: a systematic review. Breast Cancer Res Treat. 2019;178(1):1-15.
34. Albada A, Ausems MG, Bensing JM, van Dulmen S. Tailored information about cancer risk and screening: a systematic review. Patient Educ Couns. 2009;77(2):155-71.
35. Petrova D, Kostopoulou O, Delaney BC, Cokely ET, Garcia-Retamero R. Strengths and Gaps in Physicians' Risk Communication: A Scenario Study of the Influence of Numeracy on Cancer Screening Communication. Med Decis Making. 2018;38(3):355-65.
36. Ghazal S CE, Garcia-Retamero R. Predicting biases in very highly educated samples: Numeracy and metacognition. Judgment and Decision Making. 2014;9(1):15-34.
37. Petrova D, Mas G, Navarrete G, Rodriguez TT, Ortiz PJ, Garcia-Retamero R. Cancer screening risk literacy of physicians in training: An experimental study. PLoS One. 2019;14(7):e0218821.
38. Holmes A, Kelly BD, Perera M, Eapen RS, Bolton DM, Lawrentschuk N. A systematic scoping review of multidisciplinary cancer team and decision-making in the management of men with advanced prostate cancer. World J Urol. 2020.
39. Showalter TN, Mishra MV, Bridges JF. Factors that influence patient preferences for prostate cancer management options: A systematic review. Patient Prefer Adherence. 2015;9:899-911.
40. Tamirisa NP, Goodwin JS, Kandalam A, Linder SK, Weller S, Turrubiate S, et al. Patient and physician views of shared decision making in cancer. Health Expect. 2017;20(6):1248-53.
41. Cuypers M, Al-Itejawi HHM, van Uden-Kraan CF, Stalmeier PFM, Lamers RED, van Oort IM, et al. Introducing Decision Aids into Routine Prostate Cancer Care in The Netherlands: Implementation

and Patient Evaluations from the Multi-regional JIPPA Initiative. J Cancer Educ. 2019.

42. Elwyn G, Scholl I, Tietbohl C, Mann M, Edwards AG, Clay C, et al. "Many miles to go ...": a systematic review of the implementation of patient decision support interventions into routine clinical practice. BMC Med Inform Decis Mak. 2013;13 Suppl 2(Suppl 2):S14.
43. Scholl I, LaRussa A, Hahlweg P, Kobrin S, Elwyn G. Organizational- and system-level characteristics that influence implementation of shared decision-making and strategies to address them - a scoping review. Implement Sci. 2018;13(1):40.
44. Oelke M, Bachmann A, Descazeaud A, Emberton M, Gravas S, Michel MC, et al. EAU guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. Eur Urol. 2013;64(1):118-40.
45. Porter ME. What is value in health care? The New England journal of medicine. 2010;363(26):2477-81.
46. Berwick DM, Nolan TW, Whittington J. The triple aim: care, health, and cost. Health Aff (Millwood). 2008;27(3):759-69.
47. Damman OC, Jani A, de Jong BA, Becker A, Metz MJ, de Bruijne MC, et al. The use of PROMs and shared decision-making in medical encounters with patients: An opportunity to deliver value-based health care to patients. J Eval Clin Pract. 2020;26(2):524-40.
48. Damman OC, Verbiest MEA, Vonk SI, Berendse HW, Bloem BR, de Bruijne MC, et al. Using PROMs during routine medical consultations: The perspectives of people with Parkinson's disease and their health professionals. Health Expect. 2019;22(5):939-51.
49. Rutherford C, King MT, Butow P, Legare F, Lyddiatt A, Souli I, et al. Is quality of life a suitable measure of patient decision aid effectiveness? Sub-analysis of a Cochrane systematic review. Qual Life Res. 2019;28(3):593-607.
50. Ernstmann N, Herden J, Weissbach L, Karger A, Hower K, Ansmann L. Prostate-specific health-related quality of life and patient-physician communication - A 3.5-year follow-up. Patient Educ Couns. 2019;102(11):2114-21.
51. Joseph-Williams N, Elwyn G, Edwards A. Knowledge is not power for patients: a systematic review and thematic synthesis of patient-reported barriers and facilitators to shared decision making. Patient Educ Couns. 2014;94(3):291-309.
52. Davey C, Hargreaves J, Thompson JA, Copas AJ, Beard E, Lewis JJ, et al. Analysis and reporting of stepped wedge randomised controlled trials: synthesis and critical appraisal of published studies, 2010 to 2014. Trials. 2015;16:358.
53. McCambridge J, Kypri K. Can simply answering research questions change behaviour? Systematic review and meta analyses of brief alcohol intervention trials. PLoS One. 2011;6(10):e23748.
54. Puts MT, Sattar S, McWatters K, Lee K, Kulik M, MacDonald ME, et al. Chemotherapy treatment decision-making experiences of older adults with cancer, their family members, oncologists and family physicians: a mixed methods study. Support Care Cancer. 2017;25(3):879-86.

Chapter 11

Summary &

Nederlandse samenvatting

Summary

Chapter 1 consists of the general introduction and outline of this thesis. Urology is one of the specialties in which shared decision-making (SDM) has come to play a more important role over the course of recent years. In particular within the context of treatment selection for patients with localized prostate cancer, because this treatment decision is highly sensitive to preferences. Patients need to choose between surgery, external beam radiotherapy, brachytherapy or active surveillance, which all have equivalent survival outcomes, but have different risks and benefits. This thesis aimed to provide insight into the effectiveness of patient decision aids (PDAs) for various prostate diseases and to optimize the shared decision-making (SDM) process. This was done by introducing novel supportive decision-making tools and to evaluate these in various prostate diseases. This thesis is divided into four parts of which three are about SDM in benign prostate enlargement (Part I), localized prostate cancer (Part II) and advanced prostate cancer (Part III). In Part IV, suggestions for the optimalisation of the SDM process are discussed.

Compared to evidence on PDAs for prostate cancer, evidence on PDAs for men with lower urinary tract symptoms due to benign prostatic hyperplasia (LUTS/BPH) is limited and outdated. Therefore, in ***Part I,*** *a previously developed PDA for men with urinary tract symptoms due to benign prostate enlargement is evaluated and results are discussed.*

Chapter 2 presents a prospective questionnaire study that evaluates the effectiveness of a web-based PDA for men with lower urinary tract symptoms due to benign prostatic hyperplasia (LUTS/BPH). A total of 109 PDA users and 108 historical controls were analyzed. Primary outcome was *decision quality*, defined as the combination of well-informed decision and value congruent decision. Secondary outcomes were *decisional conflict*, involvement and perceived role in shared decision-making, decisional regret, and treatment choice. Implementation of the web-based PDA in clinical practice improved the *decision quality* of patients. Furthermore, PDA users perceived a less passive role and experienced lower levels of *decisional conflict* and process regret. PDA users who had not used prior medication before consulting their urologist chose lifestyle advices more often than controls.

Chapter 3 zooms in on the PDA users and reports treatment preferences before and after the use of the PDA for men with LUTS/BPH. Furthermore, feasibility of the PDA was tested among patients and clinicians. Before the PDA, 53% of the patients was undecided; half of them were able to indicate a treatment preference after PDA use. In

almost 80% the preferred treatment matched the final treatment preference. Thus, the tool supports patients in either confirming their initial preference or forming a treatment preference. In addition, most clinicians were positive about PDA feasibility. Seventy-seven percent of the clinicians would even recommend this PDA to their colleagues.

A previous study that evaluated the effectiveness of a PDA for patients with localized prostate cancer showed that one third of the patients could not make a treatment decision after completing the PDA. Moreover, one third of the patients would have wanted an explicit advice, similar to a vote match in politics (voting advice application). In response to that, ***Part II*** *describes the development of an additional quantitative values clarification method for patients with localized prostate cancer and its evaluation.*

Chapter 4 describes the developmental process of the additional values clarification method based on the analytic hierarchy process for patients with localized prostate cancer, which is used after completing the previously developed PDA. This chapter focuses on its design and the underlying theory. The ability to give patients insight into the overall value of their treatment options, by explicitly presenting scores that show how well or poorly each treatment option fits with the patients' responses makes this VCM a unique tool within the shared-decision making process.

Chapter 5 describes a prospective cohort study that evaluates the additional VCM based on the analytic hierarchy process. After diagnosis, the existing PDA was provided to patients with the additional VCM (referred to as PDA-VCM patients). Patients from a previous cluster randomized controlled trial, who only used the PDA, served as controls. A total of 119 PDA-VCM and 266 PDA patients were included. Disease specific knowledge (primary outcome), *decisional conflict*, preparation for decision-making, *decision quality*, and satisfaction and regret were assessed with questionnaires after treatment decision-making. Health literacy and numeracy and acceptability of the VCM were also evaluated. The addition of the VCM led to more prostate cancer patients being able to indicate a final treatment preference, which was more often in line with their preferences. Though, patients with lower numeracy levels may not be suitable for the use of this VCM. Hence, they could benefit from more guidance towards shared decision-making. The addition of the VCM did not result in differences between decision process outcomes.

In ***Part III****, focus is put on exploring the need for SDM in patients with advanced prostate cancer, in this case metastatic castration-resistant prostate cancer. Furthermore, the evaluation of a PDA for this patient population is described.*

Chapter 6 explores the perspectives of the multidisciplinary team (MDT) concerning SDM and PDA use in treatment decisions for older patients with metastatic castration-resistant prostate cancer (mCRPC). Treatment recommendations were assessed as well, by using hypothetical cases. In total, 170 Dutch clinicians, including urologists, oncologists, and oncology nurses completed the survey. Most agreed that these patients should always be actively involved in decision-making. The wide variation of treatment recommendations observed among the MDT suggests that mCRPC patients and their clinicians may benefit from implementation of informed SDM. Furthermore, half of the respondents found PDAs useful to facilitate the decision-making process, implicating that the development and implementation of a PDA for patients with mCRPC is an interesting field of research.

Chapter 7 entails a stepped wedge cluster randomized controlled trial that evaluates the effectiveness of a PDA for patients with mCRPC. In total, 78 PDA and 83 control patients were analyzed. Primary outcome was disease-specific knowledge; secondary outcomes included patient involvement, *value congruence, decisional conflict,* preparation for decision-making, satisfaction, anxiety, and quality of life (QoL). The added value of a geriatric screening tool (G8) and Timed Up and Go test in the decision-making process were assessed as well. Decision process outcomes, including knowledge, were comparable between groups. PDA patients' anxiety levels reduced significantly after decision-making. Also, we observed that the decision-making role of the control patients shifted from an active role to a passive one after the treatment decision was made, in contrary to PDA patients. Other secondary outcomes were comparable between groups. The additive value of geriatric screening tools in the decision-making process remains to be elucidated.

Part IV *focuses on tools that can optimize the SDM process, including decision aids.*

Chapter 8 highlights the lack of attention to patients' context, including socio-cultural factors and lived experiences, that could influence comprehension and uptake of information presented in the clinical encounter and in PDAs. As mentioned previously, PDAs include VCMs to elicit patients' values by guiding them in making tradeoffs between different treatment characteristics, however, these characteristics may not always be relevant to the individual patient. For instance, when a patient with prostate cancer babysits his grandchildren, he may not consider brachytherapy as valid treatment option. Since direct physical contact with children and pregnant women is discouraged during the first two months. Therefore, a conceptual framework, referred to as *bidirectional ask-tell-ask*, is introduced to make sure that information exchange

is no longer unilateral (with the single goal of ensuring biomedical information comprehension), but rather bilateral (with the additional goal to improve the clinician's comprehension of patients' concerns, views and context).

Chapter 9 provides a comprehensive detailed guide for developing and interpreting prediction models, based on a large dataset of real-world patients treated for mCRPC. It is suggested that personalized information on treatment outcomes and survival rates, generated from prediction models, provides a better cancer risk perception compared to general information. It would therefore be great to incorporate such models into PDAs. However, prediction model development is not a futile task and both the input of the clinician and biostatistician are essential. This guide describes an advanced method for appropriate selection of main effects and aims to bridge the gap between the statistician and clinician.

Chapter 10, the general discussion, discusses the key findings of this thesis from a diversity of perspectives. From the patient's perspective, SDM can be optimized by continuing to actively involve patients and by considering the patient's context. The implementation of the PDA for patients with LUTS/BPH can optimize the decision-making process because it provides a higher percentage of *decision quality*. The use of an additional *value clarification method* leads to more prostate cancer patients being able to indicate a final treatment preference, which more often is in line with their personal preferences.

From the clinician's perspective, SDM can be optimized by developing and using prediction models for displaying and communicating personalized treatment outcomes. However, adequate training in understanding these outcomes and communicating them to patients is essential for an optimal SDM process.

From a healthcare perspective, organizations should invest in redesigning their workflow and redistribute work roles in clinical care pathways that could lead to optimal implementation of SDM and PDAs. The emerging concept of *value-based healthcare*, with the use of patient-reported outcome measures, could contribute to this. Looking from the (clinical) researcher's perspective, the research field of SDM and PDAs can be optimized by taking into account local care pathways with their own routine information provision when evaluating the effectiveness of a new PDA. Furthermore, seeking partnership with oncology nurses to recruit patients is essential, as they are often seen as 'mediators' between physicians and patients. Lastly, the researcher must consider the many forms of bias that can occur in this research field.

Nederlandse samenvatting

Hoofdstuk 1 bevat de algemene introductie en hoofdlijnen van dit proefschrift. Urologie is één van de specialismen waarin gezamenlijke besluitvorming de afgelopen jaren een steeds belangrijkere rol is gaan spelen. Het is met name onderzocht voor patiënten met gelokaliseerde prostaatkanker waarbij de behandelkeuze zeer voorkeursgevoelig is. Deze patiënten moeten kiezen tussen een operatie, uitwendige bestraling, inwendige bestraling (brachytherapie) of *active surveillance*. Behandelopties die allemaal vergelijkbare overlevingsuitkomsten hebben, maar met verschillende voor- en nadelen gepaard gaan. Om patiënten te helpen bij deze behandelkeuze kan gebruik worden gemaakt van een keuzehulp. Keuzehulpen bevatten o.a. informatie over de ziekte en de verschillende behandelopties met voor- en nadelen. Daarnaast bevatten ze oefeningen met bijvoorbeeld stellingen waarmee patiënten kunnen achterhalen wat zij belangrijk vinden en het zwaarst laten meewegen in hun behandelkeuze (*values clarification methods*). Het doel van dit proefschrift was om inzicht te geven in de effectiviteit van keuzehulpen voor zowel mannen met plasklachten bij goedaardige vergroting van de prostaat, als ook voor (oudere) mannen met prostaatkanker. Daarnaast was het doel om het besluitvormingsproces verder te optimaliseren. Hiertoe werden nieuwe ondersteunende instrumenten in de verschillende prostaatziekten geëvalueerd. Het proefschrift is ingedeeld in vier delen, waarvan de eerste drie gaan over gezamenlijke besluitvorming bij goedaardige prostaatvergroting (Deel I), gelokaliseerd prostaatkanker (Deel II) en vergevorderde prostaatkanker (Deel III). In Deel IV worden suggesties besproken voor het optimaliseren van het besluitvormingsproces.

Vergeleken met onderzoek naar keuzehulpen voor prostaatkanker, is onderzoek naar keuzehulpen voor mannen met plasklachten bij een goedaardige prostaatvergroting veelal verouderd. In ***Deel I*** *worden daarom nieuwe resultaten van onderzoek naar de keuzehulp voor deze patiëntpopulatie beschreven.*

Hoofdstuk 2 betreft een prospectieve studie naar de effectiviteit van de online keuzehulp voor mannen met plasklachten bij een goedaardige vergroting van de prostaat (LUTS/BPH). In totaal werden 109 keuzehulpgebruikers vergeleken met 108 patiënten die standaardzorg hadden gekregen (historische controlegroep). De primaire uitkomstmaat was *decision quality*, gedefinieerd als een goed geïnformeerde behandelkeuze die overeenkomstig is met persoonlijke voorkeuren. Secundaire uitkomsten waren *decisional conflict*, betrokkenheid en rol bij gedeelde besluitvorming, spijt en uiteindelijke behandelkeuze. Implementatie van deze keuzehulp in de kliniek resulteerde in een verbetering van *decision quality*. Daarnaast bleken keuzehulpgebruikers een minder

passieve rol te ervaren, als ook minder *decisonal conflict* en hadden zij minder spijt van het besluitvormingsproces. Tot slot kozen keuzehulpgebruikers vaker voor leefstijladviezen dan controlepatiënten, mits zij eerder nog geen medicatie hadden gebruikt.

Hoofdstuk 3 zoomt in op de keuzehulpgebruikers en rapporteert de behandelvoorkeuren vóór en na het gebruik van de LUTS/BPH keuzehulp. Daarnaast wordt het gebruik van de keuzehulp geëvalueerd onder patiënten en zorgverleners. Vóór het gebruik van de keuzehulp had 53% van de patiënten geen keuze aangegeven; de helft van hen kon na keuzehulpgebruik wel een behandelvoorkeur aangeven. Bij bijna 80% kwam de behandelvoorkeur vóór en na het gebruik overeen. Kortom: de keuzehulp helpt patiënten bij het vormen van een behandelvoorkeur, maar helpt hen ook in het bevestigd krijgen van hun initiële voorkeur. Daarnaast waren de meeste zorgverleners positief over het gebruik van de keuzehulp in de praktijk. Van de zorgverleners die de vragenlijst hadden ingevuld, gaf 77% zelfs aan dat ze de keuzehulp zouden aanbevelen aan hun collega's.

*In **Deel II** wordt de ontwikkeling van een extra kwantitatieve* values clarification method *voor patiënten met gelokaliseerd prostaatkanker beschreven en de evaluatie ervan. Het idee voor de ontwikkeling hiervan is ontstaan naar aanleiding van de resultaten van een onderzoek naar een keuzehulp voor patiënten met gelokaliseerd prostaatkanker. Daaruit bleek dat een derde van de patiënten geen keuze kon maken na het doorlopen van de keuzehulp en dat een derde een expliciet advies had gewild zoals bij een kieswijzer.*

Hoofdstuk 4 beschrijft het ontwikkelingsproces van de kwantitatieve methode om de persoonlijke voorkeuren van prostaatkankerpatiënten te achterhalen (*values clarification method of* VCM). Dit is gebaseerd op de Analytische Hiërarchisch Proces (AHP) methode en wordt gebruikt na het doorlopen van de reeds bestaande keuzehulp. Het hoofdstuk richt zich op het ontwerp en de theorie achter deze VCM. Het unieke hiervan is dat het de patiënt helpt de keuze te bepalen door hen middels een tabel en grafiek inzicht te geven in hun antwoorden op voorkeursgevoelige stellingen met de daarbij passende behandeloptie.

Hoofdstuk 5 is een prospectieve cohortstudie die de aanvullende VCM evalueert in de praktijk. Na het vaststellen van de diagnose ontvingen patiënten zowel de bestaande keuzehulp als de VCM. Patiënten uit een eerder onderzoek, die alleen de keuzehulp hadden gebruikt, dienden als controlepatiënten. In totaal werden 119 interventie- en 266 controlepatiënten geanalyseerd. Na de besluitvorming werden vragenlijsten afgenomen om de volgende uitkomsten te meten: ziekte-specifieke kennis (primaire uitkomst), *decisional conflict*, voorbereiding op besluitvorming, *decision quality*, tevredenheid met

en spijt van het besluitvormingsproces. Geletterdheid en rekenvaardigheid werden ook gemeten. De toevoeging van de VCM leidde ertoe dat meer prostaatkankerpatiënten een behandelvoorkeur hadden die vaker overeenkwam met hun persoonlijke voorkeuren. Patiënten met lagere rekenvaardigheid zijn echter minder geschikt voor het gebruik van deze VCM. Zij zouden gebaat kunnen zijn bij meer begeleiding. De toevoeging van de VCM aan de bestaande keuzehulp resulteerde niet in verschillen tussen de uitkomsten van het besluitvormingsproces.

*In **Deel III** ligt de focus op het inventariseren van de behoefte aan gezamenlijke besluitvorming bij patiënten met vergevorderd prostaatkanker, in dit geval uitgezaaide castratie-resistente prostaatkanker. Ook voor deze patiëntpopulatie is een keuzehulp beschikbaar waarvan de evaluatie wordt beschreven.*

Hoofdstuk 6 onderzoekt de perspectieven van het multidisciplinaire team (MDT) met betrekking tot het gebruik van gezamenlijke besluitvorming en keuzehulpen bij de behandelkeuze voor oudere patiënten met uitgezaaide castratie-resistente prostaatkanker (mCRPC). Met behulp van hypothetische casussen werd gevraagd welke behandeling zij patiënten zouden aanbevelen. In totaal hebben 170 Nederlandse zorgverleners de enquête ingevuld, waaronder urologen, oncologen en oncologieverpleegkundigen. De meesten van hen waren het er over eens dat deze patiënten altijd actief betrokken moeten zijn bij de besluitvorming. Er was een grote variëteit aan aanbevolen behandelingen per casus tussen verschillende zorgverleners. Dit doet suggereren dat zij gebaat zijn bij de implementatie van gezamenlijke besluitvorming. Bovendien vond de helft van de respondenten keuzehulpen nuttig ter ondersteuning van het besluitvormingsproces, wat impliceert dat de ontwikkeling en implementatie van een keuzehulp voor patiënten met mCRPC een interessant en relevant onderzoeksgebied is.

Hoofdstuk 7 beschrijft daarom een *stepped wedge cluster randomized controlled trial* die de effectiviteit van een keuzehulp voor patiënten met mCRPC evalueert. In totaal werden 78 keuzehulp en 83 controle patiënten geanalyseerd. De primaire uitkomst was ziekte-specifieke kennis; secundaire uitkomsten waren patiëntbetrokkenheid, *value congruence*, *decisional conflict*, voorbereiding op besluitvorming, tevredenheid, angst en kwaliteit van leven. Ook de toegevoegde waarde van geriatrische screeningtools (G8) en Timed Up and Go-test (TUG) in het besluitvormingsproces werden geëvalueerd. De resultaten van het besluitvormingsproces waren vergelijkbaar tussen de verschillende groepen. Bij keuzehulppatiënten daalde het angstniveau significant na de behandelbeslissing in vergelijking met controlepatiënten. Verder werd geobserveerd

dat de rol van controlepatiënten in de besluitvorming verschoof van een actieve naar een passieve rol. Deze verschuiving werd niet geobserveerd in de keuzehulpgroep. De toegevoegde waarde van de G8 en TUG in dit proces behoeft nader onderzoek.

*In **Deel IV** wordt aandacht besteed aan instrumenten die het besluitvormingsproces, inclusief keuzehulpen, kunnen optimaliseren.*

Hoofdstuk 8 benadrukt het gebrek aan aandacht voor de context van patiënten die het begrip en de verwerking van informatie kunnen beïnvloeden. De eerdergenoemde *values clarification methods* in keuzehulpen omvatten niet altijd de waarden of voorkeuren die belangrijk zijn voor de behandelkeuze van de individuele patiënt. Voor een patiënt met prostaatkanker die meerdere dagen in de week op zijn kleinkinderen past, is bijvoorbeeld brachytherapie geen gewenste behandeloptie. In de eerste twee maanden wordt direct lichamelijk contact met kinderen en zwangere vrouwen namelijk afgeraden. Om meer rekening te houden met de gehele context van de patiënt wordt een nieuw concept geïntroduceerd, genaamd '*bidirectional ask-tell-ask*'. Dit zorgt ervoor dat informatie-uitwisseling niet langer eenzijdig is (dat wil zeggen vooral gericht op medische informatie), maar dat de nadruk ook komt te liggen op het verkrijgen van informatie over de zorgen, voorkeuren en de persoonlijke situatie van de patiënt door de arts.

Hoofdstuk 9 biedt een gedetailleerd stappenplan voor het ontwikkelen en interpreteren van predictiemodellen, op basis van een grote dataset met gegevens van behandelde mCRPC patiënten. Gepersonaliseerde informatie over behandeluitkomsten, te generen middels predictiemodellen, leidt namelijk tot een beter begrip van behandelrisico's bij patiënten. Het zou daarom ideaal zijn om dit te integreren in een keuzehulp. Echter, voor de ontwikkeling van zulke modellen is zowel input van de clinicus als de biostatisticus van essentieel belang. Dit stappenplan beschrijft onder andere een geavanceerde methode voor de selectie van belangrijke variabelen in het model en helpt de kloof tussen de statisticus en de clinicus te overbruggen.

Hoofdstuk 10 beschrijft de algemene discussie en bespreekt daarin de belangrijkste bevindingen van dit proefschrift vanuit verschillende perspectieven. Vanuit het perspectief van de patiënt kan besluitvorming geoptimaliseerd worden door patiënten actief te blijven betrekken en daarbij rekening te houden met de context van de patiënt. De implementatie van de keuzehulp voor LUTS/BPH kan het besluitvormingsproces optimaliseren doordat het zorgt voor een hoger percentage *decision quality*. Het gebruik van een extra *values clarification method* die patiënten inzicht geeft in hoe

hun persoonlijke voorkeuren overeenkomen met de mogelijke behandelopties leidt daarnaast tot meer patiënten die een behandelkeuze kunnen maken.

In het perspectief van de arts kan besluitvorming geoptimaliseerd worden door de ontwikkeling en gebruik van predictiemodellen voor het weergeven van gepersonaliseerde behandeluitkomsten. Voor een optimaal besluitvormingsproces is echter adequate training in het begrijpen van deze uitkomsten en het communiceren ervan naar patiënten van groot belang.

Vanuit het perspectief van de gezondheidszorg zou het opnieuw inrichten van zorgpaden kunnen leiden tot een optimale implementatie van gezamenlijke besluitvorming en keuzehulpen. Het opkomende *value-based healthcare*, met het gebruik van *patient-reported outcome measures*, zou hieraan kunnen bijdragen. Kijkend vanuit het perspectief van de (klinisch) onderzoeker kan onderzoek naar gezamenlijke besluitvorming en keuzehulpen worden geoptimaliseerd door rekening te houden met lokale zorgpaden en door samen te werken met oncologieverpleegkundigen voor het benaderen van patiënten, omdat zij vaak als 'mediators' worden gezien tussen arts en patiënt. Daarnaast dient de onderzoeker rekening te houden met de vele vormen van bias die zich kunnen voordoen in dit onderzoeksgebied.

Part VI

Appendices

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Fieke van der Wijden	University Medical Center Utrecht, Utrecht, The Netherlands *General Practitioner*

List of Publications

Does the use of a patient decision aid improve decision-making in treatment selection for older patients with metastatic Castration-Resistant Prostate Cancer? A stepped wedge cluster randomized controlled trial.
Isabel B. de Angst, Paul J.M. Kil, Huub A.A.M. Maas, Inge M van Oort, Erik B. Cornel, Kevin M Veen, Hans M Westgeest, Ilze EW van Onna, Tineke J Smilde, Romy ED Lamers, Franchette F van den Berkmortel, Jorg R Oddens, Menno A van Leeuwen, Frederiek Terheggen, Irma M Oving, Chris H Bangma, Johanna JM Takkenberg
Submitted for publication

Multi-Criteria Decision Analysis to optimize the decision aid for patients with localized prostate cancer: a prospective study with historical control group.
Isabel B. de Angst, Marieke G.M. Weernink, Erik B. Cornel, Ruben Korthorst, Janine A. van Til, Johanna J.M. Takkenberg, Paul J.M. Kil
Submitted for publication

Setting the stage for effective patient-clinician communication: a review of factors relevant to decision-making and introducing the bidirectional Ask-Tell-Ask approach.
Isabel B. de Angst, Melissa Basile, Paul J.M. Kil, Jonathan Etnel, Johanna J.M. Takkenberg, Negin Hajizadeh
Submitted for publication

Psoas hitch procedure in 166 adult patients: the largest cohort study before the laparoscopic era.
Groen VH*, Lock MTWT*, de Angst IB, Verhagen PCMS, Horenblas S, Dik P, Bosch JLHR
Accepted in BJUI Compass

A clinician's guide for developing a prediction model: A case study using real-world data of mCRPC patients.
Isabel de Angst*, Kevin Veen*, Mostafa Mokhles, Hans Westgeest, Malou Cuppen, Carin Uyl, Winald Gerritsen, Paul J.M. Kil, Johanna J.M. Takkenberg
J Cancer Res Clin Oncol. 2020 Aug;146(8):2067-2075

Case report. Rare cutaneous metastases of urothelial cell carcinoma of the bladder two years after cystectomy.
Isabel B. de Angst, Joost A. P. Leijte, Olaf J. L. Loosveld, Hans M Westgeest, Ilze E. W. van Onna
Tijdschrift voor Urologie volume 10, pages2–4(2020)

Effectiveness of a web-based treatment decision aid for men with lower urinary tract symptoms due to benign prostatic hyperplasia.
Isabel B. de Angst*, Fieke van der Wijden*, Romy Lamers, Maarten Cuypers, Marieke de Vries, Harm van Melick, Jeltje de Beij, Dennis Oerlemans, Kees van Beek, Paul Kil
Urology. 2020 Mar;137:138-145.

Treatment preferences of patients with benign prostatic hyperplasia before and after using a web-based decision aid.
Romy Lamers*, Fieke van der Wijden*, Isabel de Angst, Maarten Cuypers, Marieke de Vries, Harm van Melick, Jeltje de Beij, Dennis Oerlemans, Kees van Beek, Paul Kil
BJU Int. 2019 Jul;124(1):124-133

Should we involve patients more actively? Perspectives of the multidisciplinary team on shared decision-making for Metastatic Resistant Prostate Cancer.
Isabel B. de Angst, Paul J.M. Kil, Chris H. Bangma, Johanna J.M. Takkenberg
J Geriatr Oncol. 2019 Jul;10(4):653-658

Development and usability testing of a Multi-Criteria value clarification methods for patients with localized prostate cancer.
Isabel B. de Angst*, Marieke G.M. Weernink*, Paul J.M. Kil, Erik B. Cornel, Janine A. van Til, Johanna J.M. Takkenberg
Health Informatics J. 2020 Mar;26(1):486-498

Current training on the basics of robotic surgery in the Netherlands: Time for a multidisciplinary approach?
Brinkman W, de Angst I, Schreuder H, Schout B, Draaisma W, Verweij L, Hendrikx A, van der Poel H
Surg Endosc. 2017 Jan;31(1):281-287

A multicenter study on Leigh syndrome: disease course and predictors of survival.
Sofou K, De Coo IF, Isohanni P, Ostergaard E, Naess K, De Meirleir L, Tzoulis C, Uusimaa J, De Angst IB, Lönnqvist T, Pihko H, Mankinen K, Bindoff LA, Tulinius M, Darin N.
Orphanet J Rare Dis. 2014 Apr 15;9:52

Exome sequencing reveals a novel Moroccan founder mutation in SLC19A3 as a new cause of early-childhood fatal Leigh syndrome.
Gerards M, Kamps R, van Oevelen J, Boesten I, Jongen E, de Koning B, Scholte HR, de Angst I, Schoonderwoerd K, Sefiani A, Ratbi I, Coppieters W, Karim L, de Coo R, van den Bosch B, Smeets H
Brain. 2013 Mar;136(Pt 3):882-90

*Equal contribution

PhD portfolio

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Promotors:	Prof. dr. J.J.M. Takkenberg; Prof. dr. C.H. Bangma
Co-promotor:	dr. P.J.M. Kil

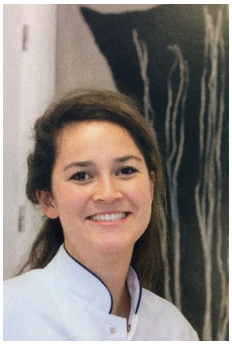
1. PhD training

	Year	Workload (ECTS)
General academic skills		
Research integrity	2018	0.3
e-BROK course	2018	1.5
English Biomedical Writing and Communication	2018	2.0
Research skills		
Master in Health Sciences, specialization clinical epidemiology, NIHES	2015-2018	70
Study Design		
Biostatistical Methods I & II		
Principles in Causal Inference		
Principles of Research in Medicine and Epidemiology		
Methods of Clinical Research		
Clinical Trials		
Health Economics		
The Practice of Epidemiologic Analysis		
Fundamentals of Medical Decision Making		
Clinical Translation of Epidemiology		
Clinical Epidemiology		
Repeated measurements in Clinical Studies		
Advanced Topics in Decision-making in Medicine		
Diagnostic Research		
Advanced Topics in Clinical Trials		
Advanced Analysis of Prognosis Studies		
Principles of Epidemiologic Data-analysis		
Quality of Life Measurement		

Conferences		
Society for Medical Decision Making 16th Biennial European Conference, London (3 days)	2016	0.9
Society for Medical Decision Making 17th Biennial European Conference, Leiden (1 day)	2018	0.3
European Association for Urology 33rd Annual meeting, Copenhagen (3 days)	2018	0.9
Oral presentations		
Regional reference meeting, cluster Utrecht	2016	0.1
Dutch Association for Urology annual spring meeting (research platform)	2017	0.6
European Association for Urology 33rd Annual meeting, Copenhagen	2018	0.3
Dutch Association for Urology annual spring meeting	2018	0.6
Society for Medical Decision Making 17th Biennial European Conference, Leiden (2 presentations)	2018	1.2
Journal club 'Gender specific differences in survival after RARC for bladder cancer'	2018	0.1
Nurses symposium, Breda	2018	0.6
Regional reference meeting, cluster Utrecht	2018	0.6
Poster presentations		
Annual research day, Elisabeth-TweeSteden Hospital	2016	0.1
Society for Medical Decision Making 17th Biennial European Conference, Leiden	2018	0.3
Seminars and workshops		
LimeSurvey course (1 day)	2017	0.3
Society for Medical Decision Making 16th Biennial European Conference, London (1 day)	2016	0.3
European Association for Urology 33rd Annual meeting, Copenhagen (1 day)	2018	0.3

2. Teaching activities		
	Year	Workload (ECTS)
Teaching		
Lecturing nurses in training on urology subjects	2016-2018	0.2
Total		**81.5**

About the author



Isabel Birgit de Angst was born on December 16th 1989. She grew up in Alkmaar and graduated from the Christelijke Scholengemeenschap Jan Arentsz in Alkmaar in 2008. Subsequently, she commenced medical school at the Erasmus University in Rotterdam. After obtaining her medical degree in 2015, she worked as a resident at the Urology Department of the Elisabeth-TweeSteden Hospital in Tilburg. At the end of her residency year the first steps for her thesis "Shared decision-making: Achieving well-balanced treatment decisions for patients with prostate disease" were taken in close collaboration with the Urology and Cardio-Thoracic Surgery Department of the Erasmus University Medical Center under supervision of dr. P.J.M. Kil, Prof. dr. J.J.M. Takkenberg and Prof. dr. C.H. Bangma. In 2016 she officially started her research project as a PhD student and, in parallel, started the clinical research master at the Netherlands Institute of Health Sciences (NIHES). Between April 2018 and June 2018 she got the opportunity to work as research scholar at the Feinstein Institute for Medical Research in New York. Under direct supervision of dr. N. Hajizadeh and dr. M. Basile she acquired knowledge and experience in an elicitation method of non-biomedical information, i.e. cultural factors, lived experience, in the shared decision-making process. From November 2018 she started working as part-time researcher and full-time resident at the Urology Department of the Amphia Hospital in Breda.

As part of her Urology traineeship, she is currently working as a resident at the General Surgery Department of the Franciscus Gasthuis & Vlietland in Rotterdam, supervised by dr. T.M.A.L. Klem. From 2022 she will continue her Urology traineeship as resident at the Urology Department of the Erasmus University Medical Center, under the supervision of dr. J.R. Scheepe.