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PhD thesis

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Patient-reported outcomes in bladder cancer: The iBLAD study.

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Summary

Bladder cancer (BC) patients often have comorbidities, limited treatment options and thus a poor prognosis. A major risk factor for developing bladder cancer is smoking which is reflected in the comorbidities of the patients. Cardiopulmonary comorbidities or renal insufficiency due to vascular or tumour obstruction challenge the patients' ability to receive oncological treatment and troubles the completion of treatment due to increased toxicity. Early management of toxicity using patient-reported outcomes (PROs) during treatment has in previous studies in general cancer populations shown to improve adherence to treatment, improve quality of life and overall survival. To test this approach in the BC population requires knowledge about quality of life (QoL) and symptoms during treatment.

The overall aim of this PhD thesis was to test the hypothesis that the active use of PROs during treatment can improve outcomes for BC patients. As a systematic approach to this aim, we performed a **systematic review** of the published literature describing QoL for muscle-invasive and metastatic BC patients to achieve an understanding of the current QoL knowledge. We found no literature describing QoL from patients in neoadjuvant chemotherapy or from patients treated for metastatic disease outside clinical trials. To close this gap in knowledge we initiated a **pilot study** to determine which PROs to use in the following prospective studies. Through a mixed-methods approach we found 45 symptomatic PROs to use in **study I**, a prospective study of BC patients receiving chemotherapy with weekly evaluations of the chosen PROs and QoL measurements. In this study, our hypotheses of the outcomes for these patients were confirmed by high rates of hospitalisations and treatment cessation. **Study II** subsequently evaluated the feasibility of electronic capture of PROs from a patient and physician perspective. The study showed high patient compliance with electronic completion of PROs but concurrently low physician compliance with the viewing of the completed questionnaires. From study I and II the most frequent PROs were identified and the development of QoL during treatment was described. Also, we investigated which symptoms have influence on QoL. We found psychological items to have the highest correlation with QoL and urinary items the weakest correlations. In **study III** we used the previously performed studies to perform a final item selection process to be used in an interventional study. We identified 15 symptomatic PROs that together with specifically defined alert thresholds comprise the intervention in **study IV**, conducted as a randomized study at four university hospitals across Denmark to test the hypothesis that active use of PROs can improve outcomes. The study is still enrolling patients and the results hereof will therefore not be reported as part of this PhD.

This PhD presents new knowledge about QoL, PRO symptoms and their correlations in BC patients receiving medical oncological treatment. Electronic PRO reporting was found feasible but further work for handling of PROs by the clinicians is warranted for successful implementation in daily clinic. Finally, a PRO item set has been defined for use during treatment for the BC patients and the initiated randomized study will show whether this tool can improve outcomes and prognosis.

Resumé

Patienter med blærekræft (BC) har ofte komorbiditeter, begrænsede behandlingsmuligheder og deraf en dårlig prognose. Rygning er den største risikofaktor for udvikling af BC hvilket afspejler sig i patienternes komorbiditeter. Kardiopulmonal komorbiditet samt obstruktive eller vaskulære årsager til renal insufficiens udfordrer patienternes muligheder for behandling samt gennemførslen heraf på grund af øget toksicitet. Tidlig håndtering af denne toksicitet ved brug af patient-reported outcome (PRO) har i nylige studier vist at kunne fastholde patienterne i behandling i længere tid, forbedre livskvaliteten og øge overlevelsen. Det kræver viden om livskvalitet og symptomer at evaluere denne tilgang hos BC patienter under behandling.

Det overordnede mål med denne ph.d.-afhandling var at teste hypotesen, at aktiv brug af PRO under behandling kan forbedre BC patienternes prognose i form af gennemførsel af behandling, hospitalsindlæggelser, livskvalitet og overlevelse. For systematisk at evaluere dette gennemførte vi et **systematisk review**, der afdækkede litteratur omkring livskvalitet for BC patienter. Vi fandt at ingen litteratur fandtes for patienter i neoadjuverende kemoterapi eller for patienter med metastatisk sygdom. For at udfylde dette hul i viden om BC patienter, udførte vi et **pilot studie**, der gennem en 'mixed-method' tilgang udvalgte 45 symptomatiske PRO til brug i **studie I.** I dette prospektive studie besvarede BC patienter de udvalgte PRO samt spørgeskemaer om livskvalitet hver uge under behandling med kemoterapi. Fra dette studie fandt vi, at en høj andel af BC patienterne bliver indlagt i løbet af deres behandlingsforløb samt at få gennemfører den planlagte behandling. I **studie II** evaluerede vi patienternes brug af elektronisk rapporterede symptomer (ePRO) og fandt at patienter havde en høj compliance, men samtidig at lægerne ikke kiggede på de indrapporterede PRO i det elektronisk system. Med data fra studie I og II identificerede vi de hyppigst rapporterede PRO samt udvikling af livskvalitet igennem behandlingen. Derudover identificerede vi hvilke symptomer der har størst indflydelse på livskvaliteten og fandt at psykologiske og kognitive symptomer har størst indflydelse, mens urologiske symptomer har ringe indflydelse på livskvaliteten. I **studie III** identificerede vi ud fra data fra de indledende studier hvilke PRO skulle bruges sammen med en specifikt defineret alert-algoritme der skulle bruges som intervention i det efterfølgende **studie IV**. Vi identificerede 15 symptomer, der ved ugentlig patientrapportering og alert-algoritme udgør interventionsarmen i studie IV, der er et randomiseret studie på fire universitetshospitaler i Danmark. Studiet inkluderer fortsat patienter, hvorfor resultaterne herfra ikke vil indgå som en del af denne ph.d.

Denne ph.d. præsenterer ny viden om livskvalitet og PRO og sammenhængen mellem disse. Elektronisk rapportering er gennemførligt hos denne ældre og komorbide gruppe af patienter, men der består et arbejde i implementering af PRO i klinisk praksis. Endeligt er et PRO redskab til brug for BC patienter i behandling med kemo- eller immunterapi blevet udviklet og det randomiserede studie vil vise, om dette redskab kan bedre prognosen for patienterne.

Manuscripts

This thesis contains the following manuscripts (I-V), based on research carried out between 2017 and 2020

MANUSCRIPT I **Taarnhøj GA**, Johansen C, Pappot H. **Quality of life in bladder cancer patients receiving medical oncological treatment; a systematic review of the literature**. Health Qual Life Outcomes. 2019 Jan 22;17(1):20. PubMed PMID: 30670040.

MANUSCRIPT II **Taarnhøj GA**, Lindberg H, Johansen C, Pappot H **Patient-reported outcomes and quality of life in bladder cancer patients receiving chemo- or immunotherapy; a real-life experience.** Under review in Cancers 24.02.20.

MANUSCRIPT III **Taarnhøj GA**, Lindberg H, Dohn LH, Omland LH, Hjøllund NH, Johansen C, Pappot H. **Electronic reporting of patient-reported outcomes in a fragile and comorbid population during cancer therapy - a feasibility study.** Under review in Health and Quality of Life Outcomes 19.11.19.

MANUSCRIPT IV **Taarnhøj GA**, Lindberg H, Johansen C, Pappot H. **Patient-reported outcomes item selection for bladder cancer patients in chemo- or immunotherapy**. J Patient Rep Outcomes. 2019 Aug 22;3(1):56. PubMed PMID: 31440865.

MANUSCRIPT V **Taarnhøj GA**, Johansen C, Lindberg H, Basch EM, Dueck A, Pappot H. **Patient reported symptoms associated with quality of life during chemo- or immunotherapy for bladder cancer patients with advanced disease.** Accepted for publication in Cancer Medicine 19.02.20.

Abbreviations

BC	Bladder cancer
CPI	Check point inhibitor
CT	Chemotherapy
CTCAE	Common Terminology Criteria of Adverse Events
EHR	Electronic health record
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ePRO	Electronic patient-reported outcome
FACT	Functional Assessment of Cancer Therapy
FDA	Food and Drug Administration
HADS	Hospital Anxiety and Depression Scale
ICHOM	International Consortium for Health Outcomes Measurement
ISOQOL	International Society of Quality of Life
IT	Immunotherapy
IVR	Interactive Voice Response
MedDRA	Medical Dictionary for Regulatory Activities
MIBC	Muscle-invasive bladder cancer
MOT	Medical oncological treatment
NCI	National Cancer Institute
NMIBC	Non-muscle invasive bladder cancer
PD(L)-1	Programmed death (ligand) protein 1
PRO	Patient-reported outcome
PRO-CTCAE	Patient-reported outcomes version of the Common Terminology Criteria of Adverse Events
QLQ-BLM30	EORTC's module for muscle-invasive bladder cancer
QLQ-C30	EORTC's general quality of life questionnaire
QoL	Quality of life
RT	Radiotherapy
TMT	Trimodal therapy
TURB	Transurethral resection of the bladder
UCC	Urothelial cell carcinoma

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Background

1.1 Bladder cancer

1.1.1 Epidemiology

Bladder cancer (BC) accounts for approximately 550.000 new cases per year worldwide, 2.500 of these are diagnosed in Denmark making it the 6th most common cancer in Denmark [1]. Bladder cancer predominantly occurs in men (75 %) and is most frequently diagnosed between the ages 50 and 80 years with a median of 73 years [2, 3]. Several risk factors for bladder cancer are known. Smoking accounts for the largest risk factor of bladder cancer as smokers have a three-fold risk of developing bladder cancer [4, 5]. A wide range of chemicals used in the steel, colour, rubber, textile and chemical industries also increase the risk of bladder cancer to different extents, as does bilharziosis, also known as infection with *Schistosoma* species [5-7].

1.1.2 Staging

The most common symptom leading to diagnosis of bladder cancer is macroscopic haematuria [8, 9]. After diagnosis, bladder cancer can be divided into non-muscle invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) indicating depth of invasion into the bladder wall. NMIBC comprises TNM-stages Tis (carcinoma in situ), Ta and T1 and accounts for appr. 70-80 % of all bladder cancer cases at diagnosis [10-12]. MIBC represents stages T2-T4 and account for appr. 20-25 % of new BC cases, in Denmark appr. 500 cases/year [12]. Five percent of patients present with metastatic disease at time of diagnosis [13]. Figure 1 graphically displays the current T (of TNM) classification [12]. However, 50-75 % of NMIBC patients later progress to MIBC and 50 % of patients will ultimately develop metastatic disease [3, 13]. The prognosis depends on stage at diagnosis. The overall estimated 5-year survival rate for all stages is 77 %, however this rate declines rapidly from T1 disease (79 %) to metastatic disease (12 %) [3]. Often synonym with BC is urothelial cancer of the upper urinary tract. In Denmark, upper tract urothelial cancer accounts for appr. 160 new cases/year and has its own staging classification and prognosis is, as for urothelial cancer of the bladder, poor with a 5-year survival of pT2/pT3 of < 50 % and < 10 % for pT4 [14].

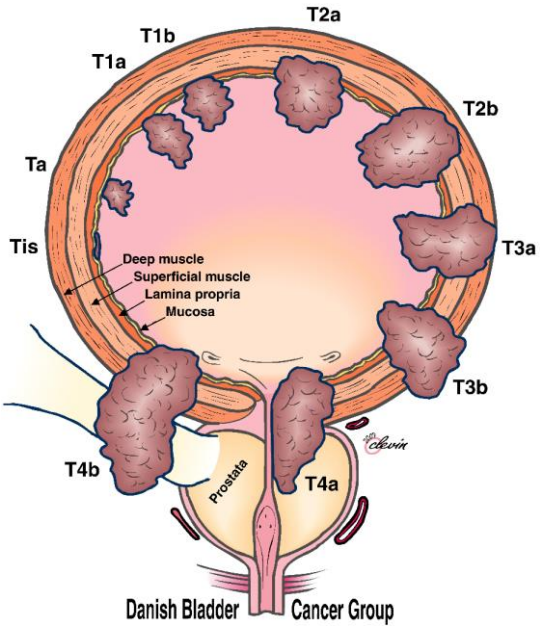

Figure 1. Bladder tumour stages according to Danish Bladder Cancer Group and the 8th edition of the TNM classification from Union International Contre le Cancer (UICC) from 2016 [12].

1.1.3 Histopathology

Urothelial cell carcinoma (UCC) is the main type of bladder cancer comprising approximately 80-90 % of all cases of BC [10, 15]. Other subtypes include adenocarcinoma, squamous cell carcinoma and small-cell carcinoma [10]. Mixed UCC variants are frequent, the most common mixed variant is UCC with squamous cell differentiation seen in up to 40 % of urothelial carcinomas [16]. Depending on the histology, treatment options may vary due to different sensitivity to chemotherapeutic agents [17, 18]. As such, UCC is the histological type best represented in clinical trials and the treatment of different histological subtypes remains controversial [17]. As an example, urothelial carcinomas with a small-cell or neuroendocrine component of more than 10 % are rare and no randomized trials support the basis of treatment recommendations for this patient group [17]. UCC is not unique to the bladder and is the main histopathological variant cancer throughout the urinary tract [16, 19]. As such, UCC is most often synonym with BC, as UCC in other parts of the urinary tract is rare (5-10 %) but share risk factors and histopathology with BC [14].

1.1.4 Treatment

Depending on stage at diagnosis, different treatment modalities may be offered. For patients with Tis-T1 NMIBC local treatment with transurethral resection of the bladder (TURB) and installation of local agents (Mitomycin C or BCG) is standard care [12, 19]. Patients with T2-T4 MIBC are treated with radical cystectomy preceded by neoadjuvant chemotherapy (CT) with combination cisplatin/gemcitabine for eligible patients (GFR > 60ml/min) [13, 20]. Patients ineligible for surgery are offered radiotherapy (RT), if possible, in combination with CT [21]. According to Danish guidelines, there are three lines of standard treatment options for patients with metastatic disease: platin-based CT, immunotherapy (IT) and vinflunine [12]. Cisplatin-eligible patients presenting with initial metastatic disease are offered first line combination cisplatin/gemcitabine CT. Likewise, eligible patients with recurrent metastatic disease and a progression free interval > 6 months after initial cisplatin-based treatment can be offered reinduction treatment with combination cisplatin/gemcitabine [12]. Cisplatin-ineligible patients presenting with metastatic disease are offered first line treatment with combination carboplatin/gemcitabine or immunotherapy (IT) with a programmed death-ligand protein 1 (PD-1/PD-L1) check point inhibitor (CPI), depending on PD-L1 expression and other comorbidities such as autoimmune conditions, neuropathy or ototoxicity [13, 22]. Patients progressing to metastatic disease after neoadjuvant cisplatin-based CT with a progression free interval < 12 months are offered second line treatment with IT. For patients unfit for platin-based CT (cisplatin or carboplatin), IT is offered, irrespective of PD-L1 molecular status as first line treatment [17, 21, 23]. Second line treatment depends on previously received regimens. If progressing after platin-based CT, IT is second line and a chemotherapeutic agent of choice, in Denmark vinflunine with an statistically superior overall survival of 6.9 v 4.6 months for best supportive care and an objective response rate of approximately 10 % in a phase III trial, is the preferred third line treatment, although not embedded into the Danish guidelines [12, 13, 24]. Other third line options include taxane-based chemotherapy, however, data supporting these chemotherapeutics stem from small phase II trials and with response rates of 0-28% [21] If progressing after IT, vinflunin is second line treatment [24]. At present there are no further standard treatment options for bladder cancer, however, a number of clinical trials with both targeted and antibody conjugate treatments are promising [25, 26].

Medical oncological treatment strategies for metastatic urothelial cancer from primary tumour in the bladder vs in other parts of the urinary tract are similar due to the main histopathological type (UCC) [14], although unique data from urethral or the upper urinary tract are sparse. Retrospective data from three RCTs has showed that location of primary tumour did not impact progression-free survival or overall survival in patients treated with platinum-based combination chemotherapy [14].

For the purpose of this PhD, patients with UCC of all parts of the urethral tract will be represented, although primarily depicted by UCC of the bladder (BC).

1.1.5 Comorbidities

Concordant with the median age of 73 years at diagnosis and main risk factor for bladder cancer (smoking), BC patients often have comorbidities in terms of cardiopulmonary or renal impairment, the latter due to vascular or obstructive causes [2, 27, 28]. The bladder cancer population is described as an elderly and frail population. As such, the most common bladder cancer patient is poorly represented in clinical trials testing systemic treatments for metastatic disease, with generally lower median ages in the clinical trials than in the total bladder cancer population [26, 27]. While the median age is now 73 years, and previously 78 years, the median age of patients enrolled into phase 3 trials to assess cisplatin-based chemotherapy for metastatic UCC has been 61-64 years [27, 29]. As a result, treatment efficacy when applying the new treatment regimens to the general UCC population not reflected by clinical trial participants has not replicated the results of previous trials [27]. Previous data suggest that early discontinuation for patients above 70 years is frequent and that age and performance status ≥ 2 increases the risk [30]. Consequently, the prognosis remains poor for bladder cancer patients with more advanced disease stages. As a result of the poor prognosis, the scientific focus has long been on new treatment options. The general UCC population outside clinical trials is thus understudied and little is known of real-life outcomes in terms of adherence to treatment, toxicity, hospitalisations and corresponding survival outcome. This information is thus important to increase supportive care for the bladder cancer patients of whom the majority are not enrolled into clinical trials.

1.2 Patient-Reported Outcomes

1.2.1 Background

For patients attending health care services for illness or disease, the presence and severity of side effects have traditionally been scored by clinicians. In particular, this practice has been exercised in the development of new pharmaceuticals, in which the toxicity of the given drug has been scored by physicians using the Common Terminology Criteria of Adverse Events (CTCAE) [31]. In oncology, the CTCAE scoring system has followed the pharmaceutic drug from use in clinical trials into daily clinic and remains the foundation of symptom scoring during active oncological treatment [31].

Data however indicates that the clinician's perspective and evaluation of a patient's symptom does not correspond well with the patient's scoring of the same symptom [32-35]. These studies report of the gap between the clinician's and patient's scoring of symptoms. Clinicians underscore the severity of the patient's symptom thereby underestimating the burden of the symptom on the patient's life [32]. Because the reliability of toxicity reports and safety of patients in clinical trials are vital, the discrepancies between patient and clinician reporting have led to awareness from authorities with the aim to improve the toxicity reporting from clinical trials. The U.S. Food and Drug Administration (FDA) therefore defined patient-

reported outcomes (PROs) as '*any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else*' in 2009 along with guidelines and recommendations for incorporating PROs into the drug development process [36].

The use of PROs is, although recently defined, not a new discipline and has existed for several decades under different names, e.g. surveys or questionnaires, acting as a passive collection of data. The use of the data collected can thus be defined as *passive* PRO. Examples of this include toxicity reporting from clinical trials including quality of life (QoL) measurements at predefined time-points in relation to treatment or CTCAE scoring during either clinical trials or daily clinic. The aim of incorporating PROs into the trial or clinic has thus been to use the PRO as an *endpoint*. The aim of this type of reporting has primarily been correct documentation and comparison of pharmaceuticals during trials [31]. While this practice has been advantageous for informing scientists, physicians and health authorities on a population level, the data collected did not benefit the supplier of data: the patient. In contrast, *active* PRO can be defined as real-time use of the PROs reported with feedback to the patient thus benefitting the patient during the period of PRO reporting through feedback on the reported symptoms facilitating either earlier handling of side effects from treatment or symptoms from disease or more personalized communication at clinical visits [37]. PROs are in such cases applied as *interventions*, in contrast to being used as an endpoint. This proactive symptom management has been proposed as a beneficial supportive care tool across diseases [38, 39]. Figure 2 graphically displays differences between the passive and active use of PROs.

Several studies have over the past years attempted to use this tool and close the gap in communication between clinician and patient by incorporating PROs into trials or clinical practice as an active and real-time use of the patient's voice [37-40].
By using these patient-reports several benefits have come to attention. A systematic review by Kotronoulas et al. from 2014 examined the value of PROs in randomized and non-randomized controlled trials and reported improved experience of patient and clinician communication, improved satisfaction with care and quality of life [39]. More recently, Basch et al. published similar results in terms of improvements of quality of life in a randomized controlled trial for metastatic cancer patients allocated to regular symptom reporting vs those allocated to regular handling of side effects. Data from the same study also showed that patients in the PRO-arm of the study had better adherence to treatment and a significant improved median survival of 31 months in the PRO-arm vs. 26 months in the control arm [41, 42].

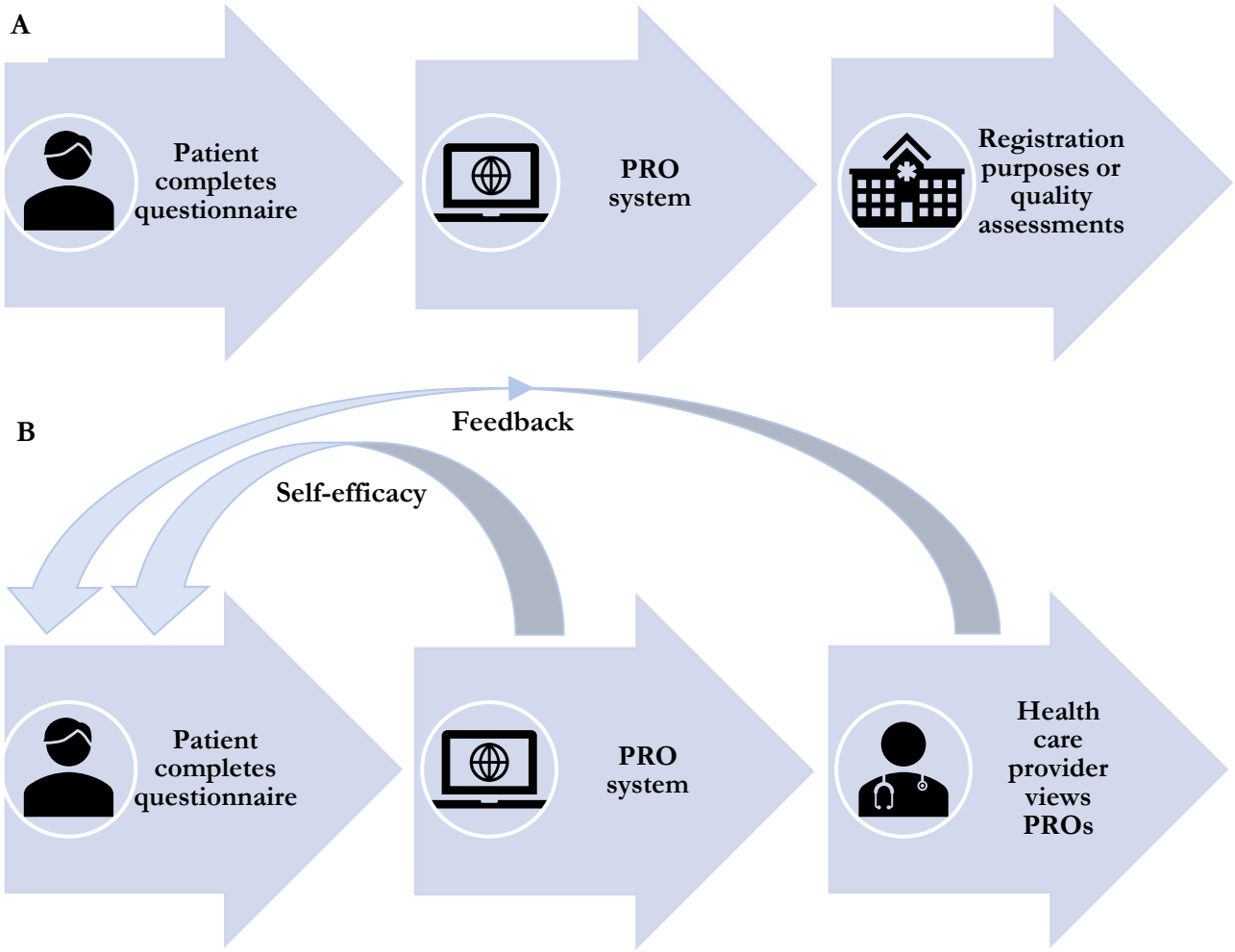

Figure 2. Examples of passive (A) vs. active (B) use of patient-reported outcomes. The bidirectional feedback arrow in B indicates the possibility of the patient contacting the hospital, e.g. as a result of the PRO system increasing self-efficacy and awareness to handle symptoms.

Later, in 2017, Denis et al. published results from a similar study in a population of lung cancer patients. This study also found a significant improved median survival of 7 months in favour of the PRO-arm (19 vs 12 months) [43, 44]. These studies have increased the interest into the use of PROs as a proactive supportive care tool substantially. However, the studies have also given rise to questions of exactly how to achieve similar benefits. The study by Basch et al. presented long median survival times for metastatic patients thus questioning the baseline characteristics of participants that would be assumed to predominantly consist of patients with a favourable prognosis, e.g. prostate and breast cancer patients [41, 42]. This further questions whether this approach could prove beneficial for all or solely subgroups of patients, depending on primary tumour site. Likewise, the study by Denis et al. followed lung cancer patients in a follow-up or maintenance therapy setting with clinical visits every three months with weekly reporting of 12 predefined symptoms from home [43]. However, the study does not disclose which

symptom questions were used or how they were chosen, thus disabling application of the approach in other settings.

1.2.2 PRO instruments

Several instruments are available to collect PROs. Quality of life measurements are examples of PRO collection that has existed for decades. The most commonly used QoL instruments in oncology are the European Organisation of Research in Treatment of Cancer (EORTC) general core questionnaire, the QLQ-C30, and the Functional Assessment of Cancer Therapy (FACT) general questionnaire, FACT-G [45, 46]. Many more instruments exist, however, not all have undergone the same extensive validation processes. In effect, the usability of such instruments is limited, as validation processes serve to reassure the end-user of the reliability and validity of the responses to the questionnaires. The validation processes also secure the readability and interpretability of the single items or full questionnaires thus ensuring that the answer given is in fact a response to the topic in question and not part of another construct [47].

PRO and QoL assessments are often used interchangeably. However, it is important to distinguish between the two. QoL will almost always be a PRO assessment, as the questionnaire in most cases is completed by the patient him- or herself. Contrarily, PRO assessments may be something quite different from QoL, as a PRO also represents single symptom items answered by the patient in accordance with the FDA definition given earlier. Whether using QoL instruments or symptom-specific PRO questionnaires, patient burden should be minimized as no surplus of information comes from patient-responses to the same symptom questions in two different questionnaires [48].

As a result of the awareness from FDA following publications of discrepancies between patient and clinician scoring of symptoms during clinical trials, the National Cancer Institute (NCI) initiated the development of a patient version of the CTCAE planned to act as a supplement to regular CTCAE scoring during clinical trials. This initiative resulted in the Patient-Reported Outcomes version of the Common Terminology Criteria (PRO-CTCAE) [49]. In the development of the PRO-CTCAE, all 790 adverse events (AEs) listed in the CTCAE were reviewed, finally identifying 78 symptomatic AEs appropriate for self-reporting. The 78 symptoms are explored further by single items on the frequency (F), severity (S), interference with daily activities (I), amount (A) or presence (P) of the given symptom, thus resulting in a total of 124 PRO-CTCAE questions [47, 49]. This instrument was developed to enhance precision and safety of toxicity reporting and supplement regular clinician CTCAE reporting in clinical trials. Acting as a library, the PRO-CTCAE is freely available for academic use on the NCI website. Although the use of the complete library has been found feasible [50], the use of such increases patient burden with lengthy questionnaires and should be avoided [48, 51]. Instead, selection of specific PROs should be undertaken with careful consideration to the aim and population. This process requires knowledge of the disease and

population and may be a decisive point in gaining the benefits presented in previous trials [37, 42, 43, 48]. The PRO-CTCAE was in 2016 translated into Danish and linguistically validated by Bæksted et al. and has since then been available alongside many other languages on the NCI website [52]. Figure 3 displays an overview of all PRO-CTCAE items.

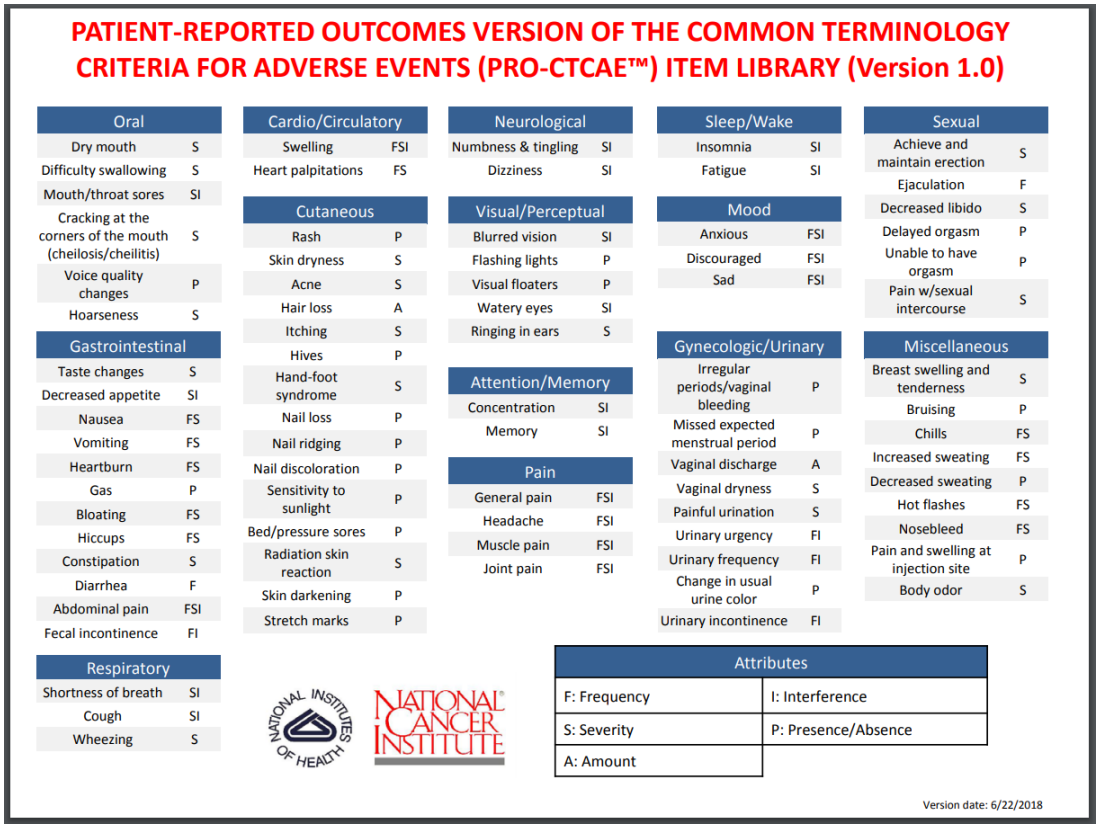

Figure 3. The full PRO-CTCAE item library. Source: National Cancer Institute.

Item selection is because of the recent focus on PROs as proactive symptom management a new discipline. Asking the right questions (and at the right time) may be the factor that determines final outcomes, as one question for a certain population may be meaningless for another population of patients [53]. Therefore, determining which items to use is essential to obtain the pre-defined endpoints, whether they are improvements in QoL, satisfaction with care or something different altogether [51, 54, 55]. For example, if changes in QoL is an endpoint of interest, knowledge about which PRO items impact QoL is imperative. Likewise, if reduction in hospitalisations is an endpoint data concerning which PRO symptoms lead to hospitalisations are essential. As item selection is a new discipline, few publications exist of the item selection process and for only a subset of diseases and settings [56, 57]. Of course, for decades multiple generic and disease-specific questionnaires have been developed but were all developed for passive collection of data as a method of describing a population and not for proactive use to obtain a predefined endpoint. The use of these questionnaires for proactive PRO management may therefore not deliver the desired results if no attention into the single items influence of the endpoint is paid. As touched upon

earlier, the item selection process in the studies by Denis and Basch has not been described in detail. From these studies therefore arise questions of how these results were achieved and how to apply the methods in other settings or populations. The benefits seen may be achieved through a number of different pathways, including correct item selection, adequate support staff to handle incoming and alarming PROs and/or an IT-system that supports the capture of electronic PROs (ePROs) at appropriate time intervals and delivers them efficiently to the clinicians [51, 58-61]. A study by Nordan et al. also suggests that the choice of appropriate PROs is vital for clinician endorsement and thus daily workflow [62]. In this study implementation of the International Consortium for Health Outcomes Measurement (ICHOM) standard item sets across disease areas created reluctance from providers accustomed to previously developed tools from speciality societies. Item and tool selection is therefore not a discipline to be taken lightly as it may determine eventual outcomes.

1.2.3 ePRO, Software & Implementation

While the collection of PROs for a long time has been on paper as part of a passive collection of data, technological developments and need for real-time use and graphic display of symptoms when using PROs proactively has urged development of software systems compatible with the electronic health records (EHR). Several vendors stand in line to promote their system to health administrators, however few have succeeded in full EHR integration which remains one of the big challenges when implementing ePROs into daily clinic [55, 58, 62, 63]. Other barriers for the use of PROs in clinic include patient and health care provider attitudes [54]. Feasibility of patient use of ePROs in one population does not guarantee smooth adaption across disease groups or even within the same patient group but in a different setting, e.g. different time points in relation to diagnosis, treatment or follow-up [55]. As such, the results from the studies by Denis and Basch have not led to subsequent implementation across diseases or borders. Likewise, multiple ePRO systems (e.g. eRAPID, KLIK, CHES, QLIC-ON, Kaiku) have been developed and proved feasible in the in-house setting the system was developed for [64-69]. These systems however remain unique to the setting in which they were developed. This suggests the presence of cultural barriers and speaks into the findings of provider reluctance with new tools as reported by Nordan et al. in the previous section [62]. A systematic review from 2019 by Warrington et al. assessed ePRO features and their associations with outcomes. The review identified 77 publications describing 41 unique ePRO systems. The review could because of heterogeneity among the systems not conclude any specific features more preferable than others to obtain improvements in outcomes [70]. However, a meta-analysis of eHealth interventions in paediatric health showed that interactive interventions are superior to purely educational features for obtaining behavioural changes or improvements in outcomes [71]. Not surprisingly, one uniform golden standard for ePRO software does not exist.

In Denmark, a publicly developed software system, Ambuflex, is available for electronic reporting of PROs. Ambuflex is a generic web-based PRO system originally developed in 2004. The software has since 2004 been implemented for out-patient follow-up for 35 cancer and non-cancer diagnoses groups across 10 hospitals in Denmark, integrated into the EHR in western Denmark [72, 73]. It sends notifications through e-Boks, a national system based on the civil registration number unique to every Danish citizen. E-Boks ensures delivery of official communication regardless geographical home address and is used for communication with authorities and companies. As a Danish citizen, it is mandatory to be an active user of e-Boks and more than 95 % of the Danish population are existing users of e-Boks [74]. Exemption from e-Boks use can be granted by authorities in certain cases, e.g. severe disability, morbidity or cognition impairment [75].

Overcoming the software issues when implementing PROs into clinic or trial is considered a vital step towards efficient and successful use of PROs [59, 62]. Several strategies for implementation of ePROs have been proposed [55, 58, 63, 76]. Of these, The International Society of Quality of Life (ISOQOL) has through a working group outlined eight key components for the implementation of PROs in routine practice and care: 1) identifying goals for the PRO collection, 2) selecting the patients, setting and time of assessments, 3) determining which questionnaire(s) to use, 4) choosing a mode for administering and scoring the questionnaire, 5) designing processes for reporting results, 6) identifying aids to facilitate score interpretation, 7) developing strategies for responding to issues identified by the questionnaire and finally 8) evaluating the impact of the PRO intervention on the practice [55]. These recommendations outline the complexity of PRO implementation and necessitates thorough planning of a PRO intervention or implementation. A systematic review by Anatchkova et al. from 2018 evaluated to what extent the use and implementation of PROs in clinical practice follow the ISOQOL guidelines. The review examined 36 randomized trials or observational studies with PRO reporting and found large discrepancies between the implementation practices in the studies and the ISOQOL guidelines. The review concludes that following the ISOQOL guidelines requires a body of evidence to guide choices before implementation.
The aim of this PhD is therefore to deliver a body of evidence about QoL and PROs in the BC population receiving medical oncological treatment. This body of evidence will support the use of PROs as an intervention in a randomized trial and perhaps followingly, the use of PROs in clinical practice.

1.3 Hypotheses

In conclusion, BC patients going through chemo- or immunotherapy are a group of patients in need of extended supportive care. The active use of PROs could be a way of achieving improvements in clinical outcomes and this concept will be the frame of this PhD.

We had the following a priori hypotheses before initiating this PhD project:

1. Limited knowledge exists of the QoL of BC patients during medical oncological treatment.
2. BC patients receiving systemic treatment have poor clinical outcomes in terms of frequent hospitalizations and poor treatment completion.
3. Electronic reporting of PROs is feasible in the BC population during treatment.
4. A set of symptoms items for weekly patient-reporting can be identified for the bladder cancer population in chemo- or immunotherapy.
5. Symptom management of BC patients can be supported by actively using PROs during treatment which will lead to better clinical outcomes for this patient group.

2

Objectives

2.1 Systematic review

The objective of our systematic review was to investigate the published literature reporting QoL during chemotherapy for muscle-invasive or metastatic BC.

2.2 Pilot study

With a mixed-methods approach the objective of the pilot study was to determine which PRO-CTCAE items to use in the following studies I & II.

2.3 Study I

The objective of study I was to initiate prospective PRO collection in a population of BC patients receiving chemotherapy while collecting information on clinical outcomes in terms of rates of hospital admissions and rates of treatment completion. These data were aimed to assist planning of study IV.

2.4 Study II

Study II was planned to test the feasibility of electronic reporting of PROs in the frail and comorbid bladder cancer population receiving chemo- or immunotherapy. The overall feasibility of this setup would inform us of how to best plan study IV. Further, based on the collected PRO data from study I and study II we aimed to describe which symptoms were frequent for the BC population during treatment and which symptoms influence QoL, as well as report the development of QoL throughout treatment.

2.5 Study III

The aim of study III was to perform a final PRO-CTCAE item selection for use in the bladder cancer population receiving chemo- or immunotherapy based on knowledge from study I and II.

2.6 Study IV

The aim of study IV was to test whether active use of PROs during treatment for bladder cancer could improve adherence to treatment, reduce hospital admission rates, improve QoL and overall survival.

2.7 Overview of studies

Figure 4 below illustrates the flow of studies included in this PhD. Each study has been designed to deliver information to the next. Ultimately study IV builds upon knowledge earned from the previous studies and will fill the gap in knowledge that the systematic review informed us of.

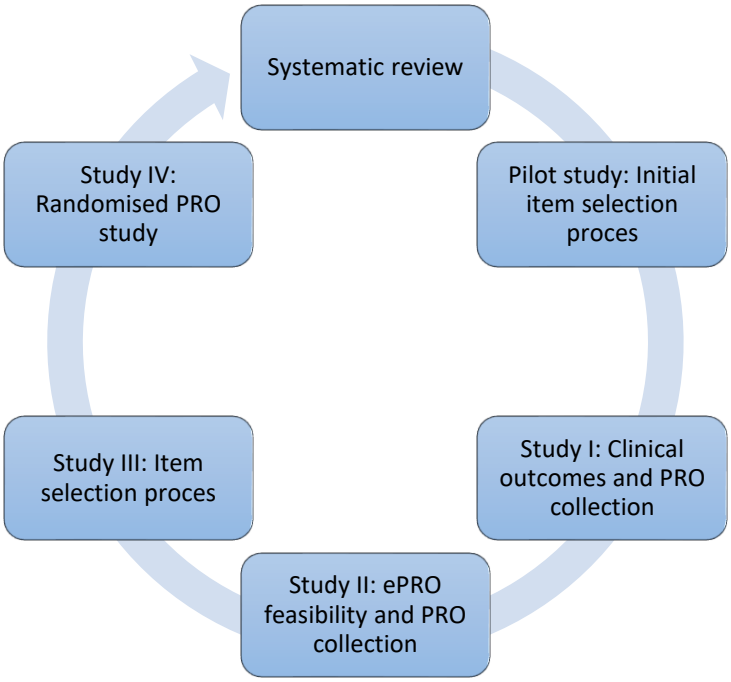

Figure 4. Overview of studies included in this PhD.

3

Patients and Methods

3.1 Systematic review

3.1.1 Search criteria

A systematic search was performed in PubMed and Embase. In order to limit the results to publications of patients undergoing medical oncological treatment (MOT) the following MeSH-, abstract- and title terms were applied:

MeSH terms	Abstract or title terms
Quality of life	Quality of life
Urinary bladder neoplasm	Bladder cancer
Chemotherapy	Chemotherapy
Drug therapy	

Table 1. Search terms in PubMed and Embase. Immunotherapy was approved as standard treatment for metastatic urothelial cancer in 2017 and therefore not part of this search string.

The results in both databases were examined by title and if found relevant the abstract was read. In order to limit the search to the relevant population and treatment modalities the following exclusion criteria were applied: not available in English, published before 2000 (allowing an overlap with previous conducted review with same topic [77-79]), only comparing surgical procedures, only involving NMIBC, only abstract available. During the procedure of reading abstracts, the studies were found relevant if they included quantitative QoL data of patients undergoing chemotherapy for MIBC. Any time point in relation to the patient's treatment was allowed: before, during or after diagnosis or treatment.

Due to a limited number of relevant studies, cross-references were checked and studies describing QoL of metastatic patients were also included.

3.1.2 Data extraction

All QoL scores from the included studies were noted. All scores on other than a 0-100 scale were converted to a 0-100 scale. Global QoL was illustrated on a 0-100 scale with increasing scores indicating better QoL whereas symptom items were illustrated on a 0-100 scale with increasing scores indicating increased impairment. One questionnaire, the FACT-BL, presented a combined score for urinary, bowel and sexual impairment. If no subgrouping into the single item scores (urinary, bowel and sexual) were elicited from the studies applying the FACT-BL, the FACT-BL score was then used multiple times as urinary, bowel

and sexual score thereby possibly over- or underestimating the given symptom. All scores for the given time point were summarized and a mean score served as the product of the included studies for the given time point in relation to diagnosis or treatment.

3.1.3 Study evaluation

All included studies were evaluated by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria. The GRADE system assesses the quality of evidence for a chosen outcome. The specified outcome for the present study was the evaluation of whether the sum of the studies included at each time point could serve as true evidence for assessing QoL or symptom burden at the given time point for the given population. The GRADE system applies the following criteria for downgrading when assessing evidence: risk of bias, inconsistency, indirectness, imprecision or apparent publication bias. The overall GRADE assessment would therefore reflect of the degree of certainty of the summarized QoL scores. The GRADE assessment was performed by author GAT and HP. The systematic review served the basis of manuscript I.

3.2 Pilot study

This study was conducted from April 2017- June 2017 at Rigshospitalet and consisted of several steps:

1. Journal audit.
   Review of medical records of patients receiving chemotherapy for bladder cancer to identify symptoms mentioned by staff. The review was predefined to include data from all patients treated at Rigshospitalet over a period of four months from January-April 2017. All symptoms mentioned in records were noted, without regard to frequency or severity.
2. Patient interviews.
   Semi-structured interviews were conducted at Rigshospitalet for patients receiving chemotherapy for bladder cancer. Interviews were concluded at time of data saturation. All symptoms mentioned by patients without regard to frequency or severity were noted.
3. Review of summary of product characteristics from European Medicines Agency (EMA) and FDA of the applied chemotherapies in the bladder cancer population.
   For the applied chemotherapies cisplatin, carboplatin, gemcitabine and vinflunine all adverse events with a frequency ≥ 10 % were included in the analysis.
4. Toxicity reports from Phase 3 randomized controlled trials in metastatic urothelial cancer for information on adverse events from immunotherapy.
   As immunotherapy was not approved as standard treatment for urothelial cancer at time of this study, data of adverse events from the applied immunotherapies were extracted from the

publications leading to approval: Bellmunt et al., Rosenberg et al [80, 81]. All symptoms CTCAE grade ≥3 reported from these trials were included in the further analysis.

Data from the above four sources were listed according to Medical Dictionary for Regulatory Activities (MedDRA) system organ class and all symptoms found corresponding to a PRO-CTCAE symptom were included in this initial set of PROs to be used in the following prospective studies I and II [49].
For an overview of the process of the pilot study, see Figure 8. The pilot study serves as the basis of the final item selection, described in detail in manuscript IV.

3.3 Study I

3.3.1 Patients

This initial prospective study enrolled patients at Rigshospitalet. Patients were eligible for enrolment if they fulfilled the following criteria:

1. Urothelial cell carcinoma of the bladder, ureter, renal pelvis or urethra, stages T2-T4, any N any M.
2. Age ≥ 18 years.
3. Initiating chemotherapy as standard neoadjuvant (combination cisplatin and gemcitabine) or metastatic treatment (combination cis- or carboplatin and gemcitabine or single agent vinflunine) (not as part of clinical trials).
4. Able to read Danish
5. No serious cognitive impairment

The study planned to enroll 30 patients, as recommended for pilot studies in previous publications [82, 83].

3.3.2 Questionnaires

Patients were asked to complete PROs weekly from home. Until approval for electronic reporting was obtained PRO collection was by paper and at time of approval of electronic reporting from The Danish National Data Protection Agency, all patients were offered completion through e-Boks and Ambuflex, an internet-based software for PRO completion. For patients completing by web, they weekly received an e-mail reminder in e-Boks with a link and a password to the questionnaire. If failing to complete the same day, reminders were sent on the following two days. For patients completing on paper, they were at each clinical visit every three weeks given three full sets of questionnaires with a date for every completion for the following three weeks.

The following PROs were completed weekly: the specifically chosen 45 PRO-CTCAE symptom questions from the pilot study, the EORTC QLQ-C30 general core questionnaire [45], the EORTC QLQ-BLM30 (organ-specific module for muscle invasive bladder cancer) [84] and the Hospital Anxiety and Depression Scale (HADS) [85], a total of 158 questions weekly. Details of EORTCs quality of life questionnaires can be found in manuscript II.

Patients terminated questionnaire completion at time of treatment cessation, for whatever reason, and completed questionnaires for a maximum of six cycles of chemotherapy.

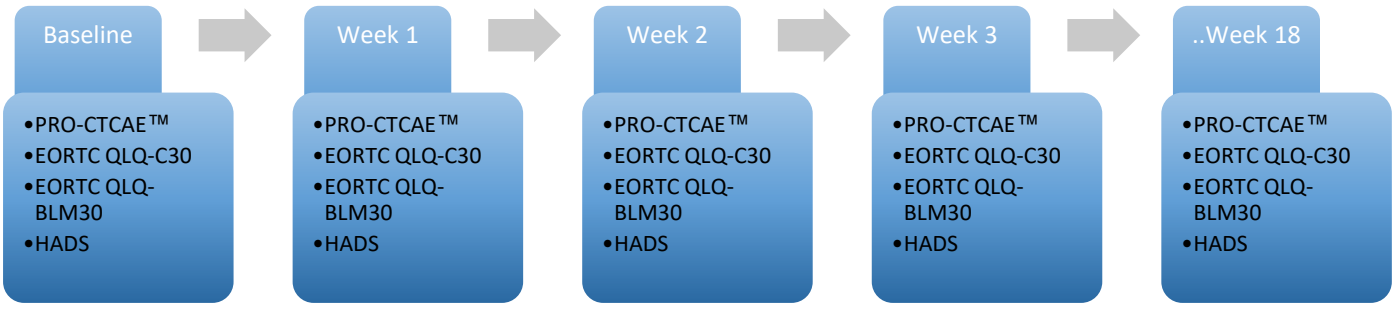

Figure 5. Flow of weekly questionnaires

The collected PROs served as a passive data collection in accordance with the aims and objectives of the study. The PRO data was therefore not visible to the clinician at patient encounters.

3.3.3 Data analysis

While the data on the clinical outcomes of BC patients from study I served as knowledge for the power calculation of study IV, the accompanying publication of study I included the patients from study II, below, in order to best engage all patient data and expand usability of the data with more power.

The QoL data was analyzed descriptively over the course of treatment and reported with a mean ± 1 standard deviations (SD) for the neoadjuvant and metastatic group separately. Differences between groups were described using Student's T-tests and development over time by linear regression. Data on most frequent PRO-CTCAE symptoms ≥ grade 2 are reported in order of falling frequency for all patients throughout treatment. These data serve as the basis of manuscript II, see appendix.

To address the aim of investigating which symptoms have impact on QoL for BC patients during oncological treatment, Spearman's analyses were performed for all aligned responses to PRO-CTCAE items and all domains of EORTC's QLQ-C30. Linear regression analysis with summarized PRO-CTCAE scores and all domains of QLQ-C30 was performed to assess the impact of overall symptom burden. These analyses were performed for the same population as in manuscript II. The results of these analyses serve as the basis of manuscript V.

3.4 Study II

3.4.1 Patients

This prospective study enrolled patients at Rigshospitalet and Herlev Hospital with the same inclusion criteria as in study I, although with two amendments:

1. Initiating chemo- *or* immunotherapy as standard treatment for locally advanced or metastatic disease (not as part of clinical trials). Chemotherapeutic agents as in study I, treatment with immunotherapy consisted of PD-1 inhibitor pembrolizumab.
2. Access to e-Boks, electronic communication with authorities.

The study planned to enroll 40 patients (20 chemotherapy / 20 immunotherapy).

3.4.2 ePRO presentation

All patients thus reported electronically through Ambuflex in this study. At every following clinical visit, all with three-week intervals, the physician was reminded that the patient had completed the questionnaire and that symptoms could be reviewed in the physician view of Ambuflex, shown below in Figure 6. Green bars indicated no or little impairment/symptom burden, yellow indicated moderate symptom burden and red bars indicated severe symptoms.

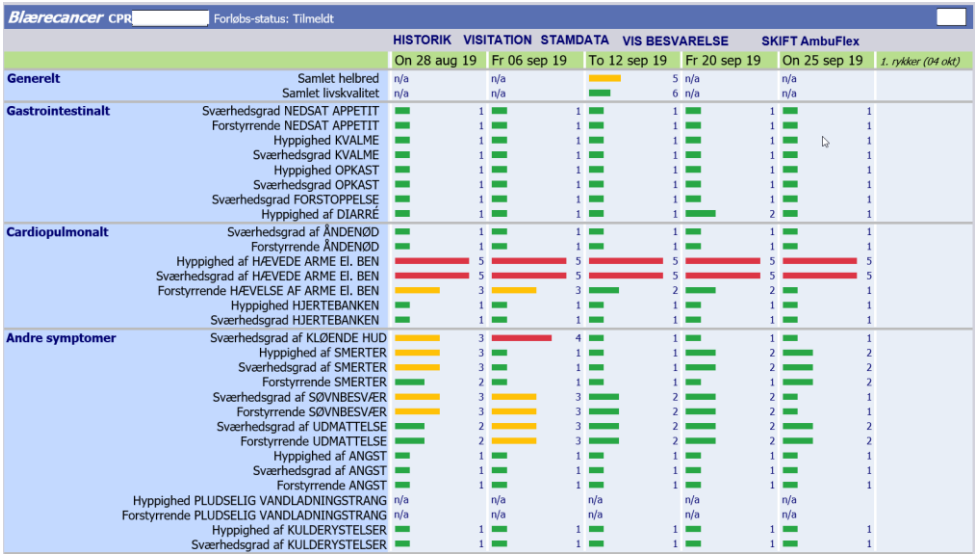

Figure 6. Clinician view of patient responses.

3.4.3 ePRO implementation

Before commencing the study, several steps were taken to ensure successful implementation of the workflow endorsing the incorporation of PROs into the clinic. The steps consisted of:

- Collective teaching of physicians and nurses about the purpose of ePROs for this patient group and how to access Ambuflex to view the patients' responses.
- One-to-one instructions of how to access Ambuflex was carried out for all physicians with clinical obligations in the uro-oncological department at Rigshospitalet and Herlev Hospital.
- Written, laminated instruction cards were present in all consultation rooms.
- All out-patient visits from patients enrolled in this study were marked with a reminder to review symptoms in Ambuflex in the electronic chart system.
- The staff at both departments were informed that questions at all times could be directed to GAT.

Figure 7. Flow of electronic patient-reported outcomes.

3.4.4 Data analysis

Patient compliance with ePROs was measured by number of questionnaires completed out of number of patients still in treatment and having received a questionnaire. Physician compliance was measured by number of logs in relation to an outpatient visit out of number of completed questionnaires in relation to each clinical visit. Study II serves as the basis of manuscript III.

3.5 Study III

For the final selection of PRO-CTCAEs for use in the randomized trial study III built on and drew information from the initial studies: pilot study – study II. By applying the 45 PRO-CTCAE symptom questions in the two prospective studies we gathered information for the current study. From study I we listed all reported PRO-CTCAE symptoms ≥ grade 2 throughout the course of chemotherapy. From study II we listed all PRO-CTCAE symptoms ≥ grade 2 that were reported in relation to a hospital admission. Hospital admissions were a focal point in this process as they were chosen as a co-primary endpoint in the randomized trial. As such, we drew information on which symptoms during oncological treatment that could lead to hospital admissions. This process was planned to secure that the final chosen item set would have an impact on the chosen endpoint in study IV. A completed questionnaire within one week of the hospital admission was considered relevant (the PRO-CTCAE question time frame is one week) and included in our final listing of symptoms for use in the final item selection process. Finally, two focus group interviews were conducted in August 2018, with uro-oncological nurses and physicians separately. The focus group interviews were semi-structured and applied the same questions about the bladder cancer patients in both groups. All symptoms mentioned by nurses or physicians were noted and included in the final item selection process, without regard to severity or frequency.

The collected listings of symptoms from the above resources were finally listed in four columns. A given symptom was included in the final selection of items if the symptom was present in 3 or more of the columns or present in only 2 but considered actionable by the study group. Examples of this process include the symptom 'pain' which was included in all four columns and therefore included in the final item set. In contrast, the symptom 'numbness and tingling' or neuropathy was included in only two of the four columns and not deemed actionable by the study group, thus this symptom was not included in the final item set. The process is illustrated by Figure 8.

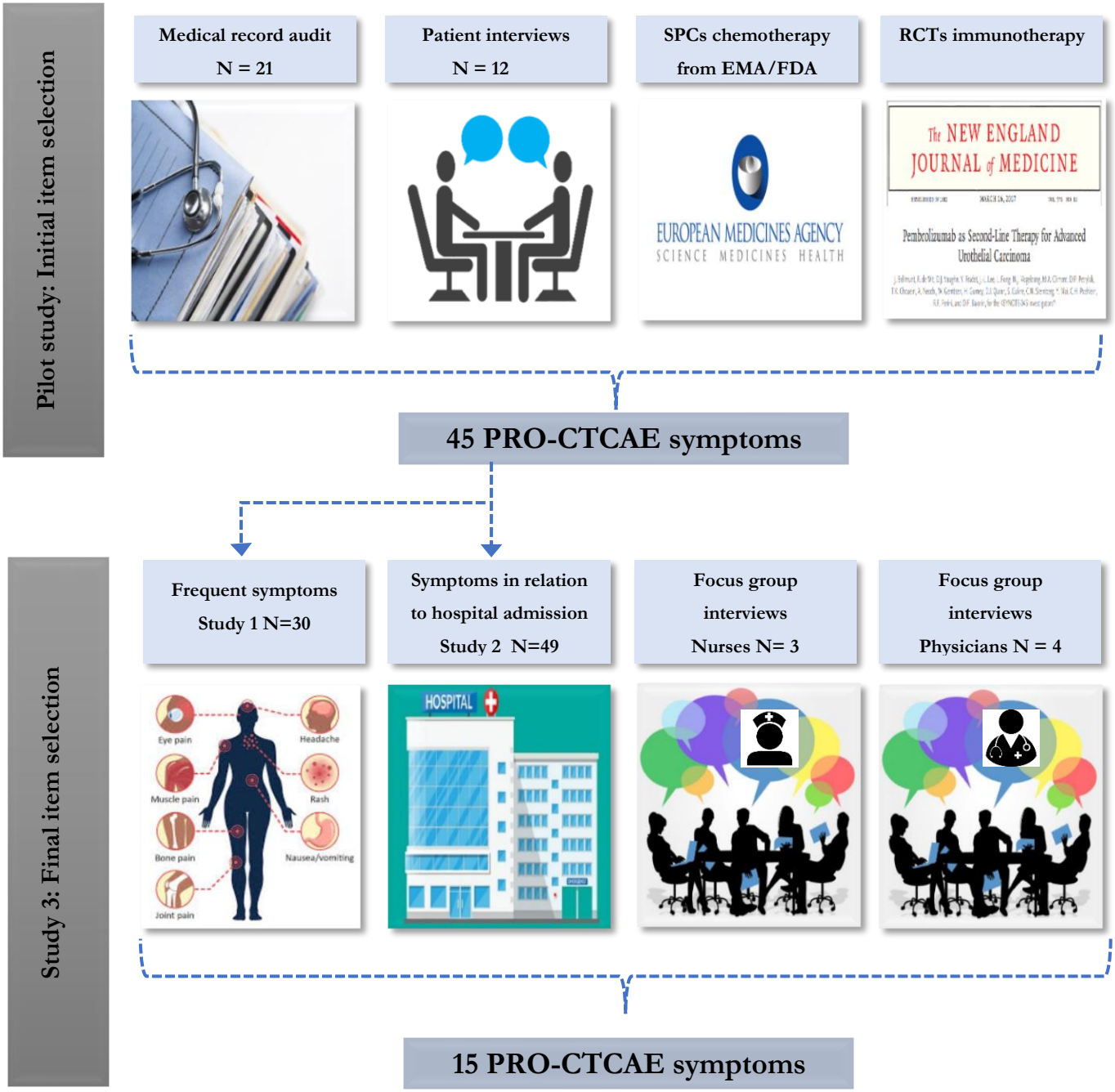

Figure 8. Overview of the pilot study and study 3, together comprising initial (pilot study) and final item selection process. SPCs: Summary of product characteristics. EMA: European Medicines Agency. FDA: US Food and Drug Administration. RCTs: randomized controlled trials: Rosenberg et al Lancet 2016, Bellmunt et al. NEJM 2017.

3.6 Study IV

From the initial studies it was clear that our hypotheses of the bladder cancer population concerning clinical outcomes were accurate. To test the hypothesis that the active use of PROs during treatment could improve these outcomes a randomized study was planned.

For study IV the same population as in study II was offered enrolment into a randomized trial with two arms, with patients being allocated 1:1 to the intervention and control arm. The study started enrolment in January 2019 and is currently enrolling and expected completement of enrolment in October 2020. The study was planned for enrolment at Rigshospitalet and Herlev Hospital but opened up at Aalborg University Hospital in April 2019 and at Odense University Hospital in May 2019 due to interest in the study from these sites. The study has been registered at www.clinicaltrials.gov with study number NCT03584659.

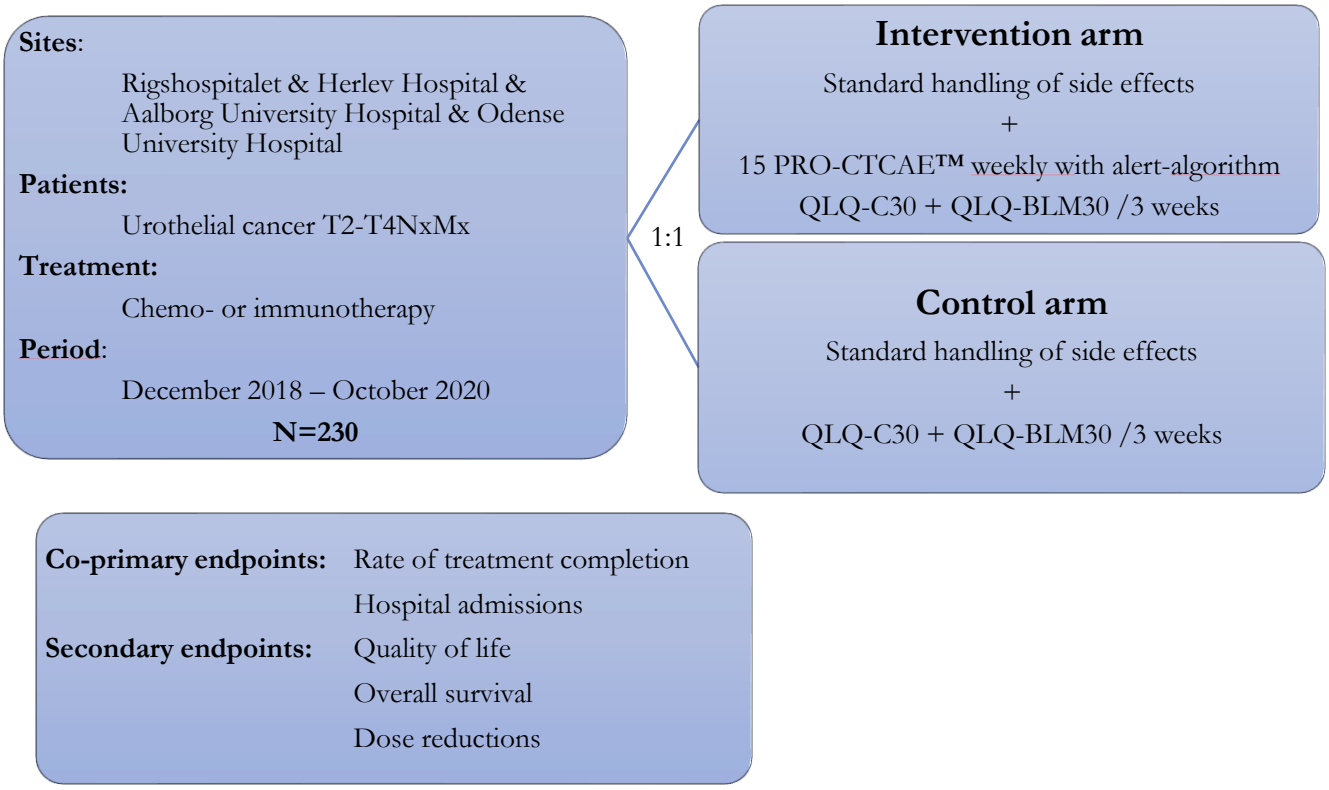

Figure 9. Overview of the randomized trial design.

Patients are at the initial clinical visit prior to start of chemo- or immunotherapy informed about the study and are subsequently asked if they want to participate at time of initiating treatment, typically the following day. After completing written informed consent patients are randomized to either the intervention arm or control arm. Both arms require electronic completion of PROs through e-Boks and if the patient does not have access to a computer or tablet to do so, a tablet is provided for the patient during the study period.

3.6.1 The intervention arm

If allocated to the intervention arm patients receive the first questionnaire the same day by receiving an email in e-Boks, as described in the methods section of study I. The frequency of questionnaires and interval between treatment cycles and accompanying clinical visits follows a fixed interval, as shown in Table 2 below:

Intervention arm	Baseline	Week 1	Week 2	Week 3	Ect.
EORTC QLQ-C30	X			X	
EORTC QLQ-BLM30	X			X	
PRO-CTCAE	X	X	X	X	X
Clinical visits/ Treatment cycles	X			X	

Table 2. Frequency of questionnaires and clinical visits for intervention arm.

If patients fail to complete the questionnaires a reminder is sent after two days.
During completion of the 15 PRO-CTCAE items from study III the patient is guided on-screen of how to handle the given symptom if the severity exceeds a predefined level of severity. The alert appears as shown below in a blue box next to the question:

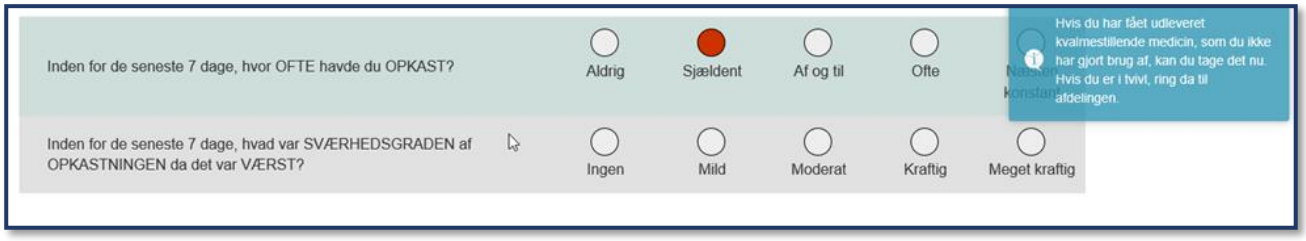

Figure 10. Patient view of questions and example of alert (blue box).

The study group predefined the threshold levels of alerts according to Table 3. Alerts are prompted to the patient at a level of severity at which the study group agreed that the symptom in question should be handled, either by the patient him/herself or by the treating department. As for the alerts, a predefined level of severity was defined concerning the colours of the 'bars' in the physician view of the Ambuflex system reflecting the severity of the response. The thresholds for the colours green/yellow/red can also be seen in Table 3.

Prior to initiation of study IV a small pilot study with five patients was conducted with the purpose of testing the alert system. The five patients were all asked to complete questionnaires according to the intervention arm for two cycles of treatment (six weeks). Semi- structured interviews were performed after

six weeks to evaluate the alerts in the software system. Any feedback given was planned to adjust the alert algorithm before initiation of the randomized study.

For all patients in the intervention arm the treating physicians are at all clinical visits reminded of responses in the Ambuflex system (as shown in Figure 6) and will have the possibility of using this information in the consultation and treatment of the patient, as in study II. In response to the PROs, the physician was not given a predefined course of action depending of the symptom and severity thereof. It is up to the physician to use these data as he or she sees fit, e.g. either as a dialogue tool to focus on the reported toxicities or as a tool to support shared decision making or simply to gain an overview of the patient's toxicity over time.

Enrolment into the intervention arm does not preclude standard procedure for handling of symptoms and side effects and the patients can at all times contact the treating department, irrespective of questionnaires completion and on-screen alerts.

Symptom nb	Symptom	Items	Alert threshold PRO-CTCAE grade	Alert wording	Number of questions	Grade threshold yellow/red
1	Decreased appetite	Severity	2	2:*	1	2/>2
		Interference with daily activities	2	2:*	2	2/>2
2	Nausea	Frequency	1+2	1: If you have been given anti-emetics that you haven't applied, please take them now. If in doubt, please contact the department. 2: *	3	2/>2
		Severity	1+2	1: If you have been given anti-emetics that you haven't applied, please take them now. If in doubt, please contact the department. 2:*	4	2/>2
3	Vomiting	Frequency	1+2	1: If you have been given anti-emetics that you haven't applied, please take them now. If in doubt, please contact the department. 2: *	5	2/>2
		Severity	1+2	1: If you have been given anti-emetics that you haven't applied, please take them now. If in doubt, please contact the department. 2: *	6	2/>2
4	Constipation	Severity	1+2	1: If you have laxative medications at home but are in doubt of how to apply them, please contact the department. 2:*	7	2/>2
5	Diarrea	Frequency	1	1:*	8	2/>2
6	Shortness of breath	Severity	2**	2:*	9	2/>2
		Interference with daily activities	2**	2:*	10	2/>2
7	Swelling	Frequency	2	2:*	11	2/>2
		Severity	2	2:*	12	2/>2
		Interference with daily activities	2	2:*	13	2/>2
8	Heart palpitations	Frequency	2	2:*	14	2/>2
		Severity	2	2:*	15	2/>2
9	Itching	Severity	2	2:*	16	>1
10	Pain	Frequency	1+2	1: If you have pain medication at home and have doubts of how to apply them, please call the department. 2: *	17	2/>2
		Severity	1+2	1: If you have pain medication at home and have doubts of how to apply them, please call the department. 2: *	18	2/>2
		Interference with daily activities	1+2	1: If you have pain medication at home and have doubts of how to apply them, please call the department. 2: *	19	2/>2
11	Insomnia	Severity	2	2:*	20	2/>2
		Interference with daily activities	2	2:*	21	2/>2
12	Fatigue	Severity	3	3:*	22	2/>2
		Interference with daily activities	3	3:*	23	2/>2
13	Anxiety	Frequency	2	2:*	24	2/>2
		Severity	2	2:*	25	2/>2
		Interference with daily activities	2	2:*	26	2/>2
14	Frequent urination	Frequency	3	3:*	27	3/>3
		Interference with daily activities	3	3:*	28	3/>3
15	Chills	Frequency	1	1:*	29	2/>2
		Severity	1	1:*	30	2/>2

Table 3. PRO-CTCAE questions and threshold for on-screen alert for intervention arm.
***: Please contact the department at which you're treated. Remember to complete the rest of the questionnaire, even though you contact the department. **: or at deterioration from baseline.**

3.6.2 The control arm

Patients assigned to the control arm follow standard procedures for handling of side effects and symptoms as informed by the treating department. For comparative reasons the patients also complete QoL questionnaires once every three weeks, as shown in Table 4 below. No on-screen alerts in response to these questionnaires are given and the physicians are not, as in the intervention arm, made aware of responses in Ambuflex. The completed questionnaires, although present in Ambuflex, are not presented to the physician with coloured bars as in the intervention arm.

Control arm	Baseline	Week 3	Week 6	Week 9	Ect.
EORTC QLQ-C30	X	X	X	X	X
EORTC QLQ-BLM30	X	X	X	X	X
Clinical visits / Treatment cycles	X	X	X	X	X

Table 4. Frequency of questionnaires and clinical visits for control arm.

3.6.3 Statistical analysis

On the basis of rates of treatment completion from study I and literature review, study IV was planned to include 230 patients. Prior data indicate that the failure rate among controls is 0,5 [42, 86, 87] and data from study I indicates a failure rate of 0,59 [88]. If the true failure rate for experimental subjects is 0,3, we will need 103 experimental subjects and 103 control subjects to be able to reject the null hypothesis that the failure rates for experimental and control subjects are equal with probability (power) 0,8. Allowing for expected attrition, 230 patients will be included, 115 patients in each group. The type I error probability associated with this test of this null hypothesis is 0,05.

For the co-primary endpoints, completion of treatment and hospitalization, the proportions of patients in each arm experiencing early treatment cessation or hospitalization will be evaluated with a Fisher's exact test. Differences between arms in QoL will be evaluated by change from baseline value to value after four cycles of treatment for the neoadjuvant group and value after six cycles of treatment for the metastatic group. If no post-baseline observation exists, the baseline value will be carried forward. If death occurs before four or six weeks, respectively, a global QoL score from QLQ-C30 of zero will be carried forward. Differences will be tested by linear mixed model regression analysis as recommended by the Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL) initiative [89]. A multivariate linear regression model with change in global QoL score as dependent variable and adjusting for age, sex, disease stage and treatment modality as covariates will also be performed. Overall survival will be assessed at one year after enrolment into the study using the Kaplan-Meier method and compared between groups using a log-rank test. Cox proportional hazard regression adjusted for age, sex, disease stage and treatment modality will be performed to assess risk of death

between the two groups. Differences in dose reductions between the two groups will be evaluated by a Fisher's exact test. The data will be analysed with the statistical software IBM SPSS version 25.

4

Summary of results and study specific discussion

This section provides a summary of the five studies included in the thesis (Table 5). The section is divided into six parts (SYSTEMATIC REVIEW - STUDY IV) presenting main results and discussion of each study.

Design	Materials and methods	Highlighted findings
	SYSTEMATIC REVIEW	
Literature review	21 publications GRADE assessment tool	No QoL data of patients in neoadjuvant treatment. No data from metastatic patients outside clinical trials.
	PILOT STUDY	
Mixed methods	Patient interviews Medical record audit Medical authority documentation Toxicity reports from randomized trials	45 PRO-CTCAE symptoms to be used in the BC population.
	STUDY I	
Prospective, single-arm	30 BC patients Rigshospitalet Chemotherapy Paper and electronic PRO reporting	Poor clinical outcomes for BC patients, stable global QoL during treatment. Identification of frequent symptoms and symptoms with correlation with QoL.
	STUDY II	
Prospective, single-arm	49 BC patients Rigshospitalet and Herlev Hospital Chemo- and immunotherapy Electronic PRO reporting	Feasible electronic PRO reporting, but poor clinician compliance with incorporation into clinic.
	STUDY III	
Mixed methods	Results from pilot study PRO symptoms from study I & II Focus group interviews	15 PRO-CTCAE symptoms identified to be used in the bladder cancer population during chemo- or immunotherapy
	STUDY IV	
Randomized controlled trial	230 BC patients 1:1 intervention vs. control arm Rigshospitalet, Herlev Hospital, Odense University Hospital, Aalborg University Hospital	Still enrolling patients, per 04.02.20 enrolled 131 patients.

Table 5. Overview of studies included in the thesis and main findings.

4.1 Systematic review

A total of 208 papers were reviewed for inclusion in the review. Fifteen papers were found eligible for the purpose of this study and a further six papers were included through cross references, resulting in 21 papers reviewed in this study. The selection of the papers included can be studied in Figure 11.

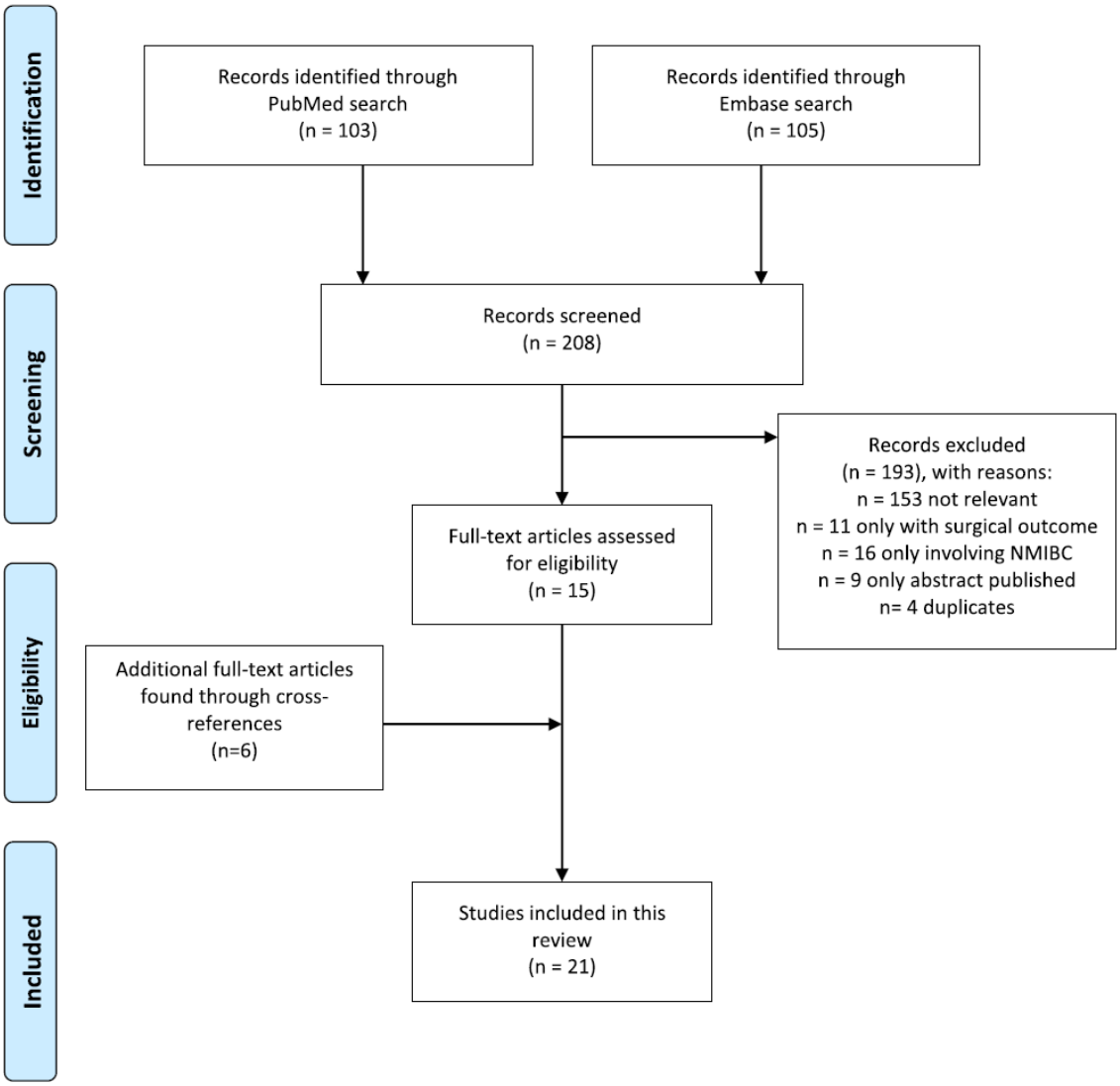

Figure 11. Flow chart in PRISMA consort diagram of study screening and selection. Taarnhøj et el. HQLO 2019.

No data were found for patients receiving neoadjuvant chemotherapy. For metastatic patients, the only published data derived from clinical trials. Data post treatment was only available for patients having undergone treatment regimens with either radiotherapy (RT), combination radio-/chemotherapy (CT) or trimodal therapy (TMT) (transurethral resection of the bladder (TURB) + RT + CT).

In the included papers, 21 different QoL instruments were used. Only 52 % of the studies included BC specific items or questionnaires. Five of the studies used non-validated questionnaires. The reported focus areas from the included instruments were global QoL (81 %), urinary symptoms (57 %), bowel symptoms

(57%), sexual function (48 %), fatigue (48 %), pain (38 %) and anxiety/depression (24 %). The reported domains were listed according to time in relation to treatment and summarized to create an overview of the QoL knowledge to date for these patients, as shown in Figure 12 below.

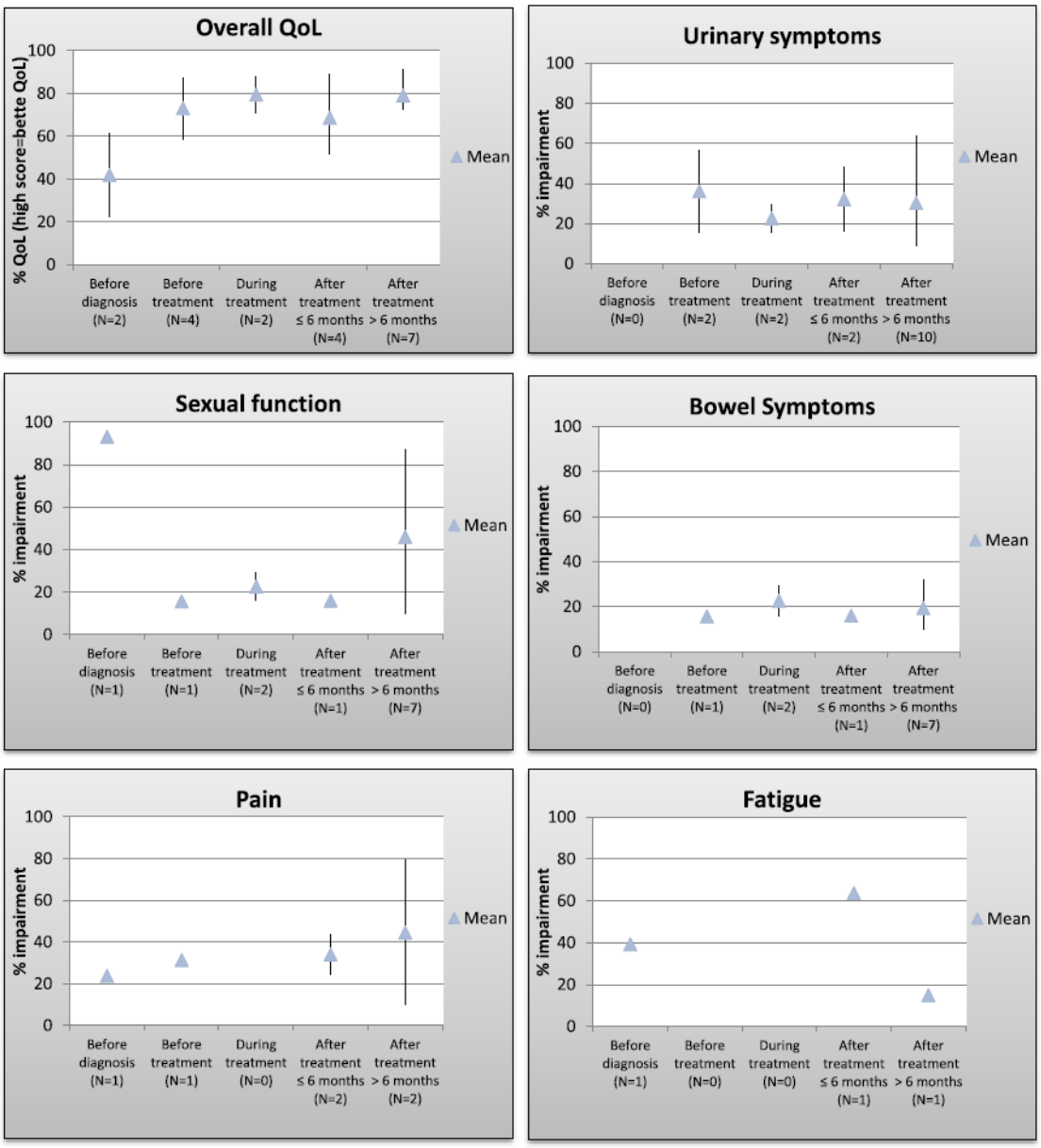

Figure 12. Quality of life domain scores in relation to treatment. Taarnhøj et al. HQLO 2019.

When evaluating each domain from the studies included at each time point by GRADE, no time points or domains were concluded to represent a high level of evidence, see Tables 3-6 in manuscript I. Global QoL was the domain represented by the most reliable studies generating very low to moderate GRADE evaluation of the studies included at each time point. Urinary, bowel and sexual domains were found only to be moderately supported by evidence post treatment for patients free of disease and having undergone RT or combination treatment. The remaining time points were evaluated as very low by

GRADE. Conclusively very little knowledge exists of the QoL of bladder cancer patients in medical oncological treatment.

This systematic review presents the gaps in knowledge for a population of patients who may benefit from extended efforts. In particular, the neoadjuvant patients are underexplored and metastatic patients outside clinical trials not represented in the present data. Also, very sparse data exists from patients during treatment, as illustrated in Figure 12. This review therefore highlights areas in which additional knowledge is needed to understand QoL for BC patients. Especially, knowledge about the impact of the reported symptom areas on quality of life could support the readability of Figure 12. Similarly, the sparse data on psychological issues creates uncertainties of the interpretation of Figure 12, as these issues are described to impact QoL in a general cancer population [90-92]. Some limitations do, however, need to be addressed. Despite efforts to gather the published knowledge of QoL for BC patients, the alignment of data from different studies, thus assuming equal weight of these studies despite large differences in populations and methods, represents a limitation. The summarized QoL values in Figure 12 may therefore only act as a careful guidance. Also, even though the search was assisted by a professional librarian, we may have found supplementary relevant literature if expanding the search to additional online libraries.

In summary, the systematic review gives new insight into the sparse knowledge of QoL for BC patients during oncological treatment. The following studies were conducted to increase this knowledge of QoL in BC patients with the overall aim of delivering information of how best to use PROs as an intervention for the BC population.

4.2 Pilot Study

As displayed in Figure 8 the pilot study resulted in 45 PRO-CTCAE symptoms aligning with the data from the four sources: medical record audit, patient interviews, medical authority documents and toxicity reports from randomized trials. The medical record audit of patients attending Rigshospitalet for treatment of bladder cancer with chemo- or immunotherapy during the three-month period from January 2017 to April 2017 consisted of 21 patient medical records. All symptoms noted by staff were noted. For the patient interviews, data saturation in the semi-structured interviews was met after interviewing 12 patients. Data extraction from the authority documents from EMA and FDA and published RCTs leading to the approval of PD-1 inhibitors as standard treatment in the metastatic bladder cancer population was performed and all symptoms from the four sources were aligned with all possible PRO-CTCAE symptoms. The alignment process can be viewed in Additional file 1 in manuscript IV. The selected PRO-CTCAE symptoms were then applied in the prospective studies I and II.

Although applying an extensive mixed-method approach one could question whether the medical record audit and patient interviews sufficed to serve as clinical input to the official documents. Additional

interviews may have resulted in other PRO-CTCAE symptoms. Also, as immunotherapy as standard treatment was not yet approved in this population, one may question if a validation of this process in the same population in a standard clinical setting now, a couple of years after implementation of IT for these patients, may result in different PRO-CTCAE symptoms. We do however encourage similar mixed-method approaches if applying the process to the same or different populations to ensure information from all involved parties.

4.3 Study I

In study I we collected PRO data and data of the clinical outcomes of BC patients during chemotherapy. Thirty patients completed informed consent, however one patient suffered from a cerebral stroke on the day of completing consent and did therefore not complete any questionnaires. Analysis was therefore performed for the remaining 29 patients.

We found that 16 patients (55 %) did not complete the planned treatment. While five of these patients (31 %) did not complete the treatment due to progression and four patients (25 %) terminated due to nephrotoxicity, the remaining seven patients (44 %) terminated treatment due to intolerable symptoms. Also, the rate of hospitalisation was high (66 %), 47 % of the hospitalisations were due to symptoms while the remaining 53 % of hospitalisations were due to nephrological or haematological toxicity or thromboembolic events, these latter events not fully preventable. These data confirmed our assumptions of the poor outcomes for these patients and were used for the power calculation of study IV.

Also from study I, we learned about the most frequently reported PRO-CTCAE symptoms grade ≥ 2 and the development of these throughout the course of chemotherapy. The reported PRO-CTCAE symptoms grade ≥ 2 were used in the final item selection process of study III, see manuscript IV.

With the aim to increase our knowledge about QoL as described in our systematic review, the PRO-CTCAE and QoL data from study I and II were combined and provide the basis of manuscripts II and V.

Manuscript II describes with data from study I & II the clinical outcomes and development of symptoms and QoL over the course of chemo- or immunotherapy. In terms of clinical outcomes, we found that the rates of treatment completion and hospitalisation were similar to those initially found for the smaller population in study I and in previous non-BC populations [42, 86, 87]. The rates of treatment cessation and hospitalisation were slightly lower in the neoadjuvant population but remained above 40 % for both outcomes. The high rates of treatment cessation and hospitalisation as a result of intolerable symptoms pinpoint the need for better symptom monitoring in this population. Proactive symptom monitoring for BC patients in neoadjuvant chemotherapy could be especially important as serious declines in QoL or performance status could compromise the patients' possibility of cystectomy. This consideration is particularly important as the overall survival benefit of neoadjuvant chemotherapy is modest (3-16 %) [93-

95] and for patients with serious declines in performance status during chemotherapy, it may be more beneficial to terminate neoadjuvant treatment early thus remaining in a performance status still suitable for cystectomy. In contrast, symptom monitoring could lead to improvement in symptoms and thus secure the full effect of the neoadjuvant treatment. Either way, symptom monitoring for the neoadjuvant population would based on our data seem prudent. For the metastatic population proactive symptom monitoring may affect several different outcomes. First, proactive symptom monitoring may result in improved symptom management leading to longer adherence to treatment thus possibly improving overall survival as seen in the studies by Basch and Denis [41-43]. In contrast, proactive symptom monitoring could lead to earlier cessation of treatment because the impact of toxicity may be captured earlier. For metastatic patients in life-prolonging oncological treatment, the benefits in survival must always be weighed against the impact on QoL. Therefore, earlier capture of symptoms may lead to treatment cessation.

The baseline global QoL data of the metastatic patients was in our study lower than that of the data from previous clinical trials (mean global QoL 54 vs. 60 (Vaughn et al.), 77 (Joly et al.) and 95 (Herman et al.) [96-98]. This difference is not surprising as there are known to be substantial differences between patients in standard treatment and clinical trials [99, 100]. When looking at the QoL development over time we found no clinically or statistically significant differences in global QoL between the two treatment modalities (immunotherapy vs. chemotherapy) at baseline (mean difference -2.4, 95 % CI: -17.5-12.6, p=0.75) or after three cycles of treatment (mean difference -2.9, 95 % CI: -23.4-17.6, p=0.77). This finding is not fully comparable to previous clinical trials as immunotherapy in clinical trials has been compared to second line chemotherapy with inferior response rates than that of cisplatin/gemcitabine which represents the primary chemotherapeutic combination in our study [98]. Thus, patients receiving chemotherapy in our study do not experience deterioration in QoL as in the phase III study by Vaughn et al. [98], please see Figure 13. These data emphasize the need for transparent reporting of more QoL data from real-life settings outside clinical trials. As no direct comparable data exists for the neoadjuvant group we compared our data with Danish and European normative QoL scores and found the scores similar despite a significant symptom burden for the neoadjuvant patients [101, 102].
The stable PRO-CTCAE symptom burden during treatment is along with the decline in urinary symptoms important information for future patients and exemplifies the need for transparent symptom reporting by patients in clinical trials thus enabling full comprehension of the planned treatment and expected toxicity for future patients.

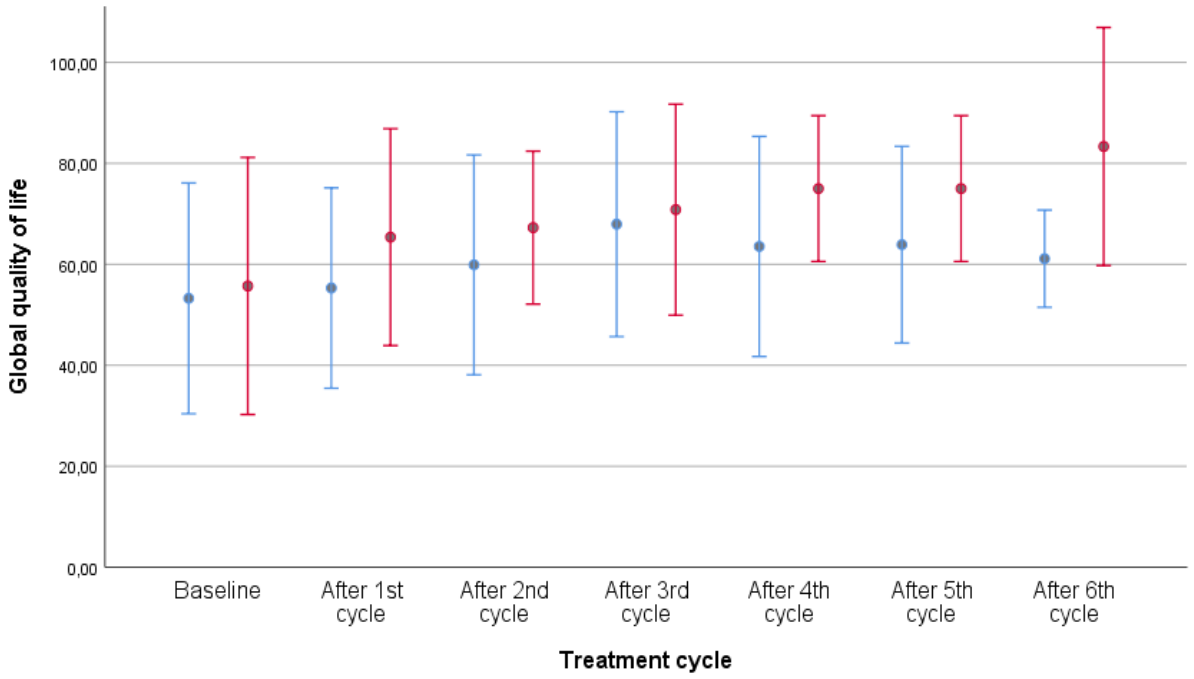

Figure 13. Development of global quality of life during treatment by treatment type, metastatic patients, n=53. Error bars represent ±1 standard deviation (SD). Blue bars: Chemotherapy Red bars: immunotherapy. From Taarnhøj et al., manuscript II.

Throughout the course of treatment 21 % (n=17 of 78) of patients reported a depression score of ≥ 11 by HADS indicating a clinical depression. For 11 of these 17 patients the high score persisted through more than one cycle of treatment thereby at a level comparable to the general population [103]. These developments also applied for anxiety. Fifteen patients scored ≥ 11 by HADS but only two patients had persisting high scores. These numbers may indicate that clinical staff have resources to resolve psychological issues with and for the patients, if the issue is presented to them thereby emphasizing the need for psychological issues to be mapped systematically with PROs. In a paediatric practice, Engelen et al. showed that the use of PROs greatly increased the discussion of psychosocial issues [104] thus strengthening the incentive to incorporate PROs into daily clinic.

These data are of course limited by the small number of patients (n=78) but remain the first real-life data for a bladder cancer population in active oncological treatment. The results support our initial hypothesis of poor clinical outcomes and confirm our further hypotheses of need for better supportive care and symptom monitoring for these patients.

With an aim of learning more about the QoL of bladder cancer patients, manuscript V looked at correlations between the reported PRO-CTCAE single items and all domains of EORTC QLQ-C30. We found that almost all PRO-CTCAE single items had significant correlations with all domains of the EORTC QLQ-C30. Specifically, psychological issues and fatigue showed the strongest correlations

whereas urinary symptoms had the weakest correlations with QoL, including subdomains. Please see Table 6 and Supplementary Table A in manuscript V. Also, our linear regression models with and without the psychological issues from Table 6 informed us that the overall symptom burden correlates with all QoL domains.

Our findings are in agreement with those of Dueck et al. from the initial validation process of the PRO-CTCAE in 2015 in which the EORTC QLQ-C30 was also used as an anchor in the test of construct validity despite the population of patients in the Dueck study being primarily prostate cancer patients [47]. The finding of weak correlations between QoL and urinary symptoms suggests that the urological patients are well prepared for these symptoms, perhaps expecting the worst. In contrast, one could hypothesize, and rightly so [104], that psychological issues do not get as much attention in daily clinic and the patients therefore are less prepared for these symptoms. Our results display that a solitary report of QoL from daily clinic or clinical trial does not cover the full picture of the patients' issues. This conception is supported by previous research indicating that certain QoL instruments may not be sensitive to specific symptom changes or change over time [105, 106]. Likewise, portraying only frequent symptoms, as identified in manuscript II, may not reflect the distress experienced due to less frequent and often psychological symptoms, as supported by a Swiss study exploring the impact of symptoms after surgery for vulvar neoplasia [107]. Depending on the aim of a given clinical trial, a singular report of QoL will either not catch symptoms in risk of progressing to e.g. urinary infections for these patients and/or overlook the psychological reasons for a decrease in QoL. This exemplifies the need for specific PROs into daily clinic as well as into clinical trial reporting as supported by a working group led by the FDA [108]. Many trials have over time reported equal QoL between two arms despite expected large differences between arms [20, 109]. This study highlights the need for incorporation of PROs into clinical trials for a more transparent picture of toxicity and into daily practice for a more individualised approach to symptom management.

While this manuscript, as the first, gives insight into correlations between PROs and QoL for BC patients in chemo- or immunotherapy, the study is limited by the number of patients and multiple responses from especially responders to treatment completing questionnaires for a longer period of time. Also, despite efforts to bring the needs of BC patients forward, these data need validation with qualitative patient and physician interviews.

Very strong (0.8-1)	Strong (0.6-0.79)	Moderate (0.4-0.59)	Weak (0.2-0.39)	Very weak (0-0.19)
	Anxiety F	Abdominal pain I	Blurred vision S	Change in urine colour P
	Concentration S	Decreased appetite I	Chills S	Constipation S
	Discouraged F	Dizziness S	Decreased libido S	Cough S
	Fatigue S	Muscle pain I	Difficulty swallowing S	Diarrea F
	Memory S	Nausea F	Dry mouth S	Hair loss A
	Sad F	Pain I	Dry skin S	Headache I
		Shortness of breath I	Heart palpitations F	Heartburn F
			Hives P	Itching S
			Hot flashes F	Mouth/throat sores I
			Increased sweating F	Pain and swelling at injection site P
			Insomnia I	Painful urination S
			Joint pain I	Ringing in ears S
			Numbness & tingling I	Urinary frequency I
			Rash P	Urinary incontinence F
			Swelling of arms or legs I	Urinary urgency I
			Taste changes S	
			Vomiting F	

Table 6. Summarized Spearman's rank-order correlations between PRO-CTCAE items and EORTC QLQ-C30 domains. PRO-CTCAE items were grouped in the above groups very weak, weak, moderate, strong, very strong if one or more item corresponded accordingly to the expected quality of life domain. Green colour represents agreement in analyses for all patients *and* patients with locally advanced disease *and* metastatic disease when analyzed separately. From Taarnhøj et al., manuscript V.

4.4 Study II

In study II we found that bladder cancer patient despite their disease burden comply well with ePRO completion. Of the 49 patients included in the analysis, the overall completion rate of questionnaires was 75%. The patient compliance remained high until after the sixth cycle of treatment. Only 2/49 (4%) patients withdrew consent to participation during the study, both patients due to problems with log-on into the Ambuflex system from home. Overall, 40 logs by clinicians were detected during the course of the study. When aligning these logs with the patients' visits, a compliance rate of ePRO views by clinicians was detected by 0-50 %, depending on cycle of treatment. No clear development of the clinician compliance was seen over time, illustrated by Figure 14, below:

This study gives real-life insight into the some of the major implementation issues the health care system is facing with the introduction of ePROs. From these data we learned that an elderly and comorbid population of patients are willing and able to report their symptoms during trying treatment, but also that

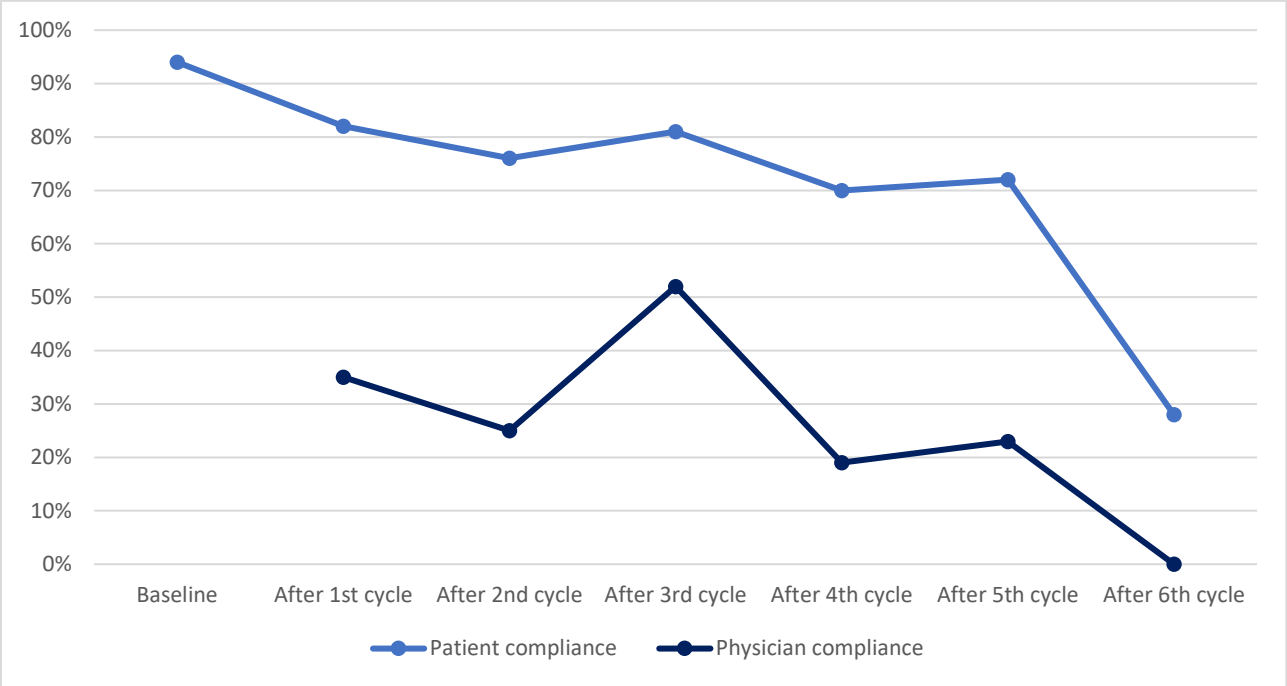

Figure 14. Patient and physician compliance with ePRO completion and views, from Taarnhøj et al., manuscript III.

feedback to their responses is needed to continue symptom reporting. Previous studies have also remarked the need for feedback to patients as a way of obtaining desired outcomes and maintaining patient engagement [37, 110, 111]. These data also illustrate the complexity of ePRO implementation. As mentioned in the introduction, Snyder et al. proposed a framework for PRO implementation in collaboration with an ISOQOL working group. The present study may have come short on the domain concerning the development of strategies for responding to issues identified by the questionnaire. We did not on beforehand develop a framework for the physicians to use in response to troublesome symptoms. Anatchkova et al. performed a systematic review in 2018 from which they report that 47 % of the included studies came short on this issue [112]. To the best of our knowledge, no data exists of the acceptance of such a framework from physicians, thus resulting in our reluctance. This is however an area that needs to be explored and further research is warranted. The low physician compliance may however also have been seen because of physician reluctance due to perceptions that PROs are time consuming during the patient visit or decrease the quality of the care delivered [73, 112]. Also, a couple of recent studies have found the need for 'a physician champion' to engage, inspire and inform fellow clinicians of the benefits and ease of PRO use to secure successful implementation [62, 110]. In the present study, this topic was only partly addressed as the study was conducted at two university hospitals and commenced before the awareness of the importance of such in the implementation process. Finally, problems with physician login into the

Ambuflex system which was integrated into an existing clinical system but at the start of the study was not embedded into the EHR may also have affected the physician compliance [59, 62].
Besides the expansion from one study site to two study sites, from study I to study II, and the familiarity gained by the staff by continuous study enrolment, the learning from this study includes the recognition that the handling of ePROs cannot solely rely on physician view and feedback to patient. This insight has been carried forward in the approach of study IV, please see below.

4.5 Study III

The final item selection process, described in detail in the methods section, resulted in selection of 15 PRO-CTCAE symptoms for weekly use in the bladder cancer population during chemo- or immunotherapy, see Table 7 & 8. As an example of the selection process the symptom 'nausea' was included in the final item set because the symptom was present in three or more of the aligned four columns: nurse focus group, physician focus group, symptoms in relation to hospitalisation and frequent symptoms throughout treatment. In contrast, the symptom 'dry skin' was not included in the final item set as it was only present in two of the four columns and not actionable by clinicians. The final 15 PRO-CTCAE symptoms were: frequent urination, fatigue, nausea, pain, decreased appetite, swelling, insomnia, shortness of breath, constipation, heart palpitations, diarrhea, chills, itching, anxious and vomiting.

This mixed method approach builds upon a wish to involve patients and clinicians in the development of a tool to be used by these exact parties and that has the potential to improve outcomes for the patients and also improve patient-clinician communication and clinician satisfaction with care [37, 39, 113, 114]. We believe that the mixed-methods approach included multiple stakeholders important to our aim. A similar approach has been carried out by Trask et al. aiming at introducing a framework for PRO-CTCAE item selection for clinical trials [57]. In this study the aim was to develop a tool for reporting in clinical trials exemplified by prostate cancer patients. A major difference between this and our study is the involvement of patients in our study and the pharmaceutical industry in the Trask study. This difference demonstrates the importance of methods used in relation to the aim and setting of the tool. The importance of the setting or endpoint a given item set is planned to be used for is also exemplified in the current item selection process. In Table 7, the fourth column represents symptoms reported in relation to hospital admissions. These symptoms are in many cases the 'third' symptom determining the inclusion of the symptom in the final item set, e.g. as is the case with insomnia, constipation and heart palpitations, in accordance with the predefined selection criteria, described in detail in the methods section. These symptoms are thus included without regard to clinician evaluation as the case is with symptoms only mentioned twice in the four columns. Of course, this methodology precludes the

hypothesis of a causal relationship between the core item set end defined endpoint. This hypothesis will however not be tested as part of this PhD.

Focus group interviews		**Overall PRO-CTCAE symptoms grade 2-4 for 29 patients* (listed by falling frequency, %)**	**PRO-CTCAE symptoms grade 2-4 in relation to hospital admission (patients receiving n=13 chemo- / n=7 immunotherapy) ****	**Final included PRO-CTCAE symptom**
Nurses, n=3	**Doctors, n=4**			
Urinary symptoms	Urinary symptoms/catheter problems/infections	Frequent urination (48)	Frequent urination (2)	**Frequent urination**
Fatigue	Fatigue	Fatigue (36)	Fatigue (9)	**Fatigue**
		Urinary urgency (30)		
		Dry mouth (25)	Dry mouth (2)	
Nausea	Nausea	Nausea (22)	Nausea (4)	**Nausea**
Pain	Pain	General pain (22)	General pain (7)	**Pain**
Decreased appetite	Decreased appetite	Decreased appetite (21)	Decreased appetite (4)	**Decreased appetite**
Swelling	Swelling	Swelling (21)	Swelling (5)	**Swelling**
	Insomnia	Insomnia (20)	Insomnia (5)	**Insomnia**
	Shortness of breath	Shortness of breath (19)	Shortness of breath (5)	**Shortness of breath**
	Constipation	Constipation (15)	Constipation (1)	**Constipation**
	Abdominal pain	Abdominal pain (15)	Abdominal pain (5)	
		Sad (15)		
	Heart palpitations	Heart palpitations (14)	Heart palpitations (1)	**Heart palpitations**
		Painful urination (13)		
		Muscle pain (12)	Muscle pain (3)	
Taste changes		Taste changes (12)	Taste changes (3)	
		Decreased libido (11)		
		Urinary incontinence (11)		
	Diarrhea	Diarrhea (11)	Diarrhea (4)	**Diarrhea**
		Chills (11)	Chills (1)	**Chills**
		Cough (10)		
		Headache (10)		
	Neuropathy	Numbness & tingling (9)		
		Dry skin (9)	Dry skin (1)	
		Discouraged (8)		
		Ringing in ears (8)		
		Itching (7)	Itching (1)	**Itching**
Anxiety		Anxious (6)		**Anxious**
		Dizziness (5)		
		Difficulty swallowing (5)		
		Increased sweating (4)		
		Mouth /throat soars (4)		
		Joint pain (4)	Joint pain (1)	
		Heartburn (3)		
		Blurred vision (3)		
		Hair loss (3)		
		Hot flashes/flushes (2)		
	Vomiting	Vomiting (2)		**Vomiting**
		Memory (1)	Memory (1)	
		Concentration (1)	Concentration (1)	
	Weight loss			
	Stomatitis			

Table 7. Final PRO-CTCAE item selection process. From Taarnhoej et al., JPRO 2019.
***Of the 30 patients enrolled in study I, only 29 initiated treatment. ** Of the 27 patients experiencing hospitalisation in study II, only 20 patients had a completed questionnaire in relation to the hospital admission.**

As remarked in the discussion of the pilot study which this study builds upon, the selection of PROs used for study IV may have been influenced by further patient interviews and medical record audits. Also, with introduction of new pharmaceuticals representing different toxicity profiles for the bladder cancer population validation of our final chosen PRO item set will be warranted [25, 26].
Finally, by comparing our 15 symptoms with the 12 symptoms used in the studies by Basch and Denis, as displayed in Table 8, it is clear that large disparities exist between the iBLAD study and the studies by Basch and Denis [42, 43]. These differences may exist due to the differences in the item selection process, of which we know little from Basch and Denis. However, differences may also exist due to the differences in diagnosis (bladder cancer, mixed metastatic disease and lung cancer) and primary endpoints of the three studies which are different for all three studies (iBLAD: hospitalisation and completion of treatment, Basch: quality of life, Denis: overall survival). The bladder cancer population may benefit from this difference as treatment and population specific questions as presented in the current study III would be expected to capture actionable symptoms more efficiently than e.g. symptoms related to an endpoint as quality of life that in our manuscript V are of a more psychological and cognitive nature. Contrarily, the mixed metastatic cancer population in the study by Basch benefitted remarkably well from a generic questionnaire. The hypothesis, as supported in manuscript V, that a generic questionnaire with symptoms shown to have moderate or strong correlations with QoL when QoL is the primary endpoint as in the Basch study underlines the importance of coherence in choice of methods and endpoints for PRO trials. One could argue that because the Basch study performed well not only in terms of QoL but also showed fewer hospitalisations and longer survival for the intervention arm, the generic questionnaire is preferable [41]. Nonetheless, several generic questions could be generated, as illustrated by the difference between the generic questionnaire introduced by Basch et al. in 2012 versus the generic questionnaire used in the randomized trial results published in 2016 [42, 51]. QoL and overall survival are secondary endpoints in the iBLAD study and will be assessed as part of the analysis after study completion and evaluated against the findings of Basch and Denis.
Planned as a systematic approach to involve patients and caregivers while taking treatment modalities into account, we do believe out final item set has a place in the bladder cancer population receiving medical oncological treatment.

iBLAD Locally advanced and metastatic bladder cancer	**Basch** [42] Mixed metastatic cancer	**Denis** [43] Locally advanced and metastatic lung cancer
Anxious		
Chills		Fever
Constipation	Constipation	
Decreased appetite	Appetite loss	Appetite loss
Diarrhea	Diarrhea	
Fatigue	Fatigue	
Frequent urination	Dysuria	
Heart palpitations		
Insomnia		
Itching		
Nausea	Nausea	
Pain	Pain	Pain
Shortness of breath	Dyspnea	Breathlessness
Swelling		Face swelling
Vomiting	Vomiting	
		Blood in sputum
	Cough	Cough
	Neuropathy	
	Hot flashes	
		Lump under skin
		Depression
		Weakness
		Weight

Table 8. Comparison of PRO symptoms used as interventions in three randomised patient-reported outcome trials. Green colour represents agreement across all three randomized trials, yellow represents agreement in two of the three randomised trials.

4.6 Study IV

The randomized trial commenced enrolment at Rigshospitalet and Herlev Hospital 22 January 2019. Due to interest in the project the study opened up for enrolment at Aalborg University Hospital in April 2019 and at Odense University Hospital in May 2019. The study is still enrolling patients and is forecasted to have completed enrolment in October 2020 after enrolment of 230 patients in the study.

The study is until now enrolling as planned:

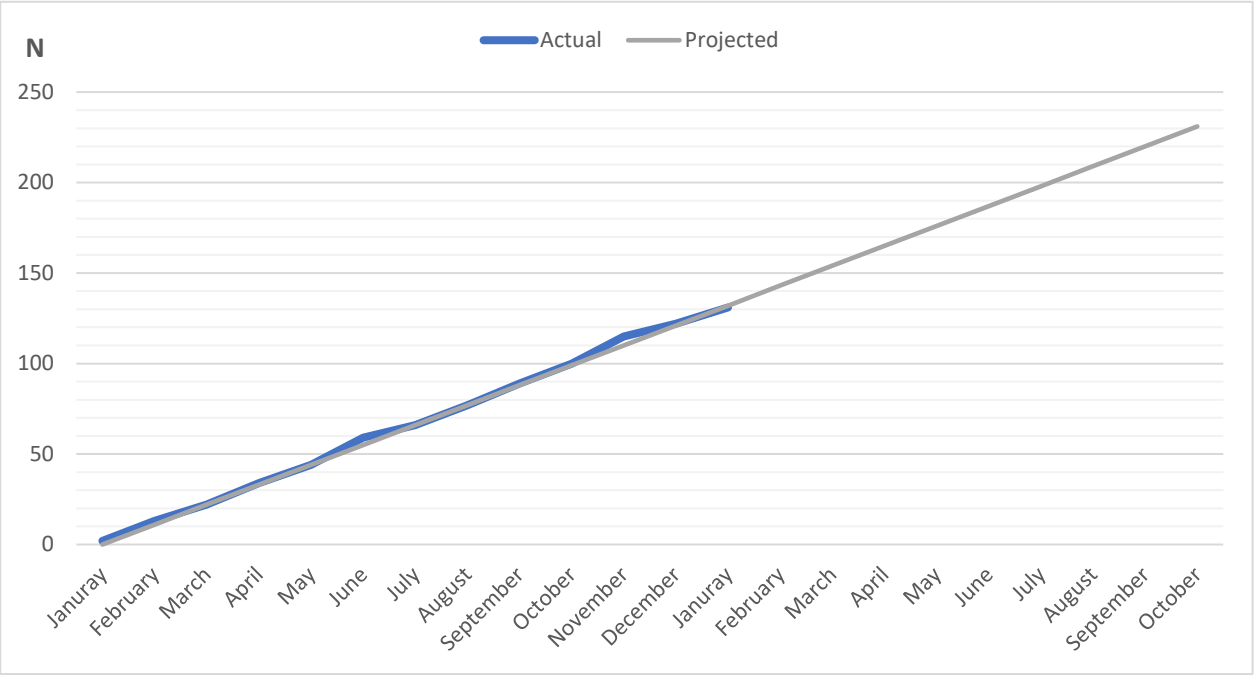

Figure 15. Recruitment diagram of study IV per 04.02.20.

Preliminary data from patients enrolled per 04.02.20:

Clinical data	All patients N=131	Intervention arm N=75	Control arm N=56
Gender			
Male	101	57	44
Female	30	18	12
Median age (years, range)	69 (40-87)	69 (45-87)	69 (40-86)
Disease stage			
Locally advanced	49	25	24
Metastatic	82	50	32
Treatment			
Cisplatin+gemcitabine	72	42	30
Carboplatin+gemcitabine	17	9	8
Vinflunine	1	1	0
Pembrolizumab	41	23	18

Table 9. Clinical data of patients enrolled into the randomized iBLAD study per 04.02.20.

5

Conclusions & Perspectives

This PhD delivers new knowledge about and to the bladder cancer population. From our systematic review we have documented the lack of real-world evidence for BC patients receiving active medical oncological treatment. The QoL and PRO data from study I and II initiates to fill this gap in knowledge. Also, the most frequent PROs during treatment have been identified and the relationship of these PROs with all domains of QoL have been established. This knowledge has the potential to be incorporated into daily clinic and clinical trials to improve supportive care and toxicity reporting during oncological treatment. Electronic symptom reporting by this elderly and comorbid BC population is feasible but the involvement of clinicians in this process requires integration of the active use of PROs into the clinical guidelines and endorsement by management. The developed PRO item set for regular symptom reporting during treatment is the first of its kind in the BC population and we believe it has a place in the treatment of BC patients, although validation of the tool is warranted.

Although there is a growing interest from policy makers to integrate PROs into daily practice and employ the potential of PROs in terms of more efficient health care, we believe that the data from this PhD is adding important information of how to achieve appropriate use of PROs in a given population. Sceptics will worry that more efficient health care with PROs impairs the quality of the care delivered, perhaps rightly so as the literature not only informs us of the gains by introducing PROs but also displays the apparent hurdles and short-comings in terms of IT software challenges and clinician scepticism [54, 73, 115]. Especially, overcoming the clinician scepticism is important as the success of PROs in daily clinic relies on engaged clinical staff and the process of PRO integration should thus respect the end users who ultimately are key to achieving the proclaimed benefits [62, 110]. Therefore, qualitative and quantitative literature unique to specific settings and populations is essential. One size does not fit all and structural changes to the health care system debilitating the quality of care are not in the patients' interests despite an eagerness to move forward and embrace new tools and technologies. The data of this PhD may assist the planning of PROs to be used in the bladder cancer population while the methods employed may inspire this planning in other cancer populations. However, evaluation of the ongoing study IV will determine to which extent the designed intervention in study III addresses the supportive care needs of the bladder cancer population as laid forward in manuscript II.

5.1 Strengths and limitations

The strengths of the studies included in this PhD include the systematic and prospective collection of data with the mixed-method approach thereby involving patients, clinicians and authorities. Patient-reported outcomes can potentially be used in many settings and this PhD displays the need for them, not only in daily practice but also in clinical trials. Without the involvement of all parties, we cannot have sufficient faith in the conclusions but more importantly, implementation into daily clinic will most likely fail if new procedures for work flow are not developed with and endorsed by the end users [116].

While this PhD brings new knowledge to the field of patient-reported outcomes and bladder cancer, there is still a need for validation of our results. Especially the QoL and PRO data from study I and II require validation due to the limited number of patients. This validation will be made with data from the ongoing study IV. Also, due to the required inclusion criteria of existing e-Boks communication in study II, a number of patients were not able to participate. These patients were most likely elderly patients or patients with impairments of physical or cognitive nature in accordance with the e-Boks exemption rules [75]. Our data is therefore not a mirror reflection of the true BC population. Requirements to data protection according to the General Data Protection Regulation demands two-factor log-in, e.g. through e-Boks, thus disabling non-e-Boks users of participating in the completion of ePROs. Interactive voice response (IVR) systems are a way of bypassing the electronic communication path and is widely used in the U.S where a large part of the population lives in an area scarce of internet signal [117]. This approach could secure input from even the most vulnerable patients; however, real-time on-screen feedback would be lost thus creating the need for a clinic-driven feedback system by allocated clinical personnel. However, with the aging of the Danish population, the number of citizens exempt from e-Boks use will diminish over time thus eliminating the problem. This does however not obliviate the fact that our data did not include data from non-participants and non-responders who are known to have poorer outcomes thereby failing to help the most vulnerable patients with the introduction of ePROs in Denmark [118-120].

Also, the low clinician compliance in study II determined by several possible factors demands awareness. As a result of the low compliance, Study IV was planned to decrease the burden on the physicians through increased patient involvement by real-time alerts on-screen for the patients instead of allocated personnel responding to alerts as in comparable previous studies [42, 43, 121]. This methodology was also considered for possible subsequent implementation following the results of study IV, as the health care system in Denmark, as in other countries, is under pressure and may not be able to allocate clinical personnel to the task. Having stated this, higher clinician compliance may likely only be achieved by endorsement of PROs in daily clinic by management and concurrent incorporation into the clinical guidelines [59, 62]. Likewise, endorsement by clinicians conceivably requires more quantitative data of the benefits in terms of work flow gained by the use of PROs in daily clinic to supplement the vast body of qualitative literature [73, 111, 113, 122].

Finally, although developed by a thorough mixed-methods approach, the final PRO item core set in manuscript IV is vulnerable to the dynamics of changes in the treatment options for BC patients. As such, a number of phase III trials with targeted and antibody conjugate treatments are currently underway and expected to change the landscape of treatment for BC patients [25, 26, 123]. With such a transition our tool will need re-evaluation and validation. Furthermore, while aiming to create a tool implementable in daily practice as well as in clinical trials we only included data from therapeutic agents used for urothelial cell carcinoma thereby leaving out possible toxicities from treatment of small-cell and neuroendocrine carcinomas of the bladder. Our PRO item set is not developed for use in this population and these subtypes of bladder cancer therefore continue to be understudied, although some toxicities may likely be the same.

5.2 Clinical implications of the studies

There are several clinical implications of the findings of this PhD. First, the systematic review highlights an area into which little attention has been paid until now. The review documents the BC patients as an understudied population and given the high incidence of the disease, further research in terms of real-life data is needed. Manuscript II delivers important insight into the clinical outcomes of BC patients during treatment with chemo- or immunotherapy and highlights a population of patients in need of intensified supportive care. Especially the reports of high rates of treatment discontinuation and hospitalisation concordant with previous literature from the metastatic BC population are alarming and exemplifies a possible benefit from concurrent QoL reports [30, 124] thereby capturing serious declines in QoL before performance status is irreversibly impaired thus securing the quality of survival for patients in life-prolonging treatment [125]. For these QoL reports to carry weight more real-life data from the BC population in standard treatment is required. Manuscript V illustrates the necessity of knowledge for full comprehension of symptomatology and QoL reports. Due to the somewhat surprising findings in this study of minimal correlations between urinary symptoms and QoL concurrent with strong correlations between psychological items and QoL, we urge for more comprehensive reports of toxicity in both clinical trials and daily clinic.

Moreover, the documentation of the most frequent PROs for this population in manuscript II could act as a source for comparison when evaluating new treatments in clinical trials or inform the patients more extensively of what to expect during standard treatment. As such, validation of our findings seems prudent. In perspective, aggregated QoL and PRO data may serve not only authorities as it has been the tradition in the past, but also inform the clinician of mean aggregated values while giving feedback on individual values as a way of shared-decision making [126, 127]. More specifically, a patient scoring low on physical function prior to initiating new oncological treatment could be informed of the prognostic value of such in relation to the treatment, thus enhancing communication of the real value of the treatment for the

specific patient [128]. The use of PROs as prognostic tool is not a new discipline, baseline QoL and specific PROs have in previous studies shown to be prognostic for survival in various cancer populations as well as in a recent systematic review [128-131]. While engaging patients in their own treatment course it becomes inescapable that all PRO data should be utilized to the benefit of the patient as well as the clinicians, administrators and authorities. A setup as described requires authority involvement to secure IT logistics and juridical endorsement [59]. The present PhD has maneuvered between these pillars of efficient PRO delivery and has required daily study management to achieve continuous involvement of all parties. This personnel-heavy structure may not be directly implementable into daily clinic but must in essence continue into daily clinic in order to achieve the prespecified objectives. In conclusion, the delivery of PROs may not be a way of reducing costs of health care but could improve the health care service delivered [37, 111]. These considerations are of course not unique to the field of cancer. This PhD should underline the complexity of PRO integration into health care altogether and be considered in the planning processes of such.

Through the conduction of this PhD old and new collaborators have taken interest into the final PRO item set for use during treatment. In the planning of new clinical trials it is therefore our hope that the Danish Bladder Cancer Group (DaBlaCa) and Dr. Matthew Milowsky as the Section Chief of the Genitourinary Oncology Service of the Bladder Cancer Advocacy Network in the U.S. will validate our findings from study III in national clinical trials or collaborate in the development of amendments to the item selection tool following introduction of new therapeutic drugs for the BC population.

While the planning of this PhD started in 2016 more recent studies have aided us in the planning of study IV. The survival results achieved by Basch et al. were hypothesized contributed to sustaining patients in treatment by improved symptom management and hence physical function [41]. We carried this hypothesis with us in the planning of study IV. However, as touched upon earlier, the direction of results for the BC population in the iBLAD study may go in either direction in terms of treatment duration. Earlier symptom management may in this population in contrast to the mixed metastatic cancer population in the study by Basch et al. lead to earlier treatment cessation because of the progressive nature of the disease and comorbid BC population but while doing so hopefully sustaining or improving the quality of life for these patients. Finally, it is also possible that our planned intervention will not have an effect in any direction. If so, an explanation for this can be that the involvement of the patients with the responsibility to act upon their own symptoms by alerts given on-screen with the aim of increasing self-efficacy will fail. One may hypothesize that the patient group is not capable or even willing to take on this responsibility or that this patient-led intervention simply cannot work in any patient population. We do not have evidence comparing an intervention as ours vs. a more clinic driven intervention as in the studies by Basch and Denis. The allocation of a study coordinator or nurse at each site responding daily to the alarming PROs

as in the Basch and Denis studies may reveal to be a necessity in obtaining predefines outcomes in PRO studies. However, a previous randomized study in a mixed breast and prostate cancer population based on electronic self-monitoring and interactive patient information and engagement succeeded in showing a difference in the chosen primary outcome of distress but failed to show any other statistically significant changes for the patients, although the trend was in favour of the intervention group [132]. Therefore, exploring the undiscovered potential in interactive interventions as in the iBLAD study may despite the difference in setup from the Basch and Denis study have a place in the health care landscape in the future. Concerning comparison of the specific items as mentioned in the results section nine symptoms from the Basch study align with symptoms in the iBLAD study. One would therefore not expect the difference of three symptom items to affect the outcome. Also, as in the Denis and Basch studies both first authors have as clinicians employed themselves as the physician champion mentioned in the literature to be vital for any PRO implementation [62, 110]. In respect of the end-users, we believe that this is a central point in achieving benefits in PRO studies. In the current study this has been sought attained by one or two key clinicians at all sites. If study IV does not show significant differences for the intervention group, the next step may be exploring *why* the intervention did not work and plan a new study in the same population as this population is in crucial need of extended supportive care as supported by the data in manuscript II. The results of study IV will be presented following inclusion and follow up of last enrolled patient expected in October 2020.

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APPENDICES A-E

APPENDIX A

Manuscript I: **Taarnhøj GA**, Johansen C, Pappot H. **Quality of life in bladder cancer patients receiving medical oncological treatment; a systematic review of the literature**. Health Qual Life Outcomes. 2019 Jan 22;17(1):20. PubMed PMID: 30670040.

APPENDIX B

Manuscript II: **Taarnhøj GA**, Lindberg H, Johansen C, Pappot H **Patient-reported outcomes and quality of life in bladder cancer patients receiving chemo- or immunotherapy; a real-life experience.** Under review in Cancers 24.02.20.

APPENDIX C

Manuscript III: **Taarnhøj GA**, Lindberg H, Dohn LH, Omland LH, Hjøllund NH, Johansen C, Pappot H. **Electronic reporting of patient-reported outcomes in a fragile and comorbid population during cancer therapy - a feasibility study.** Under review in Health and Quality of Life Outcomes 19.11.19.

APPENDIX D

Manuscript IV: **Taarnhøj GA**, Lindberg H, Johansen C, Pappot H. **Patient-reported outcomes item selection for bladder cancer patients in chemo- or immunotherapy**. J Patient Rep Outcomes. 2019 Aug 22;3(1):56. PubMed PMID: 31440865.

APPENDIX E

Manuscript V: **Taarnhøj GA**, Johansen C, Lindberg H, Basch EM, Dueck A, Pappot H. **Patient reported symptoms associated with quality of life during chemo- or immunotherapy for bladder cancer patients with advanced disease.** Accepted for publication in Cancer Medicine 19.02.20.