Quality of life in newly diagnosed bladder cancer patients

by

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Abstract

It has been postulated that bladder cancer impacts health-related quality of life (HRQoL), but research is limited. This research is particularly important as survival for non-muscle invasive bladder cancer (NMIBC) is high, and these patients will need to live with acceptable HRQoL for many years. I investigated HRQoL in 1258 muscle invasive bladder cancer (MIBC) and NMIBC patients participating in the Bladder Cancer Prognosis Programme.

Although I found no major difference in HRQoL around time of diagnosis between NMIBC and MIBC patients, I did find that different parts of HRQoL seemed to influence survival of NMIBC and MIBC. Also, patients prefer an invasive but accurate cystoscopy over a hypothetical non-invasive but less accurate urinary biomarker. Additionally, the European Organization of Research and Treatment of Cancer (EORTC) developed a quality of life questionnaire specifically for NMIBC (EORTC NMIBC-24). In this thesis, I have strengthened the structure of this questionnaire that was previously published by another UK research group. Finally, I found only a small difference in physical health between patients with incontinent and continent urinary diversion in a meta-analysis.

These findings were discussed in each of the results chapters, and put into wider context in the general discussion chapter.

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Publications arising from this thesis

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Health-related quality of life around time of diagnosis in bladder cancer patients.

Duncan Nekeman, Neil Aaronson, Lucinda Billingham, Richard Bryan, KK Cheng, Nicholas James, Maurice Zeegers.

The effect of baseline quality of life on bladder cancer survival: results from the bladder cancer prognosis programme.

Duncan Nekeman, Lucinda Billingham, Neil Aaronson, Richard Bryan, KK Cheng, Nicholas James, Maurice Zeegers.

Validation of the EORTC QLQ-NMIBC24, a quality of life questionnaire for non-muscle invasive bladder cancer patients.

Duncan Nekeman, Lucinda Billingham, Richard Bryan, KK Cheng, Nicholas James, Maurice Zeegers, Neil Aaronson.

Patients choose certainty over burden in surveillance for bladder cancer recurrence.

Duncan Nekeman, Lucinda Billingham, Neil Aaronson, Richard Bryan, KK Cheng, Nicholas James, Maurice Zeegers.

The quality of life of bladder cancer patients undergoing incontinent and continent urinary diversion techniques: a meta-analysis of 18 observational studies.

Duncan Nekeman, Maree Brinkman, Maurice Zeegers.

Presentations of work

Oral presentation of early results of Chapter 7 at the PhD tour between Maastricht University and Birmingham University at Birmingham University, 2012.

Poster presentation of Chapter 7 at the 28th annual European Association of Urology meeting in Milan, 2013.

Poster presentation of Chapter 7 at Workgroup Epidemiological Research Netherlands (WEON) in The Netherlands 2013.

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CHAPTER 1 - INTRODUCTION

1.1 Health-related quality of life

Historically, scientific research and medicine have focused on objective outcome measurements such as, mortality, cured (yes or no), blood pressure, et cetera. However, the World Health Organization (WHO) has included a focus on mental well-being as part of their definition of health: '*a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity*'.[1] Over time, patients and clinicians have had increasingly more treatment options to choose from for the same disease. Furthermore, many of these treatments do not differ much in outcome improvement, but rather differ in the impact on the patients' well-being. This increased variety in treatment options and the emphasis on mental well-being in the WHO definition of health has made patient well-being an important factor in the decision-making process.

Patient well-being has long been considered subjective and difficult to measure objectively. It is therefore not a well-defined concept and is often left open for interpretation. Over the years, different terminology has been proposed to encompass this concept from 'happiness' to 'health'. Nowadays, 'quality of life' is the most commonly used terminology, although it is still not clearly defined. Usually a differentiation is made between general quality of life and health-related quality of life, where general quality of life encompasses a broader sense of the concept and health-related quality of life relates only to the quality of life aspects, which are affected either by illness or the treatment thereof. Despite the lack of a uniform definition, it is generally accepted that health-related quality of life is a multi-faceted concept, which usually includes a physical, psychological and social aspect.

1.1.1 Measuring health-related quality of life

Health-related quality of life is a patient-reported outcome that is usually measured by means of questionnaires or semi-structured interviews. These questionnaires can differ greatly in number of items (single item vs multi-item), number of domains (single domain vs multi-domain), and measured outcome (general health-related quality of life vs disease-specific health-related quality of life).[2] This multitude of questionnaire types has resulted from a lack of standardization of measuring health-related quality of life. The lack of overall standardization of measurement may not necessarily be an issue. For example, general health-related quality of life questions may not be appropriate to adequately outline the extent of discomfort a disease or treatment brings to a patient, whereas disease-specific health-related quality of life questions may be very useful in quantifying such discomfort.

1.1.2 Quality of life questionnaires

Various quality of life questionnaires (general and disease-specific) have been validated in multiple studies and different populations. This paragraph briefly describes the available types of questionnaires.

Single domain questionnaires are meant to measure only one domain, usually general health-related quality of life (or one of its components: psychological or physical well-being). Single domain quality of life questionnaires are usually quite short, easy to analyze and interpret, and therefore easy to incorporate in studies.[3] They may also be used for a simple comparison between quality of life in patients and non-patients or even with patients suffering from a different disease. However, if general health-related quality of life is measured in a single domain, it is not possible to distinguish between

the different components (psychological vs physical). Furthermore, this may also lead to a "dilution" of the health-related quality of life. For instance, the overall health-related quality of life score may not be heavily affected if only one domain is negatively affected by the disease or treatment, while all other aspects are not. Yet the domain in question may weigh heavily in the patient's life. Another accompanying problem of single domain quality of life questionnaires is that they do not allow for identifying *why* a group of patients reports a lower health-related quality of life in a particular aspect. For instance, if bladder cancer patients would score lower on physical functioning it would be impossible to distinguish if this was due to reduced activity or perhaps urinary problems. In many situations, multi-domain questionnaires are therefore preferred.[4]

One of the most frequently used multi-domain quality of life questionnaires is the Short Form health survey (SF-36). This is a general health-related quality of life questionnaire, which contains 36 questions that measure 8 domains (Vitality, Physical Functioning, Bodily Pain, General Health Perceptions, Physical Role Functioning, Emotional Role Functioning, Social Role Functioning, Mental Health). The FACT-G is a 27-item compilation of general questions divided into four primary QOL domains (Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being). The main topic of this thesis is the quality of life in bladder cancer patients. Therefore, the work described in this thesis will mainly include the EORTC QLQ-C30, a 30-item general cancer questionnaire measuring 15 domains, and its additional disease-specific questions for non-muscle invasive bladder cancer patients (QLQ-NMIBC24). The EORTC QLQ-C30 will be described in more detail in Chapter 2, and the QLQ-NMIBC24 will be further described in Chapter 6.

1.1.3 The importance of measuring health-related quality of life

There are four main reasons why it is important to measure health-related quality of life in medical research: 1) quantifying the impact of disease burden; 2) inter- and intrapatient population comparisons; 3) assessing the effectiveness of medical interventions; and 4) improving patient-clinician communication.

It is hard for anyone not suffering from a specific disease to imagine the burden of that disease. Health-related quality of life research attempts to quantify this very subjective matter into an objective measure. As mentioned earlier, this is important in decision-making as historically most research was done in the most prevalent diseases, irrespective of the patient-perceived impact of the disease. Therefore, even though a disease might not be as prevalent, if the patient-perceived impact of the disease is significant, this should warrant enough cause for investigation. Assessing and objectively measuring health-related quality of life in patients is important in order to develop a better understanding of the impact of the disease. However, it may be even more valuable to compare health-related quality of life within and between patient populations. For instance, comparison amongst bladder cancer patients would provide insight into health-related quality of life of an individual patient compared with an average health-related quality of life in similar patients. Additionally, comparing bladder cancer patients in different hospitals or countries could allow for an evaluation of the impact of standard care in different settings. Comparison between bladder cancer patients and other cancer patients would provide information regarding the patient-perceived impact of each disease.

Recently, the scientific and medical communities have become more aware of the potential impact of health-related quality of life on health outcome and/or effectiveness

of treatments. Research has shown that lower health-related quality of life is associated with a higher mortality in the general adult population[5], in those with chronic diseases such as chronic liver disease[6], cancer in general[7], and bladder cancer specifically[8]. It is therefore all the more important that clinicians are aware of patient health-related quality of life in order to select the most effective treatment that has the least negative impact on patient quality of life. This additionally has an impact on the quality of care as suggested by Saunders et al (2015).[9] patients with a more severe condition and thus overall a poorer health-related quality of life have a worse perceived quality of care. Measuring the health-related quality of life would allow for specific (targeted) additional support.

1.2 Epidemiology of bladder cancer

Bladder cancer was the 9th most common cancer worldwide according to GLOBOCAN 2012 records. According to this data, about 430,000 new cases were identified and 165,000 bladder cancer patients died in 2012 alone. Bladder cancer is 3 to 4 times more common in men than in women, and most common in patients between 60 and 80 years old. Bladder cancer is uncommon for people younger than 50 and very rare for people under 40.

Additionally, Caucasians have the highest risk of getting bladder cancer, about twice as high as people of African descent, while people of Asian ethnicity have the lowest risk. Bladder cancer rates are significantly higher in more developed countries (Canada, Belgium, Norway, etc.), with Age Standardized Rates (ASR) of approximately 15 per 100,000, compared with less developed countries (Brazil, Chile, Thailand, etc.) where

ASRs of about 4 per 100,000 have been reported. Smoking is the number one lifestyle risk factor for bladder cancer with a 3.5 times higher risk of getting bladder cancer for somebody who smokes compared to somebody who never smoked.[10] Additionally, occupational carcinogen exposure still accounts for 5-6% of all bladder cancer cases.[11] Of these cases, the highest incidence was found in occupations in which workers are exposed to aromatic amines.[12]

1.2.1 Diagnosis

Most patients present to their general practitioner with haematuria (blood in their urine). The general practitioner will refer them to a haematuria clinic or a urology department, usually after an internal examination. The gold standard for bladder cancer diagnosis is cystoscopy, where a small camera is inserted into the urethra, which can be done under local or general anaesthesia. If any abnormalities are found, the clinician will take biopsies in order to make a diagnosis. After the diagnosis has been made depending on the stage the bladder cancer is at additional diagnostic instruments are used. For instance an ultrasound scan and computer tomography may be used to determine whether the cancer has spread beyond the bladder.[13]

1.2.2 Staging

Bladder tumours can be categorized in three main histological types: transitional cell bladder cancer, squamous cell cancer, and adenocarcinoma. Transitional cell bladder cancer, occasionally also called urothelial cancer, first develops in the bladder lining and makes up 90% of bladder cancer cases. Squamous cell carcinoma and adenocarcinoma

are rare types of cancer that account for about 5% and 1-2% of bladder cancer cases in the UK, respectively. The former is more prevalent in developing countries, like for instance Egypt where rates of a worm infection called bilharzia or schistosomiasis are high.[14] However, it seems that as the infection rate is declining so is the high number of squamous cell carcinoma, at least in Egypt.[15] Due to the rarity of these types of cancer in the UK this thesis will focus on transitional cell bladder cancer exclusively.

Bladder tumours are staged according to the Tumour Node Metastasis (TNM) system that is used for all cancers, which can be found in Table 1.1.[16]

Table 1.1 TNM classification for bladder cancer tumours

Primary tumour (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ: "flat tumour"
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscularis propria
T3	Tumour invades perivesical tissue
T4	Tumour invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
Lymph nodes (N)	
NX	Lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)
N2	Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node metastasis)
N3	Lymph node metastasis to the common iliac lymph nodes
Distant metastasis (M)	
MO	No distant metastasis
M1	Distant metastasis

When the tumour is confined to the bladder lining and connective tissue (<pT2) it is called non-muscle invasive (superficial) bladder cancer, which is prevalent in about 75% of bladder cancer patients. The remaining 25% has a tumour that has progressed into the muscle tissue (muscle invasive bladder cancer, ≥pT2).

1.2.3 Grading

The grade of the bladder tumour refers to the aggressiveness of the cancerous cells. Mostly three categories are used:

- Papilloma, also called benign papillary urothelial neoplasm of low malignant potential (PUNLMP)), which is well differentiated and not likely to progress, however it might recur.
- Low grade, which is more likely to recur and progress than papilloma.
- High grade, which is poorly differentiated and most likely to recur and progress.[16]

1.2.4 Treatments and effectiveness

Treatment of bladder cancer depends mostly on the stage at which the bladder cancer is diagnosed. For non-muscle invasive bladder cancer, the tumour(s) are usually removed during the cystoscopy, in which case diagnosis and treatment could happen at the same time. This type of treatment is usually followed by a single dose of intravesical chemotherapy in order to minimize chances of recurrence. If however histology determines that the tumour is not well differentiated, called low grade, then the doctor will usually decide to continue chemotherapy for six weeks. Moreover, if the tumour is poorly differentiated, called high grade, or pTis (Carcinoma in situ) then the most likely treatment is Bacillus Calmette-Guerin (BCG) vaccine into the bladder for six weeks, or longer depending on the effectiveness. [17]

For muscle invasive bladder cancer the two main treatment options are: surgery or radiotherapy (with or without chemotherapy).[18] With regards to oncologic outcome the

two treatments are similar. However, radiotherapy is not recommended when: pTis is present, the cancer is not responding to initial chemotherapy, the cancer is blocking both of the ureters. Surgery can be performed in two ways, the removal of the entire bladder or only part of the bladder, although this is not usually advised.

For bladder cancer that has advanced beyond the bladder, a combination of the two treatments is used, surgery and radiotherapy. Depending on how far the bladder cancer has advanced (for instance into bone) even more treatments can be combined.

1.3 Health-related quality of life – knowledge gaps in bladder cancer research

During the last several decades, there have been an increasing number of health-related quality of life studies involving cancer patients, particularly bladder cancer patients, a representative selection of which can be found in Table 1.2, Table 1.3, and 0. By far, most of these studies have been cross-sectional or retrospective studies as can be seen when comparing Table 1.2 with Table 1.3. Understandably, as these types of studies require far less resources to undertake compared with prospective cohort studies and clinical trials. However, they pose a number of disadvantages. For instance, they cannot take into account measures of health-related quality of life before or at diagnosis and are inherently subject to bias. Additionally, health-related quality of life research in bladder cancer has been focused primarily at muscle invasive bladder cancer patients as these patients' health-related quality of life is more severely affected than that of non-muscle invasive bladder cancer patients as can be seen when comparing the number of studies in Table 1.2 and Table 1.3, compared to 0. However, health-related quality of life is

arguably even more important in non-muscle invasive bladder cancer patients, where survival is relatively high. It can therefore be argued that non-muscle invasive bladder cancer patients bear the burden of the disease and any decrease in health-related quality of life for a much longer period of time than muscle invasive bladder cancer patients. Not only is it important to quantify the health-related quality of life in bladder cancer patients, it is also important to identify possible alternatives for the invasive cystoscopy, which could impact health-related quality of life.

As mentioned before, another common issue in previous research is the use of myriad quality of life questionnaires, making comparisons between different studies very difficult, if not impossible. For example, the large variety in quality of life questionnaires has prevented researchers from performing the much-needed meta-analysis to identify a urinary diversion technique, which is associated with the least decrease in health-related quality of life. Additionally, the few quality of life questionnaires that are specifically targeted at bladder cancer patients have not yet undergone extensive validation. Finally, recent studies have indicated that health-related quality of life may be a predictor of cancer survival, but more research is needed.[19-21]

Table 1.2 Prospective cohort studies of Muscle-Invasive Bladder Cancer patients

Author (year)	**Country**	**N**	**QoL measure**
Americas			
Anderson et al. (2012)[22]	United States	190	FACT-VCI
Europe			
Hardt et al. (2000)[23]	Germany	44	SF-36
Ferriero et al. (2009)[24]	Italy	38	QLQ-C30
Ferriero et al. (2010)[25]	Italy	62	QLQ-C30
Jerlstrom et al. (2010)[26]	Sweden	38	QLQ-C30
Mansson et al. (2007)[27]	Sweden/Egypt	61	FACT-BL, FACT-G & HADS
Asia			
Singh et al. (2014)[28]	India	164	QLQ-C30

Table 1.3 Cross-sectional/retrospective studies of Muscle-Invasive Bladder Cancer patients

Author (year)	Country	N	QoL measure
Americas			
Allareddy et al. (2006)[29]	United States	56	FACT-BL
Dutta et al. (2002)[30]	United States	72	SF-36 and FACT-G
McGuire et al. (2000)[31]	United States	92	SF-36
Europe			
Hobisch et al. (2000)[32]	Austria	102	QLQ-C30
Bastian et al. (2004)[33]	Germany	41	QLQ-C30
Erber et al. (2012)[34]	Germany	261	QLQ-C30
Severin et al. (2010)[35]	Germany	57	QLQ-C30
Singer et al. (2012)[36]	Germany	530	QLQ-C30
Protogerous et al. (2004)[37]	Greece	58	QLQ-C30
Vakalopoulos et al. (2011)[38]	Greece	39	SF-36
Autorino et al. (2009)[39]	Italy	79	SF-36
Sogni et al. (2008)[40]	Italy	34	QLQ-C30
Mansson et al. (2000)[41]	Sweden	66	QLQ-C30
Mansson et al. (2002)[42]	Sweden	80	FACT-BL & FACT-G
Ohrstrom et al. (2006)[43]	Sweden	11	SF-36
Pazooki et al. (2005)[44]	Sweden	27	QLQ-C30
Philip et al. (2009)[45]	United Kingdom	52	SF-36
North-Africa			
Abdelwahab et al. (2010)[46]	Egypt	25	QLQ-C30
Asia			
Arata et al. (2007)[47]	Japan	78	QLQ-C30
Fujisawa et al. (2000)[48]	Japan	56	SF-36
Hara et al. (2002)[49]	Japan	85	SF-36
Harano et al. (2007)[50]	Japan	59	SF-36
Kikuchi et al. (2006)[51]	Japan	49	FACT-BL
Miyake et al. (2002)[52]	Japan	52	SF-36
Miyake et al. (2010)[53]	Japan	80	SF-36
Miyake et al. (2012)[54]	Japan	32	SF-36
Saika et al. (2007)[55]	Japan	109	QLQ-C30
Takenaka et al. (2011)[56]	Japan	86	SF-36
Yoneda et al. (2005)[57]	Japan	48	SF-36

Table 1.4 Prospective cohort studies and cross-sectional/retrospective studies measuring Health-Related Quality of Life in Non Muscle-Invasive Bladder Cancer Patients

Author (year)	Country	N	QoL measure
Prospective cohort studies			
Bohle et al. (1996)[58]	Germany	30	MLDL
Schmidt et al. (2015)[59]	Spain	244	SF-36 & BCI
Cross-sectional/Retrospective studies			
Singer et al. (2012)[36]	Germany	210	QLQ-C30

1.4 Aim of this thesis and research questions

Therefore, the aim of this doctoral thesis is to investigate health-related quality of life around time of diagnosis in bladder cancer patients (Chapter 4) and how this relates to bladder cancer survival (Chapter 5). Chapter 6 of this thesis will describe the validation of the QLQ-NMIBC24, while Chapter 7 describes the patient's choice between a standard cystoscopy and a hypothetical non-invasive urinary biomarker test. Finally, the results section of this thesis will conclude with a meta-analysis investigating whether an ileal conduit or continent diversion has the least negative impact in health-related quality of life (Chapter 8). The work described in this thesis will answer the following research questions:

- What is the health-related quality of life around time of diagnosis in muscle invasive and non-muscle invasive bladder cancer patients (Chapter 4)?
- What is the association between health-related quality of life around time of diagnosis and bladder cancer survival (Chapter 5)?
- What are the psychometric values of the QLQ-NMIBC24 in a population of English bladder cancer patients (Chapter 6)?

- How sensitive would a non-invasive urinary biomarker have to be for bladder cancer patients to opt this over the invasive cystoscopy for bladder cancer surveillance (Chapter 7)?
- Which urinary diversion technique (ileal conduit vs continent diversion) has the least negative impact on health-related quality of life in muscle invasive bladder cancer patients (Chapter 8)?

CHAPTER 2 - METHODS

2.1 The West Midlands Bladder Cancer Prognosis Programme

The West Midlands Bladder Cancer Prognosis Programme (BCPP) was initiated by the Cancer Research UK Bladder Cancer Group, and based at the University of Birmingham. The study was approved by the Nottingham Multi-Center Research Ethics Committee reference: 06/MRE04/65 and the clinicaltrials.gov registration number is: NCT00553215. It is a large, prospective, multi-center cohort study to:

- identify determinants of recurrence and progression in non-muscle invasive bladder cancer patients;
- design a prognostic tool that could predict adverse outcomes, such as recurrence, progression and mortality;
- better understand patient-perceived impact of bladder cancer treatment and surveillance.

Additionally, blood, urine and bladder tumour samples provided with patient consent are stored in a bladder cancer tissue bank for future research purposes. Finally, simultaneous recruitment took place for a double-blinded placebo-controlled randomized-controlled trial (SELENIB) to investigate the effect of selenium and vitamin E on bladder cancer prognosis. Therefore, some BCPP patients may have also participated in the clinical trial.

2.1.1 Study team

Ten separate hospitals located across the West Midlands area, each with their own principal investigator and trained research nurse took part in this study. The hospitals were: Birmingham Heartlands Hospital in Solihull, City General Hospital in North

Staffordshire, Sandwell General Hospital in Sandwell & West Birmingham, Good Hope Hospital in Sutton Coldfield, Solihull Hospital in Solihull, Queen Elizabeth in Birmingham, Russells Hall in Dudley, Walsgrave Hospital in Coventry and Warwickshire, Burton Hospital in Burton-on-Trent, Worcesteshire Royal Hospital in Worcestershire, see Figure 2.1. The BCPP research team consisted of a chief investigator, database manager, programme manager, and other investigators whom were all university based.

Figure 2.1 Map of the study sites across the West-Midlands

2.1.2 Inclusion and exclusion criteria

To be eligible for inclusion into the BCPP cohort study patients had to be 18 years or above, male or female, able to give consent, fit for cystoscopy and surgical biopsy/resection, and present with bladder lesion with cytological evidence of high

grade malignant cells, cystoscopic or imaging characteristics compatible with urothelial cancer/TCC or an incidental finding at cystoscopy.

Patients with a previous diagnosis of cancer of the urethra, bladder, ureter or renal pelvis within the last decade, patients with HIV infection, and patients with any other condition that might interfere with the safety of the patient or evaluation of the study objectives were excluded from participation.

2.1.3 Data collection – patient characteristics

Research nurses were specifically hired to work for BCPP. They received CRF (clinical report form) and database training from the database manager. This included instruction on how to conduct semi-structured interviews and how to enter adta in the electronic database. Additionally, they were all required to have obtained GCP (good clinical practice) certification through their clinical work already. The research nurses collected detailed data on, socio-demographic information, health-related lifestyle, medical and drug history, dietary intake, social support and quality of life, using semi-structured face-to-face interviews. Bladder cancer patients received a postal questionnaire 1-2 months after diagnosis with questions about occupational and residential questions, as well as family history of cancer. Patients' medical records are continuously examined by the research nurses for information on clinical treatment, histopathology, and outcome measures, which are reported on case report forms. An overview of this information can be found in Table 2.1.

2.1.4 Data collection – health-related quality of life

The EORTC QLQ-C30 was used for the collection of the health-related quality of life data both at baseline and follow-up. The QLQ-C30 is a validated questionnaire specifically developed for measuring health-related quality of life in cancer patients. It has 30 items assessing 15 domains, of which 1 global QOL domain (Overall Health-Related Quality of Life), 5 functional domains (Physical Functioning, Role Functioning, Emotional Functioning, Cognitive Functioning, and Social Functioning), and 9 symptom domains (Fatigue, Nausea and Vomiting, Pain, Dyspnoea, Insomnia, Appetite Loss, Constipation, Diarrhoea, Financial Difficulties following cancer). All items are scored on a 4-point Likert scale, except for the global QoL domain, which is scored on a 7-point Likert scale. For the functional domains, all items pertaining to the same domain are summed and then transformed linearly in order to get a score from 0-100, where 0 is least function and 100 is best function. The same applies for the global QoL domain. For the symptom domains the method is mostly the same except that the inverse of the score is taken in order to get a score of 0 to mean the absence of symptoms and 100 meaning full presence of symptoms.

In addition to the QLQ-C30 which was used at baseline and all follow-up visits, a bladder cancer specific QLQ was used at only the follow-up visits. Depending on the type of bladder cancer (non-muscle invasive bladder cancer or muscle invasive bladder cancer) either the QLQ-BLM30 or the QLQ-NMIBC24 was used. However since the number of muscle invasive bladder cancer patients who filled out the QLQ-BLM30 was low, this thesis does not report on any data from the QLQ-BLM30. Therefore only the QLQ-NMIBC24 will be detailed. The QLQ-NMIBC24 is a non-validated add-on module for the EORTC QLQ-C30. The questionnaire consists of 24 items relating to issues specifically

affecting non-muscle invasive bladder cancer patients. A more detailed description of this questionnaire pertaining to its psychometrics can be found in Chapter 5.

Table 2.1 Measurements in the West Midlands BCPP

Phase	Measurements
Baseline (at diagnosis)	Residence GP contact information Marital status Ethnic origin Education and qualifications Life smoking history (filter, nonfilter, hand-rolled, cigar and pipe) Passive smoking Food frequency (staple, meat, fish, vegetables, fruit, dairy and other) Fluid intake (alcoholic drinks, hot drinks, soft drinks) Artificial sweeteners Vitamins and supplements Hair colouring Industrial chemicals Medications Medical history Reproductive history Social support Quality of life (EORTC QLQ-C30)
Postal (1–2 months after diagnosis)	Occupational history Residential history Family history of cancer
Follow-up (3 months after diagnosis and then yearly)	Smoking habits Food frequency (staple, meat, fish, vegetables, fruit, dairy and other) Fluid intake (alcoholic drinks, hot drinks, soft drinks) Vitamins and supplements Medications Medical history Standard gamble Social support Quality of Life (EORTC QLQ-C30, QLQ-BLM30, QLQ-NMIBC24)
Ongoing	Cystoscopy TURBT Urinary pH Cystectomy and staging investigations Local and review pathology Pre and postoperative treatments End of primary treatment Recurrence or progression Recurrence local and review pathology Death

CHAPTER 3 - DATA MANAGEMENT

3.1 Data management

Specific case reports forms were designed and used to collect patient data from semi-structured interviews at baseline and follow-up, and from patient medical files. The IT-specialists at the University of Birmingham specifically designed a study database in Microsoft Access 2007, in which the study database manager could enter all collected data. Only trained personnel such as the IT-specialists, the chief investigator of the study, and the database manager were the only people who had access to the programmable part of the database.

When needed, researchers who required access to the database in order to clean the data were trained in data management and Microsoft Access before being granted access to the database. Microsoft Access experts (University IT-specialists), the chief investigator and the data manager provided this training. The contracted research nurses could only access the database through entry forms via a Citrix web client. This ensured that the database could automatically track who made which changes. Another benefit of the research nurses accessing the database through a front-end was that input of data could be restricted and thus more unified. In addition to the BCPP patient data, research nurses recorded when a patient was seen, but declined participation in BCPP.

The database, which was developed at the start of the study, went through multiple additions of features and revisions throughout the study period. Most changes, including a log for the database manager and automated follow-up reminder, were initiated by the initial data manager, Deborah Bird.

3.1.1 Data cleaning

Due to the nature of data entry and subsequent handling, it was impossible for research nurses to alter data, which they had previously entered in the database. Therefore, one of the tasks of the database manager was to conduct data cleaning on a regular basis. From October 2010 onwards, I took over all database-managing responsibilities, including (but not limited to) searching the database for data entry mistakes and correcting them by comparing the entry to the original paper form. If the problem could not be resolved in this manner, I would contact the research nurse in order to verify the entry with the medical records. At a later stage, I wrote a program in collaboration with an external 3rd party that automatically checked all data for data entry errors according to pre-specified parameters. For instance, checks for dates of birth beyond human limits (over 150 years old or dates in the future). After the program detected these mistakes, the error was then compared with the original patient file and rectified in the same manner as before. Additionally, I checked for logical issues, e.g. an entry for non-smoking while a number of cigarettes per day was also entered.

Because the BCPP database was so large, I prioritized data which would be used in this thesis and other impending publications.

3.1.2 Data privacy and protection

According to the Caldicott principles, any group using patient data should insure the appointment of an appropriate data guardian.[60] This is to limit unnecessary access to patient identifiable data and increase data confidentiality. Furthermore, the appropriate approvals should be obtained in order to use the collected data. Within BCPP this was realised by obtaining ethical approval by the relevant committees and by appointing one database manager with full access. All other team members and collaborators only had

access to anonymised data. As the database manager, I was also responsible for creating datasets for other researchers who wanted to use the data from BCPP for their research. This eliminated the need to give external researchers access to the database and potentially compromise the data.

Formal requests outlining the research objectives, required data, proposed methods and publication plans were submitted to the BCPP study office for review. Access to the requested data was granted if approvals were obtained from the appropriate ethics committee and the BCPP Working Group following the same principles as outlined in the Caldicott Report.

3.2 BCPP in numbers

3.2.1 Baseline cohort details

Recruitment started on the 19th of December 2005 and continued until the 21st of July 2011. In this period 3317 people were assessed for their eligibility to be recruited into BCPP. Of these, 1551 people were recruited into BCPP and 1766 (53%) were excluded. In Table 3.1 the recruitment numbers per site are presented. Recruitment numbers from the Queen Elizabeth hospital were the highest.

Table 3.1 Recruitment numbers per site.

Hospital	Patients recruited	Percentage
Burton	1	0.06
Sandwell & West	134	8.64
Good Hope	242	15.6
Heart of England	103	6.64
City General	99	6.38
Queen Elizabeth	321	20.7
Dudley Group	75	4.84
Coventry & Warwickshire	222	14.31
Royal Wolverhampton	182	11.73
Worcester Acute	172	11.09

Out of the 1551 recruited patients 1398 patients filled out a baseline questionnaire, excluding 15 patients who were recruited into Selenib only and did not want to participate in the regular BCPP questionnaire follow-up. On 21st of July 2011, data collection of follow-up questionnaires was terminated. However, outcome data such as, recurrence, progression, and death were periodically collected until 28th of October 2013.

Not all patients that presented with symptoms suggestive of bladder cancer and were thus recruited into BCPP were later diagnosed with bladder cancer. Out of the 1551 people in BCPP 1285 had bladder cancer. Most common other diagnoses were: invading cancer from a different site (prostate, colon, or kidney), benign (papilloma), or a urinary tract infection. Three and a half times as many men (N=999 (77%)) were diagnosed with bladder cancer compared to women (N=286). Age at registration ranged from 26 to 95 years with a mean of 69.9 (SD= 10.8), no difference was found between male and female patients. In accordance with the West Midlands Cancer Intelligence Unit, 989 (78%) patients diagnosed with bladder cancer were diagnosed with non-muscle invasive bladder cancer, 15 (1%) with pTis (carcinoma in situ), 646 (51%) with pTa, and 328

(26%) with pT1. Of the 281 patients diagnosed with muscle invasive bladder cancer, 262 (21%) were diagnosed with pT2, 1 with pT3, and 18 (1%) with pT4.

Table 3.2 Cross tabulation of the Grade and Stage of the bladder tumours

	pTis	pTa	pT1	pT2 or higher	Total
Grade 1 (1)	0	272	6	2	280
Grade 2 (2)	0	283	77	16	376
Grade 3 (3)	12	94	243	256	605
Total	12	649	326	274	1,261

24 patients not included in this table due to missing grade and/or stage

3.2.2 Follow-up cohort details

We had 420 deaths in the cohort, of which 176 died as a direct result of the bladder cancer and 9 patients died as a result of their treatment. The remaining 222 died of other causes and 13 of unknown causes. Most common cause of death other than bladder cancer was cardiac arrest. In total 348 patients had one or multiple recurrences with 590 recurrences in total. Of 138 patients the bladder tumour had progressed, see Table 3.3. The definition of recurrence and progression as used by this study is as follows: recurrence is a new occurrence of a bladder cancer at the same or different site as the initial index primary cancer and excluding recurrences identified at the first cystoscopy. Progression is defined as a recurrence with:

- An increase in grade from grade 1/grade 2 to grade 3, or
- An increase in T-stage (determined by histopathology), or
- The new occurrence of carcinoma in situ (CIS) in a bladder previously free from CIS, or

- The new occurrence of multiple urothelial tumours following the initial diagnosis of a solitary urothelial tumour

OR:

- The need for a cystectomy because of refractory disease

OR:

- The new development of nodal and/or distant metastases (determined by imaging)

Table 3.3 Total and stage stratified number of progressions in BCPP cohort

Stage	Number of progressions
pTis	4
pTa	57
pT1	47
pT2 or higher	24
Missing	6
Total	138

Not all patients completed the entire study follow-up; in fact only 25 patients had a 5-year follow-up. A number of reasons prevented patients from reaching the five-year follow-up. There are only 6 years between recruitment in 2005 until data collection stopped in 2011, so only patients recruited in the first year of the study could have been eligible for the final questionnaire. Additionally, some patients are lost to follow-up during the study period, due to death, withdrawal, or moving homes without leaving contact details. In Table 3.4 the exact numbers of patients eligible and response rates are presented.

Table 3.4 Number of patients eligible and number of patients that responded to each questionnaire that was submitted to them.

Questionnaire	Number of Patients Eligible*	Number of Patients Responded	Percentage
Baseline	1284	1168	91%
3 month Follow-Up	1236	617	50%
1 year Follow-Up	1011	369	36%
2 year Follow-Up	651	229	35%
3 year Follow-Up	409	117	29%
4 year Follow-Up	150	25	17%
5 year Follow-Up	25	2	8%
Postal Follow-up	1236	377	31%

* Eligible patients are patients who had bladder cancer, were alive, had not withdrawn from the study, and had registered at least the appropriate amount of time for each of the follow-ups (e.g. 3 months before the 3 month follow-up).

The emphasis of this thesis is Health-Related Quality of Life therefore in Table 3.5 there is an overview of the health-related quality of life of all patients that responded to the quality of life part of the questionnaires, which was not always completed. The information provided in the table only serves to provide an overview, as it is not adjusted or stratified for any other variable. More in depth analysis of the health-related quality of life is presented in the following Chapters.

Table 3.5 Mean (SD) Health-Related Quality of Life of all patients for each follow-up period.

Domain	Baseline N=1151	3 months N=353	1 year N=237	2 years N=140	3 years N=43	4 years N=6
Global Health	67 (23)	71 (21)	69 (22)	70 (22)	66 (20)	68 (24)
Functional domains (0 worst functioning; 100 best functioning)						
Physical F	83 (21)	81 (22)	78 (23)	80 (24)	77 (23)	78 (25)
Role F	81 (29)	81 (28)	77 (31)	76 (31)	79 (27)	94 (9)
Emotional F	76 (22)	82 (20)	80 (22)	79 (24)	73 (25)	65 (23)
Cognitive F	84 (20)	84 (19)	83 (20)	83 (19)	80 (20)	86 (13)
Social F	86 (24)	84 (24)	84 (25)	81 (27)	77 (33)	81 (20)
Symptom domains (0 No symptoms; 100 worst symptoms)						
Fatigue	25 (24)	25 (25)	30 (26)	28 (23)	30 (24)	15 (20)
Nausea and vomiting	4 (12)	3 (10)	5 (13)	4 (10)	5 (13)	3 (7)
Pain	18 (26)	19 (26)	20 (28)	20 (27)	22 (26)	6 (9)
Dyspnoea	15 (25)	19 (28)	21 (25)	19 (26)	22 (30)	11 (27)
Insomnia	26 (32)	25 (32)	27 (33)	26 (28)	25 (31)	22 (27)
Appetite loss	12 (24)	10 (23)	9 (20)	11 (22)	7 (16)	17 (28)
Constipation	13 (24)	14 (25)	13 (24)	17 (25)	24 (33)	11 (17)
Diarrhoea	6 (16)	6 (17)	10 (19)	9 (19)	6 (15)	6 (14)
Financial difficulties	6 (18)	7 (18)	7 (21)	6 (19)	12 (24)	6 (14)

F represents a functional domain

CHAPTER 4 - HEALTH-RELATED QUALITY OF LIFE IN BLADDER CANCER PATIENTS AROUND TIME OF DIAGNOSIS

RESULTS FROM THE BLADDER CANCER PROGNOSIS PROGRAMME

4.1 Abstract

Introduction

Bladder cancer is the fifth most common cancer in Western society. Although survival rates are high, the high recurrence rate of bladder cancer could have a major impact on health-related quality of life. To date, the health-related quality of life of bladder cancer patients has not yet been quantified. The current study aims to quantify the health-related quality of life of bladder cancer patients around the time of diagnosis in order to create a reference value and to identify differences between non muscle-invasive bladder cancer and muscle-invasive bladder cancer.

Methods

Within the Bladder Cancer Prognosis Programme, a multi-center cohort study, socio-demographic data were collected using semi-structured face-to-face interviews. Clinicopathological information was collected prospectively. Answers to the QLQ-C30 were transformed into a scale from 0-100 (0 the worst health-related quality of life and 100 optimal health-related quality of life). Health-related quality of life data were analysed in multivariate analysis.

Results

78% of 1,160 included patients who completed the questionnaire before definitive diagnosis was made were male, the mean age of the total population was 70.4 years (range = 26-95 years), and 78% presented with non-muscle invasive bladder cancer. Despite non-muscle invasive bladder cancer having a higher health-related quality of life in every domain than muscle invasive bladder cancer, only the domain Role Functioning

was clinically significantly better in non-muscle invasive bladder cancer patients. Age, gender, and bladder cancer stage all had a significant influence on QLQ-C30 scores.

Discussion

This study has identified a baseline reference value with regard to bladder cancer patients, which allows for better evaluation of any changes in health-related quality of life as disease progresses or after treatment. However, only the domain Role Functioning was significantly better in non-muscle invasive bladder cancer patients than in muscle invasive bladder cancer patients.

4.2 Introduction

Urothelial bladder cancer is the fifth most common cancer in Western society, with a rising global incidence.[61,62] In the UK, the disease accounts for approximately 10,000 new cases and 5,000 deaths per year. The majority of patients (75-80%) present with non-muscle-invasive bladder cancer. Although not immediately life-threatening in the majority of cases, recurrence and progression of non-muscle invasive bladder cancer remain significant issues, with up to 55% of patients experiencing recurrence within five years of diagnosis.[63] Current guidelines therefore recommend long-term surveillance.[13,17] With the UK prevalence of non-muscle invasive bladder cancer estimated at 46,500 [CRUK], at any one time there will be between 35,000 and 37,000 patients requiring such surveillance.

Surveillance typically comprises of cystoscopy and urine cytology.[13,17] For patients with low-risk non-muscle invasive bladder cancer, European Association of Urology (EAU) guidelines recommend follow-up cystoscopy and urine cytology at 3 and 12 months after tumour resection (TURBT), and then annually for the next 5 years. Patients with high-risk non-muscle invasive bladder cancer undergo more intensive surveillance - every 3 months for the first 2 years, then every 4 months for the following year, every 6 months for the year after, and then annually thereafter, most likely for the rest of their lives.[64] If recurrence is detected, the tumour is resected and subsequent surveillance will start again, with the frequency determined by the risk category of the recurrence.

Each surveillance cystoscopy and urine cytology episode costs at least £533.[65] As a result, bladder cancer is the most costly cancer to treat on a per patient basis from

diagnosis to death.[66,67] Furthermore, cystoscopy itself significantly increases the burden of disease, as it is an invasive procedure that causes pain and discomfort in about one-third of patients.[68]

As survival in non-muscle invasive bladder cancer patients is high compared with other cancers, and long-term follow-up is required, this disease can be considered a chronic disease. Therefore, health-related quality of life plays a very important role. However, so far most research has focused on muscle invasive bladder cancer and in particular differences in health-related quality of life between different urinary diversions after radical cystectomy.[69-71] However, these results are difficult to interpret, as there are often no baseline reference values for comparison. For muscle invasive bladder cancer patients, survival is not as high, although health-related quality of life is affected more severely: due to more radical surgery, a higher chance of metastasis, and an overall worse prognosis, health-related quality of life is an important measure. The few manuscripts that have reported on health-related quality of life in non-muscle invasive bladder cancer patients contradict each other.[58,72] Besides the evidence being sparse, studies have often been hindered by small sample sizes, non-validated health-related quality of life questionnaires, and patients populations that are heterogeneous in terms of duration of follow-up, previous diagnoses of urothelial bladder cancer, and number of recurrences or progression.

Additionally, most studies do not take baseline health-related quality of life into account, which is important for the evaluation of any changes in a patient's health-related quality of life due to disease or treatment. Bladder cancer is a complex disease that often goes

undetected for an extended period of time, especially in female patients.[73] This could imply that bladder cancer may have already affected patients' health-related quality of life, and their health-related quality of life will not necessarily be the same as the general population even around time of diagnosis. It is therefore important to study health-related quality of life around the time the bladder cancer diagnosis is made.

One of the reasons that health-related quality of life is not often taken into account in studies could lie in the complex nature of the questionnaires used to measure health-related quality of life. More specifically, the commonly used health-related quality of life questionnaire QLQ-C30[74] has 15 separate domains that need to be compared with each other in order to provide a complete assessment of patients' health-related quality of life.

4.2.1 Aim

The current study aims to be the first to quantify the health-related quality of life around the time of diagnosis of bladder cancer patients for non-muscle invasive bladder cancer and muscle invasive bladder cancer separately.

4.3 Methods

4.3.1 Cohort

The present study is part of the West Midlands Bladder Cancer Prognosis Programme (BCPP), a multi-center cohort study in the West Midlands, UK (ethics reference: 06/MRE04/65; clinicaltrials.gov registration number: NCT00553215). Details of the

study have been published previously.[75] Briefly, adult patients (age ≥18 years) presenting at haematuria clinics in the nine participating urology centers within the region were enrolled on the basis of abnormal cystoscopic findings suggestive of bladder cancer. Those who had a previous diagnosis of cancer of the urethra, bladder, ureter or renal pelvis within the last decade, HIV infection, or any other condition that might interfere with the safety of the participant were excluded. The enrolment period was from the 19th of December 2005 to the 21st of April 2011. All participants provided written informed consent before they were included in the study.

4.3.2 Procedure

At the time of diagnosis, semi-structured face-to-face interviews to collect information on socio-demographics, health-related lifestyle, medical and drug history, dietary intake, social support and quality of life were conducted by trained research nurses. The European Organisation for the Research and Treatment of Cancer (EORTC) QLQ-C30 v3 was used for the collection of the health-related quality of life data.[76] The QLQ-C30 is a validated questionnaire specifically developed for measuring health-related quality of life in cancer patients. It has 30 items assessing 15 domains, of which 1 global health-related quality of life domain, 5 functional domains, and 9 symptom domains. The transformation of the scores is described in detail elsewhere; briefly, the answers are converted into a score from 0-100 where 100 is the best quality of life and 0 is the worst, for all domains except the 9 symptom domains, for which 100 is the most problematic symptom and 0 is no symptoms at all.[76] A difference of 10 points or more is considered clinically relevant.[77]

Medical records of each patient were reviewed by trained research nurses and clinicopathological characteristics of the bladder cancer at diagnosis were prospectively gathered on dedicated case report forms. This comprised of pT stage (according to the tumour, node, metastasis (TNM) 2002 classification system[78]), grade (according to the World Health Organization (WHO) 1973 system[79]), size of the largest tumour, and the number of visible tumours. Where early re-resection (within 3 months after first surgery for BC) indicated an invasive tumour (≥pT2) contrary to the original assessment, then the re-resection pT stage was recorded as the pT stage at diagnosis. Stage was recoded into a numerical outcome variable suitable for analysis, by coding pTa tumours with a value '0' and all other stages in sequence. In addition a separate variable was made in which stage was recoded into non-muscle invasive bladder cancer (<pT2) and muscle invasive bladder cancer (pT2+).

4.3.3 Statistical analysis

Means and standard deviations (SDs) were calculated for all domains of the QLQ-C30 to reflect reference values for muscle invasive bladder cancer and non-muscle invasive bladder cancer patients. The effect of sex, age, and stage on the 15 health-related quality of life domains from the QLQ-C30 were analysed using multivariate linear regression models. For this analysis, sex (male, female) and stage (pTis, pTa, pT1, pT2, pT3, pT4) were included as categorical variables. Statistical differences between the health-related quality of life domains and, muscle invasive bladder cancer and non-muscle invasive bladder cancer were tested using the two-group mean-comparison (ANOVA).

4.4 Results

4.4.1 Socio-demographics

During the enrolment period patients with symptoms related to bladder cancer were recruited. Out of the 1,534 recruited participants, 1,183 were subsequently diagnosed with bladder cancer. Out of these, 1,160 had filled out the questionnaire before they knew the diagnosis and could therefore be included in the analysis for the current study. The majority of the patients were male (n=906, 78.1%), the average age of the patient population was 70.4 years (range = 26-95 years). More than half of the patients were currently in a relationship (n=728, 62.8%). Most of the patients presented with non-muscle invasive bladder cancer (n=890, 78%) with pTa as the most common tumour stage (n=575, 49.6%) (Table 4.1). Interaction between age and tumour stage could not be identified.

Table 4.1 Socio-demographic characteristics of patients

	N	%
Total	1160	100
Sex		
Male	906	78.1
Female	254	21.9
Age		
Mean (SD)	70.4 (10.9)	
Range	26 - 95	
Marital status		
With partner	728	62.8
Without partner	344	29.7
Missing	88	7.5
Smoking status		
Current	228	19.7
Former	612	52.8
Never	217	18.7
Missing	94	8.8
Tumour Stage		
pTis	14	1.2
pTa	575	49.6
pT1	301	25.9
pT2	233	20.1
pT3	1	0.1
pT4	17	1.5
Missing	19	1.6
Grade		
Grade 1	254	21.9
Grade 2	336	29.0
Grade 3	540	46.5
Missing	30	2.6
NMIBC	890	76.7
MIBC	251	21.6
Missing	20	1.7

SD= Standard Deviation; IQR = Inter Quartile Range; NMIBC = Non-Muscle Invasive Bladder Cancer; MIBC = Muscle Invasive Bladder Cancer. Missing values are not explicitly reported

4.4.2 Health-related quality of life in patients non-muscle invasive bladder cancer vs muscle invasive bladder cancer

The mean overall quality of life score was 61 (SD=24) in muscle invasive bladder cancer patients, and 69 (SD=23) in non-muscle invasive bladder cancer. The functional domains for muscle invasive bladder cancer patients ranged from 72 to 81 whilst in the non-muscle invasive bladder cancer patients the same domains ranged form 76 to 86. In both groups (muscle invasive bladder cancer and non-muscle invasive bladder cancer) the worst symptoms were Fatigue and Insomnia. In general, there were few differences in health-related quality of life between non-muscle invasive bladder cancer and muscle invasive bladder cancer patients, with none of the scores differing by at least 10 points, except for Role Functioning (**Error! Reference source not found.**). However, it should be noted that muscle invasive bladder cancer always scored lower on the QLQ-C30 than the non-muscle invasive bladder cancer patients. In addition, there was a statistically significant difference in seven domains (Overall Health-Related Quality of Life, Physical Functioning, Role Functioning, Social Functioning, Fatigue, Pain, Dyspnoea, Insomnia, and Appetite Loss). The lowest reported domain was the overall health-related quality of life in both non-muscle invasive bladder cancer and muscle invasive bladder cancer, 69 and 61 out of 100, respectively. Scores in all other domains were above 75 in the non-muscle invasive bladder cancer group and above 65 in the muscle invasive bladder cancer group. More univariate comparisons of health-related quality of life stratified by tumour size, tumour number at diagnosis, and stage can be found in Appendix 11.4.

Table 4.2 Health related quality of life as measured by the EORTC QLQ-C30 for muscle invasive and non-muscle invasive bladder cancer separately.

QLQ-C30[#]	NMIBC		MIBC		
	Mean	SD	Mean	SD	
N	890		251		p-value
Overall Quality of Life	69	23	61	24	<0.001
Functional domains (0 worst functioning; 100 best functioning)					
Physical Functioning	84	20	79	23	0.005
Role Functioning	83	28	72	34	<0.001
Emotional Functioning	76	22	75	23	0.536
Cognitive Functioning	84	19	81	23	0.036
Social Functioning	86	23	81	28	0.003
Symptom domains (0 No symptoms; 100 worst symptoms)					
Fatigue	76	23	69	28	<0.001
Nausea and Vomiting	96	11	94	13	0.079
Pain	83	25	76	30	<0.001
Dyspnoea	85	24	81	29	0.015
Insomnia	76	31	67	35	<0.001
Appetite Loss	89	22	81	31	<0.001
Constipation	88	23	83	28	0.012
Diarrhoea	94	16	93	18	0.471
Financial Difficulties	95	17	93	20	0.147

MIBC = Muscle invasive bladder cancer; NMIBC = Non muscle invasive bladder cancer; SD = Standard Deviation

[#] Range of QLQ-C30 is 0-100

From Table 4.3 it is clear that age had a statistically significant effect on nearly all Functional health-related quality of life domains, except for Social Functioning. Additionally age had a statistically significant effect on Fatigue, Dyspnoea, Insomnia, Constipation, and Financial Difficulties. Increased age was detrimental in all statistically significant domains except for Financial Difficulties, Insomnia, and Emotional Functioning. The biggest effect was found in the Physical Functioning domain, where a 10-year increase in age would decrease the score by 6 points. Women had a worse outcome on every statistically significantly different health-related quality of life domain compared with men. Furthermore, gender was the only variable that had a clinical impact (>10 points difference), namely on the domain Insomnia where men scored

12.59 points higher than women. Patients with non-muscle invasive bladder cancer scored better on every single health-related quality of life domain of the QLQ-C30, although this was not always a statistically significant difference. Additionally, none of the differences were 10 points or more, which is the cut-off point for clinically significant differences.

Table 4.3 Multivariate linear regression of age, sex, and stage on each health-related quality of life domain

	Age		Sex		Stage	
	B	p value	B	p value	B	p value
Global Health	-0.19	3.93E-03	-4.72	7.71E-03	-7.65	1.71E-05
Physical F	-0.56	3.83E-21	-5.92	1.16E-04	-2.65	0.08
Role F	-0.40	1.82E-06	-2.02	0.36	-8.87	5.99E-05
Emotional F	0.20	2.06E-03	-7.34	1.43E-05	-1.13	0.50
Cognitive F	-0.16	5.54E-03	0.02	0.99	-2.10	0.17
Social F	-0.07	0.33	-3.64	4.80E-02	-4.77	1.00E-02
Fatigue	-0.27	9.84E-05	-6.19	7.52E-04	-6.04	1.07E-03
Nausea and vomiting	0.04	0.26	-5.51	7.25E-10	-1.44	0.11
Pain	-0.14	0.06	-4.85	1.49E-02	-6.89	5.84E-04
Dyspnoea	-0.37	7.47E-07	-0.59	0.76	-3.37	0.08
Insomnia	0.21	2.11E-02	-12.59	1.95E-07	-9.23	1.36E-04
Appetite loss	-0.08	0.27	-7.39	7.38E-05	-8.10	1.50E-05
Constipation	-0.34	9.13E-07	-2.98	0.10	-2.58	0.15
Diarrhoea	0.05	0.29	-2.84	2.47E-02	-1.10	0.39
Financial difficulties	0.18	2.98E-04	0.12	0.93	-2.71	4.06E-02

B= beta, unstandardized coefficient of the multivariate linear regression analyses. F represents a functional domain.

4.5 Discussion

It is important to recognize that bladder cancer patients may have a different baseline health-related quality of life compared with the general population, as the disease may already have an impact around the time of diagnosis. This study was the first to investigate health-related quality of life of bladder cancer patients with non-muscle invasive bladder cancer and muscle invasive bladder cancer at this specific time point. Interestingly, the health-related quality of life of both non-muscle invasive bladder cancer and muscle invasive bladder cancer groups was relatively high. None of the mean values for each domain fell below 60 and patients even scored above 90 on a number of domains (in both groups). Even though there are no reference data for the general population in the UK, to illustrate, this is only slightly lower than the general population data from Germany,[80] although reference data from a general Norwegian population[81] and a general Swedish population showed better values.[82] The necessity for baseline health-related quality of life reference values for bladder cancer patients might depend on cultural factors. It is generally known that Scandinavian populations have a high standard of living. It is therefore possible that this leads to a greater difference in health-related quality of life with bladder cancer patients.

No clinically significant differences (> 10 points) in health-related quality of life domains were found between muscle invasive bladder cancer and non-muscle invasive bladder cancer patients, except for Role Functioning. This might be due to the unique time point at which the questionnaire took place, namely before the histopathological confirmation of the diagnosis. Previous studies found significantly worse health-related quality of life

values between 3 to 18 months after diagnosis. [36,83] However, the disease has already affected the patients enough that a difference between non-muscle invasive bladder cancer and muscle invasive bladder cancer patients can be found in the Role Functioning domain, indicating that muscle invasive bladder cancer patients feel more restricted in fulfilling their role in society. Contrary to what might be expected, muscle invasive bladder cancer patients did not report higher pain levels or more restricted Physical Functioning.

As demonstrated by multivariate analysis, age, gender, and stage significantly influenced health-related quality of life. Overall, increased age and stage were related to worse health-related quality of life. Likewise, women generally reported worse health-related quality of life than men. However, these statistical differences did not seem to have a clinical impact (all beta coefficients < 10), with the exception of female patients, who had substantially worse scores in the Insomnia domain. Furthermore, the beta coefficient for age was relatively small per one-year difference, further implying limited clinical impact. The biggest impact of age can be found in Physical Functioning (B=0.56) and even here a 10-year difference would only alters a patient's score by 5.6 points (on a scale from 0-100).

The EORTC published a comprehensive report containing QLQ-C30 reference values for a wide variety of cancers.[84] Compared with QLQ-C30 reference values for overall cancer patients, the BCPP subjects seemed to have similar scores. Scores for prostate cancer patients in stage I-II were comparable to NMIBC patients in the BCPP cohort, although prostate cancer patients did seem to have better Physical Functioning. Overall, scores

for MIBC patients had comparable scores to stage III-IV prostate cancer patients, except for physical functioning, which was worse in prostate cancer patients. Reference values for lung cancer patients were worse than for MIBC patients in the BCPP cohort, with the exception of Cognitive Functioning, which was comparable.

As no UK QLQ-C30 data is available for bladder cancer specifically, this study aimed to provide the first data of this sort. In order to assess the representativeness of our study population, we compared our study demographics with the West Midlands Cancer Intelligence Unit data. We found no major differences with regard to age and sex (data not shown). In addition, the distribution of non-muscle invasive bladder cancer (78%) and muscle invasive bladder cancer (22%) corresponds with what is found in the literature.[85] Therefore, the results of this paper could be used as a reference population for future research into the health-related quality of life of bladder cancer patients in the UK and beyond.

4.5.1 Conclusion

This is the largest non-muscle invasive bladder cancer patient cohort that has participated in health-related quality of life research. Additionally, this study captured the health-related quality of life at a unique time point, allowing for the identification of a baseline health-related quality of life measure. Our findings suggest that health-related quality of life scores around time of diagnosis of bladder cancer patients are almost comparable to the general population of Germany and possible the UK, however QLQ-C30 data is published for the general population of the UK.

To summarise this study has identified a baseline reference value with regard to health-related quality of life around time of diagnosis for bladder cancer patients. However, only the domain Role Functioning was significantly better in non-muscle invasive bladder cancer patients than in muscle invasive bladder cancer patients.

CHAPTER 5 - THE EFFECT OF BASELINE QUALITY OF LIFE ON BLADDER CANCER SURVIVAL: RESULTS FROM THE BLADDER CANCER PROGNOSIS PROGRAMME

5.1 Abstract

Introduction

It has been hypothesized that baseline quality of life of cancer patients may be associated with cancer survival, alongside of conventional clinical factors. However, little is known about this association in the context of bladder cancer. Particularly, the association of baseline quality of life and non-muscle invasive bladder cancer has not yet been investigated. Therefore, the current study aimed to assess the association between baseline health-related quality of life and survival in muscle invasive and non-muscle invasive bladder cancer patients.

Methods

Within the Bladder Cancer Prognosis Programme, a multi-center cohort study, socio-demographic data were collected using semi-structured face-to-face interviews. The EORTC QLQ-C30 was used to assess baseline health-related quality of life of 1,276 recently diagnosed bladder cancer patients and their survival was monitored in the period between 2005 and 2014. Multivariate cox proportional hazard regression was performed to identify whether different health-related quality of life domains were associated with survival of non-muscle invasive and muscle invasive bladder cancer.

Results

A total of 1,276 patients were included (78% male), with a mean age of 69.9 years (SD=10.8 years). The mean overall health-related quality of life was 69.3 (SD=22.7) and 60.9 (SD=24.5), on a scale from 0-100(best health-related quality of life), for non-muscle invasive and muscle invasive bladder cancer, respectively. Survival of patients with the

worst health-related quality of life scores dropped to approximately 50% in the first 24 months, while survival estimates for patients with the highest overall health-related quality of life never dropped below 75% throughout the duration of the follow-up. Independent of the clinical predictors (sex, age, smoking, stage, grade, and number of tumours), a 1SD improvement in Role Functioning and Financial Difficulties would give a 16% and 20% increase in muscle invasive bladder cancer survival, respectively. Similarly, a 1SD improvement in Physical Functioning and Dyspnoea would increase non-muscle invasive bladder cancer survival by 27% and 21%, respectively.

Discussion

Certain aspects of health-related quality of life seem to influence bladder cancer survival rates independently of known clinical factors. Although further research is needed, this could lead to targeted interventions in the future, which would then improve survival rates.

5.2 Introduction

According to the latest available data from 2012, there were 430,000 new cases of bladder cancer worldwide, making it the ninth most common type of cancer[86]. Bladder cancer is generally categorized as non-muscle invasive bladder cancer when tumour stage is classified as <pT2, and as muscle invasive when tumour stage is classified as ≥pT2.

The most important determinant of survival is the tumour stage at diagnosis, where a lower stage is associated with a higher survival. Indeed, 3-year survival rates are 50% for patients with pT2 tumours, and less than 25% for patients with ≥pT3 tumours, while the 5-year survival rate for patients with <pT2 is over 80%[87]. Additionally, age and sex have been identified to play an important role in survival; men tend to have a higher survival rate than women with a difference of approximately 15%.[88] Older age at diagnosis is associated with a lower survival rate, for men 5-year survival rates drop from around 74% (15-49 years) to 40% (80-99 years), women follow a similar pattern only with lower survival rates as explained before. [89] Although it remains unclear how health-related quality of life may affect cancer survival, it is postulated that health-related quality of life might be a proxy for disease state with low health-related quality of life potentially representing a more advanced disease state associated with a higher mortality rate. However, it has recently been suggested in a review by Montazeri et al.[90] that aspects of baseline health-related quality of life could have a significant effect on the survival in a number of cancers, independently of other known risk factors.

So far, only one study has investigated the relationship between baseline health-related quality of life and bladder cancer survival specifically[8]. This particular study used the EORTC QLQ-C30 questionnaire[74], which measures health-related quality of life on 15

domains covering physical, psychological and social aspects. The authors found that the following health-related quality of life domains were independent prognostic factors for survival: Physical Functioning, Role Functioning, and Loss of Appetite[8]. However, this study was set up as a retrospective cohort in which patients from a phase III randomized-controlled trial were included. This trial included only patients with locally advanced or metastatic bladder cancer, who may not be representative of the majority of bladder cancer patients. It remains unclear whether baseline health-related quality of life is also associated with better survival rates in non-muscle invasive bladder cancer.

5.2.1 Aim

The current study aims to assess the association between baseline health-related quality of life and the survival of bladder cancer patients, independent of established clinical factors.

5.3 Methods

5.3.1 Cohort

The present study is part of the Bladder Cancer Prognosis Programme (BCPP), which is a multicenter cohort study in the West Midlands, UK. Details of the study have been published previously.[75] Briefly, adult patients (age ≥18 years) presenting at haematuria clinics in the nine participating urology centers within the region were enrolled on the basis of abnormal cystoscopic findings suggestive of bladder cancer. Those who had a previous diagnosis of cancer of the urethra, bladder, ureter or renal pelvis within the last decade, HIV infection, or any other condition that might interfere with the safety of

the participant were excluded. The enrolment period lasted from the 19th of December 2005 to the 21st of April 2011. The Nottingham Multi-center Research Ethics Committee approved the study protocol (06/MRE04/65; clinicaltrials.gov registration number: NCT00553215), and all participants provided written informed consent before they were included in the study.

5.3.2 Procedure

Around the time of diagnosis, trained research nurses collected socio-demographics, lifestyle and medical, and health-related quality of life details through semi-structured face-to-face interviews[75].

Medical records of each participant were reviewed by trained research nurses to gather information on clinicopathological characteristics of the bladder cancer at diagnosis. This comprised of pT stage (according to the tumour, node, metastasis (TNM) 2002 classification system[78]), grade (according to the World Health Organization (WHO) 1973 system[79]). In case a re-resection within three months after the first surgery of BC indicated an invasive tumour (≥pT2), in contradiction to the original assessment, then the re-resection pT stage was recorded as the pT stage at diagnosis. Additionally mortality data was retrieved from the medical records.

5.3.3 QLQ-C30

This study measured health-related quality of life using the EORTC QLQ-C30[74], a general cancer health-related quality of life questionnaire. This questionnaire has 15 domains

that included one overall health-related quality of life domain, five functional domains (Physical, Role, Emotional, Social, and Cognitive Functioning), and nine Symptom domains (Fatigue, Nausea and vomiting, Pain, Dyspnoea, Insomnia, Appetite loss, Constipation, Diarrhoea, and Financial Difficulties). The item and domain scores were recoded via linear conversion, to represent a score from 0-100, following the EORTC QLQ-C30 guidelines, where 100 is the best quality of life and 0 is the worst for all domains except the 9 symptom domains, for which 100 is the most problematic symptom and 0 is no symptoms at all. According to EORTC guidelines, domains with 50% or more missing items were not included in the analysis.[76]

5.3.4 Statistical analysis

Descriptive analyses performed on patient characteristics. Mean and standard deviation (SD) were calculated for continuous variables, i.e. sex, age and health-related quality of life. Proportions were calculated for categorical variables, i.e. smoking status, tumour stage and grade, number of tumours, and size of tumours. First a baseline model cox regression was done in order to quantify the association of overall mortality (expressed as a Hazard Ratio (HR)) and conventional clinical predictors (sex, age, smoking, stage, grade, and number of tumours). Additionally, univariate analyses, adjusted for the conventional clinical predictors, were used to identify the association between each health-related quality of life domain and mortality. Finally, stepwise multivariate cox regression identified, via the Wald-test, specifically which health-related quality of life domain explained most of the variance not explained by the conventional clinical predictors. As the clinical features and mortality rates of non-muscle invasive bladder cancer and muscle invasive bladder cancer differ significantly[17,18], all analyses were

done for both groups separately. Overall health-related quality of life was omitted as a predictor for the multivariate analyses in order to achieve model stability, as it could provide multicollinearity issues.[91] All analyses were performed in STATA 12[92].

5.4 Results

The final study population, described in Table 5.1, included 1,276 patients of which 995 (78%) were male. The age range of the total population was 26 to 95 years with a mean of 69.9 years (SD=10.8 years). The majority (N=983, 77.1%) of the patients were diagnosed with non-muscle invasive bladder cancer (<pT2), while 280 patients (22%) were diagnosed with muscle invasive bladder cancer (≥pT2), and stage was unknown for 13 patients (1%) who were subsequently excluded from the analyses including stage. Finally, a total of 336 patients died; 159 (71%) in muscle invasive bladder cancer patients and 177 (21%) in non-muscle invasive bladder cancer patients.

Table 5.1 Baseline characteristics for the study population divided into non-muscle invasive and muscle invasive bladder cancer groups. (N=1263, unknown stage and not included in table N=13)

	NMIBC (N=983)		MIBC (N=280)	
Age in years, mean (SD)	69.28 (10.8)		71.84 (10.6)	
Age in years, range	26 - 95		31 - 94	
	N	**%**	**N**	**%**
Female	208	21.2	68	24.3
Male	775	78.8	212	75.7
Smoking				
Never Smoker	208	21.2	31	11.1
Former Smoker	500	50.9	156	55.7
Current Smoker	187	19.0	56	20.0
Missing	88	8.9	37	13.2
Stage				
pTis	15	1.5	-	-
pTa	644	65.5	-	-
pT1	324	33	-	-
pT2	-	-	261	93.2
pT3	-	-	1	0.4
pT4	-	-	18	6.4
Grade				
Grade 1	274	27.9	2	0.7
Grade 2	358	36.4	12	5.7
Grade 3	337	34.3	254	90.7
Missing	14	1.4	8	2.9
Tumour size (cm)				
<=1.5	348	35.4	17	6.1
1.6-3.0	402	40.9	78	27.9
>3.0 cm	197	20.0	172	61.4
Missing	36	3.7	13	4.6
Tumour number				
One	568	57.8	176	62.8
Multiple	382	38.9	94	33.6
Missing	33	3.4	10	3.6

Table 5.2 describes the baseline health-related quality of life of the study population. The baseline health-related quality of life of muscle invasive bladder cancer patients was worse than health-related quality of life of non-muscle invasive bladder cancer patients on overall, function and symptom domains. The mean overall health-related quality of

life was 69.3 (SD=22.7) and 60.9 (SD=24.5) for non-muscle invasive and muscle invasive bladder cancer, respectively. Mean functional domain scores ranged from 76.0 (Emotional Functioning) to 86.7 (Social Functioning) for non-muscle invasive bladder cancer patients, whereas the range for muscle invasive bladder cancer patients was from 73.2 (Role Functioning) to 81.7 (Cognitive Functioning). Both non-muscle invasive and muscle invasive bladder cancer patients suffered least from Nausea and Vomiting (means 3.8 and 5.2, respectively), and most from Insomnia (means 24.1 and 31.9, respectively).

Table 5.2 Baseline EORTC QLQ-C30 scores separately for non-muscle invasive and muscle invasive bladder cancer

	NMIBC		MIBC	
	Mean	**SD**	**Mean**	**SD**
Overall Quality of Life	69.3	22.7	60.9	24.5
Functional domains (0 worst functioning; 100 best functioning)				
Physical Functioning	84.3	20.3	80.1	22.2
Role Functioning	83.0	27.4	73.2	33.1
Emotional Functioning	76.0	22.2	75.4	22.5
Cognitive Functioning	84.3	19.6	81.7	21.8
Social Functioning	86.7	23.2	81.4	26.9
Symptom domains (0 No symptoms; 100 worst symptoms)				
Fatigue	23.1	23.1	30.0	27.7
Nausea and Vomiting	3.8	11.1	5.2	12.7
Pain	16.4	24.9	22.6	29.8
Dyspnoea	14.3	24.2	19.1	28.5
Insomnia	24.1	30.7	31.9	34.6
Appetite Loss	10.2	21.8	18.1	30.2
Constipation	12.2	22.9	16.7	28.1
Diarrhoea	6.2	16.2	7.0	17.1
Financial Difficulties	5.3	16.6	7.1	20.2

Figure 5.1 indicates that overall baseline health-related quality of life might be associated with survival. Represented in this figure are four Kaplan-Meier curves, one for each quartile of overall health-related quality of life score. The first quartile

represents the bottom 25% of overall health-related quality of life scores (score <50), while the fourth quartile represents the top 25% of overall health-related quality of life scores (score >83). Patients with the worst scores, the first quartile, had the lowest survival estimates, with survival dropping to 50% in the first 24 months. Survival estimates for patients with the highest overall health-related quality of life, the third and fourth quartiles did not differ significantly from each other with survival estimates never dropping below 75% throughout the duration of the follow-up. More in-depth Kaplan-Meier curves can be found in Appendix 11.5.

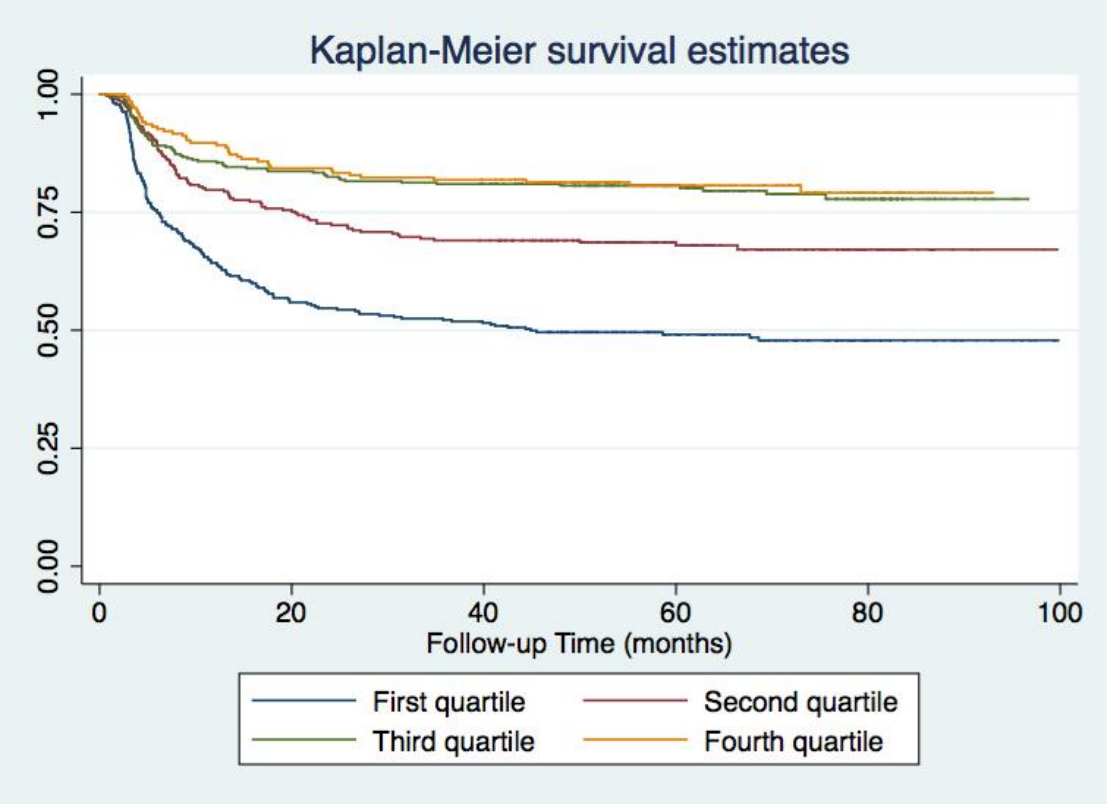


Figure 5.1 Kaplan-Meier curve for survival, divided into quartiles based on the overall quality of life of the study population
First quartile: scores <50, second quartile: scores ≥50 AND <67, third quartile: scores ≥67 AND <83, fourth quartile: scores >83.

Cox proportional hazard regression modeling showed differences between clinical predictors of overall mortality in muscle invasive bladder cancer and non-muscle

invasive bladder cancer patients (Table 5.3). Of the conventional clinical predictors of mortality only age (Hazard Ratio (HR) = 1.06; 95% Confidence Interval (CI) = 1.04 - 1.08), smoking (HR= 1.53; 95% CI = 1.04 – 2.24), and number of tumours (HR = 1.06; 95% CI = 1.00 – 1.12) were statistically significantly associated with survival in non-muscle invasive bladder cancer patients. For muscle invasive bladder cancer patients only age (HR = 1.03; 95% CI = 1.02 – 1.05) was statistically significantly associated with mortality. Univariate cox regression, shown in Table 5.4, indicated that in non-muscle invasive bladder cancer patients only emotional and cognitive functioning domains were not significantly associated with mortality. For muscle invasive bladder cancer patients, physical functioning was the only functioning domain not significantly associated with mortality. For a graphical representation of these results see Appendix

In the stepwise multivariate Cox regression models for muscle invasive and non-muscle invasive bladder cancer patients, two health-related quality of life domains were identified as significant predictors for mortality, independently of the clinical predictors; Role Functioning (HR=0.993; 95% CI=0.989-0.998) and Financial Difficulties (HR=0.991; 95% CI=0.985-0.998) for muscle invasive bladder cancer, and Physical Functioning (HR=0.985; 95% CI=0.979-0.992) and Dyspnoea (HR=0.991; 95%CI=0.985-0.996) for non-muscle invasive bladder cancer.

Table 5.3 Cox proportional hazard regression for mortality for all clinical predictors in non-muscle invasive (NMIBC; N=847 Deaths=177) and muscle invasive bladder cancer patients (MIBC; N=225, Deaths=159)

		NMIBC			MIBC		
		Hazard Ratio	(95% CI)	p-value	Hazard Ratio	(95% CI)	p-value
Sex							
	Male	1	(Base)		1	(Base)	
	Female	0.72	(0.48 – 1.07)	0.11	0.91	(0.63 – 1.30)	0.60
Age		1.06	(1.04 - 1.08)	2.93E-11	1.03	(1.02 – 1.05)	9.62E-05
Smoking							
	No	1	(Base)		1	(Base)	
	Yes	1.53	(1.04 – 2.24)	0.03	1.01	(0.70 – 1.45)	0.98
Stage							
	pTis	1.55	(0.34 – 7.09)	0.60			
	pTa	1	(Base)				
	pT1	1.35	(0.91 – 1.98)	0.13			
Grade							
	1	1.12	(0.76 - 1.66)	0.55			
	2	1	(Base)				
	3	1.11	(0.74 - 1.68)	0.61			
Number of Tumours							
	One	1	(Base)		1	(Base)	
	Multiple	1.06	(1.00 - 1.12)	0.04	0.98	(0.92 - 1.05)	0.56

Table 5.4 Univariate cox proportional hazard regression for mortality for all health-related quality of life domains of the EORTC QLQ-C30 presented separately for non-muscle invasive (NMIBC) and muscle invasive bladder cancer (MIBC) patients.

	NMIBC			MIBC		
	Hazard Ratio	(95% CI)	p-value	Hazard Ratio	(95% CI)	p-value
Overall Quality of Life	0.984	(0.978 - 0.991)	9.58E-07	0.985	(0.979 - 0.992)	7.82E-06
Physical Function	0.980	(0.975 - 0.986)	6.42E-12	0.996	(0.988 - 1.004)	0.31
Role Function	0.988	(0.984 - 0.993)	8.32E-08	0.992	(0.988 - 0.997)	7.79E-04
Emotional Function	0.998	(0.991 - 1.005)	0.52	0.991	(0.985 - 0.997)	5.78E-03
Cognitive Function	0.996	(0.989 - 1.003)	0.23	0.993	(0.987 - 0.999)	2.78E-02
Social Function	0.992	(0.986 - 0.997)	4.37E-03	0.990	(0.985 - 0.995)	1.63E-04
Fatigue	0.987	(0.982 - 0.993)	1.49E-05	0.992	(0.987 - 0.997)	7.36E-03
Nausea and Vomiting	0.991	(0.980 - 1.003)	0.16	0.987	(0.977 - 0.997)	1.02E-02
Pain	0.993	(0.988 - 0.998)	1.05E-02	0.996	(0.991 - 1.002)	0.17
Dyspnoea	0.985	(0.980 - 0.989)	2.30E-10	0.995	(0.989 - 1.001)	0.08
Insomnia	0.991	(0.987 - 0.996)	4.32E-04	0.998	(0.994 - 1.002)	0.38
Appetite Loss	0.991	(0.985 - 0.997)	2.61E-03	0.994	(0.988 - 0.999)	2.20E-02
Constipation	0.998	(0.992 - 1.003)	0.45	0.994	(0.989 - 1.000)	0.06
Diarrhoea	0.996	(0.988 - 1.004)	0.40	1.001	(0.991 - 1.011)	0.85
Financial Difficulties	0.989	(0.982 - 0.997)	4.51E-03	0.988	(0.982 - 0.994)	1.04E-04

5.5 Discussion

Health-related quality of life has been suggested to impact cancer survival, alongside of known clinical factors such as tumour stage and grade[7,8,90]. However, relatively little is known about the relationship between health-related quality of life and mortality of bladder cancer patients. With approximately 165,000 bladder cancer deaths worldwide, and nearly one-third (N=52,400) of these deaths occurring in Europe[86], it is important to identify all possible factors that could further predict mortality in bladder cancer patients.

In the current study, we found that health-related quality of life domains were indeed associated with mortality, independently of known clinical predictors. Furthermore, different health-related quality of life domains predicted survival in muscle invasive bladder cancer than in non-muscle invasive bladder cancer patients. Similar to the previous study[8], we found that Role Functioning was significantly associated with survival of muscle invasive bladder cancer patients. Additionally, Financial Difficulties was found to influence the survival curve. One SD increase in these respective domains, could improve overall survival rates by 16-20%. Potentially, Financial Difficulties represent social economic status rather than health-related quality of life, which in turn may affect survival. In contrast to the previous study[8], Physical Functioning was not associated with survival after adjusting for known clinical risk factors.

Overall mortality of non-muscle invasive bladder cancer patients was affected by their Physical Functioning and Dyspnoea. No study has looked at health-related quality of life

as a predictor for survival in non-muscle invasive bladder cancer patients previously. The effect sizes of these predictors were similar to the effect sizes of the predictors for the muscle invasive bladder cancer patients, with a HR of 0.985 for Physical Functioning and 0.991 for Dyspnoea. For Physical Functioning an improvement of 1SD would mean an increase of survival of 27%, for Dyspnoea a similar improvement would mean a an increase of 21% in survival. To put this in perspective, improving a patients' Physical Functioning could increase the survival to match a patient 4 years younger.

Even though the results of this study are intriguing, it is not without its limitations. This study only used baseline health-related quality of life, instead of the follow-up health-related quality of life, which makes it difficult to infer whether interventions targeted at improving health-related quality of life after diagnosis would be effective in increasing survival.

Additional research is needed to replicate our findings. If baseline health-related quality of life can indeed predict bladder cancer survival, health-related quality of life may be used as a predictive tool for survival. Additionally, it is possible that survival rates could be improved by improving health-related quality of life, in which case a significant number of bladder cancer patients might benefit from interventions targeted at improving health-related quality of life. Particularly, muscle invasive bladder cancer patients could benefit most, as current survival rates are relatively low. However, non-muscle invasive bladder cancer patients are the majority and even though rates are lower, absolute numbers are close together (159 deaths in muscle invasive bladder cancer vs. 177 deaths in non-muscle invasive bladder cancer).

Future research would have to determine whether improving health-related quality of life after diagnosis could improve survival rates. Additionally, if improvement of health-related quality of life after diagnosis may improve survival rates, the following step will be identifying the most effective time period for targeted interventions like, for instance support groups. In addition to improving survival rates, increased health-related quality of life may also be associated with the type of bladder cancer. Therefore, it would be interesting to investigate this association in future research.

Furthermore, some predictors (Role Functioning and Physical Functioning) for survival are related to performance status, a measure that is generally used in clinical practice. However, whereas performance status is a general measure, the QLQ-C30 provides more detail into the specific domains that impact the survival of a patient. [74]

5.5.1 Conclusion

This study found that for muscle invasive bladder cancer patients, survival can be partly predicted by the patient's perceived ability to fulfill their role in society (work or hobby) and their disease-related financial difficulties at diagnosis. For non-muscle invasive bladder cancer patients, survival is partly predicted by the patient's perceived burden of dyspnea and their perceived ability to retain physical functioning at baseline. These factors seem to influence survival rates independently of known clinical factors. The current study suggests that the association of low health-related quality of life and decreased survival may not only be due to advanced disease stage. However, further research is needed to confirm these findings and further disentangle the differences between survival of muscle invasive and non-muscle invasive bladder cancer. Additional

research into the relationship of change in health-related quality of life and bladder cancer survival is necessary to identify potential areas for intervention.

CHAPTER 6 - VALIDATION OF THE EORTC QLQ-NMIBC24, A QUALITY OF LIFE QUESTIONNAIRE FOR NON-MUSCLE INVASIVE BLADDER CANCER PATIENTS

6.1 Abstract

Introduction

Bladder cancer is the seventh most common cancer in the United Kingdom; 75% of patients present with non-muscle invasive bladder cancer. The extensive follow-up due to the ~55% recurrence rate in the first five years may have a substantial effect on their quality of life. Health-related quality of life has been suggested to be important in patient well-being. However, the only non-muscle invasive bladder cancer-specific health-related quality of life questionnaire to date has not yet been validated. This study aimed to validate the proposed domain structure of the QLQ-NMIBC24 and provide provisional reference data.

Methods

Data were used from the Bladder Cancer Prognosis Programme, a large multi-center cohort study. 405 non-muscle invasive bladder cancer patients were followed up for five years and health-related quality of life was measured at three months and then yearly thereafter with the QLQ-NMIBC24. Multi-trait scaling was performed to investigate convergent and discriminant validity and reliability was determined by Cronbach's alpha. T-tests and multi-level linear mixed models were used to test associations between demographic and clinical variables, and QLQ-NMIBC24 domains.

Results

A previously suggested domain structure by Blazeby et al. showed satisfactory psychometric values, with a convergent validity of 0.34 – 0.83, a discriminant validity of 0.01 – 0.43 and a reliability of 0.66 – 0.90. No difference was found between patients

with and without recurrence in the first year. However, age was negatively associated with sexual function and male sexual problems. Furthermore, women scored lower on sexual function than men.

Conclusion

The Blazeby domain structure seems suitable for analysis of QLQ-NMIBC24 data. Lastly, this study provides unique health-related quality of life data for the UK non-muscle invasive bladder cancer patient population measured by the QLQ-NMIBC24.

6.2 Introduction

Bladder cancer is the fifth most common cancer in Western society, with a rising global incidence.[61,62] In the UK, the disease accounts for approximately 10,000 new cases and 5,000 deaths per year. The majority of patients (75-80%) present with non-muscle-invasive bladder cancer. Although not immediately life-threatening in the majority of cases, recurrence and progression of non-muscle invasive bladder cancer remain significant issues, with up to 55% of patients experiencing recurrence within five years of diagnosis.[63] Current guidelines therefore recommend long-term surveillance. [13,17] As survival in non-muscle invasive bladder cancer patients is relatively high, compared with other cancers, and long-term follow-up is required, this disease can be considered a chronic disease.

Surveillance of low-risk non-muscle invasive bladder cancer patients involves follow-up cystoscopy and urine cytology at three and 12 months after tumour resection (TURBT), and then annually for the next five years. High-risk non-muscle invasive bladder cancer patients undergo even more intensive surveillance most likely for the rest of their lives.[13,17] If recurrence is detected, the tumour is resected and subsequent surveillance will start again, with the frequency determined by the risk category of the recurrence. Furthermore, cystoscopy itself significantly increases the burden of disease, as it is an invasive procedure that causes pain and discomfort in about one-third of patients.[68] Therefore, health-related quality of life plays a very important role in patient well-being.

Historically, health-related quality of life in bladder cancer studies has been assessed with general (cancer) health-related quality of life questionnaires, most commonly with

the Medical Outcomes Study Short Form-36 (SF-36), which is a general quality of life questionnaire.[93] However, this quality of life questionnaire has not been developed specifically with cancer patients in mind. The Quality of Life Questionnaire Cancer 30 (QLQ-C30) v3[74] is a validated questionnaire specifically developed for measuring health-related quality of life in cancer patients, developed by the European Organisation for the Research and Treatment of Cancer (EORTC). Although this quality of life questionnaire focuses on measuring health-related quality of life in cancer patients it does not measure bladder cancer-specific issues regarding health-related quality of life, such as urinary problems, bladder cancer treatment/surveillance issues, and sexual problems. Additionally, these questionnaires might not be sensitive enough to detect the variations in health-related quality of life between different stages of bladder cancer.[94]

To date, two bladder cancer-specific questionnaires are commonly used, the Bladder Cancer Index (BCI) and the Functional Assessment of Cancer Therapy – (Bladder Cancer (FACT-BL)/FACT-Vanderbilt Cystectomy Index (VCI)).[22] The BCI measures bladder cancer specific health-related quality of life, divided over three overall domains: Urinary, Bowel, and Sexual.[95] This questionnaire does not have a module specific for muscle invasive bladder cancer or non-muscle invasive bladder cancer. Both the FACT-BL and the FACT-VCI are add-on modules developed to measure bladder cancer specific issues and used in conjunction with the FACT-General. The bladder cancer specific modules are summarised into a single summary score.

The Non-Muscle Invasive Bladder Cancer-Specific Quality of Life Questionnaire (QLQ-NMIBC24) is a module of the EORTC QLQ-C30. A full description of the questionnaire

can be found in the Methods section (page 19). To date, only one study has been published in which the QLQ-NMIBC24 was validated and compared with the domain structure proposed by the EORTC.[96] Following the comparison, the authors proposed a better fitting structure, which needs replication. Particularly, evidence from populations that are more diverse in demographics and bladder cancer characteristics could add more confidence in the newly proposed domain structure.

6.2.1 Aim

The current study aims to assess the quality, reliability, and validity of the QLQ-NMIBC24 domain structure suggested by Blazeby et al.[96], in a more diverse and representative UK population.

6.3 Methods

6.3.1 Cohort

The present study was part of the Bladder Cancer Prognosis Programme (BCPP), which is a multi-center cohort study in the West Midlands, UK. Details of the study have been published previously.[75] Briefly, adult patients (age ≥18 years) presenting at haematuria clinics in the nine participating urology centers within the region were enrolled on the basis of abnormal cystoscopic findings suggestive of bladder cancer. Those who had a previous diagnosis of cancer of the urethra, bladder, ureter or renal pelvis within the last decade, HIV infection, or any other condition that might interfere with the safety of the participant were excluded. The enrolment period lasted from the 19th of December 2005 to the 21st of April 2011. The Nottingham Multi-center Research Ethics Committee

approved the study protocol (06/MRE04/65), and all participants provided written informed consent before they were included in the study.

6.3.2 Procedure

Around the time of diagnosis, trained research nurses collected socio-demographics, lifestyle and medical, and health-related quality of life details through semi-structured face-to-face interviews. These interviews were also conducted at three months and annually thereafter until the end of study.

Medical records of each participant were reviewed by trained research nurses to gather information on clinicopathological characteristics of the bladder cancer at diagnosis. This comprised of pT stage (according to the tumour, node, metastasis (TNM) 2002 classification system[78]), grade (according to the World Health Organization (WHO) 1973 system[79]). In case a re-resection within three months after the first surgery of BC indicated an invasive tumour (≥pT2), in contradiction to the original assessment, then the re-resection pT stage was recorded as the pT stage at diagnosis.

6.3.3 Non-Muscle Invasive Bladder Cancer Quality of Life Questionnaire (QLQ-NMIBC24)

The QLQ-NMIBC24 is a non-muscle invasive bladder cancer specific questionnaire was used to measure health-related quality of life. The QLQ-NMIBC24 originally consisted of 24 items that were suspected to relate to five multi-item domains (Urinary Symptoms, Malaise, Intravesical Treatment, Future Worries, Bloating and Flatulence) and eight single-item domains relating to sexual activity and intimacy problems. There were three

gender-specific items (two for males and one for females) and four items specifically for patients who were sexually intimate within the last four weeks. Since the creation of the QLQ-NMIBC24, Blazeby et al.[96] has suggested a different model with six multi-item domains (Urinary Symptoms, Malaise, Future Worries, Bloating and Flatulence, Sexual Function, and Male Sexual Problems) and five single-item domains, four relating to sexual activity and intimacy (Sexual Intimacy, Sexual Contamination Partner, Sexual Enjoyment, Sexual Function in women), and one relating to intravesical treatment issues. A graphical representation of this domain structure can be found in Table 1.

All items are scored on a 4-point Likert scale (i.e., "Not at all", "A little", "Quite a bit", "Very much"). In this paper, for all items, a higher score represents a better health-related quality of life score. The same is true for the domains to which these items belong.

Table 6.1 Domains for the Non-Muscle Invasive Bladder Cancer-Specific Quality of Life Questionnaire (QLQ-NMIBC24) as examined by Blazeby et al.[96]

	Urinary symptoms and problems							**Malaise**		**IN**	**Future Worries**				**Bloating and Flatulence**		**Sexual Function**		**SXmen**		**One item sexual problems[a]**			
item	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41**	**42**	**43**	**44**	**45**	**46**	**47**	**48**	**49**	**50**	**51**	**52**	**53**	**54**
male	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	•	•	•	
female	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			•	•	•	•

x = for all patients
• = additional items for patients who were sexually active in the past 4 weeks
IN = Intravesical Treatment
SXmen = Male Sexual Problems
[a] This category includes: Sexual Intimacy, Sexual Contamination Partner, Sexual Enjoyment, Female Sexual Problems

6.3.4 Statistical analysis

All analyses were performed in STATA 12. The item and domain scores were recoded via linear conversion, to represent a score from 0-100, following the EORTC QLQ-NMIBC24 guidelines. Missing data was imputed according to EORTC guidelines if <50% of a domain was missing. In case >50% was missing, the particular domain was not used for the analysis.[76] For the purpose of validating the questionnaire, only data from the 3-month time point was used.

Quality

Data quality was determined by assessing response rates and missing data for each item.

Reliability

Multi-trait scaling was used to assess internal consistency, item discriminant validity (item correlation with other domains) and item convergent validity (item correlation with own domain) of the questionnaire. The Cronbach's alpha is a commonly used coefficient of reliability of psychometric tests and questionnaires. Cut-offs of 0.5, 0.7 and 0.9 are generally considered poor, acceptable and excellent reliability, respectively. For this study, a Cronbach's alpha coefficient of above 0.70 was considered satisfactory reliability of the domains.

Validity

Known group comparison analysis was performed to assess the clinical validity of the QLQ-NMIBC24. Known groups were created by dividing into two groups based on the Physical Functioning scale of the QLQ-C30 (which was recorded at the same time as the QLQ-NMIBC24), patients with a PF above the median value were classed as the "high" group and patients with a median or lower value were classed as "low". A t-test was

used to assess difference in QLQ-NMIBC24 scores between patients with and without recurrence during 1 year of follow-up.

Multilevel mixed-effects linear regression was used to assess the influence of time, sex, and age on the QLQ-NMIBC24 scores, which included additional data from the 1-year follow-up.

6.4 Results

Out of the 1,536 recruited participants with symptoms related to bladder cancer, 1,280 were then diagnosed with bladder cancer, of which 984 had non-muscle invasive bladder cancer (77%). Of these, 405 had filled out at least one follow-up questionnaire (3-month or 1-year follow-up) and 308 had completed the 3-month follow-up questionnaire.

The majority of the patients were male (n=310, 77%) and the average age of the patient population was 69 years (range = 33 - 91 years). More than half of the patients (57%) were former smokers at the start of the study and 77 (19%) were current smokers. Most of the patients presented with pTa tumour stage (n=253, 64%) as can be seen in Table 2. There were no significant differences between responders and non-responders with regards to age, sex, and tumour stage, data not shown.

On average, there was a high completion rate of 95.2% (range: 89.3% - 99.7%) for the items relating to urinary problems (items 31 to 46). However, the completion rate for items relating to sexual activity (item 47 to 54) was lower with an average of 66.6% (range: 46.8% - 90.0%), see Table 6.3. Multi-item domain scores could not be calculated in 0.67% of the cases as a result of more than half of the domain being missing.

Table 6.2 Socio-demographic characteristics of patients

		N	%
Total		405	100
Sex			
	Male	310	76.5
	Female	95	23.5
Age			
	Mean (SD)	68.9 (10.2)	
	Range	33 - 91	
Smoking status			
	Current	77	19.0
	Former	229	56.5
	Never	88	21.7
	Missing	*11*	*2.7*
Tumour Stage			
	pTis	5	1.2
	pTa	253	62.5
	pT1	141	34.8
	Missing	*6*	*1.5*
Grade			
	Grade 1	93	23.0
	Grade 2	165	40.7
	Grade 3	142	35.1
	Missing	*5*	*1.2*

Table 6.3 QLQ-NMIBC24 item response frequency in percentages at 3 months

Item #	Content	Not at all	A little	Quite a bit	Very much	Missing	N
							308
Item 31	Urinate during the day	32.1	28.6	20.8	7.8	10.7	
Item 32	Urinate during the night	30.5	35.1	17.9	6.8	9.7	
Item 33	Hurry to toilet	39.9	29.5	13.0	7.8	9.7	
Item 34	Difficulty to sleep (urinate)	53.9	22.7	5.2	8.4	9.7	
Item 35	Difficulty to go out (urinate)	67.9	14.6	3.2	4.2	10.1	
Item 36	Unintentional release of urine	62.0	21.1	3.2	3.9	9.7	
Item 37	Pain urinating	63.3	16.6	5.8	3.6	10.7	
Item 38	Fever	92.9	4.2	1.6	0.3	1.0	
Item 39	Ill or unwell	70.1	23.1	3.9	1.6	1.3	
Item 40	Trouble arranging life (cystoscopies)	75.3	18.5	4.2	1.3	0.6	
Item 41	Worry about cystoscopies	46.8	39.9	10.4	2.6	0.3	
Item 42	Worried about future	26.0	52.3	13.3	7.8	0.6	
Item 43	Worry about results	28.9	48.7	13.6	8.4	0.3	
Item 44	Worry about future treatments	32.1	49.0	12.0	6.5	0.3	
Item 45	Bloated feeling	69.8	19.8	8.1	1.3	1.0	
Item 46	Flatulence	47.4	35.4	12.7	3.6	1.0	
Item 47	Interested in sex	27.3	17.2	9.7	3.6	42.2	
Item 48	Sexually active	33.1	14.9	6.5	1.6	43.8	
Item 49[a]	Difficulty erection	19.5	9.5	8.2	15.2	47.6	231
Item 50[a]	Difficulty ejaculation	30.3	4.8	4.8	6.9	53.2	231
Item 51[b]	Uncomfortable being intimate	53.5	14.1	7.0	2.8	22.5	71
Item 52[b]	Worried contamination	56.3	11.3	7.0	2.8	22.5	71
Item 53[b]	Sex enjoyable	1.4	18.3	31.0	23.9	25.4	71
Item 54[b c]	Dry vagina	30.0	30.0	20.0	10.0	10.0	10

[a] Question for men only; [b] Question for patients who have been sexually active in the last 4 weeks; [c] Question for women only

Mean scores on all domains were relatively high at all time points (range: 56 – 93), except for Sexual Function (range: 21 – 23). Furthermore, there was limited change in mean scores over time (standard deviation range: 0.0 – 1.9) as can be found in Figure 6.1 and Figure 6.2.

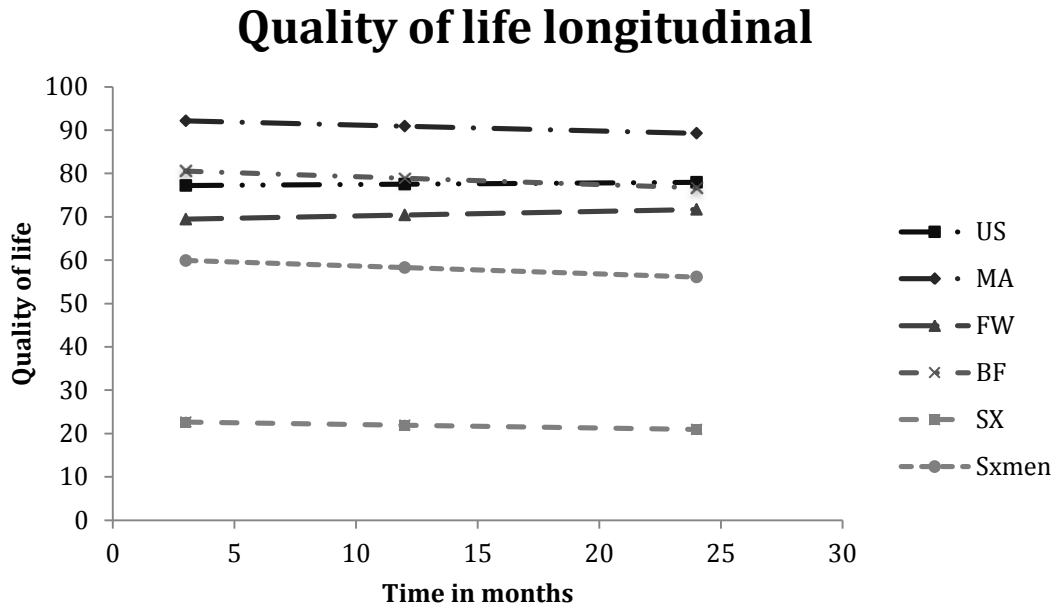


Figure 6.1 Multi-item domains of quality of life measured by the QLQ-NMIBC24 longitudinally at 3, 12, and 24 months
US: Urinary Symptoms; MA: Malaise; FW: Future Worries; BF: Bloating and Flatulance; SX: Sexual Function; SXmen: Male Sexual Problems

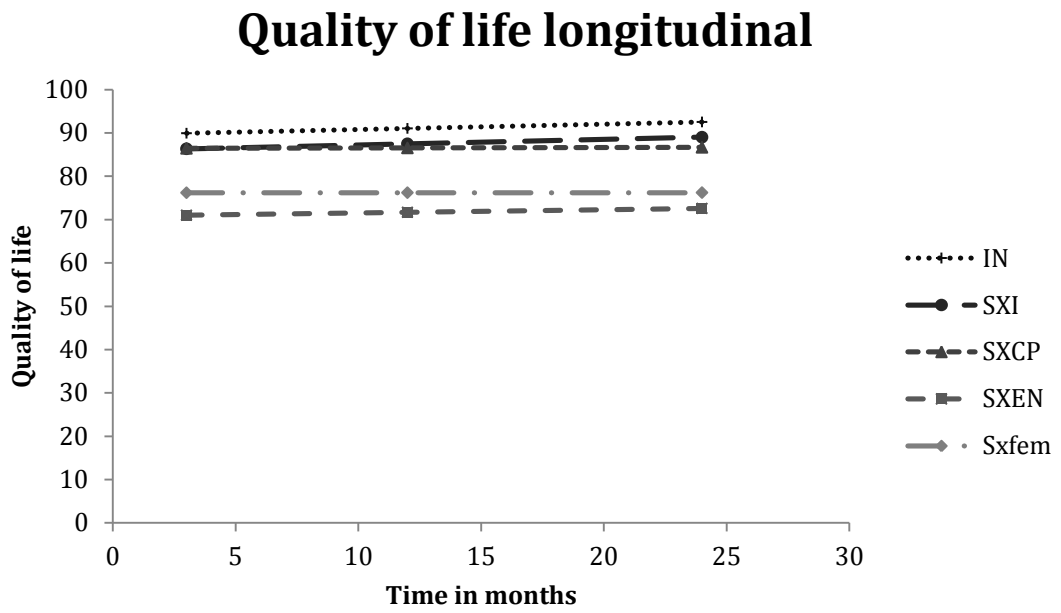


Figure 6.2 Single-item domains of quality of life measured by the QLQ-NMIBC24 longitudinally at 3, 12, and 24 months
IN: Intravesicle Treatment; SXI: Sexual Intimacy; SXCP: Sexual Contamination Partner; SXEN: Sexual Enjoyment; SXfem: Sexual Function in women

Multi-trait scaling analysis showed that the Blazeby domain structure showed acceptable psychometric values (Table 6.4). The item convergent validity, corrected for overlap, for all domains were above the 0.40 cut-off value, except for Male Sexual Problems (Urinary Symptoms: 0.54 to 0.75, Malaise: 0.46 to 0.52, Future Worries: 0.65 to 0.83, Bloating and Flatulence: 0.52 to 0.53, Sexual Function: 0.50 to 0.71, Male Sexual Problems: 0.34 to 0.47). Furthermore, there was good item discriminant validity, with correlations lower than the item convergent validity for all domains, ranging from 0.01 to 0.44. Finally, Cronbach's alpha ranged from 0.70 to 0.89.

Table 6.4 Convergent (in **bold**) and discriminant correlations for the Multi-Trait Scaling analysis QLQ-NMIBC24 at 3 months

	Scores		Correlations						
Item	Mean	SD	US	MA	FW	BF	SX	SXmen	alpha
Item 31	2.05	0.97	**0.72**	0.25	0.26	0.37	-0.01	0.07	
Item 32	2.01	0.92	**0.74**	0.26	0.27	0.31	0.04	0.16	
Item 33	1.87	0.96	**0.73**	0.30	0.20	0.31	-0.03	0.06	
Item 34	1.65	0.95	**0.75**	0.36	0.35	0.35	0.03	0.16	
Item 35	1.38	0.77	**0.72**	0.26	0.38	0.27	0.04	0.08	
Item 36	1.44	0.76	**0.54**	0.26	0.21	0.34	-0.03	-0.01	
Item 37	1.44	0.79	**0.60**	0.43	0.35	0.34	0.13	0.13	0.89
Item 38	1.09	0.36	0.20	**0.52**	0.18	0.28	0.00	-0.04	
Item 39	1.36	0.64	0.30	**0.46**	0.39	0.43	0.06	0.08	0.61
Item 41	1.69	0.76	0.16	0.23	**0.65**	0.21	0.10	0.02	
Item 42	2.03	0.84	0.22	0.34	**0.82**	0.32	0.12	0.18	
Item 43	2.02	0.88	0.24	0.26	**0.81**	0.25	0.08	0.09	
Item 44	1.93	0.84	0.33	0.30	**0.83**	0.27	0.08	0.10	0.90
Item 45	1.40	0.70	0.26	0.42	0.32	**0.52**	-0.02	-0.02	
Item 46	1.72	0.82	0.23	0.31	0.24	**0.53**	0.08	0.09	0.69
Item 47	3.18	0.93	-0.03	0.09	0.11	0.08	**0.50**	-0.14	
Item 48	3.42	0.81	-0.06	-0.03	0.03	0.05	**0.71**	-0.09	0.85
Item 49	2.36	1.25	0.12	0.15	0.10	0.29	0.10	**0.34**	
Item 50	1.75	1.14	0.10	0.21	0.17	0.16	0.23	**0.47**	0.66

Note that only multi-item domains have been taken into account during the multi-trait scaling analysis
The Blazeby scale structure was used in this analysis
SD=Standard Deviation, US=Urinary Symptoms, MA=Malaise, FW=Future Worries, BF=Bloating and Flatulence, SX=Sexual Function, SXmen=Male Sexual Problems

The low Physical Functioning group had a significantly lower mean score at 1-year follow-up compared with the high PF group on all domains except for Sexual Contamination Partner, Sexual Enjoyment, and Female Sexual Problems (Table 6.5). Patients with no recurrence within the first year consistently scored higher on each domain, except for Bloating and Flatulence, Sexual Intimicy, and Sexual Enjoyment. However, these differences were not statistically significant, except for the Male Sexual Problems domain (Table 6.6).

Table 6.5 Difference in QoL between patients with a high physical functioning score on the QLQ-C30 and a low score at 1-year follow-up

Scale	PF Group	N	Mean	SE	p-value
US	Low	113	69.57	2.29	
	High	81	91.08	1.46	1.16E-11
MA	Low	125	85.87	1.66	
	High	85	97.06	0.84	3.82E-07
IN	Low	125	67.96	2.37	
	High	84	75.17	2.33	0.039
FW	Low	125	71.60	2.25	
	High	83	84.54	2.04	8.24E-05
BF	Low	84	13.89	2.24	
	High	43	35.27	4.41	4.12E-06
SX	Low	60	46.39	4.84	
	High	38	65.79	5.33	0.010
SXMen	Low	125	89.07	2.03	
	High	82	95.53	1.50	0.022
SXI	Low	17	90.20	3.80	
	High	21	96.83	2.19	0.122
SXCP	Low	17	86.27	7.04	
	High	21	87.30	6.29	0.914
SXEN	Low	17	72.55	5.88	
	High	21	84.13	4.94	0.138
SXfem	Low	3	88.89	11.11	
	High	1	66.67	.	.

PF = Physical Functioning; High = PF score above median; Low = PF score median or lower
US: Urinary Symptoms; MA: Malaise; FW: Future Worries; BF: Bloating and Flatulance; SX: Sexual Function; SXmen: Male Sexual Problems; IN: Intravesicle Treatment; SXI: Sexual Intimacy; SXCP: Sexual Contamination Partner; SXEN: Sexual Enjoyment; SXfem: Sexual Function in women

Table 6.6 Difference in QoL between patients with and without a recurrence at 1-year follow-up

Scale	Group	N	Mean	SE	p-value
US	N	148	79.21	1.78	
	R	47	76.63	3.90	0.50
MA	N	159	91.30	1.26	
	R	52	87.82	2.29	0.18
IN	N	157	92.57	1.52	
	R	51	88.89	3.05	0.25
FW	N	159	72.54	1.84	
	R	51	66.18	4.06	0.11
BF	N	158	76.37	1.86	
	R	51	77.78	3.36	0.71
SX	N	96	21.87	2.77	
	R	31	18.82	3.69	0.57
SXmen	N	73	58.45	4.22	
	R	25	40.67	7.33	0.04
SXI	N	29	93.10	2.55	
	R	9	96.30	3.70	0.53
SXCP	N	29	87.36	5.08	
	R	9	85.19	11.26	0.84
SXEN	N	29	78.16	4.46	
	R	9	81.48	8.07	0.72
SXfem	N	3	88.89	11.11	
	R	1	66.67	.	.

N = No recurrence; R = Recurrence
US: Urinary Symptoms; MA: Malaise; FW: Future Worries; BF: Bloating and Flatulance; SX: Sexual Function; SXmen: Male Sexual Problems; IN: Intravesicle Treatment; SXI: Sexual Intimacy; SXCP: Sexual Contamination Partner; SXEN: Sexual Enjoyment; SXfem: Sexual Function in women

Table 6.7 summarises the results of the multi-level linear mixed models analyses. Follow-up time was negatively associated with the domains Malaise and Bloating and Flatulence (p-value < 0.05). Similarly, age was negatively associated with Urinary Symptomes and Sexual Enjoyment (p-value < 0.01), and Sexual Function and Male Sexual Problems (p-value < 0.001). Finally, women scored lower on the Sexual Function domain than men (p-value < 0.001). However, only the latter three associations could also be considered clinically significant.

Table 6.7 Multi-level linear mixed model longitudinal analyses of each domain

	Time (in months) coef (95% CI)	Sex coef (95% CI)	Age (in years) coef (95% CI)
US	0.04 (-0.13 – 0.19)	-0.58 (-5.47 – 4.31)	-0.32 (-0.53 – -0 .12)**
MA	-0.14 (-0.27 – -0.01)*	-0.80 (-4.06 – 2.46)	0.12 (-0.02 – 0.25)
FW	0.11 (-0.05 – 0.27)	-0.60 (-5.88 – 4.69)	0.19 (-0.02 – 0.41)
BF	-0.19 (-0.36 – -0.01)*	-3.49 (-8.14 – 1.15)	-0.02 (-0.21 – 0.17)
SX	-0.08 (-0.29 – 0.14)	-14.76 (-21.20 – -8.31)***	-0.93 (-1.18 – -0.69)***
SXmen	-0.14 (-0.49 – 0.21)	Omitted	-1.24 (-1.69 – -0.80)***
IN	0.12 (-0.05 – 0.30)	0.38 (-3.56 – 4.31)	-0.06 (-0.22 – 0.11)
SXI	0.13 (-0.24 – 0.51)	1.58 (-11.69 – 14.85)	-0.06 (-0.50 – 0.39)
SXCP	0.02 (-0.46 – 0.49)	-0.60 (-15.13 – 13.93)	-0.05 (-0.54 – 0.44)
SXEN	0.18 (-0.27 – 0.64)	2.19 (-11.28 – 0.64)	-0.66 (-1.11 – -0.20)**
SXfem	Omitted	Omitted	Omitted

US: Urinary Symptoms; MA: Malaise; FW: Future Worries; BF: Bloating and Flatulance; SX: Sexual Function; SXmen: Male Sexual Problems; IN: Intravesicle Treatment; SXI: Sexual Intimacy; SXCP: Sexual Contamination Partner; SXEN: Sexual Enjoyment; SXfem: Sexual Function in women.
* = p-value < 0.05; ** = p-value < 0.01; *** = p-value < 0.001

6.5 Discussion

Health-related quality of life has been suggested to be important in patient well-being. However, current measurement of health-related quality of life in bladder cancer patients is done with general quality of life questionnaires, which may not adequately measure bladder cancer-specific issues or detect health-related quality of life differences between bladder cancer stages. To date, only the QLQ-NMIBC24 has been specifically designed to measure health-related quality of life in non-muscle invasive bladder cancer patients on different domains.

In our population of non-muscle invasive bladder cancer patients in the West Midlands (UK), mean scores on all domains were relatively high at all time points and did not change significantly over time. This might suggest that the impact of being diagnosed with non-muscle invasive bladder cancer either dissipated before the first follow-up (at 3 months) or it is not big enough to be detected by this questionnaire. Additionally, the potential impact of the cystoscopy investigations seems negligible.

However, the QLQ-NMIBC24 is sensitive enough to pick up the differences between the low and high PF groups in our known groups comparison analyses, which reinforces that non-muscle invasive bladder cancer patients may not be as negatively impacted by their disease as one might expect. Alternatively, no clinically relevant differences were found between patients with and without recurrences at 1 year. It is possible that this is because every non-muscle invasive bladder cancer patient undergoes the same amount of cystoscopies, as the recurrences are routinely removed during these investigations.

Interestingly, in the results of the multi-level linear mixed models analyses three associations were statistically and clinically significant. Age and the female sex both negatively impacted Sexual Function, whereas age also negatively impacted Male Sexual Problems. The associations with age might naturally make sense, however, the relation between the female sex and Sexual function is a novel find.

The slight differences in results between this study and the Blazeby study may be due to differences in population, as Blazeby et al. did not include non-muscle invasive bladder cancer patients with a low risk for a recurrence and/or progression.

6.5.1 Conclusion

To summarise, the current validation study confirmed that the domain structure proposed by Blazeby et al.[96] has acceptable item convergent and discriminant validity criteria and reliability. Our study contributes data to the scarce health-related quality of life data sources for the UK non-muscle invasive bladder cancer patient population. However, the QLQ-NMIBC24 should also be validated in other countries.

CHAPTER 7 - PATIENTS CHOOSE CERTAINTY OVER BURDEN IN SURVEILLANCE FOR BLADDER CANCER RECURRENCE

7.1 Abstract

Introduction

Due to high risk of recurrence of non-muscle invasive bladder cancer, all patients undergo regular cystoscopic surveillance for early detection. As cystoscopy is invasive, costly and increases the burden of the disease significantly, there is significant research into biomarker substitutes and several are already commercially available. The implementation of such biomarkers may become a realistic option if they can be shown to demonstrate a sufficient level of sensitivity. However, the exact level that would be needed before patients would accept such biomarker surveillance is unknown.

Methods

We have studied the preferences for a urinary biomarker compared to cystoscopy at different levels of sensitivity among 437 patients with bladder cancer (354 men and 83 women) from the UK West Midlands-based Bladder Cancer Prognosis Programme. A standard gamble approach was used to estimate the minimally acceptable sensitivity of the biomarker. Additionally we used linear regression analyses to investigate whether the minimally acceptable sensitivity of such a biomarker differs as a function of sex, age, marital status, general health of the patient or social support.

Results

Almost half of the patients (183, 43%) would not wish to replace cystoscopy with a biomarker unless it was 100% sensitive. In fact, the median minimally acceptable sensitivity was 99.9999% and nearly 85% of patients wanted a sensitivity of at least 99% before preferring a urinary biomarker over a cystoscopy. The minimally acceptable

sensitivity was not associated significantly with any sociodemographic variables or with social support, and no effect modification could be identified.

Discussion

Our results indicate that patients demand more sensitive urinary biomarkers than are currently available before they would be willing to forego the more invasive and burdensome cystoscopic procedure. This is an important message to the biomarker industry.

7.2 Introduction

Bladder cancer is the fifth most common cancer in Western society, with a rising global incidence.[61,62] In the UK, the disease accounts for approximately 10,000 new cases and 5,000 deaths per year. The majority of patients (75-80%) present with non-muscle-invasive bladder cancer. Although not immediately life-threatening in the majority of cases, recurrence and progression of non-muscle invasive bladder cancer remain significant issues,[62,97,98] with up to 55% of patients experiencing recurrence within five years of diagnosis.[63] Current guidelines recommend long-term surveillance.[99,100] With the UK prevalence of non-muscle invasive bladder cancer estimated at 46,500,[101] at any one time there will be between 35,000 and 37,000 patients requiring such surveillance.

Surveillance typically comprises cystoscopy.[13,17] For patients with low-risk non-muscle invasive bladder cancer, European Association of Urology (EAU) guidelines recommend follow-up cystoscopy and urine cytology at 3 months and 12 months after tumour resection (TURBT), and then annually for the next 5 years. Patients with high-risk non-muscle invasive bladder cancer undergo more intensive surveillance of cystoscopy and urine cytology- every 3 months for the first 2 years, then every 4 months for the following year, every 6 months for the year after, and then annually thereafter, most likely for the rest of their lives. [17] If recurrence is detected, then the tumour is resected and subsequent surveillance will start again, with the frequency determined by the risk category of the recurrence. It has been estimated that each cystoscopy and urine cytology episode costs £533.[65] This surveillance in combination with the regular readmissions for transurethral resection of the tumour due to recurrences makes bladder cancer the most costly cancer to treat on a per patient basis from diagnosis to death. [66,102]

Cystoscopy itself increases significantly the burden of disease, as it is an invasive procedure that causes pain and discomfort in about one-third of patients.[68] In contrast, previous studies have shown that the only burden attributable to a non-invasive test (such as a urinary biomarker) is the waiting time for the test result.[68] For these reasons, a number of urinary biomarkers have been developed by industry in an attempt to create less burdensome and less costly non-muscle invasive bladder cancer surveillance procedures.

Urine cytology is widely used as an adjunct to cystoscopy. It has high sensitivity for detecting high-grade disease (80% - 90%), but poor sensitivity for low grade disease (about 30%).[103-105] In addition, the diagnostic qualities of these tests are known to depend upon a number of confounding factors, such as the quality of the sample and the level of expertise of the cytologist.[106]

More recently, other types of diagnostic urinary biomarkers have been developed, including soluble urine markers (BTA stat, BTA TRAK, NMP22) and exfoliated cell markers (UroVysion, ImmunoCyt/uCyt), which are all commercially-available and US FDA-approved.[107] As can be seen in Table 7.1, these biomarkers have moderate to good sensitivity. However, what is less clear is what level of sensitivity is acceptable to patients undergoing surveillance for non-muscle invasive bladder cancer, such that they would be willing to switch from cystoscopy. Biomarker-driven surveillance might become a realistic possibility if, or when, they reach a sufficient level of sensitivity.[108]

Table 7.1 Sensitivity and specificity of commercially available urinary biomarkers

Biomarker	Specificity	Sensitivity
Cytology	78-100%	12-85%
BTA stat	52-93%	24-89%
BTA TRAK	48-95%	51-79%
NMP-22	40-90%	50-91%
ImmunoCyt	62-79%	63-85%
Urovysion	65-96%	69-96%

Only two studies have previously published on this subject. Vriesema et al., in a utility analysis on 85 patients (70 men and 15 women) undergoing bladder cancer surveillance, found that 68% of their patients had a minimally acceptable sensitivity of over 99%.[109] The more cystoscopies a patient had undergone, the higher was their minimally acceptable sensitivity, suggesting that the acceptability of cystoscopy increases with patients' familiarity with and/or confidence in the procedure. In a similar utility analysis on 200 patients (119 men and 81 women), Yossepowitch et al. reported that 70% of patients had a minimally acceptable sensitivity over 99%, and only 24.5% would accept a minimally acceptable sensitivity lower than 95%.[110]

We hypothesized that patients who perceive the burden of the cystoscopy to be high would be more inclined to choose a lower minimally acceptable sensitivity. In a similar manner, patients with a low health-related quality of life would find the burden of the cystoscopy to be higher and thus choose a lower minimally acceptable sensitivity. In addition, we hypothesized patients with more social support would be willing to take more risk and thus have a lower minimally acceptable sensitivity. Education was taken into account as we hypothesized that patients with a higher education would better understand the risk associated with cystoscopy and the benefit of having a urinary biomarker, even if it comes at the cost of sensitivity.

7.2.1 Aim

The objective of this study was to assess the level of biomarker acceptability in an non-muscle invasive bladder cancer population naïve to conventional surveillance, as well as assessing factors that may affect levels of acceptability, such as sociodemographics and social support.

7.3 Methods

7.3.1 Cohort

The study presented here is part of the West Midlands Bladder Cancer Prognosis Programme (BCPP), which is an ongoing multi-center cohort study in the West Midlands region of the UK.[75] Adult patients (age >18 years) presenting with symptoms suspicious for bladder cancer (haematuria in over 80%[22]) in the 9 participating urology centers within the region were enrolled on the basis of cystoscopic findings suggestive of bladder cancer. Those who had a previous diagnosis of cancer of the urethra, bladder, ureter or renal pelvis within the last decade, HIV infection, or any other condition that might interfere with the safety of the participant were excluded. The study received ethical approval as part of BCPP (reference: 06/MRE04/65), and written informed consent was obtained from all participants.

7.3.2 Procedure

At the time of diagnosis, trained research nurses conducted semi-structured face-to-face interviews to collect information on sociodemographics, health-related lifestyle (lifetime smoking history, passive smoking, use of hair dye), medical and drug history, dietary

intake, social support and health-related quality of life. Health-related quality of life was assessed with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire, the QLQ-C30.[74] Social support was assessed with the Duke-UNC Functional Social Support Questionnaire (FSSQ).[111] The FSSQ is an eight-item instrument, scored on a 1 to 5 scale, which measures the strength of a person's social support network. Both the QLQ-C30 and the FSSQ were converted to a scale ranging from 0 to 100, with 0 as the lowest quality of life or lowest level of perceived social support and 100 as the highest. Only the overall health-related quality of life scale from the QLQ-C30 was used, as we hypothesized that the burden of the cystoscopy would affect overall health-related quality of life rather than any specific health-related quality of life domain or symptom. Participants were followed up at approximately 3 months post-baseline measurement with a similar questionnaire. During this follow-up, changes in health-related lifestyle and health-related quality of life were assessed.

7.3.3 Standard gamble

We employed a utility-based patient preference questionnaire to assess the patient's preference for cystoscopy versus a hypothetical urinary biomarker test. Patients were given a short instruction and description of a hypothetical situation (see Appendix). Using a 'standard gamble' procedure, we posed a series of questions in which the patient was asked to chose between two surveillance tests, a cystoscopy or a hypothetical urinary biomarker test.[112] The sensitivity of the hypothetical urinary biomarker's started at 100%, and decreased in each subsequent question. The definition of sensitivity was explained to the patient as the number of tumours missed by the

biomarker out of a thousand. The minimally acceptable sensitivity was defined as the lowest value of accuracy at which the biomarker was favoured over the cystoscopy.

7.3.4 Statistical analysis

Due to the non-normal distribution of the minimally acceptable sensitivity data, we used non-parametric statistical analyses to investigate the association between surveillance preference and various patient characteristics. This included the Mann-Whitney/Wilcoxon rank-sum test and Spearman's rank correlation coefficient. In addition, we conducted exploratory logistic regression analyses in which we dichotomised the outcome variable (MAS) in order to identify differences between patients that were willing to sacrifice any sensitivity (<100%) and those that were not (100% only). Stratified analyses were used to identify any possible effect modification. Lastly, sensitivity analyses were conducted where patients with a minimally acceptable sensitivity of "0%" and a minimally acceptable sensitivity of "100%" were excluded. All analyses were performed with Stata/MP version 12. A p-value of <0.05 was considered statistically significant.

7.4 Results

During the recruitment period (2005-2011), 1,536 participants were enrolled. Of these 1,536 patients, 326 were excluded because they did not have primary bladder cancer, another 23 were lost to follow-up, and 514 were excluded as they did not complete the first questionnaire, leaving 673 patients potentially available for assessment (see Figure 7.1). Of these 673 patients, 437 (65%) responded to the standard gamble section and were included in the analyses. These 437 participants were slightly different to the 236

who did not complete the standard gamble with regards to sex (p=0.05) and just about statistically significantly different with regards to age (p=0.04), whereby the non-responders were older.

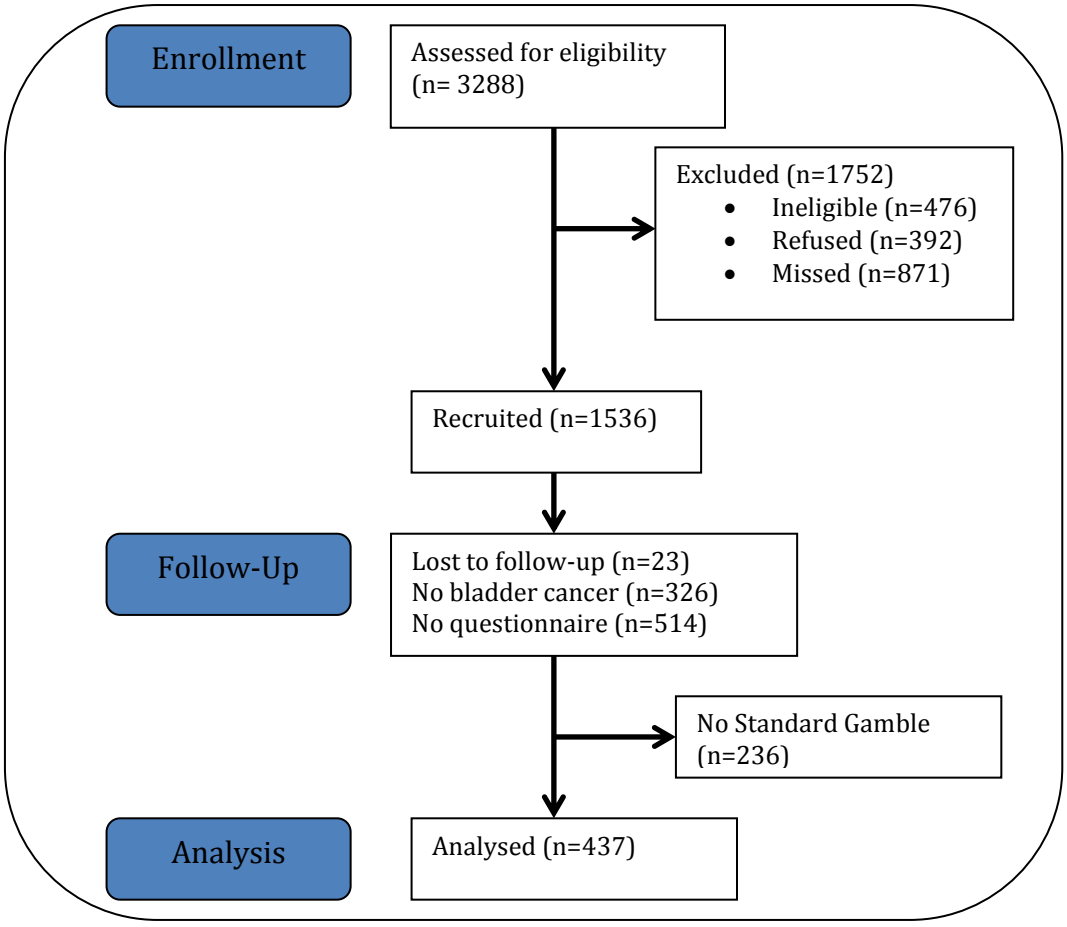


Figure 7.1 Flow diagram of patient enrolment and follow-up.

Of the 437 study participants included in the current analysis, 354 were male and 83 were female, the mean age was 69 years old, with a minimum of 33 and maximum of 90 years. 309 patients (73%) had a partner with whom they were married or living together. The median overall health-related quality of life as measured by the QLQ-C30 was 75 (interquartile range (IQR): 58 - 83), and the median social support was 100 (IQR: 88 - 100) (Table 7.2). 187 Patients (43%) would not change from a cystoscopy to a biomarker unless the biomarker had a sensitivity of 100%. In fact, the median value of

minimally acceptable sensitivity was 99.9999%, and nearly 85% of patients indicated that they would require a sensitivity of at least 99% before preferring a urinary biomarker test over cystoscopy.

Table 7.2 Patient characteristics (N=437)

Age		
Mean (SD)	68.8	(10.4)
Range	33 – 90	
Sex		
Male (%)	354	(81%)
Female (%)	83	(19%)
Marital status		
With partner (%)	309	(71%)
Without partner (%)	113	(26%)
Missing	*15*	*(3%)*
General health		
Median (IQR)	75	(58.3 – 83.3)
Range	8 - 100	
Social support		
Median (IQR)	100	(87.5 – 100)
Range	0 - 100	
Stage		
NMIBC		
pTis (%)	6	(1%)
pTa (%)	250	(57%)
pT1 (%)	139	(32%)
MIBC		
pT2 (%)	38	(9%)
Missing	*4*	*(1%)*

NMIBC=Non-muscle invasive bladder cancer
MIBC=Muscle invasive bladder cancer

We did not observe any statistically significant associations between the minimally acceptable sensitivity and age (p=0.09), sex (p=0.13), marital status (p=0.37), overall health-related quality of life (p=0.16), NVQ (p=0.17) or social support (p=0.57) and no effect modification was found. Sensitivity analyses showed similar results (no

association) except for age, which became statistically significant when either all the "100%" (p-value=0.03;rho=-0.14) answers or "0%" and "100%" (p-value=0.02;rho=-0.15) answers were excluded from the analyses. This suggests that, in these subsets of patients, increased age is associated with a lower minimally acceptable sensitivity; however this relationship was not observed in the total sample.

7.5 Discussion

Our results indicate that the large majority of patients recently diagnosed with bladder cancer demand a very high level of sensitivity before they would be willing to accept urinary biomarkers as an alternative to cystoscopy for periodic surveillance. Based on the conclusions of Vriesema et al. (2000)[109], we expected that our population of naïve cystoscopy patients would indicate a lower minimally acceptable sensitivity and therefore have a larger spread of responses. However, we observed the opposite. When comparing the results of previous studies to our results, it is clear that patients choose test certainty over test burden. In all three studies[109,110], more than 65% of the patients indicated that they would require a minimally acceptable sensitivity of over 99% (Table 7.3), and approximately 90% of patients would require a minimally acceptable sensitivity of over 90%. None of the existing biomarkers are able to consistently achieve this level of sensitivity.

Table 7.3 Minimally acceptable sensitivity distribution in the three different studies

Research group	<90	90 - <99	99 - 100	Total
Vriesema et al.	9 (10.6)	18 (21.2)	58 (68.2)	85
Yossepowitch et al.	7 (3.5)	53 (26.5)	140 (70.0)	200
Nekeman et al.	27 (6.3)	38 (8.8)	365 (84.9)	430
Total	43 (6)	109 (15)	563 (78)	715

The high percentage of patients that would not prefer a minimally acceptable sensitivity with sensitivity below 100% may reflect less than a full understanding of the concept of sensitivity, and also the fact that these patients were presented with a hypothetical situation. However, based on qualitative feedback from the research nurses who administered, it is our impression that many patients were "terrified" of missing a tumour.

It is important to note that new optical technologies (such as photodynamic diagnosis and narrow band imaging[113]) have shown that the sensitivity of conventional white light cystoscopy itself is much less than 100%, and that recurrent tumours are missed in up to 41% of patients.[114] Most patients in this study will have been unaware of the shortcomings of conventional white light cystoscopy and thus believed that readily accepted the 100% sensitivity that we used as a cystoscopy benchmark against which biomarkers were to be compared.

Even though there was only a moderate response rate (65%), we found little evidence of any significant difference between the patients who did and did not take part in the survey. Nevertheless, we cannot rule out the possibility that the minimally acceptable sensitivity of the larger population might be somewhat different from that of our study sample.

Two previous studies by Vriesema et al. and Yossepowitch et al. reported incongruent findings of associations between age and MAS, and sex and MAS; neither study was able to replicate the findings of the other[109,110]. Our study did not replicate findings of either of the two previous studies. This lack of association across the studies between the various potential risk factors and the minimally acceptable sensitivity might be due to the small variance in minimally acceptable sensitivity. Additionally, it might be possible

that we did not find an association between age and MAS, because mostly older patients did not complete the questionnaire.

Our results suggest that the bladder cancer biomarker research community, both commercial and academic, needs to improve test sensitivity substantially before such tests can be implemented into the patients' surveillance strategy. This is unlikely to be achievable with the current generation of urinary biomarkers, but may be achievable in the future with DNA-based approaches[115]. Cystoscopy is unlikely to be replaceable for the foreseeable future, but the next generation of urinary biomarkers may allow the frequency of cystoscopic surveillance to be reduced. Importantly, any evaluation of newly developed diagnostic tests should be reported following the STARD criteria to ensure optimal comparability with existing diagnostic measures.[116]

7.5.2 Conclusion

In conclusion, our study results indicate that patients demand more sensitive urinary biomarkers than are currently available, and thus patients choose certainty over burden.

CHAPTER 8 - THE QUALITY OF LIFE OF BLADDER CANCER PATIENTS UNDERGOING INCONTINENT AND CONTINENT URINARY DIVERSION TECHNIQUES: A META-ANALYSIS OF 18 OBSERVATIONAL STUDIES

8.1 Abstract

Context

High-grade muscle invasive bladder cancer requires radical cystectomy and subsequent urinary diversion. Which diversion offers the best quality of life remains uncertain.

Objective

Systematically review all relevant literature and perform a meta-analysis in order to evaluate whether the type of urinary diversion technique (continent vs incontinent) has an impact on health-related quality of life.

Evidence acquisition

Key electronic databases including Medline and Embase were searched until January 2015. References from selected articles were searched for additional articles. There were no restrictions with regard to language or study design. The main outcome was health-related quality of life measured by the EORTC QLQ-C30, the SF-36, or the FACT-G.

Evidence synthesis

Ten studies reported sufficient data for the meta-analysis. The four health-related quality of life domains that were analysed were: General Health, Physical Health, Emotional Health, and Social Health. The standardised mean difference between continent and incontinent diversion were 0.23, 0.49, -0.01, and 0.04 for General Health, Physical Health, Emotional Health, and Social Health respectively in favour of continent diversion.

Conclusion

Bladder cancer patients who have undergone continent diversion after radical cystectomy have better physical health compared to patients who have undergone incontinent diversion, albeit only slightly. Neither incontinent nor continent diversion offers a clear benefit in terms of cancer related outcomes. Other than absolute contra-indications to continent diversion, there is no reason to not perform continent diversion in case the small benefit could be perceived as a significant benefit to the patient.

8.2 Introduction

Bladder cancer is the ninth most common cancer worldwide[86] with around 30% of new cases diagnosed having muscle invasive tumours, which along with high grade or recurrent superficial disease often require radical cystectomy to improve long term survival rates. In all cases, a substitute mechanism for the bladder is needed to divert the urine from the kidneys out of the body, otherwise known as a urinary diversion technique.

In general, urinary diversion techniques can be categorized into two groups, continent (continent reservoir, and continent orthotopic neobladder) and incontinent (conduit) diversion. Incontinent conduit diversion refers to the conduit that is formed from a bowel segment to which the ureters are anastomosed. The other end of the conduit is then brought out through the abdominal wall as a stoma. A removable bag is then attached to the stoma to collect the draining urine. Traditionally a segment of the small intestine is used, although the large intestine has also been used. The ileal conduit, popularised by Bricker in 1950 [117], has been the standard incontinent urinary diversion technique until recent years. Continent diversion can be divided into two groups, continent reservoir and continent orthotopic neobladder. A continent reservoir is constructed from a bowel segment to which the two ureters are anastomosed. The reservoir itself is attached to the inside of the abdominal wall and a valve is created in order to maintain continence and for clean intermittent self-catheterization, eliminating the need for a stoma bag. A continent orthotopic neobladder is similar to the reservoir diversion in that a reservoir is created from a bowel segment, however, the outlet of the reservoir is connected to the native urethra. This allows the patient to void normally

through their native urethra, providing the native sphincter mechanism is still intact. All three urinary diversion techniques have both advantages and disadvantages. Their complications include, but are not limited to, perioperative bleeding, wound complications, urinary tract infections, metabolic complications, renal failure, urinary leakage, and stoma related problems. Yet no difference between techniques has been found with respect to cancer control and disease-specific and overall survival, making quality of life a crucial endpoint[118].

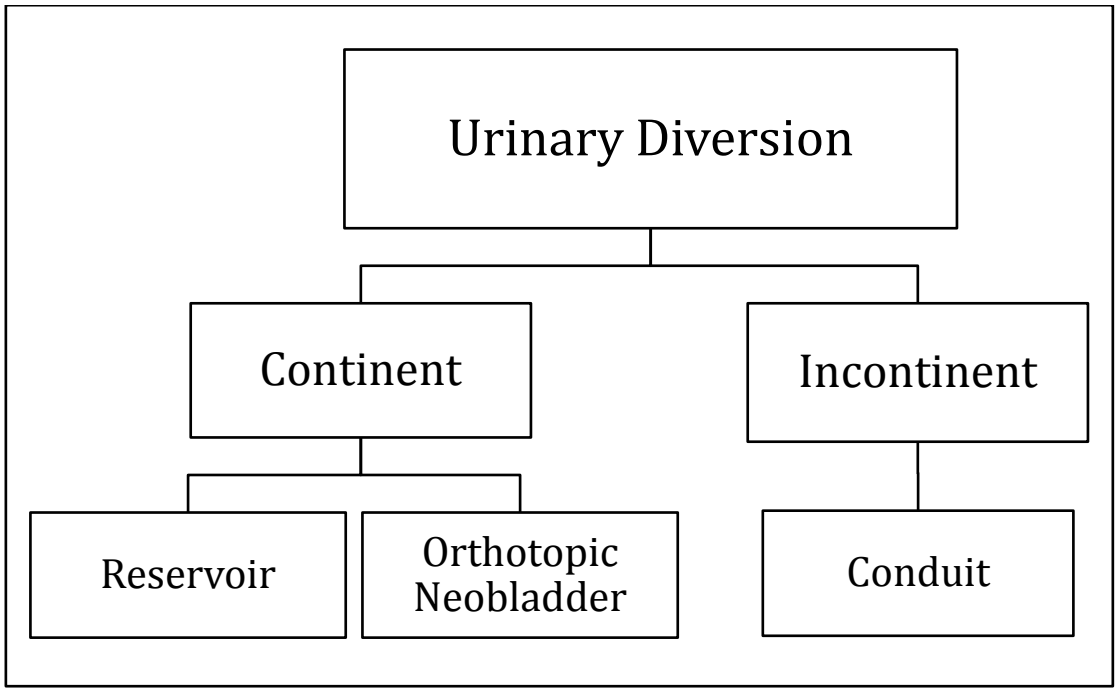


Figure 8.1 Visual representation of the different urinary diversion techniques

As there appears to be lack of consensus between urologists, the availability of quality of life data may help inform clinicians and patients on which urinary diversion technique to use. There have been numerous studies that have looked at quality of life differences between these three techniques; however, the results have been inconsistent with some having found differences between the three main techniques,[30,32] while others have not.[40,49] Although some reviews that have been published on this subject, [69,70,119-125]

none of these have tried to quantify the difference in QoL between these techniques by means of a meta-analysis. There are currently no available effect estimates for any of the different diversion techniques on which clinical decision-making could be based.

This Chapter aims to systematically review all relevant literature and perform a meta-analysis in order to determine the difference between incontinent en continent diversion techniques in terms of health related quality of life.

8.3 Methods

I performed the search, study identification and data extraction in parallel with Dr Maree Brinkman. Following each step, we discussed our results and discussed any differences. If we had not been able to resolve differences through discussion, Professor Zeegers would provide a resolution to the decision making process. However, this never occurred as we always reached a consensus.

PRISMA guidelines were followed throughout the conduct and reporting of this meta-analysis, a checklist of the PRISMA guidelines can be found in Appendix 11.11.[126]

8.3.1 Literature search

We searched Ovid Medline (from 1946), Pubmed (from 1966), and Ovid EMBASE (from 1980) until May 2015 using a predetermined search strategy specific for each search engine (Appendix 1), that included key words such as: bladder cancer and urinary neoplasms in conjunction with the interventions, conduit, pouch, reservoir, neobladder,

(in)continent diversion, (radical) cystectomy, urinary diversion, orthotopic bladder and quality of life instruments, (EORTC) QLQ-C30, SF-36, and FACT.

8.3.2 Inclusion criteria and evaluation of publications

Only peer-reviewed studies from scientific journals were eligible for inclusion in the meta-analysis. Additionally, only studies that reported health-related quality of life in human bladder cancer patients who had undergone radical cystectomy and subsequent urinary diversion were included. Furthermore, health-related quality of life had to be recorded using one of the following validated quality of life questionnaires: the EORTC QLQ-C30, the SF-36, or the FACT-G (for more details see Section 1.1.2). Although these are three different questionnaires, they have been validated to measure (some of) the same domains, which we will use in this meta-analysis. Preferably studies should have reported means and standard deviations for health-related quality of life data, however, studies were only excluded if a study reported insufficient data to calculate means and/or standard deviations. Lastly, only data reporting at least 12 months after the surgery was included.

No exclusion was made based on the co-administration of any adjuvant therapy e.g. chemotherapy and there were no language restrictions. Native speakers translated non-English reports before selection and data extraction. No study designs were excluded apart from reviews, meta-analyses and conference abstracts. In the case of multiple reports of the same study only the latest report was included. Where only partial information was given or it was unclear whether the study should be included, the

authors attempted to contact the original study investigators and requests for further information were made.

Following identification of potential studies, citation tracking was used with the references from all selected articles and hand searched for any further relevant studies using the same inclusion and exclusion criteria.

8.3.3 Data extraction

From the included studies, we extracted the following information: study design, population characteristics (e.g. sex, age), clinical characteristics (e.g. stage and grade), urinary diversion technique, mean health-related quality of life scores and standard deviations, follow-up duration.

8.3.4 Statistical analyses

Standardized mean differences

All analyses were done in Stata 12.[92] Continuous data were analysed using Hedges' g[127] standardized mean differences and their 95% confidence intervals (CI). Standardized mean differences were calculated by subtracting the mean score of the incontinent group from the continent group and dividing that by the pooled standard deviation. This resulted in a positive number if continent diversion was more favourable and a negative number if incontinent diversion was more favourable. Below is the equation used to calculate the standardised mean difference (Hedges' g):

$$d = \frac{\bar{x}_{con} - \bar{x}_{inc}}{s_{pooled}}$$

$$s_{pooled} = \sqrt[2]{\frac{(n_{con} - 1)s_{con}^2 + (n_{inc} - 1)s_{inc}^2}{n_{con} + n_{inc} - 2}}$$

$$J = \left(1 - \frac{3}{4 \times (n_{con} + n_{inc} - 2) - 1}\right)$$

$$\text{Hedges}' g = J \times d$$

To determine what was a clinically significant change for scales and questionnaires' score we used the guidelines proposed in the literature for the specific scales and questionnaires. When this information was not available or did not exist we used Cohen's [128] rule of thumb: Hedges' g ≥ .20, ≥ .50, ≥ .80 as our cut-off points for small, medium, and large effects, respectively.

Meta-analysis

The main meta-analysis was performed on studies that reported mean and SD data. If the I^2 was statistically significant and >60% (the cut-off for performing a meta-analysis), the identified source of heterogeneity was excluded, and the analysis was re-run. For the main analysis four domains, common between each quality of life questionnaire, were analysed separately. These four domains were: General Health, Physical Health, Emotional Health, and Social Health. Random effects meta-analysis was used to calculate pooled standardized mean differences and then presented in forest plots divided into groups based on the quality of life questionnaire that was used.

Sensitivity analyses

We imputed standard deviations for studies that only reported means and number of patients. We performed a sensitivity analysis to assess the potential impact of excluding studies that reported insufficient detail. Additionally, we performed a meta-analysis comparing neobladder versus incontinent diversion.

8.4 Results

8.4.1 Literature search

We identified 205 potential studies using the search strategy. A total of 41 studies remained for full text review, after eliminating duplicates (n=97), conference papers (n=34), and publications that did not meet the inclusion criteria (n=33). The full text review process excluded a further 24 articles and a handsearch of the reference lists uncovered one extra article, resulting in 17 studies identified through the literature search (see Figure 1.1). We sent letters to the authors of 25 studies to request the required details, which resulted in data from one additional study. Therefore, we included a total of 18 studies in our meta-analysis.

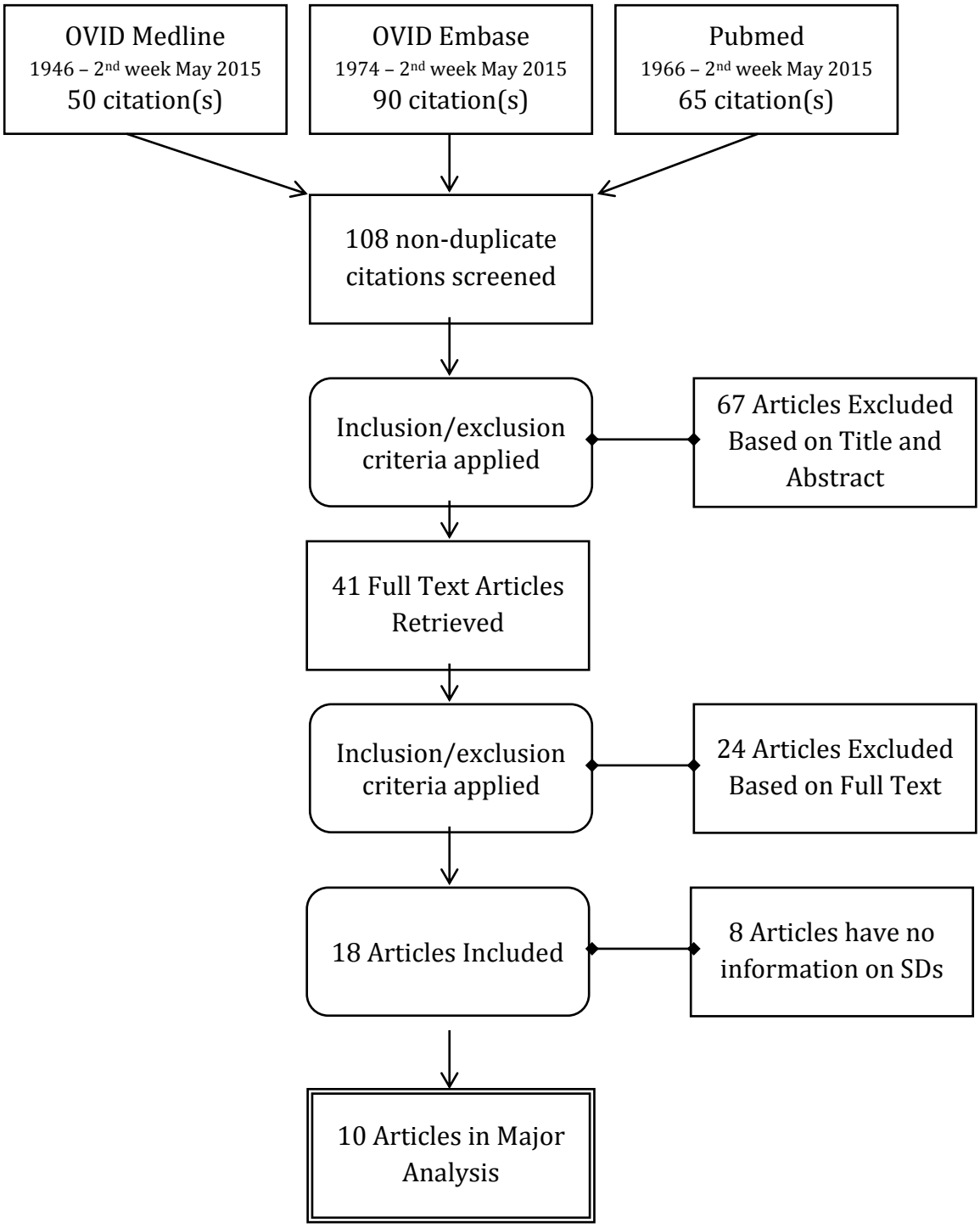


Figure 8.2 Flow diagram from database search to full-text articles included.
SDs = standard deviations

8.4.2 Description of included data

The characteristics of the included studies can be found in Table 8.1. [23,28-30,32,34-40,45,48,49,51,55,129] No clinical trials (or any other experimental designs) were identified through our searches and thus only observational studies were included. Two studies [23,28] used a prospective observational study design and the other 16 [29,30,32,34-40,45,48,49,51,55,129] used a cross-sectional or survey study design.

Out of the 18 included studies, nine used the EORTC QLQ-C30, [28,32,34-37,40,55,129] six used the SF-36, [23,38,39,45,48,49] two studies used the FACT-G [29,51]. One study [30] used both the SF-36 and the FACT-G to measure health-related quality of life, however only data for the SF-36 was reported in the article, therefore, only the SF-36 data was included.

There were five studies conducted in Japan [48,49,51,55,129], four studies in Germany [23,34-36], two each in Italy [39,40], United States of America [29,30], and Greece [37,38], and one each in the United Kingdom [45], India [28], and Austria [32].

Table 8.1 Study characteristics of all included studies

Author (year)	Country	INC	CON	QoL Questionnaire
Prospective cohort studies				
Hardt et al. (2000)	Germany	24	20	SF-36
Singh et al. (2014)	India	80	84	QLQ-C30
Total		*104*	*104*	
Cross-sectional and retrospective studies				
Allareddy et al. (2006)	United States	56	26	FACT
Arata et al. (2004)	Japan	223	107	QLQ-C30
Autorino et al. (2009)	Italy	44	35	SF-36
Dutta et al. (2002)	United States	23	49	SF & FACT
Erber et al. (2012)	Germany	24	34	QLQ-C30
Fujisawa et al. (2000)	Japan	20	36	SF-36
Hara et al. (2002)	Japan	37	48	SF-36
Hobisch et al. (2000)	Austria	33	69	QLQ-C30
Kikuchi et al. (2006)	Japan	20	29	FACT
Philip et al. (2009)	United Kingdom	24	28	SF-36
Protogerou et al. (2004)	Greece	58	50	QLQ-C30
Saika et al. (2007)	Japan	56	53	QLQ-C30
Severin et al. (2010)	Germany	36	21	QLQ-C30
Singer et al. (2012)	Germany	362	291	QLQ-C30
Sogni et al. (2008)	Italy	18	16	QLQ-C30
Vakalopoulos et al. (2011)	Greece	14	25	SF-36
Total		*1048*	*917*	
Grand total		***1152***	***1021***	

INC= Number of patients with incontinent diversion; CON= Number of patients with continent diversion.

As illustrated in Table 8.2 five studies [28,30,32,34,45] reported a statistically significant higher health-related quality of life in patients with continent diversion. Additionally these five studies all reported better Physical Health in patients with a continent diversion. Only two studies [35,38] reported a statistically significant higher health-related quality of life in patients with incontinent diversion.

Table 8.2 An overview of the results of all studies included in the review

Author (year)	General Health	Physical Health	Emotional Health	Social Health
Allareddy et al. (2006)	.	.	.	.
Arata et al. (2004)	.	.	.	.
Autorino et al. (2009)	.	.	.	.
Dutta et al. (2002)	+	+	.	+
Erber et al. (2012)	+	+	.	.
Fujisawa et al. (2000)	.	.	.	.
Hara et al. (2002)	.	.	.	.
Hardt et al. (2000)	.	.	.	.
Hobisch et al. (2000)	+	+	+	+
Kikuchi et al. (2006)	.	.	.	.
Philip et al. (2009)	.	+	.	.
Protogerou et al. (2004)	.	.	.	.
Saika et al. (2007)	.	.	.	.
Severin et al. (2010)	.	.	.	—
Singer et al. (2012)	.	.	.	.
Singh et al. (2014)	+	+	.	+
Sogni et al. (2008)	.	.	.	.
Vakalopoulos et al. (2011)	.	.	—	.

+ means in favour of continent; - means in favour of incontinent; . means no statistically significant difference

8.4.3 Main results

A total of 10 studies[23,28,29,34,36,38,40,45,48,51] reported means and standard deviation, which were included in the meta-analysis (see Appendix 11.9 for bar plots of mean scores). However, I^2 values were significantly larger than 60%. Further investigation identified the study from Singh et al. (2014) was the cause for most of the heterogeneity between the studies and therefore excluded from the meta-analysis. After exclusion of Singh et al. (2014), the meta-analysis included a total of 1063 bladder cancer patients (560 who received incontinent and 503 who received incontinent urinary diversions), with I^2 values ranging between 0% and 24.1%.

Pooled standardised mean differences for the General Health (0.08 (95% CI= -0.10 – 0.26)), Social Health (-0.13 (95% CI= -0.25 – 0.00)), and Emotional Health domains (0.04 (95% CI= -0.12 – 0.20)) were not statistically significantly different between both groups. However, Physical Health in the continent urinary diversion group was statistically significantly better than in the incontinent group with a pooled standardised mean difference of 0.30 (95% CI= 0.12 – 0.48) (Figure 1.2). Forest plots with the pooled standardised mean differences for all domains including the Singh et al (2014) study can be found in the Appendices.

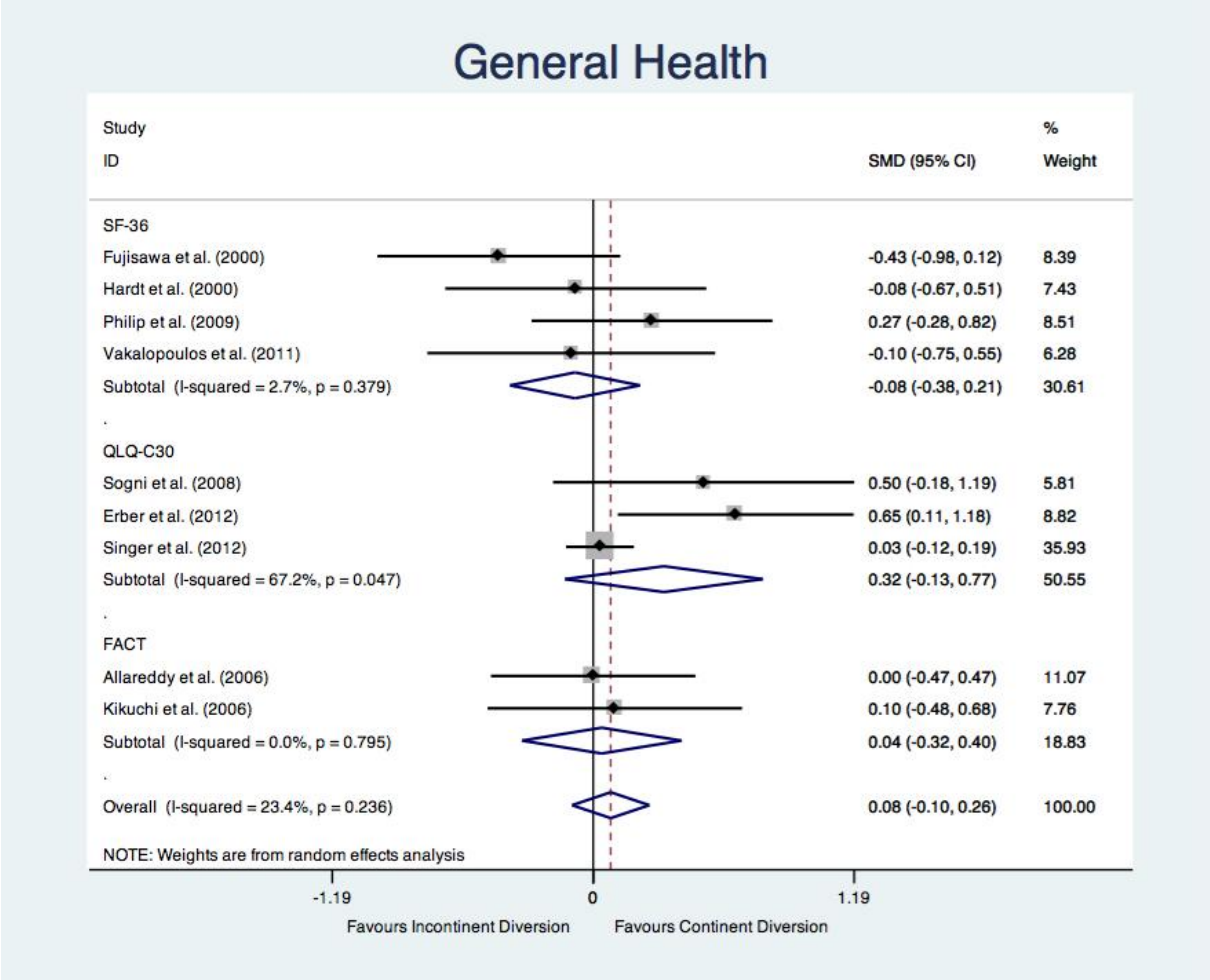


Figure 8.3 Forest plot of the pooled standardized mean differences divided by quality of life questionnaires for General Health, excluding Singh et al.

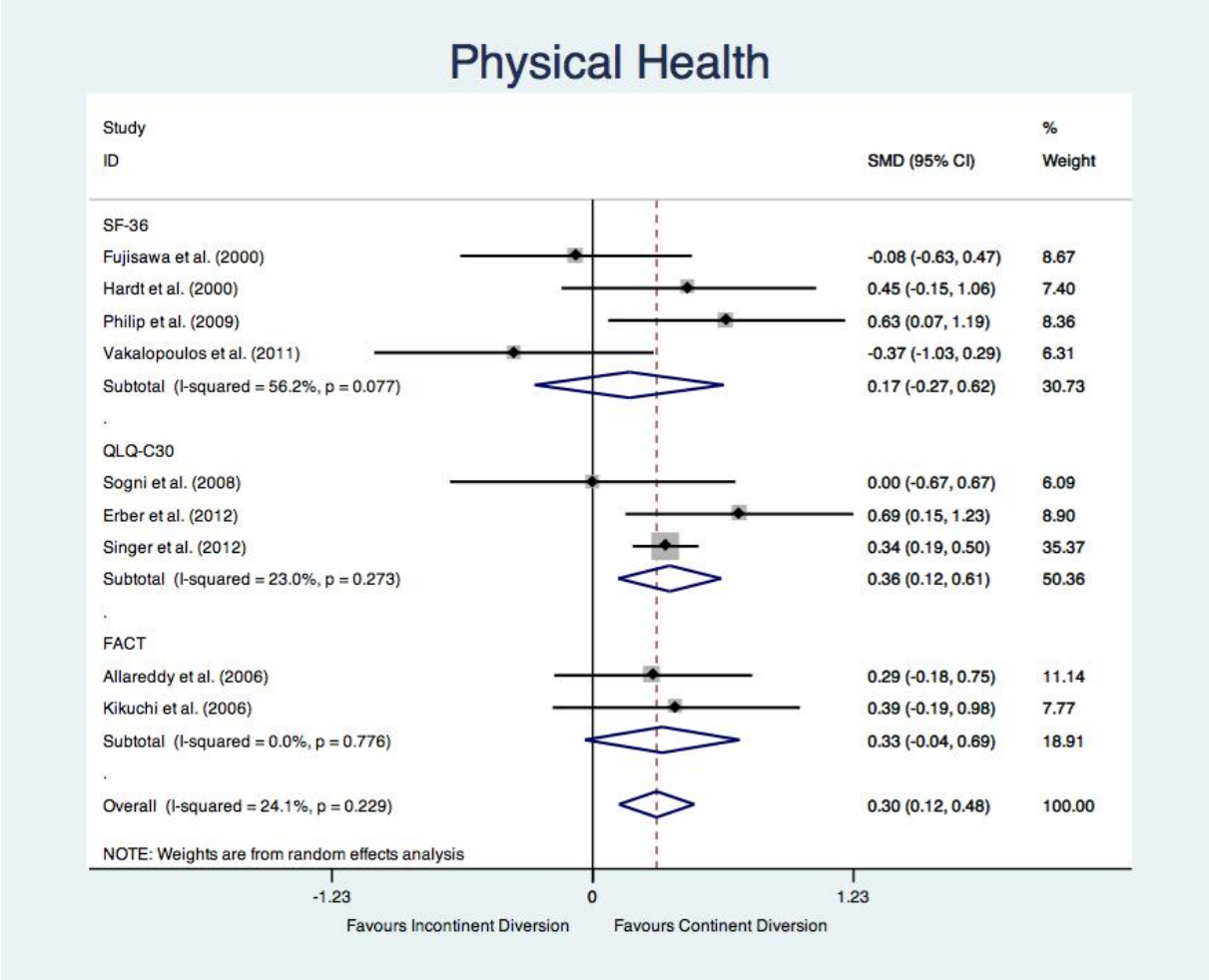


Figure 8.4 Forest plot of random effects meta-analysis with pooled standardized mean differences for the Physical Health domain.

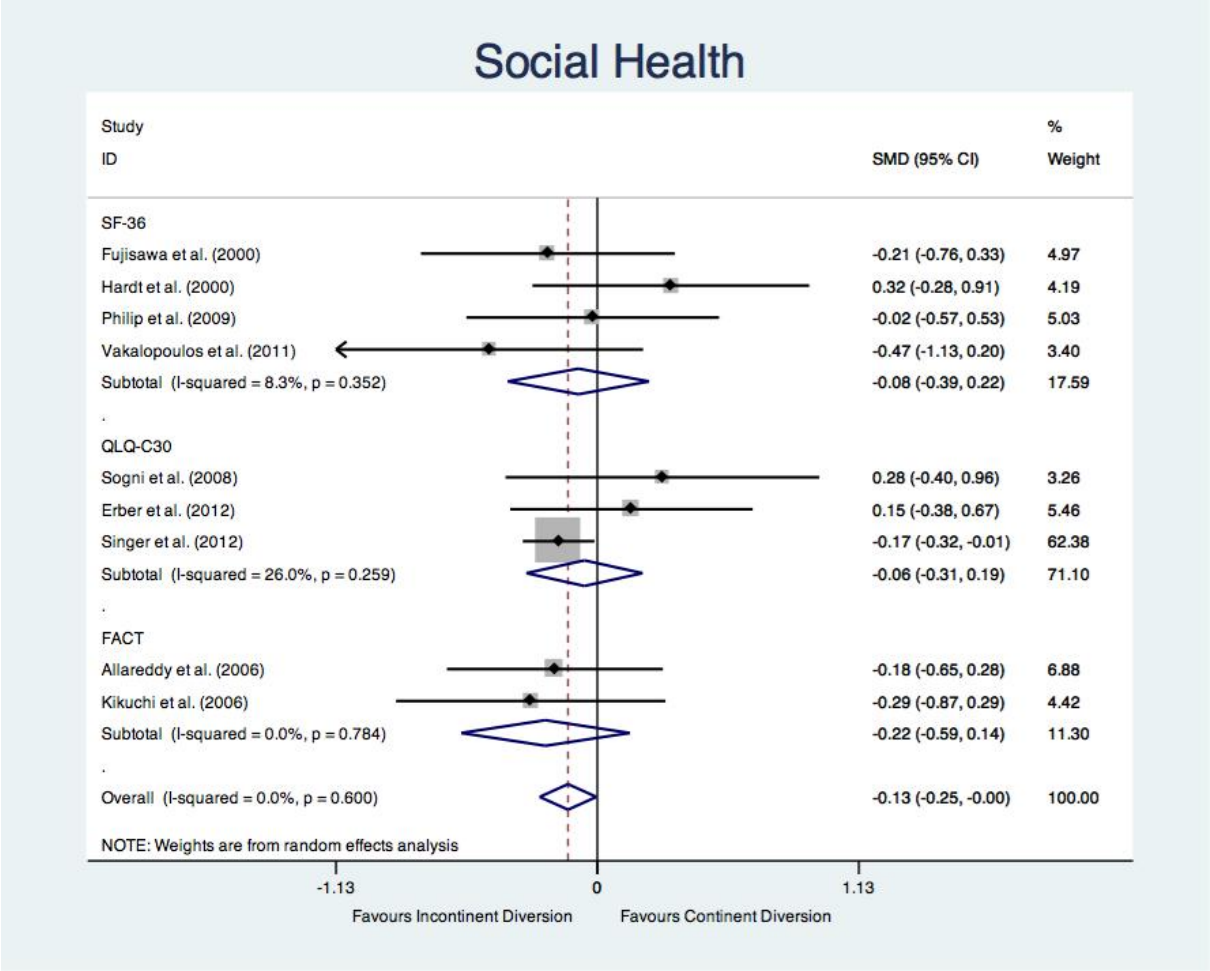


Figure 8.5 Forest plot of the pooled standardized mean differences divided by quality of life questionnaires for Social Health, excluding Singh et al.

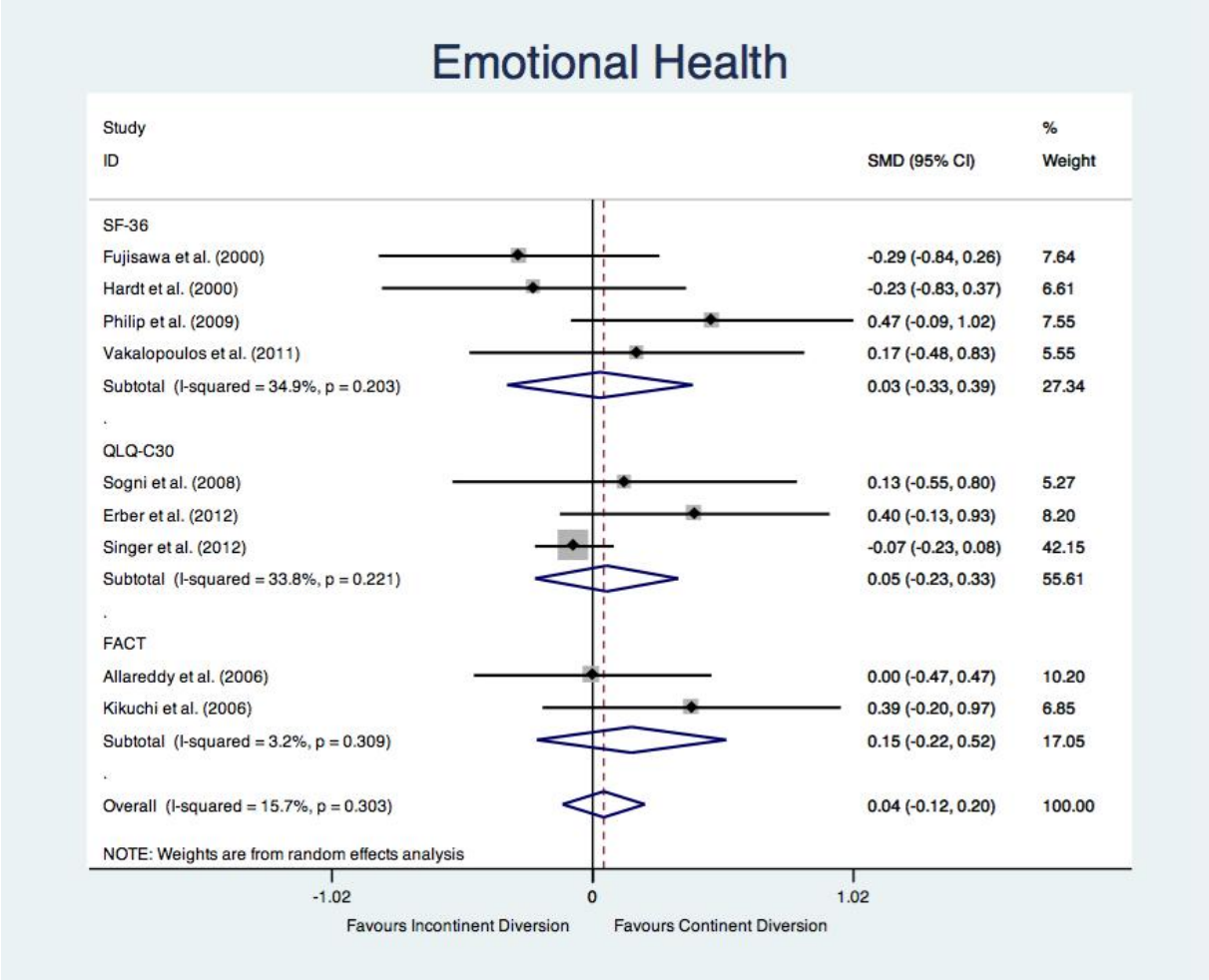


Figure 8.6 Forest plot of the pooled standardized mean differences divided by quality of life questionnaires for Emotional Health, excluding Singh et al.

8.4.4 Sensitivity analysis results

The remaining 8 studies[30,32,35,37,39,49,55,129] without reported standard deviations were included in the sensitivity analysis after imputing standard deviations. This analysis included 2169 bladder cancer patients (1150 who received incontinent and 1019 who received incontinent urinary diversion techniques). There was no significant difference between results from the meta-analysis with and from the meta-analysis without the 8 studies for which we imputed standard deviations.

Additional sensitivity analyses comparing neobladder with incontinent diversion resulted in findings very similar to continent versus incontinent diversion. When divided into subgroups based on the quality of life questionnaire that the studies used, only the pooled estimate for the studies that used the QLQ-C30 reported statistically significant differences between continent and incontinent urinary diversion.

8.5 Discussion

In this meta-analysis we investigated health-related quality of life in patients with continent and incontinent diversions following radical cystectomy for the treatment and management of urinary bladder cancer. We found that patients with a continent diversion had better Physical Health than patients with an incontinent urinary diversion, with a pooled standardized mean difference of 0.30. It might be considered intuitive that Physical Health is better in patients with a continent urinary diversion. These patients are not restricted by an external stoma that patients with an incontinent urinary diversion have. Therefore, patients with a continent diversion might be able to resume their daily activities sooner. This may facilitate a lower threshold to maintain their Physical Health, whereas patients with an incontinent diversion may face a higher threshold when resuming their daily activities following a longer recovery period.

Although the difference in the Physical Health domain was statistically significant, it was only a small difference effect according to our cut-off values. This might be due to the minimum follow-up time for all included studies being at least 12 months. Patients could have had sufficient time to adapt to their urinary diversion and regain their health-related quality of life.

Sensitivity analysis showed that only studies that used the QLQ-C30 found a significant difference between incontinent and continent diversion. However, this could also be due to the limited number of studies in each quality of life questionnaire subgroup.

8.5.1 Strengths and limitations

There have been several literature reviews [69,119,130] on this subject, the most recent of which included 21 studies.[130] However, these literature reviews included a variety of validated and non-validated questionnaires, which prevented them from performing a meta-analysis on the available data. In the current study, we only included data from validated questionnaires and this is thereby the first meta-analysis that quantified the difference between urinary diversion techniques in terms of health-related quality of life in bladder cancer patients. Although we only included validated questionnaires, our overall findings were comparable to those from the most recent literature review that also included non-validated questionnaires.[130]

Not all domains of the quality of life questionnaires were taken into account in this meta-analysis, for instance the EORTC QLQ-C30 records information for 15 domains and in this meta-analysis only four were used. It is therefore possible that this meta-analysis might have missed some differences in other domains of health-related quality of life that are not comparable across the different quality of life questionnaires. For instance, two studies found differences in the Financial Difficulties domain (EORTC QLQ-C30), even though these results were contradicting. However, two studies are not sufficient for a reliable meta-analysis.

One study by Singh et al. (2014) [28] was excluded to improve homogeneity between the included studies. With this study in the meta-analysis I^2 was as high as 92.6%, while it

was only 24.1% without this study, these results can be found in section 11.9 in the appendix. The heterogeneity this study introduced in the meta-analysis was due to the extreme differences this study found. However, the study population was comparable to populations from other included studies except that the study was conducted in India. It is possible that regional differences play a role.

Another potential limitation could be that we had not included a data quality score for each study. However, since all studies had similar study designs, it was deemed unlikely that study quality would differ much between studies. Therefore, the addition of a data quality score would have been unlikely to have made a significant impact on the results.

This meta-analysis was limited by several factors with regard to the available data. Since most studies in this meta-analysis had a retrospective study design, it is likely that the most severe cases had died before study enrolment began. Therefore, these patients who would likely have a relatively low health-related quality of life might have been underrepresented or not included at all. Most studies only included the orthotopic neobladder as continent diversion, leaving very limited data on health-related quality of life in relation to continent reservoirs. It would be useful for future studies to investigate whether there is a difference in health-related quality of life between patients with neobladder and continent reservoir diversions.

Additionally, comparison of published data was further hindered by the lack of uniform reporting of study results. Although our sensitivity analysis found that excluding studies that did not report standard deviations most likely did not significantly impact the result of the meta-analysis, it is still advisable to report standard deviations in all future studies so that no assumptions need to be made. Finally, not all studies reported

standard clinical characteristics, such as stage and grade, making it impossible to perform any meta-analyses using these variables.

8.5.2 Conclusion

In summary, bladder cancer patients who have undergone continent diversion after radical cystectomy have a higher physical health compared to patients who have undergone incontinent diversion, albeit only slightly.

Neither incontinent nor continent diversion offers a clear benefit in terms of cancer related outcomes. The only statistically significant effect found in this meta-analysis, although relatively small, is in favour of the continent diversion. Other than absolute contra-indications to continent diversion, such as renal impairment, severe hepatic dysfunction, and compromised intestinal function, there is no reason to not perform continent diversion in case the small benefit could be perceived as a significant benefit to the patient.

CHAPTER 9 - GENERAL DISCUSSION

9.1 Discussion

In this thesis I aimed to investigate various aspects of health-related quality of life in bladder cancer patients from the Bladder Cancer Prognosis Programme (BCPP). I found that:

- Health-related quality of life around time of diagnosis was generally high in bladder cancer patients and there was no statistically significant difference between health-related quality of life in muscle-invasive and non-muscle invasive bladder cancer patients;
- Patients with a higher baseline health-related quality of life had a statistically and clinically significant higher survival. Independent of other clinical predictors, Physical Functioning and Dyspnoea were the best predictors of survival in non-muscle invasive bladder cancer, while Role Functioning and Financial Difficulties were the best predictors of survival in muscle invasive bladder cancer;
- The original model for the QLQ-C30 proposed by the EORTC is not necessarily the best fitting model. Our findings supported a model containing fewer one-item domains in a heterogeneous population of non-muscle invasive bladder cancer patients, confirming findings from Blazeby et al. who performed a validation study in a homogeneous group of non-muscle invasive bladder cancer patients in the United Kingdom;
- Bladder cancer patients choose test certainty over test burden. Even in this unique population of patients who have had less than 3 cystoscopies, patients would not accept a non-invasive alternative if that meant sacrificing sensitivity;

- Although the difference between continent and incontinent diversion was relatively small, patients with continent diversion had a higher health-related quality of life after at least one-year follow-up.

These findings have been discussed in detail in the previous chapters. Therefore, this Chapter will focus more on the larger context of these results, i.e. BCPP.

9.2 Logistical issues within BCPP

Due to logistical issues in the first few years, enrollment had a slow start. Therefore many patients were enrolled later during the study period, meaning that many patients were unable to achieve the full 5-year follow-up. Additionally, the patient load was so high that it was not possible to perform the planned face-to-face follow-up. Ultimately, one research nurse did the follow-up during six months via telephone.

One of the drawbacks of limiting the access of research nurses to the database was that a lot of error handling and correcting typos had to be done by me (the database manager). This required a lot of effort and it could have been more efficient if nurses were allowed to correct their mistakes while filling in the data.

9.3 Potential bias

Cohort studies are susceptible to certain types of bias, compared with randomised controlled trials. This paragraph describes the potential bias that may have occurred during the conduct of the cohort study on which this thesis is based.

The patients filled out most questionnaires themselves, either on site or at home. However, this was not always possible. In some cases the research nurses were unable to speak to the patient face-to-face, in these cases they called the patient and filled out the questionnaire according to the answers of the patient. A consequence of this was that not all patients completed the health-related quality of life questionnaires at exactly the same time in their disease stage. I investigated if patients who answered within the time range of the planned follow-up time (± 2 months) differed from patients who answered before or after this time and found no statistical difference.

Another potential issue is that patients might respond differently to questions when asked via the telephone, or there may be a risk of nurses formulating questions in such a way that they are suggestive of a certain answer. I found no statistically significant difference between health-related quality of life data from questionnaires completed by patients, nurses, or both. Appropriate training of research nurses before the start of the study might have resulted in good conduct of these telephone interviews. Another source of bias could be the low response rate found in this study population. As can be seen in Table 3.4, the response rate drops right after the baseline measurement. After one year the response rate is only 36% which is low compared to Schmidt et al. (2015)[59] which reported a 75% response rate and Hardt et al. (2000)[23] which reported an 83% response rate after 1 year. Even though BCPP recruited a lot more patients 1551 vs 347 and 112, respectively, and you might expect a lower response rate, the response rates found in BCPP are still poor. With a low response rate comes a potential response bias, where only the highly motivated or better performing patients would respond, however during the analysis of each chapter no difference was found between responders and non-responders. This means that responses from patients were randomly missed and

therefore did not introduce bias. Personally I think there are a number of reasons for the low response rate. Mostly, there was only one dedicated research nurse at each site, meaning that whenever this person was not on site, no patients could be recruited into BCPP and no questionnaires could be administered. Additionally, the questionnaire that was used consisted of 21 pages for the initial questionnaire and 15 pages for each follow-up questionnaire. This is quite long and would take a patient roughly 15 minutes to half an hour to complete. Only a small part of this questionnaire is related to Health-Related Quality of Life.

9.3.1 Generalizability

As with almost all prospective cohort studies, people will decline to participate which could result in a bias (or lack of generalizability) of the results. In order to check whether the people that declined were different from the people that did participate, I compared our data with the West-Midlands Cancer Intelligence Unit data with regards to gender distribution, age, and stage distribution. I found that both groups were not statistically different from each other, data not shown.

Another limitation often associated with cohort studies is misclassification of the outcome. In the case of BCPP, this would be the misclassification of recurrence and progression, which is a possibility, and this should be taken into account when analyzing this data. This thesis, however, does not analyze recurrence or progression data.

Contrary to other cohort studies, the aim of BCPP is not to research the etiology of bladder cancer, instead our aim is to evaluate disease prognosis. Which in a patient's opinion is even more important as they already have the disease and want to know what they can expect and how they may improve their prognosis.

Therefore, our results do not extrapolate to the general population as other cohort studies often do. However, the results can be extrapolated to bladder cancer patients at least in the UK.

9.4 Clinical Implications

The most striking finding of this thesis, in my opinion, is that health-related quality of life in newly diagnosed bladder cancer patients is not as low as I expected and stays remarkably stable throughout the disease stages. Which leads me to believe that if someone improves their quality of life, this will almost protect them in times of need. As seen in Chapter 5.

Since baseline health-related quality of life (before the bladder cancer diagnosis) was used to investigate the effect on survival, this would mean that we should aim at improving health-related quality of life in the general population. It would therefore be interesting to compare the results of this thesis with a similar study in a country with a known high health-related quality of life, such as Sweden or Denmark. However, we could begin by improving health-related quality of life as soon as people are diagnosed with bladder cancer.

Furthermore, better Physical Health seemed to improve survival rates and in the meta-analysis I found that continent diversion was associated with better Physical Health. If this link could be further investigated and potentially confirmed in future research, this would be another argument in favour of the use of continent urinary diversion techniques whenever possible.

9.5 Future research

Even though I believe that improving health-related quality of life even after diagnosis will still help improve prognosis, there is no evidence that sustains this hypothesis. This should be the main focus of future research, as a positive result here, i.e. improving health-related quality of life improves survival, would open the door for targeted quality of life interventions. Additionally, it may be interesting to investigate how health-related quality of life is impacted by the need for multiple treatments due to unsuccessful initial treatment.

Where research at the moment is lacking is in the multitude of health-related quality of life instruments that are currently being used. Ideally, all health-related quality of life research should be done using the same questionnaire. This would make comparing different diseases with each other a lot easier, as well as comparing diseased with the general population. Realistically, however, it is unlikely that this will ever happen. Until then, we should at least agree to report our results in a uniform way.

9.6 Conclusion

In conclusion, health-related quality of life is important, and increasingly more researchers and clinicians are acknowledging this. The effect of health-related quality of life on prognosis has been presented, however, more research is needed to confirm this and thankfully more people feel the same way. At the International Psycho-Oncology Society (IPOS) their main focus is, identifying psychological, social and behavioral factors that influence tumour progression and survival. [131] However, research alone is not enough, as these results still need to be implemented into practice and this needs

cooperation from policy-makers as well. Fortunately there seems to be a trend towards bringing together researcher, clinicians, patient advocates, and policy-makers; and health-related quality of life is a high priority. My vision for the next five to ten years is that health-related quality of life of bladder cancer patients (and in general) will continue to improve and research will further quantify the effect of health-related quality of life on disease prognosis.

CHAPTER 10 - REFERENCE LIST

1. World Health Organization,. Preamble to the Constitution of the World Health Organization. in at <http://www.who.int/about/definition/en/print.html>
2. Fairclough, D. L. *Design and Analysis of Quality of Life Studies in Clinical Trials, Second Edition*. (CRC Press, 2010).
3. Fayers, P. & Machin, D. *Quality of Life*. (John Wiley & Sons, 2013).
4. Streiner, D. L. & Norman, G. R. *Health Measurement Scales: A practical guide to their development and use*. (OUP Oxford, 2008).
5. Dorr, D. A. *et al.* Use of Health-Related, Quality-of-Life Metrics to Predict Mortality and Hospitalizations in Community-Dwelling Seniors. *Journal of the American Geriatrics Society* **54,** 667–673 (2006).
6. Kanwal, F. *et al.* Health-Related Quality of Life Predicts Mortality in Patients With Advanced Chronic Liver Disease. *YJCGH* **7,** 793–799 (2009).
7. Dancey, J. *et al.* Quality of life scores: an independent prognostic variable in a general population of cancer patients receiving chemotherapy. The National Cancer Institute of Canada Clinical Trials Group. *Qual Life Res* **6,** 151–158 (1997).
8. Roychowdhury, D. F., Hayden, A. & Liepa, A. M. Health-related quality-of-life parameters as independent prognostic factors in advanced or metastatic bladder cancer. *J Clin Oncol* **21,** 673–678 (2003).
9. Saunders, C. L., Abel, G. A. & Lyratzopoulos, G. Inequalities in reported cancer patient experience by socio-demographic characteristic and cancer site: evidence from respondents to the English Cancer Patient Experience Survey. *Eur J Cancer Care (Engl)* **24,** 85–98 (2015).
10. Cumberbatch, M. G., Rota, M., Catto, J. W. F. & La Vecchia, C. The Role of Tobacco Smoke in Bladder and Kidney Carcinogenesis: A Comparison of Exposures and Meta-analysis of Incidence and Mortality Risks. *Eur Urol* (2015). doi:10.1016/j.eururo.2015.06.042
11. Brown, T., Slack, R., Rushton, L. & the, W. Occupational cancer in Britain. *Br J Cancer* **107,** S76–S84 (2012).
12. Cumberbatch, M. G. K., Cox, A., Teare, D. & Catto, J. W. F. Contemporary Occupational Carcinogen Exposure and Bladder Cancer: A Systematic Review and Meta-analysis. *JAMA Oncol* 1–9 (2015). doi:10.1001/jamaoncol.2015.3209
13. Kaufman, D. S., Shipley, W. U. & Feldman, A. S. Bladder cancer. *The Lancet* **374,** 239–249 (2009).
14. Ferguson, A. R. Associated bilharziosis and primary malignant disease of the urinary bladder, with observations on a series of forty cases. *The Journal of Pathology and Bacteriology* **16,** 76–94 (1911).
15. Salem, H. K. & Mahfouz, S. Changing Patterns (Age, Incidence, and Pathologic Types) of Schistosoma-associated Bladder Cancer in Egypt in the Past Decade. *URL* **79,** 379–383 (2012).
16. Compton, C. C. *et al. AJCC Cancer Staging Atlas*. (Springer Science & Business Media, 2012). doi:10.1007/978-1-4614-2080-4
17. Babjuk, M. *et al.* EAU Guidelines on Non–Muscle-invasive Urothelial Carcinoma of the Bladder: Update 2013. *Eur Urol* **64,** 639–653 (2013).
18. Witjes, J. A. *et al.* EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer: Summary of the 2013 Guidelines. *Eur Urol* 1–15 (2013). doi:10.1016/j.eururo.2013.11.046

19. Tarsitano, A., Pizzigallo, A., Ballone, E. & Marchetti, C. Health-related quality of life as a survival predictor for patients with oral cancer: is quality of life associated with long-term overall survival? *OOOO* **114,** 756–763 (2012).
20. Oskam, I. M. *et al.* Quality of life as predictor of survival: A prospective study on patients treated with combined surgery and radiotherapy for advanced oral and oropharyngeal cancer. *Radiotherapy and Oncology* **97,** 258–262 (2010).
21. Lemonnier, I. *et al.* Quality of life after the initial treatments of non-small cell lung cancer: a persistent predictor for patients' survival. **12,** 1–10 (2014).
22. Anderson, C. B. *et al.* Psychometric Characteristics of a Condition-specific, Health-related Quality-of-life Survey: The FACT-Vanderbilt Cystectomy Index. *URL* **80,** 77–83 (2012).
23. Hardt, J., Filipas, D., Hohenfellner, R. & Egle, U. T. Quality of life in patients with bladder carcinoma after cystectomy: first results of a prospective study. *Qual Life Res* **9,** 1–12 (2000).
24. Ferriero, M. *et al.* Early and Late Urodynamic Assessment of Padua Ileal Bladder. *URL* **73,** 1357–1362 (2009).
25. Ferriero, M. *et al.* Early and late urodynamic assessment of simplified Indiana pouch with multiple taeniamyotomies. *BJU Int* **107,** 112–116 (2010).
26. Jerlström, T., Andersson, G. & Carringer, M. Functional outcome of orthotopic bladder substitution: A comparison between the S-shaped and U-shaped neobladder. *Scand. J. of Urology & Nephrology* **44,** 197–203 (2010).
27. Månsson, Å. *et al.* Patient-Assessed Outcomes in Swedish and Egyptian Men Undergoing Radical Cystectomy and Orthotopic Bladder Substitution—A Prospective Comparative Study. *URL* **70,** 1086–1090 (2007).
28. Singh, V., Yadav, R., Sinha, R. J. & Gupta, D. K. Prospective comparison of quality-of-life outcomes between ileal conduit urinary diversion and orthotopic neobladder reconstruction after radical cystectomy: a statistical model. *BJU Int* **113,** 726–732 (2014).
29. Allareddy, V., Kennedy, J., West, M. M. & Konety, B. R. Quality of life in long-term survivors of bladder cancer. *Cancer* **106,** 2355–2362 (2006).
30. Dutta, S. C. *et al.* Health related quality of life assessment after radical cystectomy: comparison of ileal conduit with continent orthotopic neobladder. *J Urol* **168,** 164–167 (2002).
31. McGuire, M. S., Grimaldi, G., Grotas, J. & Russo, P. The type of urinary diversion after radical cystectomy significantly impacts on the patient's quality of life. *Ann. Surg. Oncol.* **7,** 4–8 (2000).
32. Hobisch, A. *et al.* Quality of life after cystectomy and orthotopic neobladder versus ileal conduit urinary diversion. *World J Urol* **18,** 338–344 (2000).
33. Bastian, P. J. *et al.* Health-Related Quality-of-Life Following Modified Ureterosigmoidostomy (Mainz Pouch II) as Continent Urinary Diversion. *Eur Urol* **46,** 591–597 (2004).
34. Erber, B. *et al.* Morbidity and Quality of Life in Bladder Cancer Patients following Cystectomy and Urinary Diversion: A Single-Institution Comparison of Ileal Conduit versus Orthotopic Neobladder. *ISRN Urology* **2012,** 1–8 (2012).
35. Severin, T., Bub, P., Jocham, D. & Kausch, I. Lebensqualität nach radikaler Zystektomie – Übersicht und Analyse einer aktuellen Serie. *Aktuel Urol* **41,** 245–251 (2010).

36. Singer, S. *et al.* Quality of life in patients with muscle invasive and non-muscle invasive bladder cancer. *Support Care Cancer* **21,** 1383–1393 (2012).
37. Protogerou, V. *et al.* Modified S-pouch neobladder vs ileal conduit and a matched control population: a quality-of-life survey. *BJU Int* **94,** 350–354 (2004).
38. Vakalopoulos, I., Dimitriadis, G., Anastasiadis, A., Gkotsos, G. & Radopoulos, D. Does intubated uretero-ureterocutaneostomy provide better health-related quality of life than orthotopic neobladder in patients after radical cystectomy for invasive bladder cancer? *Int Urol Nephrol* **43,** 743–748 (2011).
39. Autorino, R. *et al.* Health related quality of life after radical cystectomy: Comparison of ileal conduit to continent orthotopic neobladder. *European Journal of Surgical Oncology* **35,** 858–864 (2009).
40. Sogni, F. *et al.* Morbidity and quality of life in elderly patients receiving ileal conduit or orthotopic neobladder after radical cystectomy for invasive bladder cancer. *URL* **71,** 919–923 (2008).
41. Månsson, A. *et al.* Quality of life after radical cystectomy and orthotopic bladder substitution: a comparison between Italian and Swedish men. *BJU Int* **85,** 26–31 (2000).
42. Månsson, A., Davidsson, T., Hunt, S. & Månsson, W. The quality of life in men after radical cystectomy with a continent cutaneous diversion or orthotopic bladder substitution: is there a difference? *BJU Int* **90,** 386–390 (2002).
43. Öhrström, M., Davidsson, T., Mansson, W., Wohlfart, B. & Ekelund, M. Working Capacity and Well-Being after Radical Cystectomy with Continent Cutaneous Diversion. *Eur Urol* **49,** 691–697 (2006).
44. Pazooki, D. *et al.* Continent cutaneous urinary diversion is still a valid alternative after cystectomy for bladder carcinoma. *Scand. J. of Urology & Nephrology* **39,** 468–473 (2005).
45. Philip, J., Manikandan, R., Venugopal, S., Desouza, J. & Javlé, P. M. Orthotopic neobladder versus ileal conduit urinary diversion after cystectomy--a quality-of-life based comparison. *Ann R Coll Surg Engl* **91,** 565–569 (2009).
46. Abdelwahab, O. & Ahmed, M. M. M. Chimney Modification Technique for Ureterointestinal Anastomosis after Radical Cystectomy: Preliminary Evaluation of Short-Term Outcome and Impact on Quality of Life. *Curr Urol* **4,** 193–202 (2010).
47. Arata, R. *et al.* Orthotopic ileal neobladder versus sigmoidal neobladder: a 'quality of life' (QOL) survey. *Acta Med Okayama* **61,** 229–234 (2007).
48. Fujisawa, M. *et al.* Health-related quality of life with orthotopic neobladder versus ileal conduit according to the SF-36 survey. *URL* **55,** 862–865 (2000).
49. Hara, I. *et al.* Health-related quality of life after radical cystectomy for bladder cancer: a comparison of ileal conduit and orthotopic bladder replacement. *BJU Int* **89,** 10–13 (2002).
50. Harano, M. *et al.* A pilot study of the assessment of the quality of life, functional results, and complications in patients with an ileal neobladder for invasive bladder cancer. *International Journal of Urology* **14,** 112–117 (2007).
51. Kikuchi, E. *et al.* Assessment of Long-Term Quality of Life Using the FACT-BL Questionnaire in Patients with an Ileal Conduit, Continent Reservoir, or Orthotopic Neobladder. *Japanese Journal of Clinical Oncology* **36,** 712–716 (2006).

52. Miyake, H. *et al.* An evaluation of quality of life in patients who underwent orthotopic bladder replacement after cystectomy: comparison of ileal neobladder versus colon neobladder. *Urol Int* **69,** 195–199 (2002).
53. Miyake, H. *et al.* Experience with Various Types of Orthotopic Neobladder in Japanese Men: Long-Term Follow-Up. *Urol Int* **84,** 34–39 (2010).
54. Miyake, H., Furukawa, J., Muramaki, M., Takenaka, A. & Fujisawa, M. Orthotopic bladder substitution following radical cystectomy in women: Comparative study between sigmoid and ileal neobladders. *URO* **30,** 38–43 (2012).
55. Saika, T. *et al.* Health-related quality of life after radical cystectomy for bladder cancer in elderly patients with an ileal conduit, ureterocutaneostomy, or orthotopic urinary reservoir: a comparative questionnaire survey. *Acta Med Okayama* **61,** 199–203 (2007).
56. Takenaka, A. *et al.* Assessment of long-term quality of life in patients with orthotopic neobladder followed for more than 5 years. *Int Urol Nephrol* **43,** 749–754 (2010).
57. Yoneda, T. *et al.* HEALTH RELATED QUALITY OF LIFE AFTER ORTHOTOPIC NEOBLADDER CONSTRUCTION AND ITS COMPARISON WITH NORMATIVE VALUES IN THE JAPANESE POPULATION. *J Urol* **174,** 1944–1947 (2005).
58. Bohle, A., Balck, F., Weitersheim, von, J. & Jocham, D. The quality of life during intravesical bacillus Calmette-Guerin therapy. *J Urol* **155,** 1221–1226 (1996).
59. Schmidt, S. *et al.* Quality of life in patients with non–muscle-invasive bladder cancer_ One-year results of a multicentre prospective cohort study. *URO* **33,** 19.e7–19.e15 (2015).
60. The Caldicott Committee. *Report on the Review of Patient-Identifiable Information*. 1–137 (1997). at <http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4068403>
61. Ploeg, M., Aben, K. K. H. & Kiemeney, L. A. The present and future burden of urinary bladder cancer in the world. *World J Urol* **27,** 289–293 (2009).
62. van Rhijn, B. W. G. *et al.* Recurrence and progression of disease in non-muscle-invasive bladder cancer: from epidemiology to treatment strategy. *Eur Urol* **56,** 430–442 (2009).
63. Sylvester, R. J. *et al.* Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur Urol* **49,** 466–5; discussion 475–7 (2006).
64. Babjuk, M. *et al.* EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder. *European urology* **54,** 303–314 (2008).
65. Mowatt, G. *et al.* Systematic review of the clinical effectiveness and cost-effectiveness of photodynamic diagnosis and urine biomarkers (FISH, ImmunoCyt, NMP22) and cytology for the detection and follow-up of bladder cancer. *Health Technol Assess* **14,** 1–331– iii–iv (2010).
66. Riley, G. F., Potosky, A. L., Lubitz, J. D. & Kessler, L. G. Medicare payments from diagnosis to death for elderly cancer patients by stage at diagnosis. *Med Care* **33,** 828–841 (1995).
67. Svatek, R. S. *et al.* The Economics of Bladder Cancer: Costs and Considerations of

Caring for This Disease. *Eur Urol* **66,** 253–262 (2014).
68. van der Aa, M. N. M. *et al.* Patients' perceived burden of cystoscopic and urinary surveillance of bladder cancer: a randomized comparison. *BJU Int* **101,** 1106–1110 (2008).
69. Botteman, M. F., Pashos, C. L., Hauser, R. S., Laskin, B. L. & Redaelli, A. Quality of life aspects of bladder cancer: a review of the literature. *Qual Life Res* **12,** 675–688 (2003).
70. Gerharz, E. W., Månsson, Å. & Mansson, W. Quality of life in patients with bladder cancer. *Urologic Oncology: Seminars and Original Investigations* **23,** 201–207 (2005).
71. Somani, B. K., MacLennan, S. J. & N'Dow, J. Quality of Life With Urinary Diversion. *European Urology Supplements* **9,** 763–771 (2010).
72. Yoshimura, K. *et al.* Impact of superficial bladder cancer and transurethral resection on general health-related quality of life: an SF-36 survey. *URL* **65,** 290–294 (2005).
73. Lyratzopoulos, G., Abel, G. A., McPhail, S., Neal, R. D. & Rubin, G. P. Gender inequalities in the promptness of diagnosis of bladder and renal cancer after symptomatic presentation: evidence from secondary analysis of an English primary care audit survey. *BMJ Open* **3,** e002861–e002861 (2013).
74. Aaronson, N. K. *et al.* The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* **85,** 365–376 (1993).
75. Zeegers, M. P. *et al.* The West Midlands Bladder Cancer Prognosis Programme: rationale and design. *BJU Int* **105,** 784–788 (2010).
76. Fayers, P. M., Aaronson, N. K., Bjordal, K., Curran, D. & Grønvold, M. EORTC QLQ-C30 scoring manual. (1999).
77. King, M. T. The interpretation of scores from the EORTC quality of life questionnaire QLQ-C30. *Qual Life Res* **5,** 555–567 (1996).
78. Sobin, L. H., Gospodarowicz, M. K. & Wittekind, C. *TNM Classification of Malignant Tumours*. (Wiley-Blackwell, 2011).
79. Mostofi, F. K., Davis, C. J., Sesterhenn, I. A. & Sobin, L. H. Histological typing of urinary bladder tumours. (1999).
80. Schwarz, R. & Hinz, A. Reference data for the quality of life questionnaire EORTC QLQ-C30 in the general German population. *EUROPEAN JOURNAL OF CANCER* **37,** 1345–1351 (2001).
81. Hjermstad, M. J., Fayers, P. M., Bjordal, K. & Kaasa, S. Health-related quality of life in the general Norwegian population assessed by the European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire: the QLQ=C30 (+ 3). *J Clin Oncol* **16,** 1188–1196 (1998).
82. Michelson, H., Bolund, C., Nilsson, B. & Brandberg, Y. Health-related quality of life measured by the EORTC QLQ-C30--reference values from a large sample of Swedish population. *Acta Oncol* **39,** 477–484 (2000).
83. Kulaksizoglu, H., Toktas, G., Kulaksizoglu, I. B., Aglamis, E. & Unlüer, E. When should quality of life be measured after radical cystectomy? *Eur Urol* **42,** 350–355 (2002).
84. Scott, N. W. *et al.* EORTC QLQ-C30 Reference Values. 1–427 (2008).
85. Boustead, G. B. *et al.* Stage, grade and pathological characteristics of bladder

cancer in the UK: British Association of Urological Surgeons (BAUS) Urological Tumour Registry. **113,** 924–930 (2014).
86. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. *Globocan*
87. UK, C. R. Bladder cancer statistics and outlook. at <http://www.cancerresearchuk.org/about-cancer/type/bladder-cancer/treatment/bladder-cancer-statistics-and-outlook>
88. Mungan, N. A. *et al.* Gender differences in stage-adjusted bladder cancer survival. *URL* **55,** 876–880 (2000).
89. Office for National Statistics. *Statistical bulletin: Cancer Survival in Engeland: Patients diagnosed 2007-2011 and followed-up to 2012*. (2013).
90. Montazeri, A. Quality of life data as prognostic indicators of survival in cancer patients: an overview of the literature from 1982 to 2008. *Health Qual Life Outcomes* **7,** 102 (2009).
91. Van Steen, K. *et al.* Multicollinearity in prognostic factor analyses using the EORTC QLQ-C30: identification and impact on model selection. *Statist. Med.* **21,** 3865–3884 (2002).
92. StataCorp. *Stata Statistical Software: Release 12*.
93. Ware, J. E., Jr. *SF-36 Health Survey (Version 1.0) for Use in Australia*. (Australian Health Outcomes Collaboration (AHOC), 2005).
94. Guyatt, G. H., Veldhuyzen Van Zanten, S. J., Feeny, D. H. & Patrick, D. L. Measuring quality of life in clinical trials: a taxonomy and review. *CMAJ* **140,** 1441–1448 (1989).
95. Gilbert, S. M. *et al.* Development and Validation of the Bladder Cancer Index:A Comprehensive, Disease Specific Measure of Health Related Quality of Life in Patients With Localized Bladder Cancer. *J Urol* **183,** 1764–1770 (2010).
96. Blazeby, J. M. *et al.* Validation and Reliability Testing of the EORTC QLQ-NMIBC24 Questionnaire Module to Assess Patient-reported Outcomes in Non–Muscle-invasive Bladder Cancer. *Eur Urol* 1–9 (2014). doi:10.1016/j.eururo.2014.02.034
97. Bryan, R. T. & Wallace, D. 'Superficial'bladder cancer–time to uncouple pT1 tumours from pTa tumours. *BJU Int* (2002).
98. Montgomery, J. S., Weizer, A. Z. & Montie, J. E. T1 bladder cancer: advocating early cystectomy to improve oncologic control. *Urologic oncology* **28,** 466–468 (2010).
99. Birkhahn, M. *et al.* Predicting recurrence and progression of noninvasive papillary bladder cancer at initial presentation based on quantitative gene expression profiles. *Eur Urol* **57,** 12–20 (2010).
100. Robinson, V. L. *et al.* BCAN Think Tank session 2: Molecular detection of bladder cancer: the path to progress. in **28,** 334–337 (2010).
101. National Cancer Intelligence Network,. *One, five and ten year cancer prevalence by Cancer Network, UK, 2006*. (National Cancer Intelligence Network, 2010). at <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer/incidence#heading-Eight>
102. Hedelin, H., Holmäng, S. & Wiman, L. The cost of bladder tumour treatment and follow-up. *Scand. J. of Urology & Nephrology* **36,** 344–347 (2002).
103. Burchardt, M. *et al.* Current concepts in biomarker technology for bladder

cancers. *Clin. Chem.* **46,** 595–605 (2000).
104. Chao, D., Freedland, S. J., Pantuck, A. J., Zisman, A. & Belldegrun, A. S. Bladder cancer 2000: molecular markers for the diagnosis of transitional cell carcinoma. *Rev Urol* **3,** 85–93 (2006).
105. Lotan, Y. & Roehrborn, C. G. Sensitivity and specificity of commonly available bladder tumor markers versus cytology: results of a comprehensive literature review and meta-analyses. *URL* **61,** 109–18– discussion 118 (2003).
106. Kirkali, Z. *et al.* Bladder cancer: epidemiology, staging and grading, and diagnosis. *URL* **66,** 4–34 (2005).
107. Têtu, B. Diagnosis of urothelial carcinoma from urine. *Mod Pathol* **22 Suppl 2,** S53–9 (2009).
108. Bryan, R. T. *et al.* Assessment of high-throughput high-resolution MALDI-TOF-MS of urinary peptides for the detection of muscle-invasive bladder cancer. *Proteomics Clin Appl* **5,** 493–503 (2011).
109. Vriesema, J. L., Poucki, M. H., Kiemeney, L. A. & Witjes, J. A. Patient opinion of urinary tests versus flexible urethrocystoscopy in follow-up examination for superficial bladder cancer: a utility analysis. *URL* **56,** 793–797 (2000).
110. Yossepowitch, O., Herr, H. W. & Donat, S. M. Use of urinary biomarkers for bladder cancer surveillance: patient perspectives. *J Urol* **177,** 1277–82; discussion 1282 (2007).
111. Broadhead, W. E., Gehlbach, S. H., de Gruy, F. V. & Kaplan, B. H. The Duke-UNC Functional Social Support Questionnaire. Measurement of social support in family medicine patients. *Med Care* **26,** 709–723 (1988).
112. Neumann, Von, J., Morgenstern, O. & Rubinstein, A. Theory of games and economic behavior. *books.google.com* (2007).
113. Cauberg Evelyne, C. C. *et al.* A new generation of optical diagnostics for bladder cancer: technology, diagnostic accuracy, and future applications. *Eur Urol* **56,** 287–296 (2009).
114. Bryan, R. T., Billingham, L. J. & Wallace, D. M. A. Narrow-band imaging flexible cystoscopy in the detection of recurrent urothelial cancer of the bladder. *BJU Int* **101,** 702–5– discussion 705–6 (2008).
115. Costa, V. L. *et al.* Three epigenetic biomarkers, GDF15, TMEFF2, and VIM, accurately predict bladder cancer from DNA-based analyses of urine samples. *Clin. Cancer Res.* **16,** 5842–5851 (2010).
116. Bossuyt, P. M. *et al.* STARD 2015: An Updated List of Essential Items for Reporting Diagnostic Accuracy Studies. *Clin. Chem.* **61,** 1446–1452 (2015).
117. Bricker, E. M. Bladder substitution after pelvic evisceration. *Surg. Clin. North Am.* **30,** 1511–1521 (1950).
118. Bhojwani, A. G. & Mellon, J. K. Contemporary cystectomy combined with ileal conduit or bladder substitution. *Surg Oncol* **11,** 65–75 (2002).
119. Porter, M. P., Wei, J. T. & Penson, D. F. Quality of Life Issues in Bladder Cancer Patients Following Cystectomy and Urinary Diversion. *Urologic Clinics of North America* **32,** 207–216 (2005).
120. Nabi, G. *et al.* Urinary diversion and bladder reconstruction/replacement using intestinal segments for intractable incontinence or following cystectomy. *Cochrane Database Syst Rev* **1,** (2003).
121. Burkhard, F. C., Kessler, T. M., Mills, R. & Studer, U. E. Continent urinary

diversion. *Critical Reviews in Oncology/Hematology* **57,** 255–264 (2006).
122. Zietman, A. & Skinner, E. Quality of life after radical treatment for invasive bladder cancer. *Seminars in Radiation Oncology* **15,** 55–59 (2005).
123. Månsson, A. & Månsson, W. When the bladder is gone: quality of life following different types of urinary diversion. *World J Urol* **17,** 211–218 (1999).
124. Hautmann, R. E. *et al.* Urinary Diversion. **69,** 17–49 (2007).
125. Kassouf, W. *et al.* A critical analysis of orthotopic bladder substitutes in adult patients with bladder cancer: is there a perfect solution? *Eur Urol* **58,** 374–383 (2010).
126. Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G. & Grouppara, T. P. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *Journal of Clinical Epidemiology* **62,** 1006–1012 (2009).
127. Hedges, L. V. Distribution Theory for Glass's Estimator of Effect size and Related Estimators. *Journal of Educational And Behavioral Statistics* **6,** 107–128 (1981).
128. Cohen, J. *Statistical Power Analysis for the Behavioral Sciences*. (Lawrence Erlbaum Associates, 1988).
129. Arata, R., TSUSHIMA, T., SAIKA, T. & NASU, Y. The Quality of Life in Patients with Bladder Cancer after Cystectomy. *NISHINIHON …* (2004).
130. Ali, A. S., Hayes, M. C., Birch, B., Dudderidge, T. & Somani, B. K. Health related quality of life (HRQoL) after cystectomy: Comparison between orthotopic neobladder and ileal conduit diversion. *European Journal of Surgical Oncology* **41,** 295–299 (2015).
131. IPOS. International Psycho-Oncology Society. *http://www.ipos-society.org* at <http://www.ipos-society.org>

CHAPTER 11 - APPENDICES

11.1 Consent form BCPP

Bladder Cancer Prognosis Programme (BCPP)
Cancer Research UK Bladder Cancer Research Group

Chief Investigator:	**Professor KK Cheng** **University of Birmingham**
Name of your Doctor:	<Name of urologist> <Hospital name>

PATIENT INFORMATION SHEET

(Version Number: 2.0, August 2009)

We would like to invite you to take part in a clinical research study.

We are currently recruiting patients who have a bladder abnormality that is suspicious of bladder cancer.

Taking part in this study is entirely voluntary. Before you decide whether you would like to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this information leaflet.

1. What is the purpose of the study?

For the majority of patients who are diagnosed with bladder cancer, regular check-ups are required for the rest of their lives, so that if the cancer returns it can be detected early. These check-ups involve an examination of the bladder using a thin tube with a light inside that is inserted into the bladder through the water pipe (urethra). This procedure is called cystoscopy.

The dilemma for Urologists treating bladder cancer is that some bladder cancers need very frequent cystoscopies and others can be considered to be less harmful. Unfortunately, our current tests do not yet allow us to accurately predict at the outset how a patient's bladder cancer will behave in the future.

Here in the West Midlands we are undertaking a programme of research (funded by Cancer Research UK) to investigate if we can improve our ability to predict how a patient's bladder cancer will behave. This research will involve studies on your blood, urine, bladder tissue and nail clippings (these allow us to measure levels of various natural minerals contained within the body). We will use these samples to study some genetic and biological factors. We will also collect some personal details and lifestyle information using questionnaires. This information will help us to look into factors that can influence the way in which bladder cancers behave.

In order to find out if any of these factors are important, we will need to monitor your progress over the next 5 years and collect information from you regularly during your routine follow-up visits to hospital.

2. Why have I been chosen?

You have been diagnosed with a bladder abnormality that is suspicious of bladder cancer. We are hoping to collect information on patients who have been newly-diagnosed with a bladder abnormality that is suspicious of bladder cancer and who meet the requirements of the study. We intend to study at least 3400 patients over the next 3-5 years.

3. Do I have to take part?

It is up to you to decide whether or not to take part. You do not have to decide straight away. You can take this information sheet away with you. When you return to hospital before your operation, you will be asked if you would like to participate in the study. If you agree to take part you will be asked to sign a consent form. If you do decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive or your relationship with your doctor.

4. What will happen to me if I take part?

Once you have agreed to take part and have signed a consent form, the study will run alongside your standard bladder cancer treatment. When you come into hospital before your bladder operation, our researcher will talk to you about the study and will take you through a questionnaire. The questions will be on your background, medical history and lifestyle. We would need you to give us about an hour of your time to fill in this questionnaire. Before your operation we will take samples of your blood and urine.

During your operation pieces of tissue from your growth are removed from the lining of the bladder. This tissue will be sent to the pathologist at your hospital for detailed analysis under a microscope as part of your standard care. For the purposes of this study we will use a small sample of the tissue that is removed.

If the microscope analysis confirms that you have bladder cancer and if the cancer is suitable, we would then like to collect information from your medical records on any further bladder cancer treatment that you receive. After your operation we will send you a questionnaire which asks about your family history of cancer, your previous occupations and the places where you have lived. This questionnaire should take you about half an hour to fill in. We will also send you a food diary so that you can keep a record of what you eat and drink in a one week period.

We will monitor your progress at your regular hospital follow-up visits. This monitoring would involve completing a short questionnaire at the time of each follow-up visit. This follow-up questionnaire will require approximately half an hour of your time to fill it in. If it is not possible to fill it all in when you attend your follow-up appointment, we may need to telephone you at home to collect the rest of the information. If your bladder cancer returns we would once again like to take samples of your blood and urine and bladder cancer tissue. We would like to monitor you in this way for a total of 5 years.

Following your operation and depending on the outcome of the pathologist's diagnosis, we may also wish to ask you to take part in a randomised trial (our researcher will discuss this with you, if appropriate). If, after your operation, you are <u>not</u> diagnosed as having a bladder cancer, we will not ask you to participate further in this research project.

5. What do I have to do?

Other than your normal treatment, we would need you to complete our questionnaires and let us have samples of your blood, urine and nail clippings. You would also be asked to give

permission for us to use some samples of the abnormal bladder tissue that is removed during your operation.

6. What will happen to the tissue and blood samples taken as part of this study ?

The bladder tissue, blood and urine that will be collected as part of this research study will initially be stored locally at your hospital and then transferred to a central bio repository for long-term storage. Nail clipping collected will be stored centrally at the University of Birmingham.

We aim to collect together, from all of the patients who enter this research study, a large 'bank' of bladder tumour samples. The samples collected will be used, first and foremost, for research as part of the BCPP study. Such a collection or 'bank' of samples may also be very useful for research in the future that will help us to understand more about how bladder cancers behave. We would like to store and later use the samples donated as part of this study for future research, although such research projects have not yet been planned and could occur many years in the future. These future research projects may involve studies of your genes and DNA. By giving your consent for your bladder tissue, blood, urine and nail samples to be stored in the 'bank' you will be offering your samples as a gift. If, after your operation you are diagnosed as not having bladder cancer, we would still like to keep your samples for further use in approved research.

The sample stored for research will be taken from samples that remain after all the information needed by doctors diagnosing and caring for you have been obtained. The tumour, blood and urine samples are stored under strict security and are given a code, so that researchers receiving the samples do not know your name or any other personal details. Researchers who wish to use the samples that are stored in the bank will only be given access to the samples after their research has been approved by an independent Research Ethics Committee who make sure that the research is in the interest of patients and is carried out safely.

7. What are the possible disadvantages and risks of taking part?

There are no foreseeable risks of taking part. This study will run alongside your routine bladder cancer treatment and follow-up; it will not influence this process.

8. What are the possible benefits of taking part?

There is no intended immediate clinical benefit from taking part in this study. However, the information obtained from this study may result in changes in the future diagnosis, treatment, and follow-up of patients with bladder cancer. These changes may also benefit you.

9. What if new information becomes available?

This study does not influence your routine bladder cancer treatment and follow-up. However, any new discoveries or information relating to this will automatically be incorporated into the standard treatment provided by your doctors.

10. What happens when the research study stops?

When the study stops your routine bladder cancer treatment and follow-up will continue in the normal way, although it may incorporate new discoveries or information generated by this study.

11. What if something goes wrong?

As this study does not influence your routine bladder cancer treatment and follow-up, the normal National Health Service complaints mechanisms should be followed.

12. Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. If you agree to take part in this study we will need you to sign a consent form. You will be given a copy of the consent form and this information sheet to keep.

With your consent, we will be informing your GP about your participation in this study. Authorised professionals, other than those involved directly in your care, may inspect your medical notes. Information contained within your medical notes would be used only for the purposes of collecting information about your treatment and to check that the research is being carried out correctly. These authorised professionals include members of the BCPP (Bladder Cancer Prognosis Programme) research team and regulatory authority representatives.

We would like to collect some contact details from you including your current address, and telephone number. We would like to collect these details so that we can send a questionnaire to you at home and so that we can contact you before an appointment to remind you if you need to bring anything in with you to the hospital. Your contact details will be kept strictly confidential and only members of the BCPP research team would be allowed access to them.

Information on all patients entered into this study will be sent to the BCPP Study Office which is located at The University of Birmingham where it will be retained in secure storage and handled according to the 1998 Data Protection Act. No personally identifiable information will be released from the BCPP study office. Limited clinical information may be passed on to researchers within the UK. It would not be possible to identify any patient from this information and any information provided will be handled according to the normal standard of medical confidentiality and data protection.

13. What will happen to the results of the research study ?

Important results from the study will be published as they become available, which may be during the course of the study or after the study has finished, and this could possibly take several years. We intend that any results will be published in peer-reviewed journals or will be presented at meetings involved with this field of cancer research, and these publications will be available upon request from your specialist doctor. You will not be identified in any report or publication.

14. Who is organising and funding the research?

The research is being organised by The Department of Public Health and Epidemiology at The University of Birmingham, in collaboration with the Cancer Research UK Institute for Cancer Studies at The University of Birmingham, The Department of Urology at The Queen Elizabeth Hospital, Birmingham, and participating Urology Departments within the West Midlands. The research is funded by Cancer Research UK. The doctors conducting this study are not being paid for including and looking after you within this study.

15. Who has reviewed the study?

This study has been reviewed by the Nottingham Multi-centre Research Ethics Committee and by scientific experts at Cancer Research UK.

16. What if I have other concerns or would like further information?

If you have any concerns or other questions about this study or the way it has been carried out, you should contact the Urologist or the BCPP researcher at your hospital -details listed below. If you would like advice from someone independent of the study concerning your participation, you should contact <e.g. Urology CNS>.

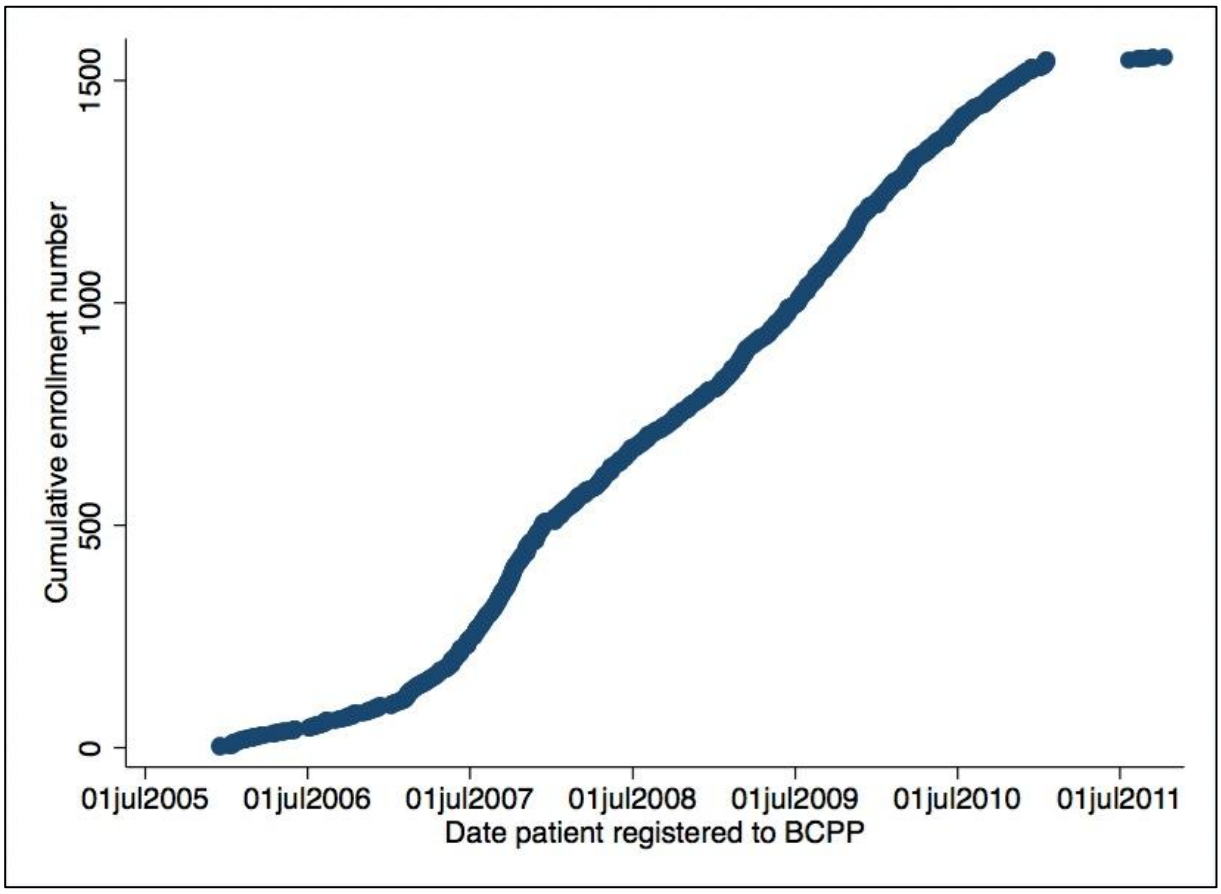
Finally, thank you for taking the time to read this information sheet and for taking part in the study, if you agree to do so.

Contact Details:

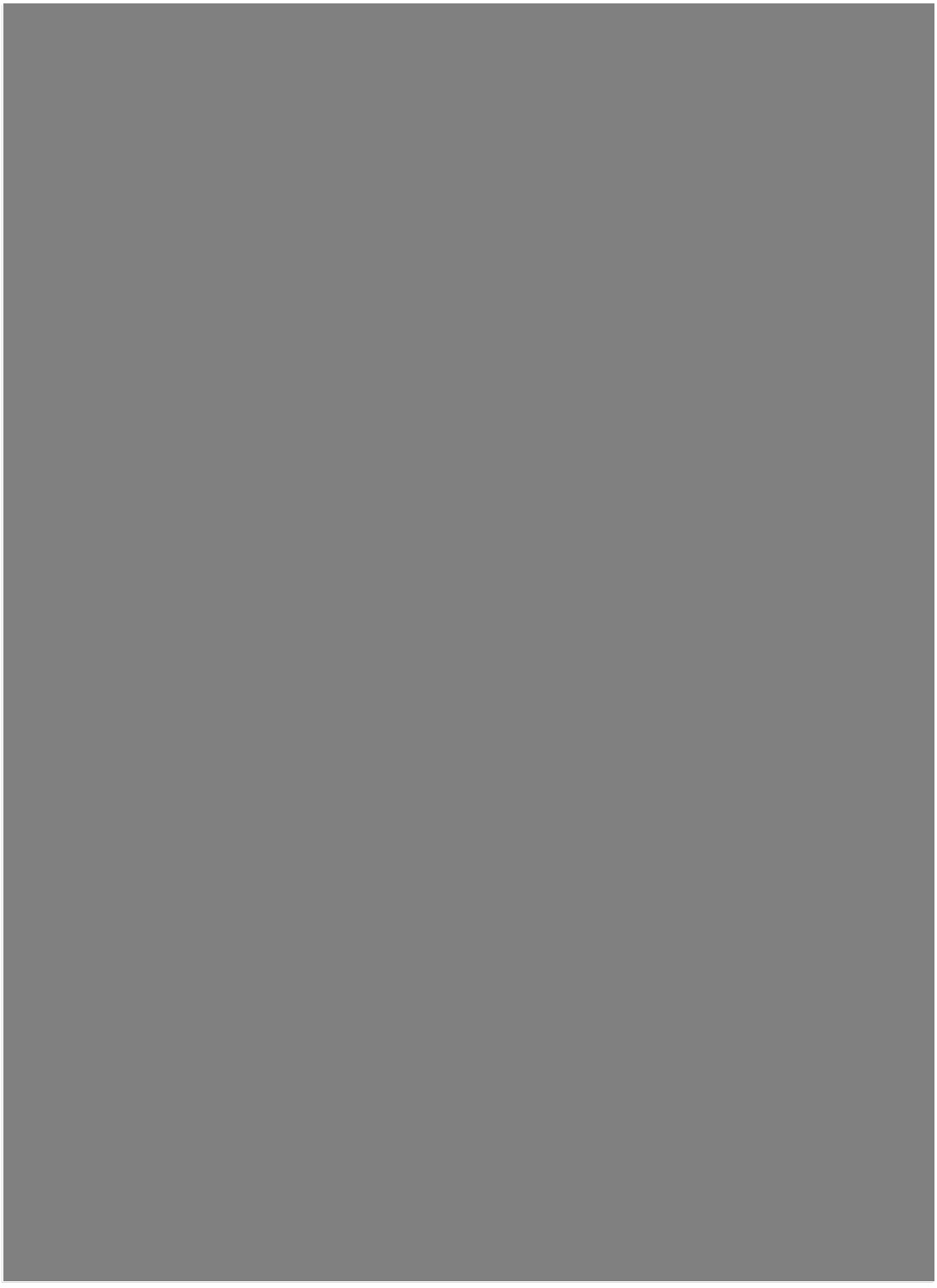
BCPP research team member: <Research Nurse/Trial Practitioner> **Tel.:** <contact number>

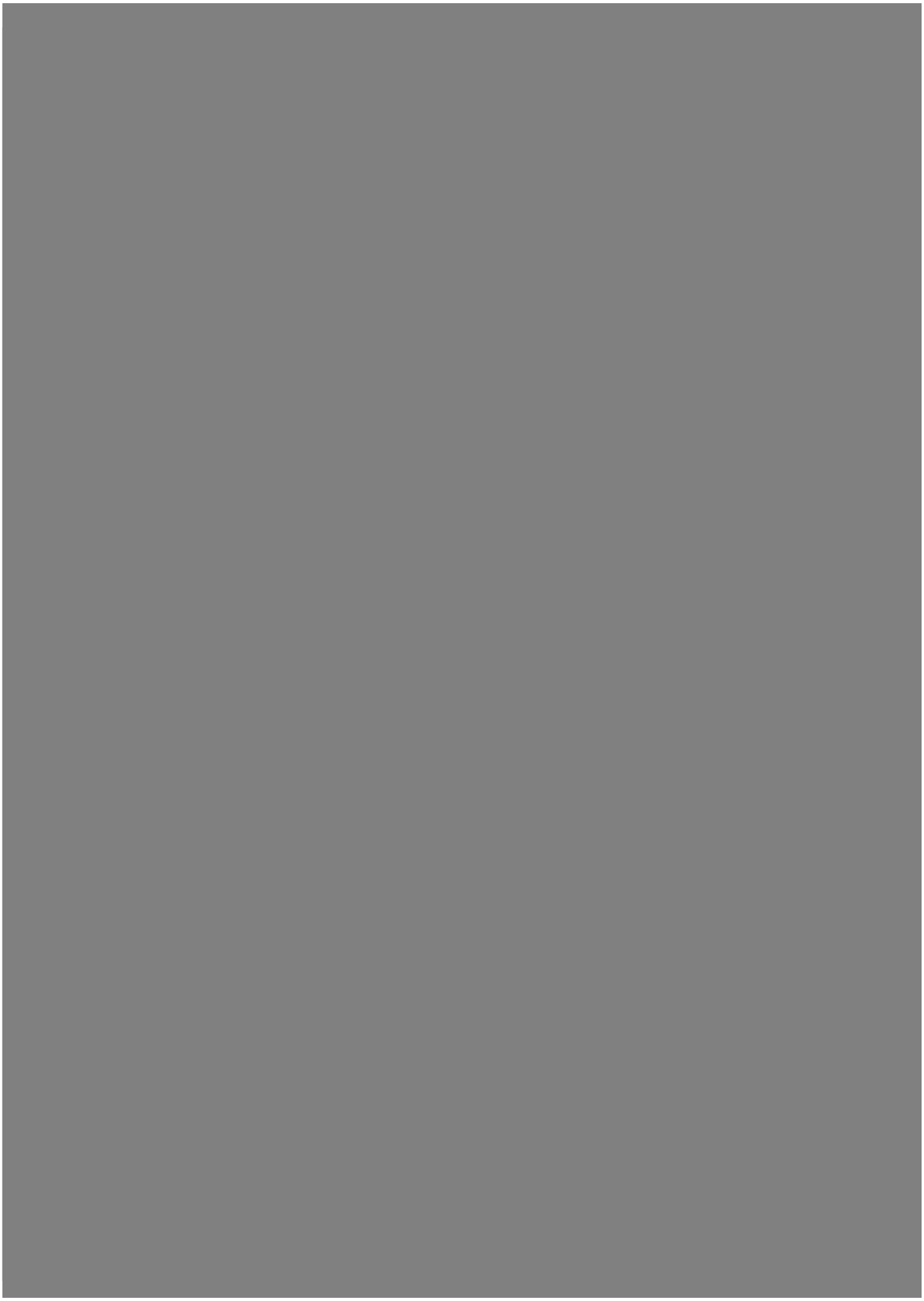
Local Investigator: <Urologist> **Tel.:** <secretary's contact number>

11.2 Cumulative enrollment graph



11.3 EORTC QLQ-C30 Specimen





11.4 Additional analysis Chapter 4

Table 11.1 Health related quality of life as measured by the EORTC QLQ-C30, tumour size comparison.

QLQ-C30#	<3cm			>=3cm		
	Mean	SD		Mean	SD	
N	560		*N*	517		p-value
Overall Quality of Life	71	21		65	24	<0.001
Functional domains (0 worst functioning; 100 best functioning)						
Physical Functioning	84	21		82	21	0.247
Role Functioning	83	27		78	31	0.003
Emotional Functioning	76	21		76	23	0.913
Cognitive Functioning	84	20		83	20	0.274
Social Functioning	87	23		84	25	0.054
Symptom domains (0 No symptoms; 100 worst symptoms)						
Fatigue	77	22		72	26	0.002
Nausea and Vomiting	96	10		95	12	0.426
Pain	84	25		80	28	0.030
Dyspnoea	86	25		83	26	0.116
Insomnia	75	30		73	34	0.227
Appetite Loss	90	22		86	27	0.024
Constipation	88	23		86	24	0.130
Diarrhoea	94	14		93	18	0.218
Financial Difficulties	94	18		95	17	0.500

SD = Standard Deviation
# Range of QLQ-C30 is 0-100

Table 11.2 Health related quality of life as measured by the EORTC QLQ-C30, pTa vs pT1 tumour stage.

QLQ-C30#	pTa			pT1			
	Mean	SD		Mean	SD		
N	575		*N*	301			p-value
Overall Quality of Life	70	22		68	24		0.185
Functional domains (0 worst functioning; 100 best functioning)							
Physical Functioning	84	20		83	21		0.375
Role Functioning	84	26		80	31		0.020
Emotional Functioning	77	22		75	23		0.201
Cognitive Functioning	85	19		83	20		0.370
Social Functioning	87	23		86	25		0.555
Symptom domains (0 No symptoms; 100 worst symptoms)							
Fatigue	77	22		75	24		0.422
Nausea and Vomiting	96	11		96	13		0.520
Pain	83	25		84	25		0.925
Dyspnoea	85	24		86	24		0.705
Insomnia	76	30		77	32		0.640
Appetite Loss	90	22		89	23		0.367
Constipation	89	22		86	25		0.094
Diarrhoea	94	16		93	17		0.274
Financial Difficulties	95	17		94	17		0.871

SD = Standard Deviation
# Range of QLQ-C30 is 0-100

Table 11.3 Health related quality of life as measured by the EORTC QLQ-C30, multiple vs one tumour.

QLQ-C30#	One		Multiple		
	Mean	SD	Mean	SD	
N	644		*N* 422		p-value
Overall Quality of Life	68	23	68	22	0.946
Functional domains (0 worst functioning; 100 best functioning)					
Physical Functioning	83	21	82	21	0.628
Role Functioning	80	29	81	29	0.805
Emotional Functioning	76	23	77	21	0.320
Cognitive Functioning	83	20	84	20	0.596
Social Functioning	86	24	86	25	0.956
Symptom domains (0 No symptoms; 100 worst symptoms)					
Fatigue	74	25	76	24	0.480
Nausea and Vomiting	96	12	96	11	0.715
Pain	81	27	83	26	0.259
Dyspnoea	83	27	85	24	0.250
Insomnia	72	32	77	31	0.025
Appetite Loss	88	25	88	24	0.738
Constipation	88	22	85	26	0.034
Diarrhoea	94	16	94	16	0.829
Financial Difficulties	94	18	95	17	0.467

SD = Standard Deviation
# Range of QLQ-C30 is 0-100

11.5 Additional Kaplan-Meier Surival curves

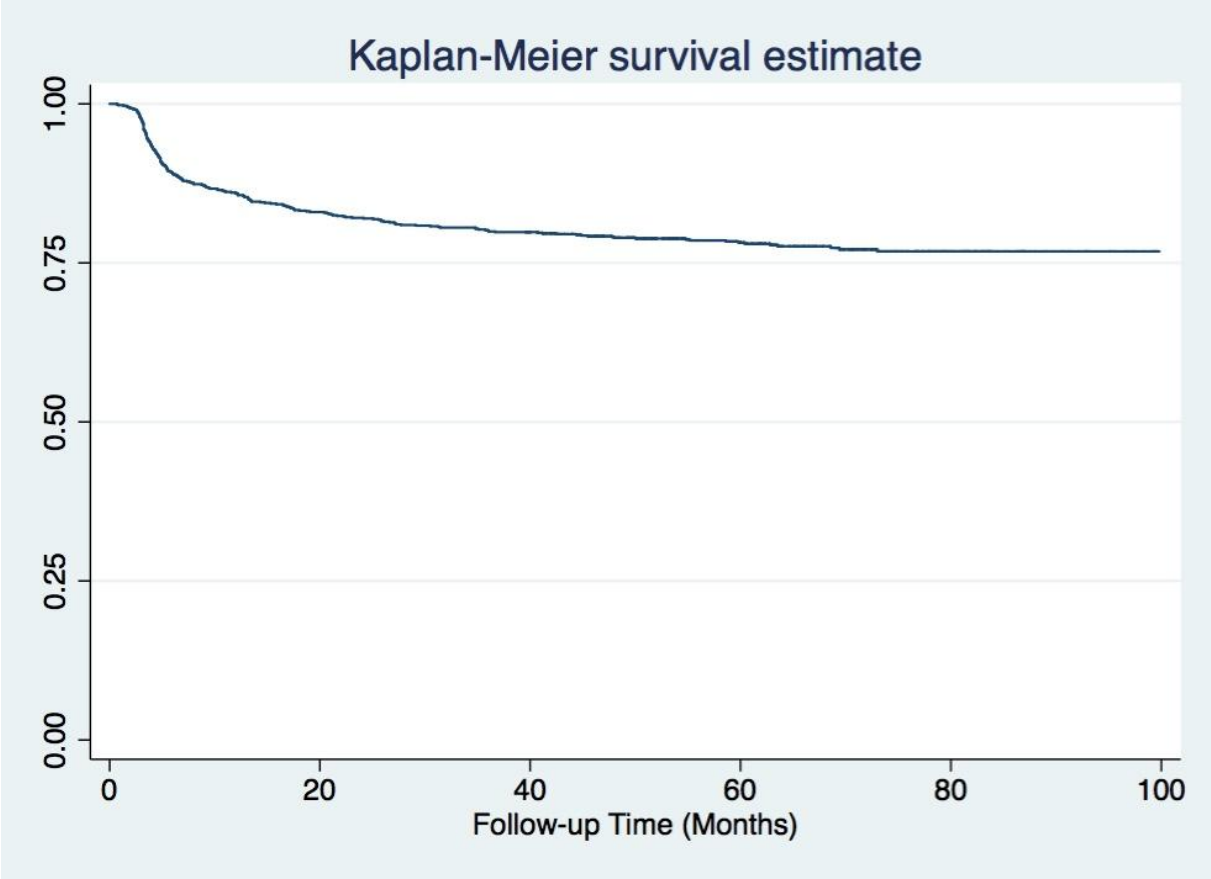


Figure 11.1 Kaplan-Meier Curve for NMIBC patients

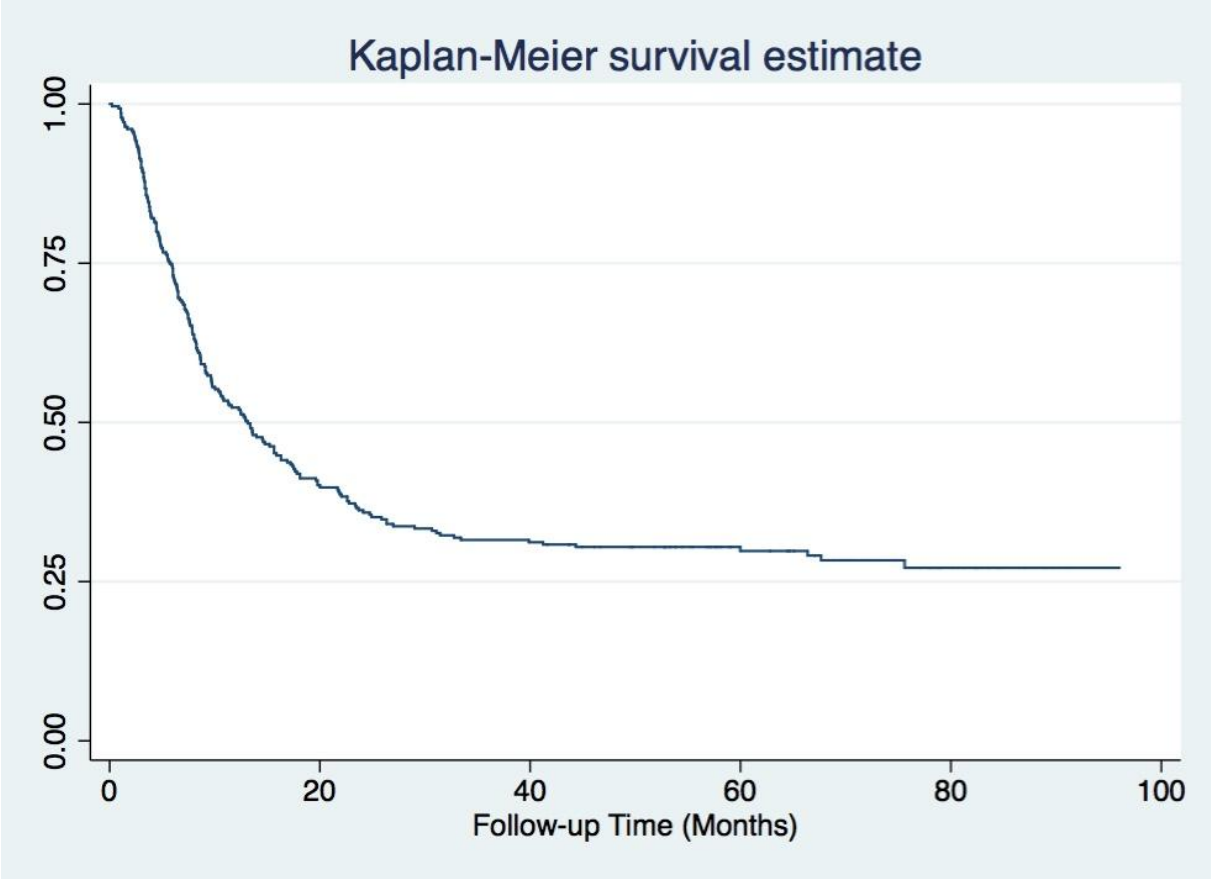


Figure 11.2 Kaplan-Meier Curve for MIBC patients.

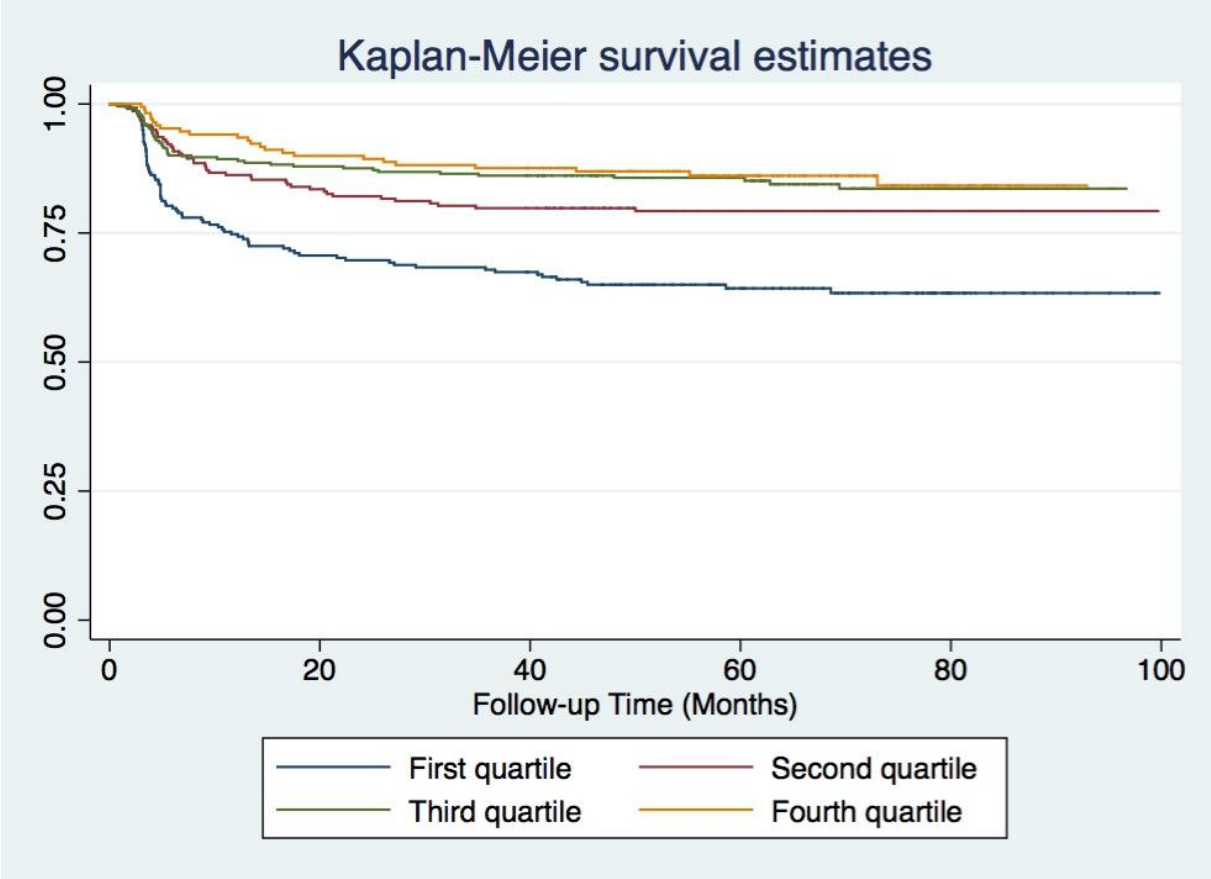


Figure 11.3 Kaplan-Meier Curve for NMIBC patients, divided into Overall Health-Related Quality of Life quartiles.

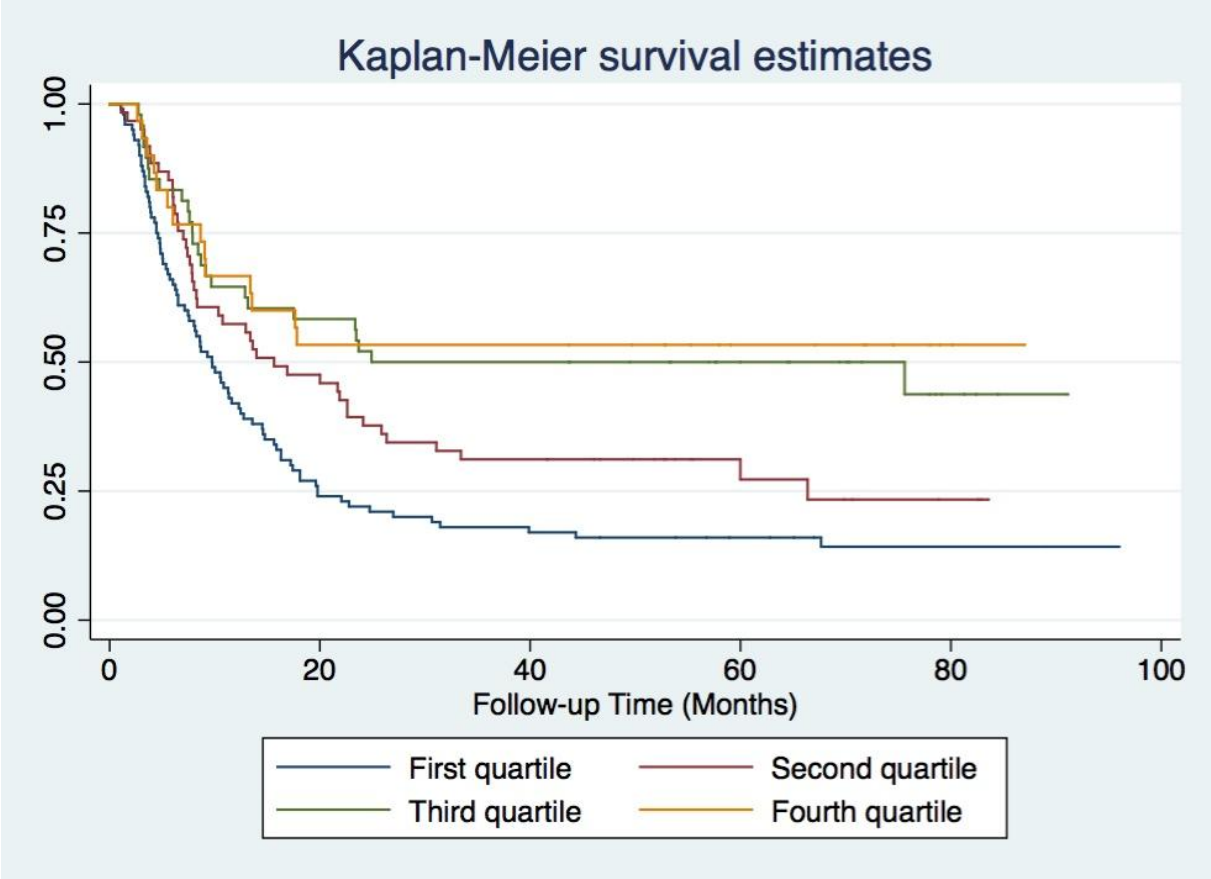


Figure 11.4 Kaplan-Meier Curve for MIBC patients, divided into Overall Health-Related Quality of Life quartiles.

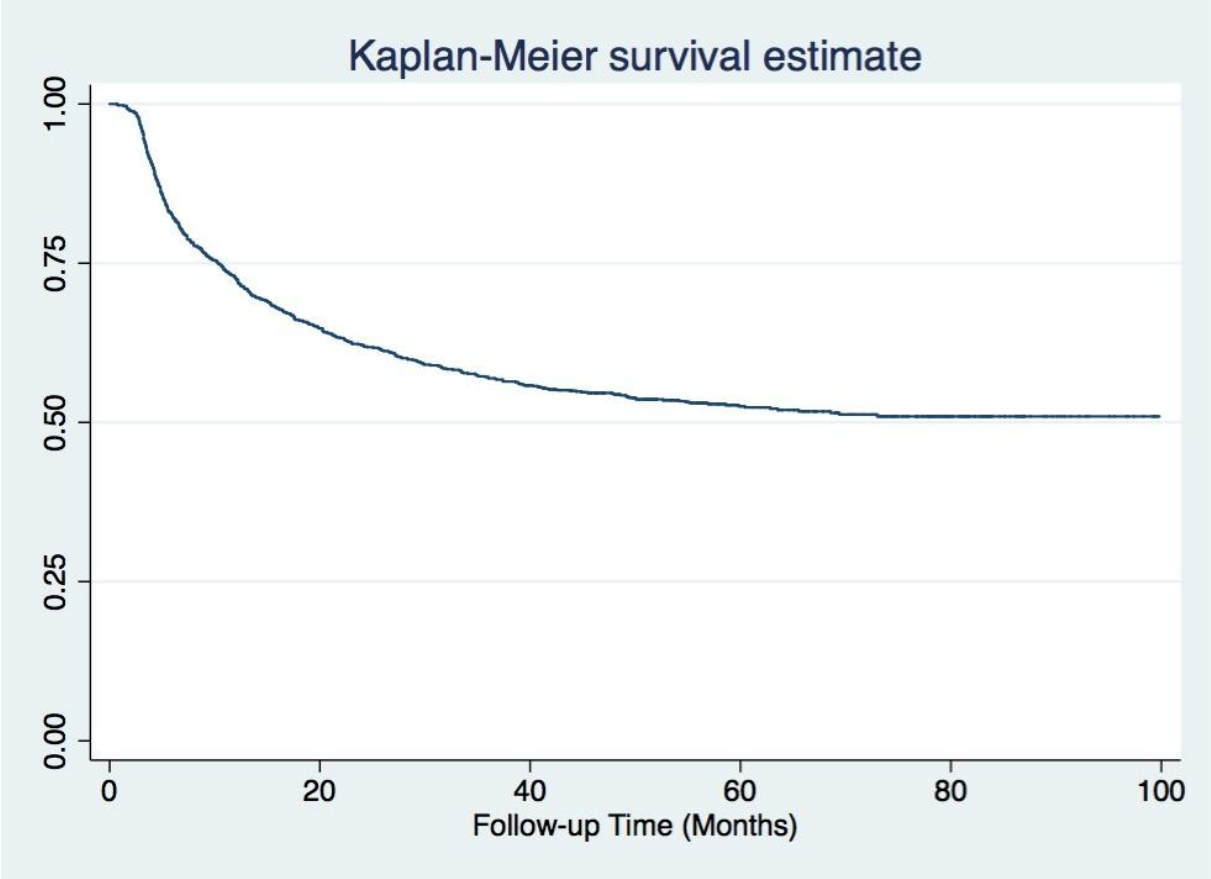


Figure 11.5 Kaplan-Meier curve of recurrence free survival for NMIBC patients

11.6 Box plot of health-related quality of life QLQ-C30 data

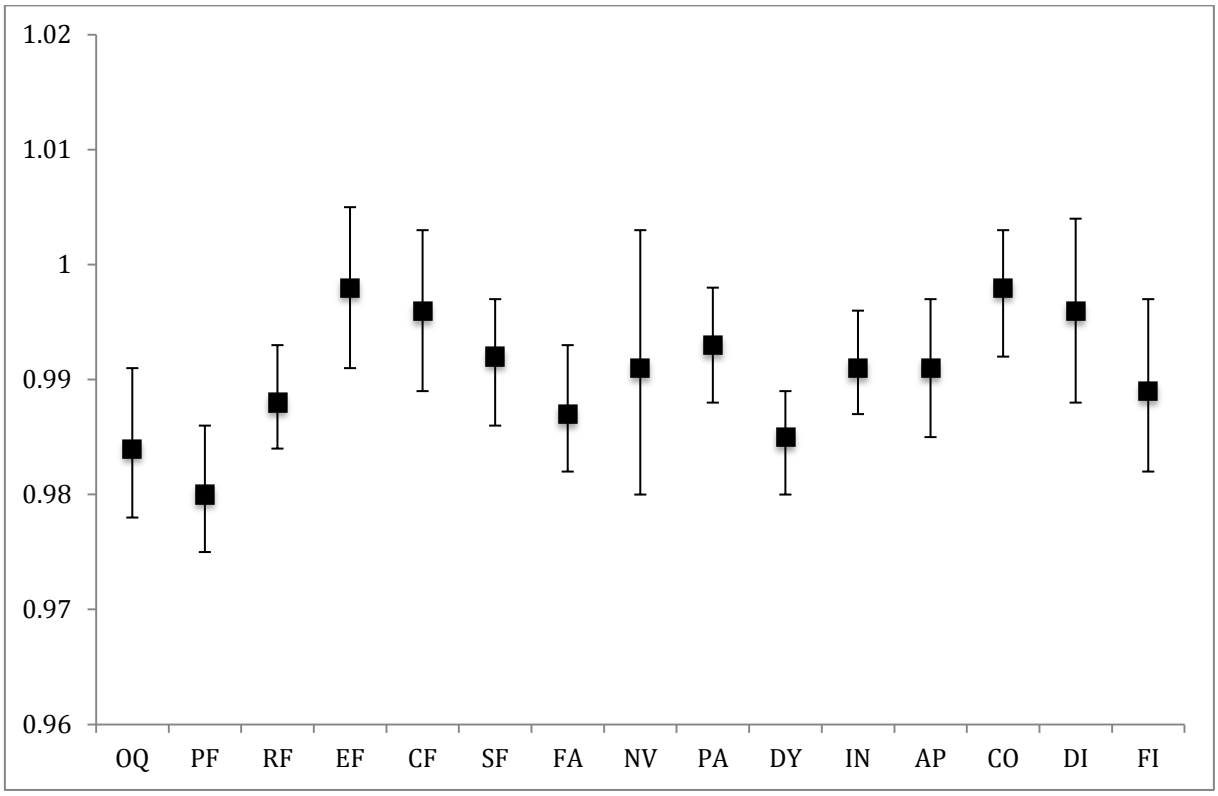


Figure 11.6 Box plot of Hazard Ratios and their 95% confidence interval of health-related quality of life domains in NMIBC patients.
OQ=overall quality of life; PF=Physical Functioning; RF=Role Functioning; EF=Emotional Functioning; CF=Cognitive Functioning; SF=Social Functioning; FA=Fatigue; NV=Nausea and Vomiting; PA=Pain; DY=Dyspnea; IN=Insomnia; AP=Loss of Appetite; CO=Constipation; DI=Diarrhea; FI=Financial Difficulties

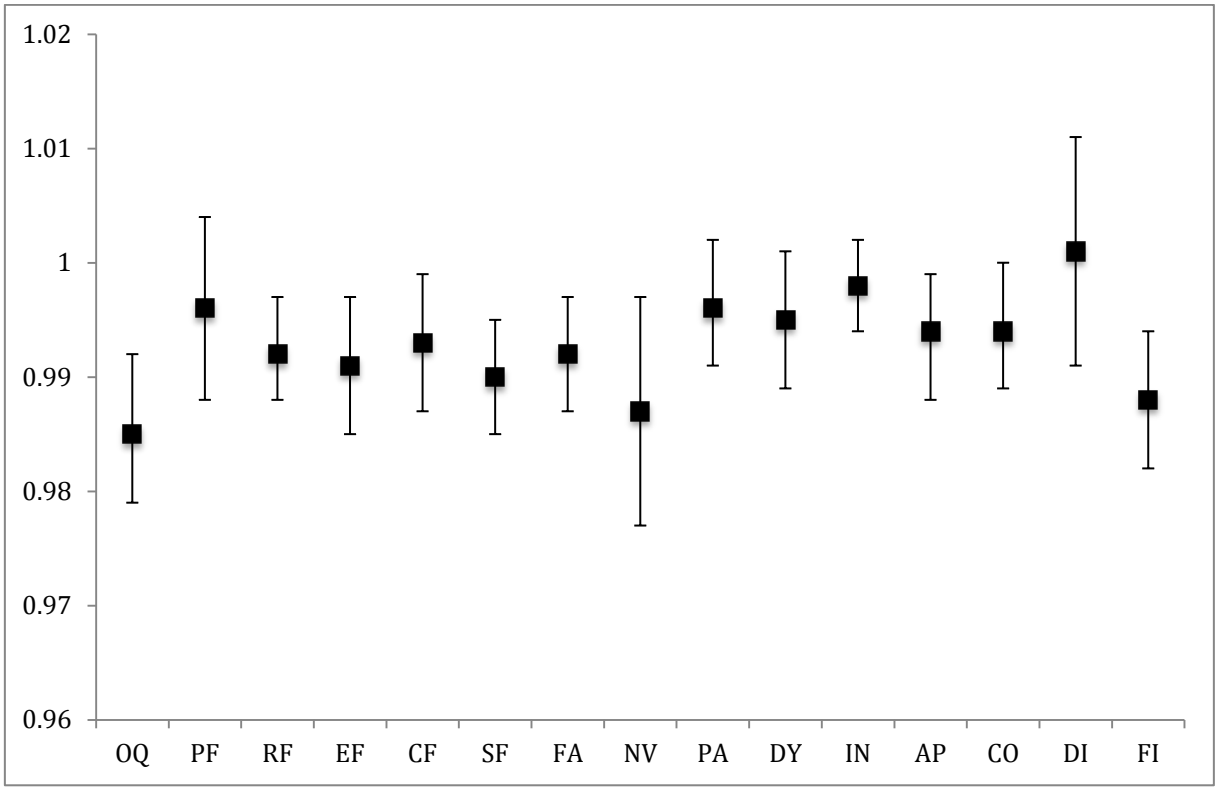


Figure 11.7 Box plot of Hazard Ratios and their 95% confidence interval of health-related quality of life domains in MIBC patients.
OQ=overall quality of life; PF=Physical Functioning; RF=Role Functioning; EF=Emotional Functioning; CF=Cognitive Functioning; SF=Social Functioning; FA=Fatigue; NV=Nausea and Vomiting; PA=Pain; DY=Dyspnea; IN=Insomnia; AP=Loss of Appetite; CO=Constipation; DI=Diarrhea; FI=Financial Difficulties

11.7 Appendix Chapter 8 – Literature search strategy for Pubmed

("urologic neoplasms"[MeSH Terms] OR ("urologic"[All Fields] AND "neoplasms"[All Fields]) OR "urologic neoplasms"[All Fields] OR "bladder cancer"[All Fields]) AND (("urinary diversion"[All Fields] OR Conduit[All Fields] OR Kock[All Fields] OR Pouch[All Fields] OR neobladder[All Fields] OR reservoir[All Fields] OR orthotopic[All Fields] OR Bricker[All Fields] OR "Le Duc"[All Fields] OR "Le Bag"[All Fields] OR Wallace[All Fields] OR Studer[All Fields] OR Indiana[All Fields] OR Hemi-Kock[All Fields] OR Mainz[All Fields]) OR ((urinary diversion[MeSH Terms]) OR (diversion AND (continen* OR orthotopic OR incontinen* OR conduit))) OR (bladder AND (continen* OR orthotopic OR substitute OR reconstruct* OR artificial OR replacement))) AND ((EORTC OR qlq OR c30 OR qlq-c30 OR (bls-24 OR "bls 24") OR (blm-30 OR "blm 30")) OR (fact-g OR fact-bl OR fact-vci OR "fact g" OR "fact bl" OR "fact vci") OR (sf-36 OR "short form 36" OR "short form-36" OR "sf 36")

11.8 Appendix Chapter 8 – Literature search Ovid

1 (urologic$ adj (cancer)).tw. or bladder cancer.mp. or exp Urinary Bladder Neoplasms/
2 urinary diversion.mp. or exp Urinary Diversion/ or conduit.mp. or pouch.mp. or neobladder.mp. or reservoir.mp. or orthotopic.mp. or Bricker.tw. or Le Duc.tw. or Le Bag.tw. or Wallace.tw. or Studer.tw. or Indiana.tw. or Hemi-Kock.tw. or Mainz.tw.
3 (diversion adj (orthotopic or continen$ or incontinen$ or conduit)).tw.
4 (bladder adj (continen$ or orthotopic or substitute or reconstruct$ or artificial or replacement)).tw.
5 eortc.tw or qlq.tw or c30.tw or qlq-c30.tw or bls-24.tw or blm-30.tw or bls 24.tw or blm 30.tw
6. (fact-g or fact-bl or fact-vci or factg or fact bl or fact vci).tw.
7. (sf-36 or short form 36 or short form-36 or sf 36).tw.
8. (sip or sickness impact profile).tw.
9. (assessment of quality of life or aqol).tw.
10. 2 or 3 or 4
11. 5 or 6 or 7 or 8 or 9
12. 1 and 10 and 11

11.9 Appendix Chapter 8 – Bar plots of mean quality of life scores per questionnaire and by continent vs incontinent urinary diversion patients

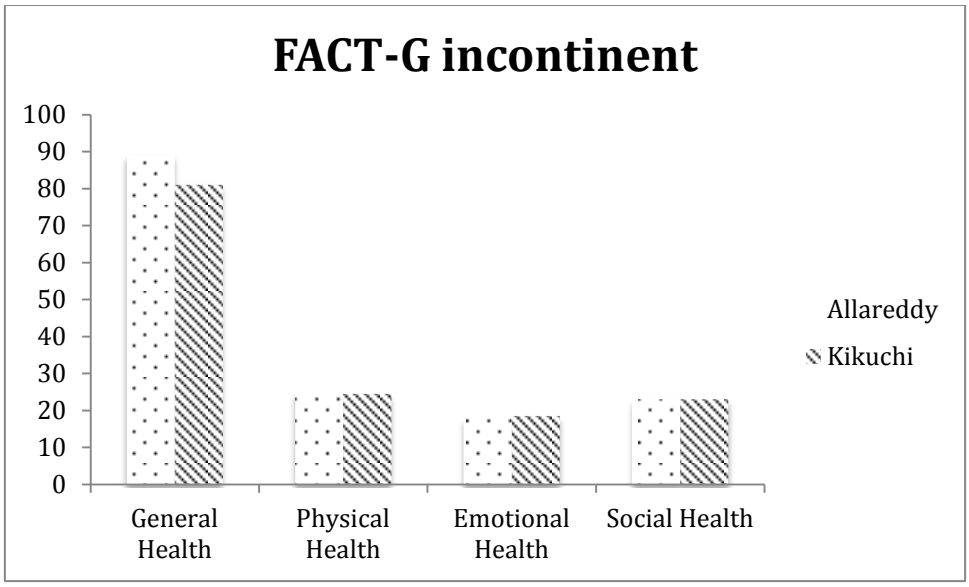


Figure 11.8 Mean FACT-G scores of incontinent urinary diversion patients included in the meta-analysis

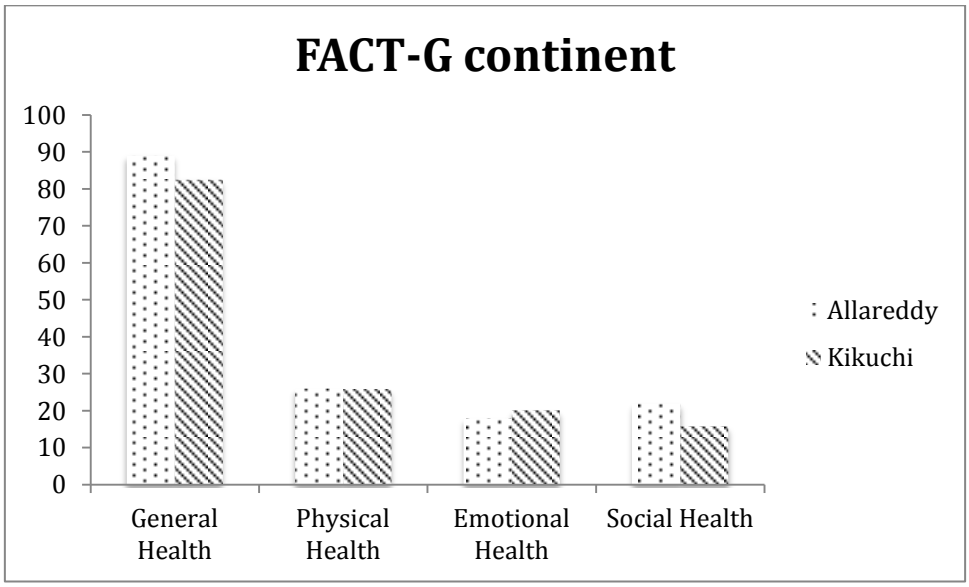


Figure 11.9 Mean FACT-G scores of continent urinary diversion patients included in the meta-analysis

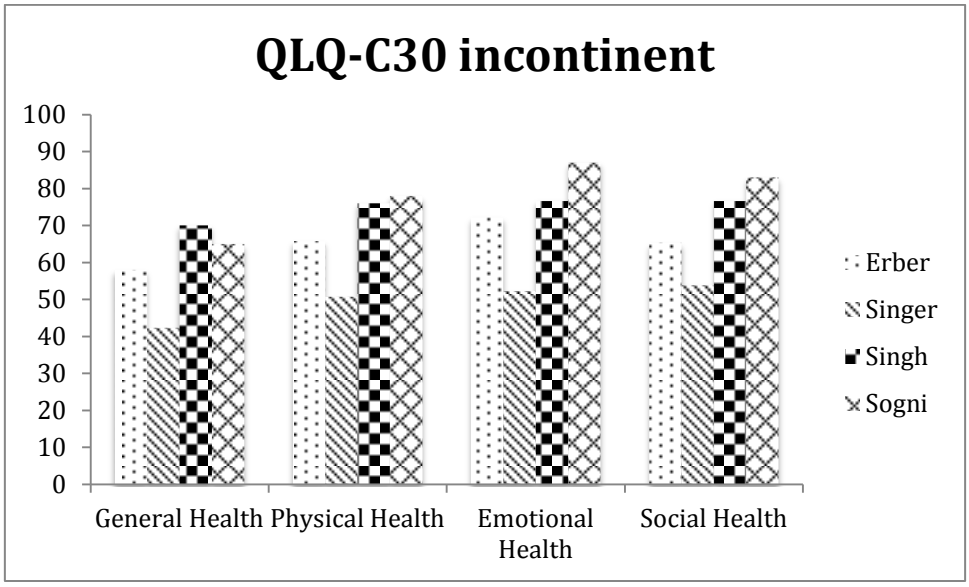


Figure 11.10 Mean QLQ-C30 scores of incontinent urinary diversion patients included in the meta-analysis

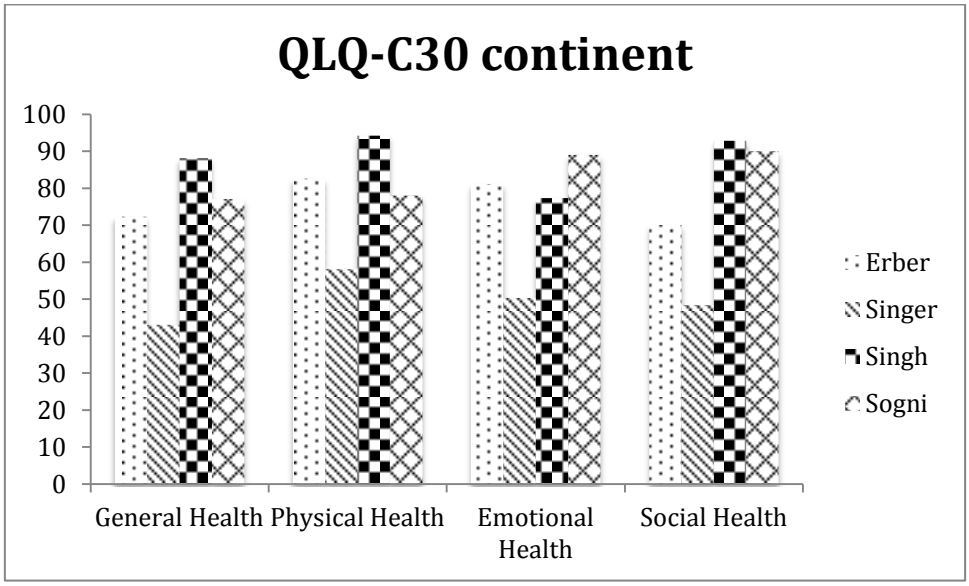


Figure 11.11 Mean QLQ-C30 scores of continent urinary diversion patients included in the meta-analysis

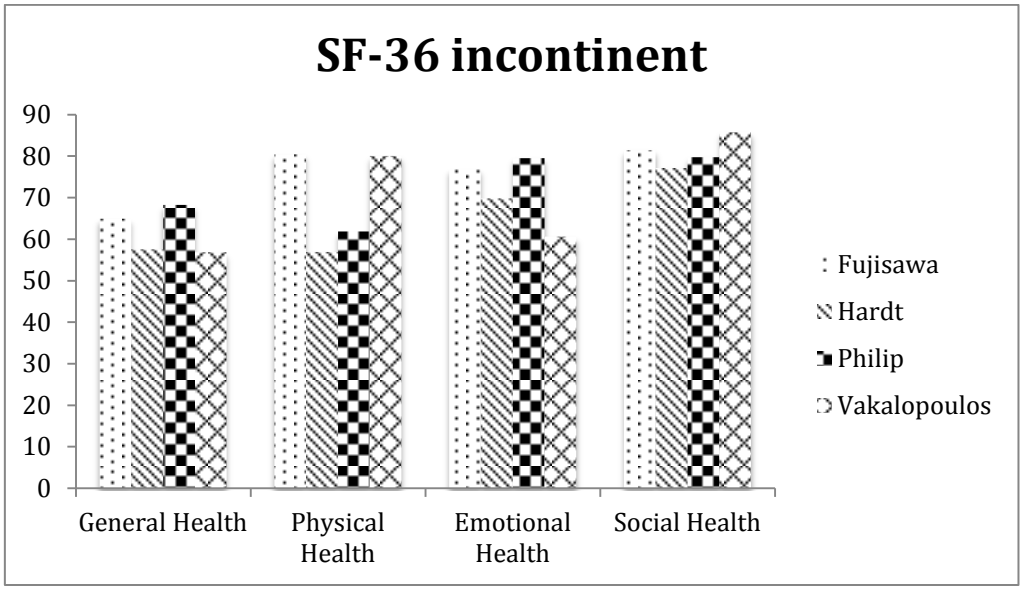


Figure 11.12 Mean SF-36 scores of incontinent urinary diversion patients included in the meta-analysis

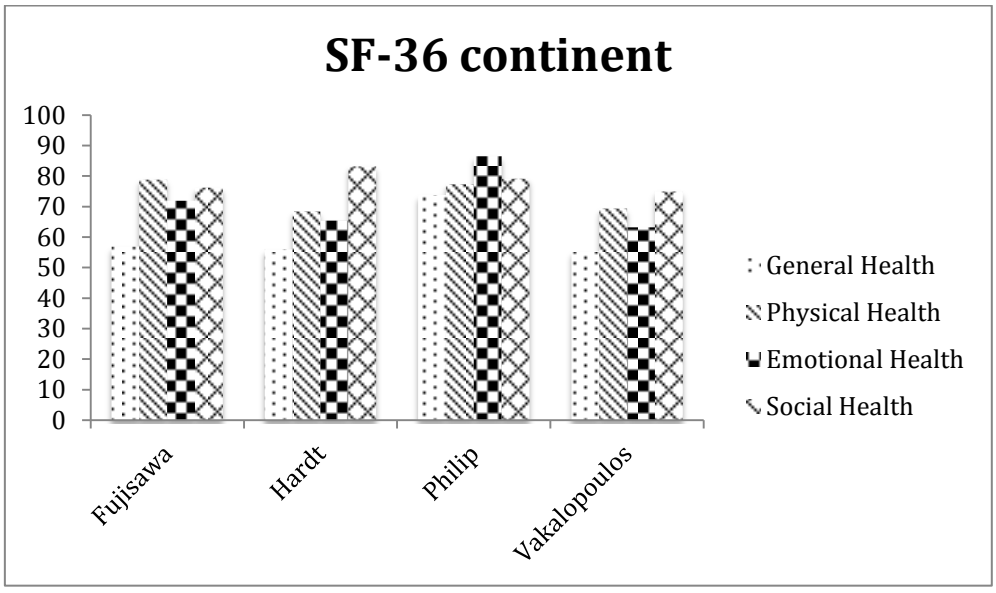


Figure 11.13 Mean SF-36 scores of continent urinary diversion patients included in the meta-analysis

11.10 Appendix Chapter 8 – Meta-analyses including Singh et al.

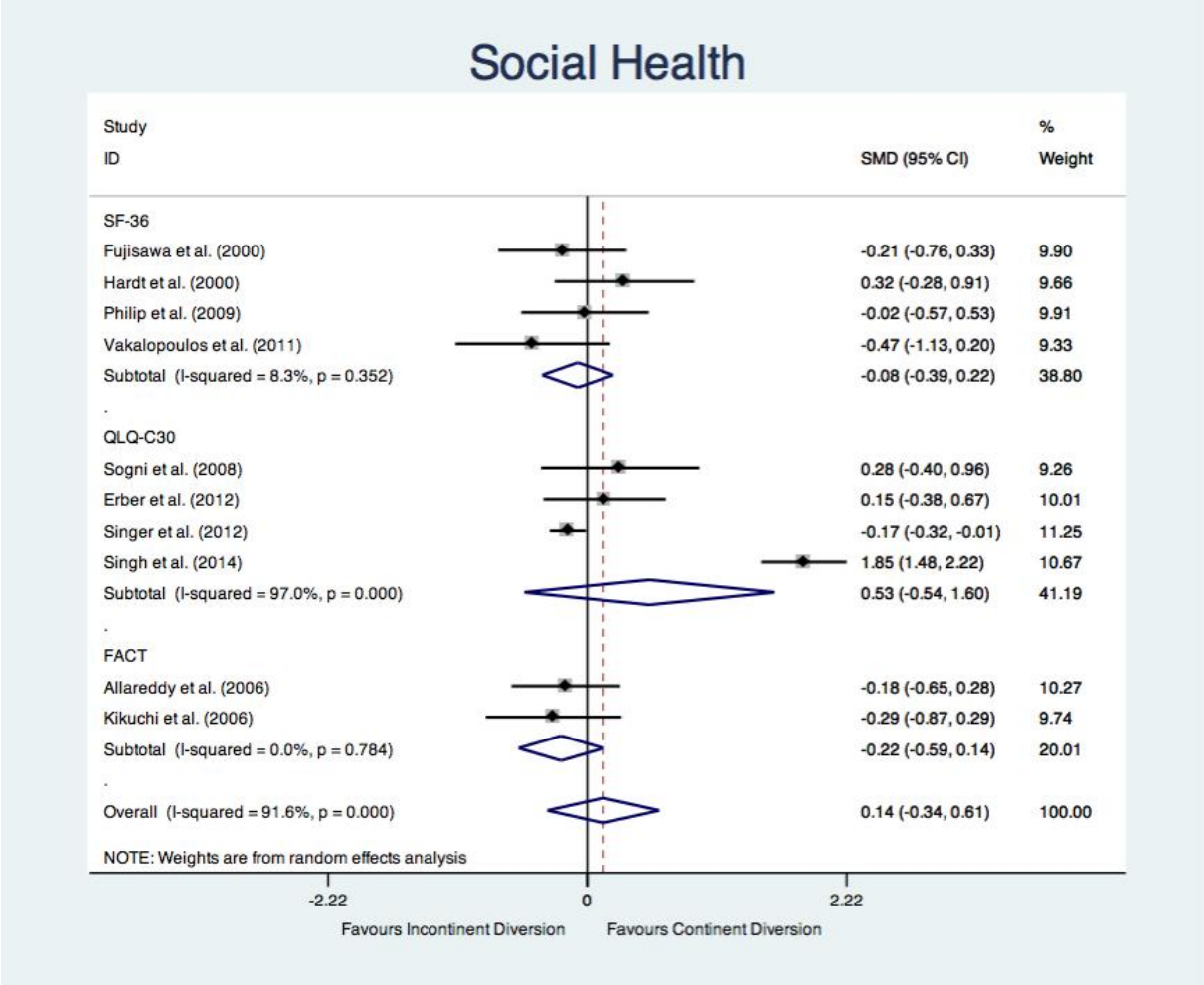


Figure 11.14 Forest plot of the pooled standardized mean differences divided by quality of life questionnaires for Social Health.

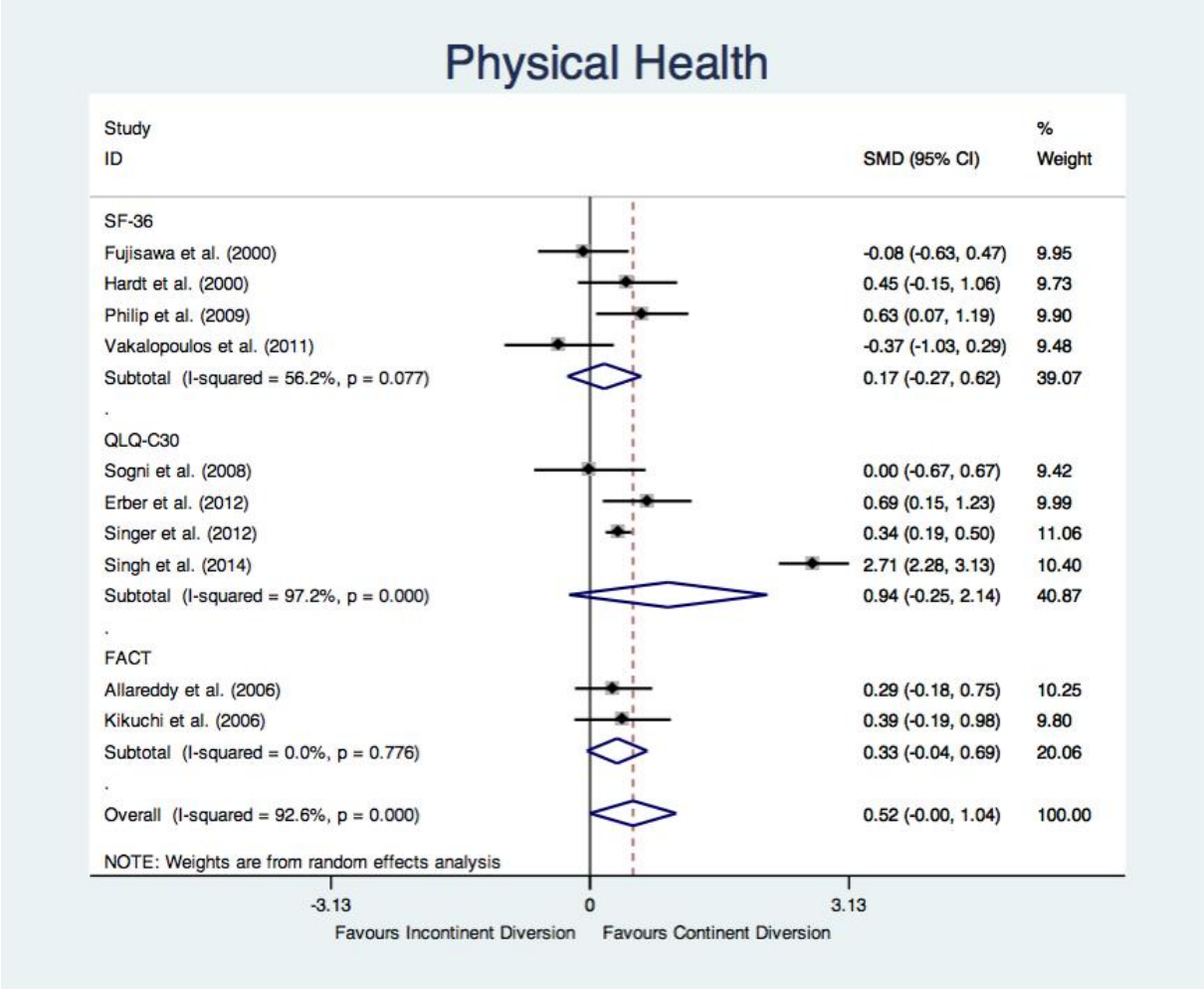


Figure 11.15 Forest plot of the pooled standardized mean differences divided by quality of life questionnaires for Physical Health.

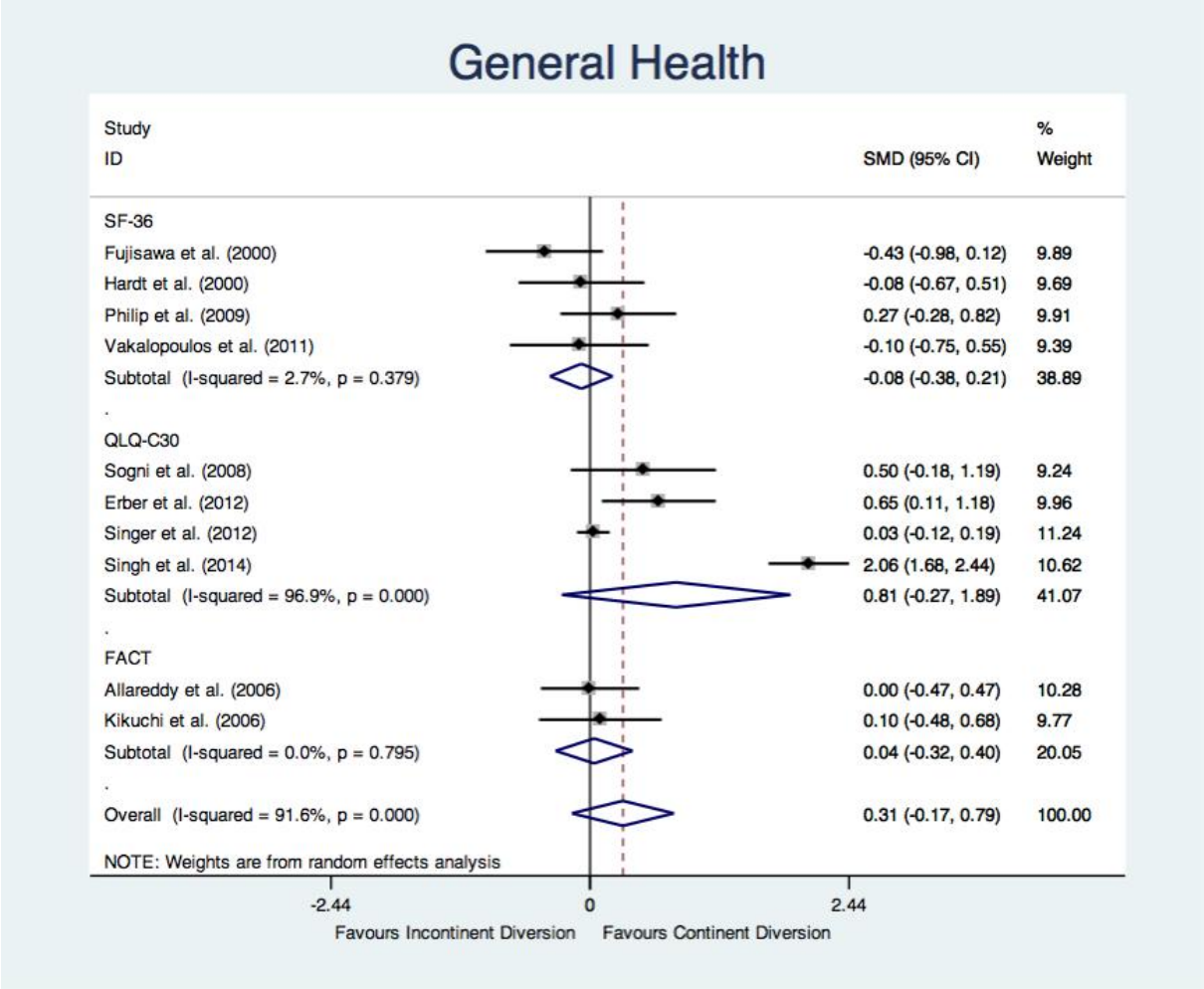


Figure 11.16 Forest plot of the pooled standardized mean differences divided by quality of life questionnaires for General Health.

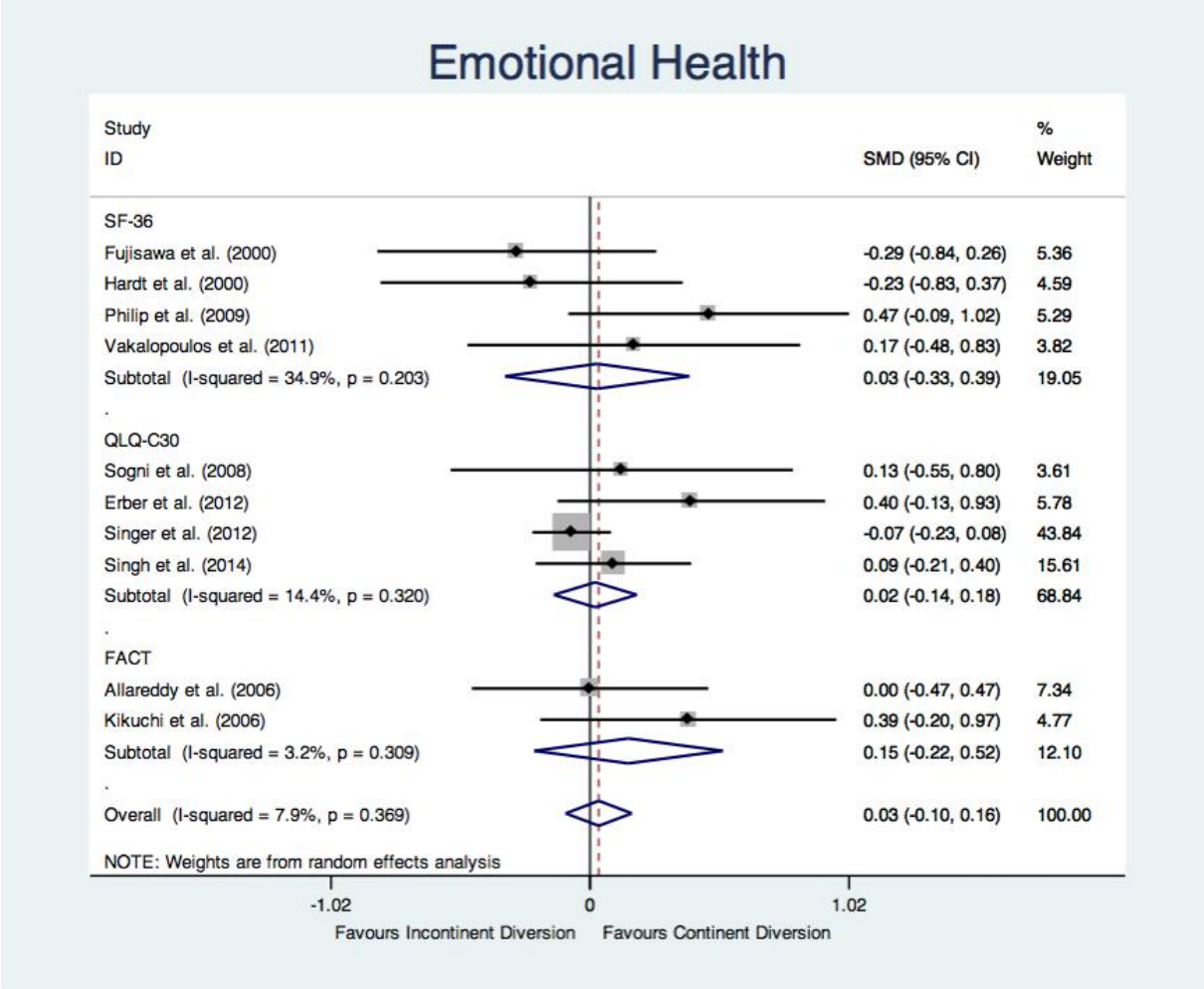


Figure 11.17 Forest plot of the pooled standardized mean differences divided by quality of life questionnaires for Emotional Health.

11.11 PRISMA checklist for Chapter 8 Meta Analysis

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	101
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	102,103
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	104 - 106
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	106
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	n/a
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	107,108
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	106,107
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	106, 107, 159
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	105 - 107
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	108

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	108
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	108
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	108, 109

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	110
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	110, 111
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	112, 113
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	114 - 118
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	114 - 118
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	118, 119
DISCUSSION			

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	119
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	120 - 122
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	122
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	n/a