Muscle-Invasive Bladder Cancer:

Quality of Care and Quality of Life in The Netherlands

Katja Goossens - Laan

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"Not everything that can be counted counts, and not everything that counts can be counted"

(Albert Einstein)

Ter nagedachtenis aan mijn vader, Ton Laan

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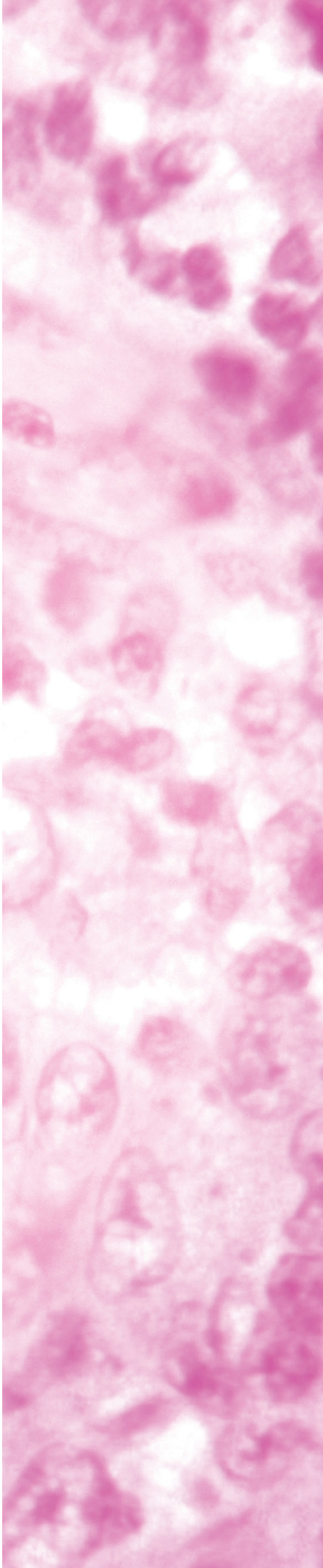
PART I

General Introduction



Chapter I

Design of this thesis

An introduction to bladder cancer: bladder cancer in the elderly.

Objective, aim and outline of this thesis

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Bladder cancer in the elderly

1 Epidemiology

Bladder cancer is the seventh most common cancer worldwide. In the Netherlands, in 2010 invasive bladder cancer was the eighth most common cancer, with an incidence of 13.7 per 100,000 persons (European Standard Rate; ESR) (Figure 1) [1]. In 2010, 2963 patients presented with invasive bladder cancer (≥T1), around 30 patients per hospital [1]. The incidence in males is four times higher than that in women. The incidence of bladder cancer in the Netherlands decreased between 1990 and 2010 for men, with a small increase for women which is consistent with rise in smoking behaviour (figure 1) Bladder cancer is often seen as a disease of 'the older man'. It is mainly diagnosed in patients older than 60 years and has a peak incidence at 85 years [2]. Indeed, the greatest risk indicator for the development of bladder cancer is age [3].

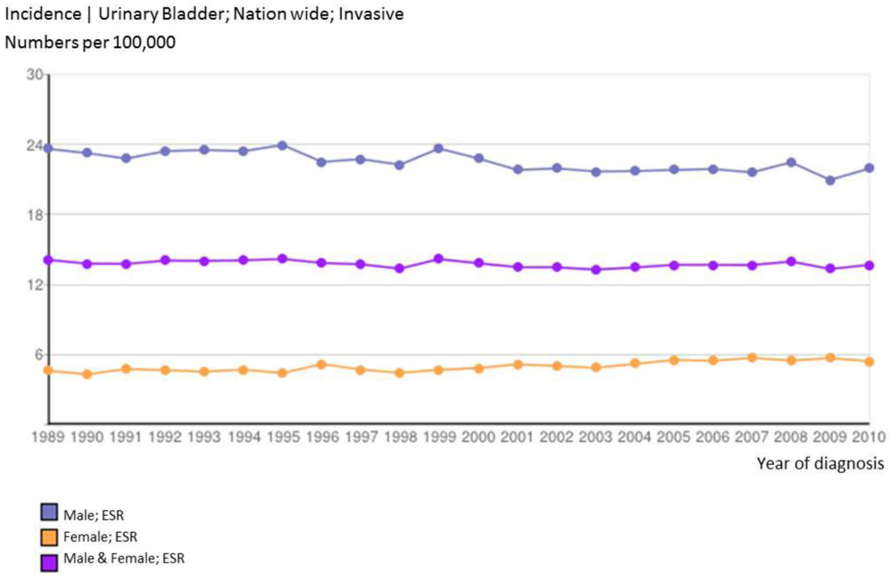

Figure 1: Incidence of invasive bladder cancer in the Netherlands, European Standard Rate (ESR).
Source: www.cijfersoverkanker.nl

2 Classification

Bladder cancer is divided into two forms: the superficial (non-muscle-invasive) and the muscle-invasive bladder cancer. About 70% of newly diagnosed bladder tumours involve a non-muscle-invasive bladder tumour, which penetrates the bladder lining only [1]. This form must be treated as early as possible; otherwise it may develop into the muscle-invasive type. One form of non-muscle-invasive bladder cancer is carcinoma in situ (CIS). If the CIS has a high-grade form of malignant potential (i.e. poorly differentiated), the chance of progression to muscle invasion is high if left untreated. The muscle-invasive tumour invades both the mucosa and the muscle of the bladder and, due to its aggressiveness and worse prognosis, requires a different treatment than the non-muscle-invasive type.

Tumours of the bladder are divided into three main histological types: 97% of the patients have an urothelial cell carcinoma, also called transitional cell carcinoma. In about 1% of the cases it will be a squamous cell carcinoma and in another 1% adenocarcinoma is found. Some exceptional cases are a form of non-differentiated cancer or a neuroendocrine tumour [3].

This general introduction only concerns urothelial cell carcinoma.

The stage of the tumour is described in the TNM classification (Table 1 and figure 2). In addition, the WHO classification subdivides the tumour into three degrees: well differentiated, moderately differentiated and poorly differentiated.

In addition to a peak incidence at 85 years, bladder cancer in the elderly patient more often presents with a poorly differentiated form. Various explanatory theories have been presented [2]. The relatively late presentation of urothelial cell carcinoma may be the result of accumulation of exposure to different carcinogens over time. Moreover, at an later age, because the bladder is less flexible there is often a residue after voiding which extends the contact time of possible carcinogens that are eventually excreted through the urine. In addition, the fluid intake of elderly patients with lower urinary tract symptoms (LUTS) is often reduced, with the hope of reducing symptoms. However, unintentionally, this allows the concentration of carcinogens in urine to increase. Last but not least, with increasing age, urothelial enzymes lose their ability to ensure inactivation to carcinogens.

Table 1. TNM classification system for bladder cancer, 2009

T –	*primary tumour*
Tx	Cannot be assessed
T0	No proof
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ
T1	Invades the lamina propria (submucosa)
T2	Invades the detrusor muscle
T2a	Invades superficially in the detrusor muscle (inner half)
T2b	Invades deep in the detrusor muscle (outer half)
T3	Invades into perivesical tissue
T3a	Microscopic
T3b	Macroscopic
T4	Invades one or more of the following structures: prostate, uterus, vagina, pelvic wall, abdominal wall
T4a	Invades prostate, uterus or vagina
T4b	Invades pelvic wall or abdominal wall
N –	*lymph glands*
Nx	Cannot be assessed
N0	None
N1	Lymph node metastasis in a single node, smaller than 2 cm
N2	Metastasis in a single lymph node larger than 2 cm, but not more than 5 cm or in multiple lymph glands
N3	Metastasis in a lymph node larger than 5 cm
M –	*remote metastases*
Mx	Cannot be assessed
M0	No distant metastases
M1	Distant metastases

Source: Schlesinger-Raab, 2008 [4].

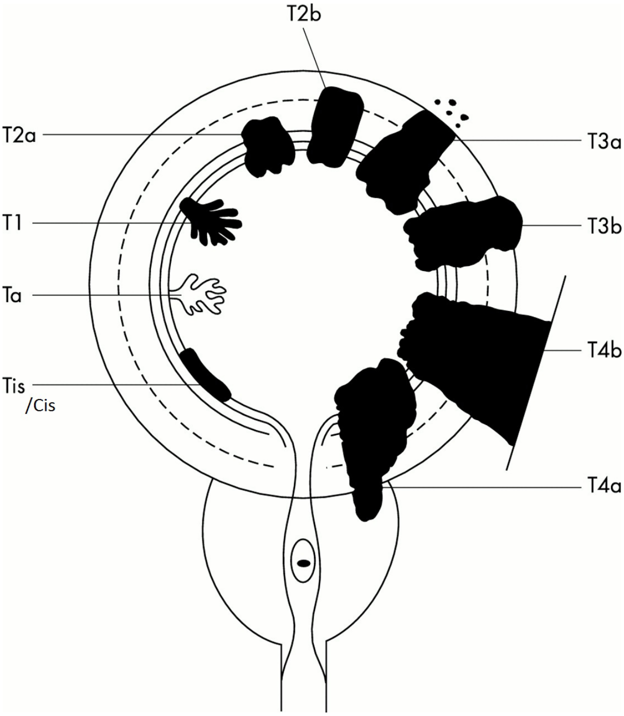

Figure 1: Classification of Malignant Tumours: the TNM classification of bladder cancer.

3 Diagnostics

Microscopic or macroscopic hematuria is the most common symptom in bladder cancer. Unlike the non-muscle-invasive type, muscle-invasive tumours often cause irritative LUTS, dysuria, and pain in the pelvic and bladder region [3].Sporadically, bladder cancer is found in patients with recurrent urinary tract infections. If a patient with a non-muscle-invasive tumour is suffering from an irritative voiding dysfunction it may be CIS, which represent 5-10% of all non-muscle-invasive tumours found per year [3]. Usually, the physical examination does not reveal a bladder tumour. Sometimes, a solid invasive tumour at the base of the bladder and pelvic wall can be palpated with bimanual examination.

The gold standard in the diagnosis of bladder cancer is the urethrocystoscopy (figure 2).

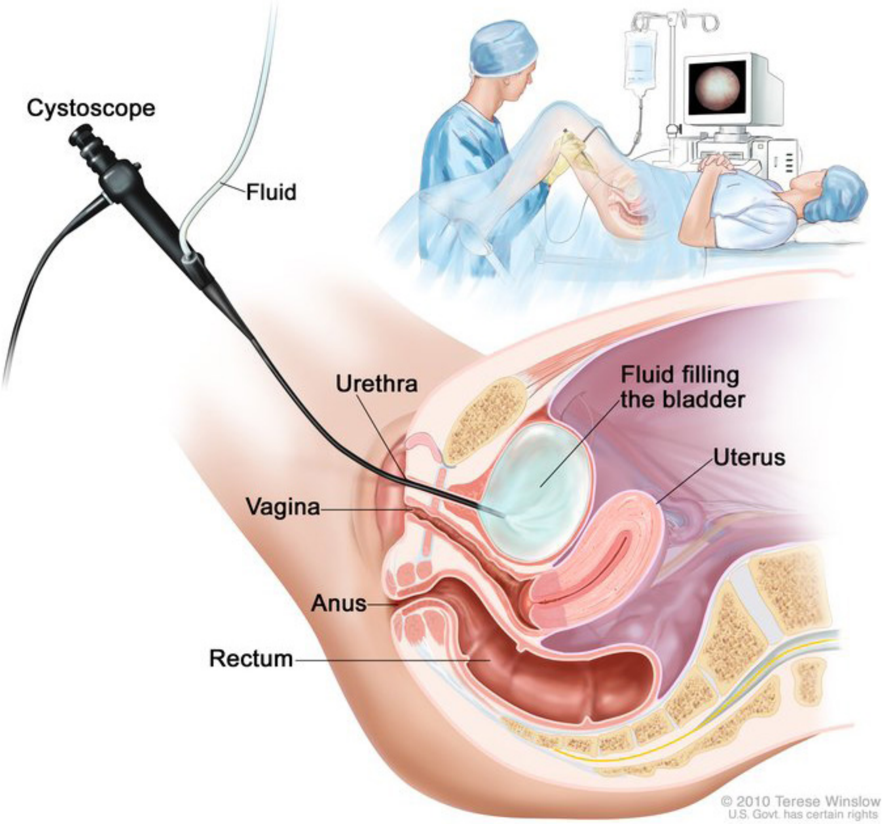

Figure 2: Flexible cystoscopy in a female patient.

With a rigid (in women) or flexible scope (men and women) the inside of the bladder is inspected for lesions on the bladder lining. Urine cytology is also performed.
Even if urine cytology shows no malignant cells, this does not rule out the presence of a bladder tumour. This is because cytology has a high sensitivity for high-grade tumours (40-90%) [5], whereas the sensitivity for low-grade tumours is somewhere between 8% and 75% [5]. In case of a positive cytology but normal cystoscopic findings, the upper urinary tract should be evaluated. Although much research has focused on the development of better tumour markers, they are not yet available for everyday use.

Due to the low sensitivity of the intravenous urogram (in which the bladder tumour is visualised as a gap in the contrast), it has been replaced by CT scan of the urinary tract [3,6]. However, a CT scan does not allow to differentiate between non-muscle-invasive and muscle-invasive tumours, and has limited value in tumour staging. For local staging an MRI scan is more accurate. In patients with a T3-T4-tumour, an abdominal CT scan and X-ray of the thorax are performed to detect metastases; with bone pain and/or increased alkaline phosphatase a bone scan is indicated [3,6].

4 Risk factors

Smoking is an important risk factor. There is a 2.5 to 3 times increased risk of developing bladder cancer in smokers [3]. Another risk factor is the occupational exposure to certain substances, such as aromatic amines (e.g. in the rubber or painting industry). There is a latency time of some 20-30 years for the development of bladder tumours. Aging automatically contributes to a prolonged exposure to carcinogens, with the potential accumulation of cellular defects that can cause neoplastic transformation [3].

5 Treatment

5.1 Treatment – General

To obtain the histological diagnosis, a TURT is performed. Under spinal or general anaesthesia the bladder is inspected using a rigid cystoscope, electrically-guided resection biopsies are taken, and then the tumour is removed. When the tumour is suspected to be non-muscle-invasive, an intravesical chemotherapy agent (e.g. mitomycin) is immediately instilled into the bladder.

Currently, there is increasing use of fluorescence cystoscopy. Before surgery, (hexa)-5-aminolevulinic acid (a porphyrin-based photosensitive substance) is instilled into the bladder; then, after inspection of the bladder under a blue light, the light turns red. This enables flat lesions (novice lesions) or CIS to be more frequently detected and resected, which may be overlooked with white light.

For older patients, TURT is mostly performed under spinal anaesthesia and, generally, is well tolerated.

5.2 Treatment – Tumour specific

Non-muscle-invasive (superficial) bladder cancer

For a very superficial bladder tumour (TaG1-2) TURT is the final treatment. During the first year the follow-up (every 3-6 months) will consist of a cystoscopy and urine cytology [3]. Based on specific risk tables with six important clinical and pathological factors, the chance of recurrence and/or progression can be estimated (Table 2) [7].

Table 2

Factors affecting the chance of a relapse/progression of tumour
• The initial number of tumours
• Tumour size
• Relapse frequency (the faster a relapse, the greater the chance of a new relapse)
• T-classification of the tumour
• Staging of the tumour
• Presence of CIS

Source: EORTC risk tables [7].

To reduce the chance of relapse for a recurrent TaG1-2 tumour, a series of intravesical instillations for up to one year is started [3,6].

For TaG3 or T1 tumours, which are liable to progress to a muscle-invasive tumour, a series of bladder instillations with BCG is started [3,6]. BCG is an immunmodulator (although its precise functioning is not yet entirely clear) which reduces the risk of recurrence and progression of bladder cancer. About 4-6 weeks after the first surgery a re-TURT will take place to establish progression, or an initial understaging of a T2 tumour in time. In case of a negative re-TURT, the BCG is continued for up to 36 instillations over a 3-year period [3,6]. According to the literature, mitomycin (MMC) and BCG instillations have a similar effect with regard to the recurrence rate: the 3-year relapse-free rate for MMC is 69% and is 66% for BCG [8]. However, BCG instillations reduce the chance of progression by 26% [8]. On the other hand, compared with mitomycin, BCG treatment more often causes serious side-effects such as urinary frequency, BCG-induced hematuria and cystitis (leucocyturia, hematuria, frequency and dysuria without demonstrable bacteriuria). BCG may also cause systemic toxicity, associated with fever, influenza symptoms, BCG-induced pneumonia, toxicity of the liver and BCG sepsis [3]. In addition, in the older patient BCG instillations are less effective; the relapse risk is 2.3 times higher for patients aged ≥ 80 years than for patients aged 60-69 years [9]. A possible explanation for this is that this BCG treatment requires an effective cell-mediated immune response, which is decreased in advanced age.

When the pathology of the re-TURT shows CIS despite BCG instillations, a second series of BCG instillations can be given. If, again, this has no effect it is recommended to treat the patient as one with muscle-invasive tumour. This occurs in about 7% of the total group of patients treated with BCG [3].

Muscle-invasive bladder cancer

Whereas treatment of the older patient with non-muscle-invasive tumours differs little from that in younger persons, the situation changes for the treatment in muscle-invasive bladder cancer. A large portion of the elderly has co-morbidity: for example, in the Netherlands, 63% of the patients have one or more serious co-morbid conditions (unpublished data Integrated Cancer Centres North and South). However, the difference in the choice of treatment compared with younger patients is based not only on the presence of co-morbidity but also on the higher biological age. Instead of a cystectomy, radiotherapy is more often offered to the elderly patient than to patients below 75 years [10]. However, there are sufficient indications to show that, in selective cases, cystectomy in the older patient is certainly possible [10,11].

Cystectomy with urinary diversion and pelvic lymph node dissection is the standard treatment for the patient with a non-metastatic muscle-invasive bladder cancer. This involves complete removal of the bladder with, in the male patient, removal of the prostate; for the female patient, this involves removal of the uterus, ovaries and adnexa, and a segment of the anterior vaginal wall. The mortality rate for cystectomy is 0.7-8.1% for the total population [12,13]. For patients aged 80 years and older a perioperative mortality of 5% is reported in high-volume centres (≥ 10 per cystectomies/year) and in specialised centres [10]. A recent study based on SEER data (Surveillance, Epidemiology and End Results database) shows a threefold and five-fold increased risk of perioperative mortality in the group of patients aged 70 and 80 years and older [14]. It is an intervention with a high complication rate of about 64% [5].

The 5-year disease-free survival rate for pT2 tumours is 72-81%, for pT3 tumours it is 35-58%, and for pT4 tumours the rate is 28-44% [3]. Performing a lymph node dissection seems to give better survival and is also of prognostic value; Skinner et al. showed that 36% of patients with positive lymph nodes achieved a survival of five years [16]. A study from 2011 shows that in patients aged 80 years or older, the lymph node dissection is frequently not performed, but that the overall cancer-specific survival advantage between all different age groups turns out to be the same when a lymph node dissection is performed [17].

When a patient is not eligible for a cystectomy due to local tumour growth, co-morbidity, poor performance status (Karnofsky score) or the choice of the patient, other options are available. The second best treatment choice is curative radiotherapy, if possible combined with chemotherapy [3,6]. The complete response rate for radiotherapy alone is 63-75%, the 5-year local control rate is 40-55%, and overall survival (five years) rate is 32-58%. For radiotherapy with chemotherapy complete remission is achieved in 61-90% of these patients and the 5-year survival rate is 45-62% [3].

There is yet another bladder-sparing treatment that is applied in case of small tumours (< 5 cm) infiltrating to the submucosa or superficial layer of the detrusor muscle (T1-2). This is a short external radiation combined with interstitial radiation therapy (brachytherapy) of the tumour area, whether or not combined with a partial bladder resection. Patients have to undergo a relatively limited operation (section alta). The results are similar to those after a radical cystectomy, and the patients generally maintain a good bladder function [3].

Chemotherapy only, or a TURT with intravesical or systemic chemotherapy, is not seen as a curative treatment method. Age alone does not form an absolute contraindication to performing a cystectomy. However, the number of elderly patients that undergoes a cystectomy is low; a study from the USA shows that only 19.7% of the group of patients aged 80 years and older is treated with a cystectomy [18].

5.3 Urinary diversion after cystectomy

There are three different forms of urinary diversions after a cystectomy: an incontinent ureteroileocutaneostomy/conduit (deviation according to Bricker), a continent pouch (Indiana pouch) or an orthotopic bladder substitution (a neobladder, i.e. a deviation of intestine constructed in the same place as the original bladder). Elderly people frequently receive an incontinent conduit, because with an orthotopic bladder substitution the patient must be able to empty his bladder with self-catheterisation [2]. Age is an important determinant for the long-term bladder capacity, nocturia and continence status after the creation of a neobladder. An explanation for these various complications could be the reduced function of the external urethral sphincter [2].

The preservation of Quality of Life (QoL) after a cystectomy is perhaps even more important for the elderly patient than the survival advantage alone. Learning to cope with a conduit or neobladder, and perhaps becoming dependent on home care, has a major impact on the patient's perceived QoL.

The effect of the different forms of urinary diversions on a patient's QoL has not yet been established. Although one review on this topic reports no difference between a continent diversion and an incontinent conduit, no randomised prospective studies are currently available [19].

5.4 (Neo) adjuvant treatment

At least 50% of the patients who undergo a cystectomy develop overt metastases within two years after diagnosis, [3,6]. A treatment strategy can be to start (neo) adjuvant chemotherapy. However neoadjuvant chemotherapy has not (yet) shown a significant improvement in survival, and for adjuvant treatment no randomised data are available [3]. In contrast, the last update of the European guidelines states that neoadjuvant chemotherapy in certain groups of patients should be considered [20]. Preoperative radiation therapy may reduce the percentage of local recurrences, but will not lead to an improved survival [3].

Metastatic disease

About 50% of the patients who undergo a cystectomy for muscle-invasive bladder cancer will develop a local relapse or metastases. Systemic chemotherapy gives a response rate of up to 70% in patients with urothelial cell carcinoma. A significant survival gain is achieved when optimal supportive care follows a survival of 4-6 months, compared with a median survival of 12-14 months with the combination of cisplatin and gemcitabine [2,3].

Toxicity with cisplatin treatment is clearly increased due to the impaired renal function with increasing age; this implies that over 40% of patients aged over 70 years are not eligible for cisplatin therapy [3]. Associated side-effects include nephrotoxicity (100%; after optimal supportive care 28-36%), ototoxicity (30%), neurotoxicity and vascular damage in the form of cardiovascular, cerebrovascular and thrombotic microangiopathy, and Raynaud's phenomena [21]. Side-effects may also include nausea, vomiting and fatigue.

Elderly patients less often receive the optimum dosage compared with younger patients, probably due to their decreased physiological reserves, co-morbidity, and changes in absorption and metabolism of the chemotherapy.

Chemotherapy regimens that do not contain cisplatin (gemcitabine alone, or with carboplatin) seem attractive despite their reduced effectiveness. More research is needed on tolerance and response rates among older patients, taking into account the co-morbidity, organ (dys)function and physiological reserves in this elderly group [2].

The disadvantage of medication-controlled studies is that there is rarely an individual dose adjustment for the elderly, or for a co-morbidity that threatens multiple organs [2]. However, carboplatin appears to be an exception to this limitation.

Furthermore, although *targeted* therapy is on the increase, it has not yet been proven meaningful in the treatment of bladder cancer.

Objective, aim and outline of this thesis

Objective

Muscle-invasive bladder cancer requires a multidisciplinary approach, whereby the trade-offs related to co-morbidity, functional and physiological reserves for each individual should determine the most appropriate treatment plan.

Quality of Life

Next to the best oncological outcome after surgery for patients is quality of life (QoL) an important outcome parameter to achieve optimal QoC [6]. The demand for optimum care is not only related to the complexity of performing a cystectomy with a urinary diversion. It starts with a worried patient entering the consultation room with (for him) life-threatening symptoms. When this first visit finally results in the decision to remove the whole bladder, a considerable amount of diagnostic and informative care has taken place: a cystoscopy, a transurethral resection of the tumour (TUR-BT), discussing the pathology result, dissemination research, and guidance in decision-making regarding the final choice of treatment. There is a need for thorough counselling of this group of patients due to the social and sexual implications of this type of surgery. This complex operation is assumed to affect the patient's QoL, health status (HS) and sexual functioning as it involves major surgery and the necessity for an incontinent or continent urinary diversion. Therefore, in patients with muscle-invasive bladder cancer undergoing cystectomy, HS and QoL (both patient-reported outcomes) are of particular interest in urologic oncology.

In these patients proper selection is essential before performing a radical cystectomy, to justify the choice of this treatment with its relatively high morbidity and mortality [6,22]. However, no well-established selection criteria are available. An option would be to take the patient's current HS and QoL into account. For example, prior to surgery to what extent is the patient already experiencing a limited QoL due to a small bladder capacity or urinary incontinence; does providing a conduit or orthotopic bladder substitution improve their QoL? Or does performing radical surgery with a urinary diversion have a negative impact on their QoL?

A person's QoL and HS are generally in part determined by that person's personality traits. Of particular interest is the trait anxiety. The trait anxiety can affect the coping mechanism of a patient diagnosed with cancer. This has been shown in breast cancer patients who score high on the trait anxiety who are offered breast conserving surgery. These patients experience a worse QoL after surgery than patients not scoring high on this trait [23]. Moreover, fatigue and depressive symptoms up to at least six months after surgery are also predicted by high scores on the trait anxiety in breast cancer patients [23]. To what extent this trait plays a role in learning to live with a conduit or orthotopic bladder substitution is unknown.

Quality of Care

An important issue in discussions on quality improvement of health care is whether or not cancer care should be regionalised in specialised 'high-volume' hospitals; especially when it involves high-risk, low-volume procedures. As said before, the radical cystectomy has an inpatient postoperative mortality rate of 0.7-8% [4,12], and postoperative morbidity occurs in 64% of the patients [15]. In the Netherlands, with about 800 radical cystectomies a year being performed in 97 hospitals, radical cystectomy qualifies not only as a high-risk, but also as a low-volume, procedure. The question arises how to manage this low number of patients to provide them with optimal treatment and what conditions must be met to achieve this goal.

Studies showed significantly different mortality and survival rates between high and low volume cystectomy providers [24,25]. These studies suggest that high-volume hospitals have better infrastructural characteristics and high-volume surgeons have more experience, resulting in better outcomes (the "practice makes perfect" principle). In the Netherlands, studies on the volume-mortality relationship for two gastro-intestinal high-complex low-volume operations, i.e. the pancreaticoduodenectomy (Whipple) and the oesophageal resection with reconstruction, have confirmed this relationship [26,27]. In addition, an American study on these two procedures, and on the elective operation for an abdominal aneurysm, showed that this positive effect on lower mortality with more operating volume is related (for as much as 50%) to the experience of the operating surgeon [28]. Volume is seen as a proxy for high quality of care and centralisation of services with high-volume providers is expected to improve outcome for these patients. This has led to the introduction of mandatory minimal volume standards for high-risk procedures, such as oesophageal resections for cancer, and local centralisation initiatives for pancreatic surgery [29,30]. This volume-outcome association is less clear for other major cancer surgeries, i.e. there is a less than two percent difference in mortality rate for nephrectomy, lobectomy and colectomy [28]. On the other hand a recent study showed for renal cancer surgery that higher volume surgeons perform relatively more partial nephrectomies and have a lower complication rate [31]. The literature on the radical prostatectomy is abundant; there is a clear association between higher hospital radical prostatectomy case volume and improved outcomes, although mortality rates are only slightly improving [32].

There is also evidence for an association between volume and outcome of cystectomy procedures for invasive bladder cancer [12,28,33,34]. Therefore, the Netherlands Organisation for Health Research and Development (ZonMw) commissioned an investigation of this association within the Dutch situation. In response to the results of this investigation showing the relationship between volume and mortality, a slow increase in the voluntary centralisation of all Dutch cystectomies occurred since 2010. Subsequently, the Dutch Association of Urologists made centralisation mandatory in 2010. Thereby becoming the first association of specialists to request minimal volume standards of a specific surgical procedure.

Measuring Quality of Care

Concerning the quality of care (QoC), mortality and morbidity have been used as proxy measures, but should not be the only criteria applied. QoC relies on a wide range of factors, all of which will influence the outcome. It is important to properly define QoC on the basis of outcome parameters and to identify the essential factors, i.e. those factors which contribute to an improved outcome. For instance, other factors can be a multidisciplinary consultation, the waiting period before surgery, the time until the pathology report is presented to the patient. Furthermore, the overall level of care in the intensive care unit and urology department may play a role. There appears to be a relationship between the mortality rate after a cystectomy and the ratio of the number of nurses/number of beds per hospital. For example, in the hospital with a high nurse per patient ratio and low volume of cystectomies per year the mortality rate was significantly lower compared with the hospital with a low nurse per patient ratio and low volume of cystectomies per year, i.e. 1.9% vs. 4.5% [12].

Aim

The aim of this thesis was to gain more insight into the level of QoC given to patients with muscle-invasive bladder carcinoma and their QoL and Health status as perceived before and after undergoing cystectomy. More specifically:
1) To what extent is quality of life in patients with muscle-invasive bladder carcinoma affected by undergoing a radical cystectomy?
2) How can process aspects of quality of care for muscle-invasive bladder carcinoma be measured in the Netherlands?
3) Is the outcome for treatment of muscle-invasive bladder cancer in the Netherlands, with emphasis on the radical cystectomy, influenced by the volume of the procedures?

Outline of this thesis

Part II Quality of Life

Chapter 2 presents a prospective study examining QoL, health status, sexual function and anxiety level in patients who presented with primary hematuria, comparing those with subsequent bladder cancer with those who turned out to have non-malignant diagnoses. The study in **Chapter 3** is a prospective case-control investigation of patients with muscle-invasive bladder cancer. Their QoL, health status, sexual function, and anxiety were measured before the diagnosis of bladder cancer was known. These patients and a matched case control group of patients were then followed until one-year post-cystectomy.

Part III Quality of Care

Part III addresses the issues and research questions on quality of care. At the start of this research in 2006, no up-to-date data were available on morbidity and mortality measured per urologist and per clinic in the Netherlands. A retrospective study was performed to establish the 30-day mortality and morbidity rates after cystectomy associated with muscle-invasive bladder cancer for the years 2001-2005 in one hospital. A subsequent prospective part of the research addressed the development of internal quality indicators to measure the quality of care in patients with invasive bladder carcinoma treated by cystectomy in clinical practice. **Chapter 4** presents and describes the results of both these studies. **Chapter 5** concerns a retrospective population-based study aimed to describe the variation in treatment policies and outcome for bladder cancer in the Netherlands. The systematic review presented in **Chapter 6** explores the volume-outcome relationship for radical cystectomy for bladder cancer. We investigated the methodological quality of the available evidence and performed a meta-analysis of the studies meeting predefined quality criteria. As the population-based study of mortality lacked information on co-morbidity, **Chapter 7** describes the effect of age and co-morbidity on treatment and survival of patients with MIBC in the South of the Netherlands. Since the systematic review also showed that there was scarce evidence on a survival-outcome relationship, **Chapter 8** describes a population-based study on survival after treatment for MIBC, taking into account the impact of hospital volume in the Netherlands.

Part IV General Discussion

Chapter 9 presents a summary and discussion of the study results including the clinical implications, as well as some suggestions for future research.

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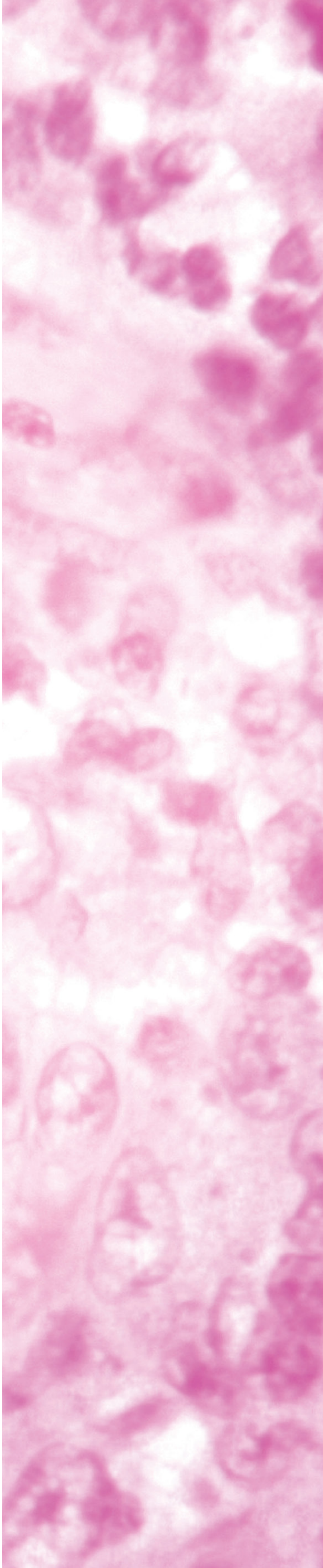
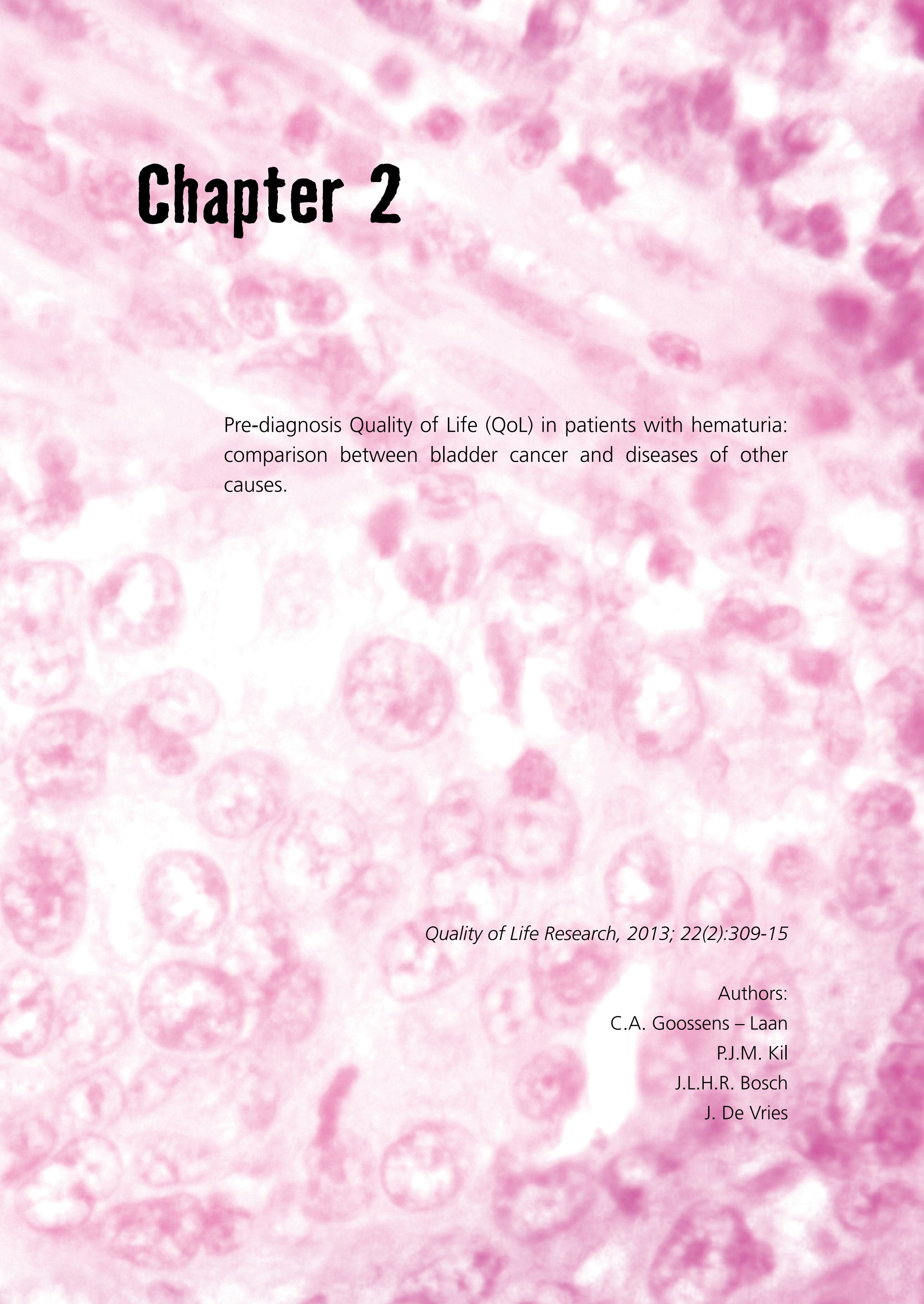
PART II

Quality of Life





Chapter 2

Pre-diagnosis Quality of Life (QoL) in patients with hematuria: comparison between bladder cancer and diseases of other causes.

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Abstract

Purpose: To examine quality of life (QoL), health status, sexual function, and anxiety in patients with primary hematuria who later appear to have bladder cancer (BC) and patients with other diagnoses.

Methods: From July 2007 to July 2010, 598 patients with primary hematuria were enrolled in this prospective, multicenter study. Questionnaires (WHOQOL-BREF, SF-12, IIEF, STAI-10-item Trait) were completed before cystoscopy. Diagnosis was subsequently derived from medical files. BC patients were compared with patients with other causes of hematuria.

Results: Cancer was diagnosed in 131 patients (21.9%), including 102 patients (17.1%) with BC. No differences were found in the WHOQOL-BREF versus SF-12 psychological or physical health domains. The erectile function was significantly worse in the BC group (9.3 vs. 14.6 for OC, $p = 0.02$). Patients with muscle-invasive BC (MIBC) had the lowest percentage anxious personalities of all BC patients ($p = 0.04$).

Conclusions: Cancer was found in 21.9% of the patients with hematuria. Pre-diagnosis patients with BC have comparable QoL and HS to patients with OC. Erectile dysfunction was highest in patients with BC. MIBC patients had the lowest percentage anxious personalities of the patients with BC.

Introduction

Bladder cancer (BC) is the 7th most common cancer worldwide. In the Netherlands, invasive BC was the 8th most common cancer in 2008 [1]. Most patients are being diagnosed after presenting with gross or microscopic hematuria [2,3]. The golden standard for diagnosis of BC is a cystoscopy of the bladder. When (muscle)-invasive bladder cancer (MIBC) is found, the therapy of choice is the radical cystectomy with bilateral pelvic lympadenectomy. Other curative treatment options are interstitial radiotherapy (IRT; e.g., brachytherapy for small solitary clinical stage II tumors) and external beam radiotherapy (EBRT). When a patient is not eligible for any of the above-mentioned therapies due to comorbidity or preference, a non-curative option usually follows: a transurethral resection of the bladder tumor (TURT) or palliative radiotherapy.

This complex operation is assumed to affect the patient’s quality of life (QoL) and health status (HS), and sexual functioning as it involves major surgery and having an incontinent or continent urinary diversion. As a result, HS and QoL, both patient reported outcomes, in patients with MIBC undergoing cystectomy are a topic of much interest in urologic oncology. A recent review of Somani et al. [4] on QoL with urinary diversion stated that there is an urgent need to establish the important determinants of QoL of this patient group.

In the few existing prospective studies, baseline QoL is assessed just prior to the cystectomy or shortly after surgery. Psychological, HS, and health-related QoL measures return to or exceed baseline values [5–7]. In none of these studies, the first measurement of QoL is done before diagnosis of BC. However, being diagnosed with cancer may already cause a changed perspective on QoL. A baseline QoL measurement point before diagnosis can give a more correct reflection of patients’ baseline QoL.

QoL is known to be influenced by health [8], culture [9], social-economic status [10], and personality [11,12]. Especially, the personality factor trait anxiety is associated with QoL. Studies among breast cancer patients have shown that an anxious personality will react differently to having cancer and undergoing major surgery and will experience a lower QoL compared with patients without such a personality [13,14].

As stated above, hematuria is the most common presenting symptom of BC. The time before cystoscopy for patients with primary hematuria can serve as a good moment for a baseline measurement in QoL-studies on BC, to use in comparison with postoperative measurements.

The aim of this multicenter study was to examine the patient reported outcome measures QoL, HS, sexual function, and dispositional anxiety in patients with BC before diagnosis was known. The comparison group was other patients with primary hematuria before cystoscopy had taken place. In addition, the diagnoses for primary hematuria were examined.

Patients and methods

Patients

All consecutive patients presenting with primary hematuria in one of six academic or large teaching departments of urology (University Medical Centre Utrecht; St. Elisabeth Hospital and Twee Steden Hospital, Tilburg; Onze Lieve Vrouwe Gasthuis, Amsterdam; Jeroen Bosch Hospital, ‘s Hertogenbosch; Catharina Hospital, Eindhoven) in the Netherlands, between July 2007 and July 2010, were eligible for this study. Exclusion criteria were age younger than 18 years, a presumed life expectancy of less than 2 years, dementia, psychiatric disorders or insufficient comprehension of the Dutch language.

Evaluation of the hematuria consisted of history and examination, urinalysis, and cytology. In addition, most patients underwent CT-IVP/urography or ultrasound and/or X-IVP depending on the preference of the individual urologist. Patients who underwent cystoscopy for evaluation of gross or microscopic hematuria were included and asked to complete a set of questionnaires on demographic features, QoL, HS, sexual functioning, and trait anxiety. Five hundred and ninety-eight patients (98.5%) gave informed consent and were asked to completed the questionnaires before undergoing a cystoscopy or radiological diagnostics, that is, before the diagnosis was known (Figure 1). Reasons given for not participating or late exclusion (after informed consent was given) were ‘questions too personal’, ‘not interested in participating after reading the questionnaire’, questionnaire not completed before diagnosis. The study was approved by the local ethics committees. All patients provided written informed consent.

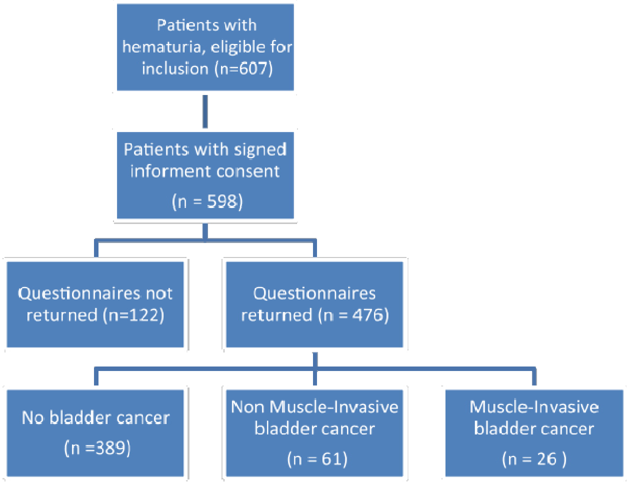

Figure 1. Flow chart study population

Questionnaires

World Health Organization Quality of Life-BREF Questionnaire (WHOQOL-BREF) [15, 16]

This questionnaire is the abbreviated version of the WHOQOL-100 and consists of 26 items covering four domains (Physical, Psychological, Social Relationships, and Environment) and a global QoL and general health facet. Patients also completed the three items from the facet sexual activity from the WHOQOL-100 that are not part of the WHOQOL-Bref. The reliability and validity are satisfactory [17], and the sensitivity to change is good [18].

RAND Medical Outcomes Study Short Form-12 (SF-12, version 2) [19]

A 12-item adaptation of the RAND 36-Item Health Survey (SF-36). The SF-12 quantifies health status into two composite scores, the Physical Component Summary (PCS) and Mental Component Summary (MCS) scales. In addition, the SF-12 quantifies health status into eight subscales, including physical functioning, emotional well-being, general health, pain, energy, social functioning, and role limitations due to physical or emotional problems. The summary scales are scored from 0 to 100 and converted to a standardized scale with a population mean of 50 and a standard deviation of 10. A higher score implies a better health status. The reliability and validity are satisfactory [19,20].

State-Trait Anxiety Inventory-Trait scale short form (STAI-10-item Trait) [21]

The STAI was originally developed to investigate anxiety phenomena in ‘normal’ adults but has also proven useful in medical and surgical patients. Trait anxiety concerns differences in individuals in the disposition to respond to stressful situations with varying amounts of stress. The 10-item trait scale (10 statements) asks people to describe how they generally feel. A trait anxiety score of more than 21 was considered high. The psychometric characteristics of this questionnaire are well established and considered good [22].

International index of erectile function (IIEF) [23]

The IIEF is a validated, self-administered questionnaire that assesses overall sexual function. It is divided into the 5 domains of erectile function, intercourse satisfaction, orgasmic function, sexual desire, and overall satisfaction. The IIEF demonstrates the sensitivity and specificity for detecting treatment-related changes in patients with erectile dysfunction [23]. After the first year of the study, it became apparent that a significant part of the patients did not participate in the study because of this questionnaire with its sexually related questions. Therefore, from September 2009 onwards new patients did not receive the IIEF questionnaire.

Demographic Questionnaire

Patients were asked to answer questions concerning age, marital status, education, and work to evaluate social-economic status.

Medical records

Data concerning medical diagnosis, tumor stage and grade after pathological examination, and treatment were obtained from the medical records of the patients with informed consent.

Statistical procedure

Independent sample *t* tests and chi-square tests were used to compare: (1) the participants and non-participants and (2) to examine QoL and HS differences between the two patient groups (bladder cancer vs. other causes of hematuria). Correction for covariates age and gender was done with anova univariate analysis. Patients with other forms of cancer were excluded from analyses. When comparing muscle-invasive versus non-muscle-invasive bladder cancer (NMIBC) versus other causes of hematuria with regard to trait anxiety, one way ANOVA was used. Analyzing MIBC to NMIBC group on high anxiety scores, independent sample *t* test was used. Analyses were performed with the Statistical Package for Social Sciences (SPSS version 15.0).

Results

Four hundred and seventy-six patients (79.6%) with hematuria participated in this study and answered the questionnaire (Figure 1). Demographics and clinical features of the participants and non-participants are shown in Table 1. Participants and non-participants only differed with regard to age, with participants being older. Diagnoses of all patients (participants and non-participants) are shown in Table 2. In 226 patients (37.8%), no pathological finding was detected. Cancer was diagnosed in 131 of the 598 patients (21.9%), including 102 patients (17.1%) with BC. NMIBC was found in 71 patients (11.9%) and MIBC in 31 patients (5.2%).

Of the participants, 110 patients had cancer (23.1%) and 87 patients had BC (18.3%). Only one patient under the age of 50 was diagnosed with BC. Most patients with BC (69.6%) were older than 60 years. Among the elderly (>75+ years), 23.5% had BC. Of the patients with BC, 78.4% were men. Demographics and clinical features of the patients with bladder cancer and with other causes are shown in Table 3.

Table 1. Demographics and clinical features of the participants and non-participants

	Participants (n = 476)	Non-participants (n = 122)	*p* value
Mean age (years ± SD)	62.5 (11.8)	59.5 (15)	**0.05**
Gender (male)	300 (63)	76 (62.3)	0.6
Diagnosis benign/malignant	353 (74.2)/110 (23.1)/13 (2.7)	101 (82.8)/21 (17.2)	0.16
Diagnosis bladder cancer	87 (18.3)	15 (12.3)	0.12
NMIBC[a]	61 (70.1)	10 (66.7)	0.13
MIBC[a]	26 (29.9)	5 (41)	0.51
Cystectomy	18 (69.2)	3 (20)	0.44
EBRT	5 (19.2)		
IRT (Brachytherapy)	3 (11.5)		
Nationality (Dutch; missing)	450 (94.5)/10 (2.1)		
Partner: yes/no/missing	378 (79.4)/77 (16.2)/21 (4.4)		
Children: yes/no/missing	393 (82.6)/71 (14.9)/12 (2.5)		
Education: low/high/missing	265 (55.7)/189 (39.7)/22 (4.6)		
Paid work: yes/no/missing	176 (37)/265 (55.7)/35 (7.3)		
Medication: yes/no/missing	345 (72.5)/118 (24.8)/13(2.7)		

(N)MIBC (non-)muscle-invasive cancer, EBRT external beam radiotherapy, IRT interstitial radiotherapy

Besides for age, percentages are between brackets

a Percentages of bladder cancer patients

p values in bold are significant

Table 2. Causes of primary hematuria

Cause	Frequency (n)	Percent
None	226	37.8
Prostatic bleeding (BPH; chronic prostatitis)	67	11.2
Calculi (renal/ureteral)	32	5.3
Calculi (bladder)	10	1.7
Cystitis/inflammation (including acute prostatitis)	85	14.2
Endometriosis	2	0.3
Use of oral anticoagulation	8	1.3
Radiation cystitis	2	0.3
Renal cyst with bleeding	3	0.5
Urethral or meatal pathology	10	1.7
Crohn’s disease	1	0.2
Bladder wall-necrosis	1	0.2
Nephrogenic cause	7	1.2
Lost to follow-up	13	2.2
Renal cancer	12	2.0
Ureteral malignancy	5	0.8
Colon cancer	3	0.5
Ovarium cancer	1	0.2
Endometrium cancer	2	0.3
Prostate cancer	6	1.0
Bladder cancer	102	17.1
Total	598	100

Table 3. Demographics and clinical features of the patients with bladder cancer and other causes

	Bladder cancer	Other causes	*p* value
Mean age (years ± SD)	66.3 (9.5)	61.3 (12.3)	**0.00**
Gender (male)	68 (77.9)	220 (62.9)	**0.01**
Nationality (Dutch)	83 (95.4)	335 (94.9)	0.62
Partner	70 (80)	284 (81)	0.33
Children	69 (79.3)	294 (83.5)	0.12
Education	27 (31)	148 (42)	0.17
Paid work	28 (31)	138 (39.2)	0.46
Medication	59 (67.8)	264 (74.8)	0.37

Besides for age, percentages are between brackets
p values in bold are significant

Patient reported outcomes

Patients' scores on QoL, health status, sexual function, and anxiety are shown in Table 4.

No significant differences were found for general QoL and the four QoL domains. The SF-12 showed no differences on HS between patients with BC versus patients with OC.

The IIEF showed a significant effect on erectile function ($p = 0.02$) and orgasmic function ($p = 0.05$). OC patients had better scores than BC. In line with this finding, erectile dysfunction was highest among patients with BC (93% vs. OC 79%).

The mean score of trait anxiety indicated normal anxiety in both groups (BC and OC). Patients with MIBC had significantly lower scores on trait anxiety compared with the other BC patients ($F = 4.94$, $p = 0.03$), only 7% of all patients with MIBC had a high anxious personality in comparison with 20% in the NMIBC group and 25% of all patients ($x2 = 1.18$, $p = 0.05$).

Table 4. Scores for quality of life, health status, sexual function, and anxiety separately for patients with bladder cancer versus patients with other non-malignant causes for hematuria

	Bladder cancer (n = 87)	Other causes (n = 353)	*p* value with co-variate model age and gender
WHOQOL-BREF			
Overall QoL and general health	3.8 (0.8) [87]	3.7 (0.8) [353]	0.31
Physical health (domain 1)	14.8 (2.8) [87]	14.5 (3.0) [350]	0.56
Psychological health (domain 2)	14.9 (2.1) [87]	14.8 (2.3) [352]	0.73
Social relationships (domain 3)	14.0 (3.4) [87]	14.4 (3.2) [351]	0.77
Environment (domain 4)	15.7 (2.2) [87]	15.8 (2.4) [351]	0.76
Sexual satisfaction	11.1 (4.4) [87]	12.1 (4.7) [351]	0.34
SF-12			
General health perceptions	46.6 (19.9) [87]	45.7 (20.3) [352]	0.70
Physical functioning	73 (30) [87]	74.4 (31) [351]	0.96
Social functioning	19.1 (18.3) [87]	19.8 (19.4) [346]	0.90
Role limitations physical	66.7 (46.2) [87]	60.5 (46.2) [351]	0.44
Role limitations emotional	90.3 (38.8) [87]	81.7 (35.2) [346]	0.10
General mental health	72.9 (16.8) [87]	70.5 (18.6) [347]	0.53
Energy/fatigue	60.7 (25.2) [87]	56.4 (25.3) [347]	0.39
Bodily pain	76.2 (22.9) [87]	75.5 (23.6) [345]	0.93
Physical component scale	65.6 (22.7) [87]	64.5 (24.9) [343]	0.80
Mental component scale	60.7 (14.9) [87]	57.2 (14.5) [342]	0.15
IIEF			
Erectile function	9.3 (8.1) [29]	14.6 (9.2) [80]	**0.02**
Patients with ED (cutoff 25 points)*	93.1 %	78.8 %	
Intercourse satisfaction	4.1 (5.1) [32]	6.8 (5.9) [87]	0.07
Orgasmic function	3.4 (3.9) [31]	5.3 (4.2) [89]	**0.05**
Sexual desire	4.5 (2.0) [29]	5.1 (2.1) [89]	0.26
Overall satisfaction	5.1 (2.5) [25]	6.2 (2.5) [81]	0.17
Trait anxiety	16.9 (4.9) [85]	17.6 [340]	0.29
High score on anxiety (score C22)	16.5 %	24.7 %	0.15

ED erectile dysfunction
Patients with other forms of cancer were excluded from analyses
Scores are represented in means. SD are between brackets
Number of questionnaires with the item completed between square brackets
p values in bold are significant
* Erectile dysfunction with cut-off point at 25 points

Discussion

We examined the QoL, HS, sexual functioning, and dispositional anxiety in patients with BC before diagnosis was known. The comparison group was other patients with primary hematuria before cystoscopy had taken place.

Quality of life and health status

In the urologic oncology community, there is no standardized assessment protocol for QoL-studies, and a wide variation exists in QoL-outcome studies [24]. A major limitation is that the few prospective studies all report a "baseline" assessment of HS and/or QoL that is done, only after MIBC is confirmed. However, the diagnosis cancer by itself is an almost certain reason for a change in QoL. It was our aim to assess QoL and HS before diagnosis in order to get a good baseline assessment. Therefore, we asked all patients with primary hematuria to complete questionnaires on QoL, HS, sexual function, and level of trait anxiety before a diagnosis was established. QoL-studies for MIBC mostly involve only HS which is not equivalent to QoL [7,25]. HS indicates where there are limitations in physical functioning as impact of the disease, whereas QoL also reflects to what extent the patients are bothered by these limitations in daily life [14,26].

The current study shows that the patients with unknown diagnosis of BC appeared to have the same baseline results on QoL and HS in comparison with the patients with other diagnosis. The BC patients perceived their sexual functioning as lower, and they also had the lowest percentage of anxious personalities.

Erectile dysfunction was highest (93.1%) and orgasmic function lowest among patients with BC compared with the patients with other diagnoses. The underlying disease, although not known by the patient, seems to have an impact on his/her sexual life. Although it is known that sexual function decreases after the cystectomy, the fact that patients already have a decrease in function before diagnosis is new information [7,27]. A history of smoking is a known risk factor for BC, and the fact that smoking can give rise to cardiovascular disease that is an important cause of erectile dysfunction could be an explanation for our finding.

Furthermore, patients with BC had the lowest percentage of anxious personalities (17%), especially patients with MIBC (7%). This may be a reason for having a higher-stage disease at presentation in the hospital as their anxiety level prevents these patients from visiting their doctor when symptoms first emerge. As this finding is based on only 26 versus 61 patients with a significance of $p < 0.03$, further research with more power is needed for confirmation.

Our study had strengths and limitations that merit comment.

This prospective study is multicenter. To our knowledge, this is the first study to investigate QoL in patients with hematuria and to investigate pre-diagnosis QoL in patients with bladder cancer. The best population to study this research question would be the general population. However, in the Netherlands in 2009, there were 5,100 cases of newly diagnosed bladder cancer, with a lifetime cumulative risk of 2% in a population of 16 million people [1]. This low risk makes screening the general population for the current research question unfeasible. As hematuria is the key symptom of bladder cancer, the population presenting with hematuria could be considered second best.

A limitation is the early withdrawal of the IIEF questionnaire. Particularly as the results of the patients who did complete the IIEF showed a difference in sexual function. Despite oral and written information about this questionnaire to patients when informing patients about the study, the proportion of patients refusing participation due to the IIEF made us decide to withdraw the list. Further limitations are that no difference is made during the inclusion between the two forms of hematuria, and the patients' smoking history is unknown.

There are multiple studies on QoL after cystectomy [7,25]. Most studies only use HRQoL questionnaires and do not compare QoL and HS in the same study population. No study has as yet addressed the issue of a baseline measurement with an unknown diagnosis, as in our study. Our study shows that pre-diagnosis QoL and HS do not differ between patients with and without bladder cancer. A follow-up study is initiated to evaluate QoL after cystectomy for BC using this baseline measurement with an unknown diagnosis and to see how QoL is affected by the surgery.

In conclusion, cancer was found in 21.9% of the patients with hematuria. Pre-diagnosis patients with BC have comparable QoL and HS to patients with OC. Erectile dysfunction was highest in patients with BC. Patients with MIBC had the lowest percentage of anxious personalities.

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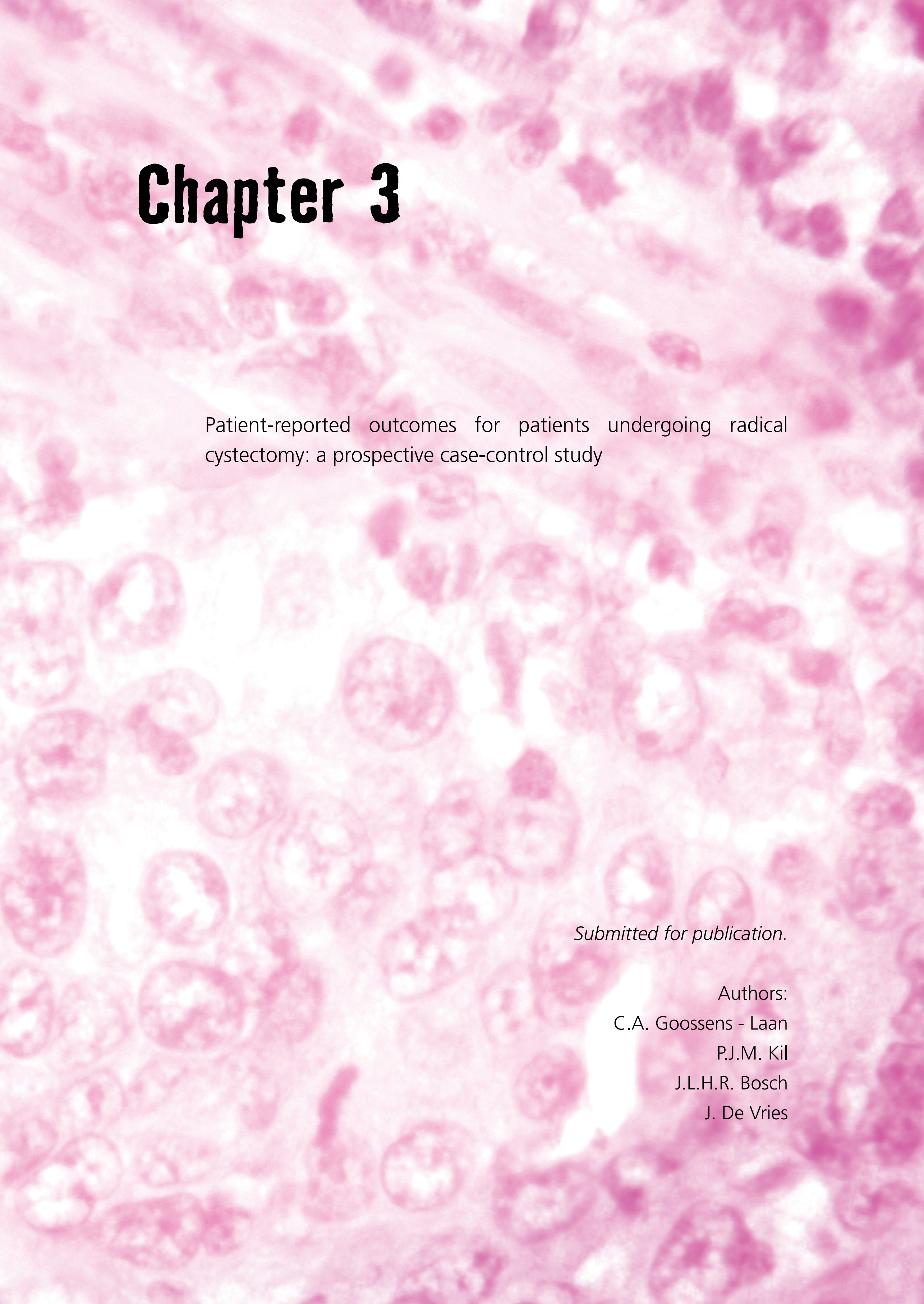

Chapter 3

Patient-reported outcomes for patients undergoing radical cystectomy: a prospective case-control study

Submitted for publication.

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Abstract

Purpose: To measure patient-reported outcomes (PROs) for patients with (muscle)-invasive bladder cancer (BC), before the diagnosis of BC was known, thus before cystectomy. The differences in outcomes between a health status (HS) and quality of life (QoL) questionnaire were examined.

Methods: From July 2007 to July 2010, 598 patients with primary hematuria were enrolled in this prospective, multi-centre case-control study. Patients undergoing radical cystectomy (RC; N=18) were compared with patients with other causes of hematuria (CC; N=20). Measurement points were before diagnosis as well as 3, 6, and 12 months postcystectomy. Questionnaires used were the WHOQOL-BREF, SF-12, IIEF, and 10-item STAI-TRAIT Scale.

Results: Prediagnosis patients who later appeared to have BC had the same QoL compared to CC patients. The pre-diagnosis physical component scale of HS and sexual function was significantly lower for RC vs. CC patient. RC patients had a better prediagnostic QoL and HS than postcystectomy at all time-points.

Conclusions: This is the first case-control study with a baseline measurement of PROs before the diagnosis BC was known. It shows lower physical health and sexual function for RC vs. CC before diagnosis is known. Until one year postcystectomy, QoL does not return to baseline level. Future studies including comorbidity and smoking history are needed to examine the generalizability of our results.

Introduction

In the Netherlands, with a population of 16.7 million, there are approximately 6000 new cases of bladder cancer each year (source: Dutch cancer registry; www.cijfersoverkanker.nl), of which 30% present as muscle-invasive bladder cancer [MIBC] [1.] The overall 5 -yr. and 10-yr. survival rate for all treatments for MIBC is 32 and 25%, respectively [2]. Gold standard therapy is radical cystectomy (RC) with some form of urinary diversion. This highly complex, low volume procedure has a mortality rate between 1.2 and 8% [3,4]. There is a postoperative morbidity rate of 64%[5], with 13% of Clavien-Dino grade 3-5 complications [6]. Alternative therapies include external beam radiotherapy (EBRT) and, in case of small solitary clinical stage II tumours (≤ 5 cm), interstitial radiotherapy (IRT; e.g., brachytherapy) is an option [7].

In today's society much importance is attached to the overall quality of care (QoC) offered to patients. Quality of life (QoL) is associated with QoC and has, therefore, become an important outcome measure of care and an important patient-reported outcome measure [8].

QoL is the perception of people on their position in life within the context of the culture and value systems in which they live and in relation to their goals, expectations, values and concerns [9]. It is a multidimensional concept involving more than direct health-related aspects [9]. In other words, QOL refers to a person's satisfaction with various aspects of his/her life and is not a direct reflection of his/her functioning.

Another widely used patient-reported outcome (PRO) is health status (HS). HS refers to the influence of disease on a person's physical, social and psychological functioning. HS is also multidimensional and directly reflects functioning. Furthermore, the concept health-related quality of life is QoL, but solely on the three main domains of QoL: i.e., physical, social, and psychological [10,11].

We have studied the QoL of patients undergoing RC. Although the literature on QoL is vastly increasing, these studies are generally of questionable quality [12,13]. Three systematic reviews on QoL indicate that the studies do not exceed level 3-4 [13,14]. As stated in the EAU-guidelines on bladder cancer, most retrospective studies do not evaluate the association between (health-related) QoL and bladder cancer-specific issues after cystectomy, such as incontinence or potency. Furthermore, important co-variates, such as a patient's age, mental status, coping ability and gender, have only rarely been considered [1]. Thirdly, being diagnosed with cancer could by itself be reason for a changed perspective on QoL. In most prospective studies the first measurement of (HR-)QoL is when the diagnosis is already known to the patient. Finally, the interpretation of HS or QoL studies can be difficult due to the variety of questionnaires used and the diversity in study design [15].

The aims of the present prospective longitudinal case-control study were: (i) to measure three patient reported outcomes: QoL, HS and sexual functioning, in patients with bladder cancer eventually undergoing cystectomy. And (ii) to examine the differences in outcomes between HS and QoL questionnaires. We hypothesize that the QoL is worse in bladder cancer patients undergoing cystectomy in comparison to a control group without bladder cancer. To meet the criticism mentioned in the EAU-guidelines, the first measurement was done before the diagnosis was known to the patient and caretaker, and the follow-up is until one year postcystectomy. Co-variates like age, gender, and trait anxiety were evaluated.

Patients and Methods

Patients

All consecutive patients presenting with primary hematuria in one of six academic or large teaching departments of urology (University Medical Centre Utrecht; St. Elisabeth Hospital and TweeSteden Hospital, Tilburg; Onze Lieve Vrouwe Gasthuis, Amsterdam; Jeroen Bosch Hospital, 's Hertogenbosch; Catharina Hospital, Eindhoven) in the Netherlands between July 2007 - July 2010, were eligible for this study. Exclusion criteria were: age younger than 18 years, a presumed life expectancy of less than two years, dementia, psychiatric disorders, or insufficient comprehension of the Dutch language.

Initial evaluation of the hematuria consisted of history and physical examination, urinalysis and cytology. In addition, most patients underwent CT-IVP/urography or ultrasound and/or X-IVP, depending on the preference of the individual urologist. Patients who came for evaluation of gross or microscopic hematuria were included, and asked to complete a set of questionnaires on demographic features, QoL, HS, sexual functioning, and trait anxiety. Five-hundred and ninety-eight patients (98.5%) gave informed consent and were asked to complete the questionnaires before undergoing a cystoscopy or radiological diagnostics, i.e. before the diagnosis was known (Figure 1). Reasons given for not participating or late exclusion (after informed consent was given) were 'questions too personal', 'not interested in participating after reading the questionnaire', or the questionnaire was not completed before diagnosis. The study was approved by the local ethics committees. All patients provided written informed consent. Patients diagnosed with other forms of cancer were excluded from the analyses.

Questionnaires

Four measurement points were included in the study; baseline (before diagnosis), and 3, 6, and 12 months postcystectomy.

World Health Organization Quality of Life-BREF Questionnaire (WHOQOL-Bref) [16,17]

This questionnaire consists of 26 items covering four domains ((24 items; Physical, Psychological, Social Relationships, and Environment) and a 2 item, global QoL and general health facet.)) Three items about sexuality from the WHO-QOL-100 were added, thereby comprehensively assessing the sexual activity. The reliability and validity of the WHOQOL-Bref are satisfactory [18] and the sensitivity to change is good [19]. One point of difference in score is clinically relevant. This questionnaire was completed at all measurement points.

State-Trait Anxiety Inventory [20]

The STAI was originally developed to investigate anxiety phenomena in 'normal' adults, but has also proven useful in medical and surgical patients. Trait anxiety concerns differences in individuals in the disposition to respond to stressful situations with varying amounts of stress. We used the 10-item STAI Trait scale [21] that asks people to describe how they generally feel. A trait anxiety score of more than 21 was considered high. The psychometric characteristics of this questionnaire are well established and considered good [21]. The trait scale was only completed at baseline measurement.

RAND Medical Outcomes Study Short Form-12 (SF-12, version 2) [22]
A 12-item adaptation of the RAND 36-Item Health Survey (SF-36). The SF-12 quantifies health status into two composite scores, the Physical Component Summary (PCS) and Mental Component Summary (MCS) scales. In addition, the SF-12 quantifies health status into eight subscales. The SF-12 Health Survey includes 12 questions from the SF-36 Health Survey (Version 1). These include: 2 questions concerning physical functioning; 2 questions on role limitations because of physical health problems; 1 question on bodily pain; 1 question on general health perceptions; 1 question on vitality (energy/fatigue); 1 question on social functioning; 2 questions on role limitations because of emotional problems; and 2 questions on general mental health (psychological distress and psychological well-being). The summary scales are scored from 0–100 and converted to a standardized scale with a population mean of 50 and a standard deviation of 10. A higher score implies a better health status. The reliability and validity are satisfactory [22,23]. This questionnaire was completed at all measurement points.

The Functional Assessment of Cancer Therapy – Bladder Cancer (FACT-Bl) [24]
The FACT-Bl is a questionnaire specially designed for patients with bladder cancer and consists of 40 questions of a general version (FACT-G) which has been validated and tested in several types of cancers. The FACT-BL itself has not been externally validated. Well-being in four domains is assessed, with patients responding to statements on a five level ordinal Likert scale, ranging from 'not at all' to 'very much'. The domains are physical, social/family, emotional, and functional. The additional concerns listed in the FACT-Bl concern urinary tract symptoms, intestinal symptoms and sexual symptoms, with a total of 10 statements, with two more for those with a stoma [25]. This questionnaire was only completed by the patients who underwent cystectomy, at 3, 6 and 12 months postcystectomy.

International Index of Erectile Function (IIEF) [26]
The IIEF is a validated, self-administered questionnaire that assesses overall sexual function. It is divided into the 5 domains of erectile function, intercourse satisfaction, orgasmic function, sexual desire and overall satisfaction. The IIEF has demonstrated

good performance as a discriminative tool and is able to detect the difference between men who are healthy volunteers and men with known erectile dysfunction. A cut of point of lower than 21 points indicates erectile dysfunction. On all measurement points the questionnaire was to be completed. After the first year of the study it became apparent that a significant part of the patients did not want to participate in the study because of this questionnaire. Therefore, from September 2009 onwards new patients did not receive the IIEF questionnaire. The facet sexual activity of the WHOQOL-Bref (see descript as part of the WHOQOL-Bref) was continued until the end of the study, and accepted well by the participants.

Demographic Questionnaire

Patients were asked at baseline to complete questions concerning age, marital status, education, and social-economic status. Case-controls were matched on above mentioned items.

Medical Records

Data concerning medical diagnosis, tumour stage and grade after pathological examination, and treatment were obtained from the medical records of the patients who provided informed consent.

Statistical Procedure

Independent sample t-tests and chi-square tests were used to compare: (i) the participants and non-participants and (ii) to examine QoL and HS differences between the two patient groups (cystectomy vs. case-controls). Analyses of variance for repeated measures were used to examine quality of life, health status, and erectile function over time. Missing data for quality of life, health status and erectile function were imputed with linear interpolation. Imputation of missing data increased the power, but did not affect the results. When comparing cystectomy vs. case-control with regard to the anxiety scores, an independent sample t-test was done. All analyses were performed with SPSS (version 15.0).

Results

Figure 1 shows the flow chart of the 476 patients (79.6%) with hematuria who participated in this study and answered the questionnaire. Demographics and clinical features of the participants and non-participants are shown in table 1. Participants and non-participants only differed with regard to age, with participants being older (p = 0.05).

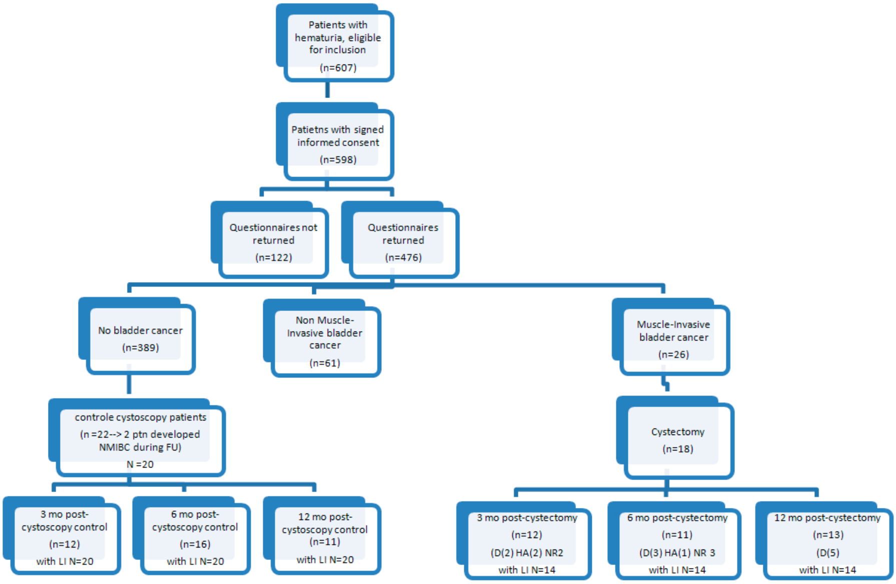


Figure 1 Flow chart for the study-participants.
Note: D: patient deceased, HA: patient admitted at hospital, LI: lineair interpolation, NR: questionnaire not returned.

Table 2 shows the demographics of the patients undergoing radical cystectomy (RC) and the case-control patients (CC). The case-control patients were older (mean age RC 62.3 vs. CC 64.9) and more often had paid work. (RC 22,2% vs. CC 50%). However, these differences were not statistically significant between the two groups. Of the 18 RC patients, five male patients received an orthotopic neobladder and 13 [9 men and 4 women] patients had an ileal conduit.

Table 1. Demographics and clinical features of the participants (returning questionnaire) and non-participants (not returning questionnaire) presenting with primary hematuria.

	Participants (n =476)	**Non-participants (n =122)**	**p-value**
Mean age (years ± SD)	62.5 (11.8)	59.5 (15)	**0.05**
Gender (male)	300 (63)	76 (62.3)	0.6
Diagnosis Benign/Malignant	353 (74.2) / 110 (23.1)	101 (82.8) / 21 (17.2)	0.16
Diagnosis Bladder cancer	87 (18.3)	15 (12.3)	0.12
*NMIBC[a]	61 (70.1)	10 (66.7)	0.13
*MIBC[a]	26 (29.9)	5 (33.3)	0.51
• Cystectomy	18 (69.2)	3 (60)	0.44
• EBRT	5 (19.2)		
• IRT (Brachytherapy)	3 (11.5)		
Nationality: Dutch/missing	450 (94.5) / 10 (2.1)		
Partner: yes/no/missing	378 (79.4) / 77 (16.2)/ 21 (4.4)		
Children: yes/no/missing	393 (82.6) / 71 (14.9) / 12 (2.5)		
Education: low/high/missing	265 (55.7) / 189 (39.7) / 22 (4.6)		
Paid work: yes/no/missing	176 (37)/ 265 (55.7) / 35 (7.3)		
Medication: yes/no/missing	345 (72.5) / 118 (24.8) / 13(2.7)		

Except for age, percentages are between brackets
[a] Percentages of bladder cancer patients

The number of lost to follow up per measurement point due to death for the RC patients is shown in figure 1. One patient died within three months due to a gastrointestinal complication postcystectomy. The other four died due to metastasis of MIBC. The reason for missing the follow-up due to hospital admission were due to the surgery or by the MIBC: one patient was first admitted with a lung embolus post-surgery and after 6 months admitted due to a pathological hip fracture. Afterwards this patient died from metastatic disease. The second patient was admitted for gastrointestinal complications after adjuvant radiotherapy.

Baseline scores

Patients' baseline scores on QoL, health status, sexual function, and anxiety are shown in table 2.

Table 2A en B. Demographics and clinical features of the study-population, and scores on (HR) QoL, sexual function and anxiety at baseline for the two patient groups.

		Cystectomy (n = 18)	**Case-controls (n = 20)**	**p-value**
Characteristic[x]				
	Mean age (years ± SD)	62.3 (8)	64.9(9.6)	0.37
	Gender; male (%)	14 (77.8)	17 (85)	0.6
	Dutch nationality	18 (100)	20 (100)	-
	Partner: yes/no/missing	14 (77.8) / 4 (22.3)/ -	17(85)/2(100)/1(5)	0.55
	Children: yes/no/missing	15 (83.4)/ 3 (16,7) / -	17(85)/3(15)/-	0.88
	Education: low/high/missing	11 (61.1) / 7 (38.9) / -	9(45)/10(50)/1(5)	0.44
	Paid work: yes/no/missing	4 (22.,2) / 13 (72.3) / 1 (5.6)	10(50)/9(45)/1(5)	0.25
	Medication: yes/no/missing	14 (77.8) / 4 (22.2) / -	16(80)/3(15)/1(5)	0.63
Scores on (HR)QoL, sexual function, and anxiety at baseline		**Cystectomy (n = 18)**	**Case-controls (n = 20)**	**p-value**
WHOQOL-Bref[xx]				
	General health and overall QoL	3.4 (0.9)	3.8 (0,7)	0.13
	Physical health (domain 1)	14.2 (3.0)	15.2 (2.3)	0.26
	Psychological health (domain 2)	15 (2.0)	14.8 (2.3)	0.81
	Social relationships (domain 3)	14.2 (3.4)	14.5 (2.7)	0.81
	Environment (domain 4)	16.0 (1.5)	16.2 (2.4)	0.86
	Sexual activity	10.8 (3.6)	11.5 (5.1)	0.66
SF12				
	General health perceptions	40.3 (19.4)	51.3 (50.0)	0.09
	Physical functioning	65.3 (28.6)	85.0 (23.5)	0.03
	Social functioning	25.6 (24.5)	13.0 (14.9)	0.06
	Role limitations physical	50 (48.7)	67.5 (43.8)	0.25
	Role limitations emotional	86.1 (44.7)	82.5 (37.3)	0.79
	General mental health	73.9 (17.5)	69.5 (23.9)	0.90
	Energy/fatigue	56.7 (24.0)	57.0 (27.0)	0.97
	Bodily pain	68.1 (30.7)	83.8 (18.6)	0.06
	Physical component scale	55.9 (24.0)	71.9 (20.0)	0.03
	Mental component scale	60.6 (13.3)	55.5 (19.2)	0.62
IIEF				
	Erectile function	6.1 (3.9) [7]	19.3 (5.7) [7]	<0.01
	Intercourse satisfaction	2.4 (4.1) [7]	8.7 (6.0) [7]	0.04
	Orgasmic function	0.9 (1.5) [7]	9.4 (0.8) [7]	<0.01
	Sexual desire	4.3 (1.8) [7]	6.6 (1.1) [7]	0.02
	Overall satisfaction	2.6 (0.9) [5]	6.8 (1.8) [5]	<0.01
Trait anxiety		15.1 (3.6) [18]	17.1 (5.3) [20]	0.20
	High score	5.6% [1]	20% [4]	0.20

* Except for age, percentages are between brackets

[xx] Scores are represented in means. Standard deviation between brackets.

Number of questionnaires with the item completed between square brackets.

Case-control patients matched for age, marital status, education, and social-economic status.

QoL and health status

WHOQOL-Bref: No significant differences were found for general QoL and the four QoL domains. However, the domain physical health showed a clinically relevant difference of 1 point between the two groups (RC 14.2 vs. CC 15.2), indicating that at baseline the physical health was lower for the patients who later appeared to have bladder cancer. Sexual activity (completed by male and female patients) was perceived equal between the two groups. (RC 10.8 vs. CC 11.5).

SF-12: The same holds for the SF-12 score. On the physical component scale of the SF-12, patients who still had to undergo RC had a significantly lower score than CC patients (55.9 vs. 70.9; $p = 0.04$). This was caused by lower scores on the physical functioning scale before cystectomy for the RC group (RC 65.3 vs. CC 85.0; $p = 0.03$).

Sexual function (male patients): In both groups the percentage of patients with pre-existing erectile dysfunction was high (RC 100% vs. CC 86%). With regard to domains of erectile function, the RC scored lower on all IIEF domains compared to the CC group, even before cystectomy.

Trait anxiety

The mean score for trait anxiety was similar in both groups (RC and CC). Only 5.6% of all RC patients had a high anxious personality compared to 20% in the CC group, but this was not statistically significant ($x^2 = 1.7$, $p = 0.19$).

Different baseline scores between RC patients

The baseline scores of the RC patients lost to follow-up due to death ($n = 5$) were significantly lower on both QoL (WHOQOL-Bref; physical health ($p < 0.00$) and environment ($p < 0.00$)) and HS (SF-12; bodily pain $p = 0.01$, energy/fatigue $p = 0.00$, physical component scale $p = 0.032$) in comparison to the other RC patients surviving one year postcystectomy ($n = 13$). No difference was found in sexual functioning.

QoL, HS and Erectile function over time

Figure 2 shows the comparison of QoL, HS and erectile function across time.

Concerning the WHOQOL-Bref, the overall QoL and general health remained stable over time. Both groups (RC vs. CC) had equal scores in this domain. For the other domains, both groups of patients had similar baseline scores, but following three months after cystectomy until 1 year, the patients who underwent cystectomy scored lower on all time points on all domains: physical and psychological health, social relationships, environment, and the facet sexual activity (Figure 2A).

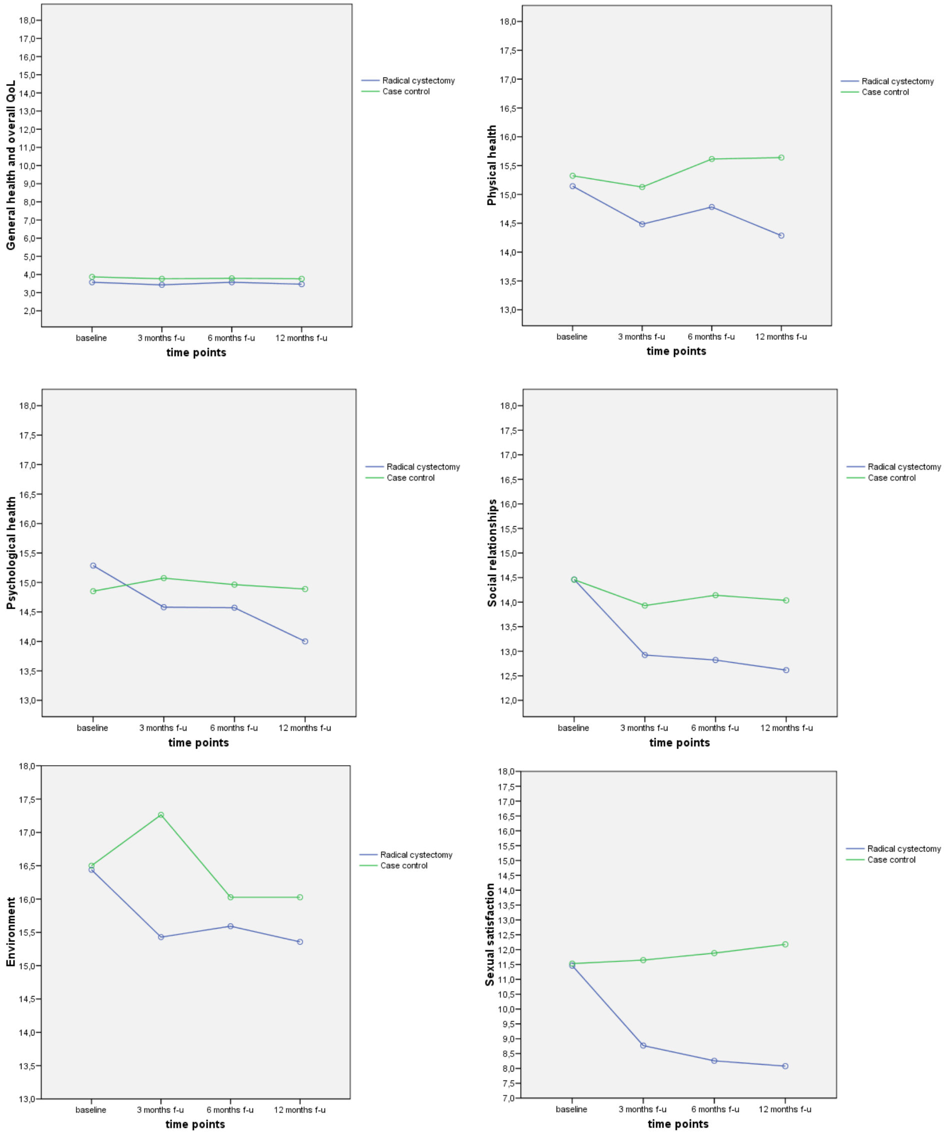
The outcome of the SF-12 short form (Figure 2B), measuring HS, showed that the perceived general health status of the patients undergoing cystectomy started at a lower baseline level, and remained stable during the follow up period. Compared with CC patients, the physical functioning, role limitations of physical functioning, and energy/fatigue showed lower end results for RC patients. Social function and general mental health were similar during the entire study. The role limitation emotional score decreasing for the RC group, compared to a non-significant increase for the CC patients. At baseline, body pain was lower for the patients undergoing cystectomy, but reached the same level as the CC group at the end of the follow-up. The scores of the physical component scale confirmed the lower baseline level of the RC group vs. the CC group. This lower level was seen on all time levels during the follow-up. For the mental component scale, the RC group started at a higher level, but after the cystectomy all levels were equal to or lower than the CC group.

With regard to the IIEF 7 RC vs. 7 CC patients completed this questionnaire at all time-points. On all fields - erectile dysfunction, intercourse satisfaction, orgasmic function, sexual desire and overall satisfaction - the RC group started, stayed and ended on a lower level than the CC patients. (Figure 2C).

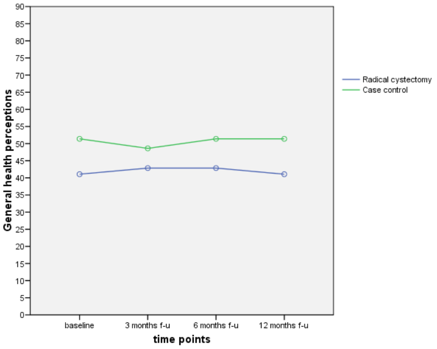
The results for the FACT-Bl of 10 patients (7 patients with an ileal conduit, and 3 patients with a neobladder) are shown in figure 3. Of the four categories, physical, social and emotional well-being remained stable over time, while functional well-being decreased slightly. The bladder cancer specific functional assessment of cancer therapy score showed an increase during the measured time period. As for the total score, it showed that six months after therapy there was a small increase in score, but after one year the score equalled the 3 months post-surgery score. (Figure 3).

Figure 2 A-C: Comparison between patients undergoing cystectomy and case-control patients on quality of life, health status and erectile function over time.

A I-VI WHOQOL-Bref



B 1-X SF-12


General health perceptions
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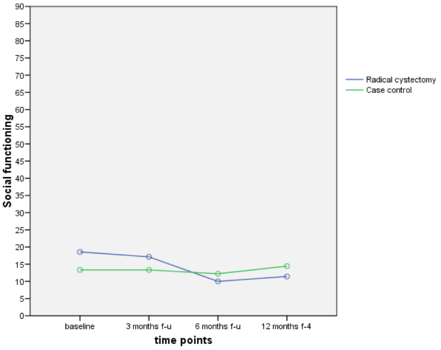
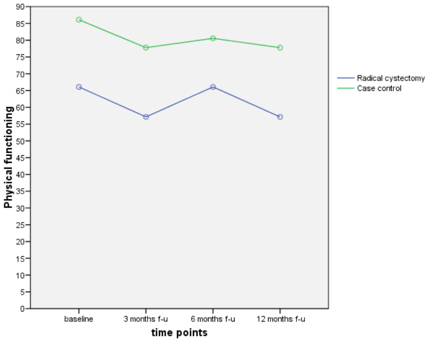
baseline
3 months f-u
6 months f-u
12 months f-u
time points
Radical cystectomy
Case control


Social functioning
90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0
baseline
3 months f-u
6 months f-u
12 months f-4
time points
Radical cystectomy
Case control


Physical functioning
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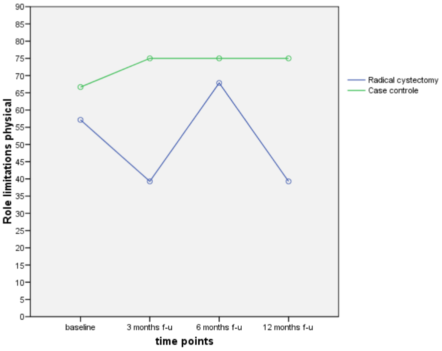
baseline
3 months f-u
6 months f-u
12 months f-u
time points
Radical cystectomy
Case control


Role limitations physical
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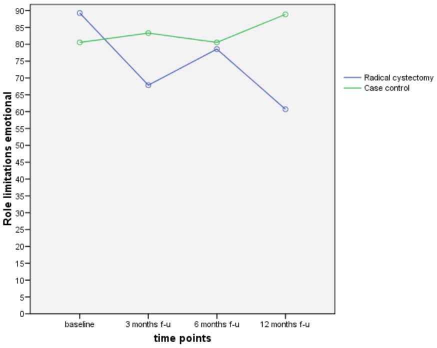
Role limitations emotional
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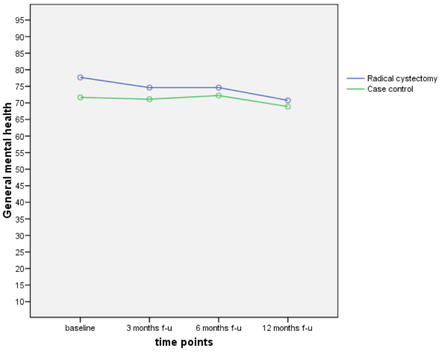
General mental health
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baseline
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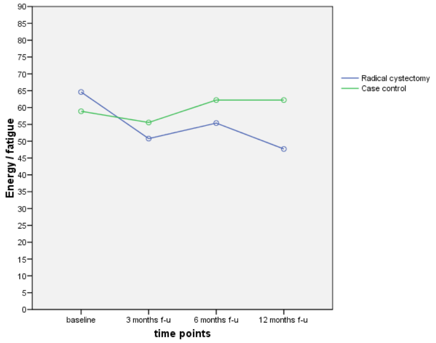
Radical cystectomy
Case control


Energy / fatigue
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5
10
15
20
25
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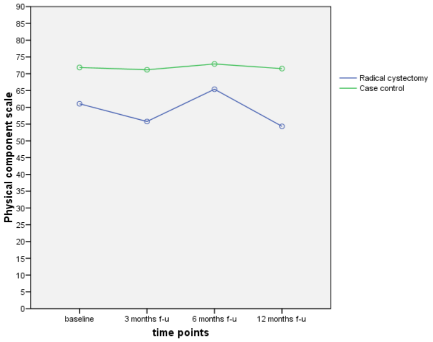
baseline
3 months f-u
6 months f-u
12 months f-u
time points
Radical cystectomy
Case control


Physical component scale
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5
10
15
20
25
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35
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50
55
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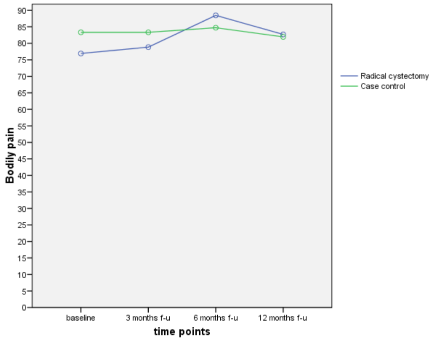
baseline
3 months f-u
6 months f-u
12 months f-u
time points
Radical cystectomy
Case control


Bodily pain
0
5
10
15
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40
45
50
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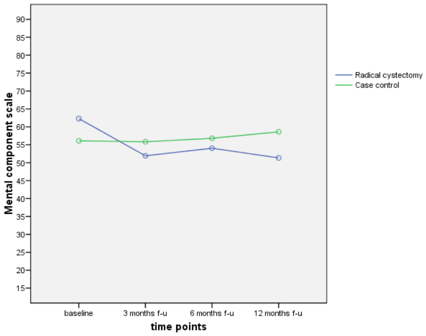
baseline
3 months f-u
6 months f-u
12 months f-u
time points
Radical cystectomy
Case control


Mental component scale
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25
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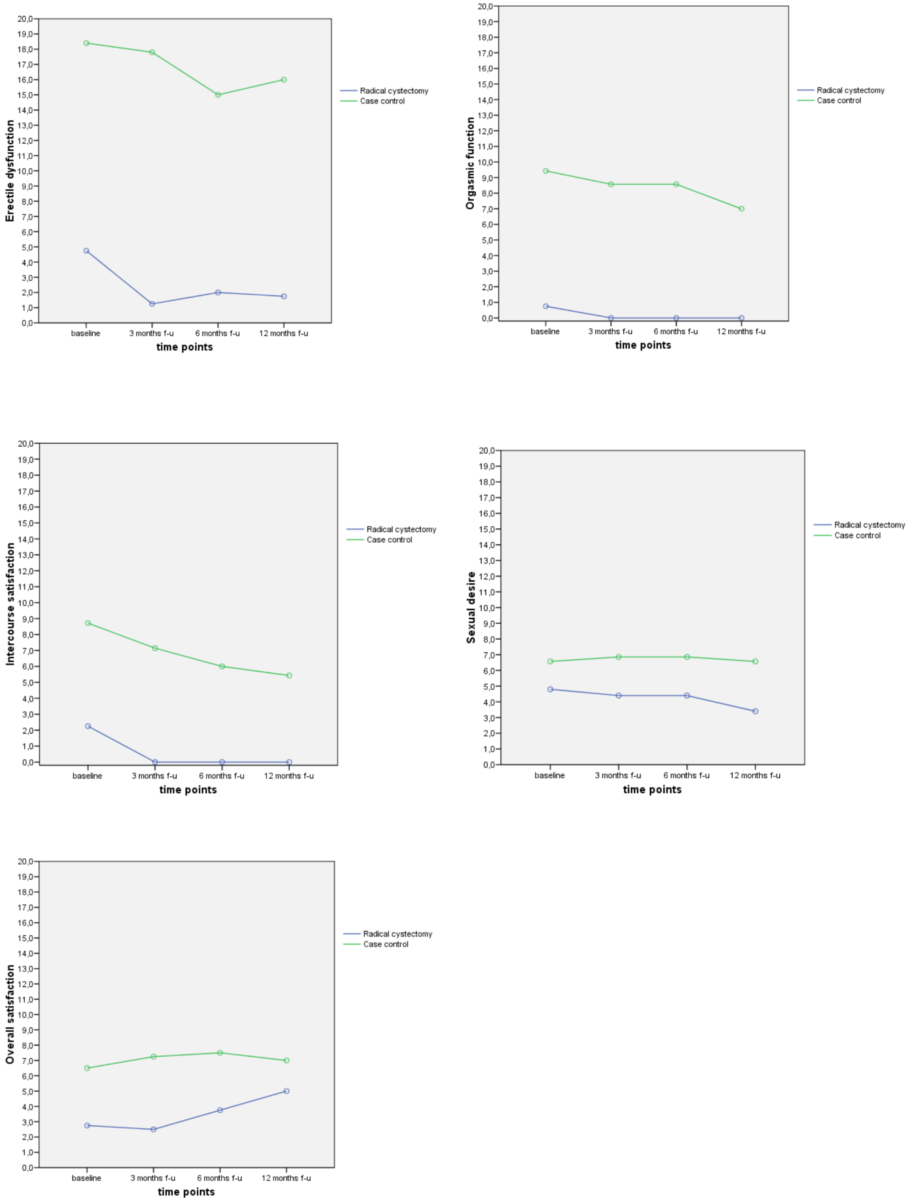
35
40
45
50
55
60
65
70
75
80
85
90
baseline
3 months f-u
6 months f-u
12 months f-u
time points
Radical cystectomy
Case control

C I-V IIEF


Erectile dysfunction
Orgasmic function
Intercourse satisfaction
Sexual desire
Overall satisfaction
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1,0
2,0
3,0
4,0
5,0
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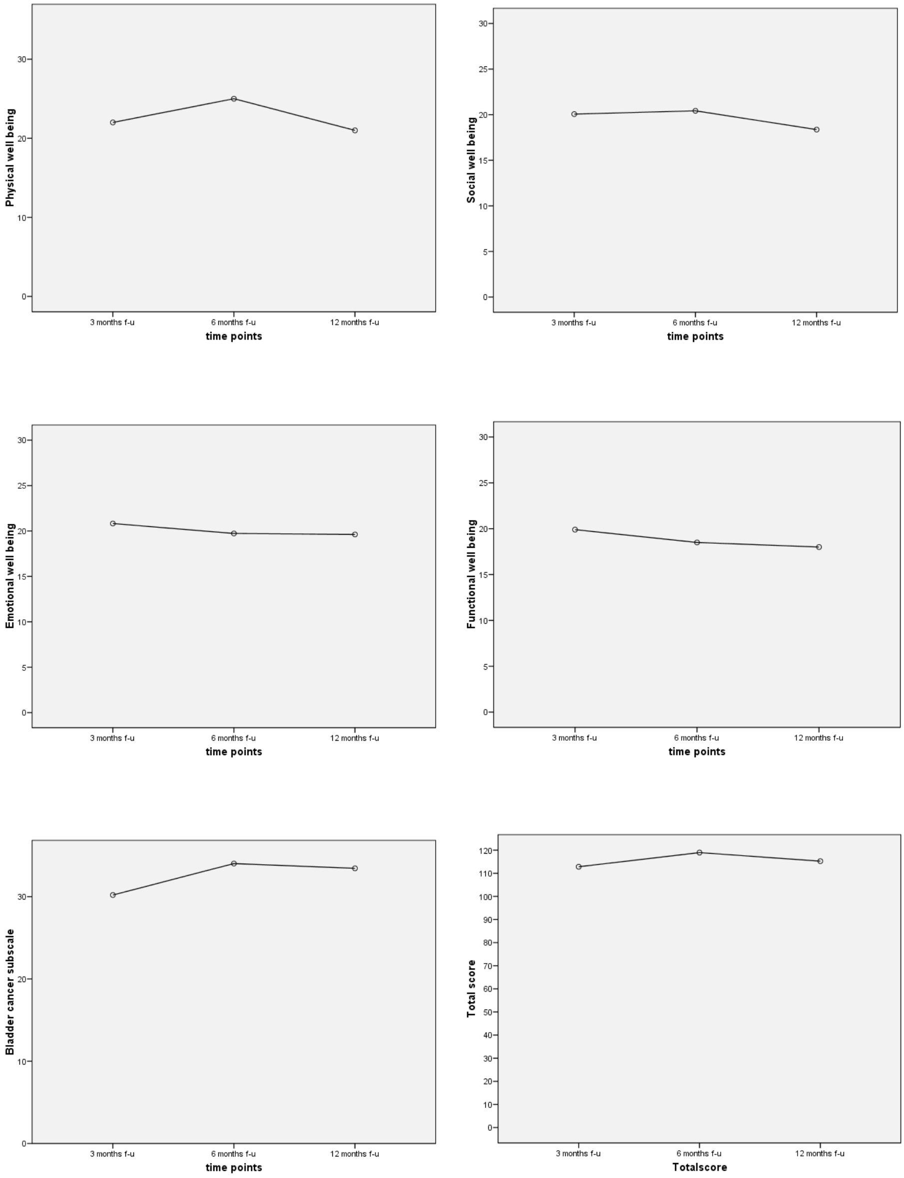
7,0
8,0
9,0
10,0
11,0
12,0
13,0
14,0
15,0
16,0
17,0
18,0
19,0
20,0
baseline
3 months f-u
6 months f-u
12 months f-u
time points
Radical cystectomy
Case control

Figure 3. I_VI FACT-BL in patients after cystectomy.



Discussion

In this prospective case-control study, the QoL, HS, sexual functioning, and dispositional anxiety were examined in patients with BC and matched. Controls with assessment points before diagnosis was known and 3, 6, 12 months postcystectomy (RC) or comparable time points (CC).

Quality of Life and Health Status

The available literature on HR-QoL following urinary diversion, is quite extensive but of debatable quality, as stated in a review by Gerharz et al [12]. Porter *et al* concluded that no prospective controlled randomized trials have yet been completed and none of the nonrandomized studies published to date adequately capture pre-treatment HRQOL, so results must be interpreted with caution [14].

QoL-studies for MIBC mostly involve only HS, which is not equivalent to QoL [12,14-15]. HS indicates where there are limitations in functioning caused by the disease, whereas QoL also reflects to what extent the patients are bothered by these limitations in daily life [15,27].

Our previous study showed that hematuria patients with unknown diagnosis of BC appeared to have the same baseline results on QoL and HS in comparison to the patients with other diagnoses than BC. The BC patients perceived their sexual functioning as lower and they also had the lowest percentage of anxious personalities [28]. The present study shows that patients with BC have an equal QoL before the diagnosis was known in comparison to CC patients (i.e., patients with other diagnoses than BC; but the present study is case-controlled). However, for HS, the physical component scale was significantly lower for RC vs. CC patients and in the WHOQOL-Bref the domain physical health showed a clinically relevant difference. An explanation may be found in the small number of RC vs. CC patients, in comparison to the large number of patients participating in the baseline study. The present study is case-controlled, giving more strength to these findings.

In a small sub-analysis of the baseline scores between RC patients who died within one year after cystectomy and RC patients who stayed alive showed that at that time point there were already differences with regard to QoL and HS scores, with patients who died scoring worse. Again, a larger study will be needed to examine the generalizability of these findings. If our findings are replicated, than a low QoL and HS could function as an indicator for worse short term survival.

The results of the FACT-Bl, measured postcystectomy, showed a physical stable score across time, while functional well-being decreased slightly. It may be that the questionnaire is not as sensitive as the other two questionnaires. The disadvantage of this disease-specific questionnaire is that a precystectomy score is possible, but no prediagnostic score. The question is whether the FACT-BL should have been applied in this study, knowing the ideal baseline cannot be used. As the generic questionnaires, with ideal baseline abilities, can be used, makes the disease-specific Fact-BL superfluous.

When looking over time at the patients with BC undergoing RC, it appeared that prediagnostic QoL and HS were better than postcystectomy, even after a follow up of one year after surgery, and shows that prediagnostic QoL and HS did not return to baseline levels at 12 months of follow up. This finding is contradictory to previous studies. One prospective study on QoL pre- and postcystectomy showed that both psychological and health-related quality of life measures came to baseline values and stabilized after a 12th-month period [29]. A second prospective study on the same subject for robotic assisted RC showed that QoL appears to return promptly to, or exceed, baseline levels at 6 months after the operation [30]. An important difference between these studies and the current study is our baseline measurement before diagnosis was known. When patients know their diagnosis, they may expect the worst en then postcystectomy, when surviving this kind of major surgery, it will always be relatively better than expected, giving no real baseline. Therefore, clinical advice to individual patients concerning their postcystectomy QoL should probably not be based on these earlier studies.

With regard to the IIEF (for male patients) and the facet sexual activity (for male and female patients), both questionnaires showed that the RC patients post-diagnosis performed worse on all items compared to CC. Only prediagnostic there was a difference between both questionnaires. RC patients started with the same baseline concerning the facet sexual activity of the QoL questionnaire. While the IIEF (HS questionnaire) showed that on all items and time points there was a difference in sexual functioning between the RC and CC patients. Because the IIEF is a widely used questionnaire, it is noteworthy that patients were willing to answer the facet sexuality questions, but on the other hand the IIEF questionnaire was a reason for many patients not to participate in our study.

A possible explanation of both the lower HS and sexual functioning could be the result of smoking in this patient category. A history of smoking is a risk factor for BC as well as for cardiovascular disease, an important cause of erectile dysfunction. Not knowing the comorbidity or smoking history of the patients is a drawback of this study, and future studies including comorbidity and smoking history are needed to examine the generalizability of our results. These results, the lower HS and sexual functioning before radical cystectomy and lower QoL postcystectomy should be taken into account and discussed with the patient, in the decision making process before choice of treatment. However, given the fact that the cystectomy is the gold standard treatment for MIBC, the abovementioned counselling may not change the choice of treatment, but the patient may benefit from being offered psychological and physical guidance throughout the disease process.

To our knowledge this is the first case-control study measuring PROs, i.e., QoL, HS, sexual functioning, and trait anxiety before the diagnosis of BC was known.
This prospective multi-centre study has a prospective follow-up with several postcystectomy assessments up to one year. Ideally, an even better baseline would be in a population not knowing they have hematuria, thus the general population. However, this is not feasible, because of the low risk of bladder cancer in the Netherlands. In 2010 there were 6600 cases of newly diagnosed bladder cancer, with a lifetime cumulative risk of 2% in a population of 16 million people [data: Dutch Cancer Registry]. As hematuria is the key symptom of bladder cancer the population presenting with hematuria was considered the best option.
The early withdrawal of the IIEF questionnaire is another limitation. Despite oral and written information about the questionnaire used in this study, the proportion of patients refusing participation due to the IIEF made us decide to withdraw the list.

However, the facet sexual activity of the WHOQOL-Bref was received and tolerated for the full duration of the study.

A major limitation is the small number of RC patients included in the study, and the loss of follow up due to hospital admissions or death of the patients due to the course of disease investigated. For the FACT-BL with a total number of participants of 10, this was even smaller. The possible explanation may be that patients are more inclined to participate in general questionnaires, than the more disease specific questionnaires.

In conclusion, this is the first case-control study measuring QoL before the diagnosis BC is known. The results of this study suggest that RC patients have a better prediagnostic QoL and HS than postcystectomy, even after a follow-up of one year after surgery. Furthermore, prediagnosis, the HS physical component scale and sexual activity for RC is lower, and the domain physical health shows a clinical difference in comparison to patients with other causes for hematuria. In this high risk, low volume procedure of the radical cystectomy with 50% 5-year survival, it is interesting to expand this research with a large number of patients and include comorbidity, and smoking history to the study to examine the generalizability of our study.

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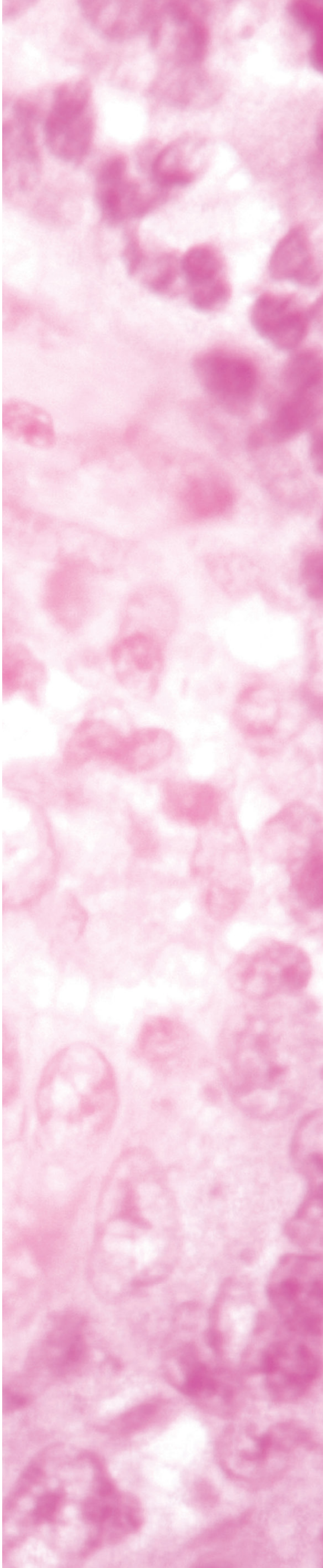
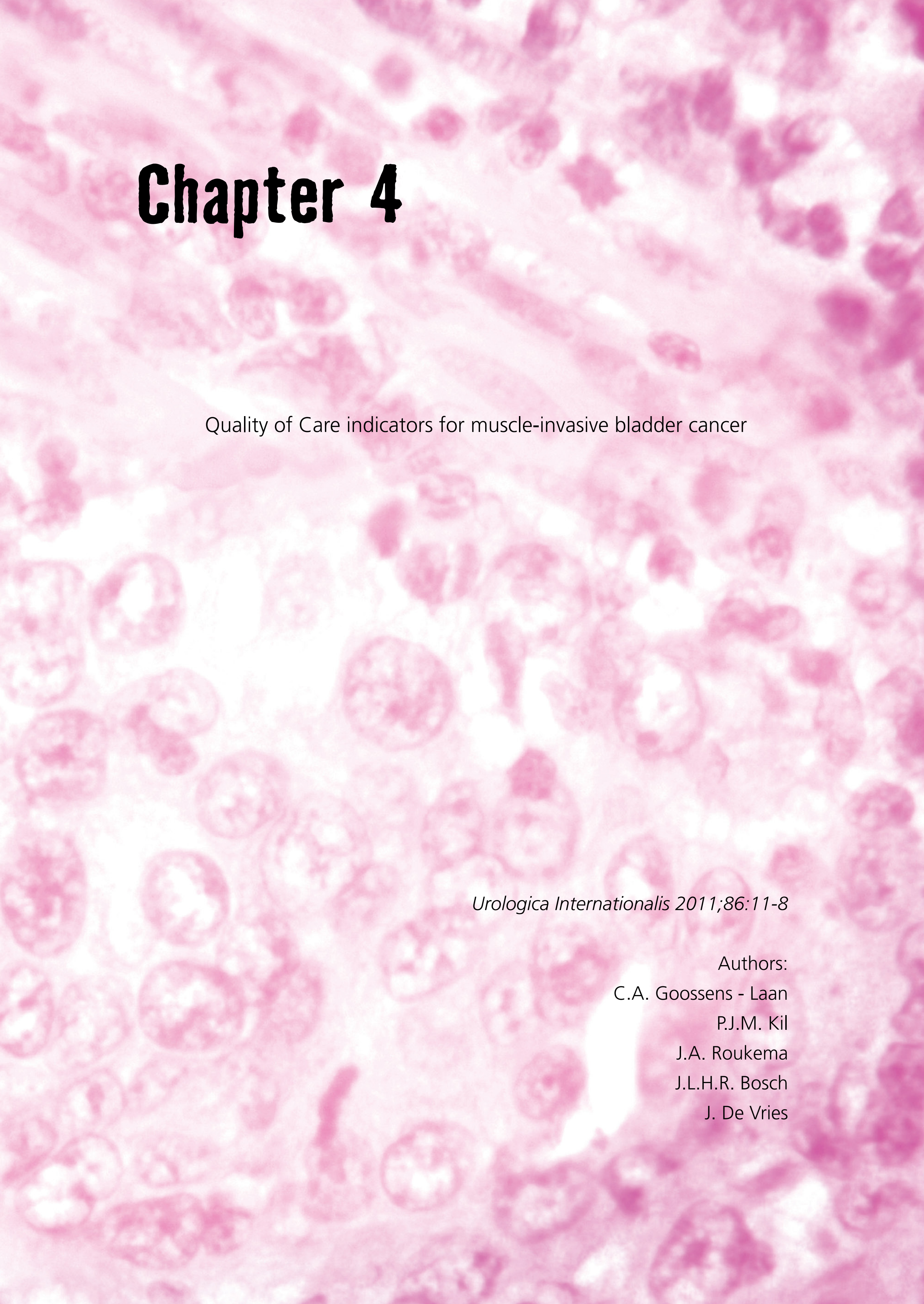
PART III

Quality of Care





Chapter 4

Quality of Care indicators for muscle-invasive bladder cancer

Urologica Internationalis 2011;86:11-8

Authors:
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J.A. Roukema
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Abstract

Objective: To define a set of quantifiable quality of care indicators (QIs) to measure the standard of care in our institute given to patients with muscle-invasive bladder cancer (MIBC).

Patients and Methods: Possible QIs were defined and selected by a multidisciplinary project group from recent literature, guidelines, and/or consensus within the project group. In a retrospective study a baseline for each QI was assessed and compared to a predefined benchmark.

Results: Four categories of QIs were selected: (1) care management, (2) accessibility and time management, (3) professional competence, and (4) patient factors. A list of 26 QIs was created. In the retrospective study, it became evident that 22 QIs failed to reach their benchmark, because of (1) an inadequate process of care (n = 5), (2) insufficient care given (n = 14), and (3) data not retrievable in retrospective study design (n = 2). Adjustments were made in the different processes of care in order to improve quality of care.

Conclusions: In the face of a complete lack of a QoC registration system for MIBC, we listed 26 quantifiable QIs, to measure QoC in our own institute. Our process of care did not meet 22 of the benchmarks, after which adjustments were made. This QoC registration method is a first step in defining applicable quality of care indicators, for implementation in the clinical practice.

Introduction

A quality of care (QoC) registration system or guidelines on how to improve and measure QoC with regard to the treatment of patients with muscle invasive bladder (MIBC) cancer do not exist. Therefore, it has not been shown that the use of a strict protocol or a multidisciplinary approach improves outcomes in terms of mortality and morbidity rates. As the definition of QoC states, it is the degree to which health care services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge [1]. To describe this optimal QoC for patients with MIBC, quality of care indicators (QIs) can be used. There is currently much discussion on QIs, how to define and measure them. And more importantly, how to demonstrate that these QIs do indeed alter the course of the disease in the long-term. Given the definition of QoC, a broad range of parameters or QIs must be selected to adequately describe the quality of care given in a certain institution. By defining these indicators, insight can be gained in the multiple elements of the provided care. Next a benchmark must be established to define minimal requirements for optimal care. After comparing the results per indicator with this benchmark, elements that are in need of improvement may be identified. The purpose of this study was to define the set of quantifiable QIs for use in our hospital and compare this set and the associated benchmarks with care provided in previous years in our institute.

Patients and Methods

Developing Quality of Care Indicators

Defining the QIs was done through a multidisciplinary approach using the Delphi method [2]. The project group included an academic urologist, a urologist of a large teaching hospital, a psychologist, an oncologic surgeon, and a urological research-physician. First, an inventory was made of resources that could serve as guidelines for defining and extracting QIs, i.e. guidelines on MIBC [3, 4], indicators formed by other project groups specialized in QIs [5], (inter-)national literature, and expert opinion (i.e. the project group). Next, based on this inventory a list of potential indicators was made, divided in different categories of QIs regarding the diagnosis, treatment and counseling of patients with MIBC [5]. For each category, indicators were discussed within the project group using the Delphi method. After defining the final QIs, benchmark values were formulated for each individual QI, using a systematic Pubmed search of the medical literature from 2001 until 2007. For each indicator, a question was formulated; e.g. for complication rate: what is the mean complication rate in recent literature? This search was limited to publications in the English language with an abstract. The final value of the benchmark was based on this literature study and/or consensus within the project group.

Retrospective Study Design and Data Collection

Secondly, a retrospective study was performed to establish baseline values for each QI and to compare these with the preset benchmark. The study was approved by the local ethics committee. Inclusion criteria were radical cystectomy for MIBC, followed by an ileal conduit or an orthotopic bladder substitution at the St. Elisabeth Hospital, Tilburg, the Netherlands, between January 2001 and January 2006. The patients were identified using the Hospital Information system and the Pathological Anatomical National Automated Archive. Data concerning the QIs was collected by one research-physician, using both in- and out- patient medical records. Clinical and logistic information (i.e. appointments and date of surgery) were obtained from the files. A prospective complication registration system was used since 2004 [6].

Results

Quality of Care Indicators

Four quality related categories were formulated: (1) care management, (2) accessibility and time management, (3) professional competence, and (4) patient factors. 'Care management' consists of indicators based on the principles of basic care for patients who will undergo a cystectomy. 'Accessibility and time management' concerns the waiting periods for diagnostic tests, results, and treatment. 'Professional competence' indicators relate to the skills of the hospital staff (e.g. urologists, nurses) taking care of the patient. The 'patient factors' category includes factors relating to comorbidity and psycho-social factors. A list of 26 QIs was divided across the four categories, including mortality and complication rates (table 1). For each individual QI, a benchmark value was established (table 1). Clarification on different QIs per category is provided below when needed.

Care Management Indicators

For this category, the benchmark for all indicators was set at 100%. The structured multidisciplinary uro-oncology consultation was implemented in 2007 and is attended by an urologist, a radiotherapist, a medical oncologist, and a radiologist. Recently, a psychologist also attended.

Accessibility and Time Management Indicators

Bladder cancer is found in two subsets of patients. Patients referred with hematuria and patients with nonspecific symptoms (i.e. abdominal pain or frequent urinary infections). It is only possible to make a time path for reference and diagnostic management for the first group, since the second group is too diverse in its presentation. For macroscopic hematuria, it is our regional policy to see the patient within 24 h, for microscopic hematuria within 14 days [7]. For the indicator ‘time from TURT (transurethral resection bladder tumor) until cystectomy’, the target is set at a maximum of 12 weeks for a cystectomy. This standard is based on findings from several studies showing that a delay in surgery greater than 12 weeks is associated with an advanced pathological stage and increased mortality [8–10]. Only one study found that a reasonable delay from the last TURT to a cystectomy is not independently associated with stage progression or with decreased survival [11].

Table 1. Quality of care indicators and the defined benchmark

Category	Description of final indicator	Benchmark
Care management		
1	outpatient consultation between surgeon and patient	100%
2	preoperative multidisplinary consultation	100%
3	postoperative multidisplinary consultation	100%
4	preoperative consultation stoma nurse	100%
5	postoperative consultation stoma nurse	100% for ileal conduit, optional for neobladder
6	informed consent	100%
7	preoperative consultation anesthesiology	100%
Accessibility and time management		
8	interval reference hematuria–1st consultation	macroscopic <24 h microscopic <14 days
9	interval 1st consultation–cystoscopy for hematuria	≤10 days
10	interval cystoscopy–TURT	≤21 days
11	interval TURT–pathology result known by patient	≤10 days
12	interval TURT–cystectomy	≤12 weeks
13	interval cystectomy–pathology result know to patient	≤10 days
Professional competence		
14	operating time	Bricker: 80% ≤300 min neobladder: 80% ≤360 min
15	lymph node dissection	100%
16	number of lymph nodes per dissection	80% ≥10 nodes
17	frozen section ureters	100%
18	positive margins cystectomy	total <10%; pT3–4 <15%; salvage <20%
19	transfusion rate	50%
20	packed cells per admission per patient	<4
21	length of hospital stay	Bricker: 80% ≤14 days neobladder or Indiana pouch: 80% ≤21 days
22	complication rate	≤64%
23	mortality rate	≤4%
24	readmission within 90 days after cystectomy	≤12%
Patient factors		
25	comorbidity registered in chart	100%
26	preoperative psychosocial screening	100%

TURT = Transurethral resection bladder tumor.

Professional Competence Indicators

Operating time is defined as the time needed to perform a lymph node dissection, cystectomy, and bladder reconstruction. Taking into account that a substantial amount of the patients have had previous abdominal procedures and will need more operating time, our target was set at 80% of the ileal conduit patients to be operated within 300 min and 80% of the orthotopic neobladder patients to be operated within 360 min [12,13]. The norm for performing a standard lymph node dissection is set at 100%, which is also a requirement in the recent Dutch Guideline, which states that all cystectomies should be performed with at least a standard lymph node dissection [14]. Progression-free as well as overall survival may be correlated with the amount of lymph nodes removed during the dissection, but interindividual differences in the number of lymph node counts by pathologists make it hard to establish a standard [4]. Herr et al. [15] suggested that at least 10–14 lymph nodes should be removed; therefore, we set the number of nodes per dissection at a minimum of 10. We set the standard at 100% for frozen section evaluation of the surgical margins of the ureter, although the updated EAU guideline states that only in case of a patient with CIS a frozen section should be performed. A standard percentage for positive cystectomy margins was adopted from Herr et al. [15], i.e. the percentage of positive margins in all cases should be less than 10%, in pT3–4 tumors less than 15% and for the salvage cystectomy less than 20%.

The mean hospital stay is highly variable according to differences in local protocols. Hospital stays between 6 and 22 days are described [13,16]. Our benchmark is based on our own protocol, where the patient is assumed to be able to perform his own stoma care 14 days postoperatively, i.e. to discharge 80% of patients within 14 days [17]. For a patient with an orthotopic neobladder we set the benchmark at 80% hospital discharge within 21 days, as after 2 weeks the transurethral catheter is removed, and the patient can be trained for continence.

Comparing retrospective-based complication studies, rates are reported to vary from 9 to 44% [18,19]. In a study with a prospective complication registration system, the rate was 64% (90 days after surgery) [20]. Due to the accuracy of prospective registration, our target is set at a maximum of 64%. When mortality rates are compared, again major differences in rates are found, varying from 0.7 to 8.1%

[13,16,18,20–26]. This variation is mostly explained by the difference in case mix and case load per hospital and per surgeon. However, when comparing case loads and mortality rates, it appears that different definitions are used. Various definitions of low-volume hospitals have been used, ranging from hospitals performing <2 to <11 cystectomies per year [13,16,18,20–26]. High volume hospitals are variously defined as hospitals performing 63 to 634 [13,16,18,20–26]. As the mean for the 30-day mortality rate found is around 4%, this was set as target value.

Patient Factors

Co-morbidity plays a key role in defining a patient's ASA classification and this indicator is set for a target of 100%. The American Society of Anesthesiologists' (ASA) physical status classification serves as a guide to predict the anesthetic/surgical risks. One reason for a multimodality approach for the patient with MIBC is the substantial amount of time that is required for thorough psychological counseling, due to the psychosocial and sexual implications of diagnosis and treatment [27]. As a consequence, preoperative psychological screening is a mandatory indicator. If the screening suggests that the patient is in need for extra social or psychological help, this is started preoperatively and will be continued during the hospital stay.

Retrospective Baseline Study

From 2001 to 2006, 58 patients underwent radical cystectomy for invasive bladder cancer. Fifty-two had MIBC (44 men, median age 64). Patient characteristics according to type of diversion are shown in table 2.

Table 2. Patient characteristics according to type of diversion

	Ileal conduit		Orthotopic neobladder		Total		p value
	n	%	n	%	n	%	
Gender							
Male	36	88	8	73	44	85	
Female	5	12	3	27	8	15	≤0.218
Pathology tumor category							
No tumor (T0)	3	7	2	18	5	10	
Organ-confined (≤T2)	14	34	9	82	23	44	
Non-organ-confined (≥T3)	24	59	0		24	46	≤0.005
Nodal status							
Negative	30	73	9	82	39	75	
Positive	11	27	2	18	13	25	≤0.556
Age, years							
Mean (SD)	65	8.3	57	11.1	64	9.5	≤0.006
Previous treatments (other then TURT)							
Radiotherapy	1	2	0	0	1	2	≤0.601
Chemotherapy	1	2	0	0	1	2	≤0.601
Iridium	3	7	0	0	3	7	≤0.355
ASA score							
1–2	26	63	11	100	37	72	
≥3	15	37	0	0	15	29	≤0.05
Total	41		11		52		

One patient had preoperative cT3GIII tumor, with no sign of lymph node invasion on the CT scan. One patient had preoperative cT1GIII, and was found to be pT2GIII after the cystectomy. One patient had recurrent CIS and showed to be pT3GIII after cystectomy. The pT0 (10%) tumors were all pT0 after the cystectomy, but were all T2GIII found by transurethral resection. The postoperative group for >pT2 was very high, as it included 3 salvage cystectomies, and 4 patients with preoperative pT2GIII N^+. 66% of the pT2 tumors found by TURT where upstaged. The 25 patients with an upstaged tumor included 44% pT3N0 (n = 11), 12% pT4N0 (n = 3), 16% pT2N+ (n = 4), 16% pT3N+ (n = 4), and 12% pT4n+ (n = 3). Baseline results are shown in table 3. After comparing the results per indicator with the benchmark, it was evident that 22 QIs failed to reach the benchmark. In as many as 7 indicators, a baseline could not be obtained, and 15 QIs were below the benchmark. Because the study was retrospective, QI1 and QI8 were not available in the charts. A structured pre- and postoperative multidisciplinary meeting for all oncological patients did not exist in our institution between 2001 and 2006 (QI2–3). The same issue occurred for indicator 7. The median perioperative blood transfusion rate was two packed cells and during the rest of the hospital stay a median of 1.5 packed cell was given. The 30-day mortality rate was 5.8%, i.e. 3 patients of the 52, all receiving an ileal conduit. Since a psychosocial screening has only recently been implemented in the clinic, no baseline was available. To improve the QoC in our institute, adjustments were made in the treatment protocol. In the category 'care management', a pre- and postoperative structured multidisciplinary consultation is implemented in which all patients with MIBC are discussed. And a pre- and postoperative visit to a specialized stoma nurse and preoperative visit to the outpatient clinic of the anesthesiologist is made mandatory. In the 'accessibility and time management' category, a strict time protocol is implemented at the outpatient clinic and ward. For the 'professional competence' category, the following changes are implemented: centralization of all cystectomies from the region Tilburg to one hospital and performed by a fixed team of 2 urologists and a standardized extended lymph node dissection (proximal border: aortic bifurcation) was performed in all patients. A new transfusion protocol was introduced hospital-wide. In the category 'patient factors', the mandatory preoperative psychological screening is implemented.

Table 3. Final quality of care indicators and results of the baseline study

Category	Indicator (benchmark)	Results of the baseline study
Care management		
1	outpatient consultation between surgeon and patient (100%)	–
2	preoperative multidisplinary consultation (100%)	–
3	postoperative multidisplinary consultation (100%)	–
4	preoperative consultation conduit nurse (100%)	62%
5	postoperative consultation conduit nurse (100%)	60%
6	informed consent (100%)	69%
7	preoperative consultation anesthesiology (100%)	– Accessibility and time management
8	interval reference hematuria–1st consultation	– (macroscopic <24 h, microscopic <14 days)
9	*interval 1st consultation–cystoscopy hematuria (≤10 days)*	*median 10 (range 3,700)*
10	interval cystoscopy–TURT (≤21 days)	median 23 (range 109)
11	interval TURT–pathology result known by patient (≤10 days)	median 14 (range 25)
12	*interval TURT–cystectomy (≤12 weeks)*	*median 6 (range 25)*
13	*interval cystectomy–pathology result known by patient (≤10 days)*	*median 9 (range 22)*
Professional competence		
14	operating time (Bricker: 80% ≤300 min; neobladder: 80% ≤360 min)	Bricker: mean 273 (70% ≤300) neobladder: mean 348 (54% ≤360)
15	lymph node dissection (100%)	92%
16	number of lymph nodes per dissection (80% ≥10 nodes)	46% >3 nodes per side
17	frozen section ureters (100%)	10%
18	positive margins cystectomy (total <10%; pT3–4 <15%; salvage <20%)	total = 23%; pT3–4 = 23%; salvage = 50%
19	transfusion rate (50%)	89%
20	packed cells per admission per patient (<4)	median 4 (range 31)
21	hospital stay (Bricker: 80% ≤14 days; neobladder or Indiana pouch: 80% ≤21 days)	Bricker: median 16 (34% ≤14) neobladder: median 22 (45% ≤21)
22	*90 days postoperative complication rate (≤64%)*	*54%*
23	30 days postoperative mortality rate (≤4%)	5.8% (3 patients)
24	readmission within 90 days after cystectomy (≤11.5%)	12% Patient factors
25	comorbidity registered in chart (100%)	–
26	preoperative psychosocial screening (100%)	–

Italics = On or above target; normal = below target. Below target due to: (1) inadequate process of care (n = 6: QI2, 3, 7, 16, 17, 26), (2) insufficient care given (n = 14: QI1, 4, 5, 6, 10, 11, 14, 15, 18, 19, 20, 21, 22, 24), and (3) data not obtained due to retrospective nature of study (n = 2: QI8, 25).

Discussion

QoC registration systems or guidelines on how to improve and measure QoC with regard to MIBC are nonexistent. In the face of a complete lack, we listed 26 quantifiable QIs to measure QoC in our own institute. The QIs were measured in a retrospective study of 52 cystectomy patients. For 22 indicators, the benchmark was not reached. Three main reasons account for this: (1) inadequate process of care (e.g. no structured multidisciplinary consultation; n = 5), (2) insufficient care given (e.g. mor- tality rate too high; n = 14), and (3) data not obtained due to retrospective nature of study (e.g. interval hematuria–1st consultation clinic; n = 2).

In respect to the process of care, a structured pre- and postoperative multidisciplinary meeting for all oncological patients did not exist in our institution between 2001 and 2006 (QI2–3). However, patients with complex pathology were discussed in a weekly multidisciplinary oncologic meeting. The same issue occurred with QI7, stating how many patients had a preoperative visit to the anesthesiologist' clinic. During the studied period, an outpatient anesthesiologist clinic did not exist, but the anesthesiologist consultation was performed the day before surgery.

To improve the QoC in our institute, the following adjustments were made in the treatment protocol:

A structured multidisciplinary consultation was implemented in 2007 after the final indicators were developed. In the same period, a consultation with a specialized stoma nurse and to the outpatient clinic of the anesthesiologist was established for all patients.

QI14 (operating time) did not reach the benchmark. In 46% of the neobladders, the operating time exceeded 360 minutes, and in 30% of the incontinent ileoconduit the 300 minutes operating time were surpassed. It is clear that this should be improved. Because increasing the number of surgeries performed by a single surgeon and increasing the volume per hospital leads to lower mortality and morbidity rates [13,16,18,20–26], a fixed team of 2 urologists started performing all cystectomies in our clinic. At the same time all patients are getting an extended lymph node dissection requiring extra time. Furthermore, centralization of all cystectomies in the region Tilburg to the St. Elisabeth Hospital was established. Our mortality rate of 6%

is comparable to the English study from McCabe (6.7%). However, in their study, the mean mortality rate dropped from 6.7 to 4.2% when surgeon volume went to 8 cases or higher a year [26]. As our mean surgeon volume was 2.5 cases a year, this could be a major reason for our higher mortality rate. Mortality rates were shown to be related to caseloads in studies from high volume centers in the USA [16,23]. The third adjustment in the category Professional competence that was made is a standardized extended lymph node dissection for all patients.

Blood loss and transfusion rates are marginally described in the literature [13,28]. Our transfusion rate between 2001 and 2006 was high (89%), and in need of improvement. Our hospital implemented a new transfusion protocol (6–5–4 rule) in 2006, e.g. all physicians and nurses have been trained and instructed to determine when an anemic patient according to his ASA classification and symptoms qualifies to get a blood transfusion. This method has reduced the transfusion rate by 49% hospital wide.

A prospective study is in progress to see if all the adjustments that have been made will result in the desired improvement of QoC resulting in more QIs reaching their benchmark.

Although this exercise has proven its value to our clinic, critical notes can be made on both the development of the QIs as for the baseline measurement. One concerns the Delphi method of reaching topic-specific consensus. The limitation is that it is only as appropriate and relevant as the expert panel involved. Also, when using this method for QIs for international purposes, an international panel from cancer centers of expertise would be a more appropriate choice. Lastly, our project group included urologists, psychologists, oncologic surgeons and research physicians, but did not include pathologists, radiotherapists and radiologists.

Also the QIs were not derived from one specific guideline in which the level of evidence influences the choice for QIs, e.g. the most important QIs having evidence that adherence to them improves survival. With the current levels of evidence in bladder cancer this high benchmark is hard to define. This means that the stronger QIs are the ones that could potentially be influencing survival, e.g. those relating to a delay in treatment and the quality of cystectomy and lymph node dissection, whereas QIs related to patient satisfaction are softer in nature.

Prognostic factors like pathologic stage, tumor grade, mean nuclear area, and lymphatic invasion are independent factors of overall and disease-free survival. We made a distinction between outcome parameters and quality of care parameters in defining the QIs; a QoC indicators should be able to change by team effort. Prognostic factors, such as tumor grade cannot be influenced.

A prospective study for the baseline study would have had the advantage that the upcoming prospective results would have been comparable.

Currently, QIs are often defined following (inter)national guideline developments with the aim to evaluate if it can be measured that implementation does indeed change practice and improve QoC. Our QIs were defined at the same time as the Dutch guideline on MIBC was developed. Our purpose of defining QIs was to see if they change practice and improve our QoC, not if the guideline can alter the course of disease.

QIs are developed to improve and guide one's own process of care and are above all being used solely by hospitals and medical professionals. This in contrast to performance indicators, which should be seen as external measurements developed by Dutch insurance companies to evaluate the performance of a care institution or hospital. In the Netherlands, there is an ongoing debate between the insurance companies and the hospitals about the use of performance indicators. When a target of a performance indicator has not been reached, this could lead to financial consequences, i.e. the hospital not getting paid for the treatment provided. So when QIs are being used in clinical practice, awareness must be raised to prevent indicator motivated actions, i.e. interventions only to reach the QIs target. The purpose of QIs is to bring quality of care to a higher standard.

Ultimately QoC indicators should be used as surrogate measures for (1) oncologic outcomes (cancer specific and overall survival), (2) patient quality of life outcomes, and (3) healthcare expenditures. Before QOC indicators are generally implemented and standardized into oncologic practice, it is imperative to document correlation between QoC and above-mentioned outcome factors.

Conclusions

In the face of a complete lack, we listed quantifiable QIs to measure QoC in our own institute for patients with MIBC, not only by assessing hospital mortality and morbidity, but with a more extensive set of outcome parameters. For each indicator a benchmark was established, based on recent literature and guidelines. In a retrospective study, a baseline measurement was set which was compared to the benchmark to get insight in the multiple elements of the provided care. Twenty-two QIs failed to reach the target and these dictated the necessary improvements. After making adjustments in our process of care, a follow up study will be initiated to evaluate the QIs in a prospective fashion. This QoC registration method is a first step in defining applicable quality of care indicators, for implementation in clinical practice.

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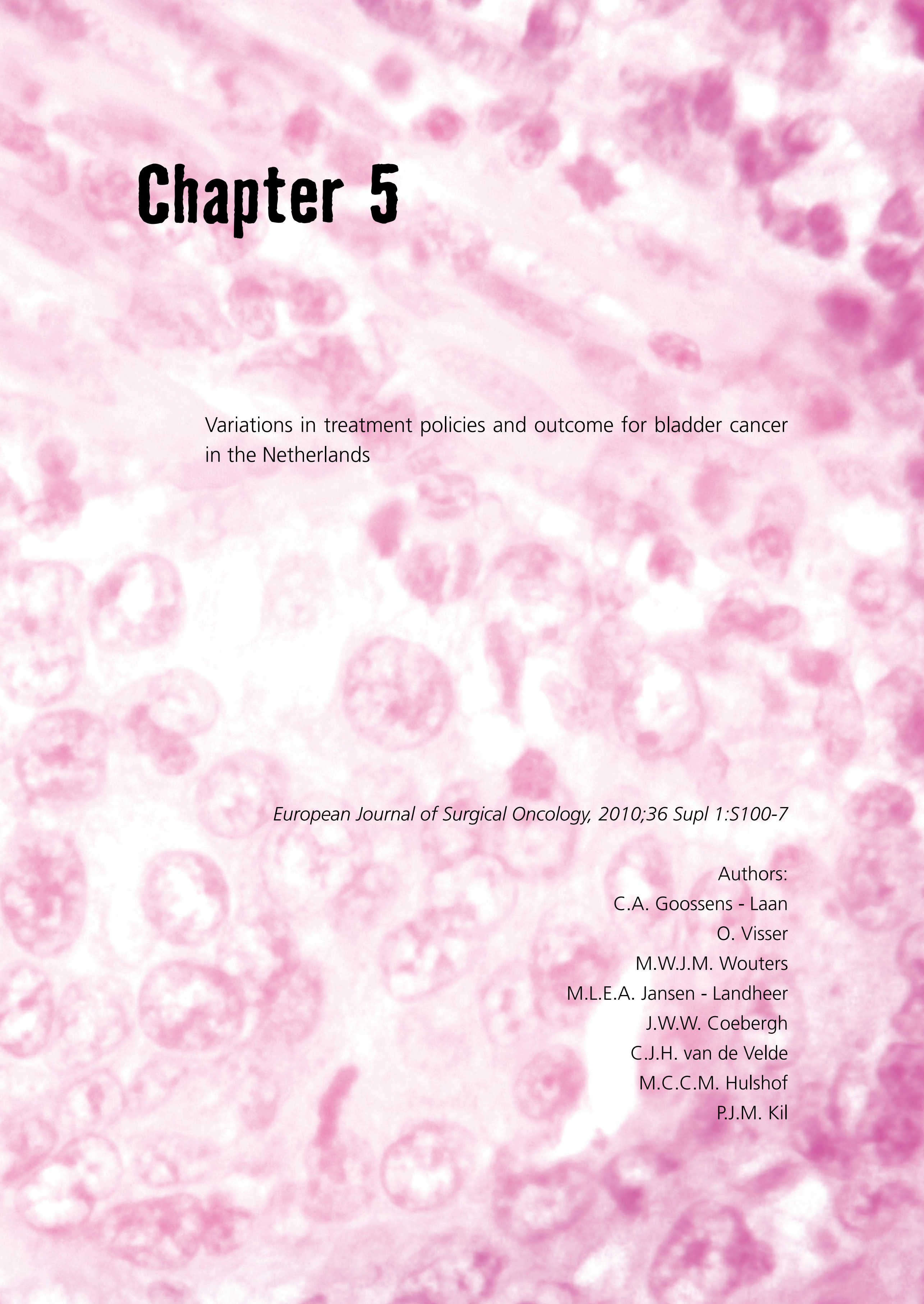

Chapter 5

Variations in treatment policies and outcome for bladder cancer in the Netherlands

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Abstract

Aim: To describe the population-based variation in treatment policies and outcome for bladder cancer in the Netherlands.

Methods: All newly diagnosed patients with primary bladder cancers during 2001-2006 were selected from the Netherlands Cancer Registry (n = 29,206). Type of primary treatment was analysed according to Comprehensive Cancer Centre region, hospital type (academic, non-academic teaching or other hospitals) and volume (≤5, 6-10 or >10 cystectomies yearly). For stage II-III patients undergoing cystectomy we analyzed the proportion of lymph node dissections and 30-days mortality.

Results: 44% of patients with stage II-III bladder cancer underwent cystectomy, while 26% were not treated with curative intent. Cystectomy was the preferred option in three of nine regions, radiotherapy in two, and two regions waived curative treatment more often. Between 2001 and 2006 the number of cystectomies increased with 20% (n = 108). Twenty-one percent (n = 663) of these procedures were performed in 44 low-volume hospitals. In 79% of the cystectomies lymph node dissections were performed, more often in high and medium-volume centers (82% and 81% respectively) than in low-volume hospitals (71%, the odds ratio being 1.5). The overall 30-days post-operative mortality rate was 3.4% and increased with older age. It was significantly lower in high- volume centers (1.2%).

Conclusion: Treatment policies for muscle-invasive bladder cancer in the Netherlands showed regional preferences and a gradual increase of cystectomy. Cystectomy albeit considered as golden standard, was performed in a minority of the muscle-invasive cases. In high-volume institutions, lymph node dissection rates were higher and post-operative mortality rates were lower.

Introduction

In the Netherlands, bladder cancer is the fifth common tumor in men, and the seventh in women [1]. While the incidence of non-invasive bladder cancer in the Netherlands has been increasing, it is decreasing for invasive bladder cancer. In recent years, the mortality rates from bladder cancer decreased among males, contrasting females [2,3].

A patient with newly diagnosed non muscle-invasive disease may be cured with local treatment only; i.e. one or multiple transurethral resections of the tumor(s) (TUR-BT) with or without subsequent bladder instillations. Cystectomy is the preferred therapy, for patients with muscle-invasive bladder cancer (MIBC) and for patients who underwent unsuccessful local treatment of non muscle-invasive bladder cancer. When a patient is not eligible for a cystectomy due to co-morbidity, or old age or patient preference, radiotherapy is the second best option [4].

Increasing evidence for a positive association between quality of care in cancer treatment in relation to volume and infrastructure [5-7] led us to explore variations in staging and treatment policies and its outcome for bladder cancer in the Netherlands.

Patients and methods

Cancer registry data

All patients with primary bladder tumours newly diagnosed in the Netherlands between January 1, 2001 and December 31, 2006 were selected from the population-based Netherlands Cancer Registry, with complete national coverage. Dutch hospitals are served in the nine regions by the largely coordinating and facilitating Comprehensive Cancer Centers (CCC). In the hospitals, registration clerks of the CCCs extract information for the registry from the medical records, notified by the Dutch National Pathology database (PALGA). A variety of data are collected, i.e. on demographics, morphology, stage at diagnosis and primary treatment (planned in the six months following diagnosis) and vital status, date of follow-up or death. Tumor site and morphology were coded according to the International Classification of Diseases for Oncology (ICD-O) [8]. Quality of data is generally considered to be high and completeness was estimated to be more than 95%.[9,10]

Hospitals and regions

Patients of all (N = 97) hospitals in the Netherlands were included in this study. Hospitals were grouped into three categories, i.e. 1) 9 academic hospitals 2) non-academic hospitals with teaching facilities for urology residents 3) other hospitals (community hospitals). The influence of a radiotherapy department on the choice of treatment was also investigated. Type of primary treatment was analysed according to geographic region (subdivided according to age and stage), hospital type and annual volume (≤5, >5-10 or >10 cystectomies yearly). Variations in treatment policies, according to age and stage were assessed in the nine regions.

Data analysis

Data analysis was done with anonymised data. Stage grouping in this study was done according to the UICC TNM classification, 6th edition [11]. cTNM was used for the diagnosis and general treatment policies including all patients and pTNM for subset analysis of cystectomy cases. Excluded from analysis were bladder tumors without histology proven diagnosis, sarcomas, lymphomas, bladder cancer only found postmortem, incomplete registrations, and tumour recurrence (except when stage 0 progressed into stage I or higher). Local treatment is defined as one or multiple transurethral resections of the tumor often followed by bladder installations. Only the initial treatment (within six months after diagnosis) for every new tumour was registered, thereby disregarding cystectomy for an initial non muscle-invasive tumour that progressed to muscle-invasive disease more than six months after the first diagnosis or a salvage cystectomy after radiotherapy. When the initial treatment took more than six months to complete, for example in case neo-adjuvant chemotherapy preceded the cystectomy, the whole treatment was registered.

Primary treatment was grouped according to local resection or no treatment (local treatment), cystectomy, radiotherapy or chemotherapy. A patient who underwent cystectomy and radiotherapy or chemotherapy was classified as cystectomy. A patient receiving radiotherapy as well as chemotherapy was classified as radiotherapy. Curative and palliative cystectomy or radiotherapy could not be distinguished.

A subset of patients was analyzed for the proportion of lymph node dissections according to surgical volume and the 30 and 60 day-mortality rate after cystectomy.

For this category the years of analysis were restricted from 2004 until 2006 as the date of cystectomy was not available for all cases in earlier years.

Statistical methods

Logistic regression analysis was performed to examine the influence of age at diagnosis (<60, 60-74, ≥75 yr), gender, stage, type of hospital, hospital volume, CCC-region on the odds of receiving surgery (cystectomy), radiotherapy, and on either surgery or radiotherapy. All analyses, including the logistic regression analyses, were performed in STATA, version 10. Results were considered statistically significant for $p < 0.05$.

Results

During 2001-2006, 29,206 patients (78% male) were diagnosed with primary bladder cancer. Six percent of all new patients were diagnosed in academic hospitals, 23% in non-academic hospitals with a teaching facility for urology and 71% in the other hospitals. Patient, hospital, regional and treatment characteristics are presented in Table 1.

Table 1. Characteristics of bladder cancer in the Netherlands, 2001-2006.

	Number of cases	%
All cases	29,206	
Year of diagnosis		
2001	4473	15.3
2002	4591	15.7
2003	4740	16.2
2004	4992	17.1
2005	5154	17.6
2006	5256	18.0
Sex		
Males	22,727	77.8
Females	6479	22.2
Age category		
<60	5745	19.7
60-74	12,780	43.8
75 or older	10,681	36.6
Clinical TNM-stage		
Tis	973	3.3
Ta	13,582	46.5
I	6267	21.5
II	4505	15.4
III	1126	3.9
IV	2349	8.0
Unknown	404	1.4
Morphological classification		
squamous cell carcinoma	343	1.2
transitional cell carcinoma	28,369	97.1
adenocarcinoma	195	0.7
undifferentiated carcinoma	107	0.4
neuro-endocrine carcinoma	192	0.7
Hospital of first diagnosis		
university hospital/oncological centre	1779	6.1
non-academic teaching hospitals	6679	22.9
other hospitals (community)	20,745	71.0
Radiotherapy facilities in the hospital		
No	23,629	80.9
Yes	5577	19.1
Comprehensive cancer centre		
1	4020	13.8
2	2351	8.0
3	2188	7.5
4	5292	18.1
5	2764	9.5
6	4436	15.2
7	4169	14.3
8	1827	6.3
9	2156	7.4

Treatment of superficial or non muscle-invasive bladder cancer

At first diagnosis, 71% of the patients had non muscle-invasive primary bladder cancer, 73% in males and 64% in females. Seventy percent of the non muscle-invasive cancers were non-invasive papillary carcinomas (Ta or stage 0a), while 30% were cancers invading the subepithelial connective tissue only (T1 or stage I). Flat tumours (carcinoma in situ or stage Tis) represented five percent of the non muscle-invasive cancers. Initial treatment of bladder cancer in the Netherlands according to stage is shown in Figure 1. The vast majority of patients with non muscle-invasive cancers received TUR-BT (with or without instillations) (Tis 94%, Ta grade 1-2 99%, Ta grade 3 97%, Ta grade unknown 96%; T1 grade 1-2 96%, T1 grade 3 90%, T1 grade unknown 91%). Cystectomy was performed in 1.5% of the patients in stage Tis, <0.5% in stage Ta and 2% in low and medium grade T1-tumours. The treatment remained unknown in 4% of patients (Tis 4%, Ta grade 1-2 1%, Ta grade 3 1%, Ta grade unknown 4%; T1 grade 1-2 1%, T1 grade 3 1%, T1 grade unknown 3%). High grade T1-tumors were diagnosed in 3043 patients (53% of all T1 tumors). Seven percent of T1G3 tumors underwent a cystectomy, and 2% received radiotherapy. A multivariate regression analysis revealed cystectomy to be performed significantly less in older patients ($\geq$75 yr; OR 0.2, $p = 0.000$) and more frequent in region 7 (OR 1.82, $p < 0.0035$) in stage T1G3.

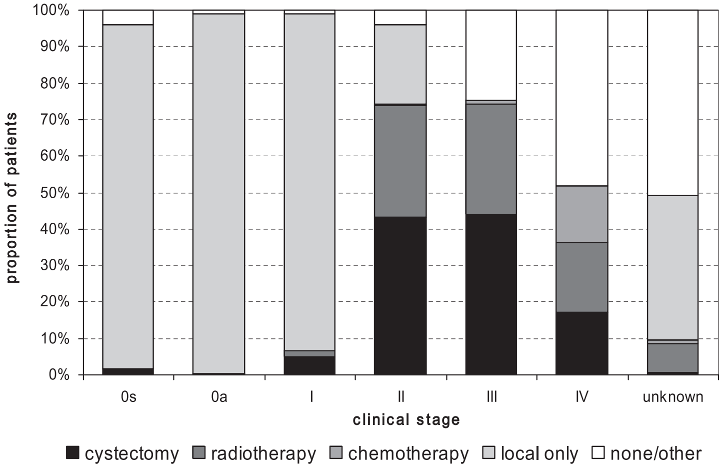

Figure 1. Treatment of newly diagnosed patients with bladder cancer according to clinical stage, the Netherlands 2001-2006.

Treatment of muscle-invasive bladder cancer

Almost 8000 patients with MIBC were diagnosed in 2001-2006 (on average 1300 annually). A cystectomy was performed in 36% of all muscle-invasive cases. In stage II 43% underwent a cystectomy, 31% received radiotherapy, <1% chemotherapy and 26% of the patients received only local treatment or no treatment. 44% of stage III patients underwent a cystectomy, 31% received radiotherapy, 1% chemotherapy, and 25% received only local treatment or no treatment. 17% of newly diagnosed patients with stage IV underwent cystectomy, while 19% received radiotherapy and 16% with chemotherapy. 48% of the stage IV patients received no therapy or only local treatment.

An increasing proportion of stage II patients underwent cystectomy, from 39% in 2001 to 47% in 2006, but remaining more or less constant in stage III (39% cystectomies in 2001 and 38% in 2006). Utilization of radiotherapy decreased from 34% to 27% in stage II and from 36% to 30% in stage III.

Figure 2 shows that the proportion of patients undergoing cystectomy for muscle-invasive cancer strongly decreased with age. In a multivariate analysis the OR of patients of 60-74 yr versus <60 yr was 0.49 ($p = 0.000$) and the OR of ≥75 yr versus <60 was 0.06 ($p = 0.000$). Radiotherapy was more often administered in older patients (60-74 yr, OR 2.0, $p = 0.000$; ≥75 yr, OR 5.2, $p = 0.000$). The chance of having one of both treatments declines with increasing age (60-74 yr, OR 0.65, $p < 0.002$; ≥75 yr, OR 0.18, $p = 0.000$).

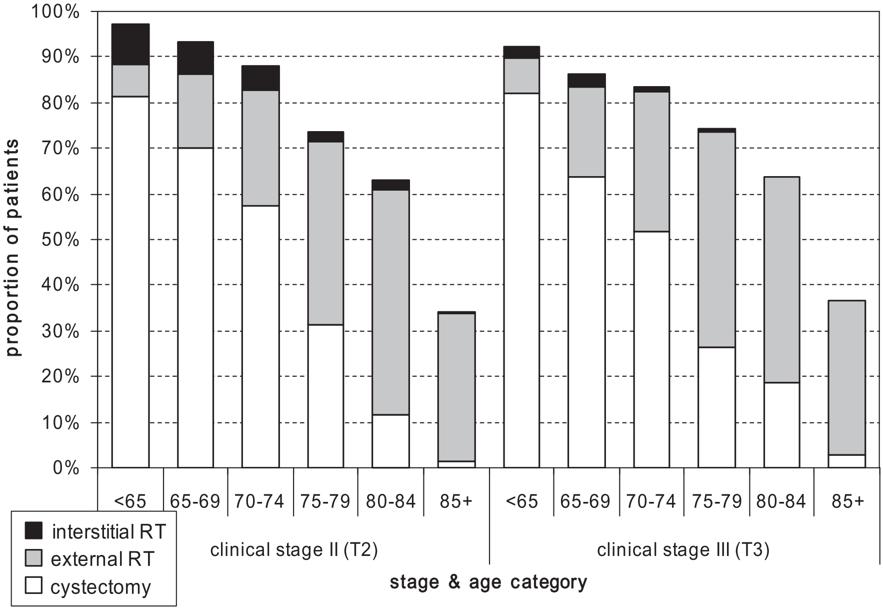

Figure 2. Proportion of clinical stage IIeIII bladder cancer patients treated with cystectomy or radiotherapy according to age category, the Netherlands 2001-2006. Interstitial radiotherapy may also be preceded by a short external radiotherapy session.

Patients were more likely to undergo a curative treatment in stage III than for stage II (OR 1.6, p = 0.000). More cystectomies were performed in comparison to radiotherapy (stage III: OR cystectomy 1.5, p = 0.000 vs. radiotherapy 0.99, p < 0.9) (Figure 3). Women more often underwent cystectomy (OR cystectomy 1.2, p < 0.016; OR radiotherapy 0.75 (p = 0.000)), contrasting radiotherapy for men.

The likelihood for receiving a specific kind of treatment is not dependent on the type of hospital where the initial diagnosis was made. The availability of a radiation department in the hospital of diagnosis did not affect the likelihood for receiving radiotherapy. However, there are strong regional preferences for specific treatments as shown for patients with stage II disease (Figure 3). Among patients below 75 yr of age 60-77% underwent cystectomy in the various regions, and 10-28% underwent radiotherapy. The chance of undergoing a cystectomy in stage II-III disease was higher in region 2, 3 and 6 in comparison to region 1 (OR 1.4, p < 0.005; OR 1.9, p = 0.000 and OR 1.3, p < 0.024). The chance of undergoing radiotherapy in stage

II-III disease was lower in region 2, 3, 6, and 8 in comparison to region 1 (OR 0.8, $p < 0.016$; OR 0.6, $p = 0.000$, OR 0.8, $p < 0.031$ and OR 0.7, $p < 0.035$, respectively). The differences in radiotherapy mainly followed differences in the application of interstitial radiotherapy (brachytherapy): the regions with a high percentage of radiotherapy were the same as those performing brachytherapy more often (region 1 and 7). In two regions (region 4 and 9) a curative treatment was performed clearly less often (OR 0.7, $p < 0.009$; OR 0.6, $p = 0.000$) than in other regions.

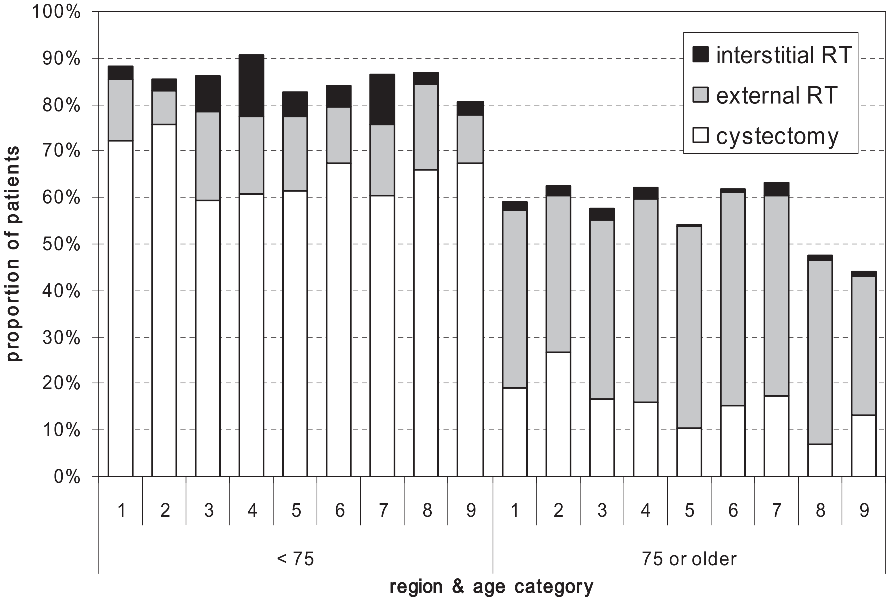

Figure 3. Regional variation in treatment of clinical stage II bladder cancer patients according to age and comprehensive cancer centre region, the Netherlands 2001-2006.

Cystectomy

Between 2001 and 2006 the total annual number of cystectomies increased 23% (from 472 to 585). Eleven percent of the cystectomies were performed in clinically non-muscle invasive disease, 77% were in clinical stage II or III (T2-T4a). Twelve percent were clinical stage IV. The proportion of clinically potentially understaged patients ranged from 44% in clinical stage I, 48% in stage II and 22% in stage III (Table 2). The proportion of clinically overstaged patients ranged from 12% in clinical stage III and 21% in clinical stage IV (Table 2).

Sixty percent of the operations were performed in community hospitals. The contribution of specialized centers was slightly increasing from 13% in 2001 to 18% in 2006. Forty-four hospitals performed an average of five or less cystectomies a year, accounting for 21% of all patients. Thirty-six hospitals performed an average of 6-10 operations a year, comprising 46% of all cystectomies in 2006. Another 13 hospitals performed more than 10 cystectomies a year (Figure 4). The proportion of patients being operated in these high-volume hospitals increased from 32% in 2001 to 36% in 2006.

Table 2. Pathological stage after cystectomy according to clinical stage of patients with bladder cancer in the Netherlands 2001-2006.

Clinical stage	Pathological stage														
	Tis		Ta		I		II		III		IV		unknown		Total
	n	%	n	%	N	%	n	%	n	%	n	%	n	%	
Tis	13	87	-	-	2	13	-	-	-	-	-	-	-	-	15
Ta	1	2	35	85	1	2	2	5	0	0	1	2	1	2	41
I					173	56	61	20	49	16	27	9	-	-	310
II					48	2	958	49	643	33	299	15	-	-	1948
III					5	1	57	11	340	66	112	22	-	-	514
IV					2	1	23	6	52	14	291	79	-	-	368
unknown					-	-	-	-	-	-	-	-	3	100	3

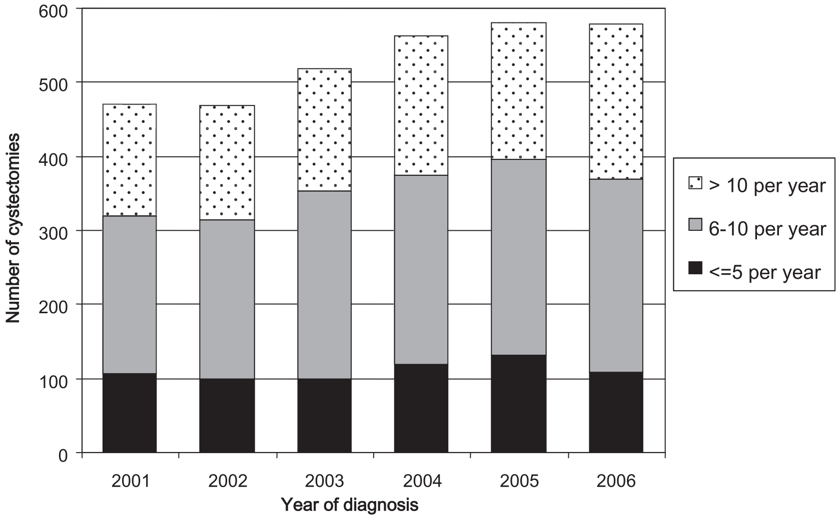

Figure 4. Number of patients who underwent cystectomy according to average annual number of cystectomies per hospital, the Netherlands 2001-2006.

Lymph node dissections were performed in 79% of all cystectomies (Table 3), more often in specialized centers in comparison to the community hospitals (OR 2.7; p ≤ 0.000), and significantly more often in median and high-volume hospitals (81% and 82%) in comparison to low-volume hospitals (71%) (OR 1.47 (6-10/yr) and OR 1.52 (≥10/yr) vs. low-volume hospitals; p = 0.027, and p = 0.043).
The overall 30-days mortality rate after cystectomy in 2004-2006 was 3.4% (Table 3). This rate rose with increasing age of the patient from 1.1% below the age of 60 to 3.1% for 60-74 yr and 7.4% for patients 75 yr or older. In the high-volume centers the mortality rate was significantly lower (1.2%; OR 0.2 vs. low-volume hospitals; p = 0.002). Mortality rates after 60 and 90 days were higher (all hospitals combined 5.7% and 7.7% and high-volume 3.1% and 4.9%), but the relative difference in mortality rate between the high, medium and low-volume hospitals remained unchanged.

Table 3. Relation of average annual volume of cystectomy with lymph node dissection and 30 day-mortality rate in newly diagnosed patients with bladder cancer in the Netherlands, 2004-2006.

Average volume	Proportion of lymph node dissections	30 day (60 day) mortality rate
≤5 per year	71%	6.4% (8.6%)
>5-10 per year	81%	3.6% (6.4%)
>10 per year	82%	1.2% (3.1%)
Total	79%	3.4% (5.7%)

Discussion

This paper summarizes the major variations in treatment policies in the period 2001-2006 for different regions and hospital types in the Netherlands. Remarkable regional differences in the choice of primary treatments were found. Availability of interstitial radiotherapy (brachytherapy) explained much of the variation in frequency of radiotherapy use in both stage II and III disease, with subsequent lower cystectomy rates in these regions (Figure 3). Nevertheless, in two regions curative treatment options (radiotherapy or cystectomy) were clearly used less often than in other regions, suggesting disparities in the chance of receiving optimal treatment for patients with bladder cancer.

No difference in choice of treatment was found in the three different types of hospitals (academic hospital, training hospital or community hospital). Lymph node dissection and mortality rates in cystectomy procedures differed with hospital volumes. Patients in high-volume centers exhibited lower mortality rates than in low-volume centers.

American and European guidelines indicate that a patient with a pT1G3 tumor should initially receive BCG intravesical therapy, although cystectomy can be considered [4,12,13].

The majority (90%) of patients with the high grade T1-tumours in our study received initially local therapy only (TUR-BT with BCG-instillations). We may conclude that this is in accordance with the current guidelines.

Radical cystectomy is considered the ‘golden standard’ for stage II and III (muscle-invasive) bladder cancer, being reinforced by recent updates of European and Dutch guidelines [4,14]. In view of these guidelines the low number of cystectomies for stage II–III MIBC cancer patients (44%) was remarkable. Even in MIBC patients below 75 years the number of cystectomies was low (stage II 65%; stage III 68%), but seems to increase over time.

However, our data is similar to a recent Swedish population-based study. The curative intent for patients with clinical stage T2-T4 bladder cancer was 41% (by means of radiotherapy (8%) or cystectomy (33%)). For patients younger than 75 yr, the curative intent of total treatment arm was 62% [15]. In comparison to the Swedish study, the Dutch percentage of cystectomy was slightly higher, moreover increasing with 8% over this study period.

Our study shows that high procedure volume for cystectomy was statistically significant and is associated with lower post-operative mortality, especially related to that in hospitals with a procedural annual volume of ≤5 cystectomies, where a 30 day-mortality of 6.4% was found. In the Netherlands there are 44 of these low-volume hospitals and together they perform 111 cystectomies a year (21% of all patients). A third of the patients (36%) underwent cystectomy in high-volume hospitals, which have a significantly lower mortality (1.2%), while most patients (46%) are operated in medium-volume hospitals with annually 6-10 cystectomies and a mortality rate of 3.6%.

Mounting evidence suggests that high procedure volume of complex operations is related with lower operative mortality after high-risk cancer surgeries (cystectomy, esophagectomy, pancreatectomy, etc.) [16,17], but the difference might partly be affected by selective referral of relatively healthy patients of higher SES. Only one Dutch study compared post-operative mortality of patients undergoing cystectomy for low-volume hospitals with an oncologic center [18]. The post-operative mortality was unsignificantly lower in the oncologic center (1.8% versus 3.5%). The present national population-based study is more suggestive because of its power.

Nevertheless, our study has several limitations. Though data on age and gender were available, our study lacks information on co-morbidities and performance status of patients. Though several studies have shown that radical cystectomy is a safe option in elderly fit patients, a poor performance status of patients might jeopardize surgical treatment and lead to a choice for radiotherapy or palliative treatment only [19-22]. A study in two CCC-regions showed co-morbid conditions in elderly patients to affect the choice of treatment (submitted). It could also be the patients preference to choose a bladder sparing approach, although there is no such differential information available within the Netherlands. Then, only the cystectomies six months after first diagnoses were taken into account, so the real cystectomy volume per hospital may be larger. Up to 30% of patients with superficial tumors evolves into ≥T1-tumors [14] of which an unknown percentage will undergo cystectomy. Though a re-biopsy is planned within 6 weeks after local resection for T1 tumors, and will take place within the six months interval after first diagnosis.

In most industrialized countries, medical disciplines, insurance companies and policy makers discuss potential improvements of patient safety and quality of health care [23]. In the literature more and more studies advocate specific volume standards for high risk cancer operations, such as ≥11 cystectomies a year [17,24,25]. In the United States the Leapfrog group, a large coalition of insurance companies encourages patients to have their operation in a high-volume referral center since 2000, but there have been no reports about actual overall improvement in outcome from these volume-based referral initiatives. Apparently, focusing on volume only, which is only a proxy for quality of care, is not enough for improving care-processes and outcome.

Moreover, complex surgical procedures like radical cystectomy have more dimensions than mortality and depend on more than hospital volume alone. Other factors include surgeon's competence, the hospitals infrastructure e.g. quality of critical care units and broad consultant expertise, the implementation of standard pathways and protocols [26].

Most important, the surgical team should be capable to handle all post-operative complications. In addition to post-operative mortality rates, patient outcome can also be measured using complication and recurrence rates, number of resected lymph nodes, surgical margins, survival rate and last but not least by the impact on quality of life [27]. To provide optimal quality of care for patients with muscle-invasive bladder cancer, quality of care indicators could be used for measuring and monitoring one's own performance [28]. The facilitating cancer registries of the Comprehensive Cancer Centers could greatly assist by independently collecting extra clinical data at regional or national scale and provide feedback to attending physicians and possible specific audits undertaken by them.

This paper summarizes the population-based variation in treatment policies for bladder cancer in the Netherlands in the period 2001-2006. Exploring population based cancer registries for differences in patterns of care can give insight in opportunities for improvement and could lead to a change in treatment strategies.

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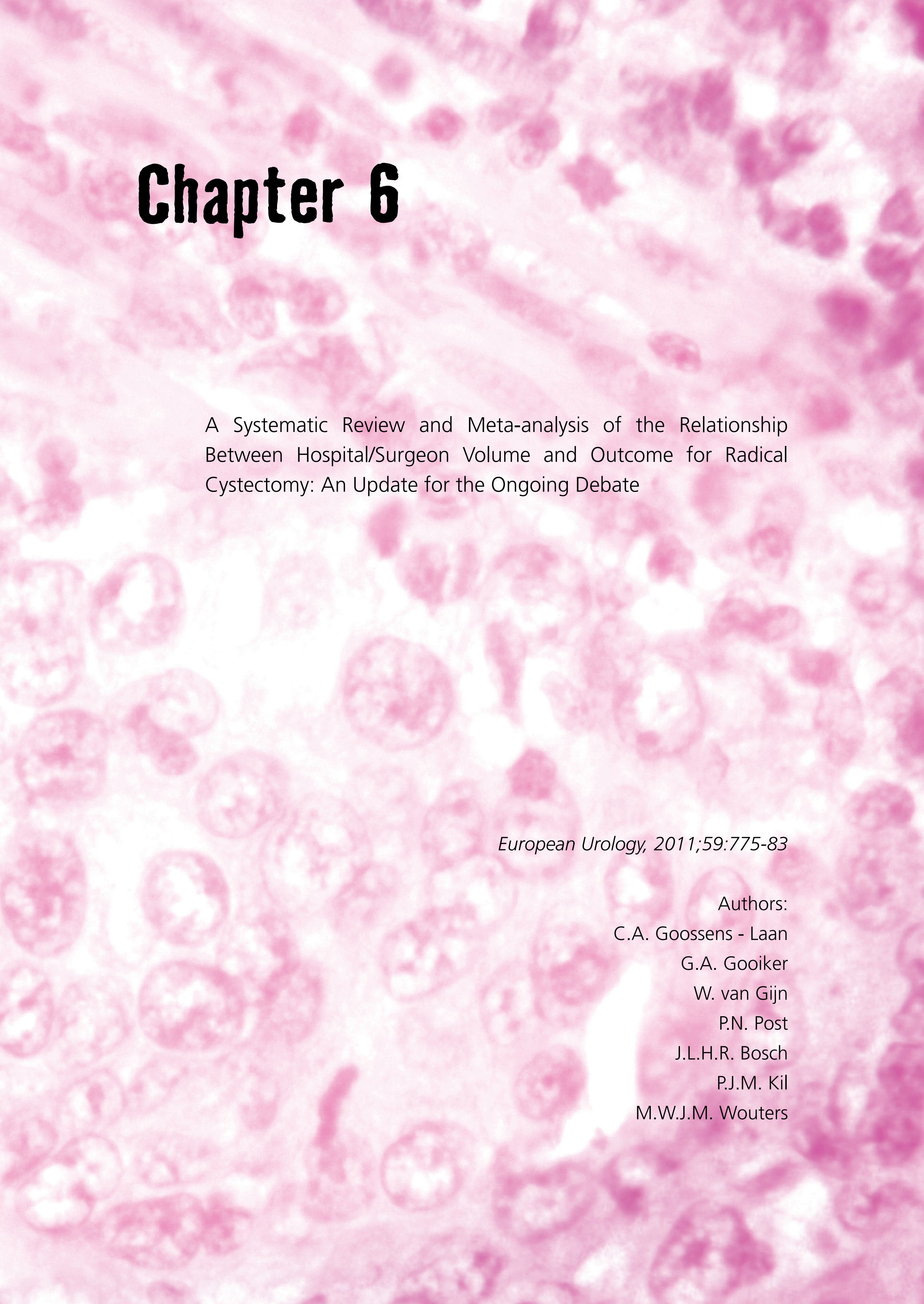

Chapter 6

A Systematic Review and Meta-analysis of the Relationship Between Hospital/Surgeon Volume and Outcome for Radical Cystectomy: An Update for the Ongoing Debate

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Abstract

Context: There is an ongoing debate about centralisation of radical cystectomy (RC) procedures.

Objective: To conduct a systematic review of the literature on the volume–outcome relationship for RC for bladder cancer (BC) with consideration for the methodologic quality of the available evidence and to perform a meta-analysis on the studies meeting predefined quality criteria.

Evidence acquisition: A systematic search was performed to identify all articles examining the effects of procedure volume on clinical outcome for cystectomy. Reviews, opinion articles, and surveys were excluded. All articles were critically appraised for methodologic quality and risk of bias. Meta-analysis was performed to calculate the overall effect of higher surgeon or hospital volume on patient outcome.

Evidence synthesis: Ten studies of good methodologic quality were included for meta-analysis. Eight studies were based on administrative data, two studies on clinical data. The results showed a significant association between high-volume hospitals and low mortality. A meta-analysis of the seven studies on hospital mortality showed a pooled estimated effect of odds ratio (OR) 0.55 (range: 0.44–0.69). The result was moderate heterogeneity (I2 = 50). A large variation in cut-off points used was observed. Sensitivity analyses did not show different effects in any of the subgroup analyses. Also, no significant differences in effect sizes were observed for different cut-off points. The data were not suggestive for publication bias. One study showed a positive effect of hospital volume on survival (hazard ratio [HR]: 0.89; $p = 0.06$). Two studies showed a beneficial effect of surgeon volume on mortality (OR: 0.55; OR: 0.64). Only one study on the impact of surgeon volume on survival was found; it showed no significant positive effect for higher volume (HR: 0.83; $p = 0.26$).

Conclusions: Postoperative mortality after cystectomy is significantly inversely associated with high-volume providers. However, additional quality criteria, such as infrastructure and level of specialisation, should be formulated to direct centralisation initiatives. The Dutch Association of Urology in 2010 implemented a national quality of care (QoC) registration programme for all patients treated by surgery for muscle-invasive BC, including multiple parameters defining QoC.

Introduction

Quality improvement of health care is currently a much-debated issue with high political impact on health care governance in many countries. An important concern is whether cancer care should be centralised in specialised "high-volume" hospitals, especially for high-risk, low-volume procedures. In the Netherlands, which has a population of 16 million, 5100 new cases of bladder cancer (BC) are diagnosed each year, of which 30% are present as muscle-invasive BC [1]. The gold standard therapy for BC is radical cystectomy (RC), which has inpatient postoperative mortality rates between 0.7% and 8% [2,3] and postoperative morbidity in 64% of the patients [4]. With approximately 600 RC procedures per year being performed in 97 hospitals in the Netherlands, RC qualifies not only as a high-risk but also a low-volume procedure. Many studies have showed significantly different mortality and survival rates between high- and low-volume providers [5,6]. In these studies, it is suggested that high-volume hospitals have better infrastructure characteristics, and high-volume surgeons have more experience, resulting in better outcomes (the "practice makes perfect" theory). Volume is seen as a proxy for high quality of care (QoC), and the expectation is that centralisation of services with high-volume providers could improve outcome for many patients. This idea has led to the introduction of minimal volume standards for high-risk procedures, such as oesophageal resections for cancer.

There is also evidence of an association between volume and outcome in cystectomy procedures for invasive BC [2,7–10]. Dutch centralisation initiatives for cystectomies are under consideration, but specific minimal volume standards are under debate.

Although the evidence on the volume–outcome relationship for the treatment of cancer seems convincing, there is solid criticism on the methodologic quality of many of these studies [5,11]. Most studies are based on administrative rather than clinical data and do not allow risk adjustment for differences in case mix between low- and high-volume providers. Moreover, a specific minimal volume standard cannot be identified [12]. However, in past years, more studies have been published on this subject, accounting for the above-mentioned limitations.

The purpose of this study was to contribute to the debate by conducting a systematic review of the literature on the volume–outcome relationship in cystectomies for BC, with consideration for the methodologic quality of the studies performed. In addition, we performed a meta-analysis on the studies meeting predefined quality criteria to analyse the strength of the association.

Evidence acquisition

Systematic search strategy

A specialised librarian and two of the investigators (GG, CG) performed a systematic search in PubMed, Embase, and the Cochrane Library to identify all relevant studies describing the association between hospital or surgeon volume and clinical outcomes. Because volume is not well indexed, a combination of Medical Subject Headings (MeSH) terms and free-text words was used (Table 1). Reference lists of relevant articles were hand-searched to identify additional articles, and the "related articles" function in PubMed was used. The last search was on 1 September 2010.

After combining the electronic library results and removing duplicates, 2112 studies remained for the primary selection. After screening, 79 studies had the (surgical) treatment of BC as the study subject.

Study selection

Two reviewers (GG and CG) independently screened titles and/or abstracts of all retrieved articles. Studies were selected using the following inclusion criteria: (1) The subject of the study is cystectomy for BC, (2) hospital or surgeon volume is reported as a variable, (3) the outcome parameter is postoperative mortality or survival, (4) the study describes multiple hospitals or surgeons, and (5) the study uses primary data (eg, editorials and systematic reviews were excluded). After the first selection, articles were obtained in full text and were further selected using three exclusion criteria. First, if multiple publications were based on the same database, the study with the highest methodologic quality was selected. In case of similar quality, the publication with the most recent study period was selected. Second, multivariate analysis had to be corrected at least for gender and age. And finally, volume had to be defined as a distinct number or cut-off value (eg, studies that defined volume as "specialisation" were excluded).

Table 1. Search terms used in the search in the databases PubMed and Embase

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Medline (PubMed)
Search 1:
(hospital volume OR surgeon volume OR surgical volume OR workload OR caseload OR procedure volume OR procedural volume)
AND
(surgical complications OR Postoperative Complications[MeSH] OR mortality OR ((Survival Rate[MeSH] OR Survival[MeSH]) OR Disease-Free Survival[MeSH]) OR Mortality[MeSH] OR Neoplasm Recurrence, Local[MeSH] OR Recurrence[MeSH] OR treatment outcome[MeSH] OR treatment outcome)
AND
(cystectomy [MeSH] OR bladder cancer OR cystectomy OR Urinary Bladder Neoplasms[MeSH] OR Urinary Bladder Neoplasms) OR ((urinary bladder neoplasms[MeSH Terms] OR urinary bladder neoplasms[All Fields] OR (bladder[All Fields] AND cancer[All Fields]) OR bladder cancer[All Fields]) AND volume[All Fields])
Search 2:
Bladder cancer AND volume
Embase
Search 1:
hospital volume.mp. OR surgeon volume.mp. OR workload.mp. OR Workload/OR caseload.mp. OR procedure volume.mp.
AND
surgical complications.mp. OR postoperative complications.mp. OR exp Postoperative Complication/OR Mortality/OR mortality.mp. OR exp Survival Rate/OR exp
Survival/OR survival.mp. OR exp Cancer Recurrence/OR neoplasm recurrence.mp. OR treatment outcome.mp. OR exp Treatment Outcome/OR surgical mortality.mp. OR exp Surgical Mortality/OR exp recurrent disease/or exp tumor recurrence/OR exp cancer survival/OR disease free survival.mp. or exp
Disease Free Survival/
AND
bladder cancer/OR exp bladder cancer/OR cystectomy.mp. OR exp cystectomy/
Search 2:
bladder cancer AND volume

MeSH = Medical Subject Headings.

Assessment of study quality and data extraction

Each study in the final selection was critically appraised following the Strengthening the Reporting of Observational Studies in Epidemiology criteria for study characteristics and methodologic quality. For each volume group, crude and adjusted outcomes were recorded for postoperative mortality and survival. Parameters for adjusted outcomes were expressed as odds ratios (OR) or hazard ratios (HR) with confidence intervals (CI) and p values.

The following characteristics were collected from each study: hospital or surgeon volume, the study period, and the number of analysed patients, hospital and surgeon names, and country. In addition, we assessed the quality of the data source (administrative or clinical data), the study design, and the degree of risk adjustment. We noted the case mix factors for which statistical adjustment was made. Case mix factors were categorised as age and gender; comorbidities; severity (tumour stage and grade); and (neo)adjuvant treatment or urgency (selective or acute admission/operation). Because patients treated at the same hospital or by the same surgeon may be more likely to experience similar outcomes, if surgical technique or supportive care practices varied among providers and these factors affected outcomes, we also checked whether the analysis accounted for clustering of outcomes [13]. We checked the inclusion criteria of the study to verify whether there was a probability of selection bias, as well.

Cut-off values for high and low volume used by the studies were noted per volume group along with how these cut-off values were determined. It was not possible to categorise the volume groups of all studies in volume categories because there was large variation in cut-off values.

Evidence synthesis

Data was analysed using Comprehensive Meta Analysis Professional v.2.2 (Biostat, Englewood, NJ, USA). Pooled estimated effect sizes were calculated using the adjusted outcomes of the highest-volume group as opposed to the lowest-volume group (reference). If the highest group was used as the reference, results were recalculated (1/effect size) to fit the statistical model. For each study, only one comparison was included. As a result, the OR of mortality or the HR of survival reflected the odds of mortality in the highest-volume group compared to the odds of mortality in the lowest-volume group. The random effect model was used to account for expected heterogeneity when pooling observational studies [14].

Heterogeneity was quantified by the I^2 test. An $I^2 > 50$ was considered notable heterogeneity [15]. Sensitivity analysis for hospital volume was conducted to further explore heterogeneity and assess the impact of subgroups (data source, case mix adjustment, study country, clustering of death, and type of definition used for mortality). Publication bias was assessed for meta-analyses with more than three studies with an Egger's regression intercept [16].

Results

Study characteristics

Our search retrieved 79 articles concerning the surgical treatment of BC. A total of 55 studies were excluded, because they examined other outcome parameters (18 studies), did not contain primary data (17 studies), described the results of a single institution or surgeon (9 studies), did not provide hospital or surgeon volume as an independent variable (8 studies), or examined a broader subject than cystectomy (ie, treatments of all BC, cystectomy combined with radiation therapy; 3 studies).

After the first selection, the remaining 24 studies underwent a more detailed evaluation. A total of nine studies were excluded because of duplicate publication from an identical database. A partial overlap between two databases was found regarding the Medicare database and the Nationwide Inpatient Sample [2,10,17,18]. However, because excluding these two studies would have resulted in loss of information, we decided not to exclude them but instead to perform a sensitivity analysis to examine the effect of including partially duplicated information. Five other studies were excluded because no multivariate risk adjustment was made (four studies) or because there was a hospital bias (one study).

Table 2 shows the characteristics of the remaining 10 studies [2,7–10,17–21]. Seven studies were included with hospital volume as the defined variable, two studies were included with surgeon volume as the independent factor, and one study was included with both hospital and surgeon volume as an independent factor. Six studies originated from the United States, two from the United Kingdom, one from Canada, and one from the Netherlands.

The definitions of high- or low-volume groups differed substantially (Table 2). Cut-off values for the highest-volume strata varied between minimal volumes of 4 to 24 procedures each year. The cut-off values of the lowest-volume strata were a maximum of one to nine procedures each year.

Table 2. Characteristics of all studies included in the meta-analysis

Author	Unit	Low	High	Period	Patients	Country	Data source	Data type	Casemix	Mortality %	Survival % (yr)	Definition Mortality
Birkmeyer 2002 [7]	Hospital	1	12	1994-1999	22349	USA	Medicare **	Administrative	CM,C,U	5.0		inpatient and 30 days
Birkmeyer 2003 [8]	Surgeon	1	4	1998-1999	6340	USA	Medicare **	Administrative	CM,C,U	4.6		inpatient and 30 days
Birkmeyer 2007 [9]	Hospital	3	8	1992-2002	2513	USA	Medicare **	Administrative	CM,C,S,U		37.2 (5)	
Elting 2005 [2]	Hospital	3	11	1999-2001	1302	USA	Texas Discharge dB	Administrative	CM,C	2.2		inpatient mortality
Fairey 2009 [19]	Surgeon	4	10	1994-2007	518	Canada	AUI RC-PLN dB	Clinical	CM,S		39 (10)	
Gilbert 2008 [17]	Hospital	2	24	1988-2003	112616	USA	NIS	Administrative	CM,U	2.8		inpatient
Goossens-Laan 2010 [20]	Hospital	5	11	2004-2006	2462	Netherlands	NCR	Clinical	S	3,4		30 days mortality *
Gore 2010 [18]	Hospital	3,5	3,8	2001-2005	27494	USA	NIS	Administrative	CM, C			in-hospital mortality
Hollenbeck 2007 [10]	Hospital	2	6	1992-1999	4465	USA	Medicare **	Administrative	CM,C,S,U	4.5		inpatient and 30 days
Mayer 2010 [21]	Hospital	9	16	2000-2006	8596	UK	HES	Administrative	CM,U	2,9		30 days mortality*
Mayer 2010 [21]	Surgeon	4	9	2000-2006	8323	UK	HES	Administrative	CM,U	2,9		30 days mortality*

dB = database; NCR: Dutch cancer registry; CM= co-morbidity, C- Clustering, S = severity, U = urgency
*30 days mortality accounted for in and outside the hospital
Medicare database: only inclusion of patient 65-99 yrs old.
*** The study of Mayer adjusted for urgency by excluding acute admitted patients; clustering was not adjusted for in model 2 (adjusting for case mix), which is used in this systematic review.

Methodologic quality of the studies

All studies had an observational design, and two used clinical data. All had sample sizes of >500 patients and were population based. However, the Medicare database only contains data on patients >65 yr of age.

In all included studies, the results were risk-adjusted for age and gender, with all but one adjusted for comorbidity. The majority (9 of 10) were adjusted for urgency of the operation, as well. Four studies were adjusted for stage and another four for (neo) adjuvant treatment. Clustering of outcomes was accounted for in six studies.

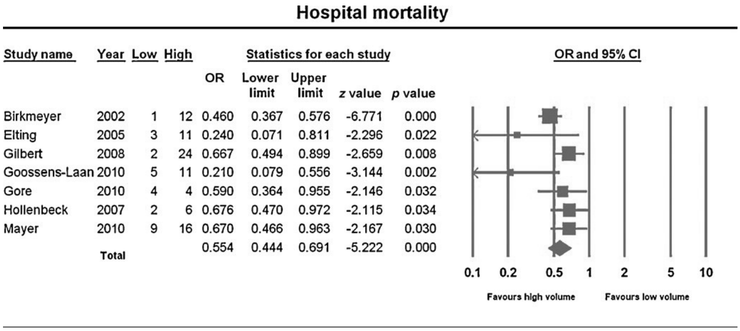
Hospital volume and outcome

Seven studies [2,7,10,17,18,20,21] regarding the association of hospital volume with postoperative mortality after cystectomy were included in the meta-analysis. The perioperative mortality varied from 2.2% to 5.0%. All studies showed a beneficial effect of hospital volume on mortality. All studies showed statistically significant differences. A single study [9] focused on the effect of hospital volume on survival, showing a trend towards better survival in high-volume hospitals, although this result was not statistically significant (HR: 0.89; 95% CI, 0.79–1.00; p = 0.06).

Pooled estimated effect size for hospital volume and mortality

Figure 1 shows the forest plot of the included studies regarding hospital volume and mortality. The pooled estimated effect was significantly in favour of the high-volume providers (OR: 0.55; 95% CI, 0.44–0.69). The analysis of the pooled effect sizes was statistically moderately heterogeneous ($I^2 = 50$).

The results of the sensitivity analysis were not sensitive to differences in any of the variables (comorbidity, country, data source, stage, urgency of the operation, and clustering). Neither were differences in definition used for mortality of influence (p = 0.79). Meta-regression failed to identify a relation between the cut-off point used and the strength of the relationship (Figure 2a and b). The effect size for studies using an upper cut-off point of 10 or 11 did not significantly differ from studies using 4 or 6 (slope for fixed effect size: p = 0.4 for >10 cystectomies per year, p = 0.3 for >4 cystectomies per year). A sensitivity analysis with exclusion of the two articles with partial overlap [10,18] did not change the effect size notably (OR: 0.51; 95% CI, 0.37–0.70).



Study name	Year	Low	High	OR	Lower limit	Upper limit	*z* value	*p* value
Birkmeyer	2002	1	12	0.460	0.367	0.576	-6.771	0.000
Elting	2005	3	11	0.240	0.071	0.811	-2.296	0.022
Gilbert	2008	2	24	0.667	0.494	0.899	-2.659	0.008
Goossens-Laan	2010	5	11	0.210	0.079	0.556	-3.144	0.002
Gore	2010	4	4	0.590	0.364	0.955	-2.146	0.032
Hollenbeck	2007	2	6	0.676	0.470	0.972	-2.115	0.034
Mayer	2010	9	16	0.670	0.466	0.963	-2.167	0.030
Total				0.554	0.444	0.691	-5.222	0.000

Figure 1. Forest plot of the included studies on hospital volume and postoperative mortality. OR = odds ratio; CI = confidence interval.

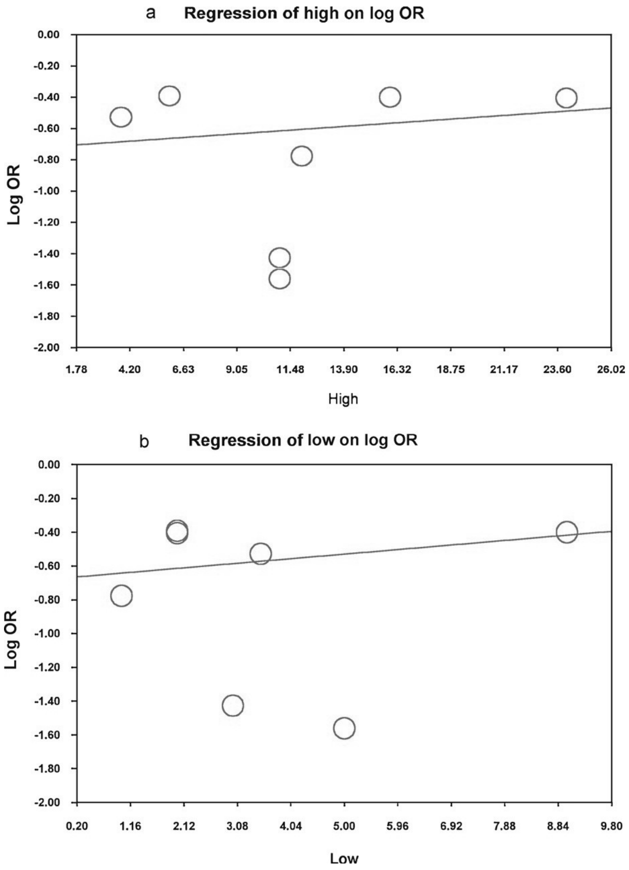


Figure 2. Meta-regression analysis on (a) high cut-off points for hospital volume (minimum number of cystectomies used) and (b) low cut-off point for hospital volume (maximum number of cystectomies used). OR = odds ratio.

Risk of publication bias

Figure 3 shows the qualitative analysis of publication bias of all studies regarding hospital volume and mortality using ORs. The data were not suggestive of publication bias.

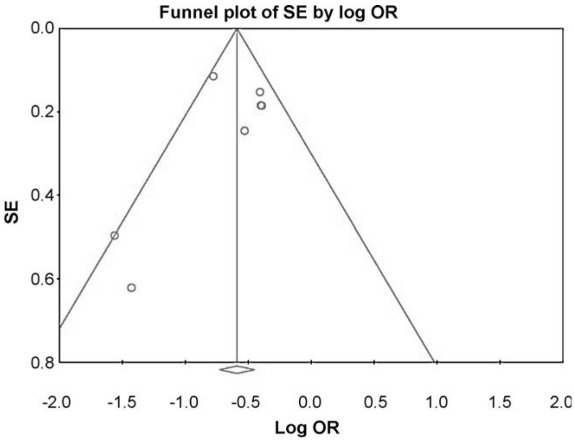


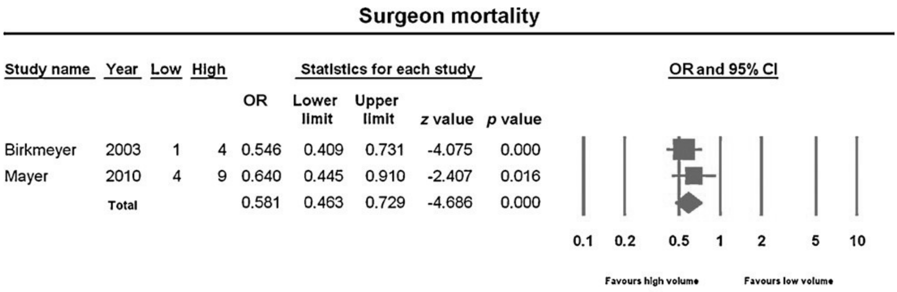
Figure 3. Analysis of risk of publication bias: funnel plot of studies included in meta-analysis on hospital volume and mortality using odds ratios. Quantitative analysis with the Egger's regression intercept showed an intercept of S1.0 with a two-sided p value of 0.45. The diagonal lines represent the 95% confidence interval (CI) around the overall effect estimate, which is indicated by the vertical line. The effect of each study is marked by a circle. Uneven distributions of the studies around 95% CI line should suggest the presence of publication bias, which is not the case in this funnel plot. Additionally, no studies lie outside this line providing evidence of such bias. In the lower left corner, negative or null studies are located; as this is not empty, again there is no potential for publication bias [14].
SE = standard error; OR = odds ratio.

Surgeon volume and outcome

Two studies [8,21] concerning surgeon volume and postoperative mortality showed a significant effect in favour of high-volume surgeons (OR: 0.55, 95% CI, 0.41–0.73 and OR: 0.64; 95% CI, 0.44–0.91, respectively). Only one study [19] was found on surgeon volume and survival; it did not show a significant effect (HR: 0.83, 95% CI, 0.6–1.14; p = 0.26).

Pooled estimated effect size for surgeon volume and mortality

Figure 4 shows the forest plot of the two studies regarding surgeon volume and mortality. The pooled estimated effect is significantly in favour of the high-volume surgeons (OR: 0.58; 95% CI, 0.46–0.73). The analysis of the pooled effect sizes was statistically moderately heterogeneous (I^2 = 50). The sensitivity analysis for surgeon volume and mortality could not be performed, as only two studies on this subject were included in our meta-analysis.



Surgeon mortality

Study name	Year	Low	High	Statistics for each study					OR and 95% CI
				OR	Lower limit	Upper limit	*z* value	*p* value	
Birkmeyer	2003	1	4	0.546	0.409	0.731	-4.075	0.000	
Mayer	2010	4	9	0.640	0.445	0.910	-2.407	0.016	
Total				0.581	0.463	0.729	-4.686	0.000	

Figure 4. Forest plot of the included studies on surgeon volume and postoperative mortality. OR = odds ratio; CI = confidence interval.

Conclusions

This systematic review and meta-analysis examined the effect of surgeon and hospital volume on the outcomes of RC procedures. It showed a strong inverse relationship between high-volume providers and postoperative mortality (inpatient and/or 30 d). For the relationship between procedural volume and long-term survival, the available literature was more limited, and only a trend for higher survival in high-volume settings was found.

Our study is the first meta-analysis on the relationship between procedural volume and outcome of cystectomies for cancer that includes studies from outside the United States. Since the last review dating from 2007, four new studies could be included, originating from Canada, the Netherlands, and the United Kingdom, making this the most up-to-date and extensive review available. Two previous systematic reviews (one with a meta-analysis) assessed the quality of the volume–outcome relationship in uro-oncology, looking at radical prostatectomies and nephrectomies in addition to cystectomies [22,23]. Our study is limited to RC procedures, although it investigates the relationship of hospital and surgeon volume on the one hand and postoperative mortality and survival on the other. In addition, we performed a sensitivity analysis, and the risk of publication bias was assessed.

All studies included in our review had an observational design, and it was challenging to deal with the heterogeneity of the eligible studies. To reduce heterogeneity, strict inclusion criteria were applied; only studies that were at least risk-adjusted for age and gender were included. The observed heterogeneity could not be explained by the type of database (administrative or clinical data), comorbidity, severity, treatment, urgency, or clustering, as shown in the sensitivity analyses. However, other factors, especially structural and process of care measures among the hospitals, seem to play a role. For example, Elting et al reported that hospitals with a high registered nurse-to-patient ratio also had a lower mortality risk. Mayer et al concluded the same and reported that a higher ratio of staffing levels of urology registrars, a shorter waiting time to surgery, and the teaching status of the hospital all accounted for lower mortality rates [2,21].

Included studies were based on administrative (n = 8) as well as clinical data (n = 2), with one clinical study even accounting for 100% of the national population [20]. The fact that four recent studies from outside the United States could be added to our review improved the generalisability of the study results.

In spite of the heterogeneity observed in the analysis, all individual estimates pointed to a substantial reduction in mortality risk among higher-volume hospitals. Therefore, not the size but the direction of the effect appeared consistent. Although a causal relationship cannot be concluded on the basis of this analysis [24,25], recommendations on minimal provider volumes are tentative. Unfortunately considerable differences in cut-off values for volume categories among the included studies were observed. High volume in one study was considered low volume in another and vice versa, and this disparity may have influenced our results. Because of these differences, it was not feasible to identify a specific minimum volume cut-off from the included studies; meta-regression failed to identify a relationship between the cut-off point used and the strength of the relationship. Moreover, the effect size for studies using an upper cut-off point of 10 or 11 did not significantly differ from studies using 4 or 6 as the high threshold. Unfortunately, no studies were identified that analysed volume as a continuous variable.

The fact that we did quite a few subgroup and meta-regression analyses might be criticised, given the small number of studies in the analyses. However, we interpreted the results of these analyses with caution. Moreover, investigation of the specific clinical differences among studies is generally preferred rather than relying on a statistical test for heterogeneity [15].

The outcomes of the present study have not been influenced by differences in the definition of mortality, as shown by the sensitivity analysis ($p = 0.79$). This finding is endorsed by Birkmeyer et al, who analysed both 30-d mortality and in-hospital mortality and performed repeat analyses using 30-d mortality alone. This effort showed that the associations between volume and outcome were largely unchanged [7], making this metric of limited influence.

The fact that we included two studies [7,17] that partly used the same database as two other studies [10,18] may also be criticised. However, because these studies only had partial overlap, excluding them would have resulted in significant loss of information. Moreover, a sensitivity analysis without the articles of Hollenbeck and Gore barely changed the effect size.

Acknowledging these limitations, the results of our meta-analysis provide evidence that with high-volume providers, the outcome of the performed cystectomies is superior to those performed by low-volume providers. An explanatory theory for the volume–outcome relationship was proposed by Luft et al. [26], who described two theories to explain the association: the practice makes perfect theory and the selective referral theory. Besides the practice makes perfect theory, it is likely that volume is an indirect indicator for other important quality characteristics of health care providers. For example, the availability of a dedicated multidisciplinary infrastructure (urology, radiology, pathology, intensive care) could have an important effect on the outcome for individual patients [27]. Hollenbeck et al. [10] showed that there are substantial differences in the perioperative care process for patients undergoing a cystectomy in high- and low- volume hospitals, especially with regard to the extent of the resection and the use of invasive monitoring techniques during and after the operation. In their study, these differences in the care process explained 23% of the volume–outcome relationship. However, the primary mechanisms remained unclear.

The selective referral theory assumes that hospitals and surgeons with superior results attract more patients. This theory could also explain our findings. With increasing transparency of the QoC provided by different hospitals, physicians can refer their patients to hospitals and surgeons with demonstrably good results. Patients are better informed and increasingly able to choose where they might receive optimal treatment. In contrast, Mayer et al showed that in the United Kingdom, where selective referral is less likely to occur, there is still reduced mortality in higher surgeon and hospital volume providers, which suggests that selective referral does not play a key role in the volume–outcome relationship [21].

The results of the present meta-analysis show a clear and consistent relationship between high-volume providers and improved mortality rates and survival. This relationship counts for both high-volume hospitals and high-volume surgeons. As shown by Birkmeyer et al, surgeon volume accounts for a relatively large proportion of the apparent effect of hospital volume (46%) and vice versa (39%) [8]. These facts offer valuable information for professionals as well as policymakers. The findings support the assumption that centralisation of BC treatment has the potential for improving the QoC.

In the United States, the shift of RC procedures to high-volume centres has already largely occurred because of the availability of residents and fellows to help in perioperative care. A second initiative driving referral is related to reimbursement.

However, the question remains whether minimal volume standards for cystectomies actually improve the QoC. As one of the three accepted domains of QoC (structure, process, and outcome), volume is a proxy for better quality but remains a poor predictor of the QoC in individual institutions [28]. With the introduction of minimal volume standards only, there is a risk of selecting hospitals with inferior outcomes that lack the facilities and expertise future referral centres need [29,30]. Therefore, a minimum volume standard should not be the only criterion in the accreditation of cystectomy centres. It is also necessary to take into account the infrastructure of the hospital and its past results. Furthermore, minimum volume standards do not take geographical spread into account and can cause logistic problems [30,31]. Nevertheless, investing in infrastructure for optimal care and maintaining a certain level of expertise within the whole medical team requires a certain number of patients.

Minimum volume standards alone thus seem an inadequate basis for centralisation. Additional quality criteria should be formulated to direct centralisation initiatives. For this purpose, the Dutch Association of Urology implemented a national QoC registration programme for all patients treated by surgery for muscle-invasive BC. As more data are needed to identify essential structural or organisational characteristics, it is of vital importance to measure the amount of care provided in the whole and different parts of the country. Such an audit registration can have direct implications for quality improvement programmes, as the next step is to develop leverage care processes that lead to better outcomes.

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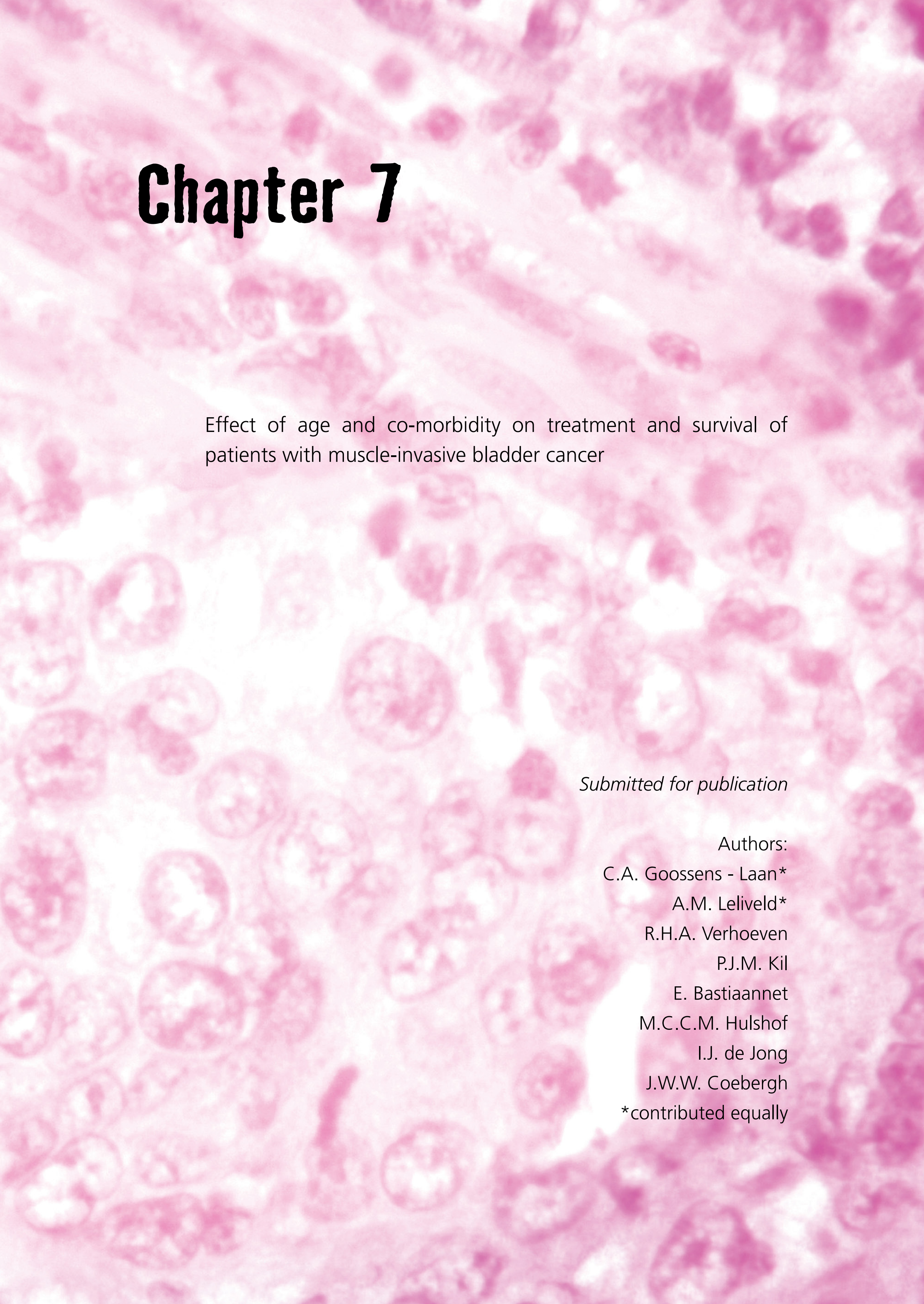

Chapter 7

Effect of age and co-morbidity on treatment and survival of patients with muscle-invasive bladder cancer

Submitted for publication

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Abstract

Introduction: This study assessed whether rising age, socioeconomic status (SES) and presence of serious comorbidity affected treatment choice and survival in a population-based series of patients with muscle-invasive bladder cancer (MIBC).

Methods: All patients diagnosed and registered with MIBC between 1995-2009 in the population-based Eindhoven cancer registry, preceding and coinciding with centralisation of cystectomy in the Netherlands were included. The independent effects of age, SES, and serious comorbidity on therapy choice and overall survival were estimated by multivariate logistic regression and multivariate Cox proportional hazard analyses, respectively.

Results: Of the 2,445 patients 38% were aged ≥75 years at diagnosis; 63% had at least one and 32% had more than one serious comorbid condition. Higher age and serious comorbidity were independent predictors for abstaining from cystectomy (61-74 versus <= 60: OR:0.8; 95%CI:0.6-1.0; >=75 versus <=60: OR:0.1; 95%CI:0.1-0.2; one comorbid condition versus none:OR:0.7; 95%CI:0.5-0.9; two comorbid conditions versus none:OR:0.6; 95%CI:0.5-0.8). Higher age is associated with more external radiotherapy and less interstitial radiotherapy. There is no independent effect of comorbidity on these latter two. Patients with a high SES were more likely to receive IRT. Increasing age, low SES and comorbidity were independent predictors for shorter survival.

Conclusion: Higher age and serious comorbidity were independent predictors for abstaining from cystectomy and decreased overall survival. SES affected treatment selection and survival. Abstaining in elderly patients with serious comorbidity may reflect sound clinical judgment. The question remains whether the good prognosis cystectomy patients also might have had a good prognosis after internal radiotherapy. An alternative opinion may be that radical cystectomy is underutilized in patients >75. Furthermore, it seems logical to investigate new strategies of chemoradiation in this growing group of patients.

Introduction

In the Netherlands, patients aged ≥65 years represent more than 80% of all cases of mortality [1]. In 2008 the most important cause of death was cancer, which accounted for 30% of all deaths. As expected, the prevalence of registered comorbidity in newly diagnosed cancer patients increased with age: 48% for patients aged 50-64 years and up to 80% for those ≥80 years [2]. The prevalence of two or more comorbid conditions also increased with increasing age from 17% to 45%, respectively [2].

In the Netherlands, bladder cancer was the seventh most common cancer in 2010 {www.cijfersoverkanker.nl}. Bladder cancer is predominantly a disease of the elderly with a peak incidence in the seventh decade of life [3]. Serious comorbidity may complicate treatment of bladder cancer. Especially patients with prior cardiac history who undergo radical cystectomy are more likely to develop complications [4]. Furthermore, patients with obstructive pulmonary disease will develop pneumonia more frequently after extensive abdominal surgery. Therefore, the management of bladder cancer in this growing group of elderly is an increasing challenge.

About 20-40% of all patients with bladder cancer will present with or progress to muscle-invasive bladder cancer (MIBC) [5]. For patients with MIBC, radical cystectomy (followed by construction of either a neobladder or an ileal conduit) remains the preferred treatment [5]. This procedure appears to be safe for elderly patients and is even feasible for patients of older age with more comorbidity [3, 6-7]. Although radical cystectomy has been suggested to have a survival benefit for selected elderly patients [8], these patients generally do not undergo this type of surgery due to the higher risk of morbidity and postoperative mortality [9-14]. Furthermore, there is a role for bladder-preserving approaches, either interstitial radiotherapy for selected patients [15] or external (chemo)radiation as alternative to radical cystectomy [16-17]; the aim of these less invasive procedures is to maintain quality of life (QoL) for the elderly while maintaining comparable local control and survival. However, randomised comparison of QoL, progression and survival outcomes between radical cystectomy and bladder-sparing approaches are sparse [16,18]. High socioeconomic status (SES) is also known to affect choice of treatment and give better survival rates for urological cancer [19].

The aim of this study is to assess the impact of age, comorbidity and SES in the choice of treatment and survival for MIBC. In 2010 a volume-based proposal for regionalisation for cystectomy was introduced in the Netherlands, the aim being to improve outcome for MIBC. From 2012 urologists in the various hospitals were required to perform more than 10 cystectomies per year which provoked a change in referral policy, and is likely to result in a change in decision-making. Thus, the present study evaluates the effect of comorbidity on the choice of treatment in a population-based series of patients with MIBC preceding centralisation in the Netherlands.

Methods

Patients

Patients diagnosed with histologically proven urothelial cell carcinoma (transurethral resection or bladder biopsy) with invasion of the detrusor muscle between 1995 and 2009 were obtained from the population-based database of the Eindhoven Cancer Registry (ECR), which covered about 10 medium to large community hospitals in which the number of practising urologists increased from 30 to 40. The nationwide Dutch network and registry of histopathology and cytopathology (PALGA) submits reports of all diagnosed malignancies to the ECR. In addition, the national hospital discharge databank (which receives discharge diagnoses of admitted patients from all Dutch hospitals) completes case ascertainment up to ≥95% [20]. After notification, registration clerks collect data on diagnosis, staging, treatment and comorbidity (diabetes, hypertension, cardiovascular disease, pulmonary disease and any other significant comorbidity) from the medical records, including pathology and surgery reports, and letters from the general practitioner plus current medication data, using a strict registration and coding manual.

Data

Data on vital status (available until 31 December 2011) were obtained from the hospital records and the mortality register of the Central Office for Genealogy (that registers all deaths in the Netherlands via the municipal population registries). Tumour stage was based on pathological information; if pathological information was missing, the clinical information was used. To draw a distinction between various comorbidities a modified Charlson score was used [2]. When no writing on the subject of comorbidity was found in the medical file of the patient, it was registered as not recorded. When comorbidity was not registered, generally due to treatment in a different region, the data was considered missing and these patients were excluded from all analyses (*n*=114). Comorbidity was categorized into none, one, and two or more comorbid conditions per patient. Next to that, subgroups of patients with the comorbid conditions of diabetes, hypertension, and cardiovascular or pulmonary diseases were analysed. No other comorbid conditions were analysed separately. An indicator for socioeconomic status (SES) developed by Statistics Netherlands was used; SES of the patient was defined at a neighbourhood level (based on six-digit postal code of residence area). On average each postal code area contains 17 households, thus covering a very small geographic area. Postal codes were assigned to four SES categories, low, intermediate, high and institutionalized. This latter category contains the postal codes of care-providing institutions, such as a nursing home. Patients for which SES was missing (*n*=41) were excluded from the analyses.

Data were entered into a separate, anonymous, password-protected database. According to Dutch law (www.Federa.org), this means no further approval from an Institutional Review Board was needed.

Statistics

Multivariate logistic regression models were used to assess whether age, SES and comorbidity were independent predictors of the choice for cystectomy, external beam radiotherapy (EBRT) or interstitial radiotherapy in bladder cancer patients, respectively. The models were adjusted for sex, period of diagnosis, SES and tumour stage. ORs (odds ratios) and 95% CI (confidence intervals) were estimated. In addition, the impact of various comorbid conditions were assessed in separate models on the probability of undergoing cystectomy, after adjustment for age, stage, sex and period of diagnosis.

To assess whether age, SES, comorbidity and therapy choice affected overall survival, a multivariate Cox proportional hazard was used to estimate hazard ratios (HR), and 95% CIs). The models were adjusted for sex, SES, tumour stage and period.

All analyses were performed in SAS version 9.3.

Results

Patient characteristics

Overall, 2,455 patients with MIBC were included; their characteristics are presented in Table 1. The majority was male (75%) and 38% were aged ≥75 years at diagnosis. Overall, 63% of these patients suffered from at least one comorbid condition and 32% had at least two comorbid conditions. For 14% of the patients, no information on comorbidity was recorded in the medical files. In patients aged ≤60, 61-74 years and ≥75 years, the percentage of patients *without* comorbidity decreased from 61% to 36% to 28%, respectively (data not in table). The percentage of patients *with two or more comorbid conditions* was 13%, 33% and 40% for those aged ≤60, 61-74 and ≥75 years, respectively (data not in table).

33% of all 2,455 patients underwent cystectomy, with 13% for patients aged ≥75 years, 43% among those aged 61-74, and 52% among those aged ≤60 (Table 1). Of the patients aged ≥75 years with no, one, and two comorbid conditions 13%, 10% and 15% underwent cystectomy, respectively (data not in table). The percentage of patients who underwent EBRT was 15%, 31% and 48% in patients aged ≤60, 61-74 and ≥75 years, respectively. The percentage of patients who underwent interstitial radiotherapy was 9%, 9% and 3% for patients aged ≤60, 61-74 and ≥75 years, respectively.

Table 1: Characteristics of patients with muscle-invasive bladder cancer according to primary treatment, diagnosed between 1995 and 2009 (n=2445) in the south of the Netherlands.

Characteristic		**Total**	**%**	**Cystectomy (%)**	**External Beam radiotherapy (%)**	**Interstitial radiotherapy (%)**
Gender	Male	1829	75	34	35	7
	Female	616	25	32	33	5
Age group	≤60 years	444	18	52	15	10
	61-74 years	1062	44	43	31	9
	≥75 years	939	38	13	48	3
Period	1995-1999	704	29	29	43	8
	2000-2004	858	35	32	35	7
	2005-2009	883	36	39	27	7
T-stage	T2	1590	65	23	39	10
	T3	582	24	60	24	3
	T4	273	11	35	32	1
TNM	Stage II	1402	57	25	43	10
	Stage III	503	21	59	24	3
	Stage IV	540	22	30	23	1
Co-morbidity	None#	919	37	38	32	8
	One	748	31	32	35	6
	Two or more	778	32	27	37	6
Type of comorbidity	Diabetes	285	12	26	39	7
	Hypertension	472	19	34	35	8
	Cardiovascular	753	31	26	39	7
	Pulmonary	315	13	27	39	5
Socioeconomic status	Low	643	26	30	38	6
	Intermediate	1002	41	38	34	6
	High	624	26	36	33	9
	Institutionalized*	176	7	12	35	6
Total		2445		33	35	7

Patient with unrecorded comorbidity included. * Patients in care-providing institutions.
Source: Eindhoven Cancer Registry.

Influence of age, SES and comorbidity on treatment choice

After adjustment for sex, period of diagnosis and stage, higher age and serious comorbidity, were independent predictors of abstaining from cystectomy, where SES was not (61-74 versus <= 60: OR:0.8; 95%CI:0.6-1.0; >=75 versus <=60: OR:0.1; 95%CI:0.1-0.2; one comorbid condition versus none:OR:0.7; 95%CI:0.5-0.9; two comorbid conditions versus none:OR:0.6; 95%CI:0.5-0.8). (Table 2).

Table 2: Multivariate logistic regression analyses of determinants of cystectomy and external or interstitial radiotherapy for patients with muscle-invasive bladder cancer.^

	Cystectomy		**External Beam radiotherapy**		**Interstitial radiotherapy**	
Factor	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Age (years)						
≤60	1.0		1.0		1.0	
61-74	0.8	(0.6 – .0.9)	2.4	(1.8 – 3.3)	0.8	(0.5 – 1.2)
≥75	0.1	(0.1 – 0.2)	5.1	(3.8 – 6.9)	0.2	(0.1 – 0.3)
Male	1.0		1.0		1.0	
Female	0.9	(0.7 – 1.2)	0.9	(0.7 – 1.1)	0.9	(0.6 – 1.3)
Period						
1995-1999	1.0		1.0		1.0	
2000-2004	1.3	(1.0 – 1.6)	0.7	(0.6 – 0.9)	1.0	(0.7 – 1.5)
2005-2009	1.9	(1.5 – 2.4)	0.5	(0.4 – 0.6)	0.9	(0.6 – 1.4)
Stage						
II	1.0		1.0		1.0	
III	4.3	(3.4 – 5.4)	0.5	(0.4 – 0.6)	0.2	(0.1 – 0.4)
IV	0.8	(0.6 – 1.0)	0.5	(0.4 – 0.6)	0.1	(0.0 – 0.2)
Comorbidity						
None	1.0		1.0		1.0	
One	0.8	(0.6 – 1.0)	1.0	(0.8 – 1.2)	0.8	(0.5 – 1.2)
Two or more	0.7	(0.5 – 0.9)*	1.0	(0.8 – 1.2)	0.9	(0.6 - 1.3)
Socioeconomic status						
Low	1.0		1.0		1.0	
Intermediate	1.2	(1.0-1.6)	0.9	(0.8-1.2)	1.0	(0.6-1.6)
High	1.1	(0.8-1.4)	0.9	(0.7-1.1)	1.6	(1.0-2.5)
Institutionalized	0.4	(0.2-0.7)	0.6	(0.4-0.9)	1.2	(0.6.-2.5)

^ Other treatment options not included in analysis
* Estimate of odds ratio (OR) is significant, when 95% confidence interval does not include 1.0
# Patient with unrecorded comorbidity included.
Source: Eindhoven Cancer Registry.

The presence of cardiovascular disease, diabetes and pulmonary disease were significantly associated with a decreased risk of undergoing a cystectomy (OR: 0.6; 95%CI:0.5-0.8; OR:0.6; 95%CI:0.5-0.9; OR:0.6; 95%CI:0.4-0.8, respectively; data not in table shown).

Higher age was an independent predictor for an increased risk for undergoing EBR. Patients aged ≥75 years showed a more than five times higher risk to undergo an EBRT as compared to patients under 60 (OR:5.1; 95%CI:3.8-6.9), and patients between age 61-74 had a more than two times higher risk to undergo an EBRT (OR:2.4; 95%CI:1.8-3.4). For interstitial radiotherapy, patients aged ≥75 years had a lower treatment rate (OR:0.2; 95%CI:0.1-0.3). There is no independent effect of comorbidity on the option of undergoing these latter two treatments.

Influence of age, SES, comorbidity and treatment choice on survival.

Table 3 shows that age, SES and comorbidity were independently associated with survival. These effects remained significant after adding treatment to the model, although the effects of age decreased. Overall, older age, female sex, advanced stage, more comorbidity and not undergoing treatment were associated with a shorter survival.

Patients treated with cystectomy, external radiotherapy or interstitial radiotherapy had a better survival independent of age, SES, and serious comorbidity (HR:0.4; 95%CI:0.4-0.5; HR:0.8; 95%CI:0.7-0.9; HR:0.4; 95%CI:0.3-0.5, respectively).

When assessing the effect of various comorbid conditions on survival (corrected for sex, age, period of diagnosis, stage, SES and cystectomy) in separate models, the presence of diabetes (HR 1.5.95% CI 1.3-1.8), cardiovascular disease (HR 1.3, 95% CI 1.2-1.5), hypertension (HR 1.1, 95% CI 1.0-1.3) and pulmonary disease (HR 1.5, 95% CI 1.3-1.7) had a significant effect on decreased survival.

Table 3. Multivariate Cox regression model of survival for patients newly diagnosed with muscle-invasive bladder cancer, in the South of the Netherlands, 1995-2009.

Variable		Model with age, sex, period and stage		Model with age, sex, period, stage and comorbidity		Model with age, sex, period, stage, comorbidity and treatment	
		HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Age in years	≤60	1.0		1.0		1.0	
	61-74	1.4	(1.2 – 1.6)	1.3	(1.2 – 1.5)	1.3	(1.1 – 1.5)
	≥75	2.9	(2.5 – 3.)	2.6	(2.3 – 3.0)	2.0	(1.7 – 2.4)
Sex	Male	1.0		1.0		1.0	
	Female	1.2	(1.1 – 1.3)	1.2	(1.1 – 1.3)	1.2	(1.1 - 1.4)
Period	1995-1999	1.0		1.0		1.0	
	2000-2004	1.0	(0.9 – 1.1)	1.0	(0.9 – 1.1)	1.0	(0.9 – 1.1)
	2005-2009	0.9	(0.8 – 1.0)	0.9	(0.8 – 1.0)*	0.9	(0.8 – 1.0)
Stage	II	1.0		1.0		1.0	
	III	1.5	(1.4 – 1.7)	1.5	(1.4 – 1.7)	1.8	(1.6 – 2.0)
	IV	3.2	(2.9 – 3.6)	3.3	(2.9 – 3.7)	3.0	(2.6 – 3.3)
Socioeconomic status	Low	1.0		1.0		1.0	
	Intermediate	0.9	(0.8-1.0)	0.9	(0.8-1.0)*	0.9	(0.9-1.0)
	High	0.8	(0.7-0.9)	0.8	(0.7-0.9)	0.7	(0.7-0.9)
	Institutionalized	1.4	(1.1-1.6)	1.4	(1.1-1.6)	1.3	(1.1-1.5)
Comorbidity	None			1.0		1.0	
	One			1.2	(1.1 – 1.4)	1.2	(1.0 – 1.3)
	Two or more			1.5	(1.3 – 1.7)	1.4	(1.3 – 1.6)
	Unknown			1.1	(1.0 – 1.3)	1.1	(0.9 – 1.3)
Cystectomy	No					1.0	
	Yes					0.5	(0.4 – 0.5)
External radiotherapy	No					1.0	
	Yes					0.8	(0.7 – 0.9)
Interstitial radiotherapy	No					1.0	
	Yes					0.4	(0.3 – 0.5)

* Estimate of hazard ratio (HR) is significant, 95% confidence interval does not include 1.0
Source: Eindhoven Cancer Registry

Discussion

Higher age and more serious comorbidity were independent predictors for abstaining from cystectomy. Besides, higher age is associated with more external radiotherapy and less interstitial radiotherapy. Patients with a high SES were more likely to receive IRT. Increasing age, low SES and comorbidity were independent predictors for shorter survival.

Although the strong association between age and comorbid condition is well established, the impact of these factors on cancer survival is not unequivocal. We found the usual clear association between age and comorbidity, i.e. the percentage of patients with ≥2 comorbid conditions at age <60 years (13%) increased threefold at age ≥ 75 years (40%). With increasing age, specific cardiovascular (i.e., atrium fibrillation, cardiac failure) and pulmonary diseases (COPD) and diabetes result in an increasingly negative influence on the patient's performance status. Hypertension exhibited only a small effect in choice of treatment, being usually treated very efficiently, and of minor interest. One of the main risk factors for the development of bladder cancer, i.e. smoking, also contributes to comorbidities such as cardiovascular and lung diseases [3;16].

MIBC is an aggressive malignancy; if left untreated its course is usually fatal with ≥85% of patients dying from their disease [16;21]. As stated before, radical cystectomy remains the gold standard of care [5]. Although abstaining from cystectomy was associated with serious comorbidity, EBRT and IRT were not. The latter two treatments can be given with serious comorbidities and age seems to be determent factor if a patient can follow this lengthy course of treatment.

For more extensive tumours (> T2b), cisplatin-based neoadjuvant chemotherapy could be considered before radical cystectomy to improve disease-specific survival. In daily practice, however, a frail elderly person probably cannot undergo cisplatin-based chemotherapy. Although its tolerance by elderly patients is unclear, cisplatin is nephrotoxic and cannot be administered to patients with decreased kidney function [5;22].

Compared to earlier population-based studies, the 35% of our patients treated with EBRT for MIBC is relatively high, whereas the 34% undergoing cystectomy is similar to the results of other series [23]. There is a group of patients not receiving a cystectomy, EBRT, or IRT, but a combination of chemotherapy followed by cystectomy, or only a transurethral resection of the tumour without additional treatment. These patients were not studied separately in the multivariate analysis.

Our results show that shorter survival was associated not only with advanced age, but also with advanced comorbidity, female sex, low SES and not undergoing cystectomy. Another study in a population-based radical cystectomy cohort of 11,260 patients, examining the rates of cancer-specific and other-cause mortality, showed age to be the main determinant of other-cause mortality [24]; this is probably because of a higher risk of dying from comorbid conditions (unfortunately not included in that study). However, cancer-specific mortality was also higher for older individuals than their younger counterparts, even after adjustment for disease stage [24]. However, the lack of data on potential confounding factors (such as administration of chemotherapy or radiotherapy) is another limitation of that study, as the elderly are often treated less aggressively.

In the present study, undergoing a cystectomy was significantly associated with longer survival. This was expected, as this is a retrospective study in which the medical specialist determined patient selection for treatment. However, undergoing cystectomy remained a significant prognostic factor after adjustment for differences in age, comorbidity and stage. After adjustment for cystectomy, high age and comorbidity were also independently associated with shorter survival. This means that only part of the prognostic effects of higher age and comorbidity can be explained by the fact that the elderly and those with comorbidity were often treated less aggressively. This suggests that the radical cystectomy was underutilized in patients older than 75. A positive effect on survival after surgery compared to EBRT was not found by two large population-based control studies [25-26].

Two other retrospective studies reported the negative influence of comorbidity on overall survival. One study of 210 patients undergoing cystectomy showed that comorbidity was an independent predictor of overall survival in multivariate analysis, while age was not [27]. Another study described a retrospective analysis of 1,121 cystectomy patients from a single institution. Higher comorbidity scores were significantly associated with increased risk of death after radical cystectomy and after adjustment for pathological stage and nodal status [28].

In contrast, another series of 106 patients underwent radical cystectomy; comorbidity measured with Charlson Comorbidity Index was independently associated with an increased risk of extravesical disease and decreased cancer-specific survival, but was not independently associated with overall survival [29]. As in our study, comorbidity did not affect short-term survival after cystectomy.

SES affected treatment selection and overall survival for patients with prostate cancer in the Southern Netherlands [19]. Presence of comorbidities only partly contributed to these differences [19,30]. For bladder cancer it has been shown that patients with low SES run more risk of suffering from, especially cardiovascular, comorbidities [30]. The present study shows again that a different treatment selection took place for high SES patients with also a better survival. As the diversity in fit vs. frail elderly patients is increasing, subsequently the need for awareness for good counselling of the patient and choosing the best treatment for the individual patient is also increasing [19,30].

The present study has both strengths and limitations. A main strength is that though being a population-based study, it allowed assessment of comorbidity status because of special efforts undertaken by the registry. Furthermore, our results are based on a large unselected population of patients with diverse treatment policies in about 10 hospitals, rather than from a single institution or clinical trial series in which patients are carefully selected making them less applicable to a general population of patients with bladder cancer. Minor limitations include the impossibility to examine disease-specific survival, and use of a modified Charlson comorbidity index [2]. Furthermore, the awareness of the need for centralisation in the Netherlands has been increasing since 2010, centralisation only occurring here and there before 2010. However, we feel that consequently provoked bias in decision-making by the urologist and radiotherapist is negligible in our cohort. Finally, after completion of data collection for this study the TNM classification system was updated, implying that earlier TNM classifications were used in this study. This may give some understaging of the patients (a pT3a tumour would be stage II), which would give worse survival for stage 2 in comparison to the new TNM classification.

The critical factor for success of any treatment for MIBC in the elderly is patient selection [30]. The question then remains whether the good prognosis for cystectomy patients also may have been good after internal radiotherapy or chemoradiation. A Dutch study on interstitial radiotherapy showed that at 1, 3 and 5 years, the disease-free probability was 85%, 68% and 61% and overall survival probability was 91%, 74% and 62%, respectively. This concerns a selected patient population (solitary, T1G3 -T3 bladder tumours, diameter<5 cm.) [15].

Accurate estimation of treatment outcome will help in counselling patients. However, despite the apparent benefits of radical cystectomy in selected elderly patients, to date no guidelines are available for patient selection [31]. Although several validated geriatric assessment scales and indicators are used for the elderly referred for chemotherapy, these tools are rarely applied to patients treated with other modalities [32]. It is reasonable to assume that for fit elderly patients radical cystectomy offers the best form of disease control [30]. Elderly patients with a poor performance status should be counselled carefully with regard to the risks and benefits of the various treatments [31]. In the future, adding novel biomarkers to the previously developed nomograms may improve the predictive accuracy of tumour progression and treatment response. Screening tools to distinguish between fit and frail patients should be adapted for the cystectomy procedure in the fit elderly only [33]. This will increase their chance of survival or prevent early death and treatment can be individualised for frail elderly patients in order to maintain optimal quality of life.

Conclusions

In this population-based study, MIBC patients who were older and had more co-morbidity less frequently underwent a radical cystectomy. This may reflect sound clinical judgment. An alternative opinion may be that radical cystectomy was underutilized in patients older than 75. Therefore, the cystectomy patients seemed better off in terms of survival, also after adjustment for age and comorbidity. Patients with higher SES underwent IRT more frequent, but the absolute numbers treated were low. The question remains whether patients with a good prognosis i.e. stage II also may have had this good prognosis after internal radiotherapy or chemoradiation.

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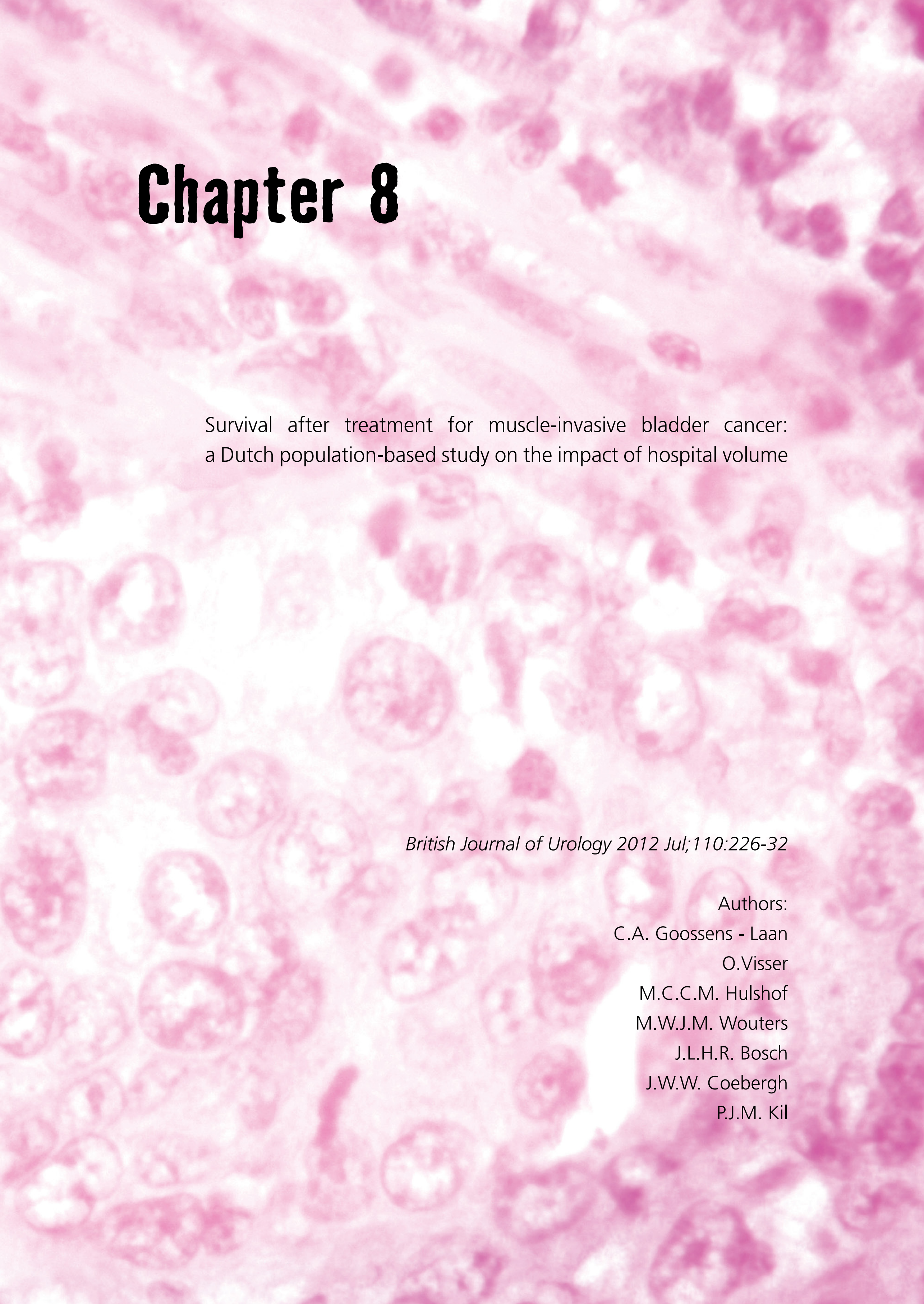

Chapter 8

Survival after treatment for muscle-invasive bladder cancer: a Dutch population-based study on the impact of hospital volume

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Abstract

Objective: To examine the volume–outcome relationship for carcinoma invading bladder muscle (MIBC) with respect to differences in survival rates among all hospitals in the Netherlands as a guide for regionalization initiatives.

Materials and methods: This population-based retrospective study included all patients (*n* = 13 033) newly diagnosed with MIBC during the period 1999–2008 in the Netherlands, selected from the Netherlands Cancer Registry.

Data were collected on demographics, morphology, stage at diagnosis and after surgery, primary treatment, vital status and date of follow-up or death.

The relative survival rate (RSR) per treatment was analysed for age, stage and hospital surgical volume.

Results: Overall 5 and 10-year RSR for all treatments of MIBC was 32% and 25%, respectively.

Although 71.7% of the patients featured stages II and III, radical cystectomy was performed in only 42% and 44% of these patients, respectively.

Relative survival for MIBC remained unchanged in the two consecutive time periods (1999–2003 and 2004–2008).

In all, 34% of patients diagnosed in low-volume hospitals (<10 cystectomies/year) underwent cystectomy vs 42% of those diagnosed in high-volume hospitals ($P = 0.000$). In a multivariate analysis long-term survival (>30 days after surgery) was significantly lower in patients after cystectomy for stage II/III in low-volume hospitals (hazard ratio [HR] 1.17, $P = 0.036$). A high lymph node count (>20) was associated with a lower risk of death (HR 0.52, $P = 0.000$).

Conclusions:

The 10-year RSR for patients with MIBC in the Netherlands was modest (25%) and has remained unchanged in the last decade.

The chance of undergoing cystectomy is significantly higher in high-volume hospitals.

Long-term survival after cystectomy is higher in high-volume hospitals.

Regionalization of bladder cancer treatments could improve overall outcomes.

Introduction

In the Netherlands in 2008 there were 5100 cases of newly diagnosed bladder cancer, with a lifetime cumulative risk of 2%. Of these, 30% were cases of carcinoma invading bladder muscle (MIBC) [1]. Radical cystectomy with bilateral pelvic lymphadenectomy is considered to be the optimum therapy for patients with MIBC or with progression to MIBC after local treatment for stage I disease. Other curative treatment options are interstitial radiotherapy (IRT), e.g. brachytherapy (for small solitary clinical stage II tumours), and external beam radiotherapy (EBRT) [2]. When a patient is not eligible for any of the above-mentioned therapies owing to co-morbidity or preference, a non-curative option usually follows: a transurethral resection of the bladder tumour (TURT) or palliative radiotherapy.

In the Netherlands in recent years, 900 radical cystectomies have been performed in 88 general and nine university hospitals [3]. During the period 2000–2006 the postoperative mortality rate ranged from 1.2% in high-volume hospitals (>10 cystectomies/year) to 6.4% in low-volume hospitals (<10 cystectomies/year) [4]. In a prospective study on complications for cystectomy, the postoperative complication rate of 64% appeared to be related to this postoperative mortality rate [5]. Annually in the Netherlands, IRT is performed 30–40 times as a primary treatment, compared with EBRT which is performed 300–350 times [3].

To guide regionalization initiatives for cystectomy, information on the influence of hospital volume on long-term survival rates for hospitals in the Netherlands is needed; therefore, data from the Netherlands Cancer Registry (NCR) were used to examine long-term (5- and 10-year) relative survival rates (RSRs) among patients undergoing different types of treatment, according to stage, age and hospital volume.

Materials and methods

Cancer registry data

All patients (*n* = 13,033) with MIBC newly diagnosed in the Netherlands between 1 January 1999 and 31 December 2008 were selected from the population-based NCR (which has had complete national coverage since 1989). Dutch hospitals were served in nine largely coordinating and facilitating Comprehensive Cancer Centres (CCCs) that host the cancer registry. Notified by the Dutch national pathology database (PALGA), registration clerks of the CCCs extract information for the registry from the medical records in the hospitals. Various data are collected, including demographics, morphology, stage at diagnosis and after treatment, primary treatment, vital status and date of follow-up or death. Tumour site and morphology are coded according to the International Classification of Diseases for Oncology [6]. Quality of data is generally considered to be high and completeness is estimated to be >95% [7,8]. Comorbidity at diagnosis is only registered in the south of the Netherlands and was therefore not available for use in the present study.
Follow-up of the vital status through the national common database of municipalities was complete until 1 February 2010. The cause of death was generally not available.

The present registration study was performed according to the privacy regulations and approved by the Privacy Commission of the NCR.

Data analysis

Data analysis of this retrospective cohort study was done using anonymized data. Stage was grouped according to the Union Internationale Contre le Cancer TNM classification, 6th edition [9]. The clinical TNM system was used for comparison of various treatment policies concerning all patients. The pathological TNM system was used for a subset analysis of radical cystectomy cases. Excluded from the analysis were patients with invasive bladder cancers with unknown stage or without histologically proven diagnosis, neuro- endocrine carcinomas, bladder sarcomas and bladder cancer only found post mortem. MIBC as a result of progression or recurrence after a previous Ta or Tis tumour was included, while progression of T1 tumours to MIBC was excluded. This was owing to registration practices, e.g. T1 is registered as an invasive tumour, as is MIBC, and progression of T1 is not accounted for as progression in the system. Only the initial treatment for every new tumour was registered, thereby disregarding cystectomy ≥ 6 months after the first diagnosis or a salvage cystectomy after radiotherapy. When the initial treatment (e.g. neo-adjuvant chemotherapy) had taken ≥6 months to complete, the (intended) cystectomy was recorded. About 20% of the cystectomies performed annually were done on T1 tumours (6%), or as secondary treatment.

Primary treatment was grouped as cystectomy, EBRT, IRT, chemotherapy only, local (intravesical) treatment only, or no/ unknown treatment. Local treatment was defined as one or multiple TURTs often followed by bladder installations. A patient who underwent cystectomy and radiotherapy and/or chemotherapy was classified as 'cystectomy'. A patient receiving radiotherapy as well as chemotherapy was classified as 'radiotherapy'. Combined EBRT and IRT was classified as 'IRT'. No information was available on the number of patients treated with palliative intent of cystectomy and/ or radiotherapy.

The hospitals were classified according to the average annual number of cystectomies performed. Hospitals with <10 cystectomies per year were classified as low volume and hospitals with ≥10 cystectomies per year were classified as high volume. The number of hospitals performing ≥20 cystectomies was too small to analyse separately.

Statistical analysis

All analyses were performed in STATA, version 10. A *P* value of <0.05 was considered to indicate statistical significance. The RSR was estimated using the Hakulinen method [10] – the ratio of observed survival to the expected survival in the general population of the Netherlands of the same age and sex – using the strs-command for STATA [11]. The absolute survival rate (ASR) was calculated using the Kaplan–Meier survivor estimator. Univariate and multivariate Cox regression analysis were performed for the risk of death for patients, conditional upon surviving ≥30 days after surgery, to examine the influence of age of diagnosis, gender, postoperative stage, residual disease and hospital volume on RSR.

Results

General

Of the 13,033 patients with MIBC, 9441 were male (72%) and the median (range) age at diagnosis was 73 (22–100) years (Table 1). The median (interquartile range) length of follow-up was 70 (40–100) months. Table 2 shows the treatment of MIBC according to clinical stage and age group. During the whole study period, 167 patients received neoadjuvant chemotherapy before undergoing cystectomy (3.6%), and 94 cystectomy patients underwent adjuvant chemotherapy (2%); however, neoadjuvant therapy increased over time and in 2008, 7% of the patients undergoing cystectomy received neoadjuvant chemotherapy.

During 2004–2008, in clinical stage II–III, the proportion was almost equal in low- and high-volume hospitals (2.4% and 2.0%, respectively). In clinical stage IV, those figures were 15% and 30%, respectively. Of the 3151 patients receiving EBRT, 118 patients (4%) received chemotherapy.

Table 1. Characteristics of patients with MIBC in the Netherlands in 1999–2008

Characteristic	Age group <75 years	 ≥75 years	Total
Sex, *n* (%)			
Males	5527 (74.5)	3914 (69.7)	9 441 (72.4)
Females	1890 (25.5)	1702 (30.3)	3 592 (27.6)
Morphological classification, *n* (%)			
Urothelial cell carcinoma	6891 (92.9)	5304 (94.4)	12 195 (93.6)
Squamous cell carcinoma	295 (4.0)	212 (3.8)	507 (3.9)
Adenocarcinoma	173 (2.3)	58 (1.0)	231 (1.8)
Undifferentiated carcinoma	58 (0.8)	42 (0.7)	100 (0.8)
Clinical stage, *n* (%)			
II	4013 (54.1)	3429 (61.1)	7 442 (57.1)
III	1036 (14.0)	873 (15.2)	1 909 (14.6)
IV	2368 (31.9)	1314 (23.4)	3 682 (28.3)
Treatment, *n* (%)			
cystectomy	3777 (50.9)	845 (15.0)	4 622 (35.5)
EBRT	1121 (15.1)	2030 (36.1)	3 151 (24.2)
IRT	301 (4.1)	59 (1.1)	360 (2.8)
Chemotherapy	542 (7.3)	68 (1.2)	610 (4.7)
Local therapy only	1091 (14.7)	1721 (30.6)	2 812 (21.6)
None/unknown	585 (7.9)	890 (15.8)	1 475 (11.3)
Total	7417	5616	13 033

Table 2. Treatment of patients with MIBC, according to clinical stage and age group, in the Netherlands in 1999–2008

	<75 years			≥75 years			All ages		
	Stage II	Stage III	Stage IV	Stage II	Stage III	Stage IV	Stage II	Stage III	Stage IV
	n = 4013	*n* = 1036	*n* = 2368	*n* = 3429	*n* = 873	*n* = 1314	*n* = 7442	*n* = 1909	*n* = 3682
Cystectomy, %	64	65	22	17	20	7	42	44	17
EBRT, %	14	17	16	39	42	24	26	28	19
IRT, %	7	1	1	2	0	0	4	1	0
Chemotherapy, %	1	2	21	0	1	4	0	1	15
Local only, %	13	7	21	35	16	29	23	11	24
None/unknown, %	1	7	20	7	22	36	4	14	25

RSRS

The RSRs of patients with MIBC for all treatments combined were 32% and 25% at 5 and 10 years after diagnosis, respectively. Figure 1A–C show the long-term RSRs according to stage and treatment. Survival was clearly inferior for patients receiving only local treatment, only chemotherapy or no oncological therapy. In clinical stage II disease the 5-year RSR after IRT was higher than after cystectomy (70% vs 57%). When only cystectomy patients with pathologically confirmed stage II MIBC were selected, the 5-year RSR was 75%.

For the age group <55 years, the 5-year ASR was 41% and the 10-year ASR was 34%; in patients aged 55–64 years the 5-year ASR was 38% and the 10-year ASR was 28%; ASRs for patients aged 65–74 years were 29% and 18% at 5 and 10 years, respectively and in patients >74 years ASRs were 14% and 5% at 5 and 10 years, respectively.

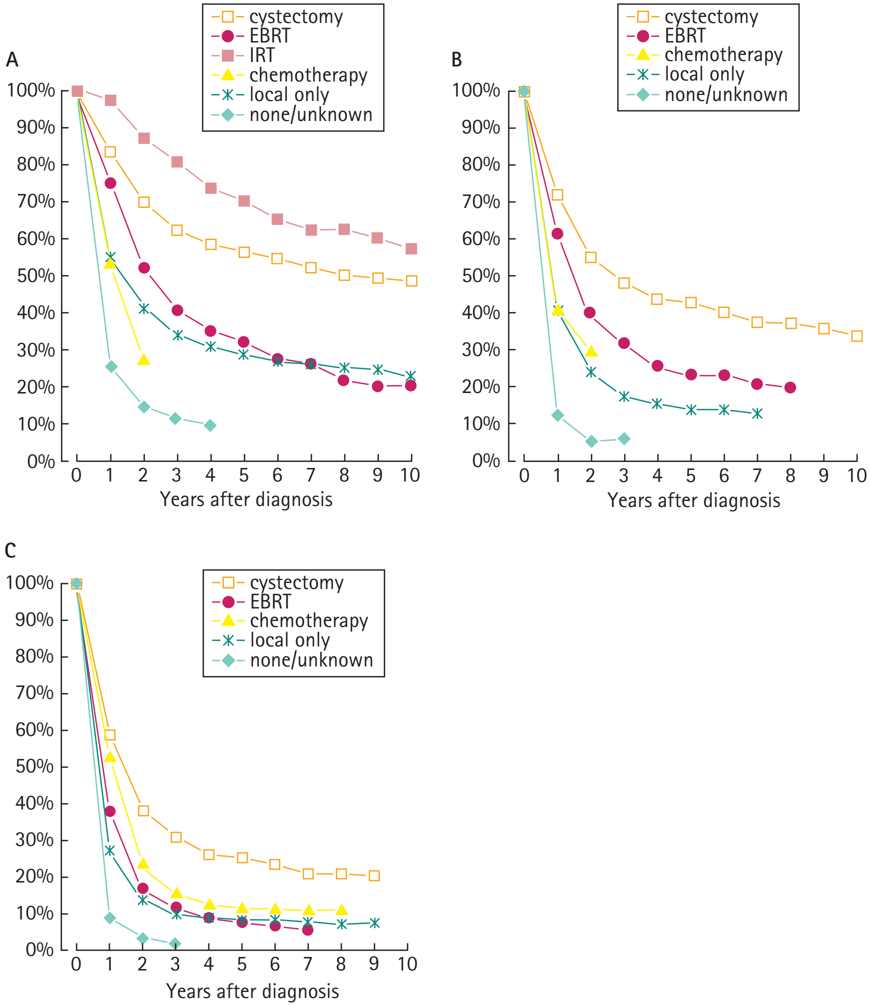

Figure 1. **A**, The RSRs of patients with MIBC clinical stage II (**A**), clinical stage III (**B**) and clinical stage IV (**C**) in the Netherlands, 1999–2008, according to primary treatment. Curves stop if the number of cases at risk is ≤15.

When comparing all patients diagnosed during 1999–2003 with those diagnosed during 2004–2008, no increase in survival was observed (31–32%). In the later period, more patients ≥75 years underwent cystectomy than in the earlier period (16% vs 12%), whereas about the same numbers in both groups received radiotherapy (35% and 34%, respectively). The 5-year RSRs for cystectomy showed no significant change: 52% (95% CI 49–54%) and 48% (95% CI 45–51%) for the earlier and later period, respectively. The 5-year RSRs for EBRT also showed little change over time: 25% (95% CI 22–28%) and 26% (95% CI 23–30%) for the earlier and later period, respectively.

Cystectomy and hospital volume

Of the 2,168 cystectomies performed between 2004 and 2008, 781 (30%) were performed in a high-volume hospital. In multivariate Cox regression analysis (>30 days after surgery) higher age, squamous cell carcinoma, higher pT stage, presence of regional/distant metastasis, residual disease and no lymph node dissection or low lymph node count were independent predictors of a lower survival rate (Table 3). Gender was not an independent predictor of lower survival.

Patients who underwent cystectomies in low-volume hospitals showed a significantly higher risk of death (>30 days after surgery) than in high-volume hospitals: hazard ratio (HR) 1.2 (95% CI 1.01–1.35; $P = 0.036$). The postoperative 30-day mortality rate was 2.9% and the 90-day mortality rate was 7.8% in low-volume hospitals.

Data on patient age, stage and therapeutic strategies, stratified according to the cystectomy volume of the hospitals, for all patients with MIBC ($n = 13\,033$), is shown in Table 4. Patients diagnosed in hospitals with a low volume of cystectomies were slightly older, while the chance of undergoing a cystectomy was significantly smaller (34%) compared with patients diagnosed in hospitals with a high volume (42%; $P = 0.000$).

Table 3. Multivariate Cox regression analysis for the risk of death after cystectomy of patients with clinical stage II or III bladder cancer, 2004–2008 (excluding patients who died <30 days after cystectomy)

		Univariate analysis		Multivariate analysis	
Characteristic	n	HR	95% CI	HR	95% CI
Sex					
Male	1593	1 (Ref.)		1 (Ref.)	
Female	575	1.08	0.94-1.25	1.11	0.96-1.29
Age group, years					
<55	265	1 (Ref.)		1 (Ref.)	
55–64	626	1.15	0.91–1.46	1.23	0.97–1.57
65–74	844	1.42	1.13–1.77	1.51	1.19–1.90
75+	433	1.84	1.44–2.33	1.82	1.41–2.35
Morphological classification					
Urothelial cell carcinoma	2039	1 (Ref.)		1 (Ref.)	
Squamous cell carcinoma	86	1.74	1.32–2.31	1.36	1.02–1.81
Adenocarcinoma	39	0.79	0.48–1.32	0.63	0.37–1.07
Undifferentiated carcinoma	4	2.03	0.65–6.29	2.91	0.93–9.14
pT stage					
T2	998	1 (Ref.)		1 (Ref.)	
T3	935	2.76	2.37–3.20	2.46	2.11–2.87
T4	235	5.1	4.21–6.16	3.69	3.00–4.55
pN stage					
N0	1806	1 (Ref.)		1 (Ref.)	
N+	362	2.09	1.80–2.42	1.84	1.56–2.17
pM stage					
M0	2157	1 (Ref.)		1 (Ref.)	
M1	11	6.60	3.53–12.3	2.55	1.32–4.91
Residual disease					
R0	1799	1 (Ref.)		1 (Ref.)	
R1/R2	169	3.20	2.66–3.86	2.02	1.65–2.48
RX	200	1.46	1.20–1.78	1.28	1.05–1.57
Hospital volume					
≥10 cystectomies per year	1529	1 (Ref.)		1 (Ref.)	
<10 cystectomies per year	639	1.21	1.05–1.40	1.17	1.01–1.35
Systemic chemotherapy					
No	2078	1 (Ref.)		1 (Ref.)	
Adjuvant	40	1.30	0.86–1.96	0.76	0.49–1.17
Neo-adjuvant	50	0.76	0.47–1.23	0.67	0.41–1.09
Lymph node dissection					
No	395	1 (Ref.)		1 (Ref.)	
Yes, 1–9 nodes	829	0.89	0.75–1.06	0.78	0.65–0.93
Yes, 10–19 nodes	405	0.73	0.59–0.89	0.62	0.50–0.78
Yes, ≥20 nodes	126	0.55	0.39–0.78	0.52	0.36–0.75
Yes, number unknown	413	0.84	0.69–1.02	0.84	0.68–1.03

Values in bold and italic are significant.

Table 4. Differences in patient age, stage, distribution on therapeutic strategies, for low- vs high-volume hospitals in the Netherlands, 1999–2008

	Low-volume hospitals, n (%)	High-volume hospitals, n (%)	P
Age group, years			
<45	183 (2)	46 (2)	
45–54	708 (7)	186 (8)	
55–64	1847 (17)	421 (19)	
65–74	3340 (31)	686 (31)	
75+	4711 (44)	905 (40)	0.002
Clinical stage			
II	6187 (57)	1255 (56)	
III	1591 (15)	318 (14)	
IV	3011 (28)	671 (30)	ns
Treatment			
Cystectomy	3684 (34)	938 (42)	
EBRT	2739 (25)	412 (18)	
IRT	311 (3)	49 (2)	
Chemotherapy	504 (5)	106 (5)	
Local therapy only	2284 (21)	528 (24)	
None/unknown	1267 (12)	211 (9)	0.000
Total	10 789	2244	

Discussion

Using data from the population-based NCR we evaluated RSRs for patients with MIBC treated with different therapeutic methods. Seven main findings emerged. (i) Total RSRs for all treatments combined at 5 and 10 years after diagnosis of MIBC were 32% and 25%, respectively. (ii) Survival was similar for groups of patients with MIBC treated with different therapeutic methods and did not change over time. (iii) Although 71.7% of the patients presented with clinical tumour stages II or III, radical cystectomy was performed in only 42% and 44% of these patients, respectively. (iv) Age appears to be an important factor in the choice of treatment strategy: patients ≤75 years underwent a cystectomy more often, while older patients were more likely to undergo radiotherapy. (v) The chance of undergoing a cystectomy was significantly lower when diagnosed in low-volume hospitals (34% vs 42%, respectively; P = 0.000). Furthermore, RSRs after cystectomy for stage II/III disease differ between low-and high-volume hospitals, with a 17% higher risk of death for patients operated in low-volume hospitals (<10 cystectomies/year; HR 1.17). (vi) Having no lymph node dissection performed or having a low lymph node count were independent predictors of lower survival (vii).

Population-based studies on survival incorporating all treatments of bladder cancer are scarce. The overall 5-year survival rates reported for stage I–IV bladder cancer range from 58 to 82% [12,13]. We measured RSR as the ratio of observed survival to the expected survival in the general population of the Netherlands of the same age and sex. Only one other population-based study (also from the Netherlands) has reported RSRs for patients with MIBC who underwent various different treatment methods. For the period 1988–2003, 5-year RSRs for stages II, III and IV were reported as 44%, 28% and 9%, respectively, and 10-year RSRs for these stages were reported as 36%, 21% and 6%, respectively [14].

The present Dutch study shows that 42% of clinical stage II patients underwent a cystectomy. A population-based study using Surveillance, Epidemiology and End Results data showed that an even lower percentage of stage II patients (21%) underwent cystectomy [15]. As radical cystectomy is the guideline-recommended treatment for MIBC, data from both of these studies imply underuse of this procedure [15].

Our earlier study [4] also reported interesting regional and/or hospital variation in the choice of treatment methods. Between regions the proportion of patients aged ≤75 years with MIBC undergoing cystectomy ranged from 60 to 77%, the proportion undergoing EBRT from 10 to 28%, and the proportion undergoing IRT from 2 to 13%.

Interstial radiotherapy is a bladder-sparing treatment in which radioactive sources are positioned in or close to a tumour. The technique was first used in the Netherlands for bladder cancer in the 1970s [16]. As this treatment is given to a selected group of patients with small (<5 cm) solitary stage II tumours (a favourable prognostic factor for MIBC), comparison of outcomes with other treatment methods should be done with great care.

Neo-adjuvant chemotherapy is a treatment option for patients with MIBC undergoing cystectomy [2]. In the present study, only a small percentage received neo-adjuvant (4%) or adjuvant (2%) chemotherapy. Chemotherapy was predominantly given in patients participating in a trial, however, an increased use of chemotherapy was observed: in 2008, 7% of the cystectomy patients received neoadjuvant chemotherapy. RSRs in the Netherlands have remained unchanged in the last 10 years [17]. This suggests little improvement, despite the development of treatment strategies such as extended lymph node dissections.

Age seems to be an important factor in the choice of treatment strategies which, in the present study, differed widely between younger and elderly patients. Although the RSR after cystectomy was superior to the RSR after the other treatment methods, local therapy and EBRT (Figure 1), only 15% of the patients aged ≥75 years underwent cystectomy. The difference in survival between treatment methods might also be attributable to selection bias. Comorbidity is negatively associated with undergoing a cystectomy and about two-thirds of the Dutch patients aged ≥75 years with MIBC also suffered from serious comorbid conditions [18]; however, multiple studies have shown that radical cystectomy is a safe option for elderly patients, even for those with comorbidity [19–21]. Good patient selection, therefore, seems to be imperative in the choice of treatment in the elderly.

In addition to the high postoperative mortality rates in low-volume hospitals reported earlier [4], survival after cystectomy seems to be lower in hospitals performing ≤10 cystectomies a year compared with higher-volume hospitals. To our knowledge, the present study is the first high-quality study showing a significant beneficial effect for survival in high-volume hospitals [22].

In multivariate analysis lymph node dissection and lymph node count were significant, showing that the process of care given to a patient, e.g. the extent of the lymph node dissection, is a prognostic factor.

With the ongoing discussion on quality of care of patients with MIBC, regionalization for cystectomy seems justified, but mortality is not the only determinant of quality of care, and procedural volume is not the only measure of quality. Underperforming high-volume providers do exist, as do low-volume providers with excellent outcomes. Minimum volume standards fall short in identifying underperforming high-volume centres and might undeservedly lead to the closure of well-performing low-volume centres. Further research is needed to look for additional quality of care indicators and should be the next step for the guiding of regionalization initiatives [23].

The present study has a few important limitations. The NCR provides population-based data from patients diagnosed with MIBC in the Netherlands, but data on the pre-treatment comorbidity status of patients with MIBC are incomplete. Comorbidity is only registered in the region of the CCC South. For patients with MIBC diagnosed in this region, a recent study (submitted) showed a negative association between comorbidity and the chance of undergoing cystectomy. The lack of comorbidity data and information on the cause of death might introduce bias if the comorbidity status of patients in high- and low-volume hospitals differ. On the one hand, if patients with high comorbidity are selectively referred to high-volume hospitals the survival outcome in those hospitals would even be better when corrected for comorbidity. On the other hand, patients with high socio-economic status and lower comorbidity might choose to be operated in a high-volume hospital, which would be the cause of the relatively favourable survival outcome of the high-volume hospitals. As little information was available to the general population on cystectomy volume during the study period, the latter effect is unlikely. It is also unlikely that low-volume hospitals selectively refer patients with low comorbidity to high- volume hospitals. A slight tendency towards increased referral to the high-volume hospitals emerged in the last few years of our study period, increasing further in 2009–2010 after publication of the hazards in high- vs low-volume hospitals in the Netherlands [4]. The assumptions regarding patient selection among the elderly with MIBC for EBRT, although very probably accurate, remain to be proven.

Other limitations of the study are inadequate control of additional confounding factors (e.g. no registration on follow-up treatments) and the impossibility of estimating disease-specific survival. Comorbidities and comorbidity-associated events represent very important causes of mortality in patients undergoing cystectomy. A recent study on cancer-specific and other-cause mortality showed that, after stratification according to disease stage and patient age, cancer-specific mortality was the main cause of mortality in all patient strata. Nonetheless, at 5 years after radical cystectomy, between 8.5% and 27.1% of deaths were attributable to other causes [24].

The use of cystectomy instead of all treatment methods to define volume measurements was based on the following reasons. The problem regarding patients undergoing EBRT is that all hospitals refer patients to radiotherapy centres, making this treatment method unsuitable for distinguishing between low- and high- volume centres. The same problem arises for brachytherapy/IRT as this treatment is given in a few specialized centres and the annual volume is low (≈150 cases in 2004–2006). Neo-adjuvant chemotherapy is also mostly given in high-volume centres, in trials that run mostly in oncological centres.

A major strength of the present study is that its results are based on the entire population in the Netherlands, of unselected patients with diverse treatment regimes.

In conclusion, less than one third of patients with MIBC in the Netherlands are being cured. Despite improved treatment strategies, no improvement in survival was observed in the last decade. Survival appears to be significantly higher in high-volume hospitals.

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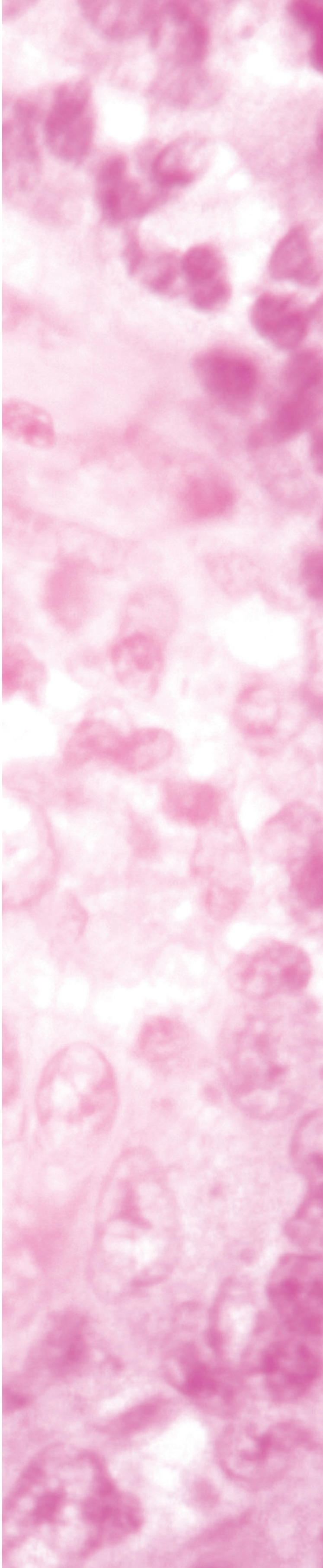
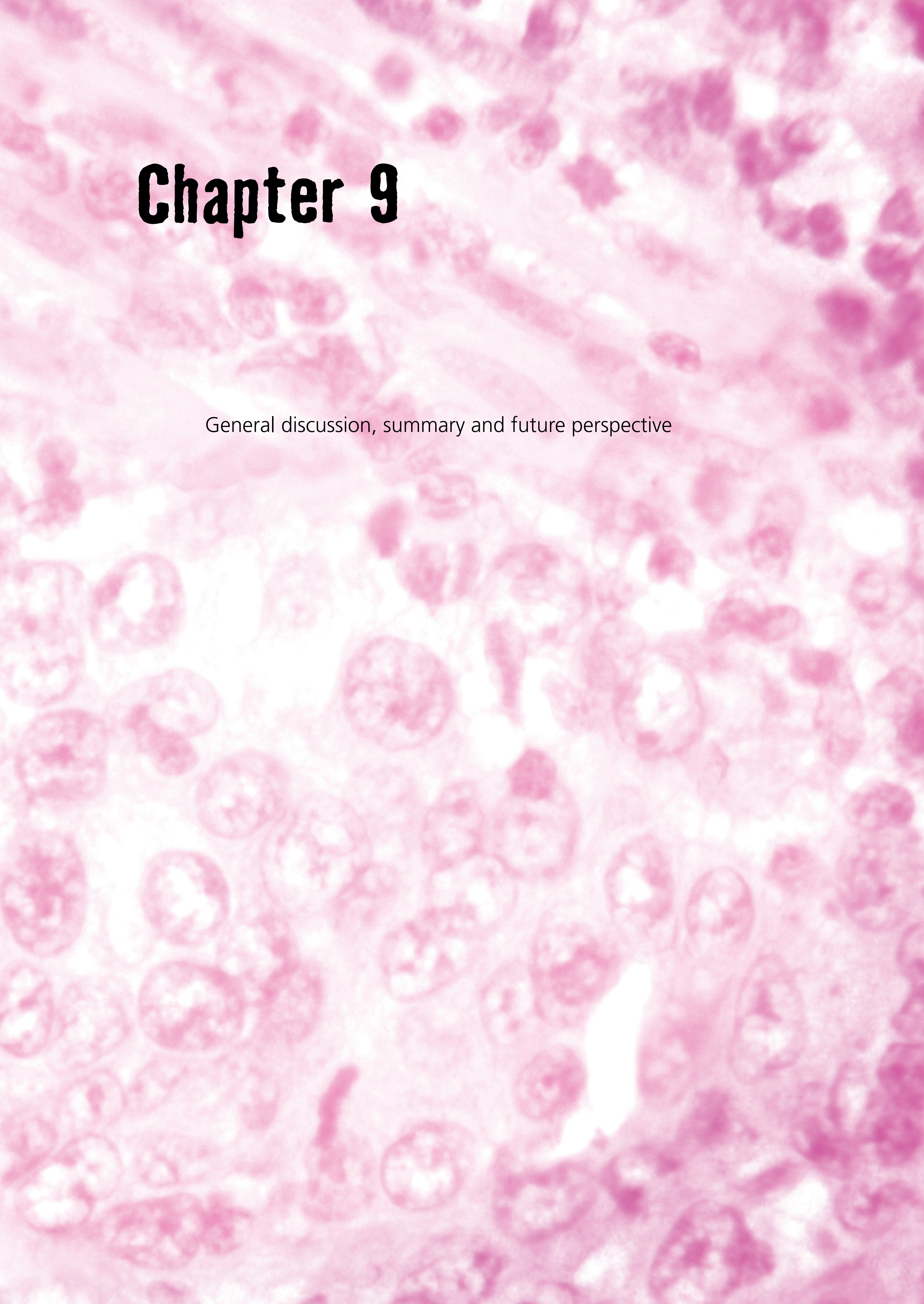
PART IV

General discussion



Chapter 9

General discussion, summary and future perspective



Quality of Care (QoC) and Quality of Life (QoL): public interest

Nowadays, it is almost impossible to find an urological journal that lacks an article on quality of care and/or quality of life. This equally applies to medical journals, congresses and even pharmaceutical commercials. In the Netherlands, the transparency in health care requested by patients and insurance companies ensures that this item is high on the political agenda, particularly QoC and quality indicators.

Regarding QoL, currently almost 60% of all patients with cancer are aged 65 years or older [1]. Muscle-invasive bladder cancer (MIBC) is a dreadful disease; in the Netherlands, the 5-year survival rate after treatment is only 32% (**chapter 8**). For those older patients that do undergo a radical cystectomy -a major surgery less often chosen for older patients (chapter 7)- it is uncertain whether the possibility of prolonged survival outweighs the negative effects on QoL.

This thesis presents the results of research aimed at gaining more insight into the level of QoC given to patients with muscle-invasive bladder cancer and their QoL and HS before and after undergoing cystectomy. Starting point were the following research questions:

1) To what extent is quality of life in patients with muscle-invasive bladder carcinoma affected by undergoing a radical cystectomy?

2) How can process aspects of quality of care for muscle-invasive bladder carcinoma be measured in the Netherlands?

3) Is the outcome of treatment of muscle-invasive bladder cancer in the Netherlands, with emphasis on the radical cystectomy, influenced by the volume of the procedures?

This general discussion presents a summary and discussion of our results in relation to the available literature on these topics.

Part I

Bladder cancer

Chapter 1 presents an introduction to the diagnosis and management of non-muscle and muscle-invasive bladder cancer. The diagnosis of bladder cancer has a major impact on a person’s functioning, and social and emotional existence, for which a multidisciplinary approach is required. For this purpose co-morbidity, and the functional and physiological reserves per person should be analysed in order to propose the most appropriate treatment plan. The objective, aim and outline of this thesis were presented.

Part II

Quality of Life (QoL)

Nowadays, because QoL is associated with QoC, QoL has become an important outcome measure of care. Before answering the third research question, first some background information is offered on how QoL in bladder cancer patients can be measured. Quality of life is the perception people have on their position in life within the context of the cultural and value systems in which they live, and in relation to their goals, expectations, values and concerns [2]. Therefore, QoL is a multidimensional concept involving much more than being simply concerned with direct health-related aspects [2]. In other words, QoL refers to a person's satisfaction with his functioning in various aspects of his life and is not a direct reflection of his performance. QoL is often confused with functional status and health status (HS). Functional status represents a person's physical functioning, whereas HS refers to the influence of disease on a person's physical, social and psychological functioning. HS is also multidimensional and directly reflects functioning. Furthermore, the concept health-related quality of life is QoL, but solely on the three main domains of QoL: i.e., physical, social, and psychological [3,4]. QoL, functional status and HS are patient reported outcomes (PROs). Patient-reported outcomes are self-reports, thus the answers come directly from patients about how they feel, function, are bothered in relation to a health condition and its therapy without the opinion of healthcare professionals or anyone else. PROs can relate to symptoms, signs, functional status, perceptions, or other aspects, such as convenience and tolerability [5].

For patients undergoing a radical cystectomy we are interested in the PRO QoL, i.e. how the person experiences the various aspects of his or her life. This is illustrated by the following example. A person has arthritis and cannot use a staircase properly (functional status). This has reduced his functioning, or his health (health status).

When measuring this person's QoL, we measure whether this person finds it problematic that he can no longer climb the stairs. Perhaps he lives in an apartment with an elevator and does not need to use the staircase.

Chapter 2 presents our results of a multicentre prospective baseline study (level 2) on QoL, HS, sexual function and trait anxiety in patients with primary hematuria of whom some later appear to have bladder cancer. These patients are compared with another group with hematuria who later appear to have a different (non-malignant) diagnosis. Bladder cancer was found in 17% of the patients. **Chapter 3** is the follow-up case-control study on QoL and HS among patients with MIBC undergoing cystectomy from a prediagnostic baseline measurement until one year postcystectomy compared to patients with non-malignant diagnosis.

QoL questionnaires

Some previous studies compared different questionnaires for QoL vs. HS to see whether the outcome scores are interchangeable [6-8]. These studies show that different questionnaires do not result in the same conclusions. This stresses the importance of using the correct questionnaire to address one's research hypothesis. For our study, we decided to use the following questionnaires: the World Health Organization Quality of Life (abbreviated version) WHOQOL-Bref, which is a general questionnaire to evaluate QoL [9,10]. To measure Health Status we chose the SF-12 questionnaire, also known as the short version of the Rand 36 [11]. Both WHOQOL-Bref and SF-12 are generic questionnaires, that can be used to measure PROs in the general population. Postcystectomy, the Functional Assessment of Cancer Therapy - Bladder Cancer (FACT-BL), a bladder cancer specific questionnaire was used to compare the results with the WOQOL-Bref and SF-12 results postcystectomy. Although better mental health status was reported by patients with an unknown diagnosis of bladder cancer, they were as satisfied with their QoL as patients with other causes of hematuria (**chapter 2**). When comparing the results between QoL and HS questionnaires, in comparison to the QoL vs. HS studies performed in patients with liver disease, intermittent claudication or breast cancer [12], the differences between the two separate questionnaires are not so evident (**chapter 2 and 3**). This may be due to the use of the SF-12 and the WHOQOL abbreviated versions, making it more difficult to detect possible differences.

Personality

QoL is known to be influenced by health [2], socio-economic status [13], culture [14] and personality [15,16]. Especially the personality factor ‘trait anxiety’ is associated with QoL, but data on bladder cancer is sparse. The State-Trait Anxiety Inventory (STAI-TRAIT) questionnaire was used to score trait anxiety [17,18]. In both **chapter 2 and 3**, the trend of a lower score on trait anxiety for bladder cancer patients was found. Between bladder cancer patients and other causes the difference in a high score for a patient on anxiety was 16.5% and 24.7% respectively. For the patients undergoing a cystectomy vs. the case-control patients, this was even more evident, 5.6% vs. 20%. Further research is needed for confirmation of this finding. If low scores on trait anxiety correlate with presence of bladder cancer, the need to increase awareness of hematuria as a possible symptom of undiagnosed bladder cancer, and of the importance to expediently analyse the cause of such hematuria, is self-evident.

In addition to choosing what concept to measure, different questionnaires are available which specify QoL or HS even further.

1) Generic questionnaires (WHOQOL-100/Bref; SF-36/12)
2) Disease-specific questionnaire (the FACT-General; Functional Assessment of Cancer Therapy or the EORTC QLQ C30)
3) Cancer specific/treatment specific questionnaire (for bladder cancer; the FACT-BL)

The downside of disease-specific questionnaires is that they are not applicable to matched controlled patients, patients before a cancer diagnosis, or “healthy” individuals. This limits the choice in what measurement time-points and control group to use. In **chapter 3** the results of the FACT-BL, measured postcystectomy, showed a physical score that is stable over time, and functional well-being decreased slightly. This in contrast to the WHOQOL-Bref and SF-12 which both showed a decreasing physical score. However, the question is whether the disease-specific FACT-BL should have been applied in this specific study knowing the ideal baseline cannot be used. As the generic questionnaires, with ideal baseline abilities, can be used, the FACT-BL is made redundant.

Sexuality

To measure sexuality, the International Index of Erectile Function (IIEF) questionnaire for erectile functioning was added to our study [19]. No validated questionnaire was available for female sexuality when our study started. So, three items of the WHOQOL-100 were added to the WHOQOL-Bref to assessing sexual satisfaction. This "facet" sexual activity can be answered by both female and male patients, in contrast to the IIEF. Because the IIEF is a widely used questionnaire, it was remarkable that this questionnaire was a reason for many patients not to participate in our study. Of the patients who did participate despite the IIEF, only 40% answered the questions of the IEFF, in comparison to the 99.5% of the participants answering the facet sexual activity (**chapter 2**). Apparently the more general questions about satisfaction with sexual activity of the WHOQOL-Bref were experienced as less intense than the specific questions on the IIEF erectile function. The results of **chapter 2 and 3** on this subject showed sexual and erectile dysfunction was highest in patients with bladder cancer. This may well be explained by a relationship with preexistent comorbidity (cardiovascular, as a result of smoking), although this cannot be confirmed in the present study because we did not collect information on patients' comorbidity status.

Quality of Life studies for bladder cancer

In the urologic oncology community there is no standardised assessment protocol for QoL studies, and there is a wide variation in QoL outcome studies [20].

Three systematic reviews on QoL show that none of the performed studies exceed level 3-4 studies [21-23]. A second major limitation is that the few prospective studies all report a 'baseline' assessment of HS and/or QoL that is measured only after MIBC has been confirmed [24-26]. However, receiving a diagnosis of cancer will almost certainly impact one's QoL. It was our aim to assess QoL and HS before diagnosis in order to get a more realistic baseline assessment. This had implications for the choice of PRO to measure and which questionnaire to use, as the FACT-BL could not be used for baseline measurement, and perhaps the motivation of the patients to answer questions on their sexuality was lower not being aware of the diagnosis behind the hematuria.

In earlier studies, psychological HS and health-related QoL measures, returned to or exceeded baseline values 12 months after cystectomy [21-26]. However, as stated earlier, none of these studies measured QoL *before* the diagnosis of bladder cancer; being diagnosed with cancer will almost certainly cause a changed perspective on QoL. A baseline QoL measurement point before diagnosis should give a more accurate reflection of a patient's baseline QoL.

The aim of this prospective longitudinal case-control study (**chapter 3**) was to measure QoL and HS in patients with an unknown diagnosed bladder cancer (eventually) undergoing cystectomy, and to evaluate co-variables like age, gender, and mental anxiety. This was the first case-control study measuring QoL before the diagnosis bladder cancer is known. The results of this study imply that radical cystectomy patients have a better prediagnostic QoL and HS than postcystectomy, even one year after surgery. The disease and cystectomy thus have a major impact on patients' lives. Therefore, one should be careful to give clinical advice to individual patients concerning their QoL postcystectomy based on earlier studies with a QoL measurement immediately before undergoing cystectomy [24-26]. One other factor that could explain the difference in outcome could be the use of different questionnaires, in these earlier studies just before and postcystectomy the FACT-BL, European Organization for Research and Treatment of Cancer QLQ-C30 [27] or personal interviews were used. As stated before, the FACT-BL in the present study was only used postcystectomy. And the EORTC QLQ-30 is a generic cancer questionnaire [27], which would not apply before diagnosis is known. Furthermore, prediagnostic, the HS physical component scale, i.e., physical functioning and sexual satisfaction for patients undergoing radical cystectomy were lower, and the domain physical health shows a clinical difference in comparison to patients with other causes for hematuria. A limitation of our study is not comparing the cystectomy to other treatment modalities of MIBC, e.g., EBRT and IRT. A second limitation is the number of patients "lost-to-follow-up" as a result of hospitalization due to complications or spread of the disease, or death due to bladder cancer.

Future perspective QoL

When considering our initial research question, i.e., to what extent is QoL in patients with muscle-invasive bladder carcinoma affected by undergoing a radical cystectomy, the answer is that QoL is negatively influenced by undergoing cystectomy. It is not yet clear if this is solely contributable to the cystectomy. The research should be expanded with a larger population including comorbidity and smoking history. In this high-risk, low-volume procedure, with a 52% 5-year survival rate (**chapter 6**), The decrease in postsurgical QoL is yet another issue to discuss with patients. As the cystectomy remains the gold standard treatment, it will probably not change the choice of the patients to undergo surgery. However, although surgery is a feasible option for the fit older patient, some patients may on the basis of this new information consider that chances of prolonged survival will not outweigh the loss of QoL, and as a result choose not to undergo surgery in favour of EBRT. For the patients who would choose cystectomy, physical training and screening for psychological problems and, if indicated, subsequent psychological counseling may improve their QoL and HS.

Part III Quality of Care

Background to development of indicators in the Netherlands

In 2005 new financial arrangements were made in the Dutch healthcare system, aiming to control the increasing costs and thus, the affordability of the system. These increasing costs are mainly caused by the expanding use and possibilities of modern technical diagnostic and treatment options, together with an increasing number of older citizens with complex medical problems. The financing system is based on demand-driven care with detailed product financing. The ratio of price, volume and quality is supposed to be accounted for by the healthcare provider using so-called indicators, i.e. measurable elements of caregiving that give an idea about the extent of the QoC provided. These indicators are called *performance indicators* and are generally used to describe the processes within the professionals own institution (so-called internal indicators), and for offering accountability to other parties (so-called external indicators).

In 2006 a project called '*Kwaliteit van Zorg in de etalage*' ('QoC on display') was started by the Quality Institute for Healthcare (CBO) and the Order of the Medical Specialists, commissioned by the Netherlands Organisation for Health Research and Development (ZON-MW) [28]. Steering groups were formed to develop disease-specific performance indicators [29]. The purpose of these external indicators was to provide insight into effectiveness and safety levels of the QoC provided by an institution, which insight -ideally- could be used in negotiations with the insurance companies.
Since 2010 the Netherlands Health Care Inspectorate requires all hospitals to provide information on these annual external quality indicators, one of them being the number of cystectomies performed per hospital on a yearly basis.

During the process of the development of these external indicators, the Dutch Association of Urologists became actively involved and took increasing responsibility. This was because some member-urologists felt that the external indicators tended to raise more questions rather than improving the transparency in the healthcare system. According to them the use of external indicators may not improve the effectiveness and safety of care for patients with bladder cancer. Questions were raised as to whether volume standards alone would lead to the desired QoC or whether other crucial factors should be involved; the need for and interest in internal QoC indicators became more apparent. The initial studies presented in this thesis were designed to answer these questions.

QoC is defined as the degree to which healthcare services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge [30]. **Chapter 4** describes the process of developing QoC indicators/internal indicators to use at hospital level to measure the QoC given. At the start of this study in 2006, there was a complete lack of QoC indicators (QIs) or a QoC registration system for MIBC. Therefore in this study QIs were defined and selected by a multidisciplinary project group based on recent literature, guidelines, and/or consensus within the project group. In a retrospective study a baseline for each QI was assessed and compared to a predefined benchmark. Afterwards the QIs were measured again (data not published). With regard to the first research question, it was shown that it is possible to measure and improve the QoC at hospital level by using QIs. This QoC registration method might thus have served as a first step in defining applicable and useful QIs for implementation in clinical practice.

In the Netherlands, as stated earlier, there is an ongoing debate about the use of performance indicators in general. When the target for a performance indicator has not been reached this could lead to financial consequences, e.g. the hospital will not get paid for certain treatments provided. Therefore, when QIs are used in clinical practice there must be increased awareness to prevent indicator-motivated actions, i.e. interventions applied only to reach that QIs target. The sole purpose of internal QIs is to raise QoC to a higher standard. Ultimately QIs should be used as a surrogate measure for:

- 1) oncologic outcomes (cancer-specific and overall survival),
- 2) patient QoL outcomes,
- 3) healthcare expenditures.

As stated in **chapter 3**, before QIs are implemented and standardised into oncologic practice, it seems essential to document correlations between QoC and the above-mentioned outcome factors.

In **chapter 5, 6 and 8** and answer is given to the second research question:

Is the outcome for treatment of muscle-invasive bladder cancer through radical cystectomy in the Netherlands influenced by the volume of the procedures?

Early 2007, commissioned by the Dutch Cancer Society, the Quality of Cancer Care Task Force of the 'Signalling Committee-Cancer' of the Dutch Cancer Society was formed. A project was started on *"Kwaliteit van kankerzorg in Nederland"* (Quality of Cancer Care in the Netherlands) [31]. The task force decided to include also a urological-oncological condition which became MIBC. Subsequently, extensive (inter)national literature research was done and, for the first time, data from the Dutch Cancer Registry (NKR) were used to investigate whether there were differences in the QoC delivered at hospital level. In the context of this project the study described in **chapter 5** was conducted. **Chapter 5** summarises the major variations in treatment policies in the period 2001-2006 for different regions and hospital types in the Netherlands.

In total, 44% of patients with stage II-III bladder cancer underwent cystectomy, while 26% were not treated with curative intent. Furthermore, 21% (n = 663) of these procedures were performed in 44 low-volume hospitals. In 79% of the cystectomies lymph node dissections were performed, more often in high-volume and medium-volume centers (82% and 81%, respectively) than in low-volume hospitals (71%; odds ratio 1.5). The overall 30-day postoperative mortality rate was 3.4% and increased with older age; this rate was significantly lower (1.2%) in high-volume centers.

Radical cystectomy is considered the gold standard treatment for stage II and III (muscle-invasive) bladder cancer, being reinforced by a recent update of the European guideline [32]. In view of this guideline the low total number of cystectomies for MIBC patients (36%) was remarkable. Even in MIBC patients aged ≤ 75 years the number of cystectomies was relatively low (stage II 65%; stage III 68%), but appeared to increase over the last decade. A drawback of our study is in the non-availability of data on co-morbidity, combined with performance status. Differences in co-morbidity could be a reason for low adherence to the cystectomy [33]. This same guideline-recommended care is underused for the radical cystectomy in the USA, as seen in a study on the SEER Medicare database [34]; only 21% of the patients underwent a cystectomy. Patient characteristics associated with a decreased chance of receiving a cystectomy included older age, higher co-morbidity and long travel distance to an available surgeon [34]. Non-adherence to a guideline is not only seen for MIBC. There is also a marked underuse of guideline-recommended care in high-grade non-MIBC [35]. A significant survival advantage was found among patients who received at least half the recommended care [36]. Efforts to improve compliance with the guidelines, as well as quality-improving initiatives such as the QoC databases and centralisation of the cystectomy, should improve the QoC given to patients with MIBC. Since the publication disclosing the variations in treatment policies there has been a shift towards centralization, with in 2010 no hospitals in the Netherlands performing less than 5 cystectomies per year.

Again by the Quality of Cancer Care Task Force of the Signalling Committee-Cancer of the Dutch Cancer Society, a second study was performed to investigate the

Volume-Outcome relationship (as reported in the literature), to contribute to the political debate on the need for centralisation of the radical cystectomy (**chapter 6**). A systematic search was made to identify all articles examining the effects of procedure volume on clinical outcome of cystectomy. We found a strong inverse relationship between high-volume providers and postoperative mortality (inpatient and/or 30-days postcystectomy). Our study is the first meta-analysis on the relationship between procedural volume and outcome of cystectomies for cancer to include studies from outside the USA. A limitation of the study was that, from the included studies, it was not possible to identify a specific minimal volume cut-off point; our meta-regression failed to identify a relation between cut-off point used and the strength of the procedural volume and outcome relationship. Unfortunately no studies were identified that analysed volume as a continuous variable. To see whether we could find an answer regarding a specific cut-off point, a sub-analysis was made for the Dutch situation (not published) using the NKR database. However, at the time of analysis only in two Dutch hospitals urologists were performing more than 20 cystectomies per year. Again, this number of hospitals was too low to determine the effect size. Since the publication of our review article, no additional publication (of good methodological quality) has been found which provides a well-established standard for a minimum threshold and/or volume. A recent study from the USA, following the trends in hospital volume and market concentration, showed that a reduction of 20% in mortality after cystectomy was achieved coinciding with the redistribution of patients to higher-volume hospitals [37].

In the existing literature, the relationship between procedural (cystectomy) volume and long-term survival showed only a trend for higher survival in high-volume settings (**chapter 6**). In **chapter 8** we described a population-based study performed in the South of Netherlands, examining long-term (5 and 10-year) relative survival among patients undergoing different types of treatment, according to stage, age and hospital volume. Hospitals with less than 10 cystectomies per year were classified as low volume and hospitals with 10 or more cystectomies per year were classified as high volume. Again, the number of hospitals performing 20 or more cystectomies was too small to analyze separately.

We found that the total relative survival rates (RSR) for all treatments combined at 5 and 10 years after diagnosis of MIBC were 32% and 25%, respectively. Thus, less than one third of patients with MIBC in the Netherlands are being cured. Age appears to be an important factor in the choice of treatment strategy: patients aged ≤ 75 years underwent a cystectomy more often, while older patients were more likely to undergo radiotherapy. The chance of undergoing a cystectomy was significantly lower when diagnosed in hospitals with a low-volume vs. high-volume for cystectomy (34% vs. 42%, respectively; p=0.000). Furthermore, the hazard ratio (HR) for cystectomy for stage II/III disease differs between low and high-volume hospitals, with a 17% higher risk of death for patients operated in low-volume hospitals (<10 cystectomies/year; hazard ratio 1.17). Finally, having no lymph node dissection or having a low lymph node count was an independent predictor of lower survival. To our knowledge, this was the first study (of good methodological quality) showing a significant beneficial effect for survival in high-volume hospitals. Therefore the tendency towards centralisation is supported by these findings and this study has served as a primary trigger to install volume norms for urologists in the Netherlands.

The selective referral theory assumes that hospitals and surgeons with superior results will attract more patients. This theory could also explain our findings of the volume-outcome relationship described in **chapters 5 and 8**. However, the literature on this subject remains controversial. A study from Canada showed that black, old, sick, poor and Medicare patients were less likely to be treated at high-volume hospitals for uro-oncologic surgery [38]. In a Korean population-based study, patients with a higher age and lower income level were significantly less likely to be treated in a high-volume hospital. The factors gender and comorbidity were not predictors for the use of a high-volume hospital [39]. These findings tend to show selective referral as having a positive effect on mortality rates in high-volume hospitals. However, a study from Boston (USA) based on the Nationwide Inpatient Sample suggests that selective referrals based on unobserved confounders (patient-level characteristics such as patient health severity, socioeconomic status) do not explain the observed negative association between procedure volume and in-hospital mortality for radical cystectomy and thus support the "practice makes perfect" hypothesis [40].

Comorbidity

There is increasing evidence that high volume of complex operations is related to lower operative mortality after high-risk cancer surgeries (cystectomy, oesophagectomy, pancreatectomy, etc.) [41,42]. As stated earlier, this difference may also be affected by selective referral of relatively healthy patients of higher socio-economic status. **Chapters 5 en 8** are based on data derived from the population-based regional cancer registries of the Netherlands. One major drawback is that these studies lack information on co-morbidities and performance status of patients, as co-morbidity is only registered in the region of the Comprehensive Cancer Centre South. Therefore, in the Southern part of the Netherlands, a study was conducted on the role of co-morbidity and is presented in **chapter 7**. We assessed the effect of age, co-morbidity and socioeconomic status (SES) in a population-based series of patients with MIBC before the period of awareness of the need for regionalisation among urologists in the Netherlands. The majority of patients with MIBC (63%) have serious pre-existent co-morbid conditions. This is comparable to the rate in newly-diagnosed cancer patients in the Netherlands, i.e. from 48% in those aged 50-64 years rising to 80% in patients aged ≥ 80 years [1]. Overall, survival for elderly patients was worse, even after adjustment for co-morbidity and cystectomy. Again, the same applies to the general Dutch population with cancer: for patients aged 65-79 years the chance of dying was twice as high as for patients aged 50-64 years [43]. However, those who underwent cystectomy had a significantly better prognosis, even after adjustment for age and co-morbidity. SES affected treatment selection and survival, showing that with high SES a different treatment selection took place (i.e., more IRT) and prolonged survival. For a proper selection for therapy, the risks and benefits of cystectomy must be thoroughly investigated in this ever-increasing group of patients. To achieve this, screening tools are being developed for individualised risk estimations in the elderly patient [44].

Regulation of the process of QoC

In 2010, coinciding with reports of our results, the conclusions were published of the final report entitled *"Kwaliteit van kankerzorg in Nederland"* (2010; Quality of Cancer Care in the Netherlands) [31]. The Signalling Committee-Cancer (SCK) indicated that, on average, cancer care in the Netherlands is of high quality. Nevertheless, there are significant gaps in care provision between the different regions and hospitals throughout the Netherlands. As a consequence, the Dutch Association of Urology decided to opt for a voluntary initiative for volume-driven centralisation, standardisation of surgical techniques, and to provide quality checks for specific urologic diseases, including the radical cystectomy for MIBC. The Quality committee and the WOU committee (*Werkgroep Oncologische Urologie*; Workforce Oncological Urology) designed a QoC registration database, following the lead of the Dutch Surgical Colorectal Audit. Comparable outcome registrations in the Netherlands (DSCA, NOV; Dutch orthopaedics complication registration) and abroad (BQS in Germany) have shown that these registration databases have a powerful quality-enhancing effect; especially when the results are presented as feedback to the individual members of the 'treatment team' [45,46]. This has a dual function; it is used for external accountability and also as mirror information and an improvement tool for the urologists. The Dutch QoC database has a feedback system that (in an anonymous manner) compares the data of one's own institution with the mean data from all other Dutch hospitals that perform cystectomies. The national database intended for prospective registration shows considerable overlap with the QIs as designed in our study and presented in **chapter 4**. The major difference is the registration of outcome parameters like the TNM stage for research purposes and for identifying case mix. It recently became mandatory to contribute to this national registration system. The aim is to use the information at the hospital level to improve local QoC and, at the national level, the Dutch Association of Urology will be able to identify early QoC problems and find ways for improvement.

Future perspective for part II QoC

Immediately following these and other studies, already many improvements have been realised, indicating the importance of QoC in health care.

The aim of our studies on QoC was to see whether volume has an impact on the outcome parameters mortality and survival, for a highly complex operation as the radical cystectomy. As **chapters 5, 6** and **8** show, volume does significantly contribute to QoC. These studies have made a contribution to the debate on centralisation.

As of 2011, the Dutch Association of Urology decided to implement volume-based centralisation norms with a minimum standard of ≥ 10 cystectomies/year, based on the findings discussed in **chapter 5**. Future studies are needed to further establish the procedural volume-outcome relationship and to investigate the cutoff point. The minimum standard of 10 is still under debate and may be raised in the near future. In England, the National Institute for Health and Clinical Excellence (NICE) recommends a volume norm of 50 pelvic cancer procedures on a yearly basis [46].

The Dutch QoC registration database for MIBC was realised in 2010. Although registration by the operating urologist seems logical, there are some drawbacks. Providing input to the database is very time-consuming, because it was designed for QoC registration but it may also be used for research purposes. Generally, at least 20 minutes are needed to register all the information concerning one patient. Also, 100% coverage is almost never achieved for each individual patient. The registration may be improved by reducing the amount of information required as input, which may enhance the total input provided by urologists (a system is only as good as its users). Or, perhaps support can be provided for the registration, such as integration with the information collected by the Netherlands Cancer Registry (NKR), to reduce the effort of gaining the information. The quality of data from the NKR is considered to be high and completeness was estimated to be over 95% [48,49].

Between 1999 and 2008 no improvement in the survival rate for surgically treated patients with MIBC was observed. The new QoC database may help elucidate where progress can be made in the coming decade. Hopefully, it also provides an answer to the issue of selective referral versus the ‘practice makes perfect’ principle.

A question still to be addressed is whether there is a difference in QoL between the different types of urinary diversions and also between the different treatment options. If the loss of QoL is not balanced by the increased survival when comparing surgical procedures with radiotherapy, the patient must be informed and counseled when making a treatment decision. Moreover, with the increasing use of robotic-assisted cystectomy, the in hospital stay, postoperative mortality rate, morbidity rates and long term survival are changing and still under investigation [50]. Furthermore, the bladder-sparing treatment with chemoradiotherapy has also emerged [51]. Thus, some of the old answers related to QoC and QoL may no longer be applicable in the near future, and many new questions are yet to be answered.

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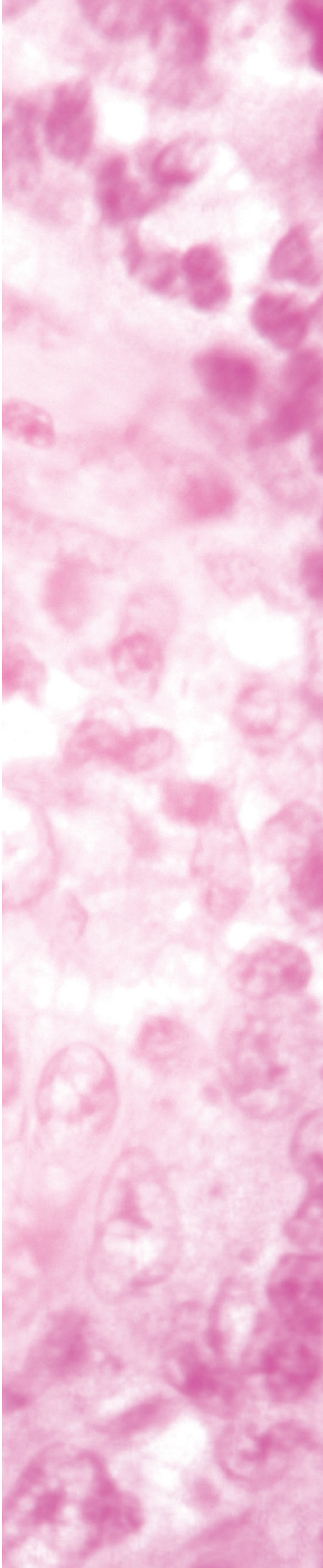
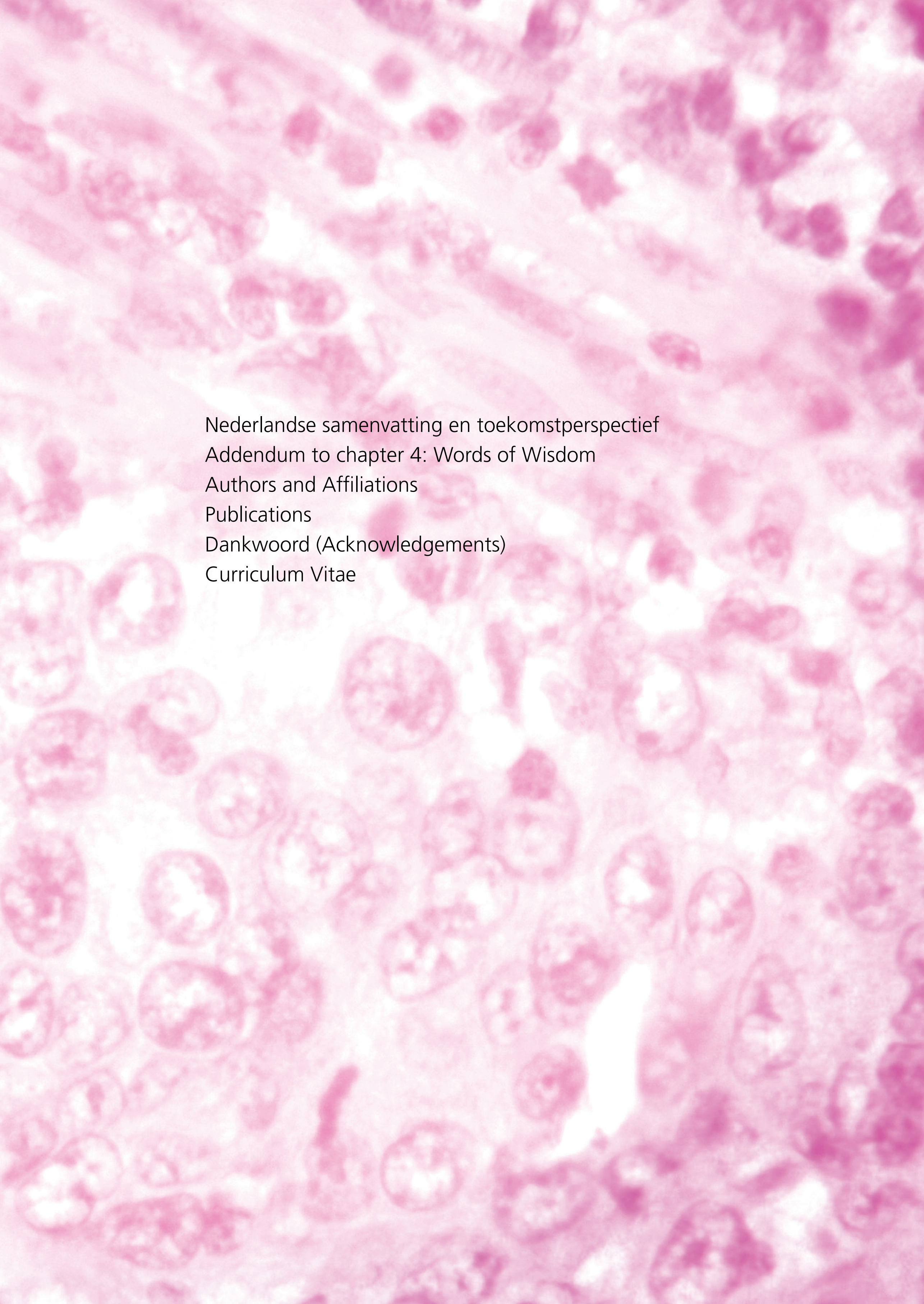
Part V

Appendices





Nederlandse samenvatting en toekomstperspectief
Addendum to chapter 4: Words of Wisdom
Authors and Affiliations
Publications
Dankwoord (Acknowledgements)
Curriculum Vitae

Kwaliteit van zorg en de kwaliteit van het leven: maatschappelijk belang

Tegenwoordig is het bijna onmogelijk een urologisch tijdschrift te vinden waarin geen artikel over kwaliteit van zorg (KvZ), kwaliteit van leven (KvL) of beide onderwerpen staat. Dit geldt ook voor medische opiniebladen, congressen en zelfs farmaceutische commercials. De vraag van patiënten en verzekeringsmaatschappijen om meer transparantie in de gezondheidszorg zorgt dat dit onderwerp hoog op de politieke agenda staat in Nederland, vooral KvZ en kwaliteitsindicatoren.

Met betrekking tot KvL zijn op dit moment bijna 60% van alle patiënten met kanker 65 jaar of ouder [1]. Spierinvasief blaaskanker is een nare ziekte; de 5-jaars overlevingskans na een behandeling is slechts 32% (**hoofdstuk 8**). Hoewel ouderen minder frequent een radicale cystectomie ondergaan (**hoofdstuk 7**) rijst de vraag of de negatieve gevolgen van deze grote chirurgische ingreep voor de kwaliteit van iemands leven wel worden gecompenseerd door de grotere overlevingskans. Dit proefschrift geeft de resultaten weer van het onderzoek naar het niveau van de kwaliteit van zorg, geleverd aan de patiënten met spierinvasief blaaskanker en hun kwaliteit van leven waargenomen voor en na het ondergaan van een radicale cystectomie.

Het doel van dit proefschrift was om de volgende onderzoeksvragen te beantwoorden:

1) In welke mate wordt bij patiënten met spierinvasief blaaskanker de kwaliteit van leven beïnvloed door het ondergaan van een radicale cystectomie?

2) Hoe kan het proces van de kwaliteit van de zorg voor spierinvasief blaaskanker in Nederland worden gemeten?

3) Worden de mortaliteit en overleving bij de behandeling van spierinvasief blaaskanker in Nederland, in het bijzonder van de radicale cystectomie, beïnvloed door het volume van de procedures?

Deze algemene discussie geeft een overzicht en bespreking van de resultaten van onze studie ten opzichte van de beschikbare literatuur over deze onderwerpen.

Blaaskanker

Deel I

Hoofdstuk 1 presenteert een introductie over blaaskanker; van de diagnostiek tot de behandeling van het niet-spier- en het spierinvasieve blaascarcinoom. De diagnose blaaskanker is van grote invloed op iemands functioneren en zijn sociaal en emotioneel bestaan. Dit maakt dat bij de behandeling een multidisciplinaire aanpak vereist is. Hierbij worden de comorbiditeit, functionele en fysiologische reserves per individu bekeken, om zo tot het beste behandelplan te komen. Verder worden doel en opzet van de studies opgenomen in dit proefschrift uiteengezet.

Deel II

Kwaliteit van leven

Vanwege de associatie van KvL met KvZ, is KvL tegenwoordig een belangrijke uitkomstparameter van zorg. Voordat de resultaten naar aanleiding van de derde onderzoeksvraag zullen worden gepresenteerd, wordt eerst achtergrondinformatie gegeven over hoe KvL gemeten kan worden bij patiënten met blaaskanker. Kwaliteit van leven staat voor de perceptie die mensen hebben op hun positie in het leven in de context van de culturele en waardesystemen waarin zij leven, en ten aanzien van hun doelstellingen, verwachtingen, waarden en zorgen. Dit maakt het een multidimensionaal concept waarbij veel meer meespeelt dan alleen maar directe gezondheid gerelateerde aspecten [2]. Met andere woorden, KvL refereert aan de tevredenheid van een persoon met verschillende aspecten van zijn/haar leven en hoeft geen directe weerspiegeling te zijn van zijn/haar functioneren. KvL wordt vaak verward met functionele status en gezondheidstoestand. Functionele status vertegenwoordigt het lichamelijk functioneren van een persoon. Gezondheidstoestand (health status; HS) vertegenwoordigt daarentegen de invloed van ziekte op iemands fysieke, sociale en psychologische functioneren. HS is net als kwaliteit van leven multidimensionaal, maar is direct gerelateerd aan functioneren. Als laatste wordt het concept “gezondheid-gerelateerde kwaliteit van leven” vaak gebruikt waarin KvL wordt gemeten uitsluitend op de volgende drie domeinen van KvL: fysiek, sociaal en psychologisch functioneren [3,4]. KvL, functionele status en HS zijn patiënt-gerapporteerde resultaten; oftewel patient reported outcomes (PROs). PROs zijn zelfrapporteringen; het antwoord komt direct van de patiënt over hoe ze zich voelen, functioneren, gehinderd zijn in hun gezondheid en conditie, en over hun behandeling zonder tussenkomst van de arts of iemand anders. PROs kunnen gerelateerd zijn aan symptomen, signalen, functionele status, perceptie en andere aspecten, zoals gemak en verdraagbaarheid [5].

Bij patiënten die een radicale cystectomie ondergaan, zijn wij geïnteresseerd in KvL, dat wil zeggen hoe de persoon de verschillende aspecten van zijn of haar leven ervaart. Ter verduidelijking het volgende voorbeeld: een persoon heeft artritis en kan een trap niet goed meer opkomen (functionele status). Dit vermindert zijn functioneren c.q. zijn gezondheid (gezondheidsstatus). Bij het meten van de KvL van deze persoon, meten we of deze persoon het problematisch vindt dat hij niet langer de trap kan beklimmen. Misschien woont hij wel in een appartement met een lift en hoeft hij geen gebruik te maken van de trap.

Hoofdstuk 2 presenteert de resultaten van een multicentrische prospectieve baseline studie (niveau 2) naar KvL, HS, seksuele functie en angst bij patiënten met primaire hematurie, die na analyse blaaskanker blijken te hebben. Deze patiënten worden vergeleken met een groep patiënten met hematurie die na diagnostiek te hebben verricht een andere (niet-kwaadaardige) diagnose blijken te hebben. Blaaskanker werd gevonden in 17% van de patiënten. **Hoofdstuk 3** bevat de resultaten van de follow-up case-control studie over KvL en HS bij patiënten met spierinvasief blaaskanker die een cystectomie ondergingen. De nulmeting werd verricht bij een nog niet bekende diagnose, en patiënten werden gevolgd tot één jaar na de radicale cystectomie, en werd vergeleken met de KvL en HS van patiënten met een niet maligne diagnose.

Kwaliteit van Leven vragenlijsten

Sommige eerdere studies vergeleken vragenlijsten over KvL tegenover HS om te zien of de uitkomsten vergelijkbaar waren [6-8]; deze studies tonen aan dat het gebruik van verschillende vragenlijsten tot andere uitkomsten leidt. Dit onderstreept het belang van het gebruik maken van de juiste vragenlijst voor het beantwoorden van de onderzoeksvraag. Voor dit proefschrift is besloten om gebruik te maken van de World Health Organization Quality of Life (verkorte versie), dit is een algemene vragenlijst om de kwaliteit van het leven te evalueren [9,10]. Voor het meten van de gezondheidsstatus werd voor de SF-12 vragenlijst gekozen, ook bekend als de korte versie van de Rand 36 [11]. Zowel WHOQOL-Bref als de SF-12 zijn generieke vragenlijsten, die gebruikt kunnen worden om patiëntgerapporteerde gegevens te verkrijgen in de algemene populatie. Na de cystectomie, werd ook de FACT-BL, een blaaskanker-specifieke vragenlijst afgenomen, om de resultaten te kunnen spiegelen aan de postcytectomie-resultaten van de WOQOL-Bref en de SF-12.

Hoewel een betere pre-diagnose mentale gezondheidsstatus werd waargenomen bij patiënten met blaaskanker, waren ze even tevreden met hun KvL als patiënten met andere oorzaken van hematurie (**hoofdstuk 2**). In vergelijking met de KvL tegenover HS studies uitgevoerd bij patiënten met leverziekten, claudicatio intermittens of borstkanker [12], waren de verschillen in uitkomst tussen de twee afzonderlijke vragenlijsten niet zo evident bij de hematurie-patient. Dit zou het gevolg kunnen zijn van het gebruikmaken van de verkorte SF-12 en de WHO-QoL versies, waardoor mogelijke verschillen lastiger te detecteren zijn.

Persoonlijkheid

KvL wordt beïnvloed door gezondheid [2], cultuur [13], sociaaleconomische status [14] en persoonlijkheid [15,16]. Vooral de persoonlijkheidskarakteristiek ‘angst’ is gerelateerd aan KvL, maar kennis hierover bij blaaskanker is beperkt voorhanden. De vragenlijst STAI-TRAIT is gebruikt om de karaktertrek angst te meten [17,18]. Zowel in **hoofdstuk 2 en 3** is gerapporteerd dat een trend is waargenomen dat de patiënten met blaaskanker lager scoorden op de karaktertrek angst dan de patiënten met overige oorzaken voor de hematurie. Het laagste percentage van een angstige persoonlijkheid werd gevonden bij patiënten met spierinvasief blaaskanker. Het verschil tussen patiënten met blaaskanker vs. andere oorzaken, was 16.5% vs. 24.7% (**hoofdstuk 2**). Bij patiënten die een cystectomie ondergingen vs. de case-control patiënten, was dit verschil nog duidelijker, 5,6% vs. 20% (**hoofdstuk 3**). Verder onderzoek is nodig om deze trend te kunnen bevestigen. Maar als deze bevinding voor de patiënt met nog onbekende diagnose voor blaaskanker blijkt te kloppen, dan zou de bewustwording van het alarmsignaal hematurie versterkt moeten worden, even als het noodzakelijke onderzoek naar de oorzaak.

Er zijn verschillende vragenlijsten beschikbaar die de concepten QoL; HS; HS-Qol; nog verder specificeren. Naast de generieke vragenlijsten (WHOQOL-100/Bref; SF-36/12), kan er ook gekozen worden voor een ziekte-specifieke vragenlijst (de FACT-General; Functional Assessment of Cancer Therapy, of een (blaas)kanker-specifieke vragenlijst (FACT-Bladder)), of een behandeling-specifieke vragenlijst. Hoe specifieker de vragenlijst, hoe kleiner de groep van patiënten die kan worden opgenomen, en hoe moeilijker het wordt om de validiteit en betrouwbaarheid van dergelijke studies vast te stellen. Het nadeel van ziekte-specifieke vragenlijsten is dat zij niet van toepassing zijn op case-control patiënten, patiënten waarbij de diagnose nog onbekend is of "gezonde" individuen. Dit beperkt de keuze in meetpunten en controlegroep. In **hoofdstuk 3** lieten de resultaten van de FACT-Bl, gemeten na de cystectomie een fysieke (HS-QoL) score zien die stabiel bleef in de tijd, terwijl het functionele welzijn licht daalde. Daartegenover staat dat de WHOQOL-Bref en SF-12 in beide gevallen een afnemende fysieke score lieten zien. De vraag is of de ziekte-specifieke FACT-BL moet worden toegepast in deze specifieke studie, wetende dat de ideale nulmeting niet kan worden gebruikt. Doordat wel generieke vragenlijsten, met wel ideale nulmeting-capaciteiten kunnen worden gebruikt, wordt de FACT-BL overbodig.

Seksualiteit

Naast de bovengenoemde vragenlijsten, werd de IIEF voor erectiele functie aan de studie toegevoegd [46]. Aan de start van dit proefschrift was er nog geen gevalideerde vragenlijst beschikbaar voor het meten van de vrouwelijke seksualiteit. Daarom werden drie vragen van de WHOQOL-100 toegevoegd aan de WHOQOL-Bref om het onderwerp seksuele bevrediging te kunnen beoordelen. Het facet "seksuele activiteit" kan worden beantwoord door zowel vrouwelijke als mannelijke patiënten in tegenstelling tot de IIEF. Omdat de IIEF is een veel gebruikte vragenlijst is, was het opmerkelijk dat deze vragenlijst een reden bleek voor veel patiënten om niet deel te nemen aan ons onderzoek. Van de patiënten die wel deelnamen ondanks de IIEF, gaf slechts 40% antwoorden op de vragen van de IEFF, in vergelijking met 99,5% van de deelnemers die het facet "seksuele activiteit" wel beantwoordden (**hoofdstuk 2**). Blijkbaar zijn de meer algemene vragen over de tevredenheid over seksuele activiteit van de WHOQOL-Bref als minder heftig ervaren dan de specifieke vragen over de erectiele functie van de IIEF.

De resultaten van **hoofdstuk 2 en 3** over dit onderwerp laten zien dat seksuele en erectiele dysfunctie het hoogst was onder patiënten met blaaskanker. Dit kan goed worden verklaard door de relatie met preexistente comorbiditeit (cardiovasculair, als gevolg van roken), hoewel dit niet kan worden bevestigd in deze studie omdat comorbiditeit niet is meegenomen in het onderzoek.

Kwaliteit van leven studies bij blaaskanker

In de uro-oncologische gemeenschap bestaat geen gestandaardiseerd protocol voor het evalueren van KvL studies en is er een grote variatie in KvL gerelateerde studies [20].

Drie systematische reviews over KvL tonen aan dat geen van de uitgevoerde studies een hoger niveau dan niveau 3-4 behaalt [21-23]. Een tweede belangrijke beperking van eerdere studies is dat de sporadische prospectieve studies een nulmeting van HS en/of KvL pas verrichtten nadat de diagnose spierinvasief blaascarcinoom was gesteld [24-26]. Gediagnosticeerd worden met kanker zal vrijwel zeker invloed hebben op een iemands KvL. Het was ons doel om de KvL en HS te beoordelen alvorens de diagnose gesteld werd om een meer realistische inschatting van de uitgangspositie c.q. baseline te verkrijgen. Dit had gevolgen voor de keuze welke vragenlijsten te gebruiken. De FACT-BL kon bijvoorbeeld niet worden gebruikt voor de door ons gekozen nulmeting. Wellicht had dit ook gevolgen voor de motivatie van patiënten om de vragen te beantwoorden over hun seksuele leven, aangezien zij nog geen diagnose hadden voor hun hematurie.

In eerdere studies keerde de psychologische HS en gezondheidgerelateerde KvL uitkomsten terug naar of overschreden de baselinewaarde na de cystectomie [21-26]. Echter, zoals eerder gezegd, geen van deze studies hebben de KvL *voor* de diagnose van blaaskanker gemeten en gediagnosticeerd worden met kanker zal vrijwel zeker leiden tot een gewijzigd perspectief op KvL. Een KvL meetpunt voor het bekend worden van de diagnose zou een meer accurate weerspiegeling moeten geven van de KvL uitgangspositie van een patiënt.

Het doel van deze prospectieve longitudinale case-control studie (**hoofdstuk 3**) was om KvL en HS te meten bij patiënten met een nog onbekende diagnose blaaskanker die (uiteindelijk) een radicale cystectomie ondergaan, en co-variabelen, zoals leeftijd, geslacht, en karaktertrek angst te evalueren. Dit was de eerste case-control studie die KVL heeft gemeten voor dat de diagnose blaaskanker bekend werd. De resultaten van deze studie suggereren dat patiënten na radicale cystectomie pre-diagnose een betere KvL en HS hebben dan postcystectomy, zelfs nog een jaar na de operatie. De ziekte en de cystectomie hebben dus een grote invloed op het leven van patiënten. Daarom moet men voorzichtig zijn om klinisch advies te geven aan individuele patiënten over hun KvL na de cystectomie gebaseerd op eerdere studies met een KvL-meting direct voor het ondergaan van de cystectomie [24-26]. Een andere factor die het verschil in uitkomst zou kunnen verklaren, kan het gebruik van andere vragenlijsten zijn. In deze eerdere studies zijn net voor en na de cystectomie de FACT-BL, of de Europese Organisatie voor Onderzoek en Behandeling van Kanker QLQ-C30 [27] gebruikt of patiënten werd een aantal interviews afgenomen. Zoals eerder vermeld, werd de FACT-BL in de huidige studie alleen gebruikt na de cystectomie. En de EORTC QLQ-30 is een algemene kankervragenlijst [27], die ook niet inzetbaar is voordat de diagnose bekend is.

De resultaten van onze studie laten zien dat pre-diagnose, fysiek functioneren en de seksuele tevredenheid voor patiënten die een radicale cystectomie ondergaan lager waren, en dat het domein fysieke gezondheid toont ook een klinisch verschil in vergelijking met patiënten met andere oorzaken voor hematurie. Een beperking van ons onderzoek is het niet vergelijken van de cystectomie met andere behandelingstechnieken van spierinvasief blaascarcinoom, bijvoorbeeld externe bestraling en brachytherapie. Een tweede beperking is het aantal patiënten dat 'lost-to-follow-up' is ten gevolge van ziekenhuisopname door complicaties of uitbreiding van de ziekte, of door het overlijden ten gevolge van de blaaskanker.

Toekomstperspectief kwaliteit van leven

Bij het beantwoorden van onze eerste onderzoeksvraag - hoe wordt de KvL bij patiënten met spierinvasieve blaascarcinoom beïnvloed door het ondergaan van een radicale cystectomie - is de conclusie dat de KvL negatief wordt beïnvloed door het ondergaan van een cystectomie. Het is nog niet duidelijk of dit uitsluitend aan de cystectomie is te wijten. Het onderzoek moet worden uitgebreid met een grotere populatie, en ook gericht zijn op een analyse van comorbiditeit en intoxicaties zoals roken.

In deze hoog-risico, laag-volume procedure met een 52% 5-jaarsoverleving (**hoofdstuk 6**), is deze informatie een kwestie om te bespreken met patiënten. De cystectomie blijft de gouden standaard behandeling, en deze informatie zal waarschijnlijk niet de keuze van de patiënt veranderen over wel of niet geopereerd willen worden. Hoewel de cystectomie haalbaar is bij de fitte oudere patiënt, kan deze nieuwe informatie mogelijk wel leiden tot een keuze voor bestraling, als een verlengde overleving niet opweegt tegen de verminderde KvL. Voor de patiënten een radicale cystectomie ondergaan, kunnen fysieke training, screening op psychische problemen en, indien geïndiceerd, psychologische begeleiding wellicht de KvL en de HS van deze patiënten verbeteren.

Deel III Kwaliteit van Zorg

Achtergrond van de ontwikkeling van indicatoren in Nederland

In 2005 werd een nieuwe financieringsmethode voor het Nederlandse gezondheidszorgsysteem ingevoerd dat gericht was op het beheersbaar houden van de toenemende kosten van de gezondheidszorg. De stijgende kosten worden enerzijds veroorzaakt door het groeiend gebruik van moderne technische diagnostiek en toegenomen behandelopties en anderzijds door het toenemend aantal ouderen met complexe medische problemen. Dit nieuwe gezondheidszorgsysteem is gebaseerd op vraaggestuurde zorg met gedetailleerde productfinanciering. De verhouding tussen prijs, volume en geleverde kwaliteit kan worden aangetoond door de zorgaanbieder met behulp van zogenaamde indicatoren, dat wil zeggen meetbare elementen van zorgverlening die een beeld over de omvang van de KvZ verstrekken. Deze indicatoren worden *prestatie-indicatoren* genoemd en worden meestal gebruikt voor het beschrijven van processen binnenin een instelling (zogenaamde interne indicatoren) of voor het verantwoording afleggen aan derden (zogenaamde externe indicatoren).

In 2006 werd een project genaamd *Kwaliteit van Zorg in de etalage* gestart door het Instituut kwaliteit gezondheidszorg (CBO) en de Orde van Medisch Specialisten, in opdracht van de Nederlandse organisatie voor gezondheidsonderzoek en ontwikkeling (ZonMw) [28]. Stuurgroepen werden gevormd voor de ontwikkeling van ziekte-specifieke prestatie indicatoren [29]. Het doel van deze externe indicatoren was om inzicht te bieden in de effectiviteit en veiligheid van de door een instelling geleverde zorg, welk inzicht door de instelling in het ideale geval gebruikt kon worden in de onderhandelingen met de verzekeringsmaatschappijen.

Sinds 2010 eist de Inspectie van de Nederlandse gezondheidszorg dat alle ziekenhuizen informatie verstrekken over deze jaarlijkse externe kwaliteitsindicatoren. Een van deze externe kwaliteitsindicatoren is het aantal cystectomieën per ziekenhuis dat per jaar wordt uitgevoerd.

Tijdens het proces van de ontwikkeling van deze externe indicatoren raakte de Nederlandse Vereniging van Urologen actief betrokken en nam zij steeds meer verantwoordelijkheid. Dit gebeurde op verzoek van de leden, aangezien sommige leden (urologen) van mening waren dat de externe indicatoren niet leidden tot een vergrote transparantie in de gezondheidszorg. Het gebruik van externe indicatoren zou wellicht helemaal geen verbetering geven in de doeltreffendheid en veiligheid van de zorg voor patiënten met blaaskanker. De vraag rees of uitsluitend de volumenorm zou moeten worden gebruikt om de gewenste KvZ te verkrijgen of dat andere cruciale factoren van belang waren; hiermee werd de noodzaak en het belang van de interne KvZ-indicatoren duidelijk.

KvZ is gedefinieerd als de mate waarin gezondheidszorg voor individuen en populaties de kans verhoogt op gewenste gezondheidsresultaten en in overeenstemming is met de huidige professionele kennis [30]. **Hoofdstuk 4** beschrijft het proces van de ontwikkeling van kwaliteitsindicatoren/interne indicatoren te gebruiken op ziekenhuisniveau, om de gegeven kwaliteit van zorg te meten. Aan het begin van deze studie, in 2006, bestonden er nog geen KvZ indicatoren (QIs; quality indicators) of een registratiesysteem van KvZ voor het spierinvasief blaascarcinoom. Daarom werden in deze studie QIs gedefinieerd en geselecteerd door een multidisciplinaire projectgroep op basis van recente literatuur, richtlijnen en consensus binnen de projectgroep. In een retrospectief onderzoek werd voor elke QI het behaalde resultaat vastgesteld en deze waarde werd vergeleken met een vooraf gedefinieerde benchmark. Daarna werden de QIs opnieuw gemeten (gegevens niet gepubliceerd). Met betrekking tot de eerste onderzoeksvraag, werd hiermee aangetoond dat het mogelijk is om KvZ te meten en te verbeteren op ziekenhuisniveau. Deze KvZ registratiemethode is een eerste stap in het definiëren van toepasbare en nuttige QI's voor gebruik in de klinische praktijk. Zoals eerder gezegd, in Nederland is er een voortdurende discussie gaande over het gebruik van prestatie-indicatoren. Als het doel van een prestatie-indicator niet bereikt wordt, kan dit leiden tot financiële gevolgen; bijvoorbeeld dat een zorgverzekeraar een ziekenhuis niet betaalt voor de geleverde zorg of in het jaar daarop niet met dit ziekenhuis wenst te contracteren. Daarom, wanneer QIs worden gebruikt in de klinische praktijk, moet men zich er van bewust zijn prestatie indicator gemotiveerde acties te voorkomen, zoals interventies die uitsluitend worden uitgevoerd om het gestelde doel van de QI te bereiken. Het enige doel van interne QIs is de KvZ naar een hoger niveau te brengen. Het ultieme doel van QI is bereikt, als het als een surrogaat maatstaf kan dienen voor 1) oncologische resultaten (kanker-specifieke en algemene overleving), voor 2) KvL parameters en voor 3) gezondheidszorg uitgaven. Zoals vermeld in **hoofdstuk 3**, voordat QIs zijn geïmplementeerd en gestandaardiseerd in de urol-oncologische praktijk, is het essentieel om verbanden te documenteren tussen KvZ en de bovengenoemde factoren.

In **hoofdstuk 5, 6** en **8** wordt een antwoord gegeven op de tweede onderzoeksvraag. Begin 2007 werd in opdracht van KWF Kankerbestrijding, door de signaleringscommissie-Kanker de werkgroep “kwaliteit van kankerzorg” opgericht. Deze heeft het project *“Kwaliteit van kankerzorg in Nederland”* gestart [31].De werkgroep verrichtte een uitgebreid (inter-)nationaal literatuuronderzoek en kon, voor het eerst, gebruikmaken van de totale landelijke data uit de Nederlandse Kankerregistratie (NKR) om te onderzoeken of er verschillen waren in de geleverde KvZ op ziekenhuisniveau. In het kader van dit project werd de in **hoofdstuk 5** beschreven studie uitgevoerd.

Hoofdstuk 5 geeft een samenvatting van de grote verschillen in behandelbeleid in de periode 2001-2006 voor de verschillende regio’s en types ziekenhuizen in Nederland. In totaal onderging 44% van de patiënten met fase II-III blaaskanker een cystectomie, terwijl 26% van de patiënten van hetzelfde stadium werd behandeld met een niet curatieve intentie.

Tevens werd 21% (n = 663) van deze procedures uitgevoerd in 44 laag-volume ziekenhuizen. In 79% van de cystectomieën werden lymfklierdissecties uitgevoerd. Dit gebeurde vaker in hoog-volume en middel-volume ziekenhuizen (82% respectievelijk 81%) dan in laag-volume ziekenhuizen (71%; odds ratio 1.5). De totale 30-dagen postoperatieve sterfte was 3,4% en nam toe bij een stijgende leeftijd. Dit postoperatieve sterftepercentage was aanzienlijk lager (1,2%) in hoog-volume ziekenhuizen.

De radicale cystectomie wordt beschouwd als de gouden standaard behandeling voor stadium II en III (spier-)invasief blaaskanker, wat wordt bevestigd door een recente update van de Europese richtlijn [32]. Met deze richtlijn in het achterhoofd is het aantal cystectomieën voor patiënten met spierinvasieve tumoren met 36% opmerkelijk laag. Zelfs in patiënten met spierinvasiviteit van de tumor en met een leeftijd jonger dan 75 jaar, was het aantal cystectomieën laag (stadium II 65%; stadium III 68%), maar dit percentage stijgt wel met het oplopen van de studiejaren. Een nadeel van onze studie is dat comorbiditeit en de sociaaleconomische status van de patiënten niet bekend waren. Verschillen in comorbiditeit zou een reden kunnen zijn voor het lage percentage cystectomieën [33]. Dat de radicale cystectomie ook onvoldoende benut wordt in de Verenigde Staten, is te zien in een studie over de SEER Medicare database [34]; slechts 21% van de patiënten onderging een cystectomie. Patiëntgerelateerde factoren die geassocieerd werden met een verminderde kans op het krijgen van een cystectomie, waren een oudere leeftijd, meer comorbiditeit en langere reisafstand naar de chirurg [34]. Het niet volgen van de richtlijn werd niet alleen gezien bij het spierinvasief blaascarcinoom. Er is duidelijk ook een verminderd opvolgen gezien van de richtlijn bij het niet-spierinvasieve hooggradige blaascarcinoom [35]. Daar staat tegenover dat er een belangrijk overlevingsvoordeel werd gevonden bij patiënten die tenminste de helft van de aanbevolen zorg ontvingen [36]. Inspanningen ter verbetering van de naleving van de richtlijnen, evenals verbetering van de kwaliteitsinitiatieven zoals de KvZ databases en centralisatie van de cystectomie, moeten de KvZ gegeven aan patiënten met spierinvasieve blaascarcinoom verbeteren. Sinds de publicatie van de variaties in het behandelingsbeleid is er een verschuiving opgetreden richting centralisatie. In 2010 waren er al geen ziekenhuizen in Nederland meer die minder dan 5 cystectomieën per jaar verrichtten.

Door de werkgroep “kwaliteit van kankerzorg” van de Signaleringscommissie Kanker van KWF kankerbestrijding werd tevens een onderzoek uitgevoerd: onderzoek naar de Volume-Uitkomst relatie bij de radicale cystectomie, om bij te dragen aan het politieke debat over de noodzaak van centralisatie van de radicale cystectomie (**hoofdstuk 6**). Een systematisch literatuuronderzoek werd uitgevoerd om alle artikelen te identificeren die de klinische resultaten onderzochten naar aanleiding van het volume c.q. het aantal radicale cystectomieën per ziekenhuis of per chirurg. Er werd een sterke omgekeerd evenredige relatie gevonden tussen ziekenhuizen/urologen met hoge volumes en het postoperatief sterftecijfer (intramurale en/of 30 dagen postoperatieve sterfte). Onze studie is de eerste meta-analyse van de relatie tussen procedureel volume en de uitkomsten van de cystectomieën met inclusie van studies buiten de VS. Een beperking van de meta-analyse is dat het uit de geïncludeerde studies niet mogelijk was om een specifiek omslagpunt voor het noodzakelijke minimumvolume te identificeren; met de meta-regressie is het niet gelukt om een relatie te identificeren tussen specifiek afkappunt qua volume en de sterkte van de relatie ten aanzien van de gevonden uitkomst. Helaas werden er geen studies gevonden die volume als een continu variabele hebben geanalyseerd. Om te zien of we een antwoord met betrekking tot een specifiek omslagpunt konden vinden, werd een sub-analyse voor de Nederlandse situatie gedaan met behulp van de NKR database (niet gepubliceerde data). Op het moment van analyse waren er slechts twee Nederlandse ziekenhuizen die meer dan 20 cystectomieën per jaar uitvoerden. Dit aantal ziekenhuizen was te laag om de grootte van het effect te bepalen. Sinds de publicatie van ons reviewartikel is geen aanvullende publicatie (van goede methodologische kwaliteit) gevonden die in een antwoord voorziet voor een minimumdrempel en/of volume. Uit een recente studie uit de VS naar de trends in volume per ziekenhuis en concentratie van zorg, bleek dat er een daling van 20% in postoperatieve sterfte na een cystectomie werd bereikt na herverdeling van patiënten naar hoog-volume ziekenhuizen [37].

In de bestaande literatuur toonde de relatie tussen procedureel volume (cystectomie) en overleving op lange termijn slechts een trend naar een betere overleving in hoog-volume-instellingen (**hoofdstuk 6**). **Hoofdstuk 8** toont de resultaten van een populatie-gebaseerde studie in Nederland die de lange termijn (5 tot 10 jaar) relatieve overleving onderzocht bij de verschillende soorten behandeling voor spierinvasief blaaskanker, geanalyseerd naar aanleiding van stadium, leeftijd en ziekenhuis volume. Ziekenhuizen met minder dan 10 cystectomieën per jaar werden geclassificeerd als laag volume en ziekenhuizen met 10 of meer cystectomieën per jaar werden geclassificeerd als hoog-volume. Wederom was het aantal ziekenhuizen dat meer dan 20 of meer cystectomieën uitvoerden te laag om afzonderlijk te analyseren.
De totale relatieve overlevingskansen (RSR) voor alle behandelingen samen waren 32% en 25%, op respectievelijk 5 en 10 jaar na de diagnose van spierinvasief blaascarcinoom. Dit betekent dat in Nederland minder dan een derde van de patiënten met spierinvasief blaascarcinoom geneest. Leeftijd lijkt een belangrijke factor te zijn bij de keuze van behandelingsstrategie: patiënten met een leeftijd jonger dan 75 jaar ondergingen vaker een cystectomie, terwijl oudere patiënten vaker radiotherapie aangeboden kregen. De kans op het ondergaan van een cystectomie was aanzienlijk lager wanneer een patiënt werd gediagnosticeerd in ziekenhuis met een laag-volume voor de cystectomie dan wanneer dit een hoog-volume ziekenhuis geschiedde. (34% respectievelijk 42%, p = 0.000). Bovendien verschilt de hazard ratio voor het ondergaan van een cystectomie voor stadium II/III ziekte tussen laag- en

hoog-volumeziekenhuizen, met een 17% hoger risico op overlijden voor patiënten behandeld in laag-volume ziekenhuizen (< 10 cystectomieën/jaar; odds ratio 1.17). Tot slot, het niet ondergaan van een lymfeklierdissectie of een laag aantal gevonden lymfeklieren in het pathologie-preparaat was een onafhankelijke voorspeller voor een kortere overleving. Naar ons weten is dit de eerste studie (van goede methodologische kwaliteit) die een significant positief effect toont ten aanzien van betere overleving na behandeling in hoog-volume ziekenhuizen. Door deze bevindingen wordt centralisatie ondersteund en heeft deze studie gediend als primaire trigger tot het stellen van volume-normen voor urologen in Nederland.

De “selectieve verwijzing theorie” gaat er vanuit dat ziekenhuizen en chirurgen met superieure resultaten meer patiënten zullen aantrekken. Deze theorie kan ook onze bevindingen uit **hoofdstuk 5 en 8** over de volume-uitkomst relatie uitleggen. De literatuur over dit onderwerp blijft echter controversieel. Een studie uit Canada toonde aan dat Afro-Amerikanen, ouderen, ziekere patiënten, armen en Medicare patiënten minder waarschijnlijk een behandeling zullen ondergaan in hoog-volume ziekenhuizen voor uro-oncologische chirurgie [38]. In een Koreaanse populatie-gebaseerde studie hadden patiënten met een hogere leeftijd en een lager inkomensniveau aanzienlijk minder kans om te worden behandeld in een hoog-volume ziekenhuis. De factoren geslacht en comorbiditeit waren geen voorspellers voor een behandeling in een hoog-volume ziekenhuis [39]. Deze bevindingen suggereren dat selectieve verwijzing een positief effect op sterftecijfers in hoog-volume ziekenhuizen zou hebben. Echter, een studie uit Boston (USA), gebaseerd op de “Nationwide Inpatient Sample” suggereert dat selectieve verwijzingen door niet geobserveerde verstrengeling/confounding op basis van patiëntkenmerken (bijvoorbeeld comorbiditeit, sociaaleconomische status) niet de waargenomen negatieve associatie tussen procedurevolume en mortaliteit (gedurende de opname) voor de radicale cystectomie verklaart en dus de hypothese “oefening baart kunst” ondersteunt [40].

Comorbiditeit

Er is steeds meer bewijs dat hoog procedureel volume gerelateerd is aan lagere operatieve sterfte na hoog-risico chirurgie voor maligniteiten (cystectomie, oesofagectomie, pancreatectomie, enz.) [41,42]. Zoals al eerder vermeld, dit verschil kan ook worden beïnvloed door selectieve verwijzing van relatief gezonde patiënten van hogere sociaaleconomische status. **Hoofdstukken 5 en 8** zijn gebaseerd op gegevens die zijn afgeleid van de op de bevolking gebaseerde regionale kankerregisters van Nederland. Een groot nadeel is dat deze studies geen informatie bevatten over de comorbiditeit en algehele conditie (performance status) van de patiënten. Comorbiditeit wordt alleen geregistreerd in de regio van het Integraal Kanker Centrum Zuid. Daarom werd in het zuidelijke deel van Nederland een studie uitgevoerd over de rol van comorbiditeit in de behandelopties van het spierinvasief blaascarcinoom. De resultaten worden gepresenteerd in **hoofdstuk 7**. Er werd gekeken naar het effect van leeftijd, comorbiditeit en sociaaleconomische status (SES) in de behandeling van een populatie gebaseerde reeks van patiënten met spierinvasief blaascarcinoom vóór de periode van de bewustwording van de noodzaak van centralisatie bij Nederlandse urologen. De meerderheid van de patiënten met spierinvasief blaascarcinoom (63%) heeft ernstige vooraf bestaande co-morbide aandoeningen. Dit is vergelijkbaar met het percentage bij nieuw gediagnosticeerde kankerpatiënten in Nederland (48% in de patiënten van 50-64 jaar; wat stijgt tot 80% in patiënten van de leeftijd 80 jaar of ouder) [1]. Over het geheel genomen was de overleving voor oudere patiënten slechter, zelfs na correctie voor comorbiditeit en het ondergaan van een cystectomie. Hetzelfde geldt voor de Nederlandse bevolking met kanker: voor patiënten in de leeftijd 65-79 jaar is de kans om te sterven twee keer zo hoog als voor patiënten in de leeftijd van 50-64 jaar [43]. Degenen die een cystectomie ondergingen hadden echter een aanzienlijk betere prognose, zelfs na correctie voor leeftijd en comorbiditeit. SES was van invloed op keuze van behandeling en op overleving. Patiënten met een hoge SES kregen een andere behandeling selectie, waaronder vaker brachytherapie, en lieten een betere overleving zien. Voor een juiste keuze voor therapie, moeten de risico's en voordelen van cystectomie grondig worden onderzocht in deze steeds groter wordende groep van patiënten. Om dat te bereiken, worden nomogrammen ontwikkeld voor individuele risico-inschattingen in de oudere patiënt [44].

Reguleren van het Kwaliteit van Zorg proces

Tijdens het tot stand komen van dit proefschrift werden in 2010 de conclusies gepubliceerd van het definitieve rapport getiteld *"Kwaliteit van kankerzorg in Nederland"* [10]. De Signaleringscommissie Kanker (SCK) gaf aan dat de gemiddelde kankerzorg in Nederland van hoge kwaliteit is. Er zijn echter grote verschillen in de zorgverlening tussen de verschillende regio's en de ziekenhuizen in heel Nederland. Dientengevolge besloot de Nederlandse Vereniging voor Urologie te kiezen voor een vrijwillig initiatief voor volume-gedreven centralisatie, standaardisatie van chirurgische technieken en voor kwaliteitscontroles voor specifieke urologische ziekten, waaronder het spierinvasief blaascarcinoom. De commissie Kwaliteit en de WOU (*Werkgroep Oncologische Urologie*) ontwierpen een KVZ registratiedatabase in navolging van Nederlandse chirurgische Colorectal Audit (DSCA). Vergelijkbare resultaatgerichte registraties in Nederland (DSCA, NOV, Nederlandse orthopedie complicatie registratie) en in het buitenland (BQS in Duitsland) hebben aangetoond dat deze registratie databases een krachtig kwaliteitsbevorderend effect hebben; vooral wanneer de resultaten worden gepresenteerd als feedback naar de afzonderlijke leden van het 'behandelteam' [45,46]. Dit urologische KvZ registratiesysteem heeft een dubbele functie: het wordt gebruikt voor externe verantwoording maar ook als spiegelinformatie en als verbeteringsinstrument voor de urologen. De Nederlandse KvZ-database heeft een effectief feedbacksysteem dat (op een anonieme manier) de gegevens vergelijkt van iemands eigen instelling met het gemiddelde van de gegevens uit alle andere Nederlandse ziekenhuizen die cystectomieën uitvoeren. De nationale database toont aanzienlijke overlap met de QIs als ontworpen in onze studie en gepresenteerd in **hoofdstuk 4**. Het grote verschil is de registratie van resultaatgerichte parameters, zoals de TNM fase voor onderzoeksdoeleinden en voor het identificeren van case mix binnen de ziekenhuizen. Onlangs is het een verplichting geworden dit nationale registratiesysteem in te vullen als men cystectomiëen uitvoert. Het doel is om de informatie verkregen op ziekenhuisniveau over lokale KvZ, en op nationaal niveau, te gebruiken om via de Nederlandse Vereniging voor Urologie vroegtijdig KvZ problemen te identificeren en verbeteringen te kunnen doorvoeren.

Toekomstperspectief kwaliteit van zorg

Naar aanleiding van deze en andere studies is er onmiddellijk veel veranderd en zijn verbeteringen gerealiseerd, wat het belang aangeeft van KvZ binnen de gezondheidszorg.

Het doel van onze studies over KvZ was om te zien of voor een zeer complexe operatie als de radicale cystectomie volume van invloed is op de uitkomstparameters sterfte- en overlevingscijfers. Zoals **hoofdstuk 5, 6** en **8** laten zien, draagt volume in belangrijke mate bij aan de KvZ. Deze studies hebben een bijdrage geleverd aan het debat over centralisatie van de ingreep. Sinds 2011 heeft de Nederlandse Vereniging voor Urologie besloten een op volume gebaseerde centralisatie toe te passen met een minimumnorm van ≥ 10 cystectomieën per jaar, op basis van de bevindingen besproken in **hoofdstuk 5**. Toekomstige studies zijn erop gericht om de relatie en het precieze cut off punt verder te definiëren. De minimumnorm van 10 wordt nog steeds bediscussieerd en zou in de toekomst kunnen worden verhoogd. In Engeland is door het Nationaal Instituut voor gezondheid en Clinical Excellence (NICE) aanbevolen een volume norm van 50 per jaar aan te houden voor oncologische operaties in het kleine bekken [46].

De Nederlandse registratiedatabase voor spierinvasief blaaskanker werd in 2010 gerealiseerd. Hoewel registratie door de behandelend uroloog logisch lijkt, zijn er enkele nadelen. Leveren van informatie aan de database is tijdrovend, omdat het niet alleen ontworpen is voor KvZ registratie, maar ook voor onderzoeksdoeleinden gebruikt wordt. In het algemeen zijn tenminste 20 minuten nodig om alle gegevens betreffende één patiënt te registreren. Daarnaast wordt 100% informatiedekking bijna nooit bereikt voor de individuele patiënt. Het systeem kan worden verbeterd door het verminderen van de informatie die aangeleverd dient te worden. Dit zal de inbreng door urologen vergroten (een systeem is slechts zo goed als haar gebruikers). Of er kan wellicht steun aan de registratie worden verleend door integratie van de gegevens die worden verzameld door de Nederlandse Kankerregistratie (NKR). De kwaliteit van de gegevens uit de NKR wordt beschouwd als hoog en volledigheid werd geschat op meer dan 95% [48,49].

Tussen 1999 en 2008 werd geen verbetering waargenomen in overlevingskansen na behandeling van spierinvasief blaascarcinoom. De nieuwe database voor KvZ zou kunnen helpen in het beantwoorden van de vraag waar vooruitgang geboekt kan worden in het komende decennium. Hopelijk kan de database ook een antwoord geven in de kwestie van de ”selectieve verwijzingtheorie” ten opzichte van het ”practice makes perfect” principe.

Tot slot

Een vraag die nog beantwoord moet worden, is of er een verschil in kwaliteit van leven bestaat tussen de verschillende typen urinedeviaties en tussen de verschillende behandelingsopties (externe radiotherapie versus cystectomie versus brachytherapie). Als het verlies van KvL niet gecompenseerd wordt door te verwachten overlevingswinst bij het vergelijken van de radicale cystectomie met (chemo)radiotherapie, moet de patiënt hierover worden geïnformeerd en geadviseerd bij het maken van een therapiekeuze. Bovendien, met het toenemende gebruik van robot-geassisteerde cystectomie, zijn de opnameduur, postoperatieve mortaliteit en morbiditeit en lange termijn overleving aan het veranderen; dit wordt nog onderzocht [50]. Verder is de blaassparende behandeling met chemoradiatie-therapie ook steeds meer in opkomst [51]. Daarom zijn enkele van de ”oude” antwoorden met betrekking tot KvZ en KvL mogelijk niet langer van toepassing in de nabije toekomst en zijn er weer veel nieuwe vragen bijgekomen om te beantwoorden.

References

See pages 174-176 of Part IV.

Addendum to chapter 4

Words of Wisdom.

Re: variations in treatment policies and outcome for bladder cancer in The Netherlands.

Professor S. Horenblas
Department of Urology, Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, The Netherlands.

Eur Urol. 2011 Feb;59(2):300. doi: 10.1016/j.eururo.2010.11.007.

Comment to: Variations in Treatment Policies and Outcome for Bladder Cancer in the Netherlands
Goossens - Laan CA, Visser O, Wouters MW, et al
Eur J Surg Oncol 2010;36(Suppl 1):S100–7

Expert's summary:

This paper describes variations in treatment policies and outcome for bladder cancer (BC) in the Netherlands. The authors used data from the population-based Netherlands Cancer Registry and selected all newly diagnosed primary BC cases between 2001 and 2007. The Netherlands Cancer Registry covers the whole country, divided in nine coordinating Comprehensive Cancer Centers (CCCs). Registration clerks at the CCCs extract information for the registry from the medical records noted in the Dutch National Pathology database.

Quality of the data is considered high, and completeness is >95%. All 97 Dutch hospitals were included and were categorized as academic, nonacademic hospitals with teaching facilities, and community hospitals. The following items were assessed: primary treatment according to CCC region, hospital type, volume of cystectomy (<5, 6–10, >10), proportion of lymph node dissection, and 30-d mortality. Of all patients with stage II–III BC, 42% underwent cystectomy, 32% were treated with radiotherapy (RT), and 26% were treated without curative intent.

The results showed a variation in treatment in the various regions: cystectomy (for stage II–III BC) was the preferred option in three of the nine regions, RT was preferred in two regions, and two regions waived curative treatment more often. In 21% of cystectomies, a lymph node dissection was not done. The overall 30-d mortality rate was 3.4%. A statistically significant difference was found between high- and low-volume hospitals (1.2% vs 6.4%).

Expert's comments

This important paper describes, for the first time, a statistically significant difference in outcome (30-d mortality) of cystectomy performed at high- and low-volume hospitals, based on data from a national cancer registry. This paper will fuel the discussion on centralization of cystectomy. Although no deliberate health care policy exists at this moment, there has already been a shift in cystectomy procedures from community hospitals to teaching and academic hospitals. This was reported for the Amsterdam region, where currently >30% of cystectomies are performed at the Netherlands Cancer Institute [1].

Until 2006, almost a quarter (21%) of cystectomies in the Netherlands were done in 44 low-volume hospitals (almost half of the 97 hospitals of the country). Remarkable differences were found in the choice of primary treatment; these differences are difficult to explain and need to be analyzed in depth. Availability of brachytherapy, a bladder-sparing modality often used in the Netherlands, explains much of the variation in frequency of RT. Additionally, the relatively low number of cystectomies for stage II–III is remarkable, considering the national guidelines, in which cystectomy is the treatment of choice. Differences in comorbidity could be the reason. This is one of the major drawbacks of this paper: no information is provided on comorbidity or performance status. Age plays an important role because the number of cystectomies decreased from 80% in patients <65 yr to <5% in patients >85 yr.

This paper marks an important change in health care. Independent national databases will become ever more important, not only on a national level but also on an individual hospital level. The time will not be far off when outcome of cancer care at individual hospitals will be monitored by independent institutions, with far-reaching consequences for individual physicians.

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Curriculum Vitae

Katja Goossens – Laan was born on August 15th, 1977 as the youngest of three children in Waddinxveen, the Netherlands. She attended secondary school at the Bonaventura College in Leiden and graduated in 1995. The same year she started medical school at Leiden University Medical Centre (LUMC). In the winter of 1999-2000 she fulfilled a research rotation at the cardiology department of Royal Infirmary, University of Edinburgh, Scotland. In 2002, she completed a clinical internship in general surgery at the Beth Israel Medical centre affiliated with Albert Einstein College of Medicine, Yeshiva University, New York, USA. After returning to the Netherlands and graduating in 2002, she worked as a house officer in general surgery and urology. In October 2005 she started her urology residency training with two years of basic surgical training at St. Elisabeth Hospital in Tilburg (Head: prof. dr. C.J.H.M. van Laarhoven). From January 2008 until December 2009 she received two years of urology training in this teaching hospital (Head: dr. P.J.M. Kil). During these years of training the research presented in this thesis was started, under supervision of co-promotor dr. P.J.M. Kil and promotors Prof. dr. J.L.H.R. Bosch, Prof. dr. J.W.W. Coebergh and mrs. Prof. dr. J. De Vries. The academic years of the residency were followed at the University Medical Centre Utrecht, under supervision of Prof. dr. J.L.H.R. Bosch. In April 2011 Katja won first place in the ESRU Campbell's Challenge at the EAU Annual Congress, a contest between European residents. She received the Moonen-award in November 2011, an award for best article published in 2010 by a urology resident in the Netherlands. In April 2012 the last few months of her residency were continued at St. Antonius Hospital in Nieuwegein (Head: dr. P.L.M. Vijverberg). In June 2012 she participated in the FEBU examination and became a fellow in the European Board of Urology. In July 2012 she became a urologist, and since October 2012 she is working at the Urology Department of Rijnland Hospital in Leiderdorp. Katja is married to Roger Goossens. They are the proud parents of three boys: Marijn, Jorg and Hidde.