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## Improving the Situation of Urinary Bladder Cancer Survivors Treated with Radical Surgery or Radical Radiotherapy

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May I Play You a Little Tune?

## Abstract

In this thesis we investigated whether the situation of urinary bladder cancer survivors can be improved. To do this, it is necessary to acquire a more specific knowledge of long-term distressing symptoms, symptom characteristics (nature, occurrence, intensity and duration), and of the corresponding symptom-induced distress, as well as the effect on well-being and the quality of life (VI). This more exact information can also be used in the pretherapeutic situation to "tailor", as far as possible, the method of treatment for the individual.

Well-being is statistically significantly lower in patients having undergone cystectomy and urostomy, both non-continent and continent, as compared to a matched control population (I). Patients treated with radical radiotherapy for urinary bladder cancer report the same lowered level of well-being (II) in contrast to patients treated with cystectomy and an orthotopic neobladder connected to the urethra; they reported well-being and a subjective quality of life as good as that of the matched control population (III). One reason for the discordance might be the feeling of reduced attractiveness in urostomy patients, a 5-fold increase in feeling unattractive being reported among them (I) as compared to no increase at all in cystectomised patients with a neobladder (III). The 6-fold increase of the feeling of reduced attractiveness in the irradiated patients as compared to matched controls might be an effect due to the increased risk for bowel symptoms. A 9-fold increased risk for defecation urgency and an 11-fold increased risk for faecal leakage were reported by the irradiated patients as compared to the matched controls (II). The risk of being affected by these symptoms was also increased in cystectomised patients with a urostomy, and a 7-fold increase of defecation urgency and faecal leakage was seen compared to matched controls (I). The risk of symptomatic urinary tract infections was increased 3-fold among the operated patients with a urostomy, i.e. 25% had at least one urinary tract infection requiring treatment during the past year (I). Virtually all men operated on were affected by sexual dysfunction, particularly erectile dysfunction, a symptom causing much distress among the affected (I+III, IV). A lower prevalence of erectile dysfunction was seen among the irradiated patients, i.e. 75% (II). Symptoms of sexual dysfunction were the most distressing kinds of symptom among urinary bladder cancer patients (IV). The prevalence of distressing symptoms was lowest for surgical patients with orthotopic neobladder substitution. The occurrence of distressing symptoms does not increase with follow-up time, but an increased symptom burden was strongly correlated with decreased well-being (V). A majority of urinary bladder cancer patients give priority to optimal survival over a reduced symptom burden (I-III).

If we refine the surgical technique during radical cystectomy and preserve (autonomic?) nerves in the pelvis, possibly the distressful bowel symptoms and the faecal leakage seen in patients operated in Sweden but not among those operated at Herlev University Hospital in Copenhagen can be eliminated. The high incidence of urinary tract infections in bladder cancer survivors possibly can be diminished by preventive measures. An orthotopic neobladder substitution and preservation of erectile nerves during surgery are further means to improve quality of life in urinary bladder cancer survivors. For those giving high priority to preserved sexual function, radical radiotherapy can be an option. During radiotherapy, diminishing the dose to the anal sphincter and rectum probably can increase quality of life in the patients that are cured. Our studies have identified additional factors that may improve the situation for urinary bladder cancer survivors, and I conclude that quality of life of urinary bladder cancer survivors probably can be improved considerably.

Key words: Bladder neoplasm, radiotherapy, cystectomy, urinary diversion, distressful symptoms, quality of life

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## List of Papers

This thesis is based on the following papers, referred to by their Roman numerals:

- I. Lars Henningsohn, Hans Wijkström, Paul W Dickman, Karin Bergmark and Gunnar Steineck  
Distressful symptoms after radical cystectomy with urinary diversion for urinary bladder cancer: A Swedish population based study  
European Urology 2001; 40: 151-162
- II. Lars Henningsohn, Hans Wijkström, Paul W Dickman, Karin Bergmark and Gunnar Steineck  
Distressful symptoms after radical radiotherapy for urinary bladder cancer  
Radiotherapy and Oncology 2002; 62: 215-225
- III. Lars Henningsohn, Kenneth Steven, Else Brohm Kallestrup and Gunnar Steineck  
Distressful symptoms and well-being after radical cystectomy with orthotopic bladder substitution as compared to a matched control population  
Journal of Urology 2002; 168: 168-175
- IV. Lars Henningsohn, Hans Wijkström, Kenneth Steven, Jörgen Pedersen, Christer Ahlstrand, Gunnar Aus, Else Brohm Kallestrup, Karin Bergmark, Erik Onelöv and Gunnar Steineck  
Relative importance of sources of symptom-induced distress in urinary bladder cancer survivors (Submitted)
- V. Lars Henningsohn, Hans Wijkström, Jörgen Pedersen, Christer Ahlstrand, Gunnar Aus, Karin Bergmark, Erik Onelöv and Gunnar Steineck  
Postoperative time, symptoms and well-being in urinary bladder cancer survivors (Submitted)
- VI. Gunnar Steineck, Karin Bergmark, Lars Henningsohn, Massoud al-Abany, Paul W Dickman, Ásgeir Helgason  
Symptom documentation in cancer survivors as a basis for therapy modifications  
Acta Oncologica 2002; 41: 244-252

Papers I, II, III and VI have been reprinted with the kind permission of the publishers.





## Introduction

Bladder cancer is the ninth most common malignant disease in the world with about 250.000 new cases each year (Parkin 1999). The management strategy for the individual patient depends on many different factors, e.g. stage and grade of the disease and the patient's physical and mental status as well as patient preferences. Depending on tumour stage and grade, urinary bladder neoplasms represent the full spectrum of malignant severity, ranging from nearly benign without mortality to extremely aggressive with high mortality. Urinary bladder neoplasms considered potentially lethal are in medically fit patients, treated with radical cystectomy or radical radiotherapy. The studies in the present thesis were conducted in patients treated by radical methods. Radical surgery requires urinary diversion by basically one of three different methods, a non-continent urostomy, a continent urostomy, both connected to the skin, or an orthotopic bladder substitution connected to the original urethra. However, one has to realize that there is no completely satisfactory replacement for a normal urinary bladder. In an attempt to increase the individual patient's quality of life, it has been proposed that organ-sparing modalities be used more often. The alternatives proposed are, for example, radical radiotherapy alone or in combination with chemotherapy (radiochemotherapy) or an extended transurethral resection of the bladder tumour with radio- and/or chemotherapy added. These modalities may as well induce long-term distressful symptoms that may affect quality of life.

### Incidence

The total cancer incidence in Sweden was 45,482 in 2000. Urinary bladder cancer accounted for 2086 of these cases (4.7%; 1547 males and 539 females) and is the fifth most common malignant disease in Sweden (Centre for Epidemiology 2002). The incidence of urinary bladder cancer has risen during the last forty years but has during recent years reach a plateau at about 23.5/100,000 inhabitants (35.3/100,000 males and 12.0/100,000 females) (Centre for Epidemiology 2002). Superficial or superficially invasive urinary bladder cancers (Tis-Ta-T1) accounts for 71% (Tis: 4%, Ta: 44%, T1: 22%) and detrusor muscle-infiltrating or non-organ-confined ones for 25% (T2-T4) (Nationellt kvalitetsregister för blåscancer - diagnosår 1999). Metastasis already at diagnosis were found in a small percentage (N+: 3% and M+: 2%). Bladder cancer is more common in the elderly, the mean age being 70, and very rare before age 45. Mortality is around 600 cases per annum in Sweden and has remained at this level during the above observation period.

### Aetiology

In theory, a substantial proportion of new cases of urinary bladder cancers are preventable. Smoking is an important risk factor for bladder cancer around the world, increasing the risk twofold (Ross 1996) to fourfold (Steineck 1988) compared to persons who have never smoked. In the USA and possibly also in Sweden, about 50% of all bladder cancers in men are explained by cigarette smoking alone. Interestingly, non-smoking tobacco does not seem to be related at all to bladder cancer (Ross 1996). In 1896, and later in epidemiological studies from the 1950s, the first group of toxic substances related to bladder cancer was identified, i.e. arylamines or aromatic amines (Case 1993), especially  $\beta$ -naphthylamine which was used earlier in the manufacture of synthetic dyes. Cigarette smoke also contains arylamines, e.g. 2-naphthylamine, and could be one explanation for the increased risk among cigarette smokers. Other factors increasing the risk of urothelial cancer are combustion gases from coal (Steineck 1990b), low intake of fruit and vegetables (Michaud 1999), ptaquiloside (a constituent in bracken fern) (Shahin 1998), arsenics (Chen 1992; Chiang 1993), some pharmacological substances such as phenacetin (Piper 1986), chlornaphazine (Thiede 1969) and cyclophosphamide (Khan 1998), radiotherapy (Kleinerman 1995), as well as chronic inflammation (Kantor 1984), e.g. induced by *Schistosoma*

haematobium causing squamous cell bladder cancer in Egypt (El Bolkainy 1981). A high intake of vitamin A supplements may be related to a lower risk of urothelial neoplasms (Steineck 1990a), as well as intake of NSAID pharmacological substances (Castelao 2000; Steineck 1995) and a high fluid intake (Michaud 1999), possibly related to an increased micturition frequency (Oyasu 1974).

#### Pathology

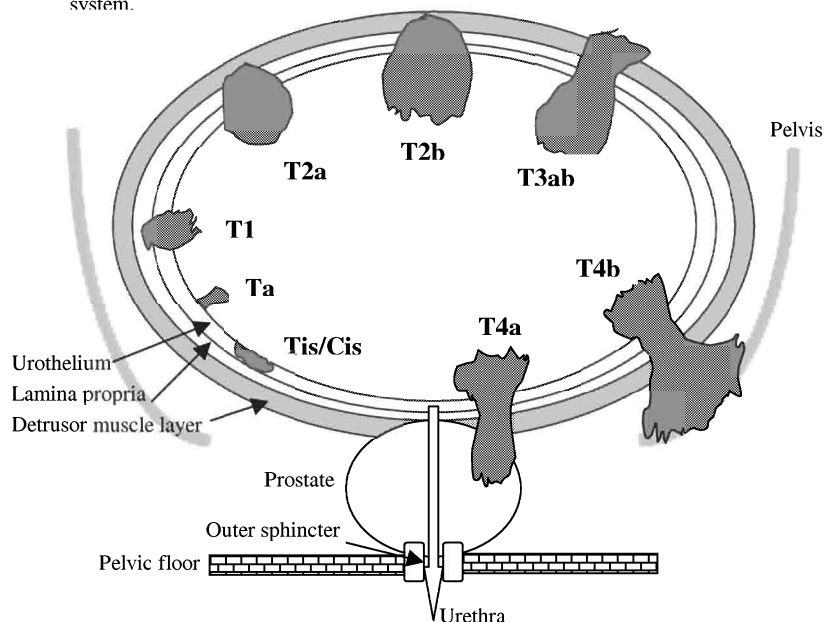
Transitional cell carcinoma (urothelial lining of the bladder) dominates and comprises 97.5% of all urinary bladder cancers in Sweden and squamous cell carcinoma accounts for 1.2% (Nationellt kvalitetsregister för blåscancer - diagnosår 1999). Other uncommon bladder tumours in Sweden are adenocarcinoma, malignant melanoma, sarcoma and lymphoma.

Single papillary/solid tumours were found in 72% and 26% were of multiple origin (Larsson 2002).

#### Classification

Urothelial cancers are categorized according to the depth of penetration into the bladder wall and the distant spread. The tumour, node and metastasis (TNM) system is the most widely used system for classification (Illustration 1) (UICC International Union Against Cancer 1997) and tumour malignancy grade is basically divided into 3 grades (G1-3) (Bergkvist 1965; Histological typing of urinary bladder tumours). Distant metastases are usually localized in the lungs, skeleton, liver and lymph nodes (Babaian 1980).

Illustration 1. Drawing illustrating the male urinary bladder and the 1997 TNM system.



#### Symptoms

Bladder cancer virtually always produces symptoms. Eighty per cent of the patients present with some form of haematuria, macroscopic or microscopic, typically painless and intermittent (Fitzpatrick 1993). Irritative symptoms like urgency, frequency and dysuria, are prevalent in 25% of the patients with bladder cancer (Farrow 1977; Utz 1970).

## Investigations

Cystoscopy in combination with urinary cytology is mandatory for the detection of bladder cancer. The pretherapeutic staging optimally also includes bi-manual palpation before and after the initial resection as well as radiological measures like computer tomography (CT) or magnetic resonance imaging (MRI) (UICC International Union Against Cancer 1997). The incidence of coexisting tumours of the upper urinary tract is about 5% (Oldbring 1989) and, consequently, procedures to exclude upper urinary tract pathology are warranted and are usually effectuated by means of an intravenous or retrograde pyelogram.

## Treatment Strategies

Superficial or superficially invasive bladder cancer is usually managed by trans-urethral resection of the bladder (TUR-B) supplemented with different instillation therapies (chemotherapy or immunotherapy) when needed. Muscle-invasive urinary bladder cancer, about 500 per year in Sweden, is a lethal disease with a 5-year survival rate of only 2% if left untreated (Marshall 1956). Consequently, it has to be treated aggressively.

## Treatment for Locally Advanced Bladder Cancer

In a population-based cohort series from Stockholm (Larsson 2002), it was shown during a 2-year period, that 37% (n=49) of 133 patients with muscle-invasive bladder cancer (T2 or more) were treated primarily with cystectomy, 14% (n=19) with radical radiotherapy, 6% (n=8) with chemotherapy, 20% (n=27) with palliative radiotherapy and 18% (n=24) with trans-urethral resection of the bladder tumour. The first line of treatment in most centres today is radical cystectomy, followed by urinary diversion using either a non-continent, continent or orthotopic technique. Some individuals resist this excenterative procedure for different reasons and, for these patients, bladder-sparing alternatives are available. Some of the bladder-sparing alternatives discussed and tested in different controlled studies are extensive TUR-B with or without radio-chemotherapy, bladder resection and chemotherapy or radical radiotherapy.

## Partial Cystectomy

Segmental resection of the bladder appears to be an attractive option because it preserves the urinary bladder. However, due to the high risk of recurrence of the urothelial cancer, it is an option only in carefully selected patients and is therefore seldom used today (Faysal 1979; Resnick 1973).

## Cystectomy

Radical cystectomy, the surgical procedure when removing the diseased bladder, is performed to minimize the risk of residual disease. The standard surgical technique includes a bilateral lymphadenectomy in addition to excision of the urinary bladder, prostate and perivesical fat. Urethra was initially routinely removed. In women, an anterior pelvic excenteration with a wide excision of the bladder in continuity with the uterus, fallopian tubes, ovaries and the anterior wall of the vagina is usually recommended but, in the patients examined in the present thesis, the vagina and internal genitals were left intact unless local spread necessitated removal. The extension of the lymphadenectomy is currently under debate, but it seems that an extended excision can cure more patients (Mills 2001; Poulsen 1998; Stein 2001). In patients operated on in Sweden, the pelvic lymphadenectomy was limited to the obturator fossa. In carefully selected cases, a procedure sparing the erectile nerves possibly might be an alternative to minimize the risk of erectile dysfunction (Colombo 2001) and incontinence/hypercontinence (Hautmann 1995).

In different reports a perioperative mortality is 2-4% (Ghoneim 1997; Hellsten 1998; Stein 2001). The overall recurrence-free 5-year survival rate has recently been shown to be 60 to 68% in cystectomized individuals (table 1) (Gschwend 2002; Poulsen 1998; Stein 2001) with recurrence rates of up to 30% (Stein 2001). It has been suggested that survival can be increased by performing cystectomy as early as possible, the disease-specific 5-year survival was 80% compared to 56% when a delayed cystectomy (> 3 months after diagnosis of invasive disease) was done (P<0.0006) (Hautmann 1998).

#### **Non-continent Urinary Diversion**

There are different methods of urinary diversion. The majority of the patients receiving a conduit were operated on by the Bricker method, using approximately 10 cm of the small intestine 30 cm from the ileocaecal valve (Bricker 1950), but the colon can also be used then utilizing 15-20 cm of the sigmoid colon (Hinman F.Jr. 1989). The ureters are connected to the proximal end of the intestinal segment inside the abdomen and the distal end of the segment is everted on the outside of the abdomen (illustration 2).

In Sweden, about 55% of all diversions were non-continent in 1999 (Nationellt kvalitetsregister för blåscancer - diagnosår 1999). Continuous propulsion of urine necessitates an external urine-collecting device/bag.

#### **Continent Urinary Reservoirs**

In order to avoid the need for a visible external appliance, such as a urostomy bag, continent reservoirs were invented. Different segments of the bowel have been used by different surgical centres. The most common reservoir in Stockholm is the one constructed according to Nils Kock (Kock 1982) utilizing about 60 to 70 cm of the ileum 50 cm proximal to the ileocaecal valve. The reservoir is made after detubularizing the intestinal segment to create a low-pressure reservoir (illustration 3). Continence is achieved by a nipple valve mechanism constructed from intersuscepted intestines. Intermittent catheterizations are needed in order to empty the reservoir, which has to be emptied at regular intervals.

In Sweden, about 19% of all diversions were continent reservoirs in 1999 (Nationellt kvalitetsregister för blåscancer - diagnosår 1999).

#### **Orthotopic Neobladder Substitution**

In an attempt reconstruct the urinary tract, i.e. urine evacuation through the urethra, as well as to completely eliminate the need for external appliances (catheters as well as bags), the reservoir was connected instead to the urethra in the next step (illustration 4). The neobladder has to be constructed like the reservoir as a low pressure one. Orthotopic neobladders have been developed by different surgeons at different surgical centres in the world utilizing different parts of the bowel (Hautmann 1988; Skinner 1991; Studer 1988). Continence is achieved by the ordinary outer sphincter mechanism and emptying occurs when the abdominal pressure is raised through straining at the same time as relaxing the sphincter. Hypercontinence as well as incontinence can occur and necessitate emptying by clean intermittent catheterizations.

Twenty-six per cent of the patients in Sweden were supplied with an orthotopic neobladder in 1999 (Nationellt kvalitetsregister för blåscancer - diagnosår 1999). It has been proposed that this technique be used more often and at some centres in the world, approximately 90% of male and female patients requiring cystectomy for bladder cancer are appropriate candidates for orthotopic diversion (Elmajian 1996; Stein 1998). Even elderly patients can be operated on by this method without increasing the mortality risk (Soulie 2002).

## Radiation Therapy

Radiotherapy in this study has been given with three different intentions. Firstly, as neoadjuvant therapy to eradicate local micrometastases to the immediate surroundings and as an attempt to downstage the tumour before cystectomy. It was in this context used until 1988. This method is no longer in use due to the absence of any evidence of an advantage (Skinner 1984a), but it can be a biasing factor when discussing long-term symptom prevalence in this study. Secondly, as short-term treatment for palliation in patients in whom the tumour was judged to be curable but the patient unsuitable for a full course of radiotherapy (Wijkström 1991). However, this method has also been disputed (Holmäng 1996; Holmäng 1997)

Thirdly, radiotherapy has been given as a cure for urinary bladder cancer. Curatively intended radical radiotherapy is usually given as a total irradiation dose of 63-70 Gray with external beams and is given with about 2 Gray fractions 5 days a week. Consequently, the treatment time is at least 6 weeks, often with a 2-week rest after approximately 40 Grays. The planning target volume is set to the gross target volume (GTV) with a 1.5-cm margin around it to be sure that the tumour is hit. There is a risk of irradiation to the surrounding structures, i.e. autonomic nerves and blood and lymph vessels, as well as intestines, rectum and the anal sphincter. Radiotherapy is given to one anterior and two oblique posterior fields. Not only surgical techniques, but also means for radiotherapy has developed a lot during the last 15 years and nowadays the GTV is individualized after target planning on computers.

Curatively intended radiotherapy was given to about 55 patients with bladder cancer in Sweden in 1999 (Nationellt kvalitetsregister för blåscancer - diagnosår 1999). The method is often used for patients not fit for radical organ-removing surgery, but today it is also being discussed as an alternative organ-sparing modality. Innovations today are combined treatment with external and interstitial treatment with high bladder tumour control rates, 69% disease free survival after 5 years (Wijnmaalen 1997). The dose per radiation fraction and the radiation technique appear to be important factors for complications (Jahnsen 1991). Severe acute bowel and late bladder toxicity has been seen in patients treated with accelerated fractionation (Moonen 1997).

The overall 5 year survival rate after radical radiotherapy has been found to be 15-34% (Grevén 1990; Holmäng 1997) with a local recurrence rate of 50-70% (table 1). Cancer recurrence might make the patient eligible for salvage cystectomy (Norlen 1985).

## Chemotherapy

A well-documented chemotherapy regimen used for bladder cancer is M-VAC (Metotrexate, Vinblastine, Adriamycin and Cisplatin) developed by Alan Yagoda at the Memorial Sloan Kettering Cancer Centre in New York (Sternberg 1985). Innovations today include chemotherapeutic protocols using gemcitabine and cisplatin (von der Maase 2000) and dose-escalation of the M-VAC protocol (Sternberg 2001). For M-VAC a 15% cure in patients with distant metastases has been reported, but probably the figure of about 2-5% is more reasonable (Nilsson 2001; Steineck 1994).

Chemotherapy as a bladder-sparing alternative has been tried. With added therapeutic options like meticulous transurethral resection of the bladder tumour, 5-year survival rates have been as high as 74% (T2-T3N0M0) including 58% with a functioning bladder, if a complete response after the resection is achieved (=T0) (Herr 1998). No comparative studies are available though (Nilsson 2001).

Adding multidrug cytotoxic therapy to cystectomy, e.g. before surgery, probably increases the 5-year survival by about 5 per cent units (Hellsten 1998; Malmström 1996).

### Chemoradiotherapy

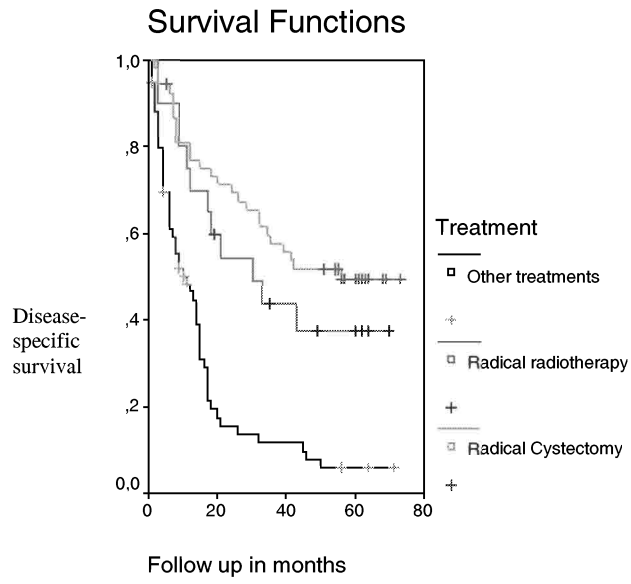
Shipley and co-workers have eradicated bladder tumours by a combination of chemotherapy and radiotherapy (Kaufman 1992; Kaufman 1993; Shipley 2002). Here, too, the primary advantage has been preserving the natural urinary bladder. In the available relatively small studies, the 5-year disease-specific survival rate has been reported to be about 50% or less (Arias 2000; Fellin 1997; Kaye 1985), but some patients will not retain a functioning bladder after the combination treatment (Fellin 1997). The combination of carboplatin and irradiation has been shown to be effective and without unacceptable toxicity (Nichols 2000; Radosevic-Jelic 1999) with a disease free survival of 35%.

### Clinical course in subgroups

The prognosis has been shown to depend on different factors, including stage and grade of the tumour (Ghoneim 1997; Stein 2001), vascular invasion (Gschwend 2002), p53 mutations (Berggren 2001) and uPA and uPAR expression (Seddighzadeh 2002). If metastases are apparent at the diagnosis, the patient usually dies within two years (Hellsten 1998).

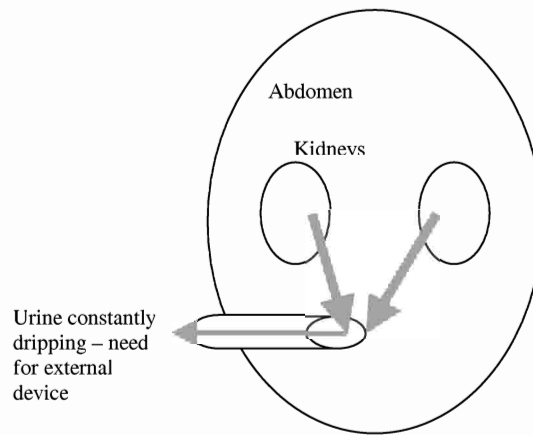
Some important factors can be discerned in a recent population based study on urinary bladder cancer cases diagnosed 1995 and 1996 in Stockholm (Larsson 2002). There were 11 out of 546 patients with tumour in situ (Tis). These were all treated with instillation therapy, two patients progressed to higher stages but no one died of the disease. Out of the 546 patients with urinary bladder cancer 34 were classified as Ta grade 1 (TaG1) and no one progressed to higher stages or died of the disease. TaG2a+b was detected in 243 (out of 546) patients, 14 progressed to higher stages and two died of the disease. TaG3 urinary bladder malignancy was found in 15 of the 546 patients, four progressed to higher stages and two died of the disease. Stage T1, superficially invasive malignancy, was found in 110 patients, 33 progressed to higher stages and 29 died of their disease. Five of the T1 patients were primary treated, within 6 months, with radical intention, i.e. cystectomy or radiotherapy. Stage T2 or higher was found in 133 out of the 546 patients and 87 of these died of urinary bladder cancer. Of the patients with T2+ stage, 51 patients had undergone cystectomy and 19 patients radiotherapy. The five-year disease-free survival was close to 50% among the cystectomized patients and somewhat below 40% among those treated with radiotherapy (figure 1). Patients having a urinary bladder cancer of stage T2 or higher not given the radical treatment modalities mentioned, had a dismal prognosis (figure 1), indicating the need for radical therapy. However, this is a non-randomized study and it is unclear how much of the difference in cancer specific survival is accounted for by confounding factors.

Figure 1. (Unpublished data, published with kind permission of Dr Pelle Larsson).



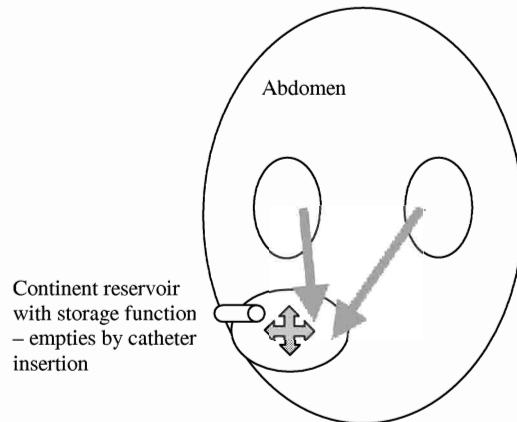
The Different Reconstructive Techniques Illustrated  
**Conduit**

Illustration 2



**Reservoir**

Illustration 3



**Orthotopic neobladder**

Illustration 4

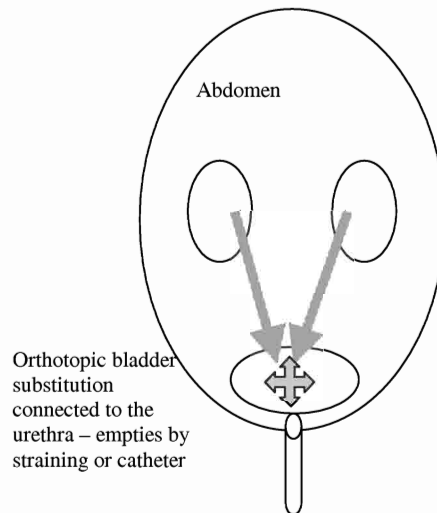




Table 1. Survival in patients treated with radical cystectomy or radical radiotherapy for urinary bladder cancer.

	Cystectomy	Cystectomy	Cystectomy	Cystectomy	Cystectomy	Radiotherapy	Radiotherapy	Radiotherapy
	10-year disease-specific survival (Gschwend 2002)	Recurrence-free 5-year survival (Stein 2001)	5-year recurrence-free survival (Poulsen 1998)	5-year disease-free survival rate (Ghoneim 1997)	5-year survival (Greven 1990)	Corrected 5-year survival rate (Malmström 1987)	Corrected 5-year survival rate (Jahnson 1991)	
	N= 686, Mean age= 64, 61	N= 1094, Median age 66, 68 (66 at 10 y)	N= 194, Median age= 62, 60	N= 1026, Mean age= 48, 48		N=38	N=319	
Overall		68 (66 at 10 y)		48	34		28	
P0		92 (86 at 10 y)						
Pis	(=95)	91 (89 at 10 y)						
Pa		79 (74 at 10 y)						
P1	(=82)	83 (78 at 10 y)		73	35 (T1)	46 (T1)	57 (T1)	
P2	(=74)	89 (87 at 10 y)		66	40 (T2)	36 (T2)	31 (T2)	
P3a	(=64)	78 (76 at 10 y)		47	35 (T3a)	13 (T3)	16 (T3)	
Organ-confined ( $\leq$ P3a)	73		75 (85% ext lgl dis vs 64% lim lgl dis*)					
P3b	(=40)	62 (61 at 10 y)		31	20 (T3b and T4)			
P4	20(P4b) – 76 (P4a)	50 (45 at 10 y)		19			6 (T4)	
Non-organ-confined ( $>$ P3a)	33		34					
N+ (lymph node involvement)	28	24	26	23	7			
Urethral recurrence			1					
5-y risk of distant metastasis		22	30					
5-y risk of pelvic recurrence		7	10					

\* ext lgl dis= extended lymph node dissection, lim lgl dis= limited lymph node dissection

### Quality of Life

The quality of life has probably always been an important concern for physicians. In clinical research, the impact of a disease and interventions on the quality of life has been reported in terms of varying toxicity (e.g. during drug therapies) and morbidity (e.g. after surgery) variables. During the last few decades, numerous survey instruments with, for example, variables defined by theories on the health-related quality of life, have been added to the research armamentarium. Thus, for different research issues, we now have a large number of different approaches to select from in designing an investigation.

In this thesis we want to improve the situation of urinary bladder cancer survivors and must therefore define things in need of improvement. In order to do this, detailed information about the current situation of the survivors is needed. Instruments producing summarized scores gives limited evidence in this regard. A lack of detail compromises interpretation and utility for refining therapy or “informing the patient”. Instead, we need an instrument that measures all possible therapy induced distressing factors in the life of the survivors, i.e. different symptoms, and their impact on well-being and the subjective quality of life. After that, it might be possible to apply resources to the most important factors, from the patients’ point of view, to improve the situation of urinary bladder cancer survivors.

Response shift, a biasing factor when using psychometric instruments, is defined as a change in the meaning of one’s self-evaluation of the quality of life as a result of: (a) a change in the respondent’s internal standards of measurement (scale recalibration in psychometric terms) or (b) a change in the respondent’s values (i.e. the importance of component domains constituting quality of life; or (c) a redefinition of life quality (i.e. reconceptualization) (Schwartz 1999; Sprangers 1999). This phenomenon is believed to have implications in quality-of-life studies as it makes comparisons over time with certain psychometric instruments incomparable due to the value shift of internal criteria. It is understandable that a patient with a life-threatening disease (e.g. cancer) may, after successful radical treatment, irrespective of treatment method, change his/her values for new things in life towards a more satisfying attitude, which in turn is seen in the results of different quality-of-life and well-being studies.

## Previous Studies

### Results from Previous Studies

#### Reports on Quality of Life, Well-being and Psychological State in Chronological Order

Kock and co-workers (Kock 1982) concluded that all 12 patients having received a continent reservoir were satisfied with their diversion, especially if previously having had another type of diversion.

Boyd and co-workers (Boyd 1987) concluded when comparing 87 patients with an ileal conduit and 85 patients with a continent Kock reservoir that the continent reservoir offers an important alternative to non-continent forms of diversion because of a poorer self-image associated with the latter in the form of a decrease in sexual desire and all forms of sexual contact. However, more than 95% of all patients were satisfied with their urostomy, irrespective of the type of diversion.

Månsson and co-workers (Månsson 1988) comparing quality of life in 40 conduit patients with 20 caecal reservoir patients found that irrespective of diversion type severe problems in all aspects of life could evolve as a result of the operation.

Nordström and co-workers (Nordström 1992a) studied 66 patients with an ileal conduit (44 due to cancer and 22 due to benign causes) using a 10-item health index. Eighty per cent considered their health to be very good or rather good (mean score 32 on a scale of 1-40) indicating a "good quality of life" according to the authors.

Bjerre and co-workers (Bjerre 1995) compared 38 patients with a neobladder and 29 with an ileal conduit after a median follow-up of 1 and 5 years, respectively, and concluded that the health-related quality of life was retained to a higher degree after bladder substitution although no statistically significant differences could be detected (90% versus 83%, respectively) in "global satisfaction with life".

Caffo and co-workers (Caffo 1996) concluded that quality of life is better after conservative therapy (radiotherapy with or without chemotherapy) than after cystectomy (with cutaneous diversion) for non-metastatic bladder cancer in a questionnaire study on 29 and 30 patients from the respective therapy group. Forty-seven per cent of the operated felt depressed and 57% anxious compared to 24% and 28%, respectively, of the conservatively treated.

Gerharz and co-workers (Gerharz 1997) addressed stoma-related issues and general aspects of the quality of life in a study of 198 patients with ileal conduits (n=128) and continent reservoirs (n=60). In a specially designed questionnaire they found a significant difference in the global quality of life ( $P=0.0009$ ) between the two groups in favour of the reservoir patients. Furthermore they found a significant correlation between urinary leakage and mental capacity, global self-assessment of the quality of life and satisfaction with one's present life.

Filipas and co-workers did not find any differences in diversion-related symptoms and global satisfaction with life on comparing 27 patients with conduits and 54 patients with reservoirs (Filipas 1997). Nor could any difference be detected in comparison with the normal German population using the earlier validated questionnaire "Quality of Life Satisfaction". Patients with a malignant disease had a lower level of satisfaction than those with a benign disease.

In a study by the Skinner group (Hart 1999), no significant difference in self-reported quality of life could be seen on comparing 25 patients with ileal conduits, 93 with cutaneous Kock pouches and 103 patients with a urethral Kock pouch.

Hobisch and co-workers (Hobisch 2000) compared the quality of life of 69 patients with an orthotopic neobladder and 33 patients with a ileal conduit using the "European Oncology

Research Trial Council Quality of Life Questionnaire – C30” (Aaronson 1993) and a specially designed disease-specific questionnaire and found the quality of life to be preserved to a higher degree after orthotopic neobladder substitution. Twenty-nine per cent of the neobladder patients, compared to 73% of the conduit patients, reported changes in their daily lives; 75% versus 33% felt absolutely safe with the urinary diversion. Physical functioning, emotional functioning, cognitive functioning, social functioning and the global quality of life were all statistically significantly in favour of the neobladder patients.

Ficarra and co-workers (Ficarra 2000) studied 155 patients after surgery for urological neoplasms. The general state of health, measured by the “General Health Questionnaire”, was significantly impaired in 12 out of 35 (34%) patients with an ileal conduit compared to 1 out of 19 (5%) with an orthotopic neobladder of the Studer type ( $P=0.01$ ). Furthermore using the “Hospital Anxiety and Depression Scale” questionnaire (Zigmond 1983), they report that the conduit patients had an increased anxiety level compared to those with a neobladder and the control group (retropubic prostatectomy for benign disease), i.e. 20% (7 out of 35 conduit patients), 5% (1 out of 19 neobladder patients) and 2% (1 out of 44 control patients), respectively, as well as an increased depression level, i.e. 14% (5 out of 35), 5% (1 out of 19) and 2% (1 out of 44), respectively.

Månsson and co-workers (Månsson 2000) found no major differences in health related quality of life comparing 33 Swedish men with 33 Italian men having undergone radical cystectomy and orthotopic bladder substitution.

Jonsson and co-workers (Jonsson 2001) used the “Short-Form-36” in 126 patients with the Kock continent cutaneous reservoir (35 due to bladder neoplasms) and found the physical and mental component scores to be as good as in age- and sex-matched historical controls. However, they also found the re-operation rate to be very high, 49%, mainly due to nipple problems.

Dutta and co-workers (Dutta 2002) examined the health-related quality of life in 72 out of 112 patients (64%) using the instruments “Short-Form-36” and “Functional Assessment of Cancer Therapy-G” and demonstrated marginal quality-of-life advantages in patients with an orthotopic neobladder (49 patients) compared to the patients with an ileal conduit (23 patients). The authors suggest a cautious analysis of their data, however, because age was a confounding factor.

In a study from Japan, Hara and co-workers (Hara 2002) scrutinized 85 men treated with orthotopic bladder substitution or an ileal conduit and found no significant difference in the health-related quality of life between the neobladder and the conduit groups using the “Short-Form-36”. Compared to the general population in the USA, significant disadvantageous differences were found in the two modules “general health” and “social functioning”. Furthermore they compared the patients’ quality of life in terms of the daytime and nighttime continence status and found no difference, suggesting that the continence status has little effect on the health-related quality of life.

Månsson and co-workers (Månsson 2002) examined the quality of life of 35 patients with a continent reservoir and 29 with a neobladder using the “Functional Assessment of Cancer Therapy-Bladder Cancer” instrument and the “Hospital Anxiety and Depression Scale” and found no differences in “quality of life”.

#### Reports on Symptoms Involving the Urinary Tract in Chronological Order

Fosså and co-workers (Fosså 1987) reported that in a study of 49 patients having undergone radical cystectomy with ileal conduit diversion, 69% (33 out of 48 patients) experienced urinary leakage.

Månsson and co-workers (Månsson 1988) reported that episodes of urinary leakage were equally common in the 40 conduit and 20 reservoir patients studied (5% and 15% respectively) but the fear of leakage was less common in the reservoir group. An unpleasant

odour was reported to occur fairly often or very often in 3 out of 40 conduit patients and in none of the reservoir patients.

Cole and co-workers (Cole 1992) studied late toxicity according to the RTOG/EORTC criteria after accelerated fractionation in 24 patients treated with radiotherapy and found 13% with grade 2 urinary toxicity (frequency and intermittent hematuria) and 20% with grade 1 urinary toxicity (microscopic hematuria).

In a study by Hautmann and co-workers (Hautmann 1993) on 211 consecutively cystectomized men with ileal neobladder 85% were continent by night and day at 3 years and clean intermittent catheterization was necessary (post voiding residual urine > 100ml) in 3.5%.

In 1995 Studer and co-workers reported their experience with an ileal low-pressure bladder substitute in 100 patients (Studer 1995) and found 92% to be continent by day (no pad, one year postoperatively) and 80% by night (maximum one pad, two years postoperatively). However, 98% of the 51 patients who underwent a unilateral or bilateral nerve-sparing procedure were continent in the daytime compared to 86% if the neurovascular bundles were sacrificed. Bacteriuria was found in 0-12% of the patients at different postoperative visits with the rate of pyelonephritis with fever being 4 occurrences in 222 person-years. Clean intermittent catheterization was required by 2% of their patients.

Bjerre and co-workers (Bjerre 1995) compared 29 ileal conduit patients with 38 neobladder patients and found a significantly higher level of distress among the conduit patients due to the risk of leakage ( $P=0.001$ ). The incidence of daytime leakage at least once a week was 10% among the conduit patients compared to 18% among the neobladder patients and the nocturnal leakage (at least once a week) was 3% versus 21%.

Hautmann and co-workers (Hautmann 1996) reported that the prevalence of hypercontinence (consequently in need for clean intermittent catheterization) was 70% among the 13 women, eligible for the analyses, operated with urethral support and nerve sparing cystectomy and an ileal neobladder.

Caffo and co-workers (Caffo 1996) studied urinary symptoms in 29 patients treated conservatively with radiochemotherapy or radiotherapy alone and found daily frequency in 44%, night frequency in 42% and difficulty controlling urination in 38%.

Danesi and co-workers (Danesi 1997) found all tumour free patients but one after combined bladder sparing treatment, radiochemotherapy, to have retained bladder function. Fifteen out of 20 studied patients were tumour free.

Wijnmaalen and co-workers (Wijnmaalen 1997) found only one patient (2%) with serious late urinary toxicity (grade 3 = frequency every hour or more often) after external radiotherapy combined with interstitial treatment, in 66 patients.

Filipas and co-workers (Filipas 1997) found that 74% of the patients with a conduit and 68% of those with a reservoir had never experienced urinary leakage.

Gerharz and co-workers (Gerharz 1997) also found in their study (see above) a significantly higher risk of urinary leakage and urinary odour,  $P<0.0001$  and  $0.0005$ , respectively, for the patients with a conduit compared to those with a reservoir.

Clean intermittent catheterization was needed in 15% out of 33 patients with orthotopic neobladders in a study by Weijerman and co-workers (Weijerman 1998). Spontaneous micturition was possible in 61% of the patients and 24% exhibited a combined pattern.

Hart and co-workers (Hart 1999) found that 23% of the patients with a urethral Kock pouch ( $N=103$ ) used pads for daytime urinary leakage while 43.6% used one and 11.7% two or more pads at night.

Leissner and co-workers (Leissner 1999) reported long-term results in 103 patients with Mainz pouch neobladders after radical cystoprostatectomy and found daytime continence to be achieved in 88% (3% were total incontinent) and nocturnal incontinence in 11%.

In 1999 the Ghoneim group analysed the function of orthotopic neobladders in 43 women (Ali-El-Dein 1999). They found that obstruction was caused primarily by an angulation between the urethra and the pouch and concluded that autonomic nerve preservation probably was not important.

In a study of 363 men 11 years after orthotopic lower urinary tract reconstruction with an ileal neobladder Hautmann and co-workers (Hautmann 1999) reported that 32% had late complications including acute pyelonephritis in 23 (6.3%) of the 290 evaluable cases. Five years after surgery, the level of continence was good during the daytime in 84% and during the nighttime in 66%. Sixteen per cent of the 290 patients were incontinent during the daytime and 18% at night five years after surgery. Clean intermittent catheterizations was performed daily by 5.6% of the patients (if having more than 200 ml of residual urine?).

The Ghoneim group studied 100 men with orthotopic bladder substitutes (El Bahnasawy 2000), 50 of whom were completely continent and 50 had enuresis without any underlying organic aetiology and concluded that post-voiding residual urine, frequency and the maximum amplitude of uninhibited contractions in the neobladder were significantly associated with nocturnal enuresis. A significant difference in bacterial growth in the urine ( $P=0.001$ ) was also noted between the continent (40% positive) and the non-continent (72% positive) patients.

Hobisch and co-workers (Hobisch 2000) reported that over a period of 4 weeks, 49% of the conduit patients versus 2% of the neobladder patients had wet clothes caused by urine leakage during the day and 33% versus 42% during the night.

In a study by Steven and Poulsen (Steven 2000) of 166 patients with orthotopic substitution, all patients were continent in the daytime and 94% at night after 5 years of follow-up. Clean intermittent catheterization was required (>100 ml post-void residual urine) in 44% of the patients at 5 years compared to 16% at 6 months. Urinary tract-related late complications were reported in 24% of the patients, the most common being urine leakage (10%). Bacteriuria was found in 24% of the patients at 5 years.

Abol-Enein and Ghoneim studied the function of orthotopic ileal neobladder reconstruction in 344 evaluable patients out of 450 (Abol-Enein 2001) and found hypercontinence (>100 ml residual urine) in 9 out of 80 women, and daytime and night-time continence in 93.3% and 80%, respectively. Pouch stones were found in 10 out of 344 patients.

In a recent relatively small study (9 young patients) Colombo and co-workers (Colombo 2001) demonstrated complete and immediate daytime and nighttime continence as well as normal bladder sensation and an absence of hesitancy in all patients after a nerve- and seminal-sparing cystectomy with orthotopic urinary reconstruction. Only one patient out of nine (11%) required clean intermittent catheterization to empty his/her neobladder. This was confirmed by pressure-flow studies capable of detecting minimal abdominal straining.

In a study involving 102 women who underwent urethra-sparing cystectomy and orthotopic urinary reconstruction, Stenzl and co-workers (Stenzl 2001) found daytime continence to amount to 82%, nocturnal continence to 72% and the clean intermittent catheterization rate to 12%. A normal voiding pattern was observed in at least 77% after a unilateral or bilateral autonomic nerve-sparing procedure.

Constantinides and co-workers (Constantinides 2001), using a modification of the ileal s-pouch as an orthotopic bladder substitute, reported that 95% and 88% of the 52 patients classified their day-, and nighttime continence, respectively, as good or satisfactory. Two patients required clean intermittent catheterization to empty their neobladder.

Hara and co-workers (Hara 2002) reported, in a subgroup of 85 men with a conduit or neobladder, 52% grade 1 continence (fully continent) in the daytime and 71% grade 1 continence at night.

### Reports on Symptoms Involving the Gastrointestinal Tract in Chronological Order

Cole and co-workers (Cole 1992) studied late bowel toxicity according to the RTOG/EORTC criteria in 24 patients treated with accelerated fractionation radiotherapy and found grade 1 (mild diarrhoea and slight rectal bleeding) in 12% of the patients.

Letocha and co-workers (Letocha 1994) studied the effects of combined systemic chemotherapy (PML) and irradiation and reported that within 3 years after the therapy 2 patients underwent sigmoideostomy due to intractable haemorrhagic proctitis.

Bjerre and co-workers (Bjerre 1995) found no statistical difference in the incidence of diarrhoea on comparing 29 ileal conduit patients with 38 orthotopic neobladder patients (10% and 16% respectively had diarrhoea).

Caffo and co-workers (Caffo 1996) found a similar prevalence of bowel symptoms when comparing 29 conservatively treated patients with 30 cystectomised patients.

Wijnmaalen and co-workers (Wijnmaalen 1997) studying late bowel toxicity after combined treatment with external irradiation combined with interstitial treatment, in 66 patients, and found no serious toxicity, i.e. grade 3 or more.

N'Dow and co-workers (N'Dow 1998) studied bowel dysfunction after urinary diversion in 71 patients with ileal conduit diversion and 82 patients with bladder reconstructions (54 with an orthotopic neobladder and 28 with enterocystoplasty). Three (4%) and two (3%) out of the 71 patients with an ileal conduit and 5 out of 54 (9%) and 6 out of 54 (11%) of the patients with an orthotopic neobladder reported defecation urgency and faecal incontinence, respectively. Diarrhoea (3 or more loose or watery bowel movements per day) was reported by 3 out of 71 (4%) patients with an ileal conduit and 7 out of 54 (13%) patients with a neobladder. This study included patients with other diagnoses than cancer, however.

Hart and co-workers (Hart 1999) found that more than 80% of the patients with conduits (N=25), reservoirs (N=93) and neobladders (N=103) "rarely" had physical symptoms such as diarrhoea, abdominal pain and rectal urgency.

The most common adverse event involving the bowel reported by Hautmann and co-workers (Hautmann 1999) in their study on 363 men 11 years after surgery, was small bowel obstruction occurring in 10 (2.7%) patients.

Abol-Enein and Ghoneim (Abol-Enein 2001) reported 3 out of 344 cases of bowel obstruction as a late complication.

### Reports on Symptoms of Sexual Dysfunction in Chronological Order

Schover and Eschenbach interviewed 9 sexually active women about sexual function before and after cystectomy (Schover 1985) and found that among those 7 women resuming sexual activity no decrease in sexual pleasure or change in the type of sexual stimulation required to produce orgasm was reported.

Fosså and co-workers (Fosså 1987) concluded that only half of the males having radical cystectomy and an ileal conduit were aware of the post-operative problems of sexual life. Two thirds of the men and women (24 out of 38) operated on reported significant changes in their sexual life.

Månsson and co-workers (Månsson 1988) found sexual problems such as disturbed relationships with partners or emotional and mental problems to be common in 30 patients with a conduit or a reservoir. In another study by the same group (Månsson 1991), sexual function was altered in all patients although the libido was diminished in only half of the patients. Six of the 28 male patients (21%) maintained their erectile function and 10 (36%) experienced orgasms.

Nordström and co-workers studied 33 males and 11 females after cystectomy and ileal conduit construction (Nordström 1992a). Three of the males (9%) and 5 of the females (45%) reported an "altered body image", 8 of the men (24%) versus none of the women reported disturbed sexual function. Twenty-six of the 29 males (90%) lost their ability to achieve

erection although 41% were able to achieve orgasm by masturbation. Five of the 6 females who were sexually active before surgery (out of the 11 operated for cancer) reported a postoperative decrease or cessation of sexual activity. The main reasons for this in the females were decreased sexual desire (5 patients), dyspareunia (3 patients), vaginal dryness (2 patients) and ceased orgasm ability (1 patient). In spite of this, only one woman considered her overall sexual life to be unsatisfactory (Nordström 1992b).

Caffo and co-workers (Caffo 1996) found that 25% of 29 patients treated conservatively, radiochemotherapy or radiotherapy alone to have erectile trouble.

Bjerre and co-workers (Bjerre 1997) did not find any significant difference between the 20 ileal conduit females and the 17 continent reservoir females concerning coitus frequency, vaginal dryness (29% vs 19%), ceased orgasmic ability (29% vs 25%) and dyspareunia (12% vs 44%).

In a study by Studer and co-workers (Studer 1995) of 100 patients, 18 out of 51 patients still had erections, although only 6 patients considered them to be as good as preoperatively.

Gerharz and co-workers (Gerharz 1997) did not find any difference in sexual activities between 61 patients with reservoirs and 131 patients with conduits ( $P=0.19$ ).

Hart and co-workers (Hart 1999) reported that 47% of the patients (see above) indicated postoperatively a moderate or high level of sexual dissatisfaction, compared to 16% before the operation.

In order to improve the quality of life of operated males, nerve and/or seminal-sparing cystectomy can be performed successfully in carefully selected young patients to reduce the morbidity due to erectile dysfunction and infertility (Colombo 2001; Schlegel 1987). Reported erectile function varies after this type of operation, from being insufficient for intercourse in 60% (Schlegel 1987) to completely sufficient in 100% (Colombo 2001).

#### Reports on Other Long-term Dysfunctions in Chronological Order

Eighty per cent of both conduit ( $N=40$ ) and reservoir ( $N=20$ ) patients stated that their stoma site was satisfactory in the study by Månsson and co-workers (Månsson 1988).

Studer and co-workers (Studer 1995) found the incidence of postoperative metabolic acidosis to be related to the length of the ileum used.

Bjerre and co-workers (Bjerre 1995) did not find any significant difference in skin problems between patients with a conduit (stomal skin) and patients with a neobladder (penile skin due to uridome usage).



## The Present Study

### Aims of the Study

The questions we attempted to answer were:

- Is it possible to improve the situation of urinary bladder cancer survivors?
- Which long-term symptoms evolve after different treatment modalities for urinary bladder cancer survivors?
- Which long-term symptoms distress the urinary bladder cancer survivors the most?
- Does long-term symptoms affect the urinary bladder cancer survivors' well-being and subjective quality of life?
- Is it possible to prevent or treat the long-term symptoms so as to improve the urinary bladder cancer survivors' well-being?
- Which treatment is the best alternative for the individual patient with a potentially life-threatening urinary bladder cancer?
- Is it possible to improve and guide future developments in surgical and radio-therapeutic technique by an epidemiological assessment of the long-term situation in urinary bladder cancer survivors?

### Patients and Methods

#### Study Bases

All patients treated with radical cystectomy for urinary bladder cancer in Stockholm County (alive on 1 January 1996 and 40-85 years old, N=294), all patients treated in the same way between 1985 and 1995 (alive on 1 January 1998) at the Örebro University Hospital (N=49), the University Hospital in Linköping (N=40), and the County Hospital Ryhov (N=21), as well as all patients (alive 1 January 1996, 40-85 years old) treated in Stockholm County with radical radiotherapy (N=71), and all patients cystectomized consecutively by one surgeon at the Herlev University Hospital in Copenhagen between 1989 and 1999 (only orthotopic bladder substitution) (N=101), were included in the study. A matched control population (age and gender) was randomly selected in Stockholm and Copenhagen (N=581). Exclusion criteria were cancer recurrence in order not to disturb patients not cured and orthotopic neobladder substitution in Sweden due to small numbers and a different new questionnaire (table 2).

Table 2. Patients and controls in the study bases.

	Control group (SE+DK) <sup>a</sup>	Stockholm Operated	Stockholm Irradiated	Örebro	Linköping	Jönköping	Copenhagen
Total no. of patients invited	581	294	71	49	40	21	101
Responding no. of patients	422 (73%)	251 (85%)	58 (82%)	45 (92%)	34 (85%)	20 (95%)	95 (95%)
Exclusion factors							
Orthotopic neobladder	-	15	-	9*	1	1	-
Cancer recurrence	-	12	9	4*	1	2	6
<b>Total no. included in the study</b>	<b>422</b>	<b>224</b>	<b>49</b>	<b>33</b>	<b>32</b>	<b>17</b>	<b>89</b>
Conduit	-	169	-	16	19	14	-
Continent reservoir	-	55	-	17	13	3	-

\* One patient with a recurrence also had an orthotopic neobladder. <sup>a</sup> SE= Sweden, DK= Denmark.

### Collection of Information

A questionnaire, previously developed on the basis of successive in-depth interviews with patients and clinicians was similar to our questionnaire on male (Helgason 1995; Helgason 1996a; Helgason 1996b) and female (Bergmark 1999) sexual function and contained 137 questions for the cystectomized patients, 139 questions for the irradiated patients and 125 questions for the controls. The questionnaire was successively examined, adjusted and validated by means of an interactive process in a face-to-face situation with patients and controls and was finally tested in two pilot studies including 45+30 individuals. It was designed to evaluate symptoms involving the urinary tract (e.g. infections, leakage and odour), the bowel (e.g. abdominal pain, diarrhoea, faecal leakage, loose stools and urgency), sexual dysfunction (e.g. reduced sexual interest, vaginal changes in women, erectile dysfunction in men and reduced orgasmic pleasure), lymphoedema and psychological state and well-being as well as potential confounding and effect-modifying factors, (e.g. education, occupation, employment status, smoking habits, concurrent diseases and their treatment) (table 3).

The questionnaire assessed (when appropriate) the characteristics of each symptom (incidence, nature, intensity and duration) (Steineck 2002). Incidence was measured on an incidence or prevalence scale, intensity on a 4-category verbal scale (none/little/moderate/much), duration by time, and distress on a 4-category verbal scale. Symptom-induced distress for selected symptoms was documented on a 4-category verbal scale. For example, the question "How often have you had sexual intercourse during the last 6 months?" had the following response alternatives: (a) I have not had sexual intercourse during the last 6 months, (b) A few times, (c) 1-2 times per month, (d) 3-4 times per month, (e) 1-2 times per week and (f) More than 2 times per week" and was followed by the distress question "If your frequency of sexual intercourse has decreased as a result of the treatment and this condition would persist for the rest of your life, how would you feel about it?" with the following response alternatives: (a) I have not noted a reduced frequency of sexual intercourse as a result of the treatment, (b) It would not distress me at all, (c) It would distress me a little, (d) It would distress me moderately and (e) It would distress me a lot."

Psychological states, energy and well-being were recorded on a 7-category visual digital scale including, for instance, the worst and best possible well-being during the preceding six months. Questions about the impact of some comprehensive entities (urinary dysfunction, bowel dysfunction and sexual dysfunction) were also included based on Helgason's study exploring the three-level approach (occurrence, distress and impact on well-being) (Helgason 1997) (illustration 6).

In a trade-off question, the treated subjects and the controls were asked to consider hypothetically the option of risking a poorer prognosis if it had been possible for them to choose to exclude radical organ-removing surgery and choose instead an alternative bladder-sparing procedure. The symptoms were said to occur or not occur while the risk of a shortened survival was specified on a vertical line (0%, 1%, 5%, 10%, 20%, 30%.....90% and 100%).

All chosen study subjects were sent a letter explaining the objectives of the study and an invitation to participate. Those who did not return the enclosed reply form within two weeks were telephoned. The questionnaire to be answered anonymously was sent by post (in Stockholm between 1 September 1996 and 30 April 1998, in Copenhagen between 1 October 1999 and 31 December 1999, and in Örebro, Jönköping and Linköping between 1 March 2000 and 31 May 2000). Treatment-related information was obtained from the patients in order to safeguard anonymity.

Table 3. Demographic variables

Characteristic	Swedish Controls	Danish Controls	Conduit	Reservoir	Neobladder	Radiotherapy
Total number in each group	310	112	218	88	89	49
Gender – proportion (%)						
Men	209/308* (68)	101/112 (90)	171/217* (79)	64/88 (74)	80/89 (90)	36/49 (74)
Women	99/308* (32)	11/112 (10)	46/217* (21)	22/88 (26)	10/89 (10)	13/49 (27)
Age – mean $\pm$ SEM (median)						
Men	73.0 $\pm$ 0.6 (74)	65 $\pm$ 1.0 (66)	71.6 $\pm$ 0.7 (72)	66.3 $\pm$ 1.3 (66)	64.1 $\pm$ 1.1 (64)	78.1 $\pm$ 0.8 (79)
Women	73.3 $\pm$ 0.9 (76)	66 $\pm$ 1.5 (69)	74.8 $\pm$ 1.4 (76)	63.6 $\pm$ 2.3 (64)	65.0 $\pm$ 1.8 (64)	80.5 $\pm$ 1.2 (81)
Marital status – proportion (%)						
Married or living with a partner	204/306 (67)	81/111 (73)	141/211 (67)	67/85 (79)	68/88 (77)	34/48 (71)
Has a partner but lives alone	18/306 (6)	7/111 (6)	30/211 (14)	6/85 (7)	3/88 (3)	3/48 (6)
Single	23/306 (8)	15/111 (14)	12/211 (6)	4/85 (5)	10/88 (11)	2/48 (4)
Widow/widower	61/306 (20)	8/111 (7)	28/211 (13)	8/85 (9)	7/88 (8)	9/48 (19)
Employment status – proportion (%)						
Working	35/304 (12)	34/107 (32)	15/191 (8)	13/72 (8)	32/84 (38)	0
On sick leave	6/304 (2)	3/107 (3)	10/191 (5)	5/72 (7)	5/84 (6)	0
Unemployed	3/304 (1)	2/107 (2)	2/191 (1)	2/72 (3)	0	0
Retired	259/304 (85)	59/107 (55)	163/191 (85)	52/72 (72)	43/84 (51)	46/46 (100)
Level of education – proportion (%)						
Primary school	145/302 (48)	21/110 (19)	118/198 (60)	40/82 (49)	16/88 (18)	30/47 (64)
Secondary school	92/302 (32)	75/110 (68)	53/198 (27)	25/82 (30)	52/88 (59)	13/47 (28)
University	65/302 (22)	14/110 (13)	25/198 (13)	17/82 (21)	20/88 (23)	4/47 (9)
Unknown	-	-	2/198 (1)	-	-	-
Born in Sweden or Denmark – proportion (%)	283/305 (93)	111/111 (100)	192/211 (81)	74/86 (86)	83/88 (94)	33/36 (92)
Preoperative irradiation	-	-	22/54 (41)	111/165 (67)	0	-
Preoperative chemotherapy	-	-	20/53 (38)	59/160 (37)	0	-
Daily smoking, one year or more - proportion (%)						
Never smoked	143/310 (46)	40/104 (39)	38/189 (20)	16/83 (19)	11/84 (13)	11/38 (29)
Former smoker	111/310 (36)	24/104 (23)	98/189 (52)	36/83 (43)	29/84 (35)	20/38 (53)
Current smoker	48/310 (15)	40/104 (39)	53/189 (28)	31/83 (37)	44/84 (52)	7/38 (18)

Percentages may not add up to 100 because of rounding. \*The gender of 2 controls and 1 patient with a conduit is unknown.

### Data Processing and Statistical Analyses

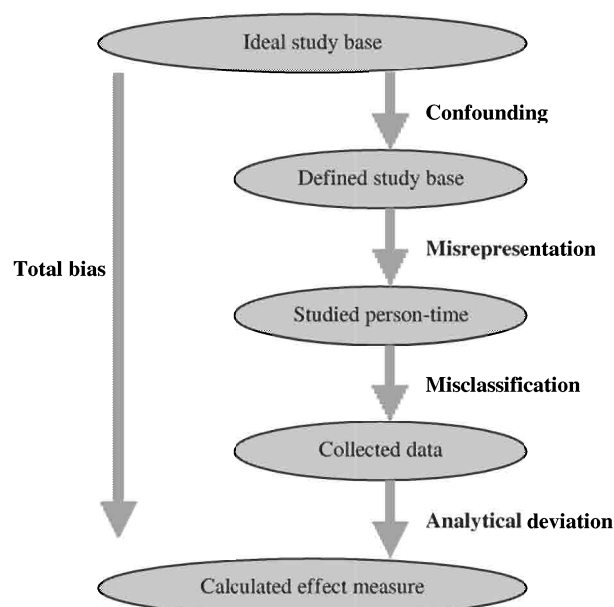
On the population level, we calculated the percentage of subjects with a certain incidence, prevalence, intensity, duration, or level of distress of a symptom. To compare groups, the outcome measures were dichotomized to estimate relative risks: the percentage of, for example, subjects operated on reporting the outcome divided by the percentage of controls reporting the same outcome. Sex- and age-adjusted relative risks, as well as the associated 95 per cent confidence intervals, were calculated by the Mantel-Haenszel method (SAS Procedures Guide; Rothman 1998). P-values were calculated using Fisher's exact test. In **study V** the results were standardized after stratification into the age intervals 49-68, 69-75 and 75 or older (by using the weight of the age distribution in the follow-up period "2-5 years" transferred into the other follow-up periods) and the Mantel-Haenszel's chi-square test, as calculated by the "linear-by-linear association"-command in SPSS (Statistical Package for the Social Sciences), was used to test if  $a \neq 0$  for the line  $y = aX + b$ .

The 7-point digital visual scales measuring well-being, anxiety, depression, energy level and the total subjective quality of life were divided into three categories: 1-2 = low, 3-5 = moderate and 6-7 = high whereupon the figures were dichotomized to compare groups as mentioned above. The prevalence of erectile dysfunction was assessed using the method described by Helgason and colleagues (Helgason 1998).

### Study Design

Steineck and co-workers (Steineck 1998) discusses biasing factors associated with epidemiological studies applicable to this study (illustration 5). The study base is the piece of reality we investigate (the total person-time at risk or a specific slice of person-time) and it is from the study base that data are collected. The ideal study base would be one without any biasing factors at all, thus giving us the right and true answers to our questions. An ideal study would be composed of "all individuals in the universe" randomly allocated. In reality, however, it is not possible to study the ideal study base so biasing factors arise when we inevitably deviate from this ideal study. The total bias can be broken down into confounding, misrepresentation, misclassification and analytical deviation.

Illustration 5. Different stages in a clinical study with corresponding biasing factors.



An imaginary situation without confounding occurs if one could simultaneously observe the same patients' response to treatment as well as no treatment. In this situation all extraneous factors would be constant and cause no confounding. Another optimal, but totally unethical, situation would be if healthy individuals could be randomized to go through a radical bladder cancer treatment or not go through such a treatment. Possible alternatives would be pseudorandomization or a before-and-after situation. In this thesis controls represent hypothetical patients before treatment and they differ from patients by not having had the disease and not having been treated. Factors related to the symptom are thus potential confounding factors. Confounding is a matter to consider in all clinical studies and can be classified as a deviation from the ideal study base when defining the specified study base. It may be introduced by a risk factor for the outcome as well as associated with the independent variable in the study base. Many different confounding factors have to be considered in our study, e.g. demographic factors like geographical region, educational status and employment status as well as other factors like age, gender, marital status, smoking, concurrent diseases and medication. Information on these and other potential confounding factors has been collected and used to detect possible confounding. Some potential confounders cannot be measured, for example, a possible response shift due to new values or tumour damage to different tissues before it was removed, e.g. the effect on rectal function. However, we consider unmeasured confounders unlikely to explain the associations obtained in the study.

In the studies of this thesis, all patients still alive having been treated for invasive bladder cancer by a special method has been included – a cohort of patients. The comparison group should be as closely alike as possible regarding all the different factors affecting outcome except the therapy. The controls were randomly selected from the normal healthy population in the same geographical region as the patients (Stockholm and Copenhagen) and frequency-matched by age and sex. This makes the comparison relevant to the clinical “patient-to-doctor” situation and the data can easily be used directly by the practising urologist. For example, if the patient wants to know what it is going to happen after the treatment, the informing doctor can use our information to the patient. Some might argue that a control population of other cancer patients (for example, rectal cancer) would be more relevant because then two cancer populations would be compared with the same expectations for the future. However, no patient I have ever had in the clinic has ever asked if he or she will have a situation “after the treatment for his or her disease comparable to that of patients with, for example, rectal cancer” – so such information is not needed in the clinical situation. We must, however, consider expectations concerning the future to be a confounding factor in this study when comparing the healthy controls with the bladder cancer survivors. The official registers in Sweden are useful to reduce selection problems in forming patient cohorts.

Misrepresentation might happen when non-participation becomes too marked. This reduces the validity if the non-participants consists of certain individuals in which there is an association between the independent variable and outcome that differs from the studied person-time. Great efforts have been made to reduce non-participation, and reasons for non-participation have been assembled and indicate a random pattern. Consequently, we see no indication that this biasing factor would be large enough to explain the associations in this study, but we cannot rule this out as a biasing factor.

Bias classified as misclassification may, or may not, be the result of measuring errors and can occur with regard to the exposure and the disease. Outcome misclassification happens when some subjects are incorrectly classified as having a symptom, or vice versa. For example, if diarrhoea is classified or recorded as diarrhoea in some patients and not as diarrhoea in others even though true diarrhoea exists in both groups. One remedy to increase the validity in this case would be to use clear concepts and easily understood scales as well as use of exactly the same questions and scales for the different populations compared. Our instruments, the questionnaires, have been tested firstly by in-depth interviewing of the patients, secondly by face-to-face validation and thirdly by pilot studies. In-depth interviews

of the patients gave us an idea of what areas and symptoms were most relevant to the patients. In the next step, a very important step, a face-to-face validation was performed in which all questions were validated in a close working situation with the studied individual and communication to find out if the subject actually understood the different questions in the same way as all other subjects taking the test. If not conceptually totally clear, the question was revised and the new modified version was tested again. In the last step, the pilot studies, all aspects of information collection were evaluated before the main study could begin. Dichotomization was used in many analyses of our data in order to make them more understandable and useful in the clinical setting. This may lead to a loss of statistical power that dilutes the risks towards 1.0 and thus cannot explain the associations found.

An inappropriate choice of statistical method could affect the last step in the “biasing ladder”. The method chosen has to be correlated with appropriate covariates to stratify, shape and adjust the results. For example, questions related to sexuality are certainly affected by age, so all these results are adjusted for age.

Lastly, the generalizability of our results could be questioned since surgical and radiotherapeutical techniques are constantly changed in order to obtain better results. This study has been made to assess long-term symptoms and therefore cannot easily be applied to the different techniques used today.

#### Symptom Documentation (**Paper VI**)

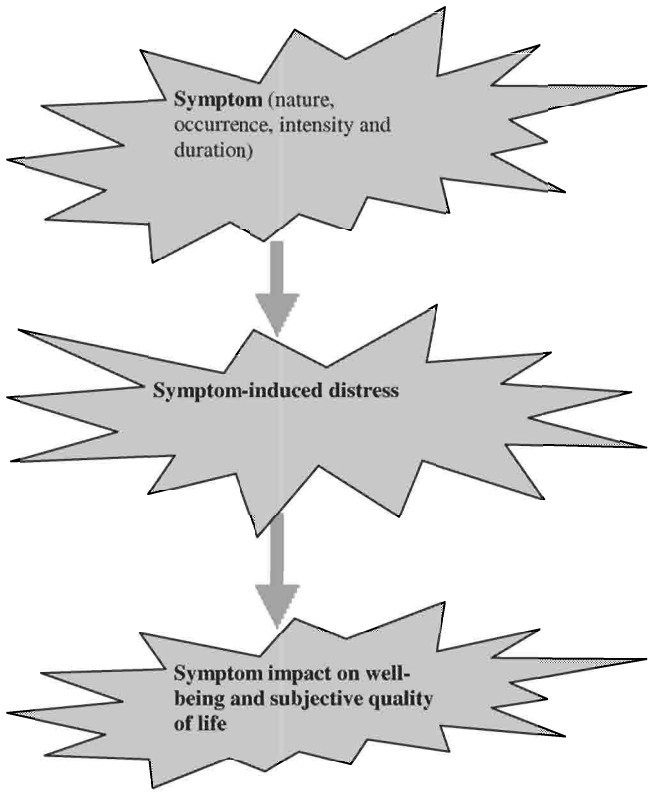
Detailed information on the occurrences of different long-term distressful symptoms related to details of the specific therapy is needed in order to suggest therapy modifications with the aim of bettering the situation for cancer survivors. In paper VI, our method of research is described in detail. We focus on the subjective long-term situation and define symptoms as a perceived abnormality. For conceptual clarity, we abandon summarizing items/scores/questionnaires and instead consider one symptom at a time. Measures of disease occurrence in the population are translated epidemiologically into measures of symptom occurrence in the individual also in order to make our findings easy to apply in the clinical situation.

A symptom has different dimensions, i.e. nature, occurrence, intensity and duration. **Nature** distinguishes one symptom from another. **Occurrence** describes how often the symptom appears and is measured in terms of incidence or prevalence. Incidence is the number of events per unit of time (e.g. number of defecations per week) and prevalence is the proportion of occasions with a condition/symptom divided by the total number of occasions (e.g. defecations with intense urgency divided by the total number of defecations). **Intensity** describes the severity of a specific symptom and can be measured on a verbal category scale (e.g. no/little/moderate/much), a visual digital (e.g. a 7-point numbered scale anchored by the worse possible and the best possible situations) or a visual analogue scale (e.g. the VAS scale for pain where no numbers but only a line is seen). **Duration** describes the time dimension of a symptom, for example how long it persists on each occasion.

In the next phase, each symptom’s specific degree of distress is evaluated in order to measure its relevance. This can either be evaluated by questions about the symptom’s effects on, for example, travel frequency or by asking to what degree the symptom would distress (no/little/moderate/much) the subject if he/she had to live with the symptom for the rest of his/her life. The distress a specific symptom causes depends not only on the dimensions mentioned above (nature/ occurrence/intensity/duration) but also on the individual’s ability to cope with them. Many factors influence this last factor, including personality characteristics, religion and social factor.

Finally, the impact of individual symptoms, as well as groups of symptoms (urinary-, bowel-, and sexually related), on well-being is assessed in the three-level approach (illustration 6) inspired by the work of Portenoy and colleagues at the Memorial Sloan Kettering Cancer Centre in New York (Portenoy 1994).

Illustration 6. The three-level approach to symptom, distress and well-being.



## Results of the Study

### Baseline Patient Characteristics and Demographic Data

The total response frequencies were 503 out of 576 (87%) patients and 422 out of 581 (73%) controls (table 2). Twenty-three patients in Sweden with orthotopic neobladders and 37 patients with cancer recurrences were excluded from the analyses. One fourth of the Swedish patients and the Swedish and Danish controls were females and three-fourths men, to be compared to the neobladder patients in Copenhagen where 90% were men and 10% women. The median age ranged from 64 years in men and women with neobladders to 81 years in women treated with radical radiotherapy (table 2). Other demographic factors such as marital status, social status, level of education and smoking habits did not differ significantly (table 3).

### Quality of Life and Well-being (Papers I-III)

Low or moderate psychological well-being was reported by 62% (33/53) of the patients with a reservoir, 48% (78/161) of the patients with a conduit, 32% (28/85) of the patients with an orthotopic neobladder and 54% (26/48) of the irradiated patients compared to 38% (157/409) of the controls (figure 2). Low or moderate physical well-being was reported by 64% of the patients with a reservoir, 65% of the patients with a conduit, 35% of the patients with an orthotopic neobladder and 77% of the irradiated patients compared to 57% of the controls (figure 3). A low or moderate energy level was reported by 81% of the patients with a reservoir, 85% of the patients with a conduit, 62% of the patients with an orthotopic neobladder and 88% of the irradiated patients compared to 69% of the controls. A moderate or high level of anxiety was reported by 26% of the patients with a reservoir, 19% of the patients with a conduit, 23% of the patients with an orthotopic neobladder and 29% of the irradiated patients compared to 20% of the controls (figure 4). Moderate or high level of depression was reported by 53% of the patients with a reservoir, 40% of the patients with a conduit, 26% of the patients with an orthotopic neobladder and 46% of the irradiated patients compared to 35% of the controls (figure 5). In response to the question about the subjective total quality of life, 30% of the patients with an orthotopic neobladder said they had a low or moderate total quality compared to 38% of the Danish controls.

Figure 2.

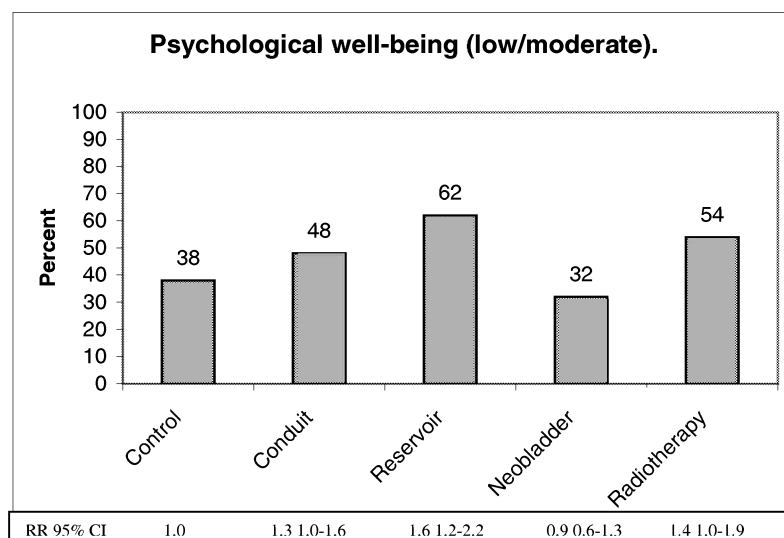




Figure 3.

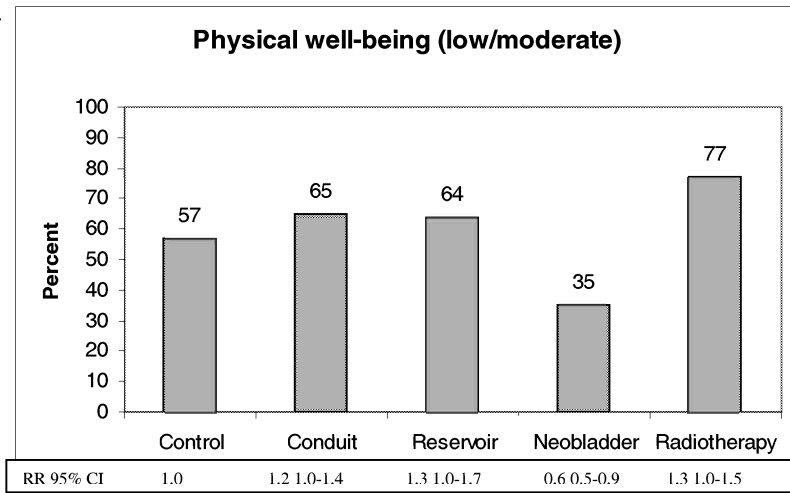


Figure 4.

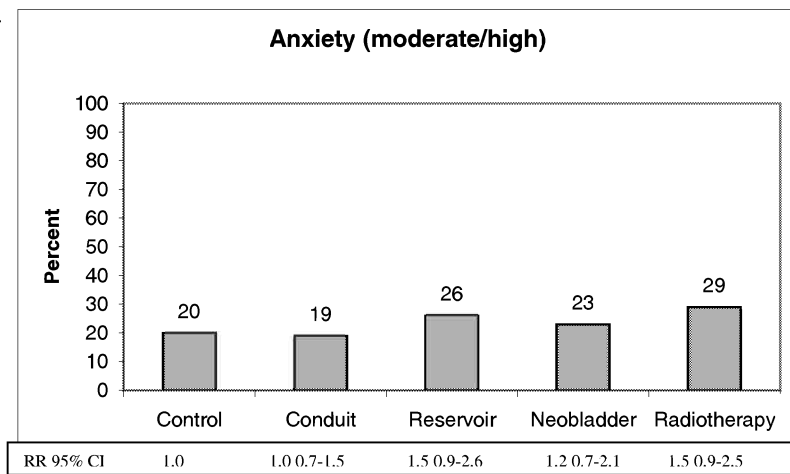
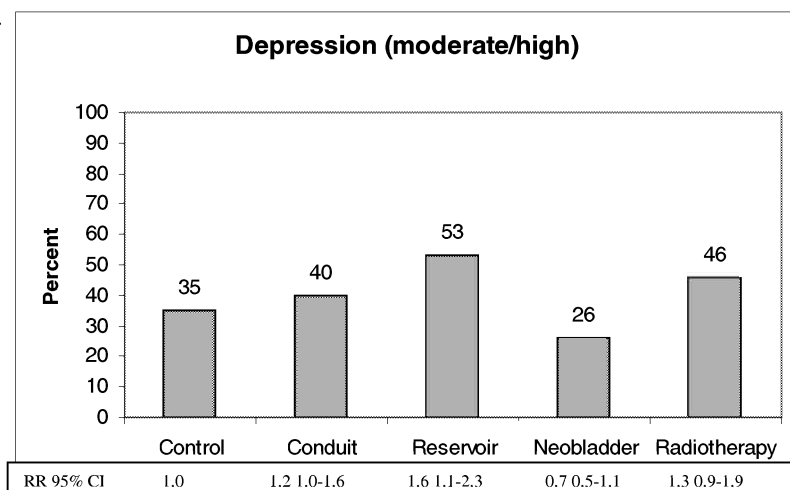
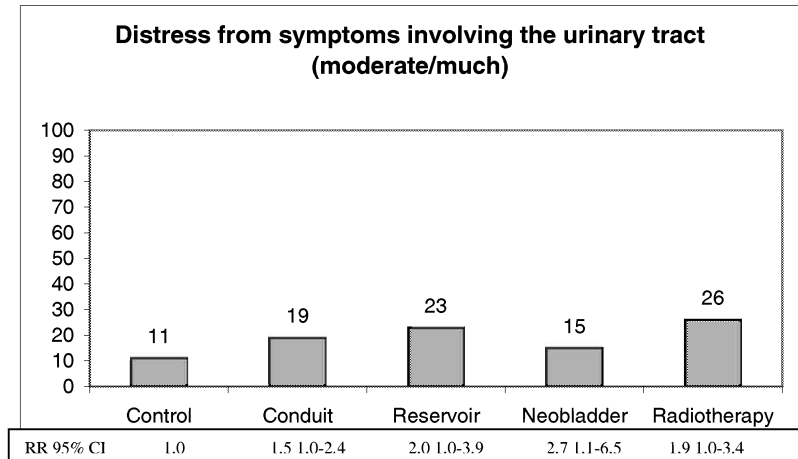


Figure 5.



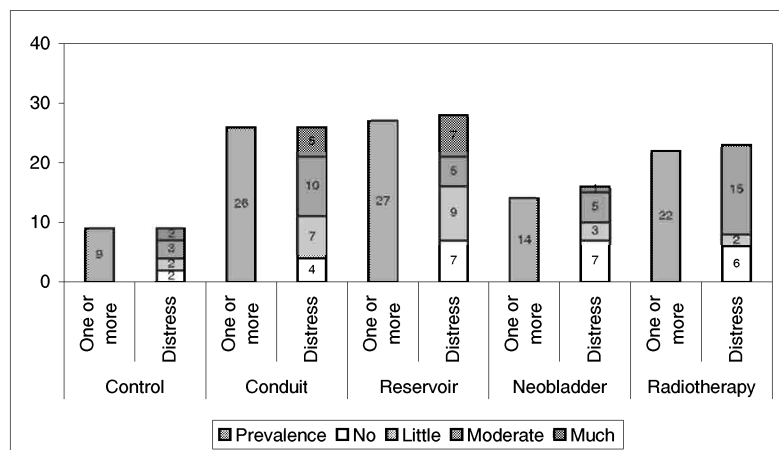
Symptoms Involving the Urinary Tract (Papers I-III)

Figure 6.



The incidence of urinary tract infections (UTIs) was increased among the treated patients. One or more UTIs during the past year were reported by 26% (41/157) of the conduit recipients, 27% (14/52) of the reservoir recipients, 14% (12/88) of the neobladder recipients and 22% (10/46) of the irradiated patients compared to 9% (28/299) of the controls (figure 7). UTIs with fever were particularly frequent among the urostomy patients with a 6-fold (27/150, 18%, conduit) and 7-fold (12/52, 23%, reservoir) increase compared to 4% (9/256) of the controls. Symptomatic UTIs were more frequent among the neobladder patients using intermittent self-catheterization than in those able to evacuate their neobladder by straining (33% versus 10%, P=0.02).

Figure 7. Urinary tract infections and the corresponding distress.



Urine odour was increased 7-fold (19/161, 12%, conduit) and 4-fold (4/52, 8%, reservoir) among the urostomy patients compared to the controls. Eight per cent (13/167) of the conduit patients reported urinary leakage (all magnitudes) at least once a month compared to 18% (10/55) of those with a reservoir, 18% (16/88) of those with a neobladder and 30% (13/44) of the irradiated patients. It was classified as moderate or large in 34% (25/72) of the

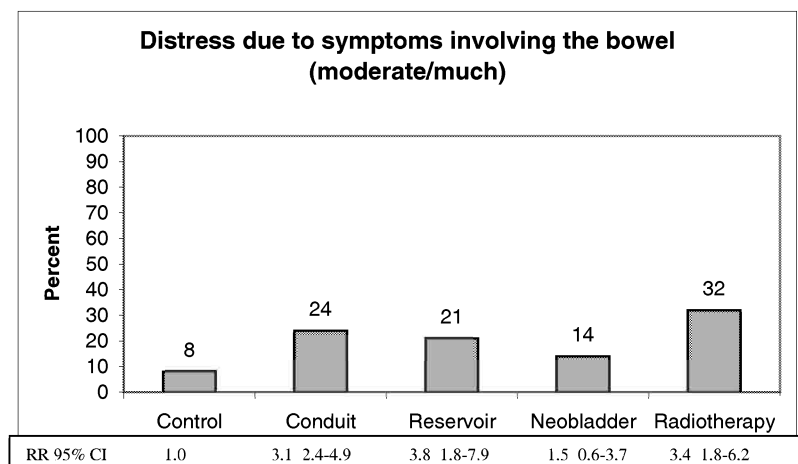
conduit patients, 19% (6/31) of the reservoir patients, 8% (7/88) of the neobladder patients and 33% (10/30) of the irradiated patients.

The prevalence of day and nighttime frequency was similar in the neobladder group to that in the controls (3% vs 3% and 15% vs 13%) but differed significantly among the irradiated patients compared to the controls (38% vs 14% and 70% vs 39%). Thirty-one per cent of the neobladder patients used sanitary pads by day and 69% by night, compared to 2% and 0% of the controls. A monthly use of sanitary pads was reported by 36% of the irradiated patients versus 7% of the controls. Calculus formation occurred in 39% of the neobladder patients. The prevalence of neobladder patients requiring intermittent self-catheterization to evacuate their neobladder (post-voiding residual urine > 100 ml) increased from 25% at 3 years to 38% at 5 years. A high anxiety level was found in this subgroup (50%) compared to those able to evacuate their neobladder by straining (7%,  $P < 0.05$ ) and to the controls (18%,  $P = 0.05$ ). The level of depression was similar in patients requiring self-catheterization (50%) and the population controls (37%) but it was significantly lower in the subgroup of neobladder patients who were able to evacuate their neobladder (0%,  $P = 0.01$ ). The prevalence of a low or moderate subjective quality of life was comparable in the two subgroups of patients and in the controls.

Overall, 32% (94/298) of the controls reported urinary symptoms. The corresponding figures were 55% (85/155) for patients with a conduit, 60% (32/52) for those with a reservoir, 72% (63/88) for those with a neobladder and 64% (30/47) for the irradiated patients (not in table). Nineteen per cent of the conduit patients, 23% of the reservoir patients, 15% of the neobladder patients and 26% of the irradiated patients reported moderate or much distress due to symptoms from the urinary tract. Adjusting for preoperative irradiation in the urostomy patients did not alter the results (data not shown).

### Symptoms Involving the Gastrointestinal Tract (Papers I-III)

Figure 8.



Defecation urgency every other time or more was reported by 18% (29/161) of the conduit patients, 6% (3/53) of the reservoir patients, 2% (2/88) of the neobladder patients and 21% (10/47) of the irradiated patients compared to 2% (6/305) of the controls. Faecal leakage (at least every month) was also increased, it was found in 9% (15/163) of the conduit patients, 8% (4/53) of the reservoir patients, 3% (3/89) of the neobladder patients and 17% (8/48) of the irradiated patients compared to 2% (5/304) of the controls. Frequent defecation (more than 14 times per week) was reported by 13% of the conduit patients, 7% of the reservoir patients,

23% of the neobladder patients and 13% of the irradiated patients compared to 3% of the controls. Diarrhoea was likewise increased: 3-fold in patients with a conduit, 2-fold patients with a neobladder, and 3-fold irradiated patients compared to the controls.

Altogether, bowel symptoms were reported by 28% (85/304) of the controls, 52% (83/160) of the conduit patients, 58% (31/53) of the reservoir patients, 38% (33/88) of the neobladder patients and 66% (31/48) of the irradiated patients (not in table). Moderate or much distress from symptoms involving the bowel was reported by 24% (38/160) of the conduit patients, 21% (11/53) of the reservoir patients, 14% (12/89) of the neobladder patients and 32% (15/47) of the irradiated patients, compared to 8% (25/304) of the controls. Twenty per cent of the preoperatively irradiated patients were moderately or much distressed by bowel symptoms compared to 22 per cent of the non-irradiated patients (not in table). The assessed bowel symptoms were altered only to a small extent (if at all) by pre-operative radiotherapy, and adjusting for this irradiation did not alter the results (data not shown).

#### Symptoms of Sexual/Genital Dysfunction in Men (**Papers I-III**)

Erectile dysfunction, i.e. impotence classified according to Dr Helgason (Helgason 1998), was prevalent in 91% of the males with a conduit, 94% of those with a reservoir, 94% of the neobladder patients and 75% of the irradiated men compared to 44% of the male controls. Low satisfaction with their present sexual life was twice as high in cystectomized men as in male controls: 66% of the male conduit patients, 77% of the male reservoir patients, 48% of the male neobladder patients and 36% of the irradiated male patients reported this condition compared to 26% of the male controls. Forty-three per cent of the irradiated patients lost their ability to ejaculate, compared to 6% of the male controls, a figure still low compared to the operated patients, nearly 100% of whom lost this ability. No or low interest in sex was reported by 62% of the male conduit patients, 40% of the male reservoir patients, 48% of the male neobladder patients and 70% of the male irradiated patients compared to 50% of the Swedish and Danish male controls. Moderate or much distress due to sexual limitations was reported by about 30% of the male patients with a conduit, by those with a reservoir, by the irradiated males and the Swedish male controls. However, 38% (29/76) of the male neobladder patients versus 6% of the male Danish controls reported this distress.

#### Symptoms of Sexual/Genital Dysfunction in Women (**Papers I-III**)

Low sexual satisfaction was reported by 25% (15/59) of the female controls compared to 21% (4/19) of the female conduit patients, 45% (5/11) of the female reservoir patients and 43% (3/7) of the female neobladder patients. Sexual interest was generally lower in women than in men: 85% (29/34) of the women with conduit, 56% (9/16) of those with a reservoir, 67% (6/9) of those with a neobladder and 100% (10/10) of the irradiated women reported low sexual interest compared to 75% (61/81) of the female controls. There was no significant difference in dyspareunia on comparing the operated women with the female controls. Insufficient vaginal lubrication at least every other time was reported by 43% (3/7) of the women with a conduit, 25% (2/8) of those with a reservoir and 50% (1/2) of the women with a neobladder, compared to 36% (10/28) of the Swedish female controls. The prevalence of intercourse was similar in the females of the neobladder group (75%) to that in the population controls (70%), and so was the prevalence of dissatisfaction with one's sexual life (43% vs 40%). Ten out of ten women (100%) treated with radiotherapy reported no or low interest in sex and none in this series reported sexual activity during the study period.

Urogenital mucosal problems in other situations than sexual were reported by 10% (3/29) of the female conduit patients, 18% (3/16) of the female reservoir patients and 13% (1/8) of the women with neobladders compared to 1% (1/76) of the female controls. Preoperative irradiation did not alter these findings (data not shown).

### Other Long Term Symptoms and Dysfunctions (**Papers I-III**)

A perceived reduction in physical attractiveness due to disease (patients and controls) or the urostomy (urostomy patients) was reported by 29% (32/110) of the men and 19% (6/32) of the women with a conduit, 51% (18/35) of the men and 13% (2/16) of the women with a reservoir, 13% (10/79) of the men and 0% (0/8) of the women with a neobladder and by 33% (11/33) of the irradiated men and 10% (1/10) of the irradiated women compared to 6% (12/195) of the male controls and 1% (1/77) of the female controls. Correspondingly, distress due to the feeling of low-level physical attractiveness was increased 2 to 4-fold in the urostomy patients, 2-fold in the male neobladder patients, 3-fold in the irradiated men and non-significantly among the neobladder and irradiated females, compared to the controls.

Surgery did not cause any increase in the prevalence of lymphoedema. "Swollen legs or lower abdomen" at least every month was reported by 14% (22/161) of the conduit patients, 7% (4/55) of the reservoir patients, 10% of the neobladder patients and 20% (10/48) of the irradiated patients, compared to 12% (35/303) of the controls. Preoperative irradiation did not significantly alter the results (not in table).

### Trade-off (**Papers I-III**)

Sixty-eight per cent (135/201) of the cystectomized individuals with a urostomy were unwilling to take any risk of shorter survival as a trade-off for alternative bladder-sparing procedures with a reduced symptom burden. The cystectomized men were more willing to trade off (53/150; 35%) than the women (13/50; 26%), and patients with a conduit were less willing to trade off (44/150; 29%) than those with a reservoir (22/50; 44%). Twenty-three of the 201 patients (12%) would retain their urinary bladder even if the risk of reduced survival was 100%. Age, social and marital status, country of birth, anxiety and depression did not significantly influence the trade-off decision. There was a tendency to higher risk-taking in patients not belonging to the Swedish state church (RR=2.2, confidence interval=1.3-3.6) (not in table). Fifty-four per cent (22/41) of the irradiated patients were unwilling to take any risk of shortened survival as a consequence of an alternative bladder-sparing procedure with a presumed reduced symptom burden compared to 39% (87/225) of the comparable controls. Age, social and marital status, country of birth, anxiety and depression did not influence the trade-off decision. Unpublished data from the Danish series show that 13% (10/75) would take the maximum risk of a shortened survival in order to retain their original bladder compared to 49% (37/75) not willing to take any such risk.

### Relative Importance of Distressful Symptoms (**Paper IV**)

Irrespective of urinary diversion, sexually related symptoms were the most distressing (highest percentage of "much distress") among the operated patients and symptoms related to the bowel among the irradiated ones. Nineteen per cent (33/174) of the conduit patients, 20% (16/81) of the reservoir patients, 19% (16/83) of the neobladder patients and 10% (4/39) of the irradiated patients reported much distress due to a reduced intercourse or orgasm frequency. Nine per cent of the controls reported the same distress. When distress of any degree was considered (low, moderate or much), 64% (27/49) of the irradiated patients had such from defecation urgency, 73% (55/77) of the neobladder patients from erectile dysfunction, 61% (49/81) of the reservoir patients from reduced intercourse frequency and 58% (81/141) of the conduit patients from erectile dysfunction. When actually affected by a symptom, 93% (13/14) classified urinary stoppage (upper and lower urinary tract retention treated with a catheter or nephrostomy) and 86% (116/135) faecal leakage as the most distressing symptom (distress of all levels).

### Symptom Burden and Well-being (**Paper V**)

In the cystectomized patients with a urostomy, reduced well-being (low/moderate) was reported by 35% of those having none or one of the symptoms studied (urinary tract infection, urinary leakage, urinary odour, abdominal pain, defecation frequency, diarrhoea, defecation urgency, faecal leakage, erectile dysfunction, vaginal dysfunction and reduced attractiveness), by 39% with two of the symptoms, by 45% with three symptoms and by 66% of those affected by four or more symptoms. The figures irrespective of symptom burden were 45% after 2-5 years of follow-up, 58% after 6-10 years of follow-up and 38% more than 10 years after surgery. The total symptom burden influenced the risk of anxiety and depression as well. Symptom prevalence (of the symptoms mentioned above) remained largely unaffected by follow-up time, an exception being defecation urgency.

## Discussion

Modifications in cancer therapy have, besides prolonging survival, been driven by efforts to reduce the risk of therapy-induced, long-term distressful symptoms. In order to do this, the new therapeutic techniques replacing the older ones, optimally causes less harm to tissues, e.g. nerves, vessels, connective tissue and organs at risk, which in turn has the effect of reducing the individual patients total subjective level of distress from different symptoms. The reduced total level of distress will then increase the individual's own perception of well-being and subjective quality of life.

To improve the situation for someone, we must collect specific information about the current situation in the affected person. In the process of gaining this knowledge, detailed questions has to be put to the population of interest and preferably also be compared with a reference population. The questions used must give us data on symptom characteristics (nature, occurrence, intensity and duration), as well as each specific symptom's own distressing capabilities (**VI**). The total level of distress from a number of symptoms, the symptom burden, affects well-being and subjective quality of life negatively (**V**).

We have found that the situation for urinary bladder cancer survivors can be improved.

Trust, a highly important feature in a good relationship with other individuals, can also be applied to patients. In this context it means that believing in the patient's own perceptions and thoughts about his/her situation, will give the us important information not only on what the most important functions/dysfunctions are for the particular patient but also on how to best help him/her by identifying his/her most important concerns.

Bladder cancer survivors treated with cystectomy and a conduit or reservoir, or radical radiotherapy classifies well-being lower than an age and sex-matched control group (**I and II**). Patients treated with radical cystectomy and orthotopic neobladder substitution classifies it at least as high as a matched control group (**III**). This could be caused by a lower total symptom burden in patients with a neobladder compared to the other treatment groups. An increased symptom burden affects well-being, anxiety and depression statistically significantly negatively (**V**). In continuing the discussion above, we have to find out the reason for this in order to help the patients. Consequently, information from psychometric domain scales with summarized scores does not supply us with enough information to know how to intervene.

With our detailed questionnaire we found an increased prevalence of nearly all symptoms asked about originating from the bowel irrespective of therapy (**I-III**). Relatively few studies in the literature have addressed the issue of bowel symptoms and dysfunction after radical surgery with urinary diversion (Bjerre 1995; Hart 1999; Hautmann 1999; N'Dow 1998). Except for the most obvious symptoms, i.e. the risk of an increased defecation frequency and diarrhoea when using varying lengths of intestine for the diversion, only one study has reported on other symptoms of bowel dysfunction (N'Dow 1998). In a subanalysis of our study (not in table) we found that symptoms involving the bowel correlated strongest of all symptoms with a low/moderate well-being (data not shown).

Increased defecation frequency and diarrhoea was statistically significantly increased among the operated patients with a conduit, a neobladder and the irradiated patients but not the reservoir patients (**I-III**). A certain length of the bowel is used for the urinary diversion reducing the intestinal reabsorption resulting in an increased risk of a looser stool passing more often than in the healthy controls. It is somewhat puzzling that no significant increase in these symptoms was seen among the patients with a reservoir, a diversion using up to 60 cm of small bowel when done according to the Kock technique (Kock 1982; Skinner 1984b). The number of patients in our study with a reservoir could have been too small so conclusions about this cannot be made. One possible explanation could be the relatively higher risk of

metabolic disturbance using a longer part of the bowel. This metabolic disturbance, including electrolytic changes, might affect motility of the remaining bowel. Ways to modify motility and absorptive symptoms from the bowel, are pharmacologic substances like bulk agents, increasing the stool volume and consistency resulting in reduced frequency and diarrhoea, anticholinergic like agents (e.g. loperamide) can reduce the intestinal movements and intestinal peptide hormones to reducing intestinal secretions, e.g. somatostatin.

Defecation urgency and faecal leakage are symptoms causing a high level of distress when they occur (**IV**). Furthermore, we found that urgency increases with postoperative time in patients treated with cystectomy and urostomy (**V**). It is reasonable to assume that they are caused by destruction or disturbance of the neural supply to the sphincter and rectum. It is possible that surgical leniency on the surrounding tissues in the lower pelvis might improve the situation of cystectomized patients and it is not unlikely that some of the differences could depend on the operating surgeon's skills. The lower total symptom burden seen in the patient group operated in Copenhagen by the same surgeon, compared to the higher symptom burden seen in the patient group operated by many surgeons in Sweden, strengthens this conclusion. One important confounding factor to consider when interpreting this result would be the different lengths of follow-up time among the Swedish patients with a urostomy (median follow-up time: 9 years) and the Danish patients with an orthotopic neobladder (median follow-up time: 4 years). We do not know how these patients will be affected after a longer follow-up time. Biasing factors for the comparison is of course also the total scenery of the care by the Danish team. An experience in the individual of good care (pre- and post-operative) can of course bias the results of the total group. Other bias might be the population differences between Danish and Swedish patients. However, the differences between the control populations in Sweden and Denmark were very modest and consequently Swedish and Danish individuals understood the questions in the same way (high validity) contradicting this as a large biasing factor (misclassification). It is furthermore not unreasonable to think that a careful dissection of autonomic nerves in the deep pelvis requires skills that improve with the surgeons experience in the "wound". Nerve-sparing cystectomies have been tried but it is not clear whether this will lower the incidence of leakage and urgency.

It is, however, not only surgical trauma causing an increased risk of defecation urgency and faecal leakage, but also radical radiotherapy for urinary bladder cancer (**II**). The same symptoms has recently been shown to be increased among patients treated with pelvic radiotherapy for other malignancies (Massoud al Abany 2002) and it is reasonable to think that a disturbed autonomic and somatic nerve function to the area, especially in the patients over 70 years old. The therapeutic technique (surgical or radiotherapeutical) can not be undone but patients struck by these symptoms might be helped by different bio-feedback strategies, usually available through the colorectal surgical units.

A statistically significantly increased risk of pain from the abdomen was seen only after radical radiotherapy (**III**) and even though intestinal adhesions frequently occur after bowel surgery, no increased risk could be detected in our studied cystectomized patients (**I and II**). If one believes that adhesions causes the increased risk of abdominal pain one must assume that they also occur after radiotherapy but due to another reason. The irradiation can cause fibrosis of the affected tissue, which in turn leads to adhesions and disturbed bowel movements. Another reason could be the disturbance of autonomic nerves to the bowel in conformity with the above discussion of urgency and leakage as well as the discussion of sexual dysfunction below.

Just remembering that these symptoms also can happen in these urinary bladder cancer survivors and bringing them out for discussion with the patient at the postoperative follow-up can visualise the problem and hopefully direct the patient towards a relief.

Multiple studies have analysed the function and symptoms of the reconstructed urinary tract after cystectomy. In our study, one of the most prevalent symptoms was symptomatic urinary tract infections (**V**) requiring treatment and as many as 15% of the surgical patients



with a urostomy were moderately or much distressed by this (I). About one out of six patients with an orthotopic bladder reconstruction (III) and one out of five irradiated patients (II) have the same condition. Some patients are repeatedly admitted to their urological ward for one to many days because of this. Patients treated with surgery or irradiation are more susceptible to bacteria than others. The most common cause in patients with a urostomy is probably bacteria introduced through the stoma from the outside, for example, by catheterization. Other causes are ureteric obstruction or retention. The risk of symptomatic infections is similar among patients on clean intermittent catheterisation and patients with a urostomy (I and III), indicating the introduction of bacteria as a cause. However, sometimes no obvious explanation can be found and it is not clear why some patients are repeatedly subjected to these distressing infections. Further studies on this issue are warranted to help the one fourth of all patients treated for urinary bladder cancer with radical therapies. Furthermore, fairly simple measures are available to try to reduce the incidence of these events, e.g. prophylactic antibiotics, acidification of the urine, hygiene techniques and a larger urinary volume.

The reason why patients treated with radical radiotherapy are more susceptible to bacteria is not clear (II). It is possible that their defence mechanisms, such as the non-adhesive surface of the urethral cells, are destroyed by the irradiation. Dörr and co-workers (Dörr 1998) found an impairment of the urothelial barrier function and associations with the bladder prostaglandin function after radiotherapy to mice bladders. Bladder prostaglandins seem to be related to normal emptying function of the bladder (Tucci 2002). It can of course also be due to destruction of a normal physiological function, for example, retention of urine due either to infravesical obstruction or secondary obstruction of the upper urinary tract, probably at the ureteral level within the irradiated area. Impaired physiological function of the lower urinary tract due to the irradiation is possible since the relative risk of urinary leakage is also increased by three times to that of the control population. Furthermore, nocturia and pollakisuria are increased in the irradiated patients, compared to the controls, thereby strengthening the hypothesis of a defective lower urinary tract physiological function. Possibly an unwanted effect of full-dose irradiation is sclerosis of the bladder outlet function as well as a sclerotic non-compliant urinary bladder causing increased frequency and bladder outlet obstruction. A slowly progressing fibrosis or “scarring” of the bladder could be responsible for these symptom combinations. Patients with these symptoms may be better characterized by an urodynamic evaluation. Possible alternatives for improvements are “bladder-training”, electrostimulation, pelvic floor exercises, pharmacological agents (alpha-receptor blockage, anticholinergics, 5-alpha-reductase inhibitors) or, as a last resort, surgical treatment, e.g. bladder augmentation or urinary diversion.

In our study, the prevalence of clean intermittent catheterization among the patients with a neobladder was 26%, a figure higher than what most other groups report (Elmajjan 1996; Hautmann 1999) probably due to a strict follow-up not allowing the residual urine to exceed 100 ml (Steven 2000). Patients on clean intermittent catheterization reported a decreased well-being compared to those not in need of the procedure. A higher limit for starting clean intermittent catheterizations should not be allowed if the risk of other distressing symptoms/diseases increases, e.g. progressive stone disease, urinary tract infections due to high residual urine or progressive renal deterioration. The ultimate goal is of course a neobladder capable of urine storage without leakage as well as one that can be emptied without stress inducing measures at a time appropriate for emptying. Preserving the sensitivity of the membranous urethra through meticulous preservation of the sphincter innervation, not only the intrapelvic extrapudendal nerve fibers, seems important (Hugonnet 2001).

Urinary leakage after urinary diversion (conduit, reservoir and neobladder) has been studied extensively by all research groups investigating the quality of life after radical cystectomy. However, symptoms emanating from the urinary tract do not seem to be as distressing and important for well-being (V). Instead, symptoms involving the bowel and

sexually related symptoms seems to be more important when considering well-being, anxiety and depression in connection with different symptoms. One reason for this might be that the patients are usually very well prepared and informed about possible negative events after urinary diversion. This alone tells us that a well-prepared and fully informed patient might have higher thresholds for a low level of well-being when afflicted with different postoperative long-term symptoms. No increase in urinary leakage could be detected when patients and controls themselves reported the occurrence of this symptom. However, in patients with a conduit and leakage, a statistically significantly higher severity (intensity) of the symptom was detected, the leakage being moderate or large in 34% of them compared to 19% of the reservoir patients and the controls. One possible reason for this is that when it occurs in the conduit patient group, it might be due to total bandage failure and at these moments all urine collected might leak out. Patients with a continent or non-continent urostomy might benefit from regular follow-up by an ostomy therapist with special interest in these problems.

Sexually related symptoms rank highest among the radically operated patients compared to other distressing symptoms, i.e. symptoms involving the bowel and the new urinary tract (IV).

The most obvious symptom among men is erectile dysfunction caused by the surgical technique rendering all patients impotent. In carefully selected patients, attempts can be made to preserve the erectile nerves without running the risk of reduced radicality (Colombo 2001). It is possible that this would increase well-being and subjective quality of life of the males operated on.

Although located within the radiation field during radical radiotherapy, the erectile nerves and vessels retain their function in a number of men with preserved sexual function: 38% of the irradiated patients had had intercourse during the previous month (II) compared to 10% of the urostomy patients (I). More than half of the irradiated males were able to ejaculate. Sexual desire was similar in the compared male groups, indicating that the desire to have sex was not affected by the different therapeutic procedures. More than half of the men using sexual aids (N=36) were moderately or much satisfied with their aid. Symptoms involving the urinary tract but not symptoms involving the bowel, affect sexual life moderately or much in male urostomy patients (28% 44/160). This effect was also seen among male patients with a neobladder (27% 21/77) and the irradiated males (19% 6/32), so the mere absence of a visible urostomy does not prevent the patient from being sexually disabled (I-III).

Impaired sexual life is as distressing in women (Bergmark 1999) as in the here studied men. This thesis includes few women (N=39 with a conduit, 17 with a reservoir, 9 with a neobladder and 13 irradiated women), and few of them have engaged in sexual activity during the study period probably due to age, thus hampering the drawing of any conclusions. Interruption of peripheral autonomic nerve fibres, oestrogen loss due to the oophorectomy sometimes performed, or preoperative irradiation are other possible explanations. Only when indicated was the anterior vaginal wall resected in this series, so this should not be the reason in our patients. van Driel and co-workers (van Driel 1993) discuss in a review article reasons for sexual dysfunction in the female after radical cystectomy. Their suggestion that the visible urostomy could be a reason is not supported in our study. Even though a narrow vaginal cylinder after resection of the anterior vaginal wall not should be the reason for female sexual dysfunction in our study, another anatomical reason could be a different vaginal direction or bending of the vagina that might cause retention of fluids and secretions that affect sexual activity and enjoyment (Sjödahl 1990).

It is possible that an increased use of sexual aids would increase the radically treated patients' well-being. A possible way of carrying this out would firstly be to remember to bring this up during the doctor-patient consultation, but also to offer follow-up visits to a specially trained nurse or sexual therapist.

No statistically significantly increased risk of lymphoedema could be detected in our patients (**I-III**), neither the operated nor the irradiated ones. Otherwise irradiation is a documented inductor of lymphoedema after treatment for other neoplasms (Johansson 2002), but the radiation fields used in our patients would probably fall outside the critical areas for inducing this distressful symptom. Surgical technique might also be the explanation here for why our patients, but not female patients treated for cervical cancer, are free of lymphoedema (Bergmark 1999).

One third of the patients with a urostomy in this study (**I**) would accept a certain decrease in survival to reduce the postoperative symptom burden and they could have been offered a bladder-sparing procedure. However, 67% (135/201) did not want to take any risk whatsoever to trade off survival for a diminished symptom burden and they must be offered the alternative causing the most survival benefit. About half of the irradiated patients (**II**) and half of the neobladder patients (**III**) would not trade off at all either. One tenth of the patients, irrespective of the group they belonged to, would have taken the chance to trade off even if there was a 100% risk of a lower survival rate (**I-III**). Controls preferred a diminished symptom burden (to maximal survival) more often than the patients, but it is possible that they would take another position if actually faced with a life-threatening disease. We do not have data from the relevant period of time, i.e. on patients with a newly diagnosed malignant tumour, so the controls represent the time before and the patients the time after the actual diagnosis. The reason for a trade-off reaction among the neobladder patients similar to that of the controls might be that they have about the same level of well-being as well as the total symptom burden as the controls. The trade-off decision was not significantly changed (effect modification) by age, social and marital status, country of birth, anxiety or depression, but "not belonging to the Swedish state church was an increasing factor (RR = 2.2, confidence interval =1.3-3.6) (not in table). These data tell us that no matter how the situation looks concerning distressful symptoms and symptom burden, most patients do not want to compromise with survival. If the figures are true, the 10% wanting to take a 100% risk of a lower survival rate in order to try another treatment (bladder-sparing treatment methods among those operated on) should have been offered alternative treatments. Those willing to compromise with survival to some degree (1-99%) might possibly be subjects fitting in different treatment protocols.

## Conclusions of the Study

- Faecal leakage, defecation urgency and abdominal pain are consequences of radical cystectomy with urostomy, when performed in Sweden. However, no excess risk of these symptoms was found in cystectomized patients in Copenhagen, Denmark, thus, applying a more lenient surgical technique in Sweden would probably improve the situation of urinary bladder cancer survivors.
- Faecal leakage, defecation urgency and abdominal pain are consequences of radiotherapy for urinary bladder cancer, as performed in Stockholm during 1977-95. Diminishing the radiation to organs at risk for these symptoms (anal sphincter, rectum, large and small bowel) would probably improve the situation of urinary bladder cancer survivors.
- A better quality of life and well-being after radical treatment for urinary bladder cancer is found in patients with orthotopic bladder substitutes following radical cystectomy compared to patients with a conduit or a reservoir or patients treated with radical radiotherapy.
- An important source of distress in cystectomized men is erectile dysfunction. Saving the erectile nerves during surgery, and thereby erectile function, would probably improve the situation of urinary bladder cancer survivors.
- Symptoms of sexual dysfunction are the most distressing group of symptoms in surgical patients, irrespective of the type of diversion. Besides intraoperative attempts to minimize erectile nerve destruction, preoperative information as well as postoperative sexual counselling can probably reduce the levels of distress involving this symptom group.
- Well-being, anxiety and depression correlates strongly with the total load of the symptom burden in urinary bladder cancer survivors treated with cystectomy and urinary diversion with a urostomy.
- If patient preferences are to optimise chances to save the sexual capacity in men, radical radiotherapy currently may be the best option.
- Despite being affected by distressing symptoms, most patients are not willing to compromise with survival.

This information can be used for:

- Improving the pretherapeutic consultation in which different radical methods are being considered.
- Changing and improving surgical techniques by means of continuous evaluation of changes in the methodology.
- Planning of the medical resources, for example, centralizing these surgical procedures.
- Improving the posttherapeutic follow-up, taking note of symptoms that may not have been discussed before in order to improve the patients' quality of life and well-being.

## Future Studies

- What causes the high incidence of urinary tract infections and the corresponding distress? Urinary tract infections are not only treatable but also in some instances preventable. An attempt to find out the most probable reasons for urinary tract infections in urinary bladder cancer survivors seems important. In studying this we can correlate clinical data, like surgical or radiotherapeutic technique, with epidemiological data received from the patients. For example, does the length of the conduit correlate to the occurrence of urinary tract infections? Other intraoperative manoeuvres might be the length of the remaining urethra and the type of anastomosis between the urethra and the bladder substitute, the extent of the dissection in the deep pelvis. Postoperative procedures of interest might be hygienic technique during urostomy care, overall hygiene, intake of substances affecting the pH of the urine, i.e. food and drinking behaviour as well as attitudes towards their own urostomy or “treated” urinary tract.
- The causes of the high incidence of symptoms involving the bowel after cystectomy with urostomy and patients treated with radical radiotherapy must be explored. Correlating the surgical journals as well as irradiation dose plans with the occurrence of these symptoms might aid in exploring the symptoms. Also here personal characteristics and behaviour (food and drinks) might be of interest, data that can be collected with our technique and type of instruments.
- Can we guide the evolution of new operative and radiation techniques to reduce, for example, the prevalence of symptoms involving the bowel? Would it be possible to visualize autonomic nerve plexa during the operation directly or indirectly. If that is the case, different dissecting techniques can be compared to one another to exactly find out which structures would benefit the most in saving.

## Swedish Summary

I denna avhandling har vi undersökt om det är möjligt att förbättra situationen för patienter behandlade för allvarlig urinblåsecancer. För att kunna göra detta måste exakt kunskap om behandlingsrelaterade stressgivande symtom och tillstånd tas fram. Symtomen mäts i sina olika dimensioner (natur, förekomst, intensitet och duration), hur mycket det stressar den drabbade samt om det påverkar den drabbades subjektiva välbefinnande och livskvalitet (VI). Denna mer exakta information om postoperativa följdverkningar vi får fram kan också användas redan i den behandlingsförberedande situationen för att så långt det är möjligt "skräddarsy" rätt behandlingsmetod till varje individuell patient.

Psykiskt och fysiskt välbefinnande är statistiskt signifikant sämre hos patienter opererade med cystektomi och urostomi, icke-kontinent eller kontinent, jämfört med en jämförbar kontrollpopulation (I). Detsamma gäller patienter som behandlats med fulldos strålbehandling mot sin cancersjukdom (II) till skillnad från danska patienter med ny konstgjord urinblåsa kopplad till urinröret, s.k. ortotopt blåssubstitut, vilka rapporterar ett likvärdigt välbefinnande som den jämförbara kontrollgruppen (III). En orsak till skillnaderna kan vara den nedsatta självkänslan hos individer med urostomi, en 5-faldig ökning av känslan att vara oattraktiv noterades hos dessa (I) emedan ingen ökning sågs hos individer med konstgjord urinblåsa kopplad till urinröret (III). Den 6-faldiga ökningen av nedsatt självkänsla hos de strålbehandlade kanske kan kopplas till den förhöjda risken för mag-tarmbesvär hos dessa patienter. En 9-faldigt ökad risk för avföringsträngningar och en 11-faldigt ökad risk för avföringsläckage rapporterades hos de strålbehandlade jämfört med kontrollpopulationen (II). Dessa symtom var också ökade hos patienter med urostomi, en 7-faldig ökning av avföringsträngningar samt avföringsläckage sågs jämfört med kontrollbefolkningen (I). En 3-faldigt ökad risk för behandlingskrävande urinvägsinfektion sågs hos de opererade med stomi, det vill säga 25 procent av dessa patienter har minst en symtomgivande urinvägsinfektion årligen (I). Alla opererade män drabbas av sexuella störningar efter detta ingrepp, framför allt erektil impotens, ett symtom som framkallar mycket stress hos de drabbade (I+III). De strålbehandlade har en lägre risk för erektil impotens, 75 procent drabbas (II). Symtom på sexuell dysfunktion tillhör de mest stressgivande symtomen dessa botade före detta cancerpatienter drabbas av (IV). Risken att drabbas av stressande symtom är lägst efter radikal kirurgi med ortotopt blåssubstitut. Förekomsten av stressande symtom ökar inte med tiden men en ökad symtombörda leder till ett försämrat välbefinnande (V). Cancerpatienter prioriterar radikalitet framför en minskad symtomförekomst (I-III).

Vid en modifiering av den kirurgiska tekniken vid radikal cystektomi, till bland annat ett bevarande av (autonoma?) nerver i lilla bäckenet, kan eventuellt risken för att drabbas av stressgivande mag-tarmsymtom och avföringsläckage minskas eller elimineras. Den höga förekomsten av symtomgivande urinvägsinfektioner hos patienter som behandlats i botande syfte för urinblåsecancer kan troligen minskas med förebyggande åtgärder. Ortotop blåssubstitution (ny konstgjord urinblåsa kopplad till urinröret) och ett bevarande av potensnerv vid kirurgi kan vidare också leda till ett bättre välbefinnande hos dessa patienter. Till dem som högt prioriterar en bevarad sexuell funktion kan fulldos strålbehandling vara ett behandlingsalternativ. Att minska stråldosen på analsfinkter och rektum kan förmodligen leda till ett ökat välbefinnande hos de strålbehandlade patienterna som botats från sin sjukdom. Våra studier har påvisat ytterligare faktorer som skulle kunna förbättra situationen för dem botats från sin urinblåsecancer och jag konkluderar att dessa individers välbefinnande och livskvalitet troligen skulle kunna förbättras avsevärt.

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