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# ON THE DETECTION AND MANAGEMENT OF URINARY BLADDER CARCINOMA

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Till Helén och Alexander

"You have never  
been in love,  
until you have seen the stars,  
reflect in the reservoirs."

Morrissey, *First of the gang to die*;8:2004.

Cover illustration by Lisa Henningsohn. "The plane of dissection for prostatic capsule and seminal sparing cystectomy".



# ABSTRACT

## On the Detection and Management of Urinary Bladder Carcinoma

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**Aims:** To describe the diagnosis and clinical course of an unselected population-based cohort of patients with newly diagnosed transitional cell carcinoma of the urinary bladder. To assess if random bladder biopsies and the detection of concomitant carcinoma in situ have an impact on management and clinical outcome in bladder cancer patients. To study the functional outcome after cystectomy performed with a prostatic capsule and seminal sparing approach. To investigate possible effects on gastrointestinal functions caused by the intestinal reconstruction in patients with orthotopic ileal neobladder.

**Patients and methods:** This study prospectively included 78% (538 patients) of all newly detected bladder cancer patients in the Stockholm region 1995 to 1996. The patients were followed for at least five years. Choice of treatment, recurrence, progression and survival were studied. The same cohort was then analyzed in order to determine possible impact of random bladder biopsies on choice of treatment and cancer-specific survival. Twenty five male bladder cancer patients who underwent prostatic capsule and seminal sparing cystectomy were evaluated by a questionnaire concerning urinary-, bowel- and sexually related symptoms. Twenty eight patients who underwent radical cystectomy and orthotopic neobladder were compared with ten patients who underwent TURBT concerning possible effects on gastrointestinal functions, such as enterohepatic circulation of bile salt, gastric emptying and gastrointestinal hormone levels.

**Results and conclusions:** In this study none of the patients with PUNLMP (WHO 1999) progressed or died, confirming the low malignant potential. In the group of patients with TaG1-G2, only 2/187 patients (1%) died of bladder cancer. In contrast, patients with TaG3 or T1G2-G3, after five years of follow-up, had a cancer-specific death rate of 30%. Patients with TaG3 or T1G2-G3 in whom random bladder biopsies were performed were more likely to be treated with intravesical BCG compared to patients without random biopsies (58% vs. 23%,  $p=0.002$ ). The Cox proportional-hazard ratio for death due to bladder cancer comparing TaG3 or T1G2-G3 patients without vs. with random biopsies was 2.5 (95% CI 1.1-5.6). For patients with muscle invasive bladder cancer the cancer-specific survival at five years was 31% and only 61% of the patients underwent a treatment with curative intention. However, our data indicates that in selected patients, prostatic capsule and seminal sparing cystectomy and orthotopic neobladder combines an appropriate oncological outcome with a satisfactory function of the lower urinary tract. When the distal ileum was removed from the gastrointestinal tract for orthotopic neobladder substitution, bile salt induced diarrhoea was found in 1/3 of the patients. Most of the patients that developed bile salt induced diarrhoea were relieved of their symptoms by cholestyramine.

**Key words:** bladder neoplasm, cystectomy, prostate sparing, urinary diversion

## LIST OF PUBLICATIONS

This thesis is based on the following original articles, referred to in the text by their Roman numerals I-IV.

- I. Per Larsson, Hans Wijkström, Andreas Thorstenson, Jan Adolfsson, Ulf Norming, Peter Wiklund, Erik Onelöv and Gunnar Steineck. A population-based study of 538 patients with newly detected urinary bladder neoplasms followed during 5 years.  
Scandinavian Journal of Urology and Nephrology 2003;37:195-201.
- II. Andreas Thorstenson, Martin C. Schumacher, Martin N. Jonsson, Per Larsson, N. Peter Wiklund, Hans Wijkström, Erik Onelöv, Gunnar Steineck and Petra J de Verdier. Random bladder biopsies - Results from a population based cohort of 538 patients.  
Submitted.
- III. Andreas Thorstenson, R. Corey O'Connor, Riitta Ahonen, Martin Jonsson, Hans Wijkström, Olof Akre, Abolfazl Hosseini, N. Peter Wiklund and Lars Henningsohn. Clinical outcome following prostatic capsule and seminal sparing cystectomy for bladder cancer in 25 men.  
In press, Scandinavian Journal of Urology and Nephrology.
- IV. Andreas Thorstenson, Hans Jacobsson, Erik Onelöv, Jens Juul Holst, Per M. Hellström and Anne-Charlotte Kinn. Gastrointestinal functions and metabolic control after construction of orthotopic ileal neobladder in bladder cancer.  
Scandinavian Journal of Urology and Nephrology 2007;41:14-19.

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## LIST OF ABBREVIATIONS

BCG	Bacillus Calmette-Guerin
c-CIS	Concomitant carcinoma in situ
CI	Confidence interval
CIS	Carcinoma in situ
CT	Computerised tomography
EAU	European association of urology
EBRT	External beam radiation therapy
GI	Gastrointestinal
GLP-1	Glucagon-like peptide-1
IARC	International agency for research on cancer
ISUP	International society of urological pathology
PSA	Prostate specific antigen
PUNLMP	Papillary urinary neoplasm of low malignant potential
PYY	Peptide YY
RIA	Radioimmunoassay
TCC	Transitional cell carcinoma
TNM	Tumour, node, metastases classification
TURBT	Transurethral resection of bladder tumour
TURP	Transurethral resection of the prostate



# 1 INTRODUCTION

Urinary bladder carcinoma has a broad spectrum of disease courses and treatments. It is the second most common urologic malignancy, only outnumbered by prostate cancer. The urologist with an interest in urinary bladder carcinoma will in his care of patients come in contact with clinical problems of different nature. The urologist has to make the right diagnosis, classify the tumor correctly, suggest a treatment with acceptable side effects and also handle side effects should they occur. This thesis concerns some of the practical issues of the detection and management of urinary bladder carcinoma that the urologist may face in the treatment of patients with bladder cancer.

## 1.1 EPIDEMIOLOGY

In Sweden approximately 2000 patients are diagnosed with urinary bladder cancer each year and about 600 patients will die due to the disease each year according to the national registry of bladder cancer (Nationellt\_Kvalitetsregister, 2006). The mean age of patients diagnosed with bladder cancer is 69 years for men and 71 years for women. In 2006 approximately 104 400 Europeans were diagnosed with urinary bladder cancer, with an estimated ratio between men and women of 3.8/1. Urinary bladder cancer is the fourth most common form of cancer among men in Europe (Ferlay *et al.*, 2007).

## 1.2 RISK FACTORS

Tobacco smoking is the most common aetiology of bladder cancer. It has been estimated that smoking causes approximately 65% of all male bladder cancer and 25% of all female bladder cancer (Silverman *et al.*, 2006). It is not clear which of the carcinogens in tobacco smoke that are involved in causing the cancer. The risk of developing bladder cancer is however enhanced whether you smoke cigarettes, pipe or cigars (Steineck *et al.*, 1988). Further, the incidence of urinary bladder cancer is directly related to the duration of smoking and number of cigarettes smoked per day, up to a threshold of 15-19 cigarettes per day, after which a plateau in the risk has been observed (IARC, 2004). Since smoking is the most common underlying factor of bladder cancer, the most important primary prevention for bladder cancer is to decrease active and passive smoking (Stenzl, 2008).

The second most common risk factor of bladder cancer is occupational exposure of carcinogenic substances. Patients with work related bladder cancer constitute of 16-24% of all bladder cancer patients in several series (Vineis *et al.*, 1991). Substances involved are benzene derivatives and arylamines (2-naphtylamine, 4-aminobiphenyle, 4,4'-methylenedianilin and ortho-toluidine) (Steineck *et al.*, 1990a). Occupations where these exposures occur include those that use dyes, rubber, textiles, paint, leather and

chemicals (Pashos *et al.*, 2002). There are also indications that professions involving exposure to combustion gases from coal, such as chimneysweepers, have an increased risk of developing urothelial cancer (Steineck *et al.*, 1990b).

External beam radiation therapy (EBRT), which for example can be given as treatment for ovarian cancer, increases the risk of secondary bladder cancer. Among patients who were treated with EBRT for prostate cancer, the incidence of bladder cancer was significantly higher compared to patients who had undergone a radical prostatectomy (Boorjian *et al.*, 2007).

Long term irritation of the bladder, by for example chronic urinary tract infection caused by an indwelling catheter, is related to development of urinary bladder cancer, especially squamous cell carcinoma (Kantor *et al.*, 1988). Schistosomiasis is endemic in Egypt and in the Middle East and is considered to be a definite cause of bladder cancer with a five times increased risk (El-Bolkainy *et al.*, 1981; Stenzl, 2008). This is why urinary bladder cancer is the most common solid tumour among male Egyptians and Egypt's foremost oncological problem (El-Bolkainy *et al.*, 1981).

### **1.3 CLASSIFICATION**

#### **1.3.1 Histology of the transitional epithelium**

The urinary tract extends from the renal pelvis to the urethra and is covered with transitional epithelium, also called the urothelium (Kumar, 1992). Normal urothelium is three to seven cell layers thick. The external layer consists of large umbrella cells. The urothelium rests on the basal membrane of the lamina propria. The lamina propria consists of subepithelial connective tissue and smooth muscle fibres named tunica muscularis mucosa (Messing, 2002). Outside of the lamina propria is the detrusor muscle (muscularis propria). When the muscularis propria contracts, the increase of intravesical pressure necessary for the micturation process is achieved. On the outside of the detrusor muscle there are fat and large venous plexa (Berrum-Svennung, 2007).

#### **1.3.2 Pathology**

There are different types of urinary bladder cancer. In Sweden 95.5% of all cases of bladder cancer are transitional cell carcinomas (TCC) (Nationellt\_Kvalitetsregister, 2006). There are also squamous cell carcinoma, adenocarcinoma and the occasional small cell carcinoma, melanoma and lymphoma of the urinary bladder (Nationellt\_Kvalitetsregister, 2006). This thesis focuses on TCC.

Classic TCC grows exophytically on the inside of the urinary bladder and may look like swaying seaweed on cystoscopy. Solitary tumours are 2-3 times more common than multiple tumours (Malmström *et al.*, 2008). The cancer can also grow as a solid tumour in the bladder wall. A special variant of TCC is carcinoma in situ (CIS or TIS).

CIS does not have an exophytic growth pattern, but is a flat tumour, often multifocal and difficult to discover on regular cystoscopy. The urologist can on cystoscopy see velvety, red, oedematous changes as a result of an inflammation in the underlying lamina propria. The use of fluorescence cystoscopy has been suggested to increase the possibility to identify CIS (Schmidbauer *et al.*, 2004). There are three different kinds of CIS:

1. Primary CIS is CIS with no previous history of bladder cancer.
2. Secondary CIS is when CIS occurs in a patient with previously diagnosed papillary tumour.
3. Concomitant-CIS (c-CIS) implicates co-existing papillary or nodular tumour and carcinoma in situ.

### 1.3.3 Tumour grading

Urothelial tumours are histopathologically classified in different grades depending on cytological and architectural criteria. Different grades have different prognosis, where papillary urinary neoplasm of low malignant potential (PUNLMP) is the most benign and carcinoma grade III is the most malignant. PUNLMP is defined as a lesion which does not fulfil the cytological criteria of malignancy, but has normal urothelial cells in a papillary way of growth.

The link between the different grading systems is shown in a somewhat simplified version in Table 1. WHO/ISUP 1998 is easily translated to WHO 1999. It is more difficult to translate WHO 1973 to WHO 1999. Certain grade 1 tumours in WHO 1973 become PUNLMP and others become grade I in WHO 1999. Additionally, some grade 2 tumours in WHO 1973 become grade I according to WHO 1999. The reason for this is the lack of rules for distinction between grade 1 and grade 2 as well as between grade 2 and grade 3 in WHO 1973 (Busch *et al.*, 2002). WHO 1999 is the system used in Sweden today.

**Table 1.** Comparisons of different grading systems for urothelial neoplasms.

WHO 1973	Modified Bergkvist 1987	WHO/ISUP 1998	WHO 1999
Papilloma	Papilloma grade 0	Papilloma	Papilloma
TCC grade 1	Papilloma with atypia grade 1	PUNLMP	PUNLMP
TCC grade 1	Urothelial carcinoma grade 2A	Urothelial carcinoma low grade	Urothelial carcinoma grade I
TCC grade 2	Urothelial carcinoma grade 2B	Urothelial carcinoma high grade	Urothelial carcinoma grade II
TCC grade 3	Urothelial carcinoma grade 3		Urothelial carcinoma grade III
	Urothelial carcinoma grade 4		

### **1.3.4 Initial symptoms, investigation and staging of tumours**

The most common initial symptom of bladder cancer is painless (“silent”) macroscopic hematuria, i.e. visible blood in the urine (Varkarakis *et al.*, 1974). There are also patients who complain about frequency, urgency, dysuria and pelvic pain. Patients with macroscopic hematuria are examined with a radiological examination of the upper urinary tracts such as contrast enhanced CT. These patients should be referred to a urologist for a cystoscopy and bladder wash cytology. If there is a macroscopic visible tumour on cystoscopy or if malignant cells are found on cytology, the next step will be a TURBT. The patient is then admitted to hospital and a resection of the tumour in the bladder is performed. Bimanual palpation under spinal anaesthesia is recommended before and after the resection. Findings on palpation are used for the staging of the tumour and influences treatment decisions. It has been shown that the presence of a palpable tumour after TURBT significantly correlates with stage T3 bladder cancer (Wijkström, 1984; Wijkström *et al.*, 1998). After TURBT the patient usually gets an instillation of a cytotoxic agent in the bladder (Babjuk *et al.*, 2008). Such an instillation can have a cytotoxic effect on free floating cancer cells in the bladder after the TURBT and may prevent reimplantation of tumour cells. The single instillation procedure has in a meta-analysis been estimated to decrease the number of patients with recurrence of bladder cancer with approximately 12% (Sylvester *et al.*, 2004). Recent findings in a study from Sweden has confirmed that 8.5 patients need to be treated with a single instillation of epirubicin to prevent one recurrence (Number Needed to Treat =8.5). However, this study also indicates that only the small sized (<5 mm) recurrences of TCC are prevented (Berrum-Svennung *et al.*, 2008).

Clinical findings and the depth of the invasion of the tumour in the bladder wall contribute with important prognostic information and are used for staging. In Table 2 the TNM-classification of 2002 is shown (Sobin *et al.*, 2002). Today this classification system is used in clinical praxis in Sweden.

**Table 2.** The 2002 TNM classification of urinary bladder cancer.

<b>T – Primary tumour</b>	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ: "flat tumour"
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
	T2a Tumour invades superficial muscle (inner half)
	T2b Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue
	T3a Microscopically
	T3b Macroscopically (extravesical mass)
T4	Tumour invades adjacent structures
	T4a Tumour invades prostate, uterus or vagina
	T4b Tumour invades pelvic wall or abdominal wall
<b>N – Lymph nodes</b>	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node 2 cm or less in greatest dimension
N2	Metastasis in a single lymph node 2-5 cm in greatest dimension or multiple lymph nodes, none more than 5 cm in greatest dimension
N3	Metastasis in a lymph node more than 5 cm in greatest dimension
<b>M – Distant metastasis</b>	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

### 1.3.5 Random bladder biopsies

In the seventies it was understood that TCC of the urinary bladder often is a multifocal disease with co-existing CIS distant from the primary tumour (Oosterlinck, 2001). Therefore it was recommended to perform random biopsies of normal appearing bladder mucosa (Loening *et al.*, 1978). The presence of c-CIS is a strong risk factor for reoccurrence and progression of the tumour in patients with bladder cancer in stages TaG3 or T1G2-G3 (Shariat *et al.*, 2007; Sylvester *et al.*, 2006). Some authors have shown that the presence of CIS can influence the treatment decision, which also can change time to recurrence and possibly time to progression (May *et al.*, 2003; Thalmann *et al.*, 2004).

The use of randomised biopsies has been questioned (Kiemeny *et al.*, 1994) and in the recently published guidelines from the EAU it is recommended not to take randomised biopsies as a routine. However, if the cytology is positive and the exophytic tumour has a non-papillary way of growing, random biopsies are recommended. Areas of the mucous membrane with an abnormal appearance should also undergo biopsy (Babjuk *et al.*, 2008).

In order to evaluate the current literature on random bladder biopsies a Pub Med search was performed. We used the mesh terms [random bladder biopsies] AND [bladder neoplasms] AND [carcinoma in situ] NOT [prostate cancer]. After exclusion of case reports, review articles, articles in other languages than English and articles more than 20 years old, there were 27 articles left for analysis. We did not find one randomised comparison between taking and not taking random biopsies. However, several interesting studies on the subject were found. In an article by van der Meiden and co-workers of the EORTC-GU group, 512 patients with low-risk tumours were registered. In 393 patients (77%) one random biopsy was performed and 6 patients (1.5%) had c-CIS. They also registered 957 patients with intermediate and high risk tumours, 602 patients (63%) underwent multiple random biopsies and 3.5% of the patients had c-CIS. They conclude that “This analysis indicates that biopsies of normal-appearing urothelium in Ta, T1 bladder cancer patients show no abnormalities in about 90%. Performing such biopsies does not contribute to the staging or to the choice of adjuvant therapy after transurethral resection.” Unfortunately, this study was not primarily designed to evaluate the effectiveness of random biopsies. Treatment and survival was not analyzed. In 32% of the patients random biopsies were not performed and there was no randomisation between taking and not taking random biopsies, why this study only can provide information on how many patients will have c-CIS if they undergo random biopsies (van der Meijden *et al.*, 1999).

Another interesting article on random biopsies was published by Witjes and co-workers. They registered 1745 Dutch patients with Ta or T1 bladder neoplasms between 1983 and 1990. In 1044 patients, four random biopsies were taken and the patients were followed for 3.4 years. In patients with normal biopsies the risk of recurrence at two years was 44.5% and in patients with dysplasia or c-CIS the corresponding risk was 47.5%. In a multivariate Cox-model the result of the biopsies was not statistically significantly associated with the risk of recurrence. In their material, 70% of the patients had Ta disease, why a possible positive effect of random biopsies may be hard to show. In this paper there was no comparison between performing vs. not performing random biopsies (Witjes *et al.*, 1992). Two years later the same authors published “Should random urothelial biopsies be taken from patients with primary superficial bladder cancer? A decision analysis”. They here form two groups of patients. In the “no-biopsy policy”, no random biopsies were performed, except for patients with T1G3 who received adjuvant treatment. In the “biopsy policy”, all patients underwent random biopsies and the choice of treatment was influenced by the presence or absence of dysplastic urothelium in the random biopsies, except for patients with T1G3 tumour who received adjuvant treatment irrespective of the result of the random biopsies. The “biopsy policy” resulted in a three year risk of recurrence and progression of 52% and 11%, respectively. The “no-biopsy policy” resulted in a three year risk of recurrence and progression of 54% and 11%, respectively. They therefore conclude that taking random biopsies at the time of TURBT has no practical value. A

limitation of this study is that all the relevant patients with T1G3 underwent both random biopsies and adjuvant treatment, why possible effects of a superior disease classification and treatment becomes hard to evaluate (Kiemeny *et al.*, 1994). In the literature search we also found publications with positive effects of random biopsies. May and co-workers followed 1033 German patients between 1998 and 2000. In their patients, 7.1% had c-CIS in the random biopsies, 7% of the patients were upstaged because of the biopsy results and in 6.8% of the patients a change of treatment was made due to the biopsy results (May *et al.*, 2003). This article shows an interesting impact on the therapeutic decisions if random biopsies are performed. However, no randomisation between taking and not taking random biopsies was done. In an article by Zieger and co-workers, 70 Danish patients with T1 disease were followed up to 17.6 years. Nearly all (98%) of the patients underwent random biopsies. Positive random biopsies could in this work predict recurrence of T1 tumour during the first six years (Zieger *et al.*, 2002). A large material of 1529 Spanish patients has been presented by Millán-Rodríguez and co-workers. The patients were registered between 1968 and 1996, 36% had Ta and 64% had T1 disease. Five cold cup biopsies of normal-looking mucosa and one biopsy of the prostatic urethra were performed. In this material 43% of the patients with G3 and 52% of the patients with c-CIS underwent BCG treatment. Multivariate analysis could show c-CIS, as one of many, prognostic factors for both recurrence, progression and mortality (Millan-Rodriguez *et al.*, 2000).

#### 1.4 PROGNOSIS

The cancer specific survival rate at five years of the 9910 patients with bladder cancer who were reported to the Swedish quality registry during the years 1997 to 2001 was 70% (Malmström *et al.*, 2008). The prognosis for the patients is dependent of the stage. The long term prognosis for patients with PUNLMP is good. PUNLMP has a negligible risk of progression, but is not completely benign, since it has a tendency to recur. In a study from Gothenburg with patients diagnosed 1987-1988, none of the patients with PUNLMP progressed during the five year long follow-up period. However, 2.4 % of the patients with grade I progressed in stage (Holmäng *et al.*, 1999). Prognostic factors for Ta and T1 tumours include number of tumours, tumour size, previous recurrence rate, presence of c-CIS, stage, grade and response to intravesical therapy. For T1 tumours a worsened prognosis has been shown if the tumour has a solid tumour pattern (i.e. without fibrovascular core formation) and/or vascular invasion (Andius *et al.*, 2007).

The natural history of CIS is less favourable. The majority of patients with CIS, who do not undergo other treatment than TURBT, will eventually have a progression of the disease (Wolf *et al.*, 1994). The natural history for bladder cancer patients in stage T1 is also disappointing. Most bladder cancers in stage T1 are of grade II or III and grow fast with a potential to recur and progress (Andius, 2006). According to an old rule of thumb; 1/3 of patients with T1 bladder cancer will be recurrence free after intravesical instillation treatment, 1/3 will have recurrence and subsequent cystectomy and 1/3 of patients will die of metastatic disease.

## *Detection and management of urinary bladder carcinoma*

Approximately 34% of Swedish patients have muscle invasive disease at diagnosis. The cancer-specific survival at five years in patients with muscle invasive bladder cancer diagnosed between 1997 and 2000 in Sweden was 27% (Malmström *et al.*, 2008). If the patient with muscle invasive bladder cancer has sufficient general health to undergo a radical cystectomy a recurrence-free survival of 56-68% at five years can be seen, as shown in Table 3 (Hautmann *et al.*, 2006; Madersbacher *et al.*, 2003; Poulsen *et al.*, 1998; Stein *et al.*, 2001). Characteristics that influence the patients' survival in muscle invasive bladder cancer are tumour stage, tumour grade and the possible spread of cancer to the lymph node system (Ghoneim *et al.*, 1997; Hautmann *et al.*, 2006). During the seventies approximately one third of patients diagnosed with muscle invasive bladder cancer had undetected metastasis at the time of the primary treatment (Prout *et al.*, 1979). Despite negative preoperative staging, 124 of 507 patients (24%) who underwent radical cystectomy at the University of Bern between 1985 and 2000, had positive lymph nodes in the final pathology (Madersbacher *et al.*, 2003). There is no efficient treatment for distally metastasised bladder cancer and the patients usually die of the disease within two years from diagnosis (Malmström *et al.*, 2008).

**Table 3.** Outcome after radical cystectomy.

Author	Institution	No. of patients, Year	Perioperative mortality	Recurrence-free survival rate at five years
Stein et al, 2001	University of Southern California, Los Angeles, US	1054 patients, 1971-1997	2.5%	68%
Poulsen et al, 1998	University of Copenhagen, Denmark	194 patients, 1990-1997	Not discussed in paper	62% vs. 56% (extended vs. limited lymph node dissection)
Hautmann et al, 2006	University of Ulm, Germany	788 patients, 1986-2003	5.1% (3-month mortality rate)	68%
Madersbacher et al, 2003	University of Bern, Switzerland	507 patients, 1985-2000	6.9% (3-month mortality rate)	62%
Unpublished	Karolinska University Hospital, Sweden	142 patients, 1998-2005	2.1% (3-month mortality rate)	62%



## 1.5 RERESECTION – “SECOND LOOK”

There is a significant risk of residual bladder tumour after the initial TURBT. Residual tumour has been observed in 44% of Nordic patients with stage T1 (Jahnson *et al.*, 2005). There is also a probability that tumours initially labelled non-muscle invasive in fact are muscle invasive (“understaging”). A repeated TURBT (“second look”) may therefore be recommended after two to six weeks (Jakse *et al.*, 2004; Malmström *et al.*, 2008). In the second-look, residual tumour and the scar after the primary TURBT should be resected. A second look should be performed if the first operation was incomplete or if the pathologist cannot see muscle in the specimen. Other indications for a second-look are if bladder cancer pTaG3 or pT1G2-G3 were diagnosed at the first operation (Babjuk *et al.*, 2008).

## 1.6 FOLLOW-UP

Careful follow-up of patients with bladder cancer is essential (Pashos *et al.*, 2002). All patients should be followed with ureterocystoscopy and bladder wash cytology three months after TURBT. If the first control cystoscopy is normal in a patient with PUNLMP, the follow-up may be terminated. If the first control cystoscopy is normal in a patient with pTaG1, annual cystoscopies are sufficient according to recent findings (Berrum-Svennung *et al.*). Patients with more serious pathology should be followed every third month with cystoscopy and bladder wash cytology for two years and after that controls may be less frequent. In patients with tumours at high risk of progression, there is a risk of tumour development in the upper urinary tract why they should be examined with x-ray annually (Babjuk *et al.*, 2008).

## 1.7 TREATMENTS

### 1.7.1 BCG

Intravesical instillation of Bacillus Calmette-Guerin (BCG) is presently the most effective pharmaceutical treatment and prophylaxis for high risk (TaG3, T1, CIS or recurrence at three months) bladder cancer (Lamm, 2002). The mechanism of the antitumour effect of BCG is not completely known, but is probably immunologically mediated (Hosseini, 2004). Previous studies have suggested that the enzyme nitric oxide synthetase is induced by BCG and may have a contributing anti-tumourous effect (Jansson *et al.*, 1998). BCG may be administered a couple of weeks after TURBT and the intravesical duration time is usually one to two hours. BCG is the recommended treatment for CIS (Schenkman *et al.*, 2004) and is the only intravesical drug with at least some effect against progression of bladder cancer (Sylvester *et al.*, 2002). In a meta-analysis of 24 trials by Sylvester *et al.*, 9.8% of patients treated with BCG had progression to muscle-invasive disease compared to 13.8% of the control patients, a

reduction of 27% in the odds of progression (OR 0.73,  $p=0.001$ ). In this meta-analysis 4863 patients were included and the control patients were heterogeneous ranging from TURBT only to the use of various chemo-immunotherapies, with mitomycin being used in approximately half of the control patients. The size of the treatment effect was similar in patients with papillary tumours and in those with CIS. However, only patients receiving some form of maintenance BCG benefited. The authors conclude that intravesical BCG significantly reduces the risk of progression after transurethral resection in patients with superficial bladder cancer who receive maintenance treatment. Thus, the authors recommend it as the agent of choice for patients with intermediate and high risk papillary tumours and those with CIS (Sylvester *et al.*, 2002). Other authors have suggested that BCG maintenance treatment is not necessary for patients with TaG1-G2 after a first negative cystoscopy (Andius *et al.*, 2004b). Other indications for treatment with BCG are stadium T1, multifocality or recurrent Ta tumours. BCG is usually administered in an induction course of one instillation every week for six weeks and then maintenance therapy up to three years (Lamm *et al.*, 2000), however several different treatment schedules exists. An alternative to BCG is the instillation of intravesical chemotherapeutic agents such as epirubicin or mitomycin. Intravesical instillation of chemotherapeutic agents are usually a less toxic alternative to BCG and can be recommended for low and intermediate risk tumours (Lamm, 2002). In a Swedish study performed in 1987-1992, 261 patients with bladder cancer were randomised to either BCG or mitomycin. In this trial, BCG was considered superior since the patients who underwent BCG treatment had fewer recurrences and longer time to treatment failure compared to the patients who were treated with mitomycin (Lundholm *et al.*, 1996). The superiority of BCG was five years later confirmed in a follow-up of the same patients (Malmstrom *et al.*, 1999).

### **1.7.2 Cystectomy**

Radical cystectomy is the standard treatment for muscle invasive bladder cancer (O'Connor *et al.*, 2001). In T1 tumours with high risk for progression, such as high grade, multifocality, c-CIS and large tumours, an immediate cystectomy is a possible treatment option (Stein *et al.*, 2008b). For patients with stage T1 and therapeutic failure of BCG, radical cystectomy is also recommended.

A traditional cystectomy on a female patient includes removal of the bladder, the distal parts of the ureters, uterus, fallopian tubes, ovaries and the anterior wall of the vagina (Skinner, 1988). If a woman has not reached menopause the ovary contralateral to the tumour can be left in situ. The urethra is extirpated in cases of CIS, tumour in the bladder neck, tumour in the prostate or tumour in the prostatic urethra. In a man the seminal vesicles and the prostate are removed during surgery. Anatomical studies have shown that nerves controlling the male potency mainly are situated on the dorsolateral aspect of the prostate (Walsh *et al.*, 1983). During the dissection of a radical cystectomy these structures can be damaged and potency is jeopardised.

### 1.7.2.1 Prostatic capsule and seminal sparing cystectomy

To decrease the risk of incontinence and impotence in patients who have undergone a cystectomy several authors have suggested a technique where the apical and dorsal parts of the prostate and seminal vesicles are spared (Colombo *et al.*, 2004). The purpose is to preserve the nerves on the dorsal aspect of the prostate and to leave the urinary sphincter intact. In a recent study from Rome, all of the 20 patients performed with this technique obtained complete continence during both night and day. All of the 20 patients were able to have intercourse a few months after the operation (Simone *et al.*, 2008). Counter-arguments against this technique have been a concern for poorer oncological results, such as for example relapse of prostate cancer, metastases and local recurrence of bladder cancer (Ghoneim *et al.*, 2008; Stein *et al.*, 2008a). In the mentioned series from Rome 6/20 patients had metastases of bladder cancer and two patients developed prostate cancer, during the 33 months long follow-up period (Simone *et al.*, 2008). In a Swedish study it was reported an occurrence of urothelial cancer in the prostate and prostatic urethra in 29% of the cystoprostatic specimens (Liedberg *et al.*, 2007). Prostate cancer has been shown in approximately 23% of the cystoprostatic specimens (Hautmann *et al.*, 2006).

An alternative technique consisting of a prior transurethral resection of the prostate (TURP) followed by cystectomy and reconstruction with a Z-ileal bladder anastomosed to the prostatic capsule has been performed in 100 patients by Vallancien and co-workers (Vallancien *et al.*, 2002). During a mean follow-up of 38 months, 20/100 (20%) of the patients died of bladder cancer. In this series 97% were fully continent (no pad) during the day and 95% voided one to two times during the night to stay dry at the one-year follow-up. Of 61 patients with previously adequate sexual function, 50 patients (82%) maintained potency with retrograde ejaculation, 6 patients (10%) had partial potency and 5 patients (8.1%) were impotent.

### 1.7.2.2 Robot-assisted radical cystectomy

The introduction of robot-assisted laparoscopic surgery has given urologists an interesting treatment option to offer patients with a need to undergo radical cystectomy. Following the rapid development of laparoscopic robot-assisted radical prostatectomy, the step to perform a radical cystectomy by robot assistance was logical. The advantages of robotic surgery are similar to the advantages in traditional laparoscopy; decreased pain and blood loss, shorter hospital stay and recovery time and smaller surgical incisions (Sherif *et al.*, 2007). With a robot-assisted technique it is feasible to perform an extended lymph node dissection and even to perform the urinary diversion intracorporeally (Jonsson *et al.*).

Cystectomy with a laparoscopic approach was first described in 1992 (Parra *et al.*, 1992). Data on oncological outcome after laparoscopic cystectomy is scarce, but suggest comparable outcomes for laparoscopic and traditional open cystectomy (Haber *et al.*, 2007). The optimal evaluation of this new treatment strategy should naturally be a randomised trial and hopefully we will see such data in the near future.

### **1.7.3 Lymph node dissection**

At the time of cystectomy a lymph node dissection of the obturator fossa have traditionally been performed in Sweden (Malmström *et al.*, 2008). Several institutions have reported this to be insufficient (Skinner, 1982). A meticulous lymph node dissection from the aortic bifurcation and down along the iliac vessels to the obturator fossa have in non-randomised studies been associated with improved survival (Poulsen *et al.*, 1998). Another reason to perform an extended lymph node dissection is to get a better determination of the stage in order to offer adjuvant chemotherapy to the appropriate patients. A promising development in this field has been the introduction of the sentinel-node technique. With this technique removal of the relevant lymph nodes can be performed, as opposed to removing large fields of tissue at random (Liedberg *et al.*, 2006; Sherif *et al.*, 2001).

For patients with lymph node positive bladder cancer, long-term survival has been shown suggesting a therapeutic role of extensive lymphadenectomy (Stein *et al.*, 2006). In a recent article by Wright and co-workers, 1260 patients with at least one positive lymph node were followed. They found an inverse association between the number of lymph nodes removed and the risk of death. Removal of more than ten lymph nodes was associated with increased overall survival (Wright *et al.*, 2008).

### **1.7.4 Urinary diversions**

When the urinary bladder has been removed a urinary diversion must be performed. In the Karolinska Hospital, we have traditionally used a technique where the distal parts of the ureters are joined according to Wallace (Wallace, 1970) and thereafter anastomosed to the urinary diversion of choice. The three most common urinary diversions used in the Stockholm area are: non-continent urinary diversion (Bricker, 1950), continent cutaneous urinary diversion (Kock *et al.*, 1982) and orthotopic neobladder (Studer *et al.*, 1995b). Traditionally, the non-continent ileal conduit introduced by Eugene Bricker in 1950, has been the most common urinary diversion and is still a frequent option. One disadvantage with an ileal conduit is the need for an external urine-collecting device, which may hamper the patient's physical activities and self image. In order to relieve the patients from the external urine-collecting device, Nils G Kock in 1975 performed the first operation with a continent cutaneous urinary diversion at Sahlgrenska University Hospital in Gothenburg (Kock *et al.*, 1982). The continent cutaneous urinary diversion is emptied several times daily by the patient. A catheter is introduced through a small stoma on the abdomen and the reservoir is evacuated. A further improvement for the patients was the introduction of orthotopic neobladders which allow the patient to micturate through the urethra in a near normal fashion. Our group have shown that patients with an orthotopic neobladder experience a better quality of life compared to patients with a urinary diversion according to Bricker or Kock (Henningsohn, 2002). It is also suggested by other authors that an orthotopic neobladder, which gives an intact body image and normal voiding through the urethra, allows patients to lead a more normal life (Hautmann *et al.*, 2007). There are other authors who disagree and argue that the quality of life is similar despite type of urinary diversion (Månsson *et al.*, 2002).

In Memorial Sloan-Kettering Cancer Center, 214 patients underwent cystectomy and orthotopic diversion and were compared to 269 patients who underwent cystectomy and ileal conduit. No difference in cancer-specific survival was seen between the groups, suggesting that the type of urinary diversion does not influence the oncological outcome (Yossepowitch *et al.*, 2003).

## **1.8 MORBIDITY AFTER CYSTECTOMY**

### **1.8.1 Postoperative mortality and morbidity**

Radical cystectomy is a major surgical procedure and as such it is commonly followed by medical and surgical complications. In a follow-up of 788 cystectomy patients from the University of Ulm, 5.1% of patients died within 90 days after surgery as shown in Table 3 (Hautmann *et al.*, 2006) and in a series of 675 patients who underwent radical cystectomy at the Duke University 1969-1990 a 30-days mortality of 2,5% was found (Frazier *et al.*, 1992). An English study confirmed that most of the postoperative deaths occurred within 90, rather than 30 days, after the cystectomy (Chahal *et al.*, 2003). Serious non-lethal complications are also common in this group of patients. Approximately one third of patients who undergo cystectomy are subjects to complications within the first thirty days after the operation. Complications may include bowel obstruction, wound rupture, infections and insufficient anastomoses (Chang *et al.*, 2002).

### **1.8.2 Late morbidity after cystectomy - Urinary incontinence**

Urinary leakage is a potential side effect feared by patients with an orthotopic neobladder. The bladder substitute has a capacity of approximately 120 ml immediately after the construction. The functional capacity increases to 450-500 ml after one year and the greater capacity is followed by improved continence. In a Swiss study were 92% of the patients continent by day and 80% continent at night (Studer *et al.*, 1995a). In the literature there is a lack of an internationally accepted definition for continence, why the number of continent patients varies in different papers.

### **1.8.3 Late morbidity after cystectomy - Sexual dysfunction**

The risk for erectile dysfunction in patients who have undergone cystectomy is substantial. Symptoms of sexual dysfunction have been shown to be the most distressing symptom group in cystectomy patients, independent of type of urinary diversion (Henningsohn, 2002). If the cystectomy is performed with a nerve sparing technique the patients' potency may be preserved. A normal erectile function can

probably improve the quality of life for bladder cancer survivors (Henningsohn, 2002). A classical nerve sparing radical cystectomy can preserve the potency in 13-52% of cystectomy patients (Colombo *et al.*, 2008).

In a patient material from Chicago, 42% of patients could achieve erections adequate for sexual intercourse after nerve sparing radical cystectomy. In this study it was also shown that the potency was more likely to return in young patients compared to older patients (Schoenberg *et al.*, 1996). Studer and co-workers have reported that 18/51 patients (35%) have preserved potency after unilateral or bilateral nerve sparing radical cystectomy, although only 12% of the patients experienced their erections as good as before the operation (Studer *et al.*, 1995a).

#### **1.8.4 Gastrointestinal function after the construction of a urinary diversion**

In the construction of a urinary diversion different parts of the intestines may be used. The distal ileum, approximately 30 cm proximal to the ileocaecal valve, is a common choice. However, the normal ileum has several important physiological functions apart from absorbing nutrients. The distal ileum is the main site for the reabsorption of bile in the enterohepatic circulation of bile acid. If a substantial part of the distal ileum is used for a urinary diversion, one consequence is that the absorption of bile will decrease and bile acids are instead passed on to the colon. Bile in the colon may cause diarrhoea and faecal urgency. In a paper from Gothenburg 1/3 of the patients developed post-operative bile-acid malabsorption after the creation of continent cutaneous reservoirs (Olofsson *et al.*, 1998). In Swedish patients it has been shown that faecal leakage, faecal urgency and abdominal pain are consequences of radical cystectomy and urinary diversion (Henningsohn, 2002).

The distal ileum is also a major site for the production and release of gastrointestinal hormones. These hormones have an inhibitory function on gastrointestinal functions, such as gastric emptying. The gastrointestinal hormones glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) are secreted to the circulation after a meal. These hormones inhibit the gastric emptying and the excretion of insulin (Naslund *et al.*, 1999; Nauck *et al.*, 1997). GLP-1 and PYY also prolong the intestinal transit time (Lin *et al.*, 2004; Savage *et al.*, 1987).

## **2 AIMS OF THE STUDIES**

### **2.1 PAPER I**

To describe the diagnosis and clinical course of an unselected population-based cohort of patients with newly diagnosed transitional cell carcinoma of the urinary bladder. To create a tumour bank of freshly frozen tumour tissue for molecular biology research.

### **2.2 PAPER II**

To assess if random bladder biopsies and the detection of concomitant carcinoma in situ have an impact on the frequency of intravesical BCG instillations or radical cystectomy; and if this affects the clinical outcome in patients with transitional cell carcinoma of the urinary bladder.

### **2.3 PAPER III**

To describe the functional outcome after cystectomy for bladder cancer performed with a prostatic capsule and seminal sparing approach.

### **2.4 PAPER IV**

To investigate the effects of radical cystectomy and orthotopic ileal neobladder construction on gastrointestinal function and metabolic control.

### **3 PATIENTS AND METHODS**

#### **3.1 PAPER I**

##### **3.1.1 Study design**

The study intended to prospectively include all newly diagnosed bladder cancer patients in the Stockholm region in 1995 and 1996. A total of 628 patients with suspected bladder neoplasms were prospectively registered. In 34 patients the histopathological examination revealed a diagnosis other than bladder neoplasm and 31 patients were excluded because of inadequate registration. In total, 563 patients (compared to 721 patients with newly diagnosed bladder cancer reported to the Swedish Cancer Registry using similar selection criteria in terms of time and geographical distribution) were left for further analysis. As all newly diagnosed bladder carcinomas are reported to the Swedish Cancer Registry, the present study cohort included  $\approx 78\%$  (563/721) of Stockholm's bladder carcinoma patients detected 1995 and 1996. As inclusion was effectuated before primary surgery in a prospective fashion, the majority of the dropouts were patients treated on an emergency basis and those in whom tumours were discovered incidentally. Thirteen patients were lost to follow-up. Another 12 patients were excluded from the regular follow-up protocol because histopathology did not show TCC, but squamous cell carcinoma, adenocarcinoma or rhabdomyosarcoma. The remaining 538 patients were followed for at least five years. All hospitals and urology units in the region agreed to participate in the study. Treatment and follow-up were performed according to a standard-of-care programme (Wijkström *et al.*, 1995). Routine pathological reports were used. Original case records were scrutinized on location in 2001.

##### **3.1.2 Statistics**

For calculating the relative hazard ratio between patients with and without a recurrence at first check-up, the Cox proportional hazards model was used. Consultations were made with statistician Erik Onelöv who performed the statistical analyses of the study.



## **3.2 PAPER II**

### **3.2.1 Study design**

The same patient cohort as described in Paper I was used. We analysed the patients according to previous results from Paper I using the four disease categories: PUNLMP, pTaG1-G2, pTaG3 or pT1G2-G3 and muscle-invasive T2+ tumours. In Paper II results were presented according to the WHO 1999 malignancy grading system (Mostofi, 1999).

For patients with newly diagnosed bladder cancer standard-of-care in the Stockholm County consisted of a diagnostic work-up including cystoscopy, bladder-wash cytology, routine blood tests, chest X-ray and intravenous urography. Computerized tomography of the abdomen and pelvis, and bone scan were only performed in patients with muscle-invasive or suspected metastatic disease. In all patients bladder tumours were first treated with a TURBT. In Stockholm, at the time of the study, there was no recommendation of second-look TURBT, but random bladder biopsies of normal appearing mucosa were recommended in all patients at the initial TURBT. It was the individual physicians who decided whether or not patients would undergo random bladder biopsies. The random biopsies were taken at the following localisations: adjacent to the bladder tumour, the right and left lateral walls, the trigone and the posterior bladder wall. The histopathological result of the random bladder biopsies were classified either as normal or as c-CIS, if CIS (G3) was found in any of the specimens.

All patients were followed with cystoscopy and cytology every three to six months for two years and cystoscopy annually thereafter. Patients with high grade tumours were followed every three months continuously. Tumour recurrences were treated with TURBT. Intravesical BCG instillations, six times at weekly intervals, were administrated if c-CIS was diagnosed by the random bladder biopsies. Patients with primary CIS, multiple tumours, frequently recurrent tumours or pTaG3 or pT1G2-G3 were also recommended intravesical instillations.

In the follow-up the following parameters were registered: Number and dates of tumour recurrences, progress in grade and stage, development of nodal or distant metastases, therapy and cause of death.

### **3.2.2 Statistics**

Statistical tests were calculated using two-tailed t-tests,  $\chi^2$  (Pearson's Chi-square test), Fisher's exact test, Cox analysis or log rank tests. A *p*-value of <0.05 was considered statistically significant. The Kaplan-Meier technique was used to calculate cancer-specific survival, in which patients who died due to intercurrent diseases were censored. Statistician Erik Onelöv performed the statistical analyses.

### **3.3 PAPER III**

#### **3.3.1 Study design**

Twenty five male patients underwent prostatic capsule and seminal sparing cystectomy as treatment of transitional cell carcinoma of the urinary bladder between 1997 and 2005. Patient selection criteria for the study included preoperative urinary continence and erectile function allowing for sexual intercourse (assessed by interview), normal digital rectal exam, serum PSA <4 ng/ml or negative octant trans-rectal ultrasound guided prostate needle biopsy if serum PSA >4 ng/ml, clinically organ-confined bladder cancer, negative intraoperative prostatic urethral margin and adequate mental capacity required to care for a continent urinary diversion. The histopathology was assessed utilizing WHO-99 guidelines (Mostofi, 1999). The patients with orthotopic neobladder were recommended to set an alarm clock at night and void every fourth hour in order to diminish the risk of night time incontinence. The original case records were retrospectively reviewed in February 2008.

The cystectomy was performed with preservation of the seminal vesicles, posterior prostate and neurovascular bundles (Spitz *et al.*, 1999). The vas deferens and seminal vesicles were used to develop the correct posterior plane for the transection of the prostate. The prostate was elliptically transected, prostatic adenomas removed and the apex and posterior prostate were left in situ. Orthotopic ileal neobladders were created (Studer *et al.*, 1995b) and ureterointestinal anastomoses were performed according to the Wallace technique (Wallace, 1970). Intraoperative frozen section analysis of the proximal urethra was conducted on all patients to ensure a negative surgical margin. Bilateral lymphadenectomy was performed and included the obturator and external iliac lymph node packets.

Urinary, bowel and sexually related symptoms were evaluated by a questionnaire distributed to the patients who had undergone prostatic capsule and seminal sparing cystectomy. The questionnaire was developed through a qualitative analysis of data retrieved by in-depth interviews with patients who had undergone radical cystectomy (Henningsohn *et al.*, 2001). The questionnaire was then tested for face-validity on patients with bladder cancer and urinary diversion. The questionnaire contained eleven questions on urinary function including one bother question, five questions on bowel function and seven questions on sexual function including one bother question.

#### **3.3.2 Statistics**

The results are presented as means with minimum and maximum range. To describe the outcome of the questionnaire percentages are given in brackets.

## 3.4 PAPER IV

### 3.4.1 Study design

During 1999 and 2000, a total of 48 patients underwent radical cystectomy and construction of orthotopic neobladder or Kock ileal reservoir for bladder cancer in our department. Twenty patients were excluded (see Table 1, Paper IV) and 28 patients (27 men, one woman) were included in the study (25 patients with orthotopic neobladder and three with Kock ileal reservoir). Ten patients endoscopically treated for non-invasive bladder cancer (TaG2) were matched for age and gender and served as controls.

Standard radical cystectomy and bilateral pelvic iliac lymphadenectomy was performed (Skinner, 1988). The orthotopic neobladders were made according to the Studer technique (Studer *et al.*, 1995b) using 50-55 cm. segments of the distal ileum, with the distal end taken approximately 30 cm proximal to the ileocecal valve. In the three patients with Kock ileal reservoir (Kock *et al.*, 1982), the ileal segment was 70 cm. To measure the enterohepatic circulation of bile salt, examination with <sup>75</sup>SeHCAT was performed (Boyd *et al.*, 1981; Ferraris *et al.*, 1986). A capsule of radioactive taurocholic acid (SeHCAT) was given orally and ten minutes later the abdominal activity was measured using a gamma camera. Seven days later a re-examination of the abdomen was done with the same gamma camera and the abdominal retention of the radionuclide between the acquisitions was calculated. At the second visit the patients ate a standardized radioactive omelette and the gastric emptying was studied (Grybäck *et al.*, 2000).

During the second visit we also took blood samples for the analysis of GLP-1, PYY, insulin and glucose. The first blood sample was taken 20 minutes before intake of the radioactive omelette and then every 10 minutes, until 120 minutes after the omelette intake. We performed RIA for the determination of plasma concentration of GLP-1 (Deacon *et al.*, 1995) and PYY (Näslund *et al.*, 1998).

For symptom evaluation all patients were sent a local questionnaire two years after the radical cystectomy. The questionnaire assessed changes in weight, bowel habits, abdominal pain, faecal urgency and the consistency and frequency of stools.

Supplementary telephone interviews were conducted three years after the radical cystectomy.

### 3.4.2 Statistics

The results were evaluated using a two-tailed *t*-test and the Mann-Whitney test.  $p < 0.05$  was considered significant. SPSS 13.0 (version 11.5.1; SPSS inc., Chicago, IL) was used for statistical analyses. Statistician Erik Onelöv performed the statistical analyses.

## 4 RESULTS AND DISCUSSION

### 4.1 RESULTS PAPER I

In this cohort, 67% (363/538) were male and 33% (175/538) were female. Median age at diagnosis was 72 years (mean 70 years; range 30-97 years). The pathological stage at diagnosis is shown in Table 4.

**Table 4.** Pathological stage at diagnosis of the patients in the cohort.

Stage	No. of patients.
CIS	11 (2%)
Ta	292 (54%)
T1	110 (21%)
T2+	125 (23%)
Total No.	538 (100%)

The result of the first control cystoscopy after the initial resection of non-invasive tumours was of prognostic value. Patients with a recurrence at the first check-up had a relative hazard ratio for stage progression of 8.1 (95% CI 4.4-16.2) and a relative hazard ratio for disease-related death of 7.5 (95% CI 3.3-17.3). Recurrent disease was present in 62% (248/402) of all patients with Ta and T1 tumour at diagnosis and patients with T1 tumours had recurrences earlier than those with Ta tumours.

Moreover, 32% (35/110) of the patients who presented with T1 tumours at diagnosis progressed to muscle-invasive disease during the follow-up period.

The calculated five year cancer-specific survival rate for the 538 patients in the cohort was 78%. No patient (0/29) with TaG1 (PUNLMP according to WHO 1999) tumour showed progression or died of bladder cancer. Only 2/187 patients (1%) with stage Ta and grade 2A (G1 according to WHO 1999) or 2B (G2 according to WHO 1999) tumour died of bladder cancer. In contrast, after five years of follow-up, patients with TaG3 (G3 according to WHO 1999) and T1G2B (G2 according to WHO 1999) tumours had disease-specific death rates of 20% and 27% respectively. The five year cancer-specific mortality for patients with T1G3 was 18/53 (34%). The overall prognosis for patients presenting with muscle-invasive tumours (T2+) was dismal, with 69% (80/116) of the patients dying of the disease. The five-year cancer-specific mortality is further described in Table 5.

**Table 5.** Five-year cancer-specific mortality of the patients in the cohort.

	Death from bladder cancer*/ Total no. (%)
TaG1 (PUNLMP WHO 1999)	0/29 (0%)
TaG2A-G2B (TaG1-G2 WHO 1999)	2/187 (1%)
TaG3-T1 (TaG3-T1 WHO 1999)	32/106 (30%)
T2+	80/116 (69%)

\*Patients who died due to intercurrent diseases were excluded.

Out of 125 patients with muscle-invasive TCC, 49 (39%) patients underwent radical cystectomy. All but three patients underwent radical cystectomy within six months. Twenty seven of the 125 patients (22%) underwent radiation or chemotherapy with curative intention. Surprisingly, only 76/125 patients (61%) of the patients with muscle-invasive tumours underwent a treatment with curative intention.

In the Cancer Registry of Stockholm during 1995 and 1996, 721 patients were registered to have a newly detected neoplasm of the urinary bladder. If the 538 patients of the bladder cancer cohort are subtracted, 183 patients remain. Of these 183 patients, 72% were male and 28% female. The median age of the patients not included in the cohort was 75 years (range 36-97 years). The histopathology of these 183 patients is shown in Table 6. The overall survival to October 2001 of these 183 patients was 113/183 (62%). The number of patients that never were included in the original study cohort stratified per hospital is shown in Table 7.

**Table 6.** Histopathology of the 183 patients that never were included in the bladder cancer cohort.

Histopathology	No. of patients
Transitional cell carcinoma	158
Squamous cell carcinoma	7
Adenocarcinoma	1
Anaplastic	3
Atypical papilloma	4
Carcinoma in situ	7
Sarcoma	1
Unidentified	2

**Table 7.** The number of patients at the different hospitals in Stockholm that never were included in the bladder cancer cohort.

Hospital	No. of patients not included	No. of patients included	No. of patients not included / Total no. of patients (%)
Danderyd Hospital	24	85	24/109 (22%)
Huddinge Hospital	16	98	16/114 (14%)
Karolinska Hospital, Solna	46	164	46/210 (22%)
Norrtälje Hospital	20	0	20/20 (100%)
Sabbatsbergs Hospital	15	0	15/15 (100%)
Stockholm South Hospital	37	169	37/206 (18%)
Small institutions/Private practitioners	25	22	25/47 (53%)
Total no. of patients	183	538	183/721 (25%)

## 4.2 DISCUSSION PAPER I

In this paper we describe the clinical and histopathological characteristics of 538 patients diagnosed with primary TCC of the urinary bladder in a defined geographical region during a period of two years. The patients in this population-based series were all diagnosed, treated and followed according to a standardized protocol (Wijkström *et al.*, 1995).

The results of the present series confirm that G2A tumours are less malignant than G2B tumours (Malmström *et al.*, 1987) when tumours of all stages are compared, although when stratified for stage we were unable to demonstrate any clinical difference in outcome between G2A and G2B tumours. The fact that many more G2B than G2A tumours invaded the lamina propria (T1) may explain that finding, as the presence of lamina propria invasion is of paramount importance for the long-term outcome of the disease (Anderström *et al.*, 1980; Zieger *et al.*, 1998).

Our data support the concept that bladder tumours with grade 1 (PUNLMP according to WHO 1999) histology are not aggressive and should not be designated as real carcinomas. In our study, none of the G1 (PUNLMP according to WHO 1999) tumours progressed and there were no disease related deaths; these tumours can in essence be recognized as PUNLMP.

Patients with T1 tumours had a dismal prognosis, with an overall cancer-specific mortality rate of 31% (30/96), although the figure was as high as 20% for TaG3 tumours as well. Only 11% (14/125) of patients with TaG3 or T1 tumours had an early cystectomy. If some of these tumours were genetically unstable but had not yet given rise to micrometastatic spread, an immediate cystectomy could probably have cured some of these patients. From a clinical standpoint, it seems that the patients in this

series with TaG3 and T1 tumours could have been treated more aggressively; a radical cystectomy could perhaps have cured some of the patients who died of bladder cancer. The result of the first cystoscopy examination after the initial resection for non-invasive tumours has considerable prognostic value, according to the British Medical Research Council study of 1989 (Parmar *et al.*, 1989). This has also been shown in Swedish patients with CIS (Andius *et al.*, 2004a). We found that patients with recurrence at the first check-up had a worse prognosis, with increased risks of stage progression and disease-related death. Patients with TaG3 and T1 tumours with recurrences at first check-up cystoscopy may be considered for cystectomy.

In our series, c-CIS was diagnosed in 9% (26/281) of patients with stage Ta and T1 tumours. In a similar cohort study reported by Holmäng *et al.* (Holmäng *et al.*, 2000), 8% of patients with stage Ta and T1 tumours had c-CIS, despite the fact that normal-looking mucosa was very rarely biopsied. Consequently, it is unclear if standardized random bladder biopsies of normal-looking mucosa add information in the primary work-up of bladder tumour patients. This issue is further analyzed in Paper II.

Among the patients with muscle-invasive bladder cancer, 39 % never underwent radical cystectomy or radiation with curative intention. This large proportion of untreated patients reflects the clinical reality, in which many patients with bladder cancer are elderly and have serious comorbidity, why they may not be able to undergo a radical treatment.

A limitation to this work is that only standard pathology was used. In a paper by van der Meijden and co-workers, 1400 patients treated in five EORTC trials were subject to review pathology. In the group of T1G3 the stage or grade was often changed after review pathology and in these patients up- or downstaging may have impact on treatment decision making (van Der Meijden *et al.*, 2000). Using reference pathology would have increased the validity of our material. The causes of death were retrieved from the death certificates. Further validity to our work would have been given if a committee of independent physicians would have decided on the cause of death.

We were unsuccessful in recruiting 22% of the bladder cancer patients in the region during 1995 to 1996 to our registry. Of the 183 patients that were not included there were more men (72% vs. 67%) and the median age was somewhat higher (75 years vs. 72 years) compared to those who were included in the cohort. A higher inclusion rate would have improved the study. This is a problem following inclusion in a prospective fashion of large cohorts that is hard to come by. The analysis of not included patients can however give more strength to the material if there are no obvious differences suggesting selection bias.

### 4.3 RESULTS PAPER II

Random bladder biopsies were performed in 326 of 538 patients (61%) and revealed c-CIS in 47 of these patients (14%). Random bladder biopsies were performed in 82% of patients with pTaG3 and pT1G2-G3 tumours compared to 57% of patients with

PUNLMP and pTaG1-G2 tumours. Mean age was statistically significantly lower (mean 66 years, SD  $\pm 11$ ) among patients in whom random bladder biopsies were performed compared to patients where no random biopsies were performed (mean 76 years, SD  $\pm 11$ ,  $p < 0.001$ ).

Patients with pTaG3 or pT1G2-G3 bladder neoplasms in whom random bladder biopsies were performed were more likely to be treated with intravesical BCG compared to patients without random biopsies (58% vs. 23%,  $p = 0.002$ ). In patients with pTaG3 or pT1G2-G3 tumours where random bladder biopsies were performed, 23 of 103 patients (22%) underwent radical cystectomy compared to 0 of 22 patients (0%) without random biopsies ( $p = 0.013$ ). Random bladder biopsies revealed c-CIS in 10 of 23 patients (44%) who underwent radical cystectomy.

Patients with pTaG3 or pT1G2-G3 bladder neoplasms with c-CIS detected by random biopsies received intravesical BCG more often than patients with normal random biopsies (87% vs. 50%,  $p = 0.002$ ). These patients, who had pTaG3 and pT1G2-G3 tumours and c-CIS, also had a lower intravesical recurrence rate during follow-up (50% vs. 85%,  $p = 0.001$ ).

The Cox proportional-hazard ratio for death due to bladder cancer comparing pTaG3 or pT1G2-G3 patients without vs. with random biopsies was 2.5 (95% CI 1.1-5.6).

Increased cancer-specific survival at five years was seen in patients with pTaG3 or pT1G2-G3 tumours in whom random biopsies were performed (77%) compared to patients without random biopsies (56%,  $p = 0.025$ , log rank test).

In the group of patients with pTaG3 or pT1G2-G3 who underwent random bladder biopsies 10/103 (10%) died due to other disease than bladder cancer. In the group of patients with pTaG3 or pT1G2-G3 who did not undergo random bladder biopsies 8/22 (36%) died due to other disease than bladder cancer. We could not find any statistically significant differences in gender, multiplicity or mean tumour size between patients with pTaG3 or pT1G2-G3 that underwent random biopsies compared to those who did not undergo random biopsies (Table 8).

**Table 8.** Multiplicity, mean tumour size and corresponding number of patients with pTaG3 or pT1G2-G3 who underwent random bladder biopsies.

		Multiplicity (No. of tumours)		Mean tumour size (cm.)	
TaG3 and T1G2- G3	Random biopsies	1 tumour	58/103 (56%)	<1.4	14/103 (14%)
		2 tumours	15/103 (15%)	1.5-3.4	55/103 (53%)
		$\geq 3$ tumours	30/103 (29%)	3.5-5	25/103 (24%)
				>5.5	9/103 (9%)
	No random biopsies	1 tumour	15/22 (68%)	<1.4	3/22 (14%)
		2 tumours	3/22 (14%)	1.5-3.4	8/22 (36%)
		$\geq 3$ tumours	4/22 (18%)	3.5-5	10/22 (45%)
				>5.5	1/22 (5%)



In patients with pTaG3 or pT1G2-G3 tumours, random bladder biopsies were performed more often in younger patients (mean age 68 years) than in older patients (mean age 80 years). In the whole group of patients with pTaG3 or pT1G2-G3 the mean age was 71 years. In order to further evaluate possible bias due to age, a mean split of the patients with pTaG3 or pT1G2-G3 was performed. We then found that in the group of patients with pTaG3 or pT1G2-G3  $\leq 71$  years who underwent random biopsies, 14 of 61 patients (23%) had c-CIS compared to 9 of 42 patients (21%)  $> 71$  years ( $p=0.86$ ,  $\chi^2$ ). All patients with pTaG3 or pT1G2-G3 who underwent random biopsies and had c-CIS underwent treatment with BCG or radical cystectomy in both age groups.

In patients with pTaG3 or pT1G2-G3  $\leq 71$  years, 3/64 patients (5%) did not undergo random biopsy and none of these patients died of bladder cancer. In patients with pTaG3 or pT1G2-G3  $> 71$  years, 19/61 patients (31%) did not undergo random biopsy, 16/19 patients (84%) did not undergo BCG or radical cystectomy and 8/19 patients (42%) died of bladder cancer.

In patients with pTaG3 or pT1G2-G3  $\leq 71$  years who underwent random bladder biopsies, 12 of 61 patients (20%) died of bladder cancer. In patients with pTaG3 or pT1G2-G3  $> 71$  years who underwent random bladder biopsies, 12 of 42 patients (29%) died of bladder cancer. In patients with pTaG3 or pT1G2-G3  $> 71$  years who did not undergo random bladder biopsies 16/19 patients (84%) did not undergo BCG or radical cystectomy and 8/19 patients (42%) died of bladder cancer.

Intravesical BCG treatment was given to significantly fewer patients  $\geq 80$  years old compared to younger patients ( $p=0.013$ , Table 9). In patients with pTaG3 or pT1G2-G3 who underwent random bladder biopsies, the younger patients were more frequently treated with BCG and the older patients died more frequently of bladder cancer.

**Table 9.** Number of patients with pTaG3 or pT1G2-G3 bladder neoplasms treated with intravesical BCG instillations stratified according to age.

Age (years)	No. of patients treated with intravesical BCG instillations / Total No. (%)
<50	4/6 (67)
50 – 59	8/11 (73)
60 – 69	24/38 (63)
70 – 79	24/47 (51)
$\geq 80$	5/23 (22)

Random bladder biopsies were performed in 10 of 34 patients (29%) with PUNLMP. None of the 10 patients was found to have c-CIS in the biopsy specimens. No patient progressed to higher tumour stage and no disease related death occurred in these 34 patients during follow-up.

In the group of patients with pTaG1-G2 random bladder biopsies were performed in 147 of 243 patients (60%) and three of these patients had c-CIS (2%). Three patients

had stage progression to T1 and two patients had stage progression to T2+. In the group of patients with pTaG1-G2 tumours two patients died due to metastatic bladder cancer, none of the dead patients was diagnosed with c-CIS.

In 66 of 125 patients (53%) with muscle-invasive (T2+) bladder cancer random bladder biopsies were performed and c-CIS was diagnosed in 21 (32%) of these patients. Cancer-specific mortality at 5 years was 81% in T2+ patients with c-CIS in the random biopsies compared to 49% in T2+ patients with normal pathology of the random biopsies.

#### **4.4 DISCUSSION PAPER II**

In this population-based cohort of patients we found that random bladder biopsies influenced treatment decisions as more patients were treated with intravesical BCG or radical cystectomy when random biopsies were performed. The cancer-specific survival at five years was higher in patients with pTaG3 or pT1G2-G3 bladder neoplasms having undergone random bladder biopsies (77%) compared to patients without (56%). The superior survival in patients with pTaG3 or pT1G2-G3 who underwent random bladder biopsies may partly be explained by the fact that more patients were treated with BCG instillations. Additionally, in patients with pTaG3 or pT1G2-G3 neoplasms the indication for radical cystectomy was partly influenced by random bladder biopsy results, since only patients with random biopsies underwent radical cystectomy.

Intravesical BCG was given to fewer patients  $\geq 80$  years old compared to younger patients ( $p=0.013$ ). In patients with pTaG3 or pT1G2-G3 who underwent random bladder biopsies, the younger patients were more frequently treated with BCG and the older patients died more frequently of bladder cancer. This finding underlines the importance of careful work-up and treatment to octogenarians.

In this study there is a difference in age between the groups of patients with pTaG3 or pT1G2-G3 in whom random biopsies were performed vs. not performed. In order to further evaluate this, a mean age split was performed. It shows that the absolute majority (95%) of patients with pTaG3 or pT1G2-3  $\leq 71$  years underwent random biopsies and this complicates the interpretation of data. However, there was no statistically significant difference in the presence of c-CIS between patients who underwent random biopsies with pTaG3 or pT1G2-G3  $\leq 71$  vs.  $> 71$  years and all patients with pTaG3 or pT1G2-G3 who underwent random biopsies and were diagnosed with c-CIS underwent treatment with BCG or radical cystectomy in both age groups. Within the age group  $> 71$  years, 42% of the patients with pTaG3 or pT1G2-G3 who did not undergo random bladder biopsies died of bladder cancer compared to 29% if random biopsies were performed. The finding that the positive influence of random biopsies on cancer-specific survival exists even after stratification for age strengthens the hypothesis that random biopsies may influence treatment decisions and thereby possibly affect the cancer-specific survival. In the group of patients with pTaG3 or pT1

who underwent random biopsy, 10% of the patients died due to competing mortality compared to 36% of the patients in the group who did not undergo random biopsy. If the patients who did not undergo random biopsy had lived longer even more patients in this group would have died due to bladder cancer. We could not find any statistically significant differences in gender, multiplicity or mean tumour size between patients with pTaG3 or pT1G2-G3 who underwent random biopsies compared the patients who did not undergo random biopsies. Further, there was no big difference in the percentage of patients who underwent random biopsies between the four large hospitals in the Stockholm County. A clinical trial with randomisation between performing and not performing random bladder biopsies is needed to further entangle the question. In patients with PUNLMP and pTaG1-G2 the cancer-specific mortality is low and these patients are rarely, if ever, candidates for intravesical BCG instillations or radical cystectomy. It would be difficult to show a beneficial effect of random bladder biopsies should such benefit exist. Our results confirm previous findings of the rarity of c-CIS in patients with PUNLMP or TaG1-G2 (Sylvester *et al.*, 2006; Zieger *et al.*, 2000), why we find the clinical value of random biopsies low in these patients. If random biopsies are recommended in all patients in the initial TURBT many patients who do not benefit from random biopsies will undergo the procedure. On the other hand it has been discussed that random biopsies are a simple task to perform without serious side effects (May *et al.*, 2003). An advantage with performing random biopsies in all patients at the initial TURBT is that no patients will be insufficiently examined. For patients with muscle-invasive bladder cancer, the presence of c-CIS should rarely, if ever, affect the decision to perform a radical cystectomy, why the clinical value of random biopsies is low also in patients with muscle-invasive bladder cancer.

#### 4.5 RESULTS PAPER III

Twenty-five men underwent cystectomy with prostatic capsule and seminal sparing approach, mean age was 55 years and mean operative time was 366 minutes (range 255-437 minutes). Average blood loss was 2310 ml (range 650-6500 ml). Mean hospital stay was 16 days (range 8-41 days). During the follow-up period (mean 72 months, range 33-129) five patients developed metastases and died of bladder cancer. Four men were diagnosed with concomitant prostate cancer. Clean intermittent catheterization was required by 4 of 21 patients (19%) due to insufficient neobladder emptying. Complete daytime continence (no pads) was reported in 17/20 (85%) patients. Complete nocturnal continence (no pads) was seen in 10/20 (50%) men. When patients were asked their feelings if their urinary status would be unchanged for the rest of their lives 18/20 (90%) reported "little or no distress". Diarrhea was noted by 7/20 (35%) men but 19/20 (95%) never had difficulties in suppressing the urge to defecate before reaching the toilet. With regard to sexual intercourse, 20/21 (95%) men remained sexually active at the time of last follow up and 14/20 (70%) of the sexually active patients experienced no difficulty with obtaining or maintaining erections and

did not require oral phosphodiesterase inhibitors. Erectile dysfunction requiring the use of oral phosphodiesterase inhibitors was reported by 5/20 (25%). In response to the question “How would you feel if your sexual limitations would persist for the rest of your life?” 8/20 (40%) responded not to have any sexual limitations and 11/20 (55%) responded to have little or no distress.

#### **4.6 DISCUSSION PAPER III**

Unlike conduit urinary diversions, the intent of bladder replacement following cystectomy is to improve post-surgical quality of life while providing comparable cancer control. Despite attempts to preserve the neurovascular bundles of the penis as well as the integrity of the external urinary sphincter, post-operative urinary incontinence and erectile dysfunction remain a significant morbidity following extirpative bladder surgery and orthotopic neobladder diversion.

We acknowledge that these patients selected for prostatic capsule and seminal sparing cystectomy tend to be younger and healthier with less advanced disease than most cystectomy cohorts. Preoperatively, 12/25 (48%) of the patients had Ta or T1 disease. All patients were potent without the need for phosphodiesterase inhibitors prior to surgery. We did not perform preoperative transurethral resection of the prostate to rule out transitional cell cancer in the prostatic urethra as described in other prostate-sparing cystectomy series (Botto *et al.*, 2004). However, all patients selected for the procedure did have a negative intraoperative frozen section of the proximal urethra.

During follow-up five patients developed metastases and died of disseminated bladder cancer. This is comparable to, or better than, other published studies. In the series of 788 patients who underwent cystectomy at the University of Ulm between 1986 and 2003, the recurrence-free survival rate was 68% at five years which compares well with the recurrence-free survival of 80% at six years in our patients (Hautmann *et al.*, 2006). However, it is not surprising since our cohort was selected to only include men with less advanced disease. Furthermore, all patients that died of metastatic disease in our series also had primary or concomitant carcinoma in situ which is known to portend a worse prognosis (Sylvester *et al.*, 2006). One can only speculate if performing a “traditional” radical cystectomy and urinary diversion would have altered the outcomes of any of the men who died of metastatic bladder cancer.

Despite performing preoperative digital rectal exam and PSA analysis on all patients and prostate biopsy on selected patients, concomitant prostate cancer was detected in 4/25 (16%) patients. Incidental prostate cancer has been reported in 18-40% of men after undergoing cystoprostatectomy for invasive bladder cancer (Kouriefs *et al.*, 2005; Montie *et al.*, 1989; Revelo *et al.*, 2004). None of the four patients diagnosed with prostate cancer in our material died from or required treatment for prostate cancer at the end of follow-up. It is likely that we could have avoided some of the problems with concomitant prostate cancer if we had taken prostate biopsies from all the patients.

In a series of 20 patients from Rome, who underwent prostatic capsule and seminal sparing cystectomy during 2002 to 2006, two patients were diagnosed with prostate cancer. In this series the quality of life was excellent with complete daytime and night time continence achieved in all patients. All of the Italian patients were reported to have had satisfactory sexual intercourse one to two months postoperatively (Simone *et al.*, 2008). Symptoms of sexual dysfunction have been shown to be the most distressing symptom group in cystectomy patients, independent of type of urinary diversion (Henningsohn, 2002).

With respect to continence and sexual function, our results are in accordance with those of previous authors (Horenblas *et al.*, 2001; Muto *et al.*, 2004; Vallancien *et al.*, 2002). It should be noted, however, that the results are likely influenced by the patient selection. For example, all patients were sexually active without pharmacological support prior to treatment, and it has been shown that postoperative continence and potency are less affected by surgery among those operated before 65 years of age (Kessler *et al.*, 2004). But with the limited dissection applied, the frequency of significant urinary and sexual dysfunction appears to go beyond what could be expected from patient selection.

Our data was retrieved during face to face interviews. As a result, patients may have diminished their complaints. There is also a risk of observer bias, although the questionnaires are designed to reduce subjectivity. Anonymous self-administered questionnaires by a neutral third party would have increased the validity of the data (Månsson *et al.*, 2004). However, in our study, the urologist who recorded the outcome data was not the same urologist that treated the patient.

In order to measure quality of life we used a questionnaire developed by our group. The questions were developed by a qualitative analysis of data retrieved by in-depth interviews with patients who had undergone radical cystectomy. The questionnaire was then tested for face-validity on patients who had undergone radical cystectomy and further refined until we were certain that all questions were correctly understood and could be answered properly. If we had used standardized questionnaires, comparisons to other groups' results would be easier.

#### 4.7 RESULTS PAPER IV

In patients who underwent radical cystectomy 7 out of 28 (25%) experienced daily diarrhea and faecal urgency. The cystectomy patients had a SeHCAT retention of  $14 \pm 3\%$  compared to the control group of TURBT patients who had  $31 \pm 8\%$  SeHCAT retention ( $p=0.013$ ). The cystectomy patients reported faecal urgency more commonly than diarrhea. During the three years following surgery 6 out of 22 (27%) patients were taking cholestyramine to control bowel symptoms, all of whom reported a good clinical effect. The six cystectomy patients who were taking cholestyramine had a mean SeHCAT retention of  $5\%$  (SD  $\pm 2\%$ ) when the medication was interrupted before the examination.

The cystectomy patients had a statistically significantly faster gastric emptying compared to controls ( $p=0.022$ ). Only one patient who had undergone radical cystectomy reported dyspeptic symptoms.

Higher plasma levels of PYY were seen in the group of cystectomy patients compared to controls ( $p < 0.001$ ). In both cystectomy patients and controls, GLP-1 and PYY increased in a similar fashion in response to the omelet meal. Further, the cystectomy patients had a slightly blunted increase in plasma insulin compared to the controls ( $p=ns$ ). Blood glucose was not affected and none of the cystectomy patients developed diabetes. The preoperative weight of the cystectomy patients ( $78 \pm 1.8$  kg) had not changed significantly at the three year follow-up assessment ( $76 \pm 2.0$  kg).

#### **4.8 DISCUSSION PAPER IV**

This study shows that the majority of patients who have undergone radical cystectomy and construction of an orthotopic ileal neobladder are likely to maintain normal bowel habits. However, a quarter of the cystectomy patients developed daily diarrhoea and faecal urgency. These findings are similar to the high prevalence of bowel symptoms in patients with Kock reservoirs earlier reported by our group (Henningsohn *et al.*, 2001). Removal of the distal ileum from the GI tract during neobladder construction impairs the enterohepatic circulation of bile, which was shown by the significantly lowered levels of SeHCAT. It has been reported that patients with a Kock ileal reservoir suffer from diarrhoea due to increased passage of bile to the colon (Olofsson *et al.*, 1998). In our series, 13 of 28 cystectomy patients (46%) had a SeHCAT level less than 10% compared to 7 of 21 (33%) in the study by Olofsson and co-workers (Olofsson *et al.*, 1998). This supports our contention that the shorter ileal segment mainly used for an orthotopic reservoir may also impair the enterohepatic circulation of bile. A resin such as cholestyramine is a reasonable treatment option in this group of patients.

Another possible mechanism for bowel disorders in this group of patients may be enhanced gastric emptying. In our limited material we could demonstrate a statistically significant tendency of more rapid gastric emptying among the cystectomy patients. It is unclear if this small difference in gastric emptying may be a contributory factor to the bowel disorders encountered.

Removal of the distal ileum is followed by changes in plasma levels of different GI hormones. Our findings showed that PYY increased in the group of cystectomy patients, but was not paralleled by an increase of GLP-1. As PYY is considered to exert an inhibitory action on gastric emptying (Savage *et al.*, 1987) it is plausible that the ileum may increase the production of PYY in order to normalize gastric emptying. These findings are surprising as both PYY and GLP-1 emanate from the same type of endocrine cells, the L-cells of the gut. Ileum transposed to the jejunum of rats has been shown to increase its production of PYY when exposed to nutrients, indicating that the ileum is the predominant site for PYY release (Strader *et al.*, 2005). In another study (Naslund *et al.*, 1998) in which plasma levels of GI hormones were measured 20 years

after jejunioileal bypass for obesity, an increase in GLP-1 was also noted. This would indicate a long lag-time for an increase of GLP-1, which may explain why we could not detect this two years after surgery.

Our present data showing stable GLP-1 levels are in line with unchanged insulin and glucose levels in the metabolic control process. The restricted increase of gastric emptying is also in line with unchanged GLP-1, as this is considered to be a major regulator of gastric emptying (Naslund *et al.*, 1999). At the same time, the high plasma levels of PYY found in the present study suggest that this peptide has only a minor influence on gastric emptying. Hence, another factor from the distal GI tract may serve as an inhibitor of gastric emptying. One possibility would be oxyntomodulin which, similarly to GLP-1, is a product of the proglucagon gene of the L-cells (Drucker, 2002; Rodier *et al.*, 1997). However, the effects of oxyntomodulin on gastric emptying have yet to be established.

One might speculate that the ileum in a dilated reservoir mistakes the urine for nutrients and enhances the basal production of PYY. However, the increase in PYY was equivalent in both cystectomy patients and controls after the test meal, which would preclude a major impact of urine on PYY release.

Another possible explanation for the finding of the raised basal levels of PYY in the cystectomy patients could be that the loss of bile acids into the faeces may increase the production of bile (Greenberger, 1989). This could secondarily lead to increased release of PYY, since one of the physiologic effects of PYY is to suppress gallbladder emptying and reduce bile salt loss (Hoentjen *et al.*, 2001).

The patients in this study reported faecal urgency more commonly than diarrhoea. Faecal urgency after radical cystectomy can possibly be caused by surgical lesions of the nerves which regulate rectal motility. Another possible cause is fibrosis in the area, which may reduce rectal compliance and normal retention of faeces. These aspects were not studied in this work.

A possibly improved study design would have been to have the cystectomy patients as their own controls. We could have made the measurements on retention of bile and gastric emptying before and after the cystectomy. In reality it may however be troublesome for patients waiting for a radical cystectomy to undergo time consuming tests, not directly needed for their operation. For our group it was also necessary to perform all the testing at one time. It could also be interesting to measure the bowel transit time, as a shorter transit time may be involved.

## **5 GENERAL DISCUSSION**

### **5.1 PUNLMP**

No patient with PUNLMP showed progression or died of bladder cancer. This strengthens the recommendation that if the first cystoscopy at three months is normal, cystoscopy controls can safely be terminated (Malmström *et al.*, 2008). No patient with PUNLMP was diagnosed with c-CIS in our cohort. This indicates that random bladder biopsies in PUNLMP patients have no clinical utility.

### **5.2 TAG1-G2**

In patients with TaG1-G2 (according to WHO 99), 1% died of bladder cancer compared to 30% in patients with TaG3-T1. This finding made us analyze the patients in four disease categories: PUNLMP, TaG1-G2, TaG3 or T1G2-G3 and T2-T4. This simple division may be helpful for clinicians in the management of bladder cancer patients.

In the group of patients with TaG1-G2, two percent of the patients were diagnosed with c-CIS. These patients are rarely, if ever, candidates for intravesical BCG instillations or radical cystectomy. This indicates that random bladder biopsies in TaG1-G2 patients have low clinical value.

### **5.3 TAG3 AND T1G2-G3**

Our data indicates that patients with TaG3 or T1G2-G3 bladder neoplasms having undergone random bladder biopsies have a superior cancer-specific survival. In the 2008 EAU Guidelines on non-muscle invasive urothelial carcinoma, patients with high grade tumour or T1 tumour should undergo a second resection (Babjuk *et al.*, 2008). A reasonable clinical practice may therefore be to take random bladder biopsies of patients with TaG3 or T1G2-G3 in the “second look” TURBT.



In patients with TaG3 or T1G2-G3 we found that the diagnosis of c-CIS resulted in a higher percentage of patients receiving intravesical BCG. Despite the presence of c-CIS, these patients had a lower intravesical recurrence rate during follow-up. This confirms that BCG is an effective treatment for CIS. We also found that fewer patients  $\geq 80$  years old underwent BCG treatment compared to younger patients and that the older patients died more frequently of bladder cancer. To increase the number of patients who undergo BCG treatment is however not an easy task. Many of the patients are octogenarians and because of their age and comorbidity deemed unsuitable for BCG. If these patients were treated by an urologist with a special interest possibly a larger number of patients would undergo BCG treatment. A consideration may be to follow all the patients regionally in one centre that specializes in the follow-up of this subgroup of patients and has easy access to intravesical instillations.

## **5.4 T2-T4**

Our data indicates that prostatic capsule and seminal sparing cystectomy combines proper oncological outcome with satisfactory function of the lower urinary tract. Symptoms of sexual dysfunction have been shown to be the most distressing symptom group in cystectomy patients (Henningsohn, 2002). The potential bias of patient selection remains and can only be definitively precluded by larger studies using an experimental design. Until such a study is performed standard radical cystectomy is the gold standard treatment of muscle invasive bladder cancer.

If a radical cystectomy is performed, recurrence-free survival at five years of 56-68% of the patients has been demonstrated. In Paper I we could show that in a population-based cohort, 39% of the patients with muscle invasive bladder cancer never underwent a treatment with curative intention. The fact that many patients with muscle invasive disease never undergo a curative treatment is important to remember when discussing the prognosis for patients with muscle invasive bladder cancer.

There are several well known side effects after a radical cystectomy. The hampered quality of life due to impotence and urinary incontinence is profoundly documented in the literature. Less is written on the different gastrointestinal disorders that may occur after a radical cystectomy. We could show that the resection of distal ileum performed for the orthotopic neobladder in bladder cancer patients, may cause bile salt induced diarrhoea. In the group of cystectomy patients 25% (Paper IV) -35% (Paper III) developed bowel disorders probably due to the decreased reabsorption of bile. A resin, such as cholestyramine, is a reasonable treatment option in this group of patients.

## **6 IMPLICATIONS AND FUTURE PERSPECTIVES**

In this thesis the detection and management of patients with bladder cancer is discussed. What needs to be acknowledged is that many of these patients could have been spared from all the side effects of treatments and many lives could have been saved if they had not been smokers. Bladder cancer is in many cases an avoidable disease. More needs to be done to alert and educate populations world wide about the public health hazards of smoking.

Our population-based data in Paper I form a clearly defined, unselected clinical basis for preclinical research. To date, 16 papers on the molecular biology aspects of the freshly frozen tumour tissue have been published. Translational collaborations between clinical urologists and preclinical biologists are needed to make further advancements regarding the molecular mechanisms behind the well known clinical aspects of bladder cancer.

In order to settle the question if random biopsies should be performed, a clinical trial with randomisation between taking and not taking random biopsies is needed. If random biopsies are recommended in all patients in the initial TURBT many patients who do not benefit from random biopsies will undergo the procedure. If random biopsies are recommended in all patients with a newly diagnosed bladder neoplasm, it makes the decision making easier for the treating physicians and more patients will undergo sufficient work-up. Until a randomised clinical trial is conducted, a reasonable option is to perform random biopsies in the second-look of patients with TaG3 or T1G2-G3. Another interesting future perspective is the use of fluorescence cystoscopy for the diagnosis of CIS. There are indications that fluorescence guided biopsies and resections are more sensitive than conventional procedures in detecting CIS (Schmidbauer *et al.*, 2004). This may help urologists in the work-up and treatment of patients with bladder cancer and the field is under development.

For selected male patients, a prostatic capsule and seminal sparing cystectomy with orthotopic neobladder substitution is a valid treatment option. The possibility of maintaining potency after the cystectomy should at least be discussed with patients of this group. There are probably many more patients in which a prostatic capsule and seminal sparing cystectomy could be considered. The numerous patients who undergo radical prostatectomy and are interested in nerve sparing procedures show that there is a large interest among cancer survivors to maintain sexual function after their treatment.

For patients with metastatic bladder cancer the current situation is less than optimal. Treatment options are few and often reduced to palliative efforts. The need for more efficient chemotherapy is vast. The field of targeted chemotherapy and immunotherapy are interesting future perspectives.

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## **9 APPENDIX (PAPER I-IV)**