

Linköping Medical Dissertations No. 1344

# **Aspects of Recurrence and Progression in Ta/T1 Urinary Bladder Cancer**

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Linköping 2013

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Printed by LiU-tryck, Linköping 2013

ISBN: 978-91-7519-738-8

ISSN 0345-0082

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# Abstract

**Aims:** To evaluate different aspects of recurrence and, when appropriate, progression in primary Ta/T1 urinary bladder cancer.

**Patients and methods:** All evaluable patients diagnosed with primary Ta/T1 urinary bladder cancer in Linköping and Norrköping between 1992 and 2007 were included prospectively in the study cohort. Histopathology results were classified according to the TNM system and were reviewed by a reference pathologist using the WHO 1999 criteria (except in the studies reported in Papers I and IV). Risk factors for local recurrence were evaluated using data from the period 1992–2001 (Paper I). Tumour size (Paper II) and bladder wash cytology (Paper III) at primary diagnosis were assessed regarding the impact on recurrence and progression, and tumour presence in the marginal resection in primary and recurrent Ta/T1 bladder cancer was investigated considering effects on recurrence in patients treated between 2001 and 2010 (Paper IV).

Furthermore, surgical experience measured as training status (resident or specialist) and surgical volume (both during the study period and lifetime) were analysed regarding their influence on recurrence and progression (Paper V).

**Results:** Tumour size  $> 30$  mm ( $p < 0.001$ ) and multiplicity ( $p = 0.021$ ) were significantly associated with local recurrence (Paper I). Tumour sizes 16–30 mm and  $> 30$  mm were correlated with recurrence ( $p = 0.003$  and  $p < 0.001$ , respectively) but not with progression (Paper II). High-grade malignant bladder wash cytology proved to be predictive of both recurrence ( $p < 0.001$ ) and progression ( $p = 0.036$ ) as was shown in Paper III. A tumour-positive marginal resection was related to overall ( $p < 0.001$ ) and local ( $p < 0.001$ ) recurrence (Paper IV). Transurethral resection of bladder tumours performed by residents was associated with recurrence ( $p = 0.004$ ) but not with progression. No differences in relation to either recurrence or progression were found for the surgical volume approach at the chosen cut-offs (Paper V).

**Conclusions:** The present studies identified new risk factors for recurrence (tumours > 15 mm, high-grade bladder wash cytology at diagnosis, tumour-positive marginal resection, and surgery performed by residents) and progression (local recurrence and high-grade malignant bladder wash cytology at diagnosis), which in the future may be integrated into follow-up schedules or risk profiles for patients with Ta/T1 urinary bladder cancer.

## Sammanfattning på Svenska

Urinblåscancer är vanlig förekommande i Sverige med 2270 nydiagnostiserade fall år 2010. Makroskopisk hematuri, d v s synligt blod i urinen är det vanligaste symptomet vid urinblåsecancer. Ungefär 73 % av alla nydiagnostiserade tumörer är yttlig växande vilket innebär att de växer i slemhinnan och underliggande bindväv men når inte blåsväggens muskellager. Tumörer kategori Ta tumörer växer ytlig i blåsslemhinnan och dessa tumörer utgör 49 % av alla nyupptäckta blåstumörer. Tumörer kategori T1 infiltrerar bindväven under slemhinnan men inte blåsväggens muskelskikt och dessa tumörer förekommer i cirka 20 % av alla nyupptäckta fall av blåscancer. Gemensamt för båda dessa tumörkategorier är att de kan fullständigt avlägsnas med transurethral resektion (operation via urinröret in till urinblåsan). Återfall av dessa tumörer antingen på samma plats som primärtumören (lokalt recidiv) eller på andra ställen i urinblåsan är vanlig förekommande och beskrivs i upp till 80 % av fallen medan progression rapporteras i upp till 56 %. I fall av T1 tumörer och höggradiga Ta tumör behövs förutom en re-resektion av tumören en kompletterande instillation av cytostatika eller immunmodulerande agens för att förhindra återfall och progression. På en hög andel återfall måste patienter med Ta och T1 urinblåscancer genomgå en cystokopi d v s en optisk undersökning av urinblåsan för att upptäcka ett recidiv i tidigt skede, med jämna mellanrum.

Genom att undersöka riskfaktorer för recidiv och progression kan man identifiera patienter med hög risk och ge dessa en mera aggressiv behandling såsom re-resektioner och kompletterande instillationsbehandling i urinblåsan. Syftet med denna avhandling var att identifiera riskfaktorer för recidiv och progression för nydiagnostiserade patienter med Ta/T1 urinblåscancer. I studien ingår alla patienter med nydiagnostiserad urinblåscancer mellan 1992 och 2007 vid sjukhusen i Linköping och Norrköping och de registrerades fortlöpande i en

populationsbaserad kohortstudie. Tumör- och patientkaraktistika noterades och analyserades med avseende på recidiv och progression i Cox proportional hazards uni- och multivariatanalyser.

I studien ingår 768 utvärderbara patienter med en median ålder av 72 år och en median uppföljningstid av 60 månader. Totalt fick 478 (62 %) patienter minst ett recidiv varav 259 (38 %) ett lokal recidiv på samma plats i urinblåsan som primärtumören. I 71 (9 %) fall progredierade tumören till muskelinvasivt stadium.

Tumörstorlek > 3 cm och flera tumörer på olika ställen i urinblåsan var associerade med lokalt recidiv. Tumörstorlek 15 – 30 mm och > 30 mm, blåssköjväska med hög malignitetsgrad vid diagnostillfälle, tumörfynd i randzonsresektatet kring tumörenbädden och operation utförd av läkare under specialistutbildning utgjorde riskfaktorer för återfall. Blåssköjväska med hög malignitetsgrad vid diagnostillfälle och lokalt recidiv på samma plats i urinblåsan som primärtumör var associerade med progression.

Patienter med nydiagnostiserad urinblåscancer och en eller flera av dessa riskfaktorer bör i tidigt skede bli föremål för kompletterande utredning såsom tidig re-resektion, adjuvant instillationsbehandling och täta cystoskopikontroller.

## Abbreviations

BCG	bacillus Calmette-Guerin
BWC	bladder wash cytology
CI	confidence interval
CIS	cancer in situ
CT	computed tomography
HR	hazard ratio
MR	marginal resection
PUNLMP	papillary urothelial neoplasm of low malignant potential
RR	relative risk
TNM	tumour node metastasis
TUR	transurethral resection
TUR-B	transurethral resection of bladder tumour
TUR-BT	transurethral resection of bladder tumour
WHO	World Health Organization

## List of papers

This thesis is based on the following original articles, which are referred to in the text by their Roman numerals:

- I. Risk factors for local recurrence in patients with pTa/pT1 urinary bladder cancer.  
Jancke G, Damm O, Rosell J, Jahnsen S.  
*Scand J Urol Nephrol.* 2008; 42(5):417–21.
- II. Impact of tumour size on recurrence and progression in Ta/T1 carcinoma of the urinary bladder.  
Jancke G, Rosell J, Jahnsen S.  
*Scand J Urol Nephrol.* 2011 Dec; 45(6):388–92.
- III. Bladder wash cytology at diagnosis of Ta-T1 bladder cancer is predictive for recurrence and progression.  
Jancke G, Rosell J, Chebil G, Jahnsen S.  
*Urology.* 2012 Sep; 80(3):625–31.
- IV. Residual tumour in the marginal resection after a complete transurethral resection is associated with local recurrence in Ta/T1 urinary bladder cancer.  
Jancke G, Rosell J, Jahnsen S.  
*Scand J Urol Nephrol.* 2012 Oct; 46(5):343–7.
- V. Impact of surgical experience on recurrence and progression after TUR-BT in non-muscle-invasive bladder cancer  
Jancke G, Rosell J, Jahnsen S.  
*Submitted*

## **Introduction**

Stage Ta/T1 urinary bladder cancer comprised approximately 69% of all cases of bladder cancer diagnosed in Sweden in 2010 (National Quality Register for urinary bladder cancer, 2010). The surveillance of Ta/T1 bladder cancer is a challenge to the urologist, because this disease has a high recurrence rate of up to 75% (Kurth et al., 2000). Tumour recurrence can be caused by persistence or re-growth of residual tumour cells after resection, new recurrence due to aggressive biology of the neoplasm, or re-implantation of circulating tumour cells during transurethral resection of a bladder tumour (Pode et al., 1986). Identifying tumours with risk patterns at primary diagnosis can help prevent recurrence and progression through the use of complementary intravesical instillation therapy, edge resection during TUR-B, re-resection, and follow-up cystoscopies at short intervals.

In the studies underlying this thesis, we investigated aspects of recurrence and progression of primary Ta/T1 urinary bladder cancer in a population-based cohort to facilitate the identification of risk tumours.

# **Carcinoma of the urinary bladder**

## **Epidemiology**

In Sweden, approximately 2,000 new cases of urinary bladder cancer are diagnosed each year, and about 75% of those patients are male (National Quality Register for Urinary Bladder Cancer, 2010). Considering all types of malignancy in this country in 2010, urinary bladder cancer had the fifth highest incidence in males and the 11th highest incidence in females (Socialstyrelsen, 2010). The age-standardized incidence rate is 10.1 per 100,000 for males and 2.5 per 100,000 for females worldwide, and it is about three to four times higher in developed countries (Ploeg et al., 2009). In Europe, the age-standardized incidence rate is highest in southern regions, where it is 27.1 in males and 4.1 in females, and the corresponding rates are 16.9 and 4.9 in northern Europe and 14.7 and 2.2 in Eastern European countries (Ferlay et al., 2004). The global mortality rate is 4 per 100,000 among males and 1.1 per 100,000 among females, and the corresponding figures in Europe are 6 and 1.3 per 100,000 (Ferlay et al., 2008). The mortality rate is declining in Europe, whereas there is evidence that the prevalence of urinary bladder cancer will increase in developing countries (Ploeg et al, 2009).

## **Aetiology**

There are several known aetiologies of urinary bladder cancer. The first association between occupational exposures and such malignancy was found by Rehn in 1895, and it is known that aromatic amines used in printing, iron and aluminium processing, industrial painting, and gas and tar production have the potential to induce the disease (Zeegers et al., 2001; Samanic et al., 2008). Notably, a trend towards a decrease in bladder cancer was seen in Western

countries after introduction of strict regulations on these agents (Kogevinas et al., 2003).

Cigarette smoking is a well-known aetiological factor that triples the risk of developing bladder cancer (Zeegers et al., 2000). The incidence of this malignancy is related to the duration of smoking and the number of cigarettes smoked per day up to 15 to 19 cigarettes, after which there is a plateau in the risk (IARC, 2004). The likelihood of developing the disease is further increased in individuals who start smoking at a young age and those who are exposed to tobacco smoke during childhood (Bjerregaard et al., 2006). Gandini et al. (2008) calculated the overall relative risk of developing bladder cancer to be 2.77 for smokers and 1.72 for former smokers compared to those who never smoked. Also, Brennan et al. (2000) observed that smoking cessation reduced the risk by 40% within 1–4 years and by 60% after 25 years.

Infection with the trematode parasite *Schistosoma haematobium* can cause squamous cell carcinomas and also urothelial carcinoma, and it represents the second most common parasitic infection after malaria, affecting about 600 million people in endemic countries in Africa, Asia, and South America (IARC, 1994). The combination of *S. haematobium* infection and high levels of smoking in Egypt contributes to the high incidence of bladder cancer in this country (Bedwani et al., 1998).

Radiation therapy, especially for prostate cancer but also for cervical cancer, can induce malignancy in the urinary bladder (Kleinerman et al., 1995). Nieder and colleagues (2005) found that the relative risk of developing bladder cancer was 1.88 after external beam radiotherapy, 1.52 after brachytherapy, and 1.85 after a combination of those two methods, as compared to radical prostatectomy.

Considering the effects of pharmacological agents, the analgesic phenacetin and its metabolite acetaminophen have been reported to be associated with the risk of bladder cancer (Castelao et al., 2000). Furthermore, the chemotherapeutic agent cyclophosphamide, which is used to treat lymphoproliferative disease and other non-neoplastic conditions, has been linked to the development of bladder cancer (Travis et al., 1995). In short, the cited investigators found a significant 4.5-fold increase in the risk of this form of cancer (95% CI = 1.5–13.6) following therapy with cyclophosphamide, and the risk was dependent on the cumulative dose.

There is some controversy regarding dietary factors and the risk of urinary bladder cancer, and no causal relationship has yet been confirmed in that context. Nonetheless, a meta-analysis performed by Steinmaus et al. (2000) did provide evidence that including vegetables and fruits in the diet can reduce the risk: low intake levels of both fruits (RR = 1.40) and vegetables (RR = 1.16) were found to be associated with an increased risk of bladder cancer.

Chronic urinary tract infection can also contribute to the development of bladder cancer, especially squamous cell carcinoma. Locke et al. (1985) noted that long-term indwelling catheters are linked to an elevated risk of bladder malignancy. However, with the exception of above-mentioned parasite *S. haematobium*, no association between the occurrence of bladder cancer and chronic bacterial or viral infections has yet been confirmed (Abol-Enein, 2008).

## **Pathology**

### Pathogenesis

The most important biological features of superficial urinary bladder cancer are multiplicity and the tendency to recurrence. According to Duggan et al. (2004),

there are currently two main theories to explain these characteristics: the clonal theory, which indicates that multifocal and recurrent tumours evolve from a single transformed cell and share a number of identical genetic mutations; and the field change or field effect theory, which suggests that exposure to exogenous or endogenous carcinogens causes a global change in the urothelium to yield multiple transformed cells that independently evolve into mature tumours. The field theory is supported by experimental results showing that loss of heterozygosity and X chromosome inactivation function independently to transform urothelial cells (Jones et al., 2005), and the clonal theory is substantiated by a study revealing the methylation patterns of the androgen receptor gene located on the X chromosome (Li et al., 1999). Several pathogenetic pathways to bladder cancer have been described as well, such as mutation of the FGF receptor 3 and deletions or mutations in TP53 (Cheng et al., 2010), and aberrant activation of phosphatidylinositol 3-kinase (Knowles et al., 2009).

### Histopathology

Histologically, the predominant type of urinary bladder cancer in Sweden is transitional cell carcinoma, which constitutes 96% of all the cases (National Quality Register for Urinary Bladder Cancer, 2006). Other types include squamous cell carcinoma (induced primarily by chronic infection with *S. haematobium*) and urachal adenocarcinoma, and occasionally small cell carcinoma, melanoma, and lymphoma of the urinary bladder.

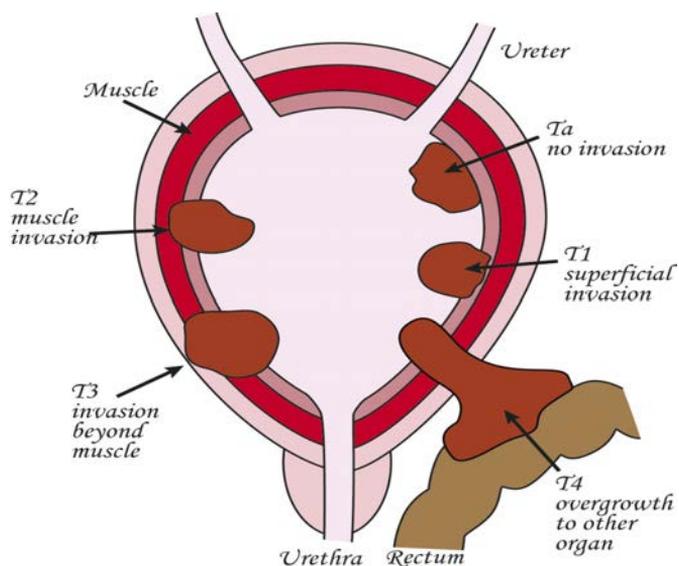
### TNM classification

The tumour, node, metastasis (TNM) classification of malignant tumours is widely used to describe the extent of cancer spread. Table 1 shows the latest revision of this staging system, which was published in 2009 and is based mainly on the 2002 version (Sobin et al., 2009). Figure 1 illustrates the different

stages of urinary bladder cancer. In Sweden in 2010, the majority of newly diagnosed cases of urinary bladder cancer in 2010 were non-muscle-invasive comprehensive Ta, T1, and carcinoma in situ (CIS), which represented 49%, 21%, and 3%, respectively, of all primary diagnoses of the disease during that year (National Quality Register for Urinary Bladder Cancer, 2010).

**Table 1.** The 2009 TNM classification of urinary bladder cancer

<b>T</b>	Primary tumour
<b>TX</b>	<b>Primary tumour cannot be assessed</b>
<b>T0</b>	<b>No evidence of primary tumour</b>
<b>Ta</b>	<b>Non-invasive papillary carcinoma</b>
<b>Tis</b>	<b>Carcinoma <i>in situ</i>: ‘flat tumour’</b>
<b>T1</b>	<b>Tumour invades subepithelial connective tissue</b>
<b>T2</b>	<b>Tumour invades muscle</b>
<b>T2a</b>	<b>Tumour invades superficial muscle (inner half)</b>
<b>T2b</b>	<b>Tumour invades deep muscle (outer half)</b>
<b>T3</b>	<b>Tumour invades perivesical tissue</b>
<b>T3a</b>	<b>Microscopically</b>
<b>T3b</b>	<b>Macroscopically (extravesical mass)</b>
<b>T4</b>	<b>Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall</b>
<b>T4a</b>	<b>Tumour invades prostate, uterus, or vagina</b>
<b>T4b</b>	<b>Tumour invades pelvic wall or abdominal wall</b>
<b>N</b>	Lymph nodes
<b>NX</b>	<b>Regional lymph nodes cannot be assessed</b>
<b>N0</b>	<b>No regional lymph node metastasis</b>
<b>N1</b>	<b>Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)</b>
<b>N2</b>	<b>Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)</b>
<b>N3</b>	<b>Metastasis in common iliac lymph node(s)</b>
<b>M</b>	Distant metastasis
<b>M0</b>	<b>No distant metastasis</b>
<b>M1</b>	<b>Distant metastasis</b>



**Figure 1.** T categories in urinary bladder cancer according to the TNM classification system (with kind permission from Hans Olsson<sup>©</sup>).

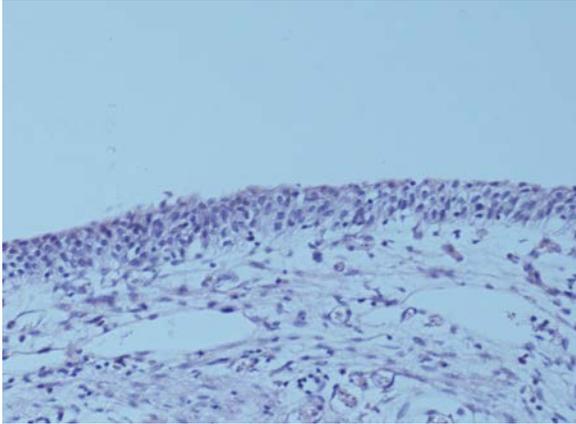
### Tumour grading

Histopathologically, urothelial tumours are classified into different grades according to cytological and architectural criteria. In 1965, Bergkvist et al. described a classification comprising grades 1 to 5 based on patterns, and later Malmström et al. (1987) presented a modification of this classification based on architectural pattern and object-related features and divided group 2 into 2 subgroups. A widely used classification was the WHO 1973 outlined in Table 2, which was introduced by Mostofi et al. (1973); drawbacks of this system were the difficulty in distinguishing between grade 1 carcinoma and papilloma, and poor definitions of the differences between grades 1 and 2, and between grades 2 and 3 (Busch et al., 2002). In 1998, the WHO/ISUP classification based on pattern and object-related features was introduced to simplify the WHO 1973 system by omitting an intermediate grade and thereby avoiding the default diagnosis by pathologists. The 1998 WHO/ISUP classification was published by the WHO in 2004 (shown in table 2) and is identical to it.

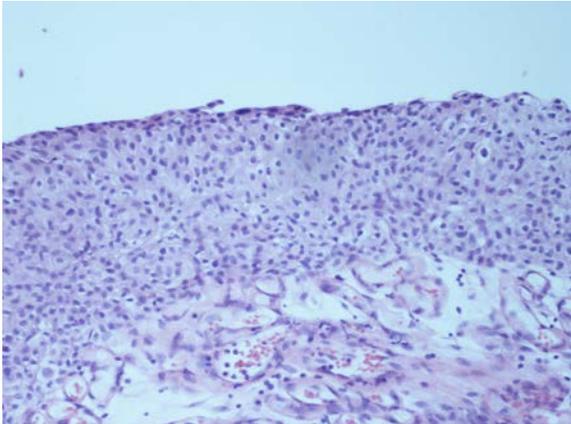
Normal appearance of the bladder urothelium and low-grade and high-grade transitional cancer of the urinary bladder are shown in Figures 2, 3, and 4, respectively. The WHO 1973 and the WHO 2004 classification cannot be translated into each other. Some tumours that are grade 1 in the WHO 1973 system are identified as PUNLMP or low-grade tumours in the WHO 2004 classification. In addition, the majority of tumours that are grade 2 in the WHO 1973 fall into the high-grade category in the WHO 2004, although some are classified as low-grade lesions (Busch et al., 2002). Another WHO classification was introduced in 1999 (Table 3), which is widely used in Sweden; this system is compatible with the WHO 2004 classification and differs primarily with regard to the division of high-grade tumours into grades 2 and 3. Use of the WHO 2004 classification is recommended. However, according to Lopez-Beltran et al. (2004), tumours should be graded using both the WHO 1973 and the WHO 2004 classification, until the latter has been validated in further clinical trials. In Sweden in 2010, classification of all primary diagnoses of transitional cancer of the urinary bladder made according to the WHO 1999 system identified 28% as grade 1, 29% as grade 2, and 40% as grade 3 tumours, 2% as papillary urothelial neoplasm of low malignant potential, and 1% could not be graded (National Quality Register for Urinary Bladder Cancer, 2010).

**Table 2.** The WHO 1973 and WHO 2004 grading systems

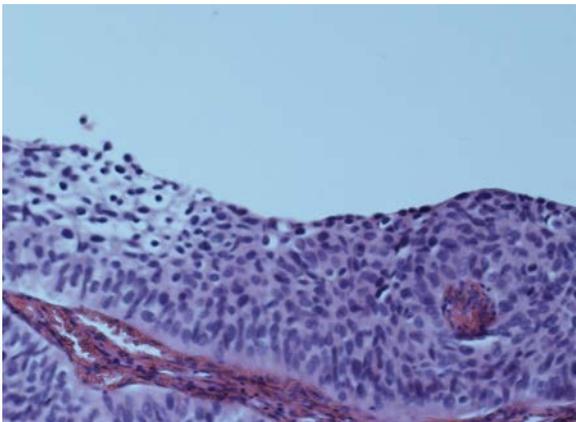
<b>1973 WHO grading</b>
Urothelial papilloma
Grade 1: well differentiated
Grade 2: moderately differentiated
Grade 3: poorly differentiated
<b>2004 WHO grading</b>
Urothelial papilloma
Papillary urothelial neoplasm of low malignant potential (PUNLMP)
Low-grade papillary urothelial carcinoma
High-grade papillary urothelial carcinoma



**Figure 2.** Urinary bladder urothelium with normal appearance.



**Figure 3.** Low-grade urinary bladder cancer.



**Figure 4.** High-grade urinary bladder cancer.

**Table 3.** Compatibility of the WHO 1999 and the WHO 2004 grading

<b>WHO 2004</b>	<b>WHO 1999</b>
Papilloma	Papilloma
Papillary neoplasm of low malignant potential (PUNLMP)	Papillary neoplasm of low malignant potential (PUNLMP)
Low-grade carcinoma	Low-grade carcinoma, grade I
High-grade carcinoma	High-grade carcinoma, grade II
High-grade carcinoma	High-grade carcinoma, grade III

*Variability in staging and grading*

Despite improvements in the tumour and grading classifications, there is wide inter-observer variability among pathologists in the classification of category Ta and T1 tumours (Murphy et al., 2002). This was also seen in an investigation of tumour grading according to the WHO 1999 classification, which showed an inter-observer agreement of 59% (Bol et al., 2003). Substantial inter-observer variability has been reported for both the WHO 1973 and the WHO 2004 grading, although the discrepancies were less pronounced in relation to the latter (May et al., 2010). The validity of the classification results can be increased by pathology review (van der Meiden et al., 2000; Lee et al., 2010).

*Ta tumour category*

Ta and T1 tumours and CIS are regarded as non-muscle-invasive bladder cancer. Stage Ta comprises tumours that are confined to the mucosa and exhibit a papillary growth pattern. Ta was the most common category of bladder cancer in Sweden in 2010, representing 49% of all primary diagnoses of the disease (National Quality Register for Urinary Bladder Cancer, 2010). In an earlier study conducted by Holmäng et al. (2001), Ta tumours were graded as PUNLMP in 26% of cases, as low-grade in 44%, and as high-grade in 30%. Holmäng and co-workers also found recurrence in 35% of patients with PUNLMP, in 71% with low-grade urothelial carcinoma, and in 73% with high-grade carcinoma, and the corresponding results for progression were 0%, 4%,

and 23%, respectively (Holmäng et al., 2001). Furthermore, Zieger et al. (2000) described recurrence in 61% of cases of primary Ta bladder cancer and progression to T1 tumour category in 19% and to muscle invasive or metastatic disease in 11%. Ta tumours identified as grade 3 (WHO 1999) or as being associated with a high-grade growth pattern must be regarded as potentially dangerous lesions that require aggressive treatment and complementary therapy.

### T1 tumour category

Stage T1 tumours infiltrate the lamina propria but not the muscle layer of the urinary bladder, and 21% of all cases of such cancer diagnosed in Sweden in 2010 were assigned to this category (National Quality Register for Urinary Bladder Cancer, 2010). Abel (1993) observed recurrence of 80% and progression of 50% within 3 years of diagnosis of T1 tumours, and Kiemeny et al. (1993) described a recurrence rate of 77% in patients with multiple, large, high-grade pT1 tumours. By comparison, Orsola et al. (2005) found lower recurrence and progression rates of 33% and 22%, respectively, in patients with T1 tumours mainly treated with BCG. In 1990, Younes proposed the following sub-staging of T1 tumours: pT1a, tumour invasion of connective tissue superficial to the level of the muscularis mucosae; pT1b, tumour invasion to the level of the muscularis mucosae; pT1c, invasion through the level of the muscularis mucosae but superficial to the muscularis propria. The author could show a 75% 5-year survival rate for level T1a and T1b compared to 11% 5-year survival for level T1c. Angulo et al. presented a two-grade sub-classification in 1995: tumour invasion confined to the lamina propria (pT1a) and tumour infiltrating into the submucosa (pT1b). He found a significantly different survival between the two sub-categories.

Andius et al. (2007) demonstrated that the vascular invasion and growth pattern (solid or papillary) of T1 tumours have independent prognostic value with

respect to both progression and disease-specific survival. Cho and colleagues (2009) found that lymphovascular invasion of the T1 tumour was significantly associated with progression and development of metastases.

Re-resection, aggressive intravesical therapy, and close follow-up are the treatments of choice in patients with T1 tumours due to the high rates of recurrence and progression associated with this tumour category. Tumours that are resistant to such treatment must be dealt with by cystectomy or radiation therapy, which could also be used as primary treatment in patients with high-risk tumours (Herr, 1999).

### *Carcinoma in situ*

CIS is a flat, high-grade, non-invasive urothelial tumour that is often multifocal and can occur anywhere in the urinary tract. It either cannot be detected visibly or presents as erythema in areas of the urinary bladder. Bladder wash cytology and random bladder biopsies or biopsies of suspicious mucosal lesions in the bladder are necessary for the diagnosis. Also, fluorescence cystoscopy can improve detection of CIS by 28% compared to standard cystoscopy (Schmidbauer et al., 2004). CIS is classified into three different types as described by Lamm et al. (1998):

1. Primary CIS with no previous or concurrent tumour; this type comprises up to 3% of all cases of bladder cancer diagnosed in Sweden (National Quality Register for Urinary Bladder Cancer, 2010).
2. Secondary CIS detected during the follow-up of patients with a previous tumour.
3. Concurrent CIS implicating the co-existence of CIS and an exophytic tumour.

The treatment of choice for CIS is intravesical BCG (Sylvester et al., 2005), which has been reported to achieve a complete response rate of 75% (Jakse et al., 2001). However, recurrent tumour with muscle invasion or metastatic disease was seen in about 50% of cases (Lamm et al., 2000; Jakse et al., 2001).

*Muscle-invasive bladder cancer (> T1 tumour category)*

T2 to T4 tumours cannot be treated by transurethral resection alone. In most Western countries, radical cystectomy is the standard treatment for non-metastatic muscle-invasive bladder cancer (Hautmann et al., 2007). In male patients, radical cystectomy comprises resection of the bladder, prostate, seminal vesicles, pelvic lymph nodes and occasionally also the urethra; in females, the resection encompasses the urinary bladder, uterus, adnexa, ventral vaginal wall, and in some cases the urethra. Urinary diversions after cystectomies were performed as follows according to a report of Hautmann et al. (2007) including more than 7,000 patients: neobladders in 47%, ileal conduit in 33%, anal diversion in 10%, continent cutaneous diversion in 8%, incontinent cutaneous diversion in 2%, and other forms of diversion in 0.1%. Corresponding diversions in Sweden in 2010 were neobladders in 15% of cases, ileal conduit in 84%, and continent diversions in 1% (National Quality Register for Urinary Bladder Cancer, 2010).

The standard lymph node dissection in bladder cancer includes the internal iliac, presacral, obturator fossa, and external iliac nodes up to the common iliac bifurcation, with the ureter as the medial border. An extended lymphadenectomy includes the mentioned nodes, as well as the nodes in the aortic bifurcation and common iliac vessels medial to the crossing of the ureter (Mills et al., 2007). The optimal extent of lymph node dissection to decrease recurrence and increase survival is not yet clear. In a study conducted at two centres, Zehnder et al. (2011) found no difference in the overall recurrence rate when comparing

lymphadenectomy up to common iliac vessels with that reaching to the inferior mesenteric artery (superextended lymphadenectomy). However, Dorin and Skinner (2010) observed that both recurrence-free and overall survival were increased in patients with extended lymphadenectomy compared to those who underwent standard lymph node dissection. Shariat et al. (2006) conducted a multicentre study and noted that the mean recurrence-free and cancer-specific survival in patients after cystectomy and lymphadenectomy were 58% and 66%, respectively. The 10-year-disease specific and overall survival were 28% and 21%, respectively in patients after cystectomy and positive lymph nodes in another series (Gschwend et al, 2002). Madersbacher et al. (2003) found that 5-year recurrence-free survival rates of 76%, 74%, 52%, and 36% in patients with T1, T2, T3, and T4 tumours, respectively. In an investigation published by Bassi et al. (1999), tumour stage and lymph node involvement were the only independent predictors of survival in patients who underwent cystectomy.

Cystectomy is not the treatment of choice in metastatic disease, and the standard treatment for these patients is instead chemotherapy. In general, approximately 10–15% of patients with bladder cancer are already metastatic at diagnosis (Rosenberg et al., 2005), and the corresponding data for muscle-invasive bladder cancer in Sweden in 2010 showed lymph-node-positive disease in 12% of cases and metastatic disease in regions other than lymph nodes in 9% (National Quality Register for Bladder Cancer, 2010).

## **Diagnosis**

### Symptoms

Macroscopic haematuria is the most common initial symptom of urinary bladder cancer (Varkarakis et al., 1974). Patients can also experience urgency, dysuria, increased frequency, pelvic pain, and pain over the kidneys as the result of ureteric obstruction due to tumour growth over the ureteric orifice.

### Cystoscopy and urinary markers

Cystoscopy is the gold standard for diagnosis of bladder cancer. All findings obtained with this method should be described in detail, considering the tumour or tumours with regard to site in the bladder, size, number, growth pattern (papillary or solid), and macroscopic evaluation (superficial or suspected muscle invasion), as well as mucosal abnormalities. The use of a bladder diagram is recommended.

To date, it seems that bladder wash cytology (BWC) is the reference standard of adjunctive tests, as reported by van Rhijn et al. (2009). Some investigators have found that, in cases involving low-grade tumours, BWC offers poor sensitivity varying from 33% to 64% (van Rhijn et al., 2005; Placer et al., 2002; Kibar et al., 2006; Leyh et al., 1999; van der Poel et al., 1998), and this is especially apparent in connection with small tumours (sensitivity 35%; Boman et al., 2002). However, in other studies, the sensitivity of BWC could be improved to 84% by combining that method with detection of p53 mutation (Prescott et al., 2001), to 96% by analysing telomerase activity (Lee et al., 1998), and to 78% by including evaluation of DD23 antigen expression (Gilbert et al., 2003). May and colleagues (2007) found that voided cytology provided inferior sensitivity of 41% compared to 59% for BWC, and corresponding sensitivities reported by Gregoire et al. (1997) were 60% and 66%, respectively. Bladder wash cytology is the gold standard regarding specificity at 94% compared to commercial tests with a specificity of 73% to 86% (van Rhijn et al., 2009). A multicentre analysis revealed differences between local and review pathologists regarding the interpretation of cytology results (Raitanen et al., 2002), and the cytological evaluation of bladder wash specimens can be hampered by factors such as low cellular yield, urinary tract infections, stones, or intravesical instillations (Lokeshwar et al., 2005).

Several urine tests based on detection of soluble or cell-associated molecular markers are commercially available for the diagnosis of bladder cancer, including UroVysion, microsatellite analysis, gene microarray, Immunocyt/uCyt+, nuclear matrix protein 22, BTA stat, BTA TRAK, cytokeratins, and survivin (Yutkin et al., 2010). However, as of yet, these tests cannot replace cystoscopy. They have higher sensitivity but lower specificity compared to BWC, although the sensitivity can be improved by using them in various combinations (Lokeshwar et al., 2005). The overall sensitivity of the tests ranges from 12% for cytokeratins to 90% for survivin and gene microarray, and the specificity varies from 28% for BTA TRAK to 100% for survivin (Yutkin et al., 2010).

### Radiological evaluation

Today, computed tomography (CT) has largely replaced conventional intravenous pyelography for evaluation of urinary bladder cancer aimed at detecting concomitant tumours in the upper urinary tract. Compared to urography, CT provides more information, especially regarding the lymph node status and adjacent organs (Nolte-Ernsting et al., 2006), but unfortunately it also exposes the patient to a higher dose of radiation. CT cannot determine the depth of invasion in muscle-invasive bladder cancer (Paik et al, 2000). In a study conducted by Swinnen et al. (2010), it was found that use of 2-deoxy-2 [F] fluoro-D-glucose position emission tomography in combination with CT (PET/CT) did not provide any advantage over conventional CT for lymph node staging in invasive bladder cancer or recurrent high-risk superficial disease. Ultrasonography is also useful for detection of renal masses and obstruction, but it cannot replace CT for diagnosis of upper urinary tract tumours.

## **Treatment**

### *Transurethral resection of bladder tumours*

TUR-B is usually performed under general or spinal anaesthesia using a monopolar electrocautery system (diam. 7 mm) with isotonic irrigation fluid. The specimen removed should be sent for pathological investigation. Small tumours (diam. < 1 cm) should be removed en bloc to help prevent the bladder mucosa and the resection region from being contaminated with circulating tumour cells, and to improve the quality of the resected specimen by reducing cautery artifacts (Thomas et al., 2008; Wilby et al., 2009). Larger lesions should be removed in fragments including the exophytic tumour, the bladder wall with detrusor muscle, and the marginal resection, which should be sent in separate containers for pathological evaluation (Babjuk, 2009). Ukai et al. (2000) and Saito (2001) proposed a transurethral technique for en bloc resections of larger tumours, and Ukai's group used a modified electrode in that context. The presence of detrusor muscle in the resection specimen is essential for correct staging and effective treatment, and thus a deep resection in the bladder muscle is recommended (Mariappan et al., 2010). Bipolar transurethral resection in bladder cancer is safe with respect to complications (Puppo, 2009), and in particular that procedure leads to less bladder perforation caused by unwanted triggering of the obturator reflex. Bladder perforation is common according to Balbay et al (2005), considering that the authors noted that radiography revealed extravasation in 58% of patients after TUR-B. However, other investigators have reported perforation rates varying from 1.3% to 4% based on clinical evaluation but not on postoperative radiological examination (Collado et al., 2000; Nieder et al., 2005; Pycha et al., 2003). Bladder perforation should be avoided under all circumstances in order to prevent perivesical fat necrosis in patients given postoperative chemotherapy instillations (Fazlioglu et al., 2009).

Bladder and prostatic urethral biopsies are not routinely recommended in patients with Ta/T1 tumours, because there is low likelihood of detecting CIS, especially in cases of low-risk tumours (van der Meijden et al., 1999). However, cold biopsies from the prostatic urethra are recommended upon suspicion of a muscle-invasive or therapy-resistant T1 tumour to facilitate planning of urinary diversion in the subsequent cystectomy (Mungan et al., 2005).

Several studies have shown that detection of bladder tumours during TUR-B can be improved by using fluorescence cystoscopy instead of white light cystoscopy (Jocham et al., 2008), which is reflected by reduction of the recurrence rate at follow-up (Daniltschenko et al., 2005; Denzinger et al., 2007). Kriegmair et al. (2002) found significantly less residual tumor during re-TUR-B 10-14 days after initial resection by using 5-aminolevulinic acid induced fluorescence endoscopy as compared to white light endoscopy. However, a recent Swedish multicentre randomized trial did not show any differences between fluorescence light guided and white light guided TUR-B in non-muscle invasive bladder cancer regarding the recurrence-free and progression-free survival rates (Schumacher et al, 2010). In addition, false-positive results can be caused by inflammation, recent TUR, and BCG instillations performed within the past 3 months (Draga et al, 2010). In the future, narrow band imaging and optical coherence tomography may prove to be suitable alternatives or adjuncts to fluorescence cystoscopy (Cauberg et al., 2009).

Bimanual palpation is recommended before and after the resection to detect or exclude stage T3 muscle-invasive tumours (Wijkström et al., 1998).

#### *Intravesical chemo- and immunotherapy*

A meta-analysis performed by Sylvester et al. (2004) showed that a single instillation of chemotherapy (epirubicin, mitomycin C, thiotepa, or doxorubicin) administered immediately after surgery decreases the risk of recurrence by 39%,

particularly in primary resections and resections of Ta tumours. However, in cases involving bladder perforation during TUR-B, immediate postoperative chemotherapy instillation can have fatal consequences (Oddens et al., 2004). Moreover, a single instillation of epirubicin after TUR can prevent only small recurrences according to Berrum-Svennung et al. (2008). In a multicentre study, Gudjonsson et al. (2009) found that a postoperative instillation of epirubicin reduced the risk of recurrence after solitary primary tumours but had no beneficial effect on recurrent or multiple tumours. However, a sub-analysis carried out by Kaasinen et al. (2002) showed a decreased risk of recurrent tumours after immediate postoperative chemotherapy, but further data are needed to evaluate the therapeutic value of postoperative chemotherapy in recurrent tumours. No particular chemotherapeutic agent has been shown to have a superior effect in reducing recurrence (Sylvester et al., 2004). The chemotherapy should be administered within 24 hours of surgery, otherwise the relative risk of recurrence is increasing two-fold (Kaasinen et al., 2002). The effect duration of risk reduction of a postoperative chemo-instillation has been calculated to 500 days in a meta-analysis (Hinotsu et al., 1999). Maintenance chemotherapy reduces the risk of recurrence both for primary and recurrent tumours in a meta-analysis by Huncharek et al., 2001. However, chemotherapy did not prevent progression (Pawinski et al., 1996). An optimal schedule for maintenance chemotherapy has not yet been determined, and thus different regimens are used.

In 1929, Pearl noted that patients with tuberculosis infection were at lower risk of malignant tumours, and nearly fifty years later Morales et al. (1976) described the recurrence-reducing effect of intravesical BCG instillations. The maintenance schedule proposed by Lamm et al. (2000) is widely used with an induction of BCG applications once per week for 6 weeks followed by a booster consisting BCG instillations once per week for 3 weeks given at 3, 6, 12, 18, 24,

30, and 36 months. The optimal number of inductions for BCG instillations and the optimal amount of boosters and duration of maintenance BCG therapy have not yet been established. BCG is the most effective intravesical treatment regarding recurrence in a meta-analysis of randomized trials (Han et al., 2006). Superiority of BCG compared to epirubicin and interferone (Duchek et al., 2010), to mitomycin C (Järvinen et al., 2009) and epirubicin (Sylvester et al., 2010) was shown in randomized trials. Furthermore, BCG immunotherapy results in a sustained and significant long-term reduction of recurrence (Järvinen et al., 2009). Considering side effects, BCG treatment frequently leads to cystitis and allergic reactions, but serious side effects are seen in less than 5% of cases, although death due to BCG sepsis has been described (van der Meijden, 2003).

#### *Follow-up of bladder cancer patients*

The initial cystoscopy should always be scheduled 3 months after primary TUR in all patients with Ta/T1 bladder cancer, because the results of that examination serve as an important indicator of recurrence and progression (Solsona et al., 2000; Holmäng et al., 2002). Patients with TaG1 disease who are free of recurrence for 5 years can be safely discharged (Mariappan et al., 2005). For patients with low-grade stage Ta tumours who are found to be tumour free at the first follow-up cystoscopy, it can suffice to perform routine follow-up with cystoscopy at 12 and 24 months after surgery (Berrum Svennung, 2007). Patients with high-grade and/or T1 tumours should undergo re-resection and then cystoscopy every third month for 2 years, thereafter follow-up examinations every 6 months for another 1–2 years, and subsequently annual follow-up throughout life (Berrum Svennung, 2007).

#### **Recurrence and progression of Ta/T1 bladder cancer**

Different pathways of recurrence have been suggested in Ta/T1 bladder cancer. Tumour recurrence can arise through persistence or regrowth of residual tumour

in the bladder after incomplete TUR, as a new lesion caused by the highly aggressive biology of the neoplasm or by re-implantation of circulating tumour cells during TUR-B (Pode et al., 1986).

Table 4 summarizes rates of recurrence and progression of Ta/T1 bladder cancer reported in the literature. The recurrence of such disease was 60% at 5 years after treatment in a population-based cohort, with rates varying from 37% for Ta grade 1 tumours to 77% for multiple large T1 tumours (Kiemeny et al., 1993). Other investigations indicated a 3-month recurrence rate of up to 36% for single tumours and up to 75% for multiple tumours (Kurth et al., 2000), and 61% recurrence of primary Ta tumours at a mean follow-up of 84 months (Zieger et al., 2000). Also, Olsson et al. (2012) noted a recurrence rate of 80% for T1 tumours in a population-based study.

Re-resection of the tumour within 4 to 6 weeks is recommended in cases involving high-grade Ta and T1 tumours. Recurrence or residual tumour tissue in the bladder has been observed at early re-resections in 44% of patients with T1 tumours in a Nordic study (Jahnsen et al., 2005) and in 52% of patients with stage T1 tumours in another series subjected to re-resection 4 to 6 weeks after primary resection (Schwaibold et al., 2006). Miladi et al. (2003) described recurrence rates as high as 83% in a series of patients who underwent re-resection, and Herr (1999) found 76% recurrent disease after re-resections. However, Grimm et al. (2003) found lower recurrence rates in re-resections with a total of 33%, varying from 27% for Ta tumour category to 53% for T1 stage in a prospective cohort study with a follow-up of 5 years. The authors concluded a recurrence- and progression-reducing effect of re-resections that becomes apparent during further follow-up, especially in cases of high risk tumours. Brausi et al. (2002) have reported that the recurrence rate at the first follow-up

cystoscopy varies considerably, and they suggested that this might be due to the quality of the TUR-B performed by the individual surgeons.

Both Kiemeny et al. (1993) and Kurth et al. (1995) found a rate of 13% for progression to muscle-invasive disease in patients with Ta/T1 urinary bladder cancer. Other authors (Zieger et al., 2000) investigating patients with primary Ta tumours found progression to T1 tumours in 19% and to muscle-invasive disease in 11%. Furthermore, Kwak et al. (2004) observed a progression rate of 44% in patients with primary T1 tumour disease, and Olsson et al. (2012) found a corresponding progression rate of 39% in patients with such tumour category in a population-based cohort.

Järvinen et al (2009) found recurrences rates of 80% for patients receiving mitomycin C compared to 59% for those receiving BCG for Ta/T1 bladder cancer in a randomized trial with a median follow-up of 8.5 years.

Corresponding progression rates were 22% in the mitomycin C group and 9% in the BCG group. Böhle et al. (2004) performed a meta-analysis comparing mitomycin C and BCG maintenance therapy for Ta/T1 superficial bladder cancer with a median follow-up time of 26 months and reported that the two treatment strategies led to progression rates of 9.4% and 7.7%, respectively. In another meta-analysis using a similar approach, Malmström et al. (2009) described progression rates of 7.0% for mitomycin C and 5.4% for BCG in patients with a median follow-up of 4.4 years. However, the impact of BCG treatment on progression of papillary tumours is not yet clear (Gontero et al., 2010).

**Table 4.** Rates of recurrence and progression in Ta/T1 bladder cancer

	<b>Recurrence (%)</b>	<b>Progression (%)</b>
<b>Ta/T1</b>		
Kiemeny et al. (1993)	60	13
<i>Single tumour</i> , Kurth et al. (2000)	36	-
<i>Multiple tumours</i> , Kurth et al. (2000)	75	-
Kurth et al. (1995)	-	13
<b>Ta tumours</b>		
Zieger et al. (2000)	61	19 T1, 11 ≥ T2
<i>PUMLMP</i> , Holmäng et al. (2001)	35	0
<i>Low grade</i> , Holmäng et al. (2001)	71	4
<i>High grade</i> , Holmäng et al. (2001)	73	23
<b>T1 tumour</b>		
Kwak et al. (2004)	71	44
Orsola et al. (2005)	33	22
Olsson et al. (2012)	80	39
<b>Recurrence in re-resections</b>		
Herr (1999)	76	-
Grimm et al. (2003)	33	-
Miladi et al. (2003)	83	-
<i>T1 tumour</i> Jahnson et al. (2005)	44	-
<i>T1 tumour</i> Schwaibold et al. (2006)	52	-
<b>Chemotherapy / BCG</b>		
<i>Böhle et al. (2004)</i>		
Mitomycin C	-	9.4
BCG	-	7.7
<i>Järvinen et al. (2009)</i>		
Mitomycin C	80	22
BCG	59	9
<i>Malmström et al. (2010)</i>		
Mitomycin C	43	7.0
BCG	43	5.4

Sylvester et al (2006) evaluated risk tables for predicting recurrence and progression in Ta/T1 bladder cancer from seven EORTC trials including 2596 patients. The following risk factors were shown to contribute to recurrence and / or progression in this investigation at 1 and 5 years: number of tumours (1, 2–7, or ≥ 8), tumour diameter (cut-off 3 cm), primary or recurrent tumour (≤ 1 or > 1

recurrence/year), tumour category (Ta or T1), concurrent CIS (yes or no), and tumour classification according to WHO 1973 (grade 1, 2, or 3). No influence was found for gender (male or female) or age (cut-off 65 years). The factors identified by Sylvester and colleagues can be used to calculate the risk for recurrence and progression at 1 and 5 years, and the prognostic value of this scoring system had been confirmed in an independent patient population (van Rhijn et al., 2010). Fernandez-Gomez et al. (2009) have proposed another tool for predicting recurrence and progression in patients receiving BCG treatment, which, in contrast to the results of Sylvester et al. (2006), showed a negative impact of age 60–70 and > 70 years, as well as female gender.

# **Aims of the present study**

## **Paper I**

To evaluate risk factors for recurrence at the same site as the primary tumour in patients with primary diagnosed Ta/T1 urinary bladder cancer.

## **Paper II**

To study the impact of tumour size on recurrence and progression in patients with a primary diagnosis of Ta/T1 carcinoma of the bladder by use of a three-size and a five-size model.

## **Paper III**

To analyse the value of bladder wash cytology performed at primary diagnosis in predicting recurrence and progression of Ta/T1 urothelial carcinoma.

## **Paper IV**

To investigate the presence of residual tumour in the marginal resection after complete transurethral resection of Ta/T1 urinary bladder cancer and to analyse the association of a tumour-positive margin resection and recurrence.

## **Paper V**

To evaluate the experience of surgeons measured as (a) training status (resident or specialist), (b) number of TUR-Bs performed during the registration period, and (c) lifetime high-volume surgeons (> 100 TUR-Bs), considering effects on recurrence and progression of primary Ta/T1 urinary bladder cancer.

## Patients

The series in this population-based cohort study comprised all evaluable patients initially diagnosed with Ta/T1 urothelial carcinoma of the urinary bladder between 1992 and 2007 at two hospitals in Östergötland County in the Southeast Healthcare Region of Sweden, which had a population of 418,000 on 31 December 2007 (Statistiska centralbyrån). The uptake area varied during the registration period. Patients treated at the hospital in the city of Motala before 2003 were not included, because the majority of the treating doctors at that facility were general surgeons without specialization in urology. The population of the cohort was 330,000 prior to 2003. After organizational changes implemented in 2003, urological surgery was no longer performed at the hospital in Motala, and hence patients at that facility who were in need of such treatment were thereafter sent to the hospitals in Linköping and Norrköping, which served a total population of 415,000 on 31 December 2003 (Statistiska centralbyrån). Thus all patients included in the present studies were treated at the hospital in Linköping or that in Norrköping.

In the Southeast Healthcare Region in 1992, new guidelines for treatment of Ta/T1 urinary bladder cancer were introduced that included a bladder chart to indicate tumour location, size, and multiplicity. Bladder mapping at primary resection was not done routinely but was performed when clinically indicated (e.g., suspected grade 3 tumour). Cases involving T1 or Ta G3 tumours were intended to undergo early re-resection with biopsies from the prostatic urethra and instillation of BCG or a chemotherapeutic agent, although that was not done routinely in the beginning of the study period. Small tumours (< 1 cm) were resected en bloc if possible, and larger lesions were fragmented. At least one postoperative cystoscopy was required for inclusion in the study. Follow-up

cystoscopy was performed at either of the two hospitals according to the 1992 guidelines for bladder cancer, which are based on the recommendations of Parmar et al. (1989). At diagnosis and when clinically indicated, the upper urinary tract was examined by intravenous urography or CT scan, or by ultrasonography in some elderly patients.

The characteristics of the tumours and patients were recorded prospectively, and updated once a year (last done in the autumn of 2011). Histopathology results were classified according to the TNM system (Eble et al., 2004) and reviewed by a uropathologist using the WHO 1999 grading criteria (World Health Organization, 1999) with exception of Papers I and IV. The research project was approved by the local medical ethics committee (File no. 03-463).

Thirty-five patients were excluded: two due to missing pathology results and the other 33 because they had not undergone follow-up cystoscopy. Twenty-eight of the 33 without follow-up cystoscopy were elderly and unable to participate in the control programme, and these patients had received evaluation on demand or had died before scheduled follow-up cystoscopy. The remaining five patients in this group had moved to other regions and may not have had the same follow-up.

Bladder mapping at primary resection was performed in 95 cases (12%).

Concurrent primary carcinoma in situ was found in 87 (11%) of the patients, and secondary carcinoma in situ was detected in 9 (1%) during further follow-up. A single intravesical instillation of chemotherapy or six instillations of BCG were given to 22 patients (3%) after primary resection. During follow-up, another 254 (33%) received intravesical instillations of either BCG or a series of chemotherapeutic agents.

The 768 evaluable patients (591 [77%] male, 177 [23%] female) included in the statistical analysis had a median age of 72 years (interquartile range 63 to 79 years) and a median follow-up time of 60 months (interquartile range 31 to 99 months).

## **Methods**

### **Paper I**

This study included all evaluable patients diagnosed with primary Ta/T1 urothelial carcinoma of the urinary bladder between 1992 and 2001 at the hospitals in the cities of Linköping and Norrköping. Recurrence was defined as reappearance of a tumour that occurred after primary resection, required TUR-B and showed pathology results stipulated for inclusion in the study. Local recurrence was classified as recurrence at the same location as the primary tumour within 18 months of the initial resection. The location of the first recurrence determined the categorisation to local or non-local recurrence also in patients with more than one recurrence during the follow-up period. The time limit of 18 months was chosen because the third quartile limit for the time from TUR-B to the first recurrence was 16 months, and to avoid missing slowly developing recurrences.

Statistical evaluation achieved by Cox proportional hazard analysis (Cox, 1972) performed in a univariate and a multivariate fashion, comparing local recurrence with non-local recurrence, and comparing local recurrence with non-local recurrence or no recurrence. In the multivariate analyses, results were considered significant at  $p < 0.05$ . The variables analysed were gender (male vs. female) and tumour multiplicity (1 vs.  $> 1$  tumour), size ( $\leq 3$  cm vs.  $> 3$  cm), category (Ta vs. T1), and grade (grade 1 vs. grade 2–3).

## **Paper II**

The series included in this study comprised all evaluable patients initially diagnosed with Ta/T1 urothelial carcinoma of the urinary bladder between 1992 and 2007. The impact of tumour size on recurrence and progression was evaluated by using two different tumour-size models, one with five size groups (1–10, 11–20, 21–30, and > 30 mm) and the other with three size groups (1–15, 16–30, and > 30 mm). The size of a tumour during TUR-B was measured by comparing the diameter of the lesion with that of the resection loop. Progression was defined as development to a muscle-invasive growth pattern.

Statistical assessments of recurrence and progression were done using Cox proportional hazard analysis (Cox, 1972) and logistic regression analysis, respectively, both conducted in a univariate and a multivariate fashion. A likelihood ratio test between the two Cox analyses was performed to validate the different cut-offs for size determination.

## **Paper III**

This investigation comprised all evaluable patients with an initial diagnosis of Ta/T1 carcinoma of the bladder made at the hospitals in Linköping and Norrköping between 1992 and 2007. The results of the bladder wash cytology (BWC) performed at primary diagnosis were registered and referred to recurrence and progression during the follow-up period. The BWC findings were categorized as normal, atypical, low grade, high grade, not representative, or missing. The data were divided into four groups according to the BWC results at diagnosis (normal or atypical; low grade; high grade; not representative or missing), which were subsequently analysed for associations with other known prognostic variables and clinical outcome, recurrence, and progression.

The sensitivity of BWC was tested and defined as the percentage of patients with malignant BWC. Low-grade and high-grade findings were considered to be malignant; normal, atypical, and non-representative cytology were regarded as negative; and missing cases were excluded. Specificity could not be evaluated, because BWC was performed at primary diagnosis in the presence of a tumour.

Recurrence and progression were assessed by Cox proportional hazard analysis (Cox, 1972) and logistic regression analysis, respectively, both performed in a univariate and a multivariate manner. Tumour grade was not included in the multivariate analysis, because it was strongly correlated with tumour category and BWC. Considering recurrence, Kaplan Meier curves and the log rank test regarding recurrence were used to illustrate the factor tumour grade stratified for BWC as a means of evaluating the relationship between these variables. Results were considered significant if the p-value was  $< 0.05$ . A Cox model for interaction analysis was created to compare BWC and tumour grade with respect to recurrence in order to ascertain whether these variables were independent of each other (Klein and Moeschberger, 2003).

#### **Paper IV**

The series of patients selected for this investigation had primary or recurrent Ta/T1 carcinoma of the urinary bladder treated between 2001 and 2010 in the Southeast Healthcare Region. The patients were chosen randomly, and data were registered prospectively. Transurethral resection was performed using a monopolar electrocautery system with isotonic irrigation fluid and white light cystoscopy. After macroscopically complete resection of the tumour, a marginal resection (MR) of 7 mm, corresponding to the diameter of the resection loop, was performed. Histopathology results were classified according to the TNM classification.

Tumour presence in the MR specimen was recorded and assessed in relation to overall recurrence and local recurrence. Tumour category was excluded from the analysis because of the low number of cases presenting with T1 tumour category. Likewise, tumour grade was excluded due to the low number of cases with grade 3 tumours.

## **Paper V**

This study included all evaluable patients initially diagnosed with Ta/T1 urothelial carcinoma of the urinary bladder between 1992 and 2007 at the hospitals in Linköping and Norrköping. The impact of surgical experience and surgical volume on recurrence and progression after TUR-B in primary non-muscle invasive bladder cancer was evaluated using three different methodological approaches focused on surgical experience, surgical volume during the registration period, and lifetime number of surgeries performed.

### *- Surgical experience*

The training status (resident or specialist) of the investigated surgeons at the time they carried out TUR-Bs was recorded and related to recurrence and progression during further follow-up.

### *-Surgical volume during the registration period*

The number of TUR-Bs (including primary and recurrent cases) performed at the two hospitals during the registration period of 1992 to 2007 was recorded separately for each surgeon, and all surgeons were categorized according to the number of TUR-Bs they carried out. In the statistical evaluation, the median number of procedures done by each surgeon, the third quartile of surgeries performed by each surgeon, and absolute numbers of > 100, > 150, and > 200 TUR-Bs were chosen as cut-offs. Furthermore, a similar analysis was conducted in which all surgeons who had worked less than one year at our institution were excluded due to difficulties in categorization.

### *-Lifetime number of TUR-Bs*

Each surgeon was categorized according to the number of TUR-Bs performed during his/her entire career thus far, as estimated by the authors. A cut-off of > 100 TUR-Bs was chosen, because that level had been used by Mariappan et al. (2010) in a previous study of educational status and outcome after TUR-B.

The results were assessed statistically by univariate and multivariate Cox proportional hazard regression analysis of recurrence and progression. Tumour grade was not included in the multivariate analysis, because it was strongly correlated with tumour category. In this population-based study, intravesical treatment had a negative predictive value for recurrence, probably due to selection bias mechanisms, and hence it was not included in the statistical evaluation.

## **Results**

### **Paper I**

A total of 472 patients were evaluable, with a mean observation time of 56 months. Intravesical instillation therapy was administered in 131 cases (28%). The first recurrence was considered as a local recurrence in 164 (35%) and as a non-local recurrence in 117 (25%). Local recurrence was associated with a higher rate of multiple tumours compared to non-local recurrence or no recurrence (35%, 23%, and 14%, respectively), tumours > 3 cm (53%, 26%, 17%, respectively), T1 tumours (36%, 23%, and 15%, respectively), and grade 3 tumours (34%, 22%, and 15%, respectively). Tumour size > 3 cm, multiplicity, and T1 category were found to be significant risk factors in the analysis performed to compare local recurrence with non-local recurrence or no recurrence ( $p < 0.0001$ ,  $p < 0.0001$ ,  $p = 0.0002$ , respectively). Furthermore,

tumour size and multiplicity were significantly correlated with recurrence in the analysis comparing local and non-local recurrence (Table 5;  $p < 0.0001$  and  $p = 0.021$ , respectively), whereas T1 category was of borderline significance ( $p = 0.048$ ).

**Table 5.** Cox proportional hazards analysis comparing local recurrence with non-local recurrence

	HR univariate	HR multivariate	P value
<b>Gender</b>			
Male	1.0	1.0	
Female	0.74 (0.49–1.11)	0.82 (0.54–1.24)	0.35
<b>Multiplicity</b>			
1 tumour	1.0	1.0	
> 1 tumour	1.57 (1.14–2.18)	1.48 (1.06–2.07)	0.021
<b>Tumour size</b>			
≤ 3cm	1.0	1.0	
> 3cm	2.38 (1.74–3.25)	1.96 (1.40–2.74)	< 0.0001
<b>Tumour category</b>			
Ta	1.0	1.0	
T1	1.89 (1.37–2.60)	1.43 (1.00–2.04)	0.048
<b>Tumour grade</b>			
1	1.0	1.0	
2–3	2.07 (1.29–3.31)	1.46 (0.88–2.41)	0.25

## Paper II

The analysis in this study included 768 evaluable patients with a mean follow-up time of 60 months. In all, 266 patients (35%) received intravesical therapy, and 25 (3%) were given such treatment before their first recurrence. Recurrence was observed in 478 (62%) patients, local recurrence in 259 (34%), and progression in 71 (9%). In both the five-size and the three-size model, larger tumours were associated with a larger number of T1 tumours, grade 3 tumours, and multiplicity, and the rates of recurrence, local recurrence, and progression increased with increasing with tumour size. No significant difference was found

in the likelihood ratio test between the two Cox analyses ( $p = 0.22$ ), demonstrating that both of the tested size models can be used. The three-size model has lower degrees of freedom (7 vs. 9), and hence it is preferable from a statistical point of view. Tumours with diameters of  $> 40$ , 31–40, and 21–30 mm were associated with significantly greater recurrence rates compared to tumours measuring 1–10 mm ( $p < 0.001$ ,  $p < 0.001$ ,  $p = 0.003$ ). The results for the three-size model were similar, showing that tumours 16–30 mm and  $> 30$  mm were significantly associated with recurrence as illustrated in Table 6 ( $p = 0.003$  and  $p < 0.001$ , respectively). No significant relationship was detected between tumour size and progression in either the five-size or the three-size model. Local recurrence and T1 tumour category had a significant impact on progression in both the five-size and three-size group analysis ( $p < 0.001$  for all).

**Table 6.** Univariate and multivariate Cox proportional hazard analysis of recurrence based on tumours divided into three different size groups

	HR univariate	HR multivariate	P value
<b>Tumour size</b>			
1–15 mm	1.0	1.0	
16–30 mm	1.51 (1.20–1.89)	1.42 (1.13–1.79)	0.003
$> 30$ mm	2.80 (2.26–3.49)	2.39 (1.90–3.00)	$< 0.001$
<b>Tumour category</b>			
Ta	1.0	1.0	
T1	1.94 (1.60–2.36)	1.61 (1.31–1.98)	$< 0.001$
<b>Multiplicity</b>			
1 tumour	1.0	1.0	
$> 1$ tumour	1.57 (1.29–1.90)	1.47 (1.22–1.81)	$< 0.001$
<b>Patient gender</b>			
Male	1.0	1.0	
Female	0.95 (0.76–1.18)	0.99 (0.80–1.24)	0.95
<b>Surgeon's experience</b>			
Resident	1.0	1.0	
Specialist	0.75 (0.59–0.96)	0.68 (0.53–0.87)	0.002
<b>Patient age</b>			
$\leq 72$ years	1.0	1.0	
$> 72$ years	1.07 (0.89–1.28)	0.98 (0.82–1.18)	0.86

### **Paper III**

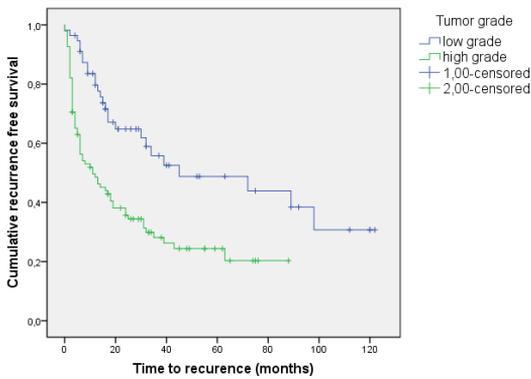
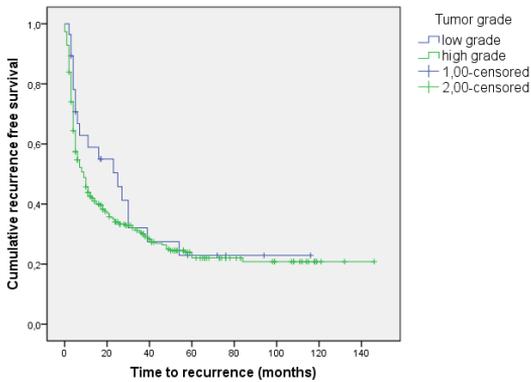
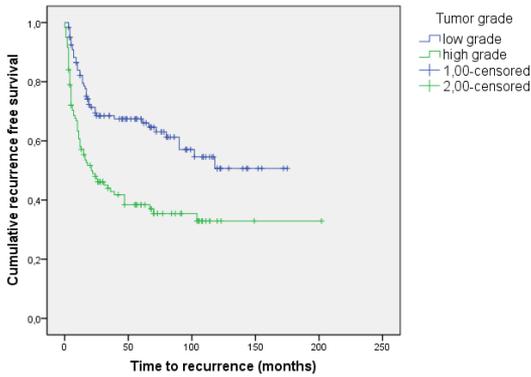
The 768 evaluable patients included in the statistical analysis had a median age of 72 years (interquartile range 63–79 years) and a median follow-up time of 60 months. The sensitivity of BWC was 60%. Recurrence was seen in 478 patients (62%) and progression in 71 (9%). Tumours with high-grade malignant BWC were associated with the highest rates of T1 tumour category (38%), high-grade tumours (91%), tumours > 30 mm (40%), and multiplicity (31%). High-grade and missing BWC were associated with recurrence (Table 7;  $p < 0.001$  and  $p = 0.008$ , respectively).

Kaplan-Meier curves of the cumulative recurrence rate according to tumour grade stratified into three different groups of BWC at diagnosis were performed: normal or atypical BWC (Figure 1A), malignant BWC (Figure 1B) and not representative or missing BWC (Figure 1C). There was a significant difference regarding recurrence between low grade and high grade tumors stratified to BWC in the log rank analyses for normal/atypical BWC and missing/not representative BWC ( $p < 0.001$  and  $p < 0.001$ , respectively). This was not found for malignant BWC ( $p = 0.33$ ). Cases presenting with malignant BWC had a higher recurrence rate than those with normal or atypical BWC and not representative or missing BWC indicating that BWC at diagnosis is an independent risk factor for recurrence.

There was no interaction effect of BWC and grade on recurrence ( $p = 0.40$ ) in the Cox model for interaction analysis implicating that BWC is a factor associated with recurrence but independent of tumor grade. High-grade malignant BWC proved to be predictive of progression ( $p = 0.036$ ).

**Table 7.** Cox univariate and multivariate analysis of recurrence in relation to the results of malignant bladder wash cytology (BWC) compared with normal/atypical BWC presented as a group and missing/not representative BWC as another group

	HR univariate	HR multivariate	P value multivariate
<b>Bladder wash cytology</b>			
Normal/Atypical	1.0	1.0	
Low grade	0.94 (0.44–2.02)	0.94 (0.44–2.01)	0.86
High grade	2.15 (1.72–2.67)	1.57 (1.23–1.99)	< 0.001
Missing/Not representative	1.63 (1.24–2.14)	1.46 (1.10–1.93)	0.008
<b>Tumour size</b>			
1–15 mm	1.0	1.0	
16–30 mm	1.51 (1.21–1.90)	1.38 (1.10–1.74)	0.006
> 30 mm	2.80 (2.25–3.47)	2.16 (1.71–2.73)	< 0.001
<b>Tumour category</b>			
Ta	1.0	1.0	
T1	1.94 (1.60–2.35)	1.40 (1.14–1.74)	0.002
<b>Multiplicity</b>			
1 tumour	1.0	1.0	
> 1 tumour	1.56 (1.29–1.89)	1.47 (1.21–1.78)	< 0.001
<b>Concomitant CIS</b>			
No	1.0	1.0	
Yes	1.39 (1.06–1.83)	1.09 (0.82–1.45)	0.56
<b>Patient gender</b>			
Male	1.0	1.0	
Female	0.94 (0.76–1.17)	1.06 (0.85–1.33)	0.58
<b>Patient age</b>			
≤ 72 years	1.0	1.0	
> 72 years	1.07 (0.89–1.28)	0.95 (0.79–1.14)	0.60



**Figure 1.** (A - up) Cumulative recurrence according to tumor grade (low and high grade) stratified by normal or atypical BWC findings at diagnosis (log-rank chi-square 17.23,  $p < 0.001$ ). (B - middle) Cumulative recurrence according to

tumor grade (low and high grade) stratified by malignant BWC findings at diagnosis (log-rank chi-square 0.96,  $p = 0.33$ ). (C - down) Cumulative recurrence according to tumor grade stratified by not representative or missing BWC findings at diagnosis (log-rank chi-square 14.05,  $p < 0.001$ ).

#### **Paper IV**

The 94 evaluable patients included in the statistical analysis in this study had a median age of 73 years (interquartile range 65 to 79 years) and a median follow-up time of 36 months (interquartile range 23 to 65 months). Primary resection was performed in 39 patients (41%) and resection for recurrent tumour in 55 (59%).

A tumour-positive MR was found in 24 patients (26%). The overall recurrence rate was 64% (60 patients) in the total material, 83% (20 patients) in cases with a positive MR, and 57% (40 patients) in those with tumour-free MR. Local recurrence was more common in the positive-MR group compared to the negative-MR group (58% vs. 19%). Compared to the patients with a negative MR, those with a positive MR had more unfavourable tumour patterns with larger proportions of T1 tumours (14% vs. 25%), grade 3 tumours (16% vs. 25%), tumours > 30 mm (10% vs. 25%), and multiple tumours (44% vs. 50%). Moreover, as shown in Table 8, multivariate Cox proportional hazard analyses indicated that having a positive MR was significantly associated with overall recurrence ( $p < 0.001$ ) and local recurrence ( $p = 0.001$ ).

**Table 8.** Cox univariate and multivariate regression analysis of recurrence in relation to tumour presence in the margin of the resection

	HR univariate	HR multivariate	P value multivariate
<b>Tumour in resection margin</b>			
No	1.0	1.0	
Yes	2.84 (1.62–4.95)	2.75 (1.56–4.85)	< 0.001
<b>Tumour size</b>			
1–15 mm	1.0	1.0	
> 15 mm	1.19 (0.71–2.00)	1.13 (0.67–1.90)	0.66
<b>Multiplicity</b>			
1 tumour	1.0	1.0	
> 1 tumour	1.20 (0.72–1.99)	1.07 (0.64–1.80)	0.79

## Paper V

The 768 evaluable patients included in the statistical analysis had a median age of 72 years (interquartile range 63 to 79 years) and a median follow-up time of 60 months (interquartile range 31 to 99 months). Recurrence was seen in 478 patients (62%) and progression in 71 (9%).

### - *Surgical experience (specialist vs. resident)*

Surgery was performed by residents in 100 cases and by specialists in 668, with recurrence in 75 (75%) and 403 (60%) patients, and progression in 9 (9%) and 62 (9%), respectively. Compared to the surgeries carried out by residents, those conducted by specialists were associated with less favourable tumour patterns that included higher rates of T1 tumours (16% vs. 27%), grade 3 tumours (12% vs. 30%), tumours > 30 mm (12% vs. 31%), and concomitant CIS (6% vs. 12%). An exception to this was multiplicity, which was noted at a higher rate in the surgeries performed by residents (33% vs. 27%).

The median number of TUR-Bs performed was 42 (interquartile range 39–44) for the seven surgeons who completed their residency at the two hospitals included in this study. A total of 36 surgeons, including 12 residents, worked at the hospitals during the registration period in this series. Surgery performed by residents was statistically associated with recurrence (HR = 0.69, 95% CI = 0.54–0.89; Table 9) but not with progression (HR = 0.72, 95% CI = 0.35–1.48).

*- Surgical volume during the registration period*

Considering the entire study period of 1992 to 2007, the median number of TUR-Bs performed per surgeon was 44 (interquartile range 13–98) when all participating surgeons (n = 36) were included but was 50 (27–118) after excluding those who worked a maximum of one year at either of the two hospitals (n = 8); the corresponding numbers for specialists were 56 (15–142) and 96 (34–161). The total number of TUR-Bs was 2,595 when all surgeons were included and 2,537 after excluding those who had worked  $\leq$  1 year at either of the hospitals. No difference in recurrence or progression was observed for high- vs. low-volume surgeons, regardless of the chosen cut-off values.

*- Lifetime number of TUR-Bs*

Considering the influence of lifetime number of TUR-Bs, 15 surgeons had performed  $>$  100 such procedures each and 21 surgeons  $\leq$  100. These 15 high-volume surgeons had carried out 576 (75%) of all the primary TUR-Bs done at the two hospitals during the registration period, and 350 (61%) of those cases showed overall recurrence, 199 (35%) local recurrence, and 55 (9%) progression. By comparison, the surgeons with  $\leq$  100 TUR-Bs each had performed 192 of the primary resections (25%), and recurrence was noted in 128 of those cases (67%), local recurrences in 60 (31%), and progression in 16 (9%). There were no significant differences regarding recurrence and progression between the groups.

**Table 9.** Cox univariate and multivariate analysis of recurrence in relation to surgical experience

	HR univariate	HR multivariate	P value multivariate
<b>Surgeon experience</b>			
Resident	1.0	1.0	
Specialist	0.75 (0.59–0.97)	0.69 (0.54–0.89)	0.004
<b>Tumour size</b>			
1–15 mm	1.0	1.0	
16–30 mm	1.51 (1.21–1.90)	1.38 (1.09–1.74)	0.006
> 30 mm	2.80 (2.25–3.47)	2.18 (1.73–2.76)	< 0.001
<b>Tumour category</b>			
Ta	1.0	1.0	
T1	1.94 (1.60–2.35)	1.50 (1.21–1.85)	< 0.001
<b>Multiplicity</b>			
1 tumour	1.0	1.0	
> 1 tumour	1.56 (1.29–1.89)	1.49 (1.22–1.81)	< 0.001
<b>Concomitant CIS</b>			
No	1.0	1.0	
Yes	1.39 (1.06–1.83)	1.13 (0.85–1.51)	0.40
<b>Bladder wash cytology</b>			
Normal	1.0	1.0	
Atypical	1.07 (0.75–1.54)	0.99 (0.69–1.43)	0.95
Malignant	2.16 (1.63–2.87)	1.50 (1.12–2.04)	0.009
Not representative	0.90 (0.36–2.24)	0.69 (0.27–1.73)	0.43
Missing	1.78 (1.27–2.47)	1.52 (1.09–2.13)	0.015
<b>Patient gender</b>			
Male	1.0	1.0	
Female	0.94 (0.76–1.17)	1.03 (0.83–1.29)	0.77
<b>Patient age</b>			
≤ 72 years	1.0	1.0	
> 72 years	1.07 (0.89–1.28)	0.94 (0.79–1.13)	0.53

# Discussion

## Paper I

Local recurrence can be the result of incomplete resection of the primary tumour, and the significant effect of tumour size on recurrence supports this conclusion. Larger tumours (> 3 cm) are technically more difficult to resect and hence may increase the risk of residual tumour cells after resection. Herr (1999) found a high frequency of residual tumour (76%) in re-resections performed within 2–6 weeks of diagnosis of primary and recurrent bladder cancer.

Multiplicity was identified as another risk factor for local recurrence, which might be explained by difficulties in achieving surgical control over all tumours during TUR-B. Brausi et al. (2002) have reported that the recurrence rate at the first follow-up cystoscopy in cases of primary and recurrent Ta/T1 bladder cancer varies widely from 7.4% to 45.8% for multiple tumours, depending on the institution. In our series, local recurrence was found in 69% of patients with planned re-resections. In cases with low-risk tumours, 110 (39%) of the patients who were not scheduled for primary re-resection developed local recurrence during further follow-up. It was not possible to determine whether this was the result of tumour cell implantation, insufficient resection, or true recurrence due to aggressive tumour biology.

## Paper II

The three-size-group model proposed in this study is easy to use in clinical practice, because 15 mm corresponds to approximately two times the diameter of the resection loop, and 30 mm corresponds to about four times that size. This model is also preferable from a statistical perspective due to the lower amount of degrees of freedom. Tumours up to 15 mm in diameter were associated with a lower risk of recurrence compared to tumours that were 16–30 or > 30 mm. The

risk tables available thus far for predicting recurrence distinguish between two tumour size categories with a cut-off level of 3 cm (Sylvester et al., 2006). However, our data suggest that another cut-off of 15 mm would give additional valuable information on recurrence. Tumour patterns regarding category, grade and multiplicity were more favourable in small lesions which contribute to the lower risk for recurrence. Expectant management of such small, low-grade, non-invasive papillary tumours can be an option according to Soloway et al., 2003. The tumours should be measured by size and not weight, as demonstrated by the findings of Gupta et al. (2008) showing no significant difference between tumours weighing 15–30 g and > 30 g with respect to recurrence and progression. Immediate intravesical instillation of chemotherapeutic agents after initial resection can influence the recurrence rate especially in smaller tumours (Berrum-Svennung et al., 2008). However, in our series only a minority of patients (3%) received intravesical agents immediate after primary TUR, and hence such treatment should not affect the recurrence rate. In contrast to results reported by van Rhijn et al. (2009), we found that tumour size did not have a significant effect on progression, despite the fact that the progression rate was 16% in patients with tumours > 30 mm compared to 7% in those whose tumours were up to 15 mm in diameter. The comparatively low number of patients with progression to muscle-invasive disease in our series may have contributed to the lack of statistical significance in the multivariate analysis.

### **Paper III**

High-grade BWC was significantly associated with recurrence and progression, irrespective of tumour grade, and it was also correlated with the highest rate of T1 tumour category (38%), high-grade tumours (91%), tumours > 30 mm (40%), multiplicity (31%), and concomitant CIS (19%). Boman et al. (2002) obtained similar results in a study of the relationship between tumour pattern and BWC, which indicated that tumour stage, grade, and size were correlated

with malignant BWC. No statistical interaction was found between tumour grade and BWC on recurrence in the present series implicating that both these variables are independently associated with recurrence.

The results of BWC in our study did not always concur with the histopathological results after TUR-B, which might be due to different tumor populations within each tumor where some are detected by pathology of the specimen and others only revealed by BWC. High-grade BWC findings (91%) showed the strongest agreement with the pathology results, which is consistent with a study by Wiener et al. (1993) demonstrating that the diagnostic accuracy of cytology is related to the histological grade of the bladder tumour.

The group missing/not representative BWC was significantly associated with recurrence ( $p = 0.008$ ). Contributing factors to the second highest recurrence rate (62%) in this group may be the comparatively large proportions of T1 tumours (21%), tumours > 15 mm (64%), and multiplicity (26%). Many of the patients in this group presented with severe haematuria as the main symptom at diagnosis and hence were hospitalized at that time, which can explain the missing cytology results.

Several studies have shown that the sensitivity of voided cytology is inferior to that of BWC (Gregoire et al., 1997; Matzkin et al., 1992; Badalament et al., 1987), and we used BWC in our investigation. BWC seems to be the gold standard of adjunctive tests according to van Rhijn et al. (2009) who presented a sensitivity of 35% for voided cytology and 58–77% for commercial tests, which can be compared with the sensitivity of 60% in our series. Furthermore, the sensitivity of BWC can be improved by combining that method with detection of p53 mutation (Prescott et al., 2001), analysis of telomerase activity (Lee et al.,

1998), and assessment of DD23 antigen expression (Gilbert et al., 2003), none of which was used in our series.

#### **Paper IV**

The high incidence of local recurrence (58%) in cases with a tumour-positive MR clearly underlines the importance of such resection, particularly with regard to the possibility of avoiding recurrence at the same site. A MR might be technically difficult and not always optimally performed.

In the investigation reported in Paper I, we found a local recurrence rate of 35%, which can be compared with a rate of 58% for the cases with a positive MR and 19% for those with a negative MR in the present series (Paper IV). The low rate of local recurrence in MR-negative cases might indicate that it is important to have a tumour-free margin around a resection area in order to prevent local recurrence.

In a study by Kolozy (1991), residual tumour was detected in 13% of patients with Ta tumours and 35% of those with T1 tumours when the surgeon performed a deep resection of the underlying bladder wall and surrounding area 2 cm lateral to the visible tumour. The corresponding proportions for such tumours in our investigation were 23% and 36%, respectively. Herr et al. (2008) have recommended the use of a 2-cm peripheral margin extending laterally into normal mucosa. However, this approach is associated with a much larger resection area and may also be related to a greater number of complications, such as postoperative bleeding, blood clot retention, and the need for blood transfusions. The optimal size of the MR is not yet clear and may be the subject of future evaluation.

According to Brausi et al. (2002), the recurrence rate at the first follow-up cystoscopy varies considerably, and one factor contributing to this disparity may be use of intravesical adjuvant treatment after TUR-B. In our series, the recurrence rate was higher in patients who received intravesical treatment (75%) than in those who did not (56%). Factors contributing to the higher recurrence rate in the former cases included unfavourable tumour patterns with more T1 and grade 3 tumours, and lesions > 30 mm in diameter (31% vs. 10%, 38% vs. 8%, and 28% vs. 19%, respectively), thus creating a negative selection bias for those patients receiving intravesical treatment.

The presence of detrusor muscle in the resection specimen is essential for correct staging and effective treatment (Babjuk, 2009; Mariappan et al., 2010), and thus a deep resection in the bladder muscle is recommended.

## **Paper V**

### *-Surgical experience (specialist vs. resident)*

Mariappan et al. (2010) found the presence of detrusor muscle in a significantly larger number of TUR-Bs performed by senior surgeons, and the rates of recurrence at the first follow-up cystoscopy or primary re-TUR-B were significantly lower for those surgeons compared to their junior counterparts (39% vs. 25%, respectively). We did not find a similar difference at the first follow-up cystoscopy and re-TUR-B, for which we noted recurrence rates of 36% and 33% after surgeries performed by residents (36 patients) and specialists (220 patients), respectively. However, in contrast to the study conducted by Mariappan et al. (2008), we did not exclude patients who were not given immediate postoperative intravesical chemotherapy or those who did not undergo follow-up cystoscopy three months after the surgery.

Brausi et al. (2002) conducted a meta-analysis of 2,928 patients randomized to different EORTC trials and found that, in cases of Ta/T1 urothelial bladder cancer, the recurrence rate at first follow-up cystoscopy after TUR-B varied considerably from 0% to 46%. This variability was partly the result of multiplicity and adjuvant intravesical treatment, but the authors suggested that it might also have been influenced by the quality of the TURs performed by the individual surgeons. This conclusion supports our data showing an experience-dependent recurrence rate. Brausi et al. (2008) subsequently reported that by implementing a dedicated teaching programme, they were able to reduce the three-month recurrence rate after surgeries performed by residents from 28% to 8%, and the corresponding reduction for senior surgeons was from 16% to 3%. Recommendations for optimizing TUR-BT have been outlined by Nieder et al. (2006) and Adiyat et al. (2010).

#### *-Surgical volume during the registration period*

We found no influence of surgeon volume on outcome after TUR for Ta/T1 bladder cancer. A possible explanation for this is that the data on TUR-Bs performed by each surgeon covered only a limited period of time, and thus it was not possible to ascertain lifetime volume. Also, some high-volume surgeons were categorized incorrectly as low-volume surgeons, because they retired during the data period, performed their duties at some other hospital, or changed sub-specialization.

#### *-Lifetime number of TUR-Bs*

It seems that the chosen cut-off of > 100 TUR-Bs in the lifetime approach eliminated the problem of incorrect categorization of the surgeons. Nonetheless, our data suggest that this cut-off was too high, because it did not reveal a difference in relation to recurrence, which was shown by the surgical experience approach with a median cut-off of 42 procedures during residency. However,

using a lower cut-off would have increased the uncertainty of the categorization, especially for surgeons working only a limited time at the current hospitals.

# Conclusions

## Paper I

Large tumours and multiplicity were independent risk factors for local recurrence. Local tumour recurrence may be a result of non-radical primary TUR-B. Re-resection within 6–8 weeks may be considered in patients with tumours > 3 cm in diameter or multiple primary tumours.

## Paper II

Tumour diameter  $\leq 15$  mm is associated with a lower risk of recurrence. Dividing tumour size into three groups provides additional information compared to the use of two size groups with a cut-off at 30 mm. In the future, it may be necessary to include additional tumour size cut-offs in risk tables used to predict recurrence.

## Paper III

High-grade malignant BWC at primary diagnosis was found to be an independent risk factor for recurrence and progression. This might be taken into consideration in future follow-up schedules. Initial BWC should be an integral part of the investigation of all newly diagnosed cases of bladder cancer.

## Paper IV

The presence of residual tumour in the MR was associated with both overall and local recurrence. The high rate of local recurrence in tumour-positive MR (58%) suggests the need for re-resection or for a larger tumour-free margin at primary resection. The optimal width of the MR may be subject of future investigations.

## **Paper V**

In this series, the outcome of TUR-B with regard to recurrence was influenced by the operative experience of the surgeon (specialist vs. resident). Surgical volume was not found to have a significant impact on recurrence or progression in any of the analyses at the chosen cut-offs. Dedicated teaching programmes, standardized checklists for the procedure, and better supervision may be necessary to eliminate these differences.

# Acknowledgements

I wish to express my gratitude to all those who helped me in the research leading to this thesis, and in particular my sincere thanks go to the following people:

**Staffan Jahson**, my supervisor and the scientific motor of the department, for great support during this project. Always open-minded and willing to discuss science and scientific problems, providing motivation by offering gentle criticism and rapid corrections, and invariably pressing the accelerator to the floor and proceeding faster than a hurricane.

**Johan Rosell**, for great help with the statistics, for always being willing to discuss statistical problems, and for being a co-author.

**Ole Damm**, for useful support and criticism of Paper I as a co-author.

**Christer Alhstrand**, the former head of the Department of Urology, for all help in general and as a kind faculty examiner at the midway review of my doctoral research.

**Oliver Gimm**, for agreeing to be external examiner at my midway review on short notice and for help with preparing for the public defence of my PhD thesis.

**Reidar Källström**, head of the Department of Urology, for supporting me in my thesis research and for taking that work into account when planning the duty roster.

**Anders Spångberg**, for valuable constructive criticism and support.

**Johan Söderholm**, for all support at my midway review.

**Patricia Ödman**, for fast and superb language correction.

**Hans Olsson**, pathologist and PhD, for helping me with numerous issues in the last phase of my disputation.

**Anneli Munther**, post-graduate coordinator, for assistance with the notification of the public defence of my thesis.

**Anneli Lindström**, Professor, for helping me with problems regarding the notification of the public defence of my thesis.

**The staff of the Department of Urology**, for all your help and support over the last few years.

And finally to my loved ones, my wife **Zara**, for your love and patience, and my children **August** and **Estrid**, for just being you.

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