ASPECTS OF TREATMENT OF
NON-MUSCLE INVASIVE BLADDER CANCER

Viveka Ströck

Department of Urology

Institute of Clinical Sciences

Sahlgrenska Academy

University of Gothenburg

Sweden

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viveka.strock@vgregion.se

To me, myself and I.

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Viveka Ströck

Department of Urology, Institute of Clinical Sciences

Sahlgrenska Academy

University of Gothenburg, Sweden

ABSTRACT

Bladder cancer is the third most common malignancy in men in Sweden and a total of 2560 patients were diagnosed with new disease in 2015. Over 95% of the tumours are of urothelial origin. Approximately 75% of the patients present with a non-muscle invasive bladder cancer (NMIBC). The first treatment is a transurethral resection of the bladder (TURB) and no further treatment is necessary for those with a non-invasive and low-grade tumour. A second resection is recommended for patients with high-grade tumours in order to verify that no muscle invasion is present. These patients require additional intravesical treatment with either chemotherapy or bacillus Calmette-Guérin (BCG) vaccine. Side-effects are common and often transient but late side-effects are rarely seen. The prognosis of NMIBC is generally good, but for high-grade tumours there is a higher progression rate. The recurrence rate is very high for NMIBC resulting in multiple TURBs with high costs. The aims of this thesis were to report a late BCG-complication not previously described and to investigate the incidence of late recurrences in BCG-treated patients. Furthermore to register the number, size and histopathology of new and recurrent tumours and to register self-reported pain perception during transurethral procedures. In the **first** paper we describe a large lesion in the bladder with a persisting mycobacterial infection in 13 patients. The majority received tuberculostatic treatment and the lesions and infections disappeared. The **second** paper is a report on a large cohort of BCG-treated patients who had a tumour-free period of at least five years at some point after BCG-treatment. We found 10.8% late recurrences, suggesting that these patients require lifelong follow-up. The **third** study was a prospective registration of the size, number and histopathology of all new and recurrent bladder tumours during 15 months. The results showed that 22% in both groups were benign or inflammatory lesions and the absolute majority of recurrences were smaller than 10 mm, which has not previously been demonstrated. The **fourth** paper consists of a prospective registration of 1572 patients with self-reported pain, experienced during cystoscopy and transurethral procedures under local anaesthesia. The pain levels at cystoscopy were generally low and in accordance with previous reports. At transurethral tumour extirpations the pain levels were higher than at cystoscopy only but still within an acceptable range. The two latter studies support the increased use of biopsies and fulguration under local anaesthesia as most recurrences are small and easily managed in the office setting.

Keywords: Bladder cancer, BCG, transurethral resection, local anaesthesia.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I.   Ströck V, Dotevall L, Sandberg T, Gustafsson CK and Holmäng S. **Late bacille Calmette-Guérin infection with a large focal urinary bladder ulceration as a complication of bladder cancer treatment**. BJU Int. 2011; 107(10): 1592-1597.

II.   Holmäng S and Ströck V. **Should follow-up cystoscopy in bacillus Calmette-Guérin-treated patients continue after five tumour-free years?** Eur Urol. 2012; 61(3): 503-507.

III.   Ströck V and Holmäng S. **A Prospective Study of the Size, Number and Histopathology of New and Recurrent Bladder Tumors**. Urology Practice. 2015; 2(5): 260-264.

IV.   Ströck V and Holmäng S. **Is bladder tumour fulguration under local anaesthesia more painful than cystoscopy only?** 2017; In manuscript.

ABBRIVIATIONS

5-ALA	5-aminolaevulinic acid
Ab	Antibody
BC	Bladder cancer
BCG	Bacillus Calmette-Guérin
CI	Confidence interval
Cis	Carcinoma in situ
CK 20	Cytokeratin 20
cT	Clinical staging
CT	Computed tomography
EAU	European Association of Urology
EORTC	European Organisation for Research and Treatment of Cancer
FDG-PET/CT	Fluorodeoxyglucose-positron emission/CT
HAL	Hexaminolevulinate
HG	High grade
HTX	Hematoxylin
IBCG	International Bladder Cancer Group
ISUP	International Society of Urologic Pathology
LG	Low grade
LVI	Lymphovascular invasion
M bovis	Mycobacterium bovis
MIBC	Muscle invasive bladder cancer
MRI	Magnetic Resonance Imaging
NMIBC	Non-muscle invasive bladder cancer
pT	Pathological staging

PDD   Photodynamic diagnosis

PUNLMP   Papillary urothelial neoplasm of low malignant potential

SCC   Squamous cell carcinoma

SNBCR   Swedish National Bladder Cancer Registry

TB   tuberculosis

TNM   Tumour, node, metastasis (classification system)

TURB   Transurethral resection of the bladder

UC   Urothelial carcinoma

UTI   Urinary tract infection

WHO   World Health Organisation

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INTRODUCTION

The incidence of urinary bladder cancer (BC) shows differences worldwide with the highest incidence in Europe, the Unites States and Egypt (1). In 2012, the incidence of BC was at number nine and the sixth most common cancer in males. The lowest rates are seen in sub-Saharan Africa, Asia and South America. The variations are mainly due to the differences in well-established risk factors for developing the disease including tobacco use, infections with *Schistosoma haematobium* and occupational exposure to aromatic amines and polycyclic aromatic hydrocarbons (2). In general, the incidence has shown a decrease in most Western countries but has increased in some eastern European and developing countries. The highest estimated mortality rates are seen in central and eastern Europe, northern Africa and western Asia (1).

In Sweden BC was the third most common malignancy in men in 2015 and a total of 2560 patients were diagnosed with new disease. Seventy-seven percent were men and the median age at diagnosis was 73 years (3, 4). The five-year survival has been fairly constant during the last decade, around 75% (5).

The majority of BCs are defined as urothelial cancers, arising from the urothelium although a few percent consists of primary squamous cell carcinoma (SCC) and adenocarcinoma (6, 7). BC usually presents as an exophytic growth and are often papillary or solid and more rarely a flat lesion.

BC is a heterogeneous disease, both concerning treatment and prognosis partly due to the depth of invasion at diagnosis and there are indications of different molecular subtypes (8). Approximately 75% of newly diagnosed BCs are confined to the urothelium or underlying lamina propria (stages Ta, T1, Tis) and defined as non-muscle invasive (NMIBC). The remaining 25% have invaded the detrusor muscle (stages T2-4) and are classified as muscle invasive (MIBC) (9).

The most common presenting symptom of BC is macroscopic haematuria and more rarely an urgency to void. Some patients are asymptomatic and detected as incidental findings at radiologic examinations performed for other reasons than urological symptoms.

Diagnosis is made by an endoscopic examination of the urinary bladder, cystoscopy, which is performed under local anaesthesia. The first treatment consists of a transurethral resection of the bladder (TURB) where the bladder tumour is resected, either completely or partially in

more advanced cases (9). This also includes a bimanual palpation of the bladder to assess the clinical stage of the tumour. The resected specimen is sent for histopathological grading and staging. For patients with Ta tumours of low-grade (LG), no further treatment is usually required. For Ta high-grade (HG) tumours and stage T1, additional treatment with intravesical instillations is administered, sometimes preceded by a re-TURB. When muscle invasion is present, a more aggressive treatment is needed; the removal of the bladder, cystectomy, with or without neoadjuvant chemotherapy. More seldom radiation therapy is given (4).

The prognosis for NMIBC varies and is generally good for those with a disease confined to the urothelium, Ta, but heterogeneous for stage T1 (10). Approximately 50% of stage T1-patients can be cured with TURB and intravesical instillations, 25% progress to a more advanced stage, requiring a more aggressive therapy and 25% will eventually die from the disease. The overall cancer specific survival for BC has been about 70% in Sweden during the last years (3).

The present thesis is focused on NMIBC, and in particular deals with intravesical treatment with bacillus Calmette-Guérin (BCG) and aspects of treatment under local anaesthesia. The different studies were approved by the local ethical committee.

DIAGNOSIS OF BLADDER CANCER

The suspicion of BC usually arises with the debut of macroscopic haematuria or persistent urgency to void in the absence of urinary tract infection (UTI). Due to a history of doctor´s delay, there is a fast track since 2015 in Sweden with a national guideline demanding health care professionals to immediately refer patients (over the age of 40 years) with symptoms of BC to a urologist (4). The goal is to simultaneously refer the patient for a computed tomography (CT) of the upper urinary tract to exclude other pathological findings. Ideally, the result of the CT is present when the patient meets the urologist for a diagnostic cystoscopy. When a BC is detected, the patient is planned for a TURB. If the CT already detected a BC, the cystoscopy is redundant and the patient is informed about the diagnosis and the planned surgery (**Figure 1**).
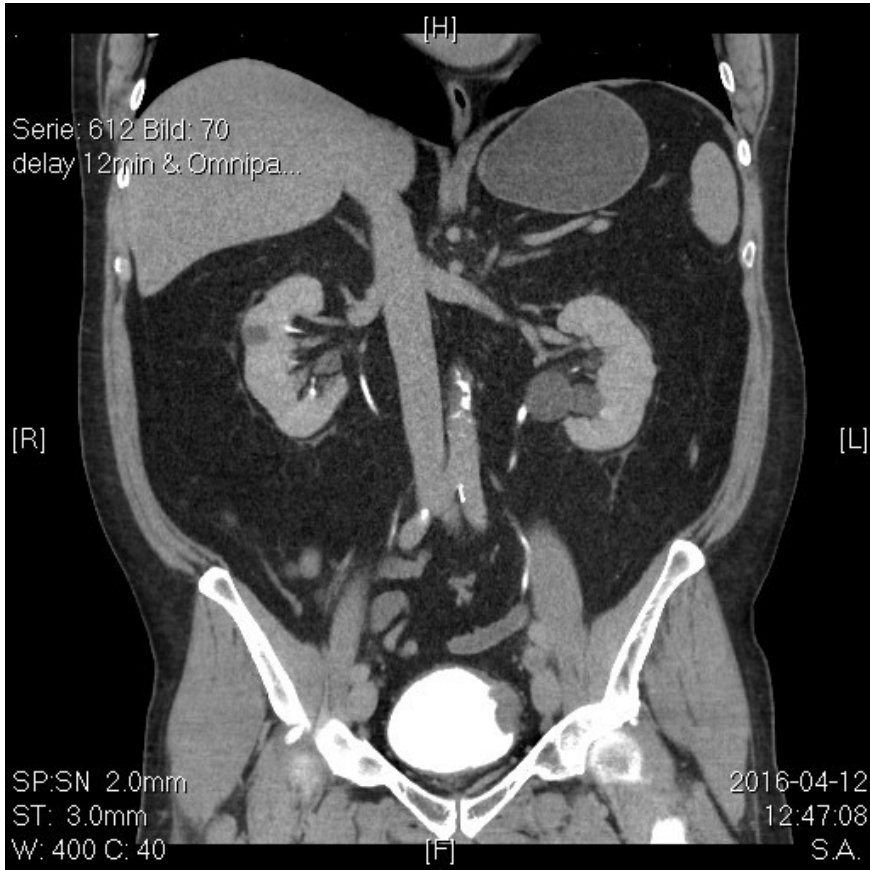
Figure 1. CT showing a BC in the left side of the bladder. After neoadjuvant chemotherapy the patient underwent cystectomy which showed pT3aN0M0.

CYSTOSCOPY AND IMAGING

The cystoscopy is performed in the outpatient clinic, under local anaesthesia with lubricant jelly containing lidocaine, with a flexible or rigid instrument. It is important to inspect the urethra and entire bladder. Any abnormal or pathological findings should be thoroughly documented and bladder wash cytology should be sent for analysis in unclear cases or when a high-grade (HG/G3) tumour is suspected, as exfoliated cells can be seen (9). Cytology is also useful for detecting flat lesions, carcinoma in situ (Cis)

In order to evaluate the staging of the disease, primarily when MIBC is suspected, CT of the abdomen and the chest is recommended, in order to detect enlarged lymph nodes or distant metastases. Unfortunately, the sensitivity is not optimal for staging, which also holds for magnetic resonance imaging, MRI. Following a TURB an oedema surrounding the bladder can be seen and mistaken for extravesical growth. Some studies have revealed an increased detection of metastasis in MIBC using fluorodeoxyglucose positron emission/CT (FDG-PET/CT) (4, 9).

CLASSIFICATION OF BLADDER TUMOURS
GRADING

The tissue samples are fixated in formaldehyde and sent to the pathology lab, where they are stained, usually with haematoxylin and eosin, which allows analysis of the tumour cells and the architecture. The grading is performed using the World Health Organisation (WHO) classification system (11). Originally defined in 1973, it was based on the degree of cellular anaplasia, where grade 1 was those who had the least degree of nuclear anaplasia, compatible with a diagnosis of malignancy. Grade 3 was applied to tumours with the most severe degree of anaplasia and grade 2 as lying in between. The WHO 1973 was the first international, systemic approach of grading urothelial cancers. This system suffered from limitations, mainly due to the poorly defined grade 2. Attempts to further define the grading resulted in adding the terms papilloma, indicating a more indolent bladder tumour, and low- versus high-grade carcinoma (12). Furthermore, the term papillary urothelial neoplasm of low malignant potential (PUNLMP) was proposed and a more refined description of flat intraepithelial lesions resulted in a two tier system of dysplasia and Cis. In 1998 the International Society of Urologic Pathology (ISUP) in collaboration with the WHO presented a consensus classification, WHO/ISUP 1998, based on the pattern and object related features of the tumours, which resulted in the definition of LG and HG carcinomas (13). In WHO 1999 the HG group was split up in HG II and HG III, but changed back in the revision of 2004 to LG/HG (**Figure 2 and 4**).
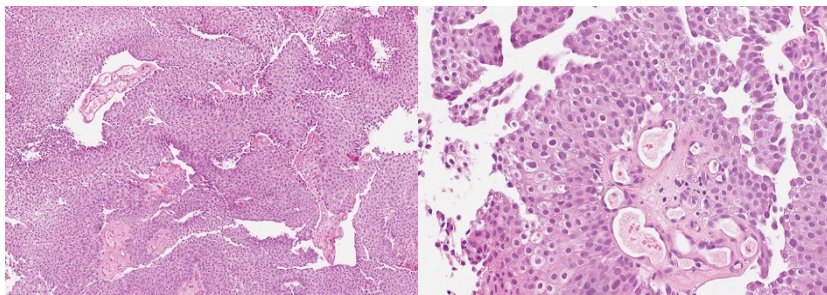
Figure 2. Papillary urothelial tumour grade 1, WHO 1999. Low variations of nuclear size and preserved polarity of the cells. Haematoxylin/eosin, original magnification x4 and x20. (By courtesy of Anders Bergström, Clinical pathology and genetics)

In the 2016 version, definitions of papillary lesion have been further defined (14).

The reasons for the continuous work on defining and redefining the grading system are several. The WHO 1973 poorly defined grade 2 and the interobserver reproducibility was low. The importance of correct grading has implications on the treatment, recurrence and progression (15).

The differences are summarized in **Figure 3.**
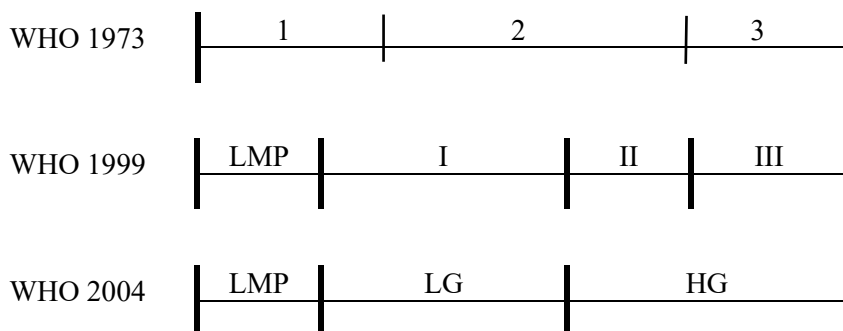
Figure 3. Relationship between the changes in the WHO classifications.

The European Association of Urology (EAU) recommends WHO 1973 or 2004/2016 grading systems (9). In Sweden both the WHO 1999 and 2004 are recommended by the Swedish National Healthcare Programme for Bladder Cancer, updated in 2015 (4).

Voided urine or bladder wash may contain exfoliated cancer-cells and can be sent for cytological analysis. Cytological examination has a high sensitivity for G3/HG-tumours (84%) but has less accuracy for G1/LG-tumours (16%), and can be used as a predictor for G3-tumours before a TURB or when Cis is suspected (9). Cytological interpretation is user-dependent and can be hampered by low cellular yield, infection, stones or previous intravesical treatment, but the specificity in experienced hands exceeds 90% (9). A negative cytology examination does not exclude malignancy in the urinary tract as the sample could contain too few cells or may not be present at all.


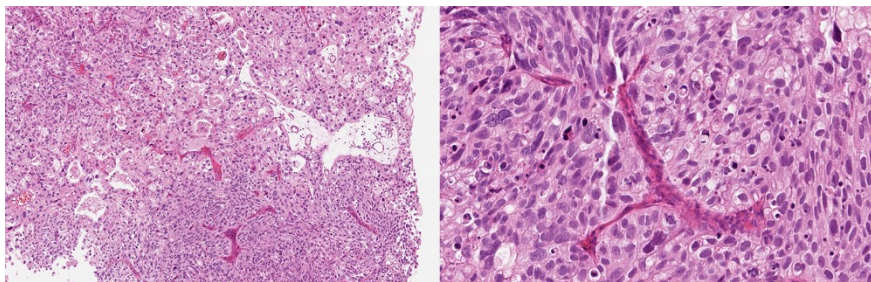
Figure 4. Papillary urothelial tumour grade 3, WHO 1999. Variations in nuclear size, more disorder and loss of polarity. Haematoxylin/eosin, original magnification x4 and x20. (By courtesy of Anders Bergström, Clinical pathology and genetics)

STAGING

Staging includes both the depth of the tumour into the bladder, or adjacent organs and the presence or lack of metastasis. The staging is decided according to the tumour, node, metastasis (TNM) classification system, as seen in **Table 1** (16).

Table 1 TNM classification system, 7th edition (2009).

T- primary tumour	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non- invasive papillary carcinoma
Tis	Carcinoma in situ
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 any of the following: prostate stroma, seminal vesicles, uterus,
	vagina, pelvic wall, abdominal wall
	T4a Tumour invades prostate stroma, seminal vesicles, uterus or vagina
	T4b Tumour invades pelvic wall or abdominal wall
N- Regional lymph nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator,
	external iliac or presacral)
N2	Metastasis in multiple lymph nodes in the true pelvis
N3	Metastasis in common iliac lymph node(s)
M- Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

The pathological staging (pT) is assessed from the histopathological report and radiologic imaging. Assessment of the clinical stage (cT) is performed by bimanual palpation at the time for TURB. At the time for surgery, a description of the location in the bladder, macroscopic appearance of the tumour, including size and numbers should also be included. Both cT and pT are of uttermost importance to determine the correct treatment strategy and hence the prognosis of the disease, although accurate tools for calculating the prognosis are lacking (17).

NMIBC includes stages Ta, Tis and T1, and although Ta has a high recurrence rate, the prognosis is overall good. For both Cis and T1 the prognosis is worse as these have a considerably higher risk to progress to muscle invasive disease. There are also reports that indicate a necessity for further staging of T1 tumours, defining the depth of invasion beyond the basal membrane (18, 19).

SUBTYPES AND NON- UROTHELIAL BLADDER CANCERS

Up to 90-95% of all bladder cancers are of urothelial origin, although there are more rare subtypes that display variations in morphology and growth pattern (14). The nested variant of urothelial carcinoma is characterized by cytologically bland cells, infiltrating as disorderly arranged nests or tubules. It is important to identify these as they can mimic benign urothelial proliferation, but are usually presented as locally advanced tumours with poor clinical outcome. Another variant is the micropapillary urothelial carcinoma (UC) which displays as small nests of tumour cells within lacunae. These are commonly associated with lymphovascular invasion (LVI) and are clinically aggressive and should be treated likewise (14).

The remaining BCs are squamous cell carcinoma (SCC) and adenocarcinoma (0.5-2%). The SCC is further divided in two subtypes, one associated with bilharzia (infection with *s haematobium*) leading to higher incidence where the parasite is endemic- the Middle East, South East Asia and South America (7).

BLADDER TUMOUR MARKERS

There has been extensive research to find bladder tumour markers in the hope of both early detection and to decrease the numbers of cystoscopies for follow-up. The ideal tumour marker should have a high detection rate of malignancy and high accuracy (high specificity and sensitivity). It should also be technically easy to use, non-invasive and ideally reducing the cost for surveillance. In the case of follow-up, a marker should be able to detect a recurrence at an early stage, primarily for the high-risk tumours, as these have the highest risk for progression. For low- or intermediate-risk tumours, early detection of a recurrence may reduce the number of resections done under general or spinal anaesthesia. So far the standard non-invasive marker is still cytology, with a specificity over 90%, although the sensitivity is reported to be 11-76% (18). The reason for the high range of sensitivity is mainly due to the low detection rate for G1/LG-tumours, but is more accurate for G3/HG-tumours. The results of cytological examinations are dependent on the presence of exfoliated tumour cells, which seem to be present more often in bladder wash cytology, compared to voided urine (20). One should also keep in mind that a negative cytological examination does not exclude malignancy in the urinary tract. So far, no urinary molecular tests are accepted for detection or follow-up for BC according to the EAU guidelines.

HISTOPATHOLOGY

The standard preparation of bladder tissue samples is fixation in formaldehyde, embedded in paraffin and stained with haematoxylin (HTX) and eosin (21).

The preparation enables the pathologist to evaluate the urothelial cells under the microscope to determine the grade of malignancy and the relationship to the underlying tissue. The evaluation of grade is made by analysing architectural abnormalities (order/disorder among the cells, polarisation), the appearance of the nuclei (pleomorphism, prominent, enlarged) and the number of mitoses (22). Immunohistochemistry analyses may provide further support in determining if the tumour is of urothelial origin. One is cytokeratin 20 (CK 20) which usually stains urothelial tumours evenly but it is negative for papillomas. To distinguish between reactive dysplasia and Cis, CK 20 along with GATA 3 may be helpful, but the recommendation is still that diagnosis should rely on the morphological interpretation. There are also other markers that stain more positive, the higher the grade, such as p53 and Ki-67 (23).

TREATMENT OF BLADDER CANCER
RISK GROUP STRATIFICATION

In order to calculate the risk for recurrence and progression the European Organisation for Research and Treatment of Cancer (EORTC) has developed a calculator (24). Low-risk tumours are primary, solitary, Ta, LG/G1, less than 3 cm and no Cis. High-risk tumours are any of: T1-tumours, HG/G3-tumours, Cis, multiple and recurrent and large (>3 cm) TaG1-2 tumours (9). Intermediate-risk tumours are those who are not defined in low-or high-risk. This stratification is important as it helps in determining the correct treatment for each patient.

TURB

The TURB is usually performed in an operating room under general or spinal anaesthesia, using a resectoscope (**Figure 5**).

Figure 5. Resectoscope for TURB. It can be used with 0, 12 or 30 degrees optics.

If the tumour is very small, it is possible to take biopsies, with subsequent fulguration and thereby remove it completely at cystoscopy (25). The specimen biopsied/resected is sent for histopathological analysis, yielding stage (pT) and grade.

The primary goal of TURB is to completely resect all tumour, which should be documented regarding location in the bladder, size, appearance, multiplicity and bimanual palpation when a MIBC is suspected.

The surgery is usually performed under spinal or general anaesthesia and starts with the inspection of the whole urothelial lining, including the urethra. It is important to have the correct instrument, resectosope or cold cup biopsy forceps when indicated. Cauterisation should be kept to a

minimum as this can result in heat damage to the tissue and thus provide difficulties for the pathological evaluation. In cases of small tumours, the resection should be performed in one piece, including the underlying tissue. Larger tumours are resected in sections; the exophytic parts, the underlying tissue including detrusor muscle and the margins of the tumour site. Separate biopsies from the bladder neck and prostatic urethra are recommended when there is a suspicion of Cis, when there are abnormalities in the prostatic urethra/bladder neck and in cases of positive cytology but no visible tumour in the bladder. In the latter case, the use of fluorescence-guided (PDD) biopsies are recommended (9). If a tumour is located on the lateral walls of the bladder, there is a risk of stimulating the obturator nerve, resulting in an activation of the adductor muscles and risk of bladder perforation. It is therefore important to have sufficient muscle relaxation. Some argue that the use of bipolar resection reduces the risk of obturator stimulation as well as yielding less heat damage to the tissue, although larger studies are lacking (26, 27).

The resected tissue is sent for histopathological grading and staging and it is important to get detrusor muscle within the specimen although not mandatory for TaG1-tumours. The different fractions should be referred in separate containers for correct evaluation. The pathological report should include stage, grade, the presence of Cis, if there is detrusor muscle found in the specimen, any unusual histological pattern and the presence of LVI.

A second resection should be performed after an incomplete first TURB, if the tumour is pTaG3-T1 or if no detrusor was present in the specimen except in pTaG1 and primary Cis (9). Residual tumour is found in a majority of patients after the first TURB and understaging is common- up to 25% primarily reported as pT1 are upstaged to pT2 after second resection (28). The risk of understaging has been reported to be even higher when no muscle was found at first resection. Correct staging is of great importance in determining the recurrence and progression rates and deciding the accurate treatment in each case.

In cases of very large or locally advanced tumours, complete resection may not be possible and the focus should be on achieving local control of the tumour and get enough tissue for diagnosis in order to plan for radical treatment such as cystectomy, with or without additional oncological treatment.

BIOPSIES AND TURB UNDER LOCAL ANAESTHESIA

Before any transurethral procedure, the routine is to instil 2% lidocaine gel in the urethra, both for lubrication and anaesthesia (29). This is sufficient anaesthesia for those where only cystoscopy or a small biopsy is performed. In cases where multiple or deeper biopsies are needed, additional anaesthesia is administered. One method is to instil 60 ml lidocaine (20 mg/ml) into the bladder at least ten minutes prior to the procedure (25). This method provides enough analgesia for multiple biopsies and/or fulgurations at multiple sites in the bladder and is easy to perform. If solitary and/or larger tumours are found, a submucosal injection with local anaesthetic can be used as was shown by Engberg et al in 1983 (30). Injections can be made with 1-2 ml at multiple sites around the base up to 20 ml, which also provides a hydro-dissection of the tumour from the underlying tissue. This technique can be used for TURB in the office setting, for selected patients (31, 32). At our department we have over 20 years of experience of bladder tumour treatment under local anaesthesia managing bladder tumours up to a few centimetres (33). The technique is not suitable for all tumours, such as those located laterally or in the dome of the bladder as this requires more manipulation of the instrument, which can cause pain and discomfort, especially in men. Brausi et al used additional injections of lidocaine in the bladder neck to increase the tolerability and their results showed that 60% of the patients perceived no or mild pain (31). Nearly all patients at our department presenting with a bladder tumour under a few centimetres are offered surgery under local anaesthesia when the urologist finds it appropriate. In our experience, most patients accept, as the option of coming back another day for general surgery and maybe an overnight stay sounds less appealing. Usually no catheter is inserted after the procedures under local anaesthesia and the patients can leave the clinic with standard postoperative information (32).

The benefits of treating patients under local anaesthesia are multiple. As mentioned above, no hospital stay is needed and it is less time consuming compared to surgery under general anaesthesia, which also can cause side-effects. In elderly patients or patients with severe comorbidity, general anaesthesia may be associated with higher risks. Another benefit is the cost reduction, in one study reported to be 70% (33).

NEW TECHONOLOGIES

To enhance visibility during cystoscopy and TURB, new technologies have been developed. Photodynamic diagnosis (PDD) or fluorescence cystoscopy requires the instillation of a solution in the bladder, hexaminolevulinic acid (HAL) or 5-aminolaevulinic (5-ALA) prior to the planed examination which is then performed using blue-violet light (380-440 nm). PDD has a higher sensitivity for detecting BC and is reported to reduce the numbers of recurrences at follow-up (34). The specificity is lowered by the fact that HAL and 5-ALA also is absorbed by inflammatory lesions, both acute and chronic, which hampers the evaluation of patients treated with instillations, and can also show false positivity at certain angles. The studies on PDD has to a great extent been sponsored by the industry. The Swedish guidelines advocates the use of PDD in newly diagnosed patients where cystectomy is not the obvious treatment, positive cytology in the absence of visible tumour, multiple tumours and at follow-up for Cis or multiple tumours (4).

Narrow band imaging (NBI) is another method of enhancing the detection of BC and is based on filtering white light into two bandwidths, 415 and 540 nm. The light is absorbed by haemoglobin, and due to the fact that most BC′s are highly vascularised it enhances the contrast between tumour and normal mucosa. Recent findings suggest that due to increased detection the recurrence rate is lowered, but only in low-risk patients (35). NBI has the same limitations as PDD, but has the advantage of requiring no prior instillation and is incorporated in newer equipment. Neither the EAU nor Swedish guidelines recommend NBI (4, 9).

INTRAVESICAL INSTILLATION
SHORT HISTORY OF BCG

BCG is a tuberculosis vaccine that was developed in the early twentieth century by Albert Calmette (1863-1933) and Camille Guérin (1872-1961). *Mycobacterium tuberculosis* and *mycobacterium bovis (m bovis)* are known as tubercle bacilli, which cause tuberculosis (TB) in mammals. In 1908 Calmette, a bacteriologist, started working with Guérin, who was a veterinarian, at the Pasteur Institute in Lille, France. Together they isolated a strain of *m bovis* from an infected cow and after work with the growth medium they had grown a less virulent strain in 1915. They administrated this early vaccine to several cows, demonstrating its protection against TB (36). Further work showed that the strain was

nonvirulent but genetically stable and they named it BCG. After 231 passages they began animal studies, and in 1921 administrated it orally to a child, whose mother had passed away from TB. The child showed no adverse reaction and strong with confidence Calmette and Guérin continued their work and another 217 Parisian children received the vaccine, without complications. The results were published in 1924 and the mass production was initiated by the Pasteur Institute. Due to lack of methods to preserve the live cultures, it required continuous passages, which resulted in a variety of strains until the sixties, when new technique for preservation emerged. The strains were named after the site of origin and manufacturer e g, Danish, Chicago (Tice), Toronto (Connaught) and RIVM (Holland) (36).

The connection between cancer and BCG was observed in 1929, when Pearl in an autopsy study found that the frequency of cancer was lower in those with TB. The discovery was interesting but a year later, a tragedy occurred in Germany, which brought further investigations to a halt at that time (36). In Lübeck more than 70 children died following BCG-vaccination, unfortunately the vaccine had been contaminated by a virulent strain of *m tuberculosis* due to a laboratory error. In the fifties, research was resumed on animal studies by Lloyd Old, who found that BCG activates macrophages to inhibit or destroy cancer cells (37). By the late 1960s, clinical trials on acute lymphoblastic leukemia and melanoma showed promising results and by 1971, Berton Zbar published further studies (38). It was Zbar who defined the criteria for successful BCG therapy; close contact between the tumour cells and BCG, a host capable of adequate immune response, adequate numbers of viable BCG bacilli, a limited tumour burden and no serious side-effects. Encouraged by this, Morales conducted a small study, published in 1976, on seven patients (39). Initially there were nine patients but two were excluded due to incomplete follow-up. Five of the patients were included for recurrence prevention, the rest due to residual tumour. Despite the few numbers, the results were impressive, showing only one recurrence during 41 patient months, compared to 22 in 71 patient months before the study. This work lead to further randomized studies in the USA (40).

INTRAVESICAL TREATMENT WITH BCG

Treatment with BCG is recommended in patients with intermediate- and high-risk tumours, although the optimal schedule for treatment is yet to be established. BCG has been shown to prevent recurrences of NIMBC

and eradicate Cis, but its role in preventing progression is still under debate (41). BCG is first given as an induction course, consisting of six weekly instillations, starting 2-3 weeks after TURB, with a dwell time of one to two hours. The rationale behind this schedule is that when Morales performed the study from 1976, the vaccine was packaged in vials of six, and he found that the side-effects subsides within a few days (36). Maintenance is recommended by the EAU for intermediate-risk tumours for one year, given for three weeks at months 3, 6 and 12, and in high-risk tumours for three years, with additional treatment for three weeks at months 18, 24, 30 and 36 (9). Oddens et al evaluated whether a one-third dose is still as effective as full-dose and if this could reduce the side-effects. Unfortunately the toxicity was not lowered with the lower dose, even if the effect did not seemed to be altered (42). Maintenance for up to three years is recommended for maximum efficacy, but has been questioned, as Herr et al reported in 2011 (43). Their figures after induction only showed similar results compared to those receiving maintenance, although 32% received additional induction therapy. Another study showed that if the three and six month cystoscopy after induction therapy showed no tumour, no further maintenance was required, although some patients received three additional weekly instillations (44).

The contraindications for BCG-treatment are TURB within two weeks, traumatic catheterization, haematuria, urethral stenosis, active TB, prior BCG sepsis and immunosuppression, although there is retrospective evidence that immunocompromised patients still safely can be treated with BCG (41).

BCG-TREATMENT IN SWEDEN

The Swedish guidelines are in accordance with the EAU, recommending maintenance after the induction (4). However, in the latest edition from 2015 there is a reference to the study by Holmäng, where a total of nine instillations is advocated (44). There is an emphasis on individual assessment on those with increased risk for progression. In patients where a recurrence is found at the first cystoscopy after BCG, there are still some patients who could benefit from further instillations, but for T1 and Cis, the risk for progression is high and early cystectomy should be considered.

In Sweden the aim is that a minimum of 75% of patients with T1-tumours should be treated with intravesical instillations, but the most

recent reports from 2014-15 show that only 50-60% were treated (3). A retrospective, population-based study showed that BCG is underused especially in patients 75 years or older and those treated in low-volume hospitals (45). The study was performed on patients treated during 1997-2006, and the latest national reports shows increasing numbers, and hopefully further improvements can be achieved in the following years.

BCG-REFRACTORY TUMOURS

There are at present no accurate means of predicting which patients benefit from BCG-treatment until the first cystoscopy at three months. In patients with primary Cis who present with Cis at three months, an additional BCG-course may achieve a complete response in more than 50% of cases (9). If there is Cis again at six months, the tumour should be considered as BCG-refractory. Other circumstances where BCG should be considered as failure are; if a MIBC is detected during follow-up, a HG NMIBC is present at three months, a HG tumour appears during BCG-treatment and a HG recurrence after BCG-treatment. Patients who have HG recurrences more than one year after completed maintenance or have a LG recurrence during treatment are not considered BCG-refractory. There is currently no evidence that a change to another intravesical agent will yield a better outcome in these patients and they should be offered cystectomy.

SIDE-EFFECTS OF BCG TREATMENT

In a large EORTC study over 60% of the BCG-treated patients reported local side-effects (46). The most reported symptoms are cystitis and frequency, and attempts have been made to decrease the rate by giving the tuberculostatic agent isoniazid, although with no success and the unfortunate side-effect of transient liver function disturbances (47). Another study used ofloxacin as prophylaxis and showed that the adverse events were reduced although the study was small, and long term efficacy was not studied (48). Further efforts have been made by using oxybutynin to decrease the symptoms but rather disappointingly the treated patients had worse outcome, and lowering the dose has not shown any effect either (49). Although troublesome for the patient, cystitis or frequency does not necessitate the cessation of BCG, although postponing the treatment is recommended, with or without antibiotics and/or NSAIDs. A few percent report epididymitis/prostatitis where the recommendation is

to suspend the BCG-instillations and start treatment with anti-TB agents (41). Haematuria is also one of the more common side-effects where the BCG-treatment should be delayed until the urine clears. A few percent also report skin rash, where in severe cases, treatment should be suspended.

Systemic side-effects are seen in 30% where the most common are general malaise, fever, chills and flu-like symptoms (46). There are many reports of more rare, and more severe systemic side-effects such as lung infection, BCG-sepsis, mycotic aneurysms, hepatitis and bladder contracture (50).

Most side-effects occur within the first year of treatment and some have claimed that it is a common reason for stopping the instillations, but it could not be confirmed in a large EORTC study, where only 7-8% stopped due to side-effects, with no differences between those receiving full or one-third dose (42). One study reduced the dwell-time to <30 minutes in patients who had pronounced side-effects after the preceding instillation and found a reduction in the reports on fever, chills, dysuria and overall time to recovery, but no difference in frequency or haematuria (51).

INTRAVESICAL CHEMOTHERAPY

There are several other solutions used for intravesical instillations, such as mitomycin or epirubicin, which are chemotherapeutic agents. They act by destroying circulating tumour cells after TURB and are recommended in some patients as a single immediate instillation (52). Some data suggest that postoperative irrigation has a similar effect (52). This treatment only prevents recurrences if there is no history of more than one recurrence per year and does not alter the progression rate. Intravesical chemotherapy is also recommended as maintenance, and several studies have been performed to evaluate optimal efficacy. Unfortunately, the optimal schedule, dose, interval or specific chemotherapeutic agents remain unclear (53). The challenges in establishing optimal treatment is partly due to the fact that the studies use different schedules, chemotherapeutic agents and doses which makes conclusions difficult. The existing data suggest that if maintenance is used, a maximum of one year is sufficient to prevent recurrences.

In Sweden, 40 mg mitomycin diluted in sterile water is recommended, dwell time 1-2 hours, once a week for six to eight weeks (4).

The benefits of intravesical therapy are not equal to BCG, as it does not reduce the progression rate. However, new techniques with device-assisted chemotherapy have been developed and suggest increased an efficacy, but should still be considered to be at an experimental stadium so far (9, 54).

SIDE-EFFECTS OF INTRAVESICAL CHEMOTHERAPY

The most studied intravesical chemotherapeutic therapy is mitomycin, but the side-effects appear to be similar for the different agents. The most reported symptoms are gross haematuria, dysuria, frequency, urgency, suprapubic discomfort and pelvic pain, which collectively are known as chemical cystitis (55). In some studies it is reported in up to 25% of the cases but the figures are uncertain as many studies are inconsistent in reporting side effects. Other side-effects are skin rash, malaise, perivesical fat necrosis, fistula formation and necrosis of corpus spongiosum. Some side-effects can persist for months or even years after treatment, such as bladder wall ulcerations and calcifications, but these are not always symptomatic (55).

SYSTEMIC TREATMENT
RADICAL CYSTECTOMY

Radical cystectomy is usually performed when muscle invasion has been found, but can be a treatment option in certain cases of NMIBC. At cystectomy the bladder is removed, usually with lymphadenectomy, and a urinary diversion is performed. In Sweden approximately 87% receive an ileal conduit and 11% an ortotopic bladder substitute (56). Some patients with NMIBC have a higher risk for progression; concomitant Cis, multiple T1 and/or G3-tumours, residual T1 tumour at second resection, deep infiltration in the lamina propria, the presence of LVI and micropapillary tumours (24, 57). These patients should at an early stage be informed of the higher risk for progression and be presented with the alternative of primary cystectomy. On the other hand, some argue that certain patients respond well to local therapy with TURB and BCG, and have a more favourable prognosis, in which cases an assessment could be made at the three and six month controls (44, 57). Individual assessment

is also of great importance, as some patients have severe comorbidity and therefore are not suitable for greater surgery.

Radical cystectomy is associated with complications and since 2013 all cystectomies and complications are reported to a national registry, which is mandatory. A study of the cystectomies performed in Sweden during 1997-2002 was published in 2012, including those operated on within three months from diagnosis and were M0 (58). A comparison between the study and the latest registry report reveals that the proportion of ileal conduit has increased from 63 to 87% and ortotopic bladder substitute decreased from 22 to 11% (56). The median perioperative blood loss has decreased from 2313 ml to 700 ml, and the percentage of reoperations decreased from 24 to 12%. The overall 90 day mortality has been fairly constant at 5% over the last decades.

SYSTEMIC CHEMOTHERAPY AND RADIATION

The purpose of neo-adjuvant chemotherapy is to reduce micro-metastasis and to increase the long term survival for those with MIBC (59). There are several chemotherapeutic agents used, and usually a combination of different agents is used, often with cisplatin. As the treatment is associated with potential side-effects, the patients should have a good performance status and normal kidney function.

Radiation therapy can be an option for patients not fit for surgery or for those who refuse cystectomy. The treatment is intense and side-effects are common, with symptoms from the bladder and rectum. Radiation shows decreased cancer specific survival, compared to cystectomy (60).

RECURRENCE AND PROGRESSION

In clinical practice, deciding the correct treatment for each patient comes with several challenges, as it depends on multiple factors. NMIBC has a high recurrence rate and the time from TURB to an intravesical recurrence is called recurrence-free survival. The progression has previously been poorly defined as some have considered a recurrence with a higher grade as a progression and some as an increase in stage. In 2014, a proposal was made by the International Bladder Cancer Group (IBCG) to define progression as an increase in stage from Cis or Ta to T1, development of T2 or greater or lymph node disease (N+) or distant metastasis (M1) or an increase in grade from low to high (61). The time

from diagnosis of NMIBC to progression is called progression-free survival.

In Sweden all patients with primary BC have been included in the Swedish National Bladder Cancer Registry (SNBCR) since 1997 where information on TNM, grade (according to WHO 1999) and primary treatment are reported (3). Since 2009 a questionnaire has been distributed annually to the units treating NMIBC in order to provide follow-up data on recurrence (confirmed by histology or treated by fulguration) and progression (defined as MIBC and/or regional lymph nodes larger than 2 cm or the presence of histologically verified lymph node metastasis or distant metastasis) occurring within five years after diagnosis.

A study based on 5839 patients with NMIBC diagnosed between 2004 and 2007 was conducted in 2015, based on SNBCR (62). Overall, recurrence was reported in 50% of the patients with variations from 37-56% in different regions. The statistical analyses showed that recurrence was associated with TaG2 and T1 disease, no intravesical treatment and treatment in certain regions. Nine percent of the patients progressed, associated with older age, higher stage and grade, but the risk decreased with intravesical therapy. The results showed unexpectedly large differences in local recurrences between the healthcare regions. Some plausible reasons are discussed by the authors such as differences in intravesical treatment and a lower rate of T1 tumours in the regions with fewer recurrences. There are also differences in the incidence of BC between the regions, with a nearly three-fold higher incidence in the Southern region compared to the north, where the relative risk of recurrence is lower although there is a higher risk of progression. The authors speculate whether there could be some explanations found in regional differences in smoking habits, body mass index as well as unmeasurable biological disparities. Hopefully further studies will reveal more answers and show improved results with less regional differences.

RISK STRATIFICATION

The most used models for calculating both the risks for recurrence and progression have been developed by the EORTC and the Club Urológico Español de Trataimento Oncológico (CUETO). The EORTC risk score was presented in 2006 and based on seven randomized studies including 2596 patients with stages Ta, T1 or Cis (24). Although many patients were included, there were some differences in the treatment schedules in

the studies, a total of 78% received intravesical instillations but only a minority of them BCG. A single tumour was seen in 56% of the patients, 18% reported to be more than three centimetres in size and 42.7% had stage T1. In this population recurrences were seen in 47.8% of the patients and progression in 10%.

A few years later the CUETO scoring model was reported, based on four randomized studies including 1062 patients with stages Ta, T1 and Cis (63). All patients received intravesical BCG, with the intention of six additional instillations following induction, although only 73% received more than 10 instillations. A single tumour was seen in 49% of the patients, 45% over three centimetres in size and 77% had stage T1. They reported recurrences in 32% of the patients and 13% progressed. Both studies used progression to stage T2 as definition of progress and based the grading on WHO 1973.

The EORTC scoring system is based on findings of number of tumours, tumour size, prior recurrence rate, T category, concomitant Cis and grade. The CUETO scoring system is similar although other factors such as sex and age are also incorporated there.

A large retrospective, multi-institutional study showed that both scoring systems tend to overestimate both recurrence and progression, demonstrating the urgent need of more accurate tools (17). Another report from 2014, which evaluated the two scoring systems concluded that both reasonably can predict progression while prediction of recurrence was less accurate, thus concluding that other means for prediction are needed (64).

FOLLOW-UP

Patients with NMIBC are recommended follow-up with cystoscopy on a regular basis, as no non-invasive method has been proven to replace it. Early detection of MIBC and HG-tumours is essential because any delay in diagnosis and treatment worsens the prognosis. Low-risk tumours pose no immediate danger to the patients and early detection is less important, some authors propose expectant management in selected cases, as these tumours have a low growth rate (65, 66). There is an increased risk of tumours in the upper tract for those with multiple or high-risk tumours in the bladder. The findings at first cystoscopy at three months are important prognostic indicators of recurrence and progression. The Swedish guidelines are very similar to the EAUs recommendations and are

summarized below (4, 9). The first cystoscopy is planned three months after TURB or six weeks after completed induction instillation therapy.

For PUNLMP and TaG1 tumours that are solitary, less than three centimetres and no recurrence at three months the recommendations are that the subsequent cystoscopy should be after nine months and if negative, yearly up until five years. For PUNLMP, follow-up can be terminated after one year.

For TaG2, and TaG1 tumours that fulfil at least one of: multiple primary tumours, tumour size >3 cm or recurrence at first follow up, the first cystoscopy should be at six weeks after instillation therapy. Then at another three months and then twice a year for two years and annually in years 2-10.

Cis, TaG3 and T1 tumours are recommended follow-up every three months with cystoscopy and cytology for two years, then twice a year up until five years. Thereafter long term follow-up on an individual basis since these patients have a higher risk of recurrence and progression even after many tumour-free years.

When a recurrence is detected, follow-up should resume from the beginning again.

CT is not recommended in Sweden during follow up, although it is stated that it should be performed generously in high risk patients. The EAU guidelines are more rigorous and recommend yearly upper tract imaging.

COST

According to a review in 2003 the cost per patient with BC from diagnosis to death is the highest of all cancers (67) The overall cost of BC patients differs between countries due to variations in routines and health care systems although the need of regular follow-up accumulates over time to great costs (68). An evaluation of the diagnosis, treatment and follow-up stated that more studies are needed in certain areas to calculate cost effectiveness, including optimal BCG-maintenance schedule, urinary markers and the use of PDD (68). In a Swedish publication it was reported that the care concerning cystectomies accounted for 34%, transurethral procedures for 40% and follow up cystoscopies for 13% of the total cost (69). They found that the cost for transurethral resections and extirpations were five times higher when the patient was hospitalized compared to day-care surgery and thus economic savings could be

achieved in increasing the number of patients treated on an outpatient basis.

SURVIVAL

There are several ways of estimating the survival. The overall survival are those with, in this case BC, that still are alive at a certain time. The cancer specific survival are those with BC that still are alive at a certain time after diagnosis, but excluding those who have died from other causes. The latest report from SNBCR shows that the five-year overall survival has increased from 54% to 59%, for those diagnosed between 1997-2010 (3). These figures are crude as they include all patients diagnosed with BC, but generally both the cancer specific and the overall survival rates increases with LG and low stage tumours. In the report from 2015, the five-year cancer specific and overall survival for those with pTaG1 was >95 % and 79% and corresponding figures for pT1G3 were 78% and 58%. The lowest overall survival is seen in those with metastatic BC with figures of <20% five years after diagnosis. There are however gender related differences. A study that published data from the SNBCR showed that women have a lower cancer specific survival than men, and in spite of women having a higher rate of aggressive tumours, a smaller proportion received optimal treatment (70). The reasons are probably complex and the authors indicated in their final remarks that no conclusions could be drawn from the existing data.

AIMS OF THE THESIS

The treatment of NMIBC have not altered in any significant way during the last few decades. Although technical innovations have facilitated diagnosis and follow-up, the health care systems have not changed accordingly. BCG improved the treatment with fewer recurrences but the optimal regime is still unknown after more than 40 years of general use.

Ethical approval was granted from the local ethical committee for all four studies.

The overall aim of the thesis was to investigate aspects of treatment and follow-up of NMIBC.

PAPER I

To report a late BCG complication previously not reported in the literature.

PAPER II

To investigate the incidence of recurrence and progression in BCG-treated patients who had been tumour-free for five years.

PAPER III

To prospectively report on the size, number and histopathology of new and recurrent bladder tumours.

PAPER IV

To prospectively register self-reported pain levels at cystoscopy and cystoscopy with biopsies and/or fulguration in an office-based setting.

PATIENTS AND METHODS

PAPER I

Between 1986 and 2008 a total of 858 patients were treated with intravesical BCG at our department at Sahlgrenska University Hospital. Among the treated patients we identified 12 patients who developed a late BCG infection with a focal lesion in the bladder. An additional case from a small county hospital was also included. The BCG-treatment consisted of induction therapy, with six weekly instillations and up until 1996 most patients received monthly maintenance up to a year. The maintenance was thereafter reduced to three weekly additional instillations. The dwell time was two hours except for the patients with bothering side-effects, where it was reduced to 1-30 minutes.

We used the Danish strain 1331 (Statens Seruminstitut, Copenhagen, Denmark) in 80 patients until 1993 which then was replaced by BCG-Tice (OncoTice®, Organon Technica, Boxtel, Belgium), which was used in 454 patients. Between 2003-2008 a total of 320 patients received BCG-RIVM (Medac GmbH, Wedel, Germany). In 2008, four patients were treated with a mixture of the two latter strains.

The follow-up after the induction therapy consisted of a first cystoscopy after six weeks including bladder wash cytology. Subsequently, follow-up was performed at 3-6 months intervals for 2-3 years and thereafter annually.

If a suspicion of BCG infection arose, the patient was equipped with three flasks and instructed to sample early morning urine on three different days. The urine was sent for mycobacterial culture, which had to be specified on the referral sheet.

The biopsies performed were embedded in paraffin and stained with a polyclonal antibody (Ab), primary Ab tuberculosis, and in some cases Ziehl-Neelsen staining was used which detects acid-fast bacilli.

For comparison of differences between the different strains and infection rates, the chi-squared test was used.

PAPER II

All patients with NMIBC treated with at least one intravesical BCG-instillation in the Gothenburg area between 1986 until 2003 were included, n=542, except for a few treated in a private hospital.

We used the Danish strain 1331 (Statens Seruminstitut, Copenhagen, Denmark) until 1993 which then was replaced by BCG- Tice (OncoTice®, Organon Technica, Boxtel, Belgium). Since 2003 we use BCG-RIVM (Medac GmbH, Wedel, Germany). The intention was to give all patients induction therapy and then maintenance, provided they had a negative first cystoscopy at three months. Maintenance was given in 39% of the cases and consisted of monthly instillations up to a year until 1996, and thereafter three weekly instillations. For recurrences another three to six weekly instillations were sometimes given. Some patients with bothering side-effects had the dwell time reduced or treated with a lower dose.

Follow-up for the first 2-3 years consisted of cystoscopy and cytology every 3-6 months and thereafter yearly evaluations at least for five years when some urologists prolonged the interval to every other year. The follow-up was continued until 10-20 tumour-free years, although for patients in poor general condition it was terminated earlier. Upper tract imaging was not performed on a regular basis, only in cases with gross haematuria or unexplained malignant cytology. The clinical records for those still alive were updated in 2011 and for the deceased, death certificates were retrieved when needed.

Recurrence was defined as a tumour in the lower or upper urinary tract with histopathological evidence of urothelial malignancy or positive cytology. A fulgurated lesion was also defined as a recurrence. Progression was defined as stage T2 or higher or evidence of metastatic disease. Patients were censored on the date of surgery if they underwent cystectomy without prior progression or if intravesical chemotherapy was given, on the date of the first instillation.

For the statistical comparison between the groups, traditional variables were analysed using the Fisher exact test for dichotomous variables, and the Mantel-Haenszel chi-square test for ordered categorical variables and the Mann-Whitney U-test for continuous variables. For time to recurrence, Kaplan-Meier curves were constructed and differences between groups were tested with the log-rank test. For continuous variables, Cox proportional hazard regression was performed to find significant effect on time to recurrence.

PAPER III

We performed a prospective, population-based study of all patients presenting with a suspected malignant tumour in the bladder at our department during 15 consecutive months from the 1st of January 2010 (population 656 720 in 2010). The majority of all TURBs in the city are performed at our hospital, the remainder at two smaller, private hospitals.

The tumour size, number and whether it was new or recurrent was documented and a database was created. To estimate the size, which was recorded in three dimensions when possible, we used the instruments as a guide (resection-loop 7 mm, biopsy forceps 4.5-5 mm depending on manufacturer, fulguration electrode 1.5 mm). The database was updated with results from the histopathological report, according to the TNM 2009 system and WHO 1999.

We separated the groups into urothelial tumour, including PUNLMP, other malignant tumour, atypia, inflammation and benign/normal. Atypia was an intermediate group, combined with bladder wash cytology where there was dysplasia although not enough for a malignant diagnosis. The histopathological examinations were performed by one experienced pathologist who re-evaluated all T1 tumours at the weekly conferences held between the authors and the pathologist.

All TURBs, biopsies and/or fulgurations were recorded, but any repeat resection of the same tumour is excluded from calculation. For calculation of tumour volume we used the formula for an ellipsoid and the chi-square test for comparison between the groups (71).

PAPER IV

We prospectively collected our data from the 1st of January 2010 until the 31st of March in 2011 from patients scheduled for cystoscopy at our outpatient clinic. The majority was follow up for BC, although a large proportion of the patients were referred due to gross haematuria.

Exclusion criteria were if any other intervention was performed at the same visit (dilatation of the urethra, insertion or removal of stents, transrectal ultrasound or lithotripsy) or when both flexible and rigid instrument were used.

All patients received 2% lidocaine gel into the urethra a few minutes prior to the procedure, 20 g for males and 10 g for females. The cystoscopies were performed in the lithotomy position and the patients were able to follow the procedure on the screen. Men were examined with either a flexible or a rigid instrument and women with rigid only.

The examinations started as diagnostic cystoscopies and if a small, suspected tumour was seen, the patient was offered immediate removal. The intention was always to take cold-cup biopsies before fulguration. Some patients received additional local anaesthesia, either with instillation of 60 ml of 2% lidocaine or submucosal injections of 1-30 ml of 1% lidocaine, at the discretion of the urologist. Medium-sized tumours were in some cases operated by the most experienced urologists with a Ch 24 resectoscope.

Immediately after the procedure, the patients were asked to evaluate their pain levels, using a Visual Analog Scale (VAS) score and to answer the question "if you have to go through the same procedure again, would you rather do it in the same way or under general anaesthesia?"

A database was created including age, gender, anaesthesia, VAS-score, type of instrument, indication for the procedure, tumour size and number. The records were later completed with the histopathological findings, using the TNM 2009 and WHO 1999.

Number and percentage were given for categorical variables and mean, standard deviation, median and range for continuous variables.

Since the same patient might appear more than once in the material, Generalized Estimating Equations models were used. For analyses of prediction of pain score the same models were used with a log-link function. Descriptively, the estimated values with 95% Confidence intervals (CIs) were given per group as well as Risk Ratios with 95% CIs and p-values between groups. All tests were two-tailed and p-values <0.05 were considered statistically significant.

RESULTS

PAPER I

The median age at the first BCG-treatment was 77 years (range 45-86 years) for the 13 patients compared to a median age of 73 years for the whole cohort. They were all males despite the fact that the whole cohort included 29% females. Eight out of the 13 patients had at least one concomitant disease and three had previously been treated for lung TB. All patients had HG tumours and 54% had stage T1, compared to 25% T1 in all BCG-treated patients.

The first three patients were treated with BCG-TICE and the others with BCG-RIVM. Thus three out of 454 (0.7%) treated with BCG-TICE and ten out of 320 (3.1%) treated with BCG-RIVM developed a persistent BCG infection in the bladder, p<0.01. The number of instillations given was 6-9, with a mean dwell time of 95 minutes (range 1-180).

The median time from the first instillation to a visible lesion in the bladder was 8 months (range 2-34), from the last BCG-instillation to a positive urine culture 14 months (range 3-34) and from a visible lesion to positive urine culture 9 months (range 0-29). Not all patients had a positive culture at first, although all showed positive results when the culture was repeated. All patients had side-effects, seven of them transient, but for six patients the symptoms persisted with frequency, urgency or dysuria (data from one patient missing).

The lesions were solitary and always at the site for previous resections, although seven of the patients had had multiple tumours and hence several resection sites. The size varied from 10-50 mm in diameter and were triangular or oval in shape, the majority with a yellow central area and slightly raised, hyper-vascular edge, **Figure 6**.

Bladder wash cytology was analysed in all cases; in one case only normal cells were found, four had atypical findings and the rest showed inflammatory cells. Six of the patients underwent TURB or biopsies to exclude malignancy and in five patients the histopathological report showed granulomatous inflammation and an ulcer in one. Only two of the five inflammatory lesions were positive for Zielh-Neelsen and TB antibodies.
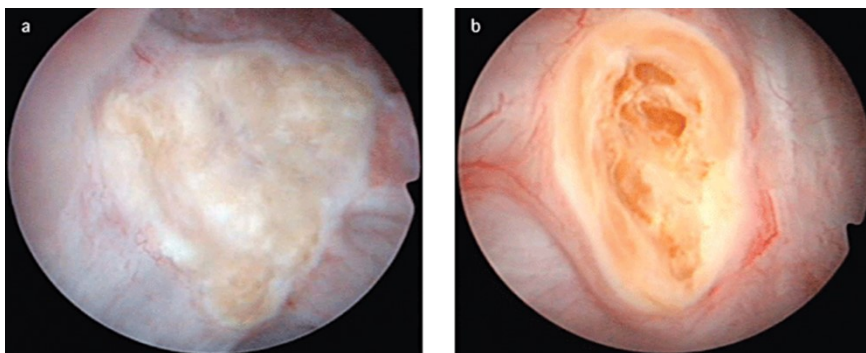
Figure 6. Macroscopic appearance of BCG lesions. Still from cystoscopy.

None of the patients had symptoms of disseminated infection and all had urinary cultures positive for *m bovis,* which was sensitive to rifampicin and isoniazid. Eight patients were at the time for the study treated with these antibiotics for six months in combination with pyridoxine, which reduces the risk of neuropathic side effects. All eight had negative urinary cultures for *m bovis* 2-4 months after treatment.

One patient experienced deteriorated renal function and rifampicin was replaced by ciprofloxacin, to which the strain was sensitive. Another patient experienced several side-effects and the treatment was discontinued after six weeks. One patient did not receive tuberculostatic treatment as he underwent radiation therapy for another malignancy.

Out of the eight patients who had completed the treatment, five no longer had a visible lesion in the bladder at follow up. The previous lesions were replaced by a dark red area in two patients and in one the lesion was still visible although smaller in size. The remaining patients had not yet been submitted to follow up at the time for the study.

Four of the patients appeared to have a reduced bladder capacity although it was not studied in a systemic way, and three had persistent frequency. These symptoms were not affected by the tuberculostatic treatment.

Nine of the patients remained recurrence free during the study period, three had recurrences of TaG1-G3 tumours and one progressed to MIBC

and underwent cystectomy. Three patients died of other causes than BC and one of an unknown cause. The median follow up was 43 months (range 15-100).

PAPER II

The median age at the induction of BCG-treatment of all 542 patients was 72 years and 77 % were male. The recurrence rate per year was calculated from BCG-induction to the last follow up and was 0.36 recurrences per year for the whole cohort. During the first five years, 57 patients (10.5%) died of BC and 96 (17.7%) died of inter-current disease and corresponding numbers for years 6-25 was 32 (5.9%) and 150 (27.7%). At the end of the study a total of 207 (38.2%) patients were still alive.

There were 338 patients without a tumour-free period of five years, and of them 24% progressed to at least stage T2 and 8.9% who were diagnosed with an upper tract tumour.

A total of 204 patients had a tumour-free period of at least five consecutive years at some point after the first BCG-treatment although 74 patients (36.3%) had recurrences during the first five years. Age at the time for BCG-induction was the only variable that had a prognostic significance for a tumour-free period of more than five years, p<0.0001.

Of the 22 patients (10.8%) with late recurrences, 17 had tumours in the bladder, one in the urethra, three in the ureter and one in the renal pelvis. The recurrence rate for the 204 patients, calculated from after the tumour-free period and ending on the date of the last follow-up, was 0.04 recurrences per year. Of the 17 with BC recurrence, 11 were small sized G1-tumours and five patients recurred with Cis. Two of the latter underwent cystectomy due to BCG-failure and were still alive at the end of the study as well as the third and fourth patient. The fifth patient died of stroke 20 months after the additional BCG. One of the 17 patients with BC recurrence progressed to stage T2 and received systemic chemotherapy and cystectomy but died of disease.

At 10 years after the first BCG-instillation, 82.3% of the patients with initial TaG1-G2 tumours and 91.3% of patients with initial TaG3/Cis/T1 tumours remained tumour-free. The corresponding figures at 15 years are 65.4% and 86.0%, respectively.

Fifty-nine of the 204 patients received BCG-treatment for the primary tumour, and only one of these (1.7%) had a late recurrence. For the remaining 145 patients, who were treated after multiple recurrences, 21 patients (14.5%) had late recurrences. Primary versus recurrent tumour was the only variable that had a statistical significance for late recurrence, p=0.02.

PAPER III

During the 15-month period a total of 579 transurethral operations were registered in 432 patients. The median age was 74 years (range 25-95) and 69% were male. Tumour size was missing in 25 cases either due to difficulties in estimating the borders of the suspected lesion or when random biopsies were taken due to malignant cells in bladder wash cytology. For every patient with a newly diagnosed BC, an estimated ratio of 1.3 operations for recurrent tumours was recorded. The ratio increased to 1.4 when fulgurated lesions were included and to 1.5 when the atypia group was included.

A total of 248 operations were performed in 233 patients with no previous history of BC. Repeat resections were performed in 13 patients (15 operations). There were 167 confirmed urothelial tumours and the median size of those was 20 mm and 61% were solitary.

For suspected recurrences a total of 326 operations were performed in 229 patients. Repeat resections were performed in seven patients (eight operations). Sixty-eight patients were treated for at least two recurrences during the period. There were 214 confirmed urothelial malignancies and the median size of those was 10 mm and 45% were solitary.

In both groups of suspected tumours, 22% were either benign or inflammatory lesions.

The number and distribution of the histopathological findings are shown in **Table 2**. Atypia includes lesions that are neither benign nor malignant.

Table 2 Number of suspected new and recurrent tumours

Histopathological diagnosis	No New (%)		No Recurrent (%)		Totals
Urothelial malignancy[1]	167	72	214	66	381
Other malignancy[2]	8	3	-	-	8
Atypia	8	3	26	8	34
Inflammation	34	15	45	14	79
Benign/normal	16	7	26	8	42
No histology	-	-	15	5	15
Totals	233	100	326	100	559

[1]Includes Cis

[2]Primary tumour in colon, prostate, cervix uteri or lymphoma

Of all the recurrent urothelial tumours, seven percent were three centimetres or larger compared to 46% of the new. The differences between tumour sizes are shown in **Figure 7**.
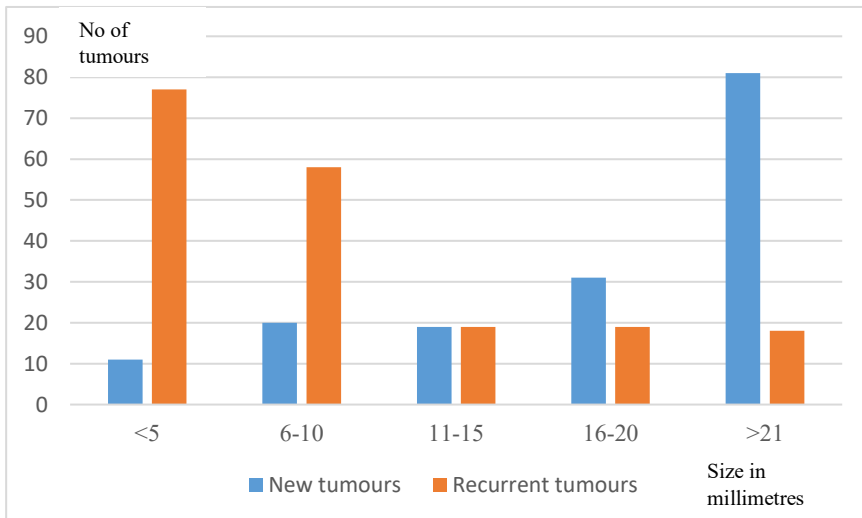
Figure 7. Relationship between tumour sizes of new (n=167) and recurrent (n=214) urothelial tumours.

We measured the tumours in three dimensions and calculated the tumour volume. For the newly diagnosed tumours, 68% had a volume ≥1 ml and the corresponding value for the recurrent was 12% (p <0.001).

PAPER IV

Out of 2005 visits, 433 were excluded, thus yielding 1572 evaluable visits. There were 1314 cystoscopies with a median patient age of 70 years (range 16-100), 65% were male. A total of 258 biopsies and/or fulgurations were recorded with a median age of 75 years (range 25-95) and 66% male.

Severe pain (VAS 7-10) was reported in 2.4% in the cystoscopy group and 7% in the biopsy group. There were no differences between males and females, only between the groups, where the biopsy groups scored more than 80% higher values.

One percent of the patients in the cystoscopy group (with a VAS range 2-10) and 7% in the biopsy group (VAS range 3-10) stated that they would rather repeat the procedure under general anaesthesia.

The median VAS score in the cystoscopy group was 1, and 86% reported VAS 0-3. Corresponding figures for the biopsy group was 2 and 65%.

In the biopsy group a total of 40% received additional anaesthesia with lidocaine instillations and/or submucosal injections, although they had the same VAS distribution as the other patients. Eight TURBs were performed (one showed Cis and the others TaG1-3) and 15 out of the 258 were fulgurated only. The histopathological findings showed 59% urothelial tumours, 21% inflammation, 10% benign, 9% atypia and 1% other malignancy.

DISCUSSION

PAPER I

This paper describes large mycobacterial lesions in the bladder with persisting infection in BCG-treated patients, findings which have not been reported previously. There have been some reports of scattered granulomata and multiple ulcers as well as disseminated BCG-infections (72, 73).

Urine cultures after BCG-treatment are positive for mycobacteria in 16% of the patients at day six following an instillation and Bowyer et al found 3% positive cultures at 16.5 months (74). Cultures of bladder biopsies are sometimes performed but seem to yield less positive results. There are also reports on PCR techniques showing that BCG DNA can be detected in the bladder wall in one third of the patients at two years, although the significance of this remains unclear (74).

Studies and case reports of persisting BCG-infection are surprisingly only on male patients. This could be a random finding although it also leads to speculation if the prostate could act as a reservoir, harbouring bacteria. A study from 1997 found that in BCG-treated patients subjected to cystoprostatectomy, 75% had a granulomatous inflammation in the prostate, which we find in many of our patients as well, although it was not studied in the present report (75). One may also speculate whether the reports are solely on males due to the fact that a majority of BC patients are male.

All patients in our study had HG BC and nearly half of them stage T1, which was also found in the five case reports from Bowyer et al (72). A possible explanation could be that these patients had an impaired immune system, more susceptible to a persistent BCG-infection. Eight of our patients also had various comorbidities, such as diabetes mellitus, possibly adding to a higher risk of prolonged infection.

Not all of our patients had local symptoms and the association between symptoms and the visible lesion is not evident. Following the tuberculostatic treatment all the symptomatic patients reported a clear improvement, in some cases up to a few years after. On the other hand, the one patient who did not receive the treatment also reported a clear improvement. At follow-up, the lesions were growing smaller and eventually could not be seen in all but one patient, who still had a small

reddish area at the previous lesion site. Surprisingly it vanished in the one who did not receive tuberculostatic treatment as well, although he still had a positive culture for mycobacteria two years after the initial diagnosis of the persisting infection. No firm conclusions can be made from single cases although speculations arise about the significance of long-term antibiotics that are required for eradicating the mycobacteria, with potential serious side effects.

The different BCG strains differ from each other and from the original strain from 1921 although a meta-analysis could not show any large differences in efficacy or side effects (76). In our small material the majority had been treated with BCG-RIVM and possibly the virulence has increased compared to BCG-TICE, although to our knowledge no more reports of persistent BCG-infection has been reported in Sweden recently. We have had a few more cases at our clinic following our publication and that could be due to our awareness of this rare side-effect.

The study was small and no firm conclusions can be made. We are still unaware of which patients benefit from anti TB-treatment when these lesions and positive mycobacterial cultures are found.

PAPER II

Here we present the outcome for 204 patients who were tumour-free for over five years after BCG treatment.

Some authors have reported on late recurrences after >10 tumour-free years but the number was either not stated, or was small (10, 77). One study reported on late recurrences and progression and identified 176 patients who had received BCG-treatment with a tumour-free period of more than five years (78). In accordance to our figures they noted that early recurrences were not uncommon, followed by a tumour-free period. They also performed upper tract imaging on a regular basis, but found only one patient (0.4%) with upper tract tumour, in our material 1.5%. This contrasts to another study were they found 18% upper tract tumours in patients with initially HG Ta tumours after up to 181 months (10). These differences could be explained by a higher risk for upper tract tumours in patients with an active HG BC, as in Herr´s study (10). There seems to be a lower risk for those patients who have had a tumour-free period for more than five years as in the present study and Matsumoto´s, indicating that upper tract imaging on a regular basis could be questioned (78).

Maintenance has been shown to decrease early recurrences although data suggests that the effect weakens over time, as demonstrated by Lamm et al who reported 76% recurrences in the maintenance arm after 10 years, compared to 83% in the non-maintenance arm (79). Besides, the optimal maintenance schedule is yet to be defined. The risk factors for late recurrences do not seem to be equal to those for early recurrences, as Matsumoto reported and we found only an increased risk for the patients who received BCG after multiple recurrences (78).

Concerning late progression it has been reported, although the tumour-free period was not clearly specified (10, 79, 80). We identified 0.5% BC progression compared to Matsumoto´s 3.4% after at least five tumour-free years (78).

In our material we divided the patients with primary TaG1-2 into one group and those with TaG3, Cis, T1 into another as they differ in long term prognosis. The former group has a more favourable prognosis and follow up may be discontinued after five tumour-free years. If so, the patients should be instructed to return if haematuria occurs. In our study the LG recurrences were identified during follow up and were small and thus easy to immediately treat under local anaesthesia. Concerning the latter group, they are at higher risk for HG recurrence which potentially could be life threatening. We suggest continued yearly follow-up for these patients, as long as they are reasonably healthy otherwise, i e available for potential curative treatment. The recurrence rate in our material for these patients was low, on the other hand, a flexible cystoscopy is well tolerated. Bladder wash cytology should be included in the follow-up schedule.

Individual aspects should be taken in consideration when deciding the follow-up schedule. There is a need for further studies of costs and identifying risk factors for late recurrences.

The limitations of this study are that it is retrospective although including approximately 99% of all BCG treated patients in a large geographical area. A second evaluation of the histopathological specimens was not performed, although the primary investigation was performed by a pathologist with special interest in BC.

Considering the results from the third paper where we found that 22% of all suspected tumours were benign or normal, one could question the decision of including the fulgurated lesions in the definition of recurrences in this study. However, other studies have used the same

definition why it seems likely that the true recurrence rate is somewhat lower than reported.

PAPER III

Data on newly diagnosed BC can be found in the literature but the present study also includes comparative information of recurrences. Our data could differ from other urology units as there are factors that could influence the size, number and histopathology of BC. If there are longer intervals between cystoscopies, the larger a tumour could grow, although the median growth rate reported by Soloway et al was 1.25 mm per month (65). Interestingly they reported that eight tumours could not be seen at follow up and they speculate whether these had been misdiagnosed. In our material there were 22% benign or normal findings even though it was suspected to be a tumour and 86% of the operations were performed or supervised by a specialist in urology. Perhaps the eight missing tumours from Soloway´s study were inflammatory lesions. The results from another study reported that 17.5% of the suspected tumours were benign (81). It seems reasonable to always take biopsies from suspected lesions rather than only fulgurate and presume that it is a recurrence, as this may affect the follow-up intervals.

Intravesical chemotherapy or BCG may reduce the number and size of recurrent tumours. The ratio of 1.4 operations for recurrences for every new tumour has at our department been reduced from a ratio of 2.4 during the last decade (69). An increased use of intravesical treatment could possibly explain this decline in the recurrence rate.

There are several studies presenting data on newly diagnosed tumours. A study from 2011 included data from 768 new Ta-T1 tumours including size, histopathology and multiplicity (82). The tumours had a median size of 20 mm, 28% were multiple and 28% larger than 30 mm, which is in accordance to our data on new tumours. Reports on recurrences are usually based on a selected group of patients and most often focused on recurrence and progression rates and seldom as detailed as the present study (4, 82, 32).

Determining the size of a bladder tumour can be difficult, even when using instruments as a guide. A study was performed comparing different methods of measurement and using a urethral catheter as the objective measure (83). They found that compared to the estimation at cystoscopy, preoperative ultrasound and at TURB, the most reliable measurement was

made by the operating surgeon. Our estimates should consequently be fairly accurate. Another weakness in our study is the calculation of tumour volume, using the formula for ellipsoids (71). We chose this as we measured the tumours in three dimensions and they were more often ellipsoid rather than spherical, but it should be considered as an approximation.

The present study confirms what most urologists already have presumed-that a recurrence usually is smaller than a new tumour. We believe that a majority of these patients could be treated in the office using local anaesthesia. We have a long tradition of these procedures and there are other authors as well encouraging an increased use of extirpation and fulguration under local anaesthesia (32, 84). The procedure is usually well tolerated and reduces costs considerably (25, 85, 86).

PAPER IV

There has been other reports on experienced pain during cystoscopy, mostly on men (87, 88). Last year a study was published on women undergoing both flexible and rigid cystoscopy, and as for men, they were more likely to experience less pain at flexible cystoscopy (89). However, this is to our knowledge the first report presenting data on pain experience during extirpation of small sized bladder tumours, showing that it is well tolerated in the majority of cases.

In order to decrease the pain and discomfort at cystoscopy, studies have been undertaken with various methods and results. Two authors reported studies on whether watching the cystoscopy at a separate screen could reduce pain levels, with different results (90, 91). Two other studies investigated the effect of listening to music and both concluded that it reduces VAS scores (92, 93). Oral administration of non-steroid anti-inflammatory drugs has also been reported to reduce pain levels. It may prove difficult to completely eradicate pain and discomfort as the patients are in an exposed situation.

The instillation of lidocaine prior to transurethral procedures has been reported to reduce pain (25, 33). The procedures can be further facilitated by a submucosal injection of lidocaine, as shown by several authors (30, 31). In our opinion it gives excellent analgesia at TURB in the office, although the discomfort of moving the instrument still exist. Brausi et al used additional injections at the bladder neck to reduce this (31).

There are several weaknesses in the present study. One is that we should have asked for pain levels prior to the procedure as Seklehner did (87). The results could be biased as the questions were asked by the staff present during the cystoscopy. We did not have the information on all patients about their previous experience with cystoscopy or transurethral surgery. It would have been interesting to know since one study found that the first time cystoscopy was the strongest predictor of severe pain (88). The additional local anaesthesia for some patients was used in a sporadic manner, when the urologist thought it appropriate, rather than in a systematic way. Another weakness is that we used cystoscopes with different diameters, we should have thought about using the same or registered the diameter for each patient, as this might have affected the experienced discomfort or pain.

The strengths of this prospective study is the high number of patients and that we recorded the VAS score also among patients subjected to biopsy and fulguration.

CONCLUSIONS

PAPER I

The study reports a late BCG-infection with a concomitant large ulceration in the bladder in 1.8% of all the BCG-treated patients at our clinic. When lesions of uncertain origin are discovered in such patients we recommend mycobacterial urinary cultures and biopsies of the lesions. The effect of the antibiotic treatment was good, as was the oncological outcome. Further studies are needed to evaluate possible differences between the BCG strains and their side effects.

PAPER II

A tumour free period of more than five years after BCG-treatment is a good prognostic sign although late recurrences are not rare. This study supports earlier reports that suggested that follow-up should continue beyond five tumour-free years in selected patients.

PAPER III

The absolute majority of all suspected bladder tumour recurrences are less than 10 mm, LG or benign. These data support the potential of treating more patients under local anaesthesia in the office resulting in significant cost reduction.

PAPER IV

Our results of VAS scores after cystoscopy are in accordance with other authors, showing that it is a well-tolerated procedure. The pain levels for patients treated with biopsy and fulguration are higher but still within well accepted limits. This confirms the extended use of transurethral procedure under local anaesthesia in patients with small tumours.

FUTURE PERSPECTIVES

Intravesical BCG has been used globally since the late 1970s with great success and benefit for patients with NMIBC. Despite this, there are still aspects that should be investigated further, such as the optimal maintenance schedule and whether there are differences between the BCG strains. Perhaps the different strains have slightly different effect on various populations. Early identification of patients that are BCG-refractory is important in order to determine another treatment strategy and hopefully, future studies will provide more knowledge. Further studies on device-assisted chemotherapy may possibly report positive results for this group of patients, especially since there has been a shortage of BCG and these studies are therefore important for all NMIBC patients.

In Sweden the number of patients receiving BCG-treatment is still not within the desired level, although the use has increased during the last years. There is an awareness that there are regional and gender related differences and it is important to study these questions further in order to identify the reasons for this. Future studies will hopefully provide an increased knowledge about the causes and minimize differences in treatment and survival.

The first paper in this thesis suggests that prolonged BCG-infections following intravesical treatment may be underdiagnosed. A greater awareness is essential in order to establish the true rate. When an atypical lesion is found in the bladder, and histopathology reveals inflammation, some may be content with the affirmation of ruling out malignant disease rather than to do further investigations of the nature of inflammation. Identifying the late BCG-infections could potentially lead to a decrease of late, permanent side effects such as bladder contraction. On the other hand, we have since the first publication identified a few more patients with positive mycobacterial cultures up to five years after BCG-treatment, with no visible lesion or local symptoms. How long can the cultures remain positive? Do we have to treat all patients with positive mycobacterial cultures or should we consider these patients as any other with an asymptomatic urinary infection, not requiring antibiotics?

Follow-up schedules are suggested in guidelines but many factors can affect the adherence to these. The difference between a scheduled visit for cystoscopy at three or six months is less important for low risk tumours, but of greater importance for high risk tumours. The duration of follow-up is another problem and five years of tumours-free controls may

be enough for some patients. It was evident in our material that BCG-treated patients still have a risk of late recurrence in spite of being tumour-free for more than five consecutive years. It raises a question of whether it is possible to identify these individuals at an early stage. It would be ideal to be able to terminate the follow-up for those not at risk for late recurrence, but at present we simply do not have the answer.

It is evident for a reader of the third and fourth paper that we strongly believe in the benefits of treating certain BC patients under local anaesthesia. We have over 20 years of experience and the patients seem satisfied with the swift removal of the tumour and they always get the choice of returning another day for a TURB under general anaesthesia. There are some factors essential for these procedures besides a dedicated urologist, such as having experienced nurses and proper equipment readily available. The most important factor is choosing the right patient, who should be well informed of the procedure and be as relaxed as possible. The tumour should not be too large or in a difficult location, requiring extensive manipulation of the instrument, especially in male patients. Education and encouragement may possibly contribute to an increased use of procedures under local anaesthesia.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Urinblåsecancer är den vanligaste cancersjukdomen i urinvägarna och i Sverige får ca 2500 personer diagnosen årligen. Det vanligaste debut symptomet är synligt blod i urinen, men även täta trängningar från blåsan förekommer. Diagnosen ställs oftast genom att man tittar in via urinröret in i blåsan med ett cystoskop. Man kan i vissa fall även upptäcka en blåstumör på en datortomografi som kan vara utförd av olika anledningar. Den första behandlingen består av en hyvling av blåstumören, transuretral resektion, TURB, varvid tumören hyvlas bort och vävnaden skickas för mikroskopisk undersökning.

Med stadieindelning menas hur djupt en tumör växer i vävnaden och om den sitter på blåsslemhinnans yta kallas det tumör-stadie Ta. Om tumören växer invasivt in i slemhinnan kallas det stadie T1. Dessa stadier går under samlingsnamnet icke muskel-invasiv blåscancer, vilket utgör ca 75% av alla nydiagnostiserade blåstumörer i Sverige. Vid stadie T2 eller högre växer tumören in i blåsans muskulatur eller igenom och utanför. Den mikroskopiska undersökningen ger svar på stadiet men även på hur allvarligt förändrade tumörcellerna är, vilket benämns gradering. Det finns olika klassifikationssystem för gradering och i Sverige använder vi det som heter WHO 1999 och WHO 2004. I detta arbete används WHO 1999 där man använder en skala som går från grad 1-3, där grad 1 (G1) är den mest beskedliga och grad 3 (G3) mest aggressiv.

Vid icke muskelinvasiv blåscancer är prognosen god jämfört med de som har stadie T2 eller värre. Muskelinvasiv sjukdom behandlas mer aggressivt, oftast med borttagande av blåsan och i vissa fall även cellgifter. Vid de mer beskedliga TaG1-tumörerna räcker TURB som enda behandling. Vid TaG3-T1 ges kompletterande behandling med blåssköljningar, instillationer. Man använder antingen en lösning av cellgifter eller tuberkulosvaccin, BCG, som består av försvagade mykobakterier. Behandlingen ges via en kateter som förs in i blåsan och lösningen tappas ut efter 1-2 timmar. Instillationen upprepas en gång i veckan under sex veckors tid och oftast ges sedan ett kompletterande antal behandlingar. Tyvärr är det vanligt med biverkningar, ff a de första dagarna efter behandling, t ex i form av trängningar och influensaliknande symptom. Syftet med instillationerna är att det minskar risken för återfall och vid BCG-behandling minskas även risken för progression, d v s att sjukdomen blir mer aggressiv. Återfall är mycket vanliga och vissa faktorer ökar risken, som högre stadie och grad men

även storlek och antal. Det finns rekommendationer för hur ofta dessa patienter ska undersökas och under hur lång tid uppföljningen ska pågå, men det har funnits vissa oklarheter avseende när det kan anses vara säkert att avsluta kontrollerna. Vid återfall får man göra en ny hyvling och eventuellt upprepa instillationerna. Vid små tumörer går det att ta bort dem direkt vid ett mottagningsbesök via cystoskopet i lokalbedövning.

Det första arbetet beskriver 13 patienter där vi fann en avvikande förändring i blåsan. Då vävnadsprover togs visade den mikroskopiska undersökningen att det rörde sig om en inflammation, orsakad av BCG. Deras urinprov innehöll levande BCG-bakterier, trots att det i vissa fall hade gått flera år sedan den senaste BCG-behandlingen. De fick behandling med antibiotika av den typ som ges mot tuberkulos och av de sju patienter som hade symptom från blåsan gick dessa över efter avslutad kur. Under den fortsatta uppföljningen såg man att förändringarna i blåsan försvann.

Det har varit oklart hur lång uppföljningen av tumörfria, BCG-behandlade patienter ska vara och det var frågeställningen för den andra publikationen. Data från 542 BCG-behandlade patienter analyserades varvid 204 befanns ha varit tumörfria i minst fem efterföljande år. Av dessa fick ca 11% senare återfall. Studien visar att man kan rekommendera längre uppföljning för vissa patienter trots att de haft en längre sammanhängande tumörfri period.

I det tredje arbetet beskrivs data från alla misstänkta nyupptäckta och återkommande blåstumörer. Studien visar att en ny tumör i snitt är 20 mm i diameter jämfört med 10 mm för ett återfall. De mikroskopiska undersökningarna visar även att 22% av det man uppfattar vara tumör i själva verket är godartat eller inflammation.

Självupplevd smärtskattning vid cystoskopi med eller utan provtagning av blåstumör var fokus för det fjärde arbetet. Studien visar att majoriteten av de som genomgår cystoskopi upplever lite eller ingen smärta. För de som även genomgick vävnadsprovtagning var det endast något mer smärtsamt men fortfarande inom helt acceptabla nivåer. De två sista arbetena stödjer utökandet av behandling av små blåstumörer i lokalbedövning.

ACKNOWLEDGEMENTS

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