

Best practice in the treatment of nonmuscle invasive bladder cancer

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Abstract: Bladder carcinoma is the most common malignancy of the urinary tract. Approximately 75–85% of patients with bladder cancer present with a disease that is confined to the mucosa (stage Ta, carcinoma *in situ*) or submucosa (stage T1). These categories are grouped as nonmuscle invasive bladder cancer (NMIBC). Although the management of NMIBC tumours has significantly improved during the past few years, it remains difficult to predict the heterogeneous outcome of such tumours, especially if high-grade NMIBC is present. Transurethral resection is the initial treatment of choice for NMIBC. However, the high rates of recurrence and significant risk of progression in higher-grade tumours mandate additional therapy with intravesical agents. We discuss the role of various intravesical agents currently in use, including the immunomodulating agent bacillus Calmette-Guérin (BCG) and chemotherapeutic agents. We also discuss the current guidelines and the role of these therapeutic agents in the context of higher-grade Ta and T1 tumours. Beyond the epidemiology, this article focuses on the risk factors, classification and diagnosis, the prediction of recurrence and progression in NMIBC, and the treatments advocated for this invasive disease.

Keywords: carcinoma in situ, chemotherapy, immunotherapy, noninvasive bladder tumour, transurethral resection

Epidemiology

The incidence rate of a cancer is defined as the number of new cases diagnosed per 100,000 people per year. Bladder carcinoma is the most common malignancy of the urinary tract.

Bladder cancer is nearly three times more common in men than in women [Jamal *et al.* 2005]. The worldwide age standardized incidence rate (ASR) is 10.1 per 100,000 for men and 2.5 per 100,000 for women [Ploeg *et al.* 2009]. In men, it is the fourth most common cancer after prostate, lung and colorectal cancers, accounting for 6.6% of all cancer cases. In women it is the ninth most common cancer, accounting for 2.4% of all cancers [Jamal *et al.* 2005]. In Europe, the highest incidence (ASR) has been reported in the western (23.6 in men and 5.4 in women) and southern (27.1 in men and 4.1 in women) regions, followed by northern Europe (16.9 in men and 4.9 in women). The lowest incidence is observed in

eastern European countries (14.7 in men and 2.2 in women) [Ferlay *et al.* 2004].

Approximately 75–85% of patients with bladder cancer present with a disease that is confined to the mucosa [stage Ta, carcinoma *in situ* (CIS)] or submucosa (stage T1). These categories are grouped as nonmuscle invasive bladder cancer (NMIBC). Of these, approximately 70% present as stage Ta, 20% as T1 and 10% as CIS. Previously, these were categorized as superficial bladder cancers, but following a consensus meeting during the SIU, this name was changed, because ‘superficial’ has a more benign feeling and NMIBC better describes the different potentials of bladder tumours [Soloway, 2007].

Risk factors

Many of the aetiological factors for the development of bladder tumours are known and urologists

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Table 1. Tumour, node, metastasis (TNM) classification 2009.**T – Primary tumour**

Ta: noninvasive papillary carcinoma

Tis: carcinoma *in situ*

T1: tumour invades subepithelial connective tissue

T2: tumour invades muscularis

a: superficial muscle (inner half)

b: deep muscle (outer half)

T3: tumour invades perivesical tissue (beyond muscularis)

a: microscopically

b: macroscopically (extravesical mass)

T4: tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall

a: Prostate, uterus, vagina

b: Pelvic wall, abdominal wall

N – Lymph nodes

Nx: regional lymph nodes cannot be assessed

N0: no regional lymph nodes metastases

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 a common iliac lymph node

M – Distant metastasis

M0: no distant metastasis

M1: distant metastasis

should be aware of the types of occupational exposure that might be related to urothelial carcinogens. Aromatic amines were the first to be recognized. High-risk groups include workers in the following industries: printing, iron and aluminium processing, industrial painting, gas and tar manufacturing [McCahy *et al.* 1997; Zeegers *et al.* 2001; Samanic *et al.* 2008]. Another prominent risk factor is cigarette smoking, which triples the risk of developing bladder cancer [Bjerregaard *et al.* 2006; Puente *et al.* 2006]. Smoking leads to a higher mortality rate from bladder cancer during long-term follow up, even though, in a multivariate analysis, the prognostic effect of smoking was weaker than that of other factors, such as stage, grade, size and multifocality of the tumour [Aveyard *et al.* 2002]. Former cigarette smokers have a reduced incidence of bladder cancer compared with active smokers. [Augustine *et al.* 1988]. However, the reduction of this risk down to baseline (age adjusted) takes nearly 20 years after cessation of smoking, a period far longer than for the reduction of risk of cardiovascular disease and lung cancer after smoking has stopped. From a clinical standpoint it is important to realize that not only does smoking increase the risk for developing bladder cancer but also failure to quit smoking once a diagnosis is made predicts a more

ominous outcome, even in those diagnosed with noninvasive initial cancers [Fleshner *et al.* 1999].

Classification

Tumour, node, metastasis classification

The 2002, tumour, node, metastasis (TNM) classification approved by the Union International Contre le Cancer has been widely accepted. This version was updated in 2009, but there were no changes for bladder tumours (Table 1) [Sobin *et al.* 2009].

Histological grading of nonmuscle invasive bladder urothelial carcinomas

In 1998, a new classification of noninvasive urothelial tumours was proposed by the World Health Organization (WHO) and the International Society of Urological Pathology (ISUP) (1998 WHO/ISUP classification) and published by the WHO in 2004 (Table 2) [Epstein *et al.* 1998; Sauter *et al.* 2004].

The 2004 WHO classification of the flat lesions includes urothelial hyperplasia, reactive urothelial atypia, and atypia of unknown significance,

Table 2. World Health Organization (WHO) grading in 1973 and 2004.**1973 WHO grading**

Urothelial papilloma

Grade 1: well differentiated

Grade 2: moderately differentiated

Grade 3: poorly differentiated

2004 WHO grading

Flat lesions

Hyperplasia (flat lesion without atypia or papillary aspects)

Reactive atypia (flat lesion with atypia)

Atypia of unknown significance

Urothelial dysplasia, urothelial carcinoma *in situ*

Papillary lesions

Urothelial papilloma (which is a completely benign lesion)

Papillary urothelial neoplasm of low malignant potential (PUNLMP)

Low-grade papillary urothelial carcinoma

High-grade papillary urothelial carcinoma

dysplasia and CIS. Among noninvasive papillary urothelial lesions, the 2004 WHO grading differentiates between papillary urothelial neoplasm of low malignant potential (PUNLMP) and low-grade and high-grade urothelial carcinomas. PUNLMPs are defined as lesions that do not have cytological features of malignancy but show normal urothelial cells in a papillary configuration. Although they have a negligible risk for progression, they are not completely benign and still have a tendency to recur. The intermediate grade (grade 2), which was the subject of controversy in the 1973 WHO classification, has been eliminated [Burger *et al.* 2008; Pan *et al.* 2010]. It was shown that the 2004 WHO classification had a better reproducibility than the WHO 1973 classification [Hudson *et al.* 1995]. The prognostic value of both grading systems (WHO 1973 and 2004) has been confirmed. Attempts to demonstrate better prognostic value of one system over another, however, have yielded controversial results [Burger *et al.* 2008; Pan *et al.* 2010; May *et al.* 2010; Otto *et al.* 2011]. The majority of clinical trials published to date on TaT1 bladder tumours have been performed using the 1973 WHO classification, and therefore, the guidelines are based on this scheme. Until the prognostic role of WHO 2004 is validated by more prospective trials, both classifications are recommended for use.

Characteristics of stages Ta, T1, Tis

Stage Ta tumours are confined to the urothelium, have a papillary configuration of their exophytic part and do not penetrate from the urothelium into the lamina propria or the detrusor muscle. They are usually of low grade. Although recurrence is common, especially in the setting of multiplicity, progression is rare. Three to eighteen percent of Ta tumours are high grade, with an average of 6.9% [Sylvester *et al.* 2005a]. The most important factor for progression is grade, not stage.

Stage T1 tumours generate from the urothelium but penetrate the basement membrane, which separates the urothelium from the deeper layers. T1 tumours invade into the lamina propria, but not so deep that they reach the detrusor muscle. They are usually papillary; a nodular or sessile appearance suggests deeper invasion. There is significant potential for understaging in patients with nonmuscle invasive tumours, especially for those that appear to be stage T1. Many tumours are found to be more extensive than the transurethral resection (TUR) specimen indicated when patients undergo cystectomy. About one-third of patients believed to have nonmuscle invasive disease at the time of cystectomy were found to actually have muscle invasion, only half of which were organ confined [Stein *et al.* 2001].

Carcinoma *in situ* (Tis) is a high-grade (anaplastic) carcinoma confined to the urothelium, but with a flat nonpapillary configuration. Unlike a papillary tumour, Tis appears as reddened and velvety mucosa and is slightly elevated but sometimes not visible. Tis can be local or diffuse. Primary Tis (no previous or concurrent papillary tumours) can be distinguished from secondary Tis (with a history of papillary tumours) and concurrent Tis (in the presence of papillary tumours). It is high grade by definition. Although confined to the urothelium in the same manner as stage Ta, Tis is regarded as a precursor lesion for the development of invasive high-grade cancer. Between 40% and 83% of patients with Tis will develop muscle invasion if untreated, especially if associated with papillary tumours [Althausen *et al.* 1976]. Some studies have reported worse prognosis in concurrent CIS and T1 tumours compared with primary CIS and in extended CIS [Losa *et al.* 2000; Griffiths *et al.* 2002; Solsona *et al.* 2000]. Various publications have shown that the response to intravesical treatment with Bacillus Calmette-Guérin (BCG) or chemotherapy is an important prognostic factor for subsequent progression and

death caused by bladder cancer. Approximately 10–20% of complete responders to BCG instillations will eventually still progress to muscle-invasive disease [Van Gils-Gielen *et al.* 1995; Hudson *et al.* 1995; Solsona *et al.* 2000].

Diagnosis

The most common presenting symptom of bladder cancer is painless macroscopic haematuria, which occurs in about 85% of patients [Varkarakis *et al.* 1974]. However, haematuria is mostly intermittent so a negative result on one or two specimens has little meaning in ruling out the presence of bladder cancer. The symptom complex of bladder irritability and urinary frequency, urgency and dysuria is the second most common presentation and is usually associated with diffuse CIS or invasive bladder cancer. However, these symptoms almost never occur without (at least) microscopic haematuria. A history of macroscopic haematuria and microscopic haematuria in high-risk patients requires further investigation of the entire urinary tract.

Cystoscopy

All patients suspected of having bladder cancer should have a cystoscopic evaluation. The diagnosis of bladder cancer ultimately depends on cystoscopic examination of the bladder and histological evaluation of the resected tissue. Cystoscopy is initially performed in the office, using flexible instruments. The diagnosis of CIS is made by a combination of cystoscopy, urine cytology and histological evaluation of multiple bladder biopsies [Kurth *et al.* 1995]. If a bladder tumour has been visualized in earlier imaging studies, diagnostic cystoscopy can be omitted because the patient will undergo a TUR anyhow. A careful description and documentation of the findings is necessary, including the site, size, number and appearance (papillary or solid) of the tumours, as well as a description of mucosal abnormalities. Use of a bladder diagram is recommended.

Urinary cytology – urinary molecular marker tests

Urine cytology is obtained at baseline and to establish the likelihood of high-grade disease. Malignant urothelial cells can be observed on microscopic examination of the urinary sediment or bladder washings. The limitations of microscopic cytology are due to the cytological normal appearance of cells from the well differentiated tumours and

because well differentiated cancer cells are more cohesive, they are not readily shed into the urine. Therefore, microscopic cytology is more sensitive in patients with high-grade tumours or CIS. The sensitivity of cytology in CIS detection is over 90%. False-positive cytology may occur in up to 10% of patients and is usually due to urothelial atypia, inflammation, presence of stones in the urinary tract or changes caused by radiation therapy or chemotherapy [Koshikawa *et al.* 1989]. Cytology should be performed on fresh urine with adequate fixation. Morning urine is not suitable because of the frequent presence of cytolysis.

Molecular urinary markers have not improved the combination of cystoscopy and cytology with relation to detection of bladder tumours. The sensitivity of tests can be improved by using multiple diagnostic marker tests, as suggested by the International Consensus Panel on Bladder Tumour Markers [Lokeshwar *et al.* 2005], but this will increase costs and it is not clear which tumours are detected and which are still missed. Although it is hoped that by further research these tests can soon make the transition from the laboratory to the clinic, it is essential to evaluate their costs to determine whether they can provide a low-cost and reliable alternative to current cystoscopy methods [Hong and Loughlin, 2008].

Imaging

Renal and bladder ultrasound may be used during initial work-up in patients with haematuria. At the time of initial diagnosis of bladder cancer, computed tomography (CT) urography [or intravenous urogram (IVU)] should be performed only in selected cases (e.g. tumours located in the trigone or high-risk tumours). Especially in muscle-invasive tumours of the bladder and in upper tract tumours, CT urography gives more information than IVU (including status of lymph nodes and neighbouring organs). However, CT urography has the disadvantage of higher radiation exposure compared with IVU. In most centres CT urography has replaced time-consuming IVU investigations.

Therapy

Transurethral resection of bladder tumours

TUR of bladder tumours (TUR-BT) under regional or general anaesthesia is the initial treatment for visible lesions and is performed to remove all visible tumours and to provide specimens for

pathological examination to determine stage and grade. Bimanual examination of the bladder should be performed under anaesthesia before prepping and draping unless the tumour is clearly small and noninvasive, and should be repeated after the resection. Fixation or persistence of a palpable mass after resection suggests locally advanced disease. The strategy of resection depends on the size of the lesion. Small tumours (<1 cm) can be resected *en bloc*; the specimen contains the complete tumour plus a part of the underlying bladder wall. Some experts believe that deep resection is not necessary in small, apparently low-grade lesions with a previous history of TaG1 tumour. Larger tumours should be resected separately in fractions, which include the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle, and the edges of the resection area. The specimens from different fractions must be referred to the pathologist in separate containers to enable a correct diagnosis to be made. Cauterization should be avoided as far as possible during TUR to prevent tissue destruction. Complete and correct TUR-BT is essential to achieve a good prognosis [Brausi *et al.* 2002]. It has been confirmed that absence of detrusor muscle in the specimen is associated with a significantly higher risk of residual disease and early recurrence [Mariappan *et al.* 2010].

Complete visualization to plan the resection is now facilitated by the initial flexible cystoscopy. In the past it was recommended that a 70° rod lens be used, which allowed maintenance of the anatomic relationships. Bipolar electroresection allows TUR in saline and minimizes the risk of the obturator reflex that can lead to bladder perforation [Shiozawa *et al.* 2002; Miki *et al.* 2003]. The use of general anaesthesia with muscle-paralyzing agents or anaesthetic block of the obturator nerve also prevents obturator reflex for tumours located at the lateral wall of the bladder. Resection of diverticular tumours presents a particular risk of bladder wall perforation and accurate staging is difficult to achieve because the underlying detrusor is absent. Invasion beyond the lamina propria immediately involves perivesical fat or stage T3a. Partial or radical cystectomy should therefore be considered for high-grade diverticular tumours.

Complications of transurethral resection of bladder tumours

Intraoperative complications. The major complications of uncontrolled haematuria and clinical bladder perforation occur in less than 5% of cases.

Cauterization is used for the bleeding site. The vast majority of perforations are extraperitoneal, but intraperitoneal perforation is possible when resecting tumours at the dome [Collado *et al.* 2000]. Management of extraperitoneal perforation is usually possible by prolonged urethral catheter drainage. Intraperitoneal perforation is less likely to close spontaneously and often requires open surgical repair. To prevent bladder perforation it is necessary to perform the resection if the bladder is not overdistended.

Postoperative complications. Minor bleeding and irritative symptoms are common side effects in the immediate postoperative period, but sometimes clot retention can occur, especially if an extensive resection was performed. When tumours are located at or near the ureteral orifice, obstruction of the upper tract can occur. Therefore, in these situations a postoperative ultrasound should be performed.

Bladder and prostatic urethral biopsies

Biopsies of any suspicious areas are an important part of a complete evaluation. CIS can present as a velvet-like, reddish area that is indistinguishable from inflammation, or it might not be visible at all. It can be present as an isolated lesion without exophytic tumour or it can accompany TaT1 tumours. When abnormal areas of urothelium are seen targeted 'cold cup' biopsies or biopsies with a resection loop should be taken. Biopsies from normal-looking mucosa, so-called random biopsies (R-biopsies), should be performed in patients with positive (high-grade) urinary cytology and in the absence of visible tumour in the bladder. It is recommended that R-biopsies are taken from the trigone, the bladder dome, the right, left, anterior and posterior bladder walls, and the prostate in men. The current consensus is that random biopsies are not indicated in low-risk patients, that is, those with low-grade papillary tumours and negative cytology. The likelihood of detecting CIS, especially in low-risk tumours, is extremely low (<2%) [van der Meijden *et al.* 1999]. Also, cold cup biopsies from normal-looking mucosa should be performed when the exophytic tumour has a non-papillary appearance. Material obtained by random or directed biopsies must be sent for pathological assessment in separate containers. In CIS, the coherence and adherence of epithelial cells is decreased, and this feature often results in denuded biopsies when taken by cold

cup or a resection loop [Levi *et al.* 2001]. Involvement of the prostatic urethra and ducts with urothelial cancer in men with NMIBC has been reported [Solsona *et al.* 1996].

Although the exact risk of prostatic urethra or duct involvement is not known, it seems to be higher if the tumour is located on the trigone or bladder neck, in the presence of bladder CIS and multiple tumours [Matzkin *et al.* 1999; Mungan *et al.* 2005]. In these cases and when cytology is positive, with no evidence of tumour in the bladder, or when abnormalities of prostatic urethra are visible, biopsies of the prostatic urethra are recommended. The biopsy is taken from abnormal areas and from the precollicular area (between the 5 and 7 o'clock position) using a resection loop. Also, a prostatic urethral biopsy using the cutting loop may be performed if orthotopic bladder creation is anticipated for high-risk disease [Holzbeierlein *et al.* 2000].

Fluorescence cystoscopy

Endoscopically, urologists can suspect malignancy based only on the presence of visible changes such as tumours or 'red spots'. The imperfect sensitivity of cystoscopy potentially explains the high rate of cancer recurrence soon after 'complete' removal of all visible tumours.

Photodynamic diagnosis (PDD) is performed using violet light after intravesical instillation of 5-aminolaevulinic acid or hexaminolaevulinic acid. Previous studies have confirmed that fluorescence-guided biopsy and resection are more sensitive than conventional procedures for detection of malignant tumours, particularly for CIS [Jichlinski *et al.* 2003; Schmidbauer *et al.* 2004; Hungerhuber *et al.* 2007].

PDD is most useful for detection of CIS, and therefore, it should be restricted to patients who are suspected of harbouring a high-grade tumour; for example, for biopsy guidance in patients with positive cytology or with a history of high-grade tumour. Because of conflicting data on the reduction in recurrence rate using PDD in papillary tumours, the use of PDD is still questioned in these cases [Stenzl *et al.* 2010; Witjes *et al.* 2010]. The additional costs of the equipment and instillation for PDD should be taken into account.

Narrow band imaging (NBI) is a new endoscopic technique that is used to improve the detection of

NMIBC. NBI uses light of a narrow bandwidth with centre wavelengths in the blue and green spectrum of light to increase the contrast of the mucosa and small vascular structures with a high resolution, without the use of intravesical instillations. NBI cystoscopy, in addition to white light cystoscopy, improves the detection of NMIBC and might lead to a more complete resection, thereby possibly resulting in fewer early tumour recurrences. However, further validation of the technique is required with comparative studies [Cauberg *et al.* 2011].

Second resection

There is a significant risk of residual tumour after the initial TUR of TaT1 tumours [Brausi *et al.* 2002; Miladi *et al.* 2003]. Repeat TUR-BT is usually appropriate in the evaluation of T1 tumours because a repeat TUR can demonstrate worse prognostic findings in up to 25% of specimens [Schwaibold *et al.* 2000]. A second TUR should be considered when the initial resection is incomplete; for example, when multiple and/or large tumours are present, or when the pathologist has reported that the specimen contains no muscle tissue (TaG1 excluded). Furthermore, a second TUR should be performed when a high-grade or T1 tumour has been detected at initial TUR [Kulkami *et al.* 2010]. Previous studies have demonstrated that a second TUR can increase recurrence-free survival [Grimm *et al.* 2003; Lopez-Beltran *et al.* 2004; Divrik *et al.* 2006].

There is no consensus about the strategy and timing of a second TUR. Most authors recommend resection 2–6 weeks after the initial TUR. The procedure should include resection of the primary tumour site.

Recurrence progression

TaT1 tumours. Patients with a TaT1 bladder tumour are divided into low-risk, intermediate-risk and high-risk groups [Millán-Rodríguez *et al.* 2000a, 2000b]. When using these risk groups, however, no distinction is usually drawn between the risk of recurrence and progression. Although prognostic factors indicate a high risk for recurrence, the risk of progression might still be low, and other tumours might have a high risk of recurrence and progression. To predict separately the short-term and long-term risks of recurrence and progression in individual patients, the European Organization for Research and Treatment

Table 3. Weighting used to calculate recurrence and progression scores.

Factor	Recurrence	Progression
Number of tumours		
single	0	0
2–7	3	3
>8	6	3
Tumour diameter		
up to 3 cm	0	0
more than 3 cm	3	3
Prior recurrence rate		
Primary	0	0
<1 per year	2	2
>1 per year	4	2
Category		
Ta	0	0
T1	1	4
Concurrent CIS		
No	0	0
Yes	1	6
Grade (WHO 1973)		
G1	0	0
G2	1	0
G3	2	5
Total score	0–17	0–23

CIS, carcinoma *in situ*; WHO, World Health Organization.

of Cancer (EORTC)-Genitourinary (GU) Group developed a scoring system and risk tables (Tables 3–5) based on the six most significant clinical and pathological factors [Sylvester *et al.* 2006]:

1. tumour size,
2. prior recurrence rate,
3. T-category,
4. presence of concurrent CIS,
5. tumour grade,
6. number of tumours.

Carcinoma in situ. Patients with CIS are always categorized in the high-risk group. Without any treatment, approximately 54% of patients with CIS progress to muscle-invasive disease [Lamm *et al.* 1992]. Unfortunately, there are no reliable prognostic factors that can be used to predict the course of the disease and specify the most dangerous cases. Various publications have shown that the response to intravesical treatment with BCG or chemotherapy is an important prognostic factor for subsequent progression and death caused by bladder cancer [Van Gils-Gielen *et al.* 1995;

Hudson and Herr, 1995; Solsona *et al.* 2000; Chade *et al.* 2010]. Approximately 10–20% of patients who have a complete response eventually progress to muscle-invasive disease compared with 66% of those who do not respond [Van Gils-Gielen *et al.* 1995; Hudson and Herr, 1995; Solsona *et al.* 2000].

Adjuvant treatment

Perioperative intravesical therapy

It is believed that tumour cell implantation immediately after resection is responsible for early recurrences and this has been used to explain the observation that initial tumours are most commonly found on the trigone and lower side walls of the bladder, whereas recurrences are often located near the dome [Heney *et al.* 1981]. Thus the assumption is that intravesical chemotherapy can kill these cells before implantation. A high variability in the 3-month recurrence rate has been demonstrated, indicating that TUR is probably incomplete in a large number of cases due to overlooked tumours or recurrences in a high percentage of patients [Brausi *et al.* 2002]. Therefore, adjuvant therapy should be considered in all patients and resection techniques improved. It needs to be shown that an improvement in resection technique (a complete resection of all tumours) is perhaps more important than adjuvant instillations. The choice of therapy may be considered on an individual basis according to what risk is acceptable for the patient and the urologist.

One immediate instillation of chemotherapy within 6–24 h of TUR was shown to significantly reduce recurrence rate compared with TUR alone [Sylvester *et al.* 2004]. Further studies are required, however, to determine the definitive role of immediate chemotherapy before BCG or further chemotherapy instillations in intermediate- and high-risk groups. There is no single chemotherapeutic drug that is superior with regard to efficacy. Mitomycin C, epirubicin and doxorubicin have all shown a beneficial effect [Sylvester *et al.* 2004]. So, an early immediate instillation is indicated in tumours at low risk of progression (single, primary, papillary lesions) as the only intravesical treatment and in those presumably at intermediate risk, for which a single instillation is considered as the initial stage of further intravesical therapy. In tumours that are presumably at high risk of recurrence/progression (solid lesions,

Table 4. Probability of recurrence according to total score.

Recurrence score	Probability of recurrence at 1 year (%)	Probability of recurrence at 5 years (%)	Recurrence risk group
0	15	31	Low risk
1–4	24	46	Intermediate group
5–9	38	62	Intermediate group
10–17	61	78	High risk

Table 5. Probability of progression according to total score.

Progression score	Probability of progression at 1 year (%)	Probability of progression at 5 years (%)	Progression risk group
0	0.2	0.8	Low risk
2–6	1.0	6.0	Intermediate group
7–13	5.0	17.0	High risk
14–23	17.0	45.0	High risk

positive urinary cytology), an immediate instillation is an option because it can have a positive impact on recurrence rate through prevention of tumour cell implantation. However, whether this immediate instillation in combination with a course of further adjuvant treatment improves the outcome compared with a course of adjuvant treatment alone remains to be determined.

In case a bladder perforation is suspected after the TUR-BT or if significant haematuria is present, the immediate postoperative chemotherapy instillation should be omitted.

Additional adjuvant intravesical chemotherapy

For patients at low risk of tumour recurrence (and without a suspected bladder wall perforation), a single immediate instillation of a chemotherapeutic agent is considered the standard treatment. No further treatment should be given in these patients before subsequent recurrence. For other patients, however, a single immediate instillation remains an incomplete treatment because the likelihood of recurrence and/or progression is considerable. The effect of the immediate instillation of chemotherapy occurs during the first and second year [Solsona *et al.* 1999; Hinotsu *et al.* 1999]. The choice between further chemotherapy and immunotherapy largely depends on the risk that needs to be reduced: recurrence or progression. A combined analysis of the EORTC-GU Group and Medical Research Council data, comparing intravesical

chemotherapy with TUR alone, demonstrated that chemotherapy prevents recurrence but not progression [Pawinski *et al.* 1996]. The ideal duration and intensity of the instillation schedule remains undefined [Sylvester *et al.* 2008]. The available data do not support any treatment longer than 1 year. If chemotherapy is given, the drug should be used at its optimal pH and the concentration of the drug maintained during instillation by reducing fluid intake. One of the instillation schedules used in an adjuvant setting is weekly mitomycin C 40 mg for 6 weeks, and in the case of negative cystoscopy, monthly instillations for 1 year.

Intravesical BCG immunotherapy

Intravesical immunotherapy results in a massive local immune response characterized by induced expression of cytokines in the urine and bladder wall and by an influx of granulocytes and mononuclear cells. BCG is an attenuated mycobacterium developed as a vaccine for tuberculosis. The vaccine is reconstituted with 50 ml of saline and should be administered through a urethral catheter under gravity drainage soon thereafter because aggregation occurs [Ratliff *et al.* 1994]. The exact antitumour action of BCG has not been elucidated until now, but several groups have demonstrated that an increase in T helper 1 urinary cytokines (e.g. gamma, interleukin-2) following BCG instillations predicts an improved outcome [de Reijke *et al.* 1996; Ratliff *et al.* 1986; Haaff *et al.* 1986].

Four meta-analyses have confirmed that BCG after TUR is superior to TUR alone or TUR and chemotherapy for the prevention of recurrence of NMIBC in patients with Ta and T1 tumours [Shelley *et al.* 2001; Han *et al.* 2006], at high risk of tumour recurrence [Shelley *et al.* 2004] and intermediate- or high-risk status [Böhle *et al.* 2003]. Also, there are studies which have confirmed the superiority of BCG over the combination of epirubicin and interferon [Duchek *et al.* 2010], mitomycin C [Järvinen *et al.* 2009] or epirubicin [Sylvester *et al.* 2010] alone for prevention of tumour recurrence, in intermediate- and high-risk tumours. Although BCG is a very effective treatment, there is a consensus that not all patients with NMIBC should be treated with BCG due to the risk of toxicity. Ultimately, the choice of treatment depends on the patient's risk of recurrence and progression (see Tables 4 and 5). The use of BCG does not alter the natural course of tumours at low risk of recurrence (see Tables 4 and 5), and could be considered to be overtreatment for this patient category. In patients with tumours at high risk of progression, for whom cystectomy is not an option, BCG including at least 1 year of maintenance is indicated.

In patients at intermediate or high risk of recurrence and intermediate risk of progression, BCG with 1 year of maintenance is more effective than chemotherapy for prevention of recurrence; however, it has more side effects than chemotherapy. For this reason BCG with maintenance and intravesical chemotherapy both remain an option. The efficacy of BCG after TUR-BT for high-risk papillary disease has been demonstrated in several series of T1 lesions, with recurrence rates of 16–40% and progression rates of 4.4–40%, a substantial improvement compared with TUR-BT alone [Cookson and Sarosdy, 1992; Pansadoro *et al.* 1995; Herr, 1997; Jimenez-Cruz *et al.* 1997; Gohji *et al.* 1999; Hurler *et al.* 1999].

For optimal efficacy, BCG must be given in a maintenance schedule, consisting of weekly instillations for 6 weeks and three weekly instillations at month 3, 6 and 12, if cystoscopy and cytology are negative [Böhle *et al.* 2003; Malmström *et al.* 2009; Sylvester *et al.* 2010]. If a recurrence is found at the 3-month cystoscopy, again 6 weeks of BCG instillations can be given followed by the maintenance schedule as described above. In the EORTC-GU Group meta-analysis, only patients who received maintenance BCG benefited. Induction BCG instillations are classically given

according to the empirical 6-weekly induction schedule that was introduced by Morales in 1976 [Morales *et al.* 1976]. The optimal number of induction instillations and the optimal frequency and duration of maintenance instillations remain unknown [Zlotta *et al.* 2000]. Treatments usually begin 2–4 weeks after the TUR-BT, allowing time for the re-epithelialization to minimize the potential for intravasation of live bacteria [Lamm, 1992a, 1992b]. In the event of a traumatic catheterization, macroscopic haematuria and symptomatic urinary tract infection, the treatment should be delayed for several days.

BCG toxicity

Serious side effects are encountered in less than 5% of patients and can be effectively treated in virtually all cases [van de Meijden *et al.* 2003]. The side effects can be divided into local (e.g. voiding complaints, haematuria) and systemic side effects (e.g. fever, hepatitis, pneumonitis, allergic reactions). Major complications can appear after systemic absorption of the drug. Thus, BCG should not be administered during the first 2 weeks after TUR-BT in patients with macroscopic haematuria, symptomatic urinary tract infection or after traumatic catheterization. BCG should not be used in immunocompromised patients (immunosuppression, HIV) [Lamm *et al.* 1992]. Although these are the recommendations, personal experience has revealed no major side effects in patients undergoing renal transplantation. Before applying intravesical BCG therapy the urologist should be aware of how to recognize and treat BCG-induced complications.

Morbidity secondary to intravesical BCG may present both locally and systemically. Most patients suffer a self-limited irritative voiding syndrome. Often there are not unified criteria for the management of BCG side effects. Irritative voiding symptoms are among the most frequent symptoms, generally self-limited, but if these persist (>48 h) the urologist will have to treat them depending on their intensity and duration with symptomatic therapy (e.g. anticholinergics). Macroscopic haematuria is not infrequent and diminishes with an expectant approach and water intake, however a urinary tract infection or residual tumour should be excluded. A febrile syndrome, if present, is usually self-limited to the first 24–48 h and below 38.5°C without general status affection. The majority of local and systemic side effects are seen during the induction

and the first half year of maintenance. During further maintenance BCG toxicity does not increase and instillations are generally well tolerated [Van der Meijden *et al.* 2003]. Recognition of risk factors, particularly traumatic catheterization or concurrent cystitis, that result in systemic BCG absorption, as well as the prompt and appropriate treatment of early side effects should significantly decrease the incidence of severe toxicity [Lamm *et al.* 1992].

Patients who develop mild symptoms of cystitis following BCG instillation, even if accompanied by low-grade fever, usually do not require specific therapy other than analgesics. As noted above, symptoms usually resolve within 48 h.

Acute fever higher than 39.0°C may occasionally develop but does not necessarily signify BCG infection. In this setting it may be impossible to distinguish an infectious from a noninfectious event. Such patients are best seen, evaluated and sometimes hospitalized for observation. Empiric therapy with a fluoroquinolone antibiotic should be considered until the etiology of the fever is established. A fluoroquinolone will treat the majority of non-BCG bacterial urinary tract infections and has reasonable antimycobacterial activity.

The cardinal sign of BCG infection is a relapsing fever with drenching night sweats persisting beyond 48 h. For acute symptoms or those that persist beyond 48 h, antituberculous therapy should be prescribed. Knowing when to administer and when to withhold BCG will prevent most complications, but even when all precautions are taken, some complications will occur. The initial step in the treatment of infectious complications is the use of isoniazid. Routine prophylactic isoniazid should not be given because animal studies have confirmed that immune stimulation, and presumably antitumour activity, can be inhibited by isoniazid prophylaxis. However, when cystitis persists for more than 2 days or is so severe that it does not respond to symptomatic treatment, isoniazid 300 mg daily is used to control the symptoms, prevent progressive infection and avoid the overgrowth of BCG, which can result in excessive organisms and suppression of the immune response. If symptoms progress despite isoniazid treatment or do not begin to abate within 1–2 weeks, rifampicin 600 mg daily is added. Rifampicin is given from the beginning in patients with potentially severe extravesical BCG infection such as pneumonitis, hepatitis or nephritis. In

patients with symptoms such as fever, malaise or bladder irritation that respond within a few days, it is generally necessary to continue antituberculous antibiotics for only 2 weeks [Lamm, 1992a, 1992b; Rodriguez *et al.* 2009]. Patients with extravesical infection and those who do not respond promptly to treatment are treated for 3 months, and those with severe or deep-seated infection are treated for 6 months. Patients with disseminated infection should also be hospitalized and treated with antituberculous agents with or without glucocorticoids. Patients who develop infectious complications severe enough to require antituberculous therapy should generally not receive further BCG bladder instillations.

Prophylactic ofloxacin decreased the incidence of moderate to severe adverse events associated with BCG intravesical therapy. Compliance with induction and maintenance therapy may be improved by adjuvant ofloxacin therapy. However, long-term comparative studies with other preventive strategies must be carried out to confirm these findings [Colombel *et al.* 2006].

Several attempts to decrease BCG-induced toxicity have been published. The Spanish group found that dose reduction of BCG resulted in less toxicity with similar efficacy in low- and intermediate-risk patients. However, in high-risk patients the full dose is still advised [Martinez-Pineiro, 2002]. Another strategy could be to reduce the number of instillations (two instead of six during the induction weeks) because the immune reaction was shown to be more favourable in mice [de Boer *et al.* 2005].

Carcinoma in situ

If concurrent CIS is found in association with muscle-invasive bladder cancer, therapy is determined according to the invasive tumour. The detection of CIS with TaT1 tumours increases the risk of recurrence and progression of TaT1 tumours [Sylvester *et al.* 2006; Fernadez-Gomez *et al.* 2009] and further treatment is mandatory. CIS cannot be cured by an endoscopic procedure only. Histological diagnosis of CIS must be followed by further treatment, either intravesical BCG instillations or radical cystectomy. No consensus exists about whether conservative therapy (intravesical BCG instillations) or aggressive therapy (cystectomy) should be done, especially in combination with concurrent high-grade papillary tumours. There is a lack of randomized trials comparing

instillation therapy and early cystectomy as immediate primary treatment. Tumour-specific survival rates after early cystectomy for CIS are excellent, but as many as 40–50% of patients might be over-treated [Van der Meijden *et al.* 2005].

The American Urological Association Guidelines and the European Association of Urology (EAU) guidelines supported BCG as the preferred initial treatment option for CIS [Smith *et al.* 1999; Sylvester *et al.* 2005b].

Treatment of failure following intravesical therapy

Patients with high-grade Ta, T1 or CIS are at high risk for recurrence and, more importantly, progression. Thus, both the American Urological Association and the EAU recommend initial intravesical treatment with BCG followed by maintenance therapy for a minimum of 1 year. The complete response rate to BCG therapy in patients with high-risk NMIBC can be as high as 80%. However, most patients with high-risk disease suffer from recurrence. Treatment with BCG is considered to have failed in the following situations:

1. When a muscle-invasive tumour is detected during follow up.
2. When a high-grade, nonmuscle invasive tumour is present at both 3- and 6-month follow up. In patients with a tumour present at 3 months, an additional BCG course can achieve a complete response in over 50% of cases, both in patients with papillary tumours and CIS [Herr *et al.* 2003], but with increasing risk of progression [Gallagher *et al.* 2008; Lerner *et al.* 2009].
3. Any worsening of the disease under BCG treatment, such as a higher number of recurrences, higher T-stage or higher grade, or the appearance of CIS, in spite of an initial response.

In patients whose condition fails to respond to conservative treatment with noninvasive recurrences and who refuse surgical therapy or are not suitable candidates for surgery, the treatment options become even more complicated. Patients with non-muscle invasive recurrence of urothelial bladder carcinoma after intravesical chemotherapy can benefit from BCG instillations [Huncharek *et al.* 2004].

However, if this treatment fails again, the treatment options are limited and include an

alternative immunotherapy regimen, low-dose BCG plus interferon-alpha [Gallagher *et al.* 2008], chemotherapy with intravesical gemcitabine [Mohanty *et al.* 2008; Di Lorenzo *et al.* 2010] or docetaxel [Barlow *et al.* 2009]. Device-assisted therapy with electromotive mitomycin C given sequentially with BCG might not only reduce the recurrence rate but also reduce progression and disease-specific mortality, although currently there is no trial in a specific population with 'BCG failure' [Yates and Roupret, 2010].

Another bladder-preserving treatment is chemotherapeutic instillations combined with hyperthermia [Witjes *et al.*, 2009; Colombo *et al.* 2011]. It was shown that in patients with primary CIS whose condition failed to respond to BCG-CIS treatment with chemotherapy using the Synergo® system (Synergo® Medical Enterprises, Amstelveen, The Netherlands), complete responses of around 50% after 2 years could be achieved. However, more data are needed. To achieve a more homogeneous heating of the bladder we have started a trial with external hyperthermia in combination with mitomycin instillations. The results of this approach are awaited.

To date, however, further research is necessary for all conservative secondary treatment options to determine which might be the most efficacious. All conservative treatments should be considered investigational. Currently, cystectomy remains the standard of care for high-risk patients whose condition has failed to respond to BCG therapy [Lightfoot *et al.* 2011].

Urine markers have been studied extensively to help diagnose bladder cancer and thereby decrease the need for cystoscopy. However, no marker is available at present that can sufficiently warrant this. Several urinary markers have higher but still insufficient sensitivity compared with cytology. To identify an optimal marker that can delay cystoscopy in the diagnosis of bladder cancer, large prospective and standardized studies are needed [Tilki *et al.* 2011]. The same is true for prognostic markers, which could help in selecting patients who need aggressive therapy from the beginning to prevent delay of effective treatment and increasing the risk to the patient.

The role of early cystectomy

Many cases of high-grade NMIBC will progress to invasion and with the risk of cancer death.

Although the initial response rate to BCG therapy in patients with CIS can be above 80%, patients whose condition fails to respond have a 50% chance of disease progression and a higher likelihood of disease-specific mortality [Catalona *et al.* 1987; Nadler *et al.* 1994]. Therefore, some experts consider it reasonable to propose immediate cystectomy to patients with NMIBC who are at high risk of progression. According to the risk tables of the EORTC (Tables 3–5) these patients have multiple recurrent high-grade tumours, high-grade T1 tumours or high-grade tumours with concurrent CIS. In these patients the following treatment options should be discussed: immediate cystectomy and conservative treatment with BCG instillations. Patients should be informed about the benefits and risks of both approaches.

Delay of cystectomy in these patients might lead to decreased disease-specific survival [Raj *et al.* 2007]. In patients in whom cystectomy is performed at the time of pathological high-risk nonmuscle-invasive disease, the 5-year disease-free survival exceeds 80% [Stein *et al.* 2001; Madersbacher *et al.* 2003; Hautmann *et al.* 2006; Shariat *et al.* 2006a, 2006b, 2006c; Ghoneim *et al.* 2008].

Follow up

Cystoscopy is the hallmark of surveillance

The EAU recommendations for follow up in patients after TUR of NMIBC are [Leblanc *et al.* 1999; Zeeger *et al.* 2000; Oge *et al.* 2000; Holmang *et al.* 2001; Fujii *et al.* 2003; Borhan *et al.* 2003; Soloway *et al.* 2003; Gofrit *et al.* 2006; Sylvester *et al.* 2006]:

1. Patients with TaT1 tumours at low risk of recurrence and progression (Tables 3–5) should have a cystoscopy at 3 months. If negative, the following cystoscopy is advised 9 months later, and then yearly for 5 years.
2. Patients with TaT1 tumours at high risk of progression and those with CIS should have a cystoscopy and urinary cytology at 3 months. If negative, the following cystoscopy and cytology should be repeated every 3 months for a period of 2 years, and every 6 months thereafter until 5 years, and then yearly. Yearly imaging of the upper tract is recommended.
3. Patients with TaT1 tumours at intermediate risk of progression (about one-third of all

patients) should have an in-between follow-up scheme using cystoscopy and cytology, which is adapted according to personal and subjective factors.

4. During follow up in patients with positive cytology and no visible tumour in the bladder, R-biopsies or biopsies with PDD (if equipment is available) and investigation of extravesical locations (CT urography, prostatic urethra biopsy) are recommended.

A number of tumour markers have shown the ability to improve upon the sensitivity of cytology, but specificity is lower for most. Because of these facts, there are no markers that are accurate enough to replace cystoscopy or cytology in the follow up of NMIBC. Change in lifestyle habits can be advised and the most important are an increase in fluids, smoking cessation and a low-fat diet.

New imaging developments

Optical coherence tomography

Optical coherence tomography (OCT) is a novel, real-time endoscopic imaging modality that permits delineation of microarchitectural features of bladder lesions. It may provide an extension of conventional cystoscopy by allowing noninvasive examination of bladder tissue at microscopic resolution (10–20 μm) [Goh *et al.* 2008]. It is not possible to examine the whole bladder using OCT, but it could be helpful to decrease the high number of false-positive biopsies if photodynamic diagnosis is used because OCT can provide the urologist with direct information on the architecture of the suspect area. Since this technique looks at the microarchitecture of the lesions in the bladder, it could also be used to grade the tumours in a more objective manner because the grading systems are known to be subject to a high inter- and intra-observer variability. Based on OCT-measured optical attenuation [$\mu(t)$], the grade of bladder urothelial carcinoma could be assessed in real time [Cauberg *et al.* 2010].

Raman molecular imaging

Raman molecular imaging (RMI) is an optical technology that combines the molecular chemical analysis of Raman spectroscopy with high-definition digital microscopic visualization. This approach also permits visualization of the physical architecture and molecular environment of cells in the urine. In 1995, Feld and colleagues

first recorded Raman spectra from the bladder. They showed that bladder cancer has a greater nucleic acid content and lower lipid content than normal bladder urothelium [Feld *et al.* 1995]. Urothelium, lamina propria and muscle layers could be clearly distinguished based on Raman spectra. Lamina propria spectra were dominated by signal contributions of collagen and the smooth muscle layer showed strong signal contributions of actin. The urothelium had a relatively strong lipid signal contribution. This technology can be applied *in vivo* by thin, flexible fibre optic catheters for analysis of the molecular composition of the normal and pathological bladder without the need for biopsies [de Jong *et al.* 2002]. A three-group algorithm constructed by Raman spectroscopy differentiated normal bladder, cystitis and urothelial carcinoma/CIS with over 90% sensitivity and specificity. In addition, this could accurately characterize urothelial carcinoma into low (G1/G2) or high (G3) grade and superficial (pTa) or invasive (pT1/pT2) stage. It has the potential to provide immediate pathological diagnoses during TUR-BT [Crow *et al.* 2004].

Draga and colleagues studied the feasibility of Raman spectroscopy for the diagnosis of bladder cancer *in vivo*. They demonstrated that high-volume Raman spectroscopy could be used *in vivo* as an objective clinical tool for real-time staging of bladder cancer invasion [Draga *et al.* 2010a, 2010b].

New drugs

Apaziquone

Apaziquone is a promising drug for intravesical use in patients with NMIBC [Witjes and Kolli, 2008]. The complete response of a marker lesion in 67% of patients was followed by a recurrence-free rate of 56.5% at 1-year follow up and 49.5% at 2-year follow up. These long-term results are good in comparison with the results of other ablative studies [Hendricksen *et al.* 2009]. Early recurrences after treatment with apaziquone are infrequent and the interval to recurrence is significantly longer compared with the historical recurrence rates for these patients. Larger prospective randomized trials are warranted to confirm these results [Jain *et al.* 2009]. Local side effects were comparable to side effects due to other chemotherapy instillations [van der Heijden *et al.* 2006].

Gemcitabine

Gemcitabine seems especially promising for the treatment of intermediate-risk NMIBC. Gemcitabine has a molecular weight of 299 D, lower than that of commonly used intravesical chemotherapeutic agents such as mitomycin C (389 D) and doxorubicin (589 D). This may enable gemcitabine to penetrate the bladder mucosa with beneficial effects in the treatment of early invasive bladder cancer (T1 disease). At the same time the molecular weight is high enough to prevent significant systemic absorption in an intact bladder [Contero and Frea, 2006]. The safety of gemcitabine is tested in different instillation schemes, drug concentrations and administered volumes. Its safety profile is excellent, with good tolerability and minimal toxicity up to 2000 mg/50 ml for 2 h instillations. In comparison with other drugs, the ablative efficacy of gemcitabine is good. The first studies on prophylactic efficacy in intermediate-risk, high-risk and BCG-refractory patients are promising but limited by the small number of patients studied. Exploring phase II and comparative randomized phase III studies should provide additional information on gemcitabine and its benefit to clinical practice [Hendricksen and Witjes, 2007].

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Conflict of interest statement

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References

- Althausen, A.F., Prout, G.R. Jr and D" Daly, J.J. Non-invasive papillary carcinoma of the bladder associated with carcinoma in situ. *J Urol.* 1976 Nov; 116(5): 575–580.
- Augustine, A., Hebert, J.R. and Kabat, G.C. Wynder, EL. Bladder cancer in relation to cigarette smoking. *Cancer Res.* 1988 Aug 1; 48(15): 4405–4408.
- Aveyard, P., Adab, P., Cheng, K.K., Wallace, D.M., Hey, K. and Murphy, M.F. Does smoking status influence the prognosis of bladder cancer? A systematic review. *BjU Int.* 2002 Aug; 90(3): 228–39. Review.
- Barlow, L., McKiernan, J., Sawczuk, I. and Benson, M. (2009) A single-institution experience with induction and maintenance intravesical docetaxel

- in the management of non-muscle-invasive bladder cancer refractory to bacille Calmette-Guérin therapy. *BJU Int* 104: 1098–1102.
- Bjerregaard, B.K., Raaschou-Nielsen, O., Sørensen, M., Frederiksen, K., Christensen, J. and Tjønneland, A. Tobacco smoke and bladder cancer—in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer*. 2006 Nov 15; 119(10): 2412–6.
- Böhle, A., Leyh, H., Frei, C., Kühn, M., Tschada, R. and Pottek, T. Single postoperative instillation of gemcitabine in patients with non-muscle-invasive transitional cell carcinoma of the bladder: a randomised, double-blind, placebo-controlled phase III multicentre study. *Eur Urol*. 2009 Sep; 56(3): 495–503. Epub 2009 Jun 21.
- Borhan, A., Reeder, J.E. and O’Connell, M.J., Wright, K.O., Wheelless L.L. di Sant’Agnese P.A. *et al.* Grade progression and regression in recurrent urothelial cancer. *J Urol*. 2003 Jun; 169(6): 2106–2109.
- Brausi, M., Collette, L., Kurth, K., van der Meijden, A.P., Oosterlinck, W. and Witjes, J.A. Variability in the recurrence rate at first follow-up cystoscopy after TUR in stage Ta T1 transitional cell carcinoma of the bladder: a combined analysis of seven EORTC studies. *Eur Urol*. 2002 May; 41(5): 523–31.
- Burger, M., van der, Aa M.N., van Oers, J.M., Brinkmann, A., van der Kwast, T.H. and Steyerberg, E.C. Prediction of progression of non-muscle-invasive bladder cancer by WHO 1973 and 2004 grading and by FGFR3 mutation status: a prospective study. *Eur Urol*. 2008 Oct; 54(4): 835–43. Epub 2007 Dec 26.
- Catalona, W.J., Hudson, M.A., Gillen, D.P., Andriole, G.L. and Ratliff T.L. Risks and benefits of repeated courses of intravesical bacillus Calmette-Guérin therapy for superficial bladder cancer. *J Urol*. 1987 Feb; 137(2): 220–224.
- Cauberg, E.C., de Bruin, D.M., Faber, D.J., de Reijke, T.M., Visser, M., de la Rosette, J.J. and van Leeuwen, T.G. (2010) Quantitative measurement of attenuation coefficients of bladder biopsies using optical coherence tomography for grading urothelial carcinoma of the bladder. *J Biomed Opt* 15: 066013.
- Cauberg, E.C., Mamoulakis, C., de la Rosette, J.J. and de Reijke, T.M. (2011) Narrow band imaging-assisted transurethral resection for non-muscle invasive bladder cancer significantly reduces residual tumour rate. *World J Urol* 29: 503–509.
- Chade, D.C., Shariat, S.F., Godoy, G., Savage, C.J., Cronin, A.M. and Bochner, B.H. Clinical outcomes of primary bladder carcinoma in situ in a contemporary series. *J Urol*. 2010 Jul; 184(1): 74–80.
- Cho, K.S., Seo, H.K., Joung, J.Y., Park, W.S., Ro, J.Y. and Han, K.S. Lymphovascular invasion in transurethral resection specimens as predictor of progression and metastasis in patients with newly diagnosed T1 bladder urothelial cancer. *J Urol*. 2009 Dec; 182(6): 2625–30. Epub 2009 Oct 17.
- Collado, A., Chéchile, G.E., Salvador, J. and Vicente J. Early complications of endoscopic treatment for superficial bladder tumors. *J Urol*. 2000 Nov; 164(5): 1529–1532.
- Colombel, M., Saint, F., Chopin, D., Malavaud, B., Nicolas, L. and Rischmann, P. (2006) The effect of ofloxacin on bacillus Calmette-Guérin induced toxicity in patients with superficial bladder cancer: results of a randomized, prospective, double-blind, placebo controlled, multicenter study. *J Urol* 176: 935–939.
- Colombo, R., Salonia, A., Leib, Z., Pavone-Macaluso, M. and Engelstein, D. Long-term outcomes of a randomized controlled trial comparing thermochemotherapy with mitomycin-C alone as adjuvant treatment for non-muscle-invasive bladder cancer (NMIBC). *BJU Int*. 2011 Mar; 107(6): 912–918. doi: 10.1111/j.1464-410X.2010.09654.x. Epub 2010 Oct 4.
- Cookson, M.S. and Sarosdy, M.F. (1992) Management of stage T1 superficial bladder cancer with intravesical bacillus Calmette-Guérin therapy. *J Urol* 148: 797–801.
- Crow, P., Uff, J.S., Farmer, J.A., Wright, M.P. and Stone, N. (2004) The use of Raman spectroscopy to identify and characterize transitional cell carcinoma in vitro. *BJU Int* 93: 1232–1236.
- de Boer, E.C., Rooyackers, S.J., Schamhart, D.H., de Reijke, T.M. and Kurth, K.H. BCG dose reduction by decreasing the instillation frequency: effects on local Th1/Th2 cytokine responses in a mouse model. *Eur Urol*. 2005 Aug; 48(2): 333–338.
- de Jong, B.W., Bakker Schut, T.C. Wolffenbutter, K.P. Nijman, J.M. Kok, D.J. and Puppels, G.J. (2002) Identification of bladder wall layers by Raman spectroscopy. *J Urol* 168: 1771–1778.
- de Reijke, T.M., de Boer, E.C., Kurth, K.H. and Schamhart, D.H. Urinary cytokines during intravesical bacillus Calmette-Guérin therapy for superficial bladder cancer: processing, stability and prognostic value. *J Urol*. 1996 Feb; 155(2): 477–482.
- Di Lorenzo, G., Perdonà, S., Damiano, R., Faiella, A., Cantiello, F. and Pignata, S. Gemcitabine versus bacille Calmette-Guérin after initial bacille Calmette-Guérin failure in non-muscle-invasive bladder cancer: a multicenter prospective randomized trial. *Cancer*. 2010 Apr 15; 116(8): 1893–900.
- Divrik, R.T., Yildirim, Ü., Zorlu, F. *et al.* (2006) The effect of repeat transurethral resection on recurrence and progression rates in patients with T1 tumours of the bladder who received intravesical mitomycin: a prospective, randomized clinical trial. *J Urol* 175: 1641–1644.

- Draga, R.O., Grimbergen, M.C., Kok, E.T., Jonges, T.N., van Swol, C.F. and Bosch, J.L. Photodynamic diagnosis (5-aminolevulinic acid) of transitional cell carcinoma after bacillus Calmette-Guérin immunotherapy and mitomycin C intravesical therapy. *Eur Urol.* 2010 Apr; 57(4): 655–60. Epub 2009 Oct 6.
- Draga, R.O., Grimbergen, M.C., Vijverberg, P.L., van Swol, C.F., Jonges, T.G., Kummer, J.A. and Ruud Bosch, J.L. (2010b) In vivo bladder cancer diagnosis by high-volume Raman spectroscopy. *Anal Chem* 82: 5993–5999.
- Duchek, M., Johansson, R., Jahnson, S., Mestad, O., Hellström, P. and Hellsten, S. Bacillus Calmette-Guérin is superior to a combination of epirubicin and interferon-alpha2b in the intravesical treatment of patients with stage T1 urinary bladder cancer. A prospective, randomized, Nordic study. *Eur Urol.* 2010 Jan; 57(1): 25–31. Epub 2009 Oct 6.
- Epstein, J.I., Amin, M.B., Reuter, V.R. and Mostofi, F.K. The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. Bladder Consensus Conference Committee. *Am J Surg Pathol.* 1998 Dec; 22(12): 1435–48.
- Feld, M.S., Manoharan, R. and Salenius, J. (1995) Detection and characterization of human tissue lesions with near infra-red Raman spectroscopy. *Adv Fluorescence Sensing Technol II*(SPIE 2388): 99–102.
- Fernandez-Gomez, J., Madero, R., Solsona, E. et al. (2009) Predicting nonmuscle invasive bladder cancer recurrence and progression in patients treated with bacillus Calmette-Guérin: the CUETO scoring model. *J Urol* 2009 182: 2195–2203 “<http://www.ncbi.nlm.nih.gov/pubmed?term=%22Fleshner%20N%22%5BAuthor%5D>” Fleshner N, HYPERLINK “<http://www.ncbi.nlm.nih.gov/pubmed?term=%22Garland%20J%22%5BAuthor%5D>” Garland J, HYPERLINK “<http://www.ncbi.nlm.nih.gov/pubmed?term=%22Moadel%20A%22%5BAuthor%5D>” Moadel A, HYPERLINK “<http://www.ncbi.nlm.nih.gov/pubmed?term=%22Herr%20H%22%5BAuthor%5D>” Herr H, HYPERLINK “<http://www.ncbi.nlm.nih.gov/pubmed?term=%22Ostroff%20J%22%5BAuthor%5D>” Ostroff J, HYPERLINK “<http://www.ncbi.nlm.nih.gov/pubmed?term=%22Trambert%20R%22%5BAuthor%5D>” Trambert R, HYPERLINK “<http://www.ncbi.nlm.nih.gov/pubmed?term=%22O’Sullivan%20M%22%5BAuthor%5D>” O’Sullivan M, HYPERLINK “<http://www.ncbi.nlm.nih.gov/pubmed?term=%22Russo%20P%22%5BAuthor%5D>” Russo P. HYPERLINK “<http://www.ncbi.nlm.nih.gov/pubmed/10590376>” \l “#” \o “Cancer.” Cancer Influence of smoking status on the disease-related outcomes of patients with tobacco-associated superficial transitional cell carcinoma of the bladder. *Cancer.* 1999 Dec 1; 86(11): 2337–45.
- Fujii, Y., Kawakami, S., Koga, F., Nemoto, T. and Kihara, K. Long-term outcome of bladder papillary urothelial neoplasms of low malignant potential. *BJU Int* 2003 Oct; 92(6): 559–562.
- Gallagher, B.L., Joudi, F.N., Maymí, J.L. and O’Donnell, M.A. (2008) Impact of previous bacille Calmette-Guérin failure pattern on subsequent response to bacille Calmette-Guérin plus interferon intravesical therapy. *Urology* 71: 297–301.
- Ghoneim, M.A., Abdel-Latif, M., el-Mekresh, M., Abol-Enein, H., Mosbah, A. and Ashamalla, A. Radical cystectomy for carcinoma of the bladder: 2,720 consecutive cases 5 years later. *J Urol.* 2008 Jul; 180(1): 121–7. Epub 2008 May 15.
- Gofrit, O.N., Pode, D., Lazar, A., Katz, R. and Shapiro, A. Watchful waiting policy in recurrent Ta G1 bladder tumors. *Eur Urol.* 2006 Feb; 49(2): 303–6; discussion 306–307. Epub 2006 Jan 6.
- Goh, A.C., Tresser, N.J., Shen, S.S. and Lerner, S.P. (2008) Optical coherence tomography as an adjunct to white light cystoscopy for intravesical real-time imaging and staging of bladder cancer. *Urology* 72: 133–137.
- Gohji, K., Nomi, M., Okamoto, M., Takenaka, A., Hara, I. and Okada, H. Conservative therapy for stage T1b, grade 3 transitional cell carcinoma of the bladder. *Urology.* 1999 Feb; 53(2): 308–13.
- Gontero, P. and Frea, B. Actual experience and future development of gemcitabine in superficial bladder cancer. *Ann Oncol.* 2006 May; 17 Suppl 5: v123–128. Review.
- Griffiths, T.R., Charlton, M., Neal, D.E. and Powell, P.H. Treatment of carcinoma in situ with intravesical bacillus Calmette-Guérin without maintenance. *J Urol.* 2002 Jun; 167(6): 2408–12.
- Grimm, M.O., Steinhoff, C., Simon, X., Spiegelhalder, P., Ackermann, R. and Vogeli T.A. Effect of routine repeat transurethral resection for superficial bladder cancer: a long-term observational study. *J Urol.* 2003 Aug; 170(2 Pt 1): 433–7.
- Han, R.F. and Pan, J.G. (2006) Can intravesical bacillus Calmette-Guérin reduce recurrence in patients with superficial bladder cancer? A meta-analysis of randomized trials. *Urology* 67: 1216–1223.
- Hautmann, R.E., Gschwend, J.E., de Petriconi, R.C., Kron, M. and Volkmer, B.G. Cystectomy for transitional cell carcinoma of the bladder: results of a surgery only series in the neobladder era. *J Urol.* 2006 Aug; 176(2): 486–92; discussion 491–2.
- Hendricksen, K., van der Heijden, A.G., Cornel, E.B., Vergunst, H., de Reijke, T.M. and van Boven, E. Two-year follow-up of the phase II marker lesion study of intravesical apaziquone for patients with non-muscle invasive bladder cancer. *World J Urol.* 2009 Jun; 27(3): 337–42. Epub 2009 Feb 13.

- Heney, N.M., Nocks, B.N., Daly, J.J., Prout, G.R. Jr, Newall, J.B., Griffin, P.P., Perrone, T.L. and Szyfelbein W.A. Ta and T1 bladder cancer: location, recurrence and progression. *Br J Urol.* 1982 Apr; 54(2): 152–157.
- Hinotsu, S., Akaza, H., Ohashi, Y. and Kotake, T. Intravesical chemotherapy for maximum prophylaxis of new early phase superficial bladder carcinoma treated by transurethral resection: a combined analysis of trials by the Japanese Urological Cancer Research Group using smoothed hazard function. *Cancer.* 1999 Nov 1; 86(9): 1818–26.
- Holmäng, S. Follow-up of patients with noninvasive and superficially invasive bladder cancer. *Semin Urol Oncol.* 2000 Nov; 18(4): 273–279.
- Holzbeierlein, J.M. and Smith, J.A. Jr. Surgical management of noninvasive bladder cancer (stages Ta/T1/CIS). *Urol Clin North Am.* 2000 Feb; 27(1): 15–24, vii–viii. Review.
- Hong, Y.M. and Loughlin, K.R. (2008) Economic impact of tumor markers in bladder cancer surveillance. *Urology* 71: 131–135.
- Hudson, M.A. and Herr, H.W. (1995) Carcinoma in situ of the bladder. *J Urol* 153: 564–572.
- Hungerhuber, E., Stepp, H., Kriegmair, M., Stief C., Hofstetter, A. and Hartmann, A. Seven years' experience with 5-aminolevulinic acid in detection of transitional cell carcinoma of the bladder. *Urology.* 2007 Feb; 69(2): 260–4.
- Hurle, R., Losa, A. and Manzetti, A. and Lembo, A. (1999) Intravesical bacille Calmette-Guérin in Stage T1 grade 3 bladder cancer therapy: a 7-year follow-up. *Urology* 54: 258–263.
- Jain, A., Phillips, R.M., Scally, A.J., Lenaz, G., Beer, M. and Puri, R. (2009) Response of multiple recurrent TaT1 bladder cancer to intravesical apaziquone (EO9): comparative analysis of tumor recurrence rates. *Urology* 73: 1083–1086.
- Järvinen, R., Kaasinen, E., Sankila, A. and Rintala, E. FinnBladder Group. Long-term efficacy of maintenance bacillus Calmette-Guérin versus maintenance mitomycin C instillation therapy in frequently recurrent TaT1 tumours without carcinoma in situ: a subgroup analysis of the prospective, randomised FinnBladder I study with a 20-year follow-up. *Eur Urol.* 2009 Aug; 56(2): 260–5. Epub 2009 Apr 16.
- Jemal, A., Murray, T., Ward, E., Samuels, A., Tiwari, R.C., Ghafoor, A., Feuer, E.J. and Thun, M.J. Cancer statistics, 2005. *CA Cancer J Clin.* 2005 Jan-Feb; 55(1): 10–30.
- Jichlinski, P., Guillou, L., Karlsen, S.J., Malmström, P.U., Jocham, D. and Brennhovd, B. Hexyl aminolevulinic acid fluorescence cystoscopy: new diagnostic tool for photodiagnosis of superficial bladder cancer—a multicenter study. *J Urol.* 2003 Jul; 170(1): 226–9.
- Jimenez-Cruz, J.F., Vera-Donoso, C.D., Leiva, O., Pamplona, M., Rioja-Sanz, L.A., and Martinez-Lasierra, M. Intravesical immunoprophylaxis in recurrent superficial bladder cancer (Stage T1): multicenter trial comparing bacille Calmette-Guérin and interferon-alpha. *Urology.* 1997 Oct; 50(4): 529–35.
- Koshikawa, T., Leyh, H. and Schenck, U. (1989) Difficulties in evaluating urinary specimens after local mitomycin therapy of bladder cancer. *Diagn Cytopathol* 5: 117–121.
- Kulkarni, G.S., Hakenberg, O.W., Gschwend, J.E., Thalmann, G., Kassouf, W. and Kamat, A. An updated critical analysis of the treatment strategy for newly diagnosed high-grade T1 (previously T1G3) bladder cancer. *Eur Urol.* 2010 Jan; 57(1): 60–70. Epub 2009 Sep 1.
- Kurth, K.H., Schellhammer, P.F., Okajima, E. *et al.* (1995) Current methods of assessing and treating carcinoma in situ of the bladder with or without involvement of the prostatic urethra. *Int J Urol* 2(Suppl. 2): 8–22.
- Lamm, D.L., van der Meijden, P.M., Morales, A., Brosman, S.A., Catalona, W.J. and Herr, H.W. Incidence and treatment of complications of bacillus Calmette-Guérin intravesical therapy in superficial bladder cancer. *J Urol.* 1992 Mar; 147(3): 596–600.
- Leblanc, B., Duclos, A.J., Bénard, F., Côté, J., Valiquette, L., Paquin, J.M. *et al.* Long-term followup of initial Ta grade 1 transitional cell carcinoma of the bladder. *J Urol.* 1999 Dec; 162(6): 1946–1950.
- Lerner, S.P., Tangen, C.M., Sucharew, H., Wood, D. and Crawford, E.D. Failure to achieve a complete response to induction BCG therapy is associated with increased risk of disease worsening and death in patients with high risk non-muscle invasive bladder cancer. *Urol Oncol.* 2009 Mar-Apr; 27(2): 155–9. Epub 2008 Mar 4.
- Levi, A.W., Potter, S.R., Schoenberg, M.P. and Epstein, J.I. Clinical significance of denuded urothelium in bladder biopsy. *J Urol.* 2001 Aug; 166(2): 457–60.
- Lightfoot, A.J., Rosevear, H.M. and O'Donnell, M.A. Recognition and treatment of BCG failure in bladder cancer. *Scientific World Journal.* 2011 Mar 7; 11: 602–613.
- Lokeshwar, V.B., Habuchi, T., Grossman, H.B., Murphy, W.M. and Hautmann, SH, Hemstreet G.P. 3rd, Bladder tumor markers beyond cytology: International Consensus Panel on bladder tumor markers. *Urology.* 2005 Dec; 66(6 Suppl 1): 35–63.
- Lopez-Beltran, A., Bassi, P., Pavone-Macaluso, M. and Montironi, R. (2004) Handling and pathology reporting of specimens with carcinoma of the urinary

- bladder, ureter, and renal pelvis. *Eur Urol* 45: 257–266.
- Losa, A., Hurle, R. and Lembo, A. (2000) Low dose bacillus Calmette-Guérin for carcinoma in situ of the bladder: long-term results. *J Urol* 163: 68–72.
- Madersbacher, S., Hochreiter, W., Burkhard, F., Thalmann, G.N., Danuser, H. and Markwalder, R. Radical cystectomy for bladder cancer today—a homogeneous series without neoadjuvant therapy. *J Clin Oncol*. 2003 Feb 15; 21(4): 690–6.
- Malmström, P.U., Sylvester, R.J., Crawford, D.E., Friedrich, M., Krege, S. and Rintala, E. An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesical mitomycin C versus bacillus Calmette-Guérin for non-muscle-invasive bladder cancer. *Eur Urol*. 2009 Aug; 56(2): 247–56. Epub 2009 Apr 24.
- Martínez-Piñero, J.A., Flores, N., Isorna, S., Solsona, E., Sebastián, J.L., Pertusa, C. *et al*, for CUETO (Club Urológico Español de Tratamiento Oncológico). Long-term follow-up of a randomized prospective trial comparing a standard 81 mg dose of intravesical bacille Calmette-Guérin with a reduced dose of 27 mg in superficial bladder cancer. *BJU Int*. 2002 May; 89(7): 671–680.
- Matzkin, H., Soloway, M.S. and Hardeman, S. Transitional cell carcinoma of the prostate. *J Urol*. 1991 Nov; 146(5): 1207–1212.
- May, M., Brookman-Amis, S., Roigas, J., Hartmann, A., Störkel, S. and Kristiansen, G. Prognostic accuracy of individual urologists in noninvasive urinary bladder carcinoma: a multicentre study comparing the 1973 and 2004 World Health Organisation classifications. *Eur Urol*. 2010 May; 57(5): 850–8. Epub 2009 Mar 31.
- McCahy, P.J., Harris, C.A. and Neal, E. (1997) The accuracy of recording of occupational history in patients with bladder cancer. *Br J Urol* 79: 91–93.
- Miki, M., Shiozawa, H., Matsumoto, T. and Aizawa, T. Transurethral resection in saline (TURis): a newly developed TUR system preventing obturator nerve reflex *Nihon Hinyokika Gakkai Zasshi*. 2003 Nov; 94(7): 671–7.
- Miladi, M., Peyromaure, M., Zerbib, M., Saighi, D. and Debré, B. The value of a second transurethral resection in evaluating patients with bladder tumours. *Eur Urol*. 2003 Mar; 43(3): 241–5.
- Millán-Rodríguez, F., Chéchile-Toniolo, G., Salvador-Bayarri, J., Huguete-Pérez, J. and Vicente-Rodríguez J. Upper urinary tract tumors after primary superficial bladder tumors: prognostic factors and risk groups. *J Urol*. 2000 Oct; 164(4): 1183–7.
- Millán-Rodríguez, F., Chéchile-Toniolo, G., Salvador-Bayarri, J., Palou, J., Algaba, F. and Vicente-Rodríguez, J. Primary superficial bladder cancer risk groups according to progression, mortality and recurrence. *J Urol*. 2000 Sep; 164(3 Pt 1): 680–4.
- Mohanty, N.K., Nayak, R.L., Vasudeva, P. and Arora, R.P. (2008) Intravesical gemcitabine in management of BCG refractory superficial TCC of urinary bladder—our experience. *Urol Oncol* 26: 616–619.
- Morales, A., Eidinger, D. and Bruce, A.W. (1976) Intracavitary bacillus Calmette-Guérin in the treatment of superficial bladder tumors. *J Urol* 116: 180–183.
- Mungan, M.U., Canda, A.E., Tuzel, E., Yorukoglu, K. and Kirkali, Z. Risk factors for mucosal prostatic urethral involvement in superficial transitional cell carcinoma of the bladder. *Eur Urol*. 2005 Nov; 48(5): 760–3. Epub 2005 Jul 1.
- Nadler, R.B., Catalona, W.J., Hudson, M.A. and Ratliff, T.L. Durability of the tumor-free response for intravesical bacillus Calmette-Guérin therapy. *J Urol*. 1994 Aug; 152(2 Pt 1): 367–373.
- Nativ, O., Witjes, J.A., Hendricksen, K. *et al*. (2009) Combined thermo-chemotherapy for recurrent bladder cancer after bacillus Calmette-Guérin. *J Urol* 182: 1313–1317.
- Nguyen, C.T. and Jones, J.S. (2008) Defining the role of NMP22 in bladder cancer surveillance. *World J Urol* 26: 51–58.
- Oge, O., Erdem, E., Atsü, N., Ahin, A. and Ozen, H. Proposal for changes in cystoscopic follow-up of patients with low-grade pTa bladder tumor. *Eur Urol*. 2000 Mar; 37(3): 271–274.
- Otto, W., Denzinger, S., Fritsche, H.M., Burger, M., Wieland, W.F, Hofstädter, F. *et al*. (2010) The WHO classification of 1973 is more suitable than the WHO classification of 2004 for predicting survival in pT1 urothelial bladder cancer. *BJU Int* 107: 404–408.
- Pan, C.C., Chang, Y.H., Chen, K.K., Yu, H.J., Sun, C.H. and Ho, D.M. Prognostic significance of the 2004 WHO/ISUP classification for prediction of recurrence, progression, and cancer-specific mortality of non-muscle-invasive urothelial tumors of the urinary bladder: a clinicopathologic study of 1,515 cases. *Am J Clin Pathol*. 2010 May; 133(5): 788–95.
- Pansadoro, V., Emiliozzi, P., Defidio, L., Donadio, D., Florio, A., Maurelli, S. *et al*. Bacillus Calmette-Guérin in the treatment of stage T1 grade 3 transitional cell carcinoma of the bladder: long-term results. *J Urol* 154: 2054–2058.
- Pawinski, A., Sylvester, R., Kurth, K.H., Bouffou, C., van der Meijden, A. and Parmar, M.K. A combined analysis of European Organization for Research and Treatment of Cancer, and Medical Research Council randomized clinical trials for the prophylactic treatment of stage TaT1 bladder cancer. European

- Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group and the Medical Research Council Working Party on Superficial Bladder Cancer. *J Urol*. 1996 Dec; 156(6): 1934–40, discussion 1940–1.
- Ploeg, M., Aben, K.K.H. and Kiemeny, L.A. (2009) The present and future burden of urinary bladder cancer in the world. *World J Urol* 27: 289–293.
- Puente, D., Harge, P., Greiser, E. *et al.* (2006) A pooled analysis of bladder cancer case–control studies evaluating smoking in men and women. *Cancer Causes Contr* 17: 71–79.
- Raitanen, M.P., Aine, R., Rintala, E., Kallio, J., Rajala, P. and Juusela, H. Differences between local and review urinary cytology in diagnosis of bladder cancer. An interobserver multicenter analysis. *Eur Urol*. 2002 Mar; 41(3): 284–9.
- Raj, G.V., Herr, H., Serio, A.M. *et al.* (2007) Treatment paradigm shift may improve survival of patients with high risk superficial bladder cancer. *J Urol* 177: 1283–1286.
- Raj, G.V., Herr, H., Serio, A.M., Donat, S.M., Bochner, B.H. and Vickers A.J. Treatment paradigm shift may improve survival of patients with high risk superficial bladder cancer. *J Urol*. 2007 Apr; 177(4): 1283–6; discussion 1286.
- Ratliff, T.L., Ritchey, J.K., Brandhorst, J. and Hanna, M.G. Jr (1994) Time-dependent aggregation of reconstituted BCG vaccine. *J Urol* 152: 2147–2150.
- Rodríguez, F., Palou, J., Martínez, R., Rodríguez, O., Rosales, A., Huguet, J. and Villavicencio H. Practical guideline for the management of adverse events associated with BCG installations. *Arch Esp Urol*. 2008 Jun; 61(5): 591–6.
- Samanic, C.M., Kogevinas, M., Silverman, D.T., Tardón, A., Serra, C. and Malats, N. Occupation and bladder cancer in a hospital-based case-control study in Spain. *Occup Environ Med*. 2008 May; 65(5): 347–53. Epub 2007 Oct 19.
- Sauter, G., Algaba, F., Amin, M. *et al.* (2004) Tumours of the urinary system: non-invasive urothelial neoplasias. In: Eble, J.N., Sauter, G., Epstein, J.I. and Sesterhenn, I. (eds) *WHO classification of Tumours of the Urinary System and Male Genital Organs*. Lyon: IARCC Press, pp. 29–34.
- Schips, L., Augustin, H., Zigeuner, R.E. *et al.* (2002) Is repeated transurethral resection justified in patients with newly diagnosed superficial bladder cancer? *Urology* 59: 220–223.
- Schlomer, B.J., Ho, R., Sagalowsky, A. *et al.* (2010) Prospective validation of the clinical usefulness of reflex fluorescence in situ hybridization assay in patients with atypical cytology for the detection of urothelial carcinoma of the bladder. *J Urol* 183: 62–67.
- Schmidbauer, J., Witjes, F., Schmeller, N., Donat, R., Susani, M. and Marberger, M. Improved detection of urothelial carcinoma in situ with hexaminolevulinat fluorescence cystoscopy. *J Urol*. 2004 Jan; 171(1): 135–8.
- Schmitz-Drager, B.J., Beiche, B., Tirsar, L.A. *et al.* (2007) Immunocytology in the assessment of patients with asymptomatic microhaematuria. *Eur Urol* 51: 1582–1588.
- Schumacher, M.C., Holmäng, S., Davidsson, T., Friedrich, B., Pedersen, J. and Wiklund, N.P. Transurethral resection of non-muscle-invasive bladder transitional cell cancers with or without 5-aminolevulinic Acid under visible and fluorescent light: results of a prospective, randomised, multicentre study. *Eur Urol*. 2010 Feb; 57(2): 293–9. Epub 2009 Nov 6.
- Schwaibold, H.E., Sivalingam, S., May, F. and Hartung, R. The value of a second transurethral resection for T1 bladder cancer. *BJU Int*. 2006 Jun; 97(6): 1199–1201.
- Shariat, S.F., Karakiewicz, P.I., Palapattu, G.S., Lotan, Y., Rogers, C.G. and Amiel, G.E. Outcomes of radical cystectomy for transitional cell carcinoma of the bladder: a contemporary series from the Bladder Cancer Research Consortium. *J Urol*. 2006 Dec; 176(6 Pt 1): 2414–22; discussion 2422.
- Shariat, S.F., Karam, J.A. and Lerner, S.P. (2008) Molecular markers in bladder cancer. *Curr Opin Urol* 18: 1–8.
- Shariat, S.F., Palapattu, G.S., Amiel, G.E., Karakiewicz, P.I., Rogers, C.G. and Vazina, A. Characteristics and outcomes of patients with carcinoma in situ only at radical cystectomy. *Urology*. 2006 Sep; 68(3): 538–42. Epub 2006 Sep 18.
- Shelley, M.D., Kynaston, H., Court, J., Wilt, T.J., Coles, B. and Burgon, K. A systematic review of intravesical bacillus Calmette-Guérin plus transurethral resection vs transurethral resection alone in Ta and T1 bladder cancer. *BJU Int*. 2001 Aug; 88(3): 209–16.
- Shelley, M.D., Wilt, T.J., Court, J. *et al.* (2004) Intravesical bacillus Calmette-Guérin is superior to mitomycin C in reducing tumour recurrence in high-risk superficial bladder cancer: a metaanalysis of randomized trials. *BJU Int* 93: 485–490.
- Shiozawa, H., Aizawa, T., Ito, T. and Miki, M. A new transurethral resection system: operating in saline environment precludes obturator nerve reflexes. *J Urol*. 2002 Dec; 168(6): 2665–7
- Smith, J.A. Jr, Labasky, R.F., Cockett, A.T., Fracchia, J.A., Montie, J.E. and Rowland, R.G. Bladder cancer

- clinical guidelines panel summary report on the management of non-muscle invasive bladder cancer (stages Ta, T1 and T1S). The American Urological Association. *J Urol*. 1999 Nov; 162(5): 1697–1701.
- Sobin, L.H., Gospodariwicz, M. and Wittekind, C. (eds) (2009) *TNM Classification of Malignant Tumors*. UICC International Union Against Cancer. 7th edn. Oxford: Wiley-Blackwell, pp. 262–265.
- Soloway, M.S. It is time to abandon the “superficial” in bladder cancer. *Eur Urol*. 2007 Dec; 52(6): 1564–5. Epub 2007 Jul 17.
- Soloway, M., Bruck, D.S. and Kim, S.S. (2003) Expectant management of small recurrent, non-invasive papillary bladder tumours. *J Urol* 170: 438–441.
- Solsona, E., Iborra, I., Dumont, R., Rubio-Briones J., Casanova, J. and Almenar, S. The 3-month clinical response to intravesical therapy as a predictive factor for progression in patients with high risk superficial bladder cancer. *J Urol*. 2000 Sep; 164(3 Pt 1): 685–9.
- Solsona, E., Iborra, I., Ricos, J.V. *et al.* (1996) Extravesical involvement in patients with bladder carcinoma in situ: biological and therapy implications. *J Urol* 155: 895–899.
- Solsona, E., Iborra, I., Ricós, J.V., Monrós, J.L., Casanova, J. and Dumont, R. Effectiveness of a single immediate mitomycin C instillation in patients with low risk superficial bladder cancer: short and long-term followup. *J Urol*. 1999 Apr; 161(4): 1120–3.
- Solsona, E., Iborra, I., Ricós, J.V., Monrós, J.L., Dumont, R. and Almenar, S. Extravesical involvement in patients with bladder carcinoma in situ: biological and therapy implications. *J Urol*. 1996 Mar; 155(3): 895–9; discussion 899–900.
- Stein J.P., Lieskovsky G., Cote R., Groshen S., Feng A.C. and Boyd S. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. *J Clin Oncol*. 2001 Feb 1; 19(3): 666–75.
- Stenzl, A., Burger, M., Fradet, Y., Mynderse, L.A., Soloway, M.S. and Witjes, J.A. Hexaminolevulinate guided fluorescence cystoscopy reduces recurrence in patients with nonmuscle invasive bladder cancer. *J Urol*. 2010 Nov; 184(5): 1907–13. Epub 2010 Sep 17.
- Sylvester, R.J., Brausi, M.A., Kirkels, W.J., Hoeltl, W., Calais Da Silva, F. and Powell, P.H. Long-term efficacy results of EORTC genito-urinary group randomized phase 3 study 30911 comparing intravesical instillations of epirubicin, bacillus Calmette-Guérin, and bacillus Calmette-Guérin plus isoniazid in patients with intermediate- and high-risk stage Ta T1 urothelial carcinoma of the bladder. *Eur Urol*. 2010 May; 57(5): 766–73. Epub 2009 Dec 18.
- Sylvester, R.J., van der Meijden, A., Witjes, J.A., Jakse, G., Nonomura, N. and Cheng, C. High-grade Ta urothelial carcinoma and carcinoma in situ of the bladder. *Urology*. 2005 Dec; 66(6 Suppl 1): 90–107.
- Sylvester, R.J., van der Meijden, A.P., Witjes, J.A. and Kurth, K. Bacillus calmette-guerin versus chemotherapy for the intravesical treatment of patients with carcinoma in situ of the bladder: a meta-analysis of the published results of randomized clinical trials. *J Urol*. 2005 Jul; 174(1): 86–91; discussion 91–2.
- Sylvester, R.J., van der Meijden, A.P., Oosterlinck, W., Witjes, J.A., Bouffieux, C. and Denis, L. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur Urol*. 2006 Mar; 49(3): 466–5; discussion 475–7. Epub 2006 Jan 17.
- Tilki, D., Burger, M., Dalbagni, G., Grossman, H.B., Hakenberg, O.W., Palou, J. *et al.* (2011) Urine markers for detection and surveillance of non-muscle-invasive bladder cancer. *Eur Urol* 60: 484–592.
- van der Heijden, A.G., Moonen, P.M., Cornel, E.B., Vergunst, H., de Reijke, T.M., van Boven, E. *et al.* (2006) Phase II marker lesion study with intravesical instillation of apaziquone for superficial bladder cancer: toxicity and marker response. *J Urol* 176: 1349–1353.
- van der Meijden, A., Oosterlinck, W., Brausi, M., Kurth, K.H., Sylvester, R. and de Balincourt, C. Significance of bladder biopsies in Ta,T1 bladder tumors: a report from the EORTC Genito-Urinary Tract Cancer Cooperative Group. EORTC-GU Group Superficial Bladder Committee. *Eur Urol*. 1999 Apr; 35(4): 267–71.
- Van der Meijden, A., Sylvester, R., Collette, L. *et al.* (2000) The role and impact of pathology review on stage and grade assessment on stages Ta and T1 bladder tumors: a combined analysis of 5 European Organization for Research and Treatment of Cancer Trials. *J Urol* 164: 1533–1537.
- van der Meijden, A.P., Sylvester, R., Oosterlinck, W., Solsona, E., Boehle, A. and Lobel, B. EAU guidelines on the diagnosis and treatment of urothelial carcinoma in situ. *Eur Urol*. 2005 Sep; 48(3): 363–71.
- van der Meijden, A.P., Sylvester, R.J., Oosterlinck, W., Hoeltl, W. and Bono, A.V. EORTC Genito-Urinary Tract Cancer Group. Maintenance Bacillus Calmette-Guerin for Ta T1 bladder tumors is not associated with increased toxicity: results from a European Organisation for Research and Treatment of Cancer Genito-Urinary Group Phase III Trial. *Eur Urol*. 2003 Oct; 44(4): 429–34.
- van Gils-Gielen, R.J., Witjes, W.P., Caris, C.T., Debruyne, F.M., Witjes, J.A. and Oosterhof, G.O. Risk factors in carcinoma in situ of the urinary bladder. Dutch South East Cooperative Urological Group. *Urology*. 1995 Apr; 45(4): 581–6.

- Van Rhijn, B.W.G., van der Kwast, T.H., Kakiashvili, D.M. *et al.* (2010a) Pathological stage review is indicated in primary pT1 bladder cancer. *BJU Int* 106: 206–211.
- Varkarakis, M.J., Gaeta, J., Moore, R.H. and Murphy, G.P. Superficial bladder tumor. Aspects of clinical progression. *Urology*. 1974 Oct; 4(4): 414–420.
- Witjes, A., Hendricksen, K., Gofrit, O., Risi, O. and Nativ, O. Intravesical hyperthermia and mitomycin-C for carcinoma in situ of the urinary bladder: experience of the European Synergo working party. *World J Urol*. 2009 Jun; 27(3): 319–324. Epub 2009 Feb 22.
- Witjes, J.A., Redorta, J.P., Jacqmin, D., Sofras, F., Malmström, P.U. and Riedl, C. Hexaminolevulinat-guided fluorescence cystoscopy in the diagnosis and follow-up of patients with non-muscle-invasive bladder cancer: review of the evidence and recommendations. *Eur Urol*. 2010 Apr; 57(4): 607–14. Epub 2010 Jan 22.
- Yates, D.R. and Roupret, M. (2010) Failure of bacille Calmette-Guérin in patients with high risk non-muscle-invasive bladder cancer unsuitable for radical cystectomy: an update of available treatment options. *BJU Int* 106: 162–167.
- Zeegers, M.P., Swaen, G.M., Kant, I., Goldbohm, R.A. and van den Brandt, P.A. Occupational risk factors for male bladder cancer: results from a population based case cohort study in the Netherlands. *Occup Environ Med*. 2001 Sep; 58(9): 590–6.
- Zeegers, M.P., Tan, F.E., Dorant, E. and van Den Brandt, P.A. The impact of characteristics of cigarette smoking on urinary tract cancer risk: a meta-analysis of epidemiologic studies. *Cancer*. 2000 Aug 1; 89(3): 630–9.
- Zlotta, A.R., van Vooren, J.P., Huygen, K., Drowart, A., Decock, M., Pirson, M., Jurion, F., Palfliet, K., Denis, O., Simon, J. and Schulman, C.C. What is the optimal regimen for BCG intravesical therapy? Are six weekly instillations necessary? *Eur Urol*. 2000 Apr; 37(4): 470–77.
- Zlotta, A.R., Fleshner, N.E. and Jewett, M.A. (2009) The management of BCG failure in non-muscle-invasive bladder cancer: an update. *Can Urol Assoc J* 3(6 Suppl. 4): S199–S205.