European Association of Urology

GUIDELINES ON BLADDER CANCER*

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1. BACKGROUND

The incidence of bladder carcinoma is rising in Western countries. In 1996, approximately 53,000 patients were diagnosed with bladder cancer in the USA (1), 9,000 in France (2), 2,000 in Sweden (3) 8,000 in Spain (4) and 1,120 in Belgium. Approximately 75–85% of patients present with disease confined to the mucosa (stage Ta–Tis) or submucosa (stage T1). The other 15–25% have muscle invasion or nodal disease (stages T2–T4, N+) at presentation (1). The management of superficial bladder cancer (SBC) has become more complex, with urological opinion differing with regard to initial investigation, treatment and follow-up.

2. CLASSIFICATION

The tumour node metastases (TNM) 1992 classification approved by the Union International Contre le Cancer (UICC) was widely accepted (6). TNM 97 (Table 1) (7) differs from TNM 92 in the T2 stage, which now includes all bladder wall infiltration (T2a inner half, T2b outer half).

Table 1: 1997 TNM classification of urinary bladder cancer

Primary tumour		
Ta		Non-invasive papillary
Tis		In situ: ‘flat tumour’
T1		Subepithelial connective tissue
T2		Muscularis
	T2a	Inner half
	T2b	Outer half
T3		Beyond muscularis
	T3a	Microscopically
	T3b	Extravesical mass
T4		Other adjacent structures
	T4a	Prostate, uterus, vagina
	T4b	Pelvic wall, abdominal wall
Lymph nodes		
N1		Single = 2cm
N2		Single > 2–5 cm, multiple = 5 cm
N3		> 5 cm
Distant metastasis		
M1		Distant metastasis

The World Health Organization (WHO) histological classification is generally applied throughout most of the world (Table 2).

Table 2: Histological grading of World Health Organisation and International Pathology Concensus Committee 1988(5)

PTNM pathological classification
The pT, pN, and pM categories correspond to the T, N, and M categories.

G	**Histopathological grading**
GX	Grade of differentiation cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3–4	Poorly differentiated/undifferentiated

More than 90% of bladder cancers are transitional cell carcinoma (TCC); the remainder are squamous cell or adenocarcinoma (8).

Bladder tumours are considered superficial (Tis–Ta–T1) or infiltrative (T2–T3–T4) based on cystoscopy, transurethral resection (TUR), imaging studies and histopathological findings.

Definition ambiguities of superficial and infiltrative tumours

A papillary tumour confined to the mucosa is classified as stage Ta according to the TNM system. Tumours that have invaded the lamina propria are classified as stage T1. As Ta and T1 can be removed by TUR, they are grouped under the heading SBC for therapeutic purposes. Also included under this heading are flat, high-grade tumours confined to the mucosa, commonly classified as carcinoma in situ (CIS) (8). However, molecular biology techniques, and clinical experience have demonstrated the highly malignant, invasive potential of CIS and T1 lesions (9,10).

Inter- and intra-observer variability in staging and grading

Despite well-defined criteria for the diagnosis of TCC, there is significant variability among pathologists in terms of defining dysplasias and CIS. There is also important inter-observer variability in classifying stage T1 versus Ta tumours and grading tumours (11–14). As a consequence, our group strongly recommends that the urologist reviews histological findings with their pathologist.

3. RISK FACTORS

Carcinoma of the bladder is unique among human neoplasms in that many of its aetiological factors are known and the urologist should be aware of the types of occupational exposures to urothelial carcinogens that occur (15). Aromatic amines were the first to be recognized. At-risk groups include workers in the following industries: printing, iron foundry, aluminium smelting, industrial painting, gas and tar manufacturing. The use of standard questionnaires is advised in order to take an occupational history of patients with bladder cancer (16).

Another prominent risk factor is cigarette smoking. Smoking leads to higher mortality 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 (17). Patients with initial grade III tumours were significantly more likely to be heavy smokers than those with less aggressive disease (18).

4. DIAGNOSIS

4.1 Early detection and symptoms

Early symptom recognition in bladder tumours is a key to better prognosis (19,20). An educational programme designed for the general population and primary care practitioners is crucial to promote early diagnosis. Haematuria is the most common finding in bladder cancer. The degree of haematuria does not correlate with the extent of the disease. It may be grossly visible to the patient or simply found on routine urinalysis. Any degree of haematuria, however, requires evaluation for bladder cancer, even if another potential cause of haematuria (e.g. renal calculus, bacterial cystitis) is found.

Bladder cancer may also present symptoms of voiding irritability. Patients may complain of urgency, dysuria and increased urinary frequency. Although these symptoms are more commonly indicative of bacterial cystitis, negative bacterial cultures with persistence of symptoms, with or without haematuria, should prompt investigation for the possible presence of bladder cancer including CIS (21).

The policy regarding asymptomatic microscopic haematuria is still unclear, except in patients over 50 years of age, who should be examined by a urologist (22,23). The incidence of underlying malignancy in patients over 50 years with asymptomatic microscopic haematuria is approximately 5%, while an incidence of around 10% is found in those with symptomatic microscopic haematuria (24).

Screening for asymptomatic haematuria is not recommended because its positive predictive value is too low (0.5%) to warrant mass screening (23,25,26). However, routine screening for microscopic haematuria may be indicated for populations exposed to bladder carcinogens, including heavy smokers.

4.2 Physical examination

Physical examination, including digital rectal examination and bimanual pelvic palpation, is recommended when haematuria is found. However, 85% of patients with bladder cancer initially present with superficial disease. Therefore, physical examination plays a limited role in the diagnosis, except to exclude co-existing pathology (27).

4.3 Imaging

Intravenous pyelography IVP

Large tumours may be seen as filling defects in the bladder or may restrict symmetrical bladder wall expansion during filling in invasive tumours. Intravenous pyelography (IVP) is also used to detect filling defects in the calices, renal pelvis and ureters, and hydronephrosis, which may indicate the presence of a ureteral cancer or a muscle-invasive bladder cancer at the ureteral orifice (28,29). The necessity to perform routine IVP at initial diagnosis is now questioned because of the low incidence of important findings obtained with this method (30,31).

Ultrasonography

Ultrasonography has been used with increasing frequency as the initial means of urinary tract imaging, not only because it avoids the use of contrast agents, to which some patients may be allergic, but also because more sensitive transducers have allowed improved imaging of the upper urinary tract and bladder. Transabdominal ultrasound permits characterization of renal masses, detection of hydronephrosis and visualization of intraluminal filling defects in the bladder. Combined with plain abdominal film, it was found to be as accurate in the diagnosis of the cause of haematuria as IVP, and proved to be more pertinent in detecting bladder tumours (32,30).

Computed tomography CT

Computed tomography (CT) scanning may be part of the evaluation of invasive bladder tumours and the evaluation of pelvic and abdominal lymph node metastasis. Its usefulness in predicting the local extent of the disease is reduced by artefactual abnormalities in the perivesical tissues. These may result from inflammatory processes caused by prior resections and can lead to overstaging (32).

CT scanning may permit the evaluation of lymph node enlargement, but it does not provide reliable information on the microscopic aspects of disease. Thus, sensitivity in detecting nodal metastasis has been low. On this basis, the major use of CT has been relegated to the detection of enlarged lymph nodes and possible liver metastases (33).

Bone scan

The clinical significance of a routine bone scan before total cystectomy in infiltrative tumours is questionable except in the presence of an increased alkaline phosphatase level or in patients suffering from bone pain (34).

4.4 Urinary cytology

Examination of a voided urine or bladder barbotage specimen for exfoliated cancer cells is particularly useful when a high-grade malignancy or CIS is present (35,36). Specimens for cytology should be provided when the patient is well hydrated to optimize the appearance of the cancer cells.

Urinary specimens for cytology should not be obtained from the first-voided morning specimen. Even if upper tract or bladder imaging studies are negative, findings of positive urinary cytology may indicate a source of cancer anywhere in the urinary tract, from the calyx, through the ureters, into the bladder and urethra. Moreover, negative voided urinary cytology does not necessarily exclude the presence of a low-grade bladder tumour (36). Cytological interpretation can be problematic; low cellular yields, atypia, degenerative changes and therapeutic alterations contribute to the difficulty (37). These reasons stimulate the research on more reliable tests on urine to detect urothelial malignancies.

4.5 New tests to replace cytology

Many studies in the last few years have focused on evaluating urinary markers. Tests for bladder tumour antigen, NMP 22 (Nuclear Matrix Protein), fibrin-degradation products, Quanticyt and Immunocyt, are now already commercially available. Most of these tests have a better sensitivity for detecting bladder cancer, but specificity is much lower. Hence false-positive tests can lead to unnecessary imaging and bladder biopsies. It remains unclear if these tests offer additional information which is useful for decision-making, treatment and prognosis of superficial bladder tumours as prospective multicentre data are lacking (38). Combining these new markers may optimize their performance, allowing the advantages of one test to correct the shortcomings of another. However, as Brown (39) commented, “until an obvious winner is declared in the race to find a bladder tumour marker, urinary cytology will remain the gold standard screening method.”

4.6 Cystoscopy and TUR

The diagnosis of bladder cancer ultimately depends on cystoscopic examination of the bladder and pathological evaluation of the resected lesion. Cystoscopy may initially be performed without anaesthesia when assessing a patient for bladder cancer. If a bladder cancer has been visualized in earlier imaging studies or if urinary cytology has previously been found to be positive, diagnostic cystoscopy can be omitted and the

patient scheduled for cystoscopy and biopsy or tumour resection under anaesthesia.

With the patient anaesthetized a bimanual examination should be performed, first to assess whether or not a mass is palpable in the bladder and, if so, whether or not it is fixed to the pelvic wall. Bimanual examination may be performed both before and after TUR. The presence of a palpable mass after resection implies that there is an extravesical tumour. It may be of particular interest to follow the results of pre-cystectomy irradiation (40). TUR of the bladder tumour should be performed so as to maximize the preservation of architectural detail and the relationship of the tumour to the various layers of the bladder wall. The extent to which the tumour involves the various layers of the bladder wall has traditionally primarily been used for staging bladder cancer and determining prognosis. For pathological evaluation, the more superficial component of the tumour should be resected separately from its deeper component.The use of cautery current should be minimized to preserve pathological detail and avoid cautery artefact.

Biopsy specimens of the tumour and suspected area should be taken to map the extent of the disease. Both cold cup biopsies to preserve the histological architecture and TUR biopsies to determine the extent of the disease should be performed (41). Random biopsies of normal mucosa are indicated in the presence of positive cytology, even in the absence of a tumour, or in any non-papillary tumour. Random biopsies in patients with solitary papillary lesions are contra-indicated because of the absence of additional information (42) and because they may be hazardous, as lesions to the mucosa can provoke implantation of tumour cells (43). Prostatic urethra biopsies by TUR are indicated if there is suspicion of Tis of the bladder in view of the high frequency of involvement of the prostatic urethra (44).

4.7 RECOMMENDATIONS

1. Mandatory evaluations

- Physical examination (including digital rectal and pelvic examination)
- Renal and bladder ultrasonography and/or IVP
- Cystoscopy with description of the tumour: size, site, appearance (a diagram of the bladder should be included)
- Urinalysis
- Urinary cytology
- TUR with:
  - biopsy of the underlying tissue
  - random biopsies in the presence of positive cytology, large or non-papillary tumour
  - biopsy of the prostatic urethra in cases of Tis or suspicion of it

2. When the bladder tumour is muscle infiltrative and radical treatment is indicated, the following tests are mandatory

- Chest X-ray
- IVP and/or abdominal/pelvic CT scan
- Liver ultrasonography
- Bone scan if symptoms are present or alkaline phosphatase level is elevated

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5. TREATMENT

After the diagnostic work-up, it should be evident whether the bladder tumour is superficial (Ta-T1), CIS or invasive (more than T1). Further treatment and follow-up for these three groups is completely different. The highest T and G categories detected in the bladder define the treatment.

- Ta-T1 are superficial bladder tumours. Treatment will be directed towards the prevention of recurrence and progression.
- T1 G3 has a high tendency to progress. The role of early cystectomy is still a matter of debate.
- Tis is a potentially highly malignant disease that can still be treated in the majority of cases, with bladder instillations of bacillus Calmette-Guérin (BCG). A cystectomy is necessary when this fails to cure the disease after two cycles of 6-8 weekly instillations.
- Tumours of T2 or higher category are infiltrating tumours and cystectomy will be necessary in the majority of cases. Bladder preservation can be an option in selected cases.
- N+ and metastatic disease require additional therapeutic approaches.

5.1 Treatment of Ta-T1 lesions

The therapeutic regimen for Ta-T1 lesions will take into account the risk of disease recurrence and progression (prognostic factors of the tumours), side-effects and cost effectiveness. The recurrence rate of SBC, even after adequate treatment, is widely documented (1,2). The risk of progression to invasive cancer is low in the

majority of cases, but goes up to 50% in high-grade T1 G3 (2,3), which represents around 10% of cases.

The risk of disease recurrence and progression can be predicted on the basis of clinical and pathological data, which become available at the initial TUR and diagnostic work-up of the SBC. They are called the prognostic factors of the SBC.

Prognostic factors

Several large groups of clinical investigators in the field of SBC have identified prognostic factors that allow the identification of different prognostic categories (4-8). Several important parameters of prognostic value are easy to assess. For disease recurrence they are, in descending importance, the:

1. Number of tumours present at diagnosis
2. Recurrence rate in the previous period; a recurrence at 3 months
3. Size of the tumour: the larger the tumour, the higher the risk of recurrence
4. Anaplasia grade of the tumour

For evolution to invasive disease, the anaplasia grade and T-category are of utmost importance. Tumours at the bladder neck have a worse prognosis than elsewhere (9). Based on prognostic factors, SBC can be divided into the following risk groups:

- Low-risk tumours: single, Ta, G1, < 3 cm diameter
- High-risk tumours: T1, G3, multifocal or highly recurrent, CIS
- Intermediate: all other tumours, Ta-T1, G1-G2, multifocal, > 3 cm diameter

One single chemotherapeutic instillation immediately after TUR in all papillary SBC

One single instillation with epirubicin or mitomycin C within 6 h of TUR is able to reduce the disease recurrence rate by about 50% and is therefore advocated in all SBC cases, except when bladder perforation is suspected (10,11). BCG is contra-indicated because of the danger of general side-effects in the presence of open wounds in the bladder.

In intermediate-risk tumours that need further instillation, an early instillation can reduce the need for maintenance therapy (12). Immediate instillation after TUR with a chemotherapeutic agent should be encouraged in all cases.

Single Ta-T1, G1 smaller than 3 cm diameter and papillary tumours need no further treatment as the recurrence rate in this group is very low (< 0.2/year after one single instillation immediately after TUR).

A 4-8 week course followed by monthly instillation with chemotherapeutic agents in intermediate- and high-risk tumours

Tumours with a high risk of recurrence, i.e. recurrent multiple Ta-T1, G1-G2, should be treated with a 4-8 week course of bladder instillation. Severe bladder irritation is a reason to delay or stop the treatment to avoid invalidating symptoms for the patient and later bladder contraction. Side-effects are related to the intensity of the treatment regimen.

Maintenance chemotherapy

The usefulness of repeated instillations with chemotherapeutic agents is not clearly defined. In highly recurrent tumours or those with a high risk of progression, continuation of monthly instillations after the first induction course is advocated. Maintenance therapy lasting longer than 6 months did not improve the reduction in disease recurrence rate and prevention of progression achieved with an early instillation after TUR in SBC at intermediate risk (12). There is no proof that chemotherapeutic instillations lasting longer than 6 months are worthwhile if no recurrence is noticed. Intravesical therapy may be effective mainly by reducing the hazard of recurrence in the first phase after therapy.

Treatment of disease recurrence

On recurrence, the initial instillation schedule is restarted. In cases of highly recurrent tumours or multiple recurrence, a change to BCG therapy is advocated because of its proven results in these circumstances (13,14). Progression of T1 tumours involves muscle infiltration and should be treated accordingly.

Chemotherapeutic agents used for bladder instillations

Several chemotherapeutic agents have been found to provoke chemoresection of SBC marker lesions. None have been found to be superior to the others. The most frequently used agents are mitomycin C, epirubicin and doxorubicin.

The chemotherapeutic agents are dissolved in 30-50 mL of physiological solution or water and are kept in the bladder for 1-2 h. The commonly advocated doses for mitomycin C are 2-40 mg, for epirubicin, 50-80 mg and 50 mg for doxorubicin, but real dose-response curves are lacking. The patient is encouraged not to drink before the instillation to avoid diluting it.

In terms of side-effects, chemical cystitis is related to the intensity of the regimen, i.e. concentration and frequency, and occurs with all the drugs used. It heals spontaneously in most instances after stopping the treatment. A contracted bladder can appear in patients who develop serious chemical cystitis. An allergic skin reaction occurs frequently on the hands and in the genital region with mitomycin C. Washing the hands and genital region after micturition is useful in order to avoid this.

BCG instillations

The mechanism of BCG activity is not yet understood, although most evidence suggests a form of immunotherapy. It has been found to be more effective in high-risk SBC. It is also currently accepted that BCG prevents disease progression (15,17). It is not confirmed by the results of other studies (14).

Six-weekly induction instillations of BCG are necessary to provoke an immunological response and three cycles are necessary as a booster to obtain a good immunological reaction. In papillary T1-Ta, G1-G2 lesions, the dose can be reduced to 25% with the same effectiveness as the full dose and fewer general side-effects (18,19,20). No differences among different strains of BCG have been demonstrated.

Side-effects are mostly local irritation of the bladder, but general flu-like symptoms can occur as well as some rare severe complications, such as BCG sepsis, prostatitis, orchitis and hepatitis (16). For this reason, BCG should not be used when open wounds are present in the bladder or urethra, for instance shortly after TUR or when macroscopic haematuria is present. It is advisable to wait 14 days after TUR of the bladder before starting BCG therapy. For the same reason, BCG is not indicated in low-risk groups in which the potential danger of BCG does not counterbalance its advantage.

Lower disease recurrence rates have been reported after BCG maintenance therapy of up to 3 years. Boosters of BCG were given at 3, 6, 12, 18, 24, 30 and 36 months (17). Whether or not this heavy schedule is necessary for all patients is uncertain. It is possibly the treatment of choice for high recurrent and high-risk SBC.

Chemotherapy may still be effective after failure of BCG therapy and vice versa. Sequential chemotherapy followed by BCG is under investigation, but has not yet been validated.

Immunomodulating agents

Other immunomodulating agents that have proved to be successful in the prevention of disease recurrence and that are as active as chemotherapeutic agents include: interferon, interleukin, and keyhole limpet haemocyanin.

5.2 Treatment of Tis

The current standard treatment of Tis consists of BCG instillations given over a 6-week period. Complete remission is obtained in up to 70% of cases. If cytology and biopsies remain positive, another cycle may produce an additional 15% complete remission. Maintenance therapy with booster cycles at 3, 6, 12, 18, 24, 30 and 36 months are advocated to prevent recurrence of this highly malignant disease. If cure is not achieved after this second cycle or if there is early disease recurrence, cystectomy with urethrectomy is indicated. In 70% of cases, however, it is possible to preserve the bladder.

5.3 Treatment of T1 G3 bladder tumours

T1 G3 bladder tumours have a high tendency to progress and therefore some experts tend to carry out early cystectomy with excellent survival rates. Nevertheless, it has been demonstrated that 50% of patients can conserve their bladder with bladder instillations of chemotherapeutic agents or BCG therapy (13-17). The T1 G3 tumours that really need early cystectomy are not clearly defined, but certain factors can influence the decision, such as the solid or papillary appearance of the tumour, the high recurrence rate and multiplicity of tumours and the presence of concomitant Tis.

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5.5 Radical cystectomy

Background

Generally, radical cystectomy is the gold standard treatment in most countries for muscle-invasive bladder tumours. However, renewed interest in quality-of-life issues has increased interest in bladder preservation treatments (1,2). Urologists in certain countries, such as the USA and Germany, favour early cystectomy, while others, such as those in the UK (3), appear to use radiotherapy and/or chemotherapy as the first choice and reserve cystectomy for salvage treatment. Also, performance status and age can influence the choice of therapy, with cystectomy being reserved for younger patients without concomitant disease. In one population-based analysis, it was found that more than 60% of the patients with muscle-infiltrating tumours were considered unsuitable for radical cystectomy (4). Bladder-sparing surgery together with neoadjuvant or adjuvant chemotherapy and/or radiation may be a reasonable alternative to radical cystectomy.

Indications

The primary indication for cystectomy is muscle-invasive bladder cancer T2-T4a, N0-NX, M0. Other indications are high-risk superficial tumours (T1 G3 and BCG-resistant Tis) and extensive papillary disease that cannot be controlled with conservative measures. Whether p53 can help select patients with pT1 tumours who may benefit from early cystectomy remains controversial (5,6). Salvage cystectomy is indicated for non-responders to non-surgical therapies or relapse after bladder-sparing treatments, as well as for non-transitional cell carcinomas, as these tumours generally respond less well to chemotherapy and radiotherapy than TCC. Contra-indications for cystectomy are major co-morbidity and patients not willing to accept the surgical risks. The overall staging error between clinical and pathological stages was as high as 44% in one series (7) and has been found to be highest for tumours in the T2 category (8). The frequency of regional lymph node metastases depends on the T-stage, ranging from less than 10% in T1 to almost 33% in the T3-T4 category.

Technique

Radical cystectomy consists of removal of the bladder and neighbouring organs, such as the prostate and seminal vesicles in men and uterus and adnexa in women. The distal part of the ureters is also usually resected and in cases with CIS, a frozen section of the margin is advisable. The indications for urethrectomy are controversial and have been reduced presumably because of the advent of bladder substitution. Currently, urethrectomy is recommended if the tumour involves the bladder neck in women (8) and the prostatic urethra in men. Recent reports indicate that the decision to perform urethrectomy may be based on the results of a frozen section of the urethral margin; however; these studies are hampered by their short follow-up times (10,11). The urethra may also be excised as a secondary procedure. Studies suggest that radical cystectomy with preservation of sexual function can be performed in some men (12).

Radical cystectomy also includes a dissection of the regional lymph nodes, which can give valuable prognostic information. There are several issues regarding this procedure, including the intention, the anatomical extent and the impact on the remaining operative procedure of the lymphadenectomy. Is the intention of this procedure diagnostic or curative? Its use in the diagnostic setting has been based on the poor prognosis of patients with positive nodes. Its therapeutic effect has not been fully documented. There are some reports of a relatively good prognosis in cases with very limited lymph node involvement and this has stimulated the proponents of curative dissection (13). The limited lymph node dissection consists of removing the tissue in the obturator fossa. Others (14,15) favour extended lymphadenectomy with removal of the obturator, internal, external and common iliac nodes, the pressacral nodes, and the lymph nodes at the aortic bifurcation. They reported that extended lymphadenectomy improved survival in patients with tumours confined to the urinary bladder.

The results of lymph node staging can influence how the procedure is completed. Those who favour a frozen section will change the rest of the operation if positive nodes are verified, e.g. no cystectomy will be performed or a simpler type of urinary diversion will be chosen. The other group argue the pitfalls of frozen sections and the advantage of tumour debulking with respect to the patient's quality of life. No controlled studies exist supporting the curative value of lymph node dissection, thus only limited dissection is recommended.

Morbidity and mortality

The operative mortality has decreased during the last few decades; it was 3.7% in the European Organization for Research and Treatment of Cancer (EORTC) Medical Research Council (MRC) trial (16) and 2.3% and 1.2% in the Nordic Cystectomy trials I and II, respectively (17). Early morbidity is around 30% (18,19) and is usually transient. Late morbidity is mainly due to the urinary diversion. The risk of impotence is high and age dependent (20).

Survival rates

The 5-year survival rate is usually reported to be in the range of 40-60% and has not improved significantly in

recent times. The use of pre-operative radio- or chemotherapy has not changed the outcome. In a recent report, the 5-year survival rates with no pre-operative therapy were 75% for stage pT1, 63% for stage pT2, 31% for stage pT3 and 21% for stage pT4 disease (21). Approximately 10% of cystectomy specimens are without tumour (stage pT0) due to radical TUR. Whether or not this confers a survival advantage is controversial (22,23). Tumour stage and nodal involvement are the only independent predictors of survival (24). P53 overexpression and mutation do not appear to be superior to staging as prognostic markers (25,26).

5.6 RECOMMENDATIONS

1. Radical cystectomy in T2-T4a, N0-NX, M0 and recurring T1 G3 and Tis.
2. No pre-operative radio- or chemotherapy.
3. Limited lymph node dissection.
4. Preservation of the urethra if margins are negative.

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5.8 Urinary diversion after radical cystectomy

Four treatment options are presently considered after cystectomy: an ileal conduit; a continent pouch; a bladder reconstruction; or ureterosigmoidostomy. The long-term quality of life outcomes for patients with the first three options, which are the major approaches, have recently been studied (1-3). Regardless of the type of urinary diversion, the majority of patients reported good overall quality of life, little emotional distress and few problems with social, physical or functional activities. Problems with urinary diversion and sexual functioning were identified as being the most common. No prospectively controlled randomized studies between the major alternatives have been performed. Bladder reconstruction seems to have become the first option in many centres.

Contra-indications to more complex procedures are debilitating neurological and psychiatric illnesses, short life expectancy and impaired liver or renal function. Patients undergoing continent urinary diversion have to have the motivation and skill to learn self-catheterization. Contra-indications to orthotopic bladder substitutes are TCC of the prostatic urethra, widespread CIS, high-dose pre-operative irradiation, complex urethral stricture and intolerance to incontinence.

Ileal conduit

The ileal conduit is a reliable treatment option with established efficacy. After long-term follow-up, however, 20% of patients develop stomal complications and 30% of the renal units become dilated (4). The disadvantage of the ileal conduit is mainly cosmetic.

Conventional ureterosigmoidostomy

This procedure became obsolete due to a high incidence of upper urinary tract infections and the risk of developing malignancy in the bowel. Bowel frequency and urge incontinence were also common. Recent modifications have been reported to decrease these complications, however, the procedure has become a standard option in selected centres (5,6).

Continent pouch

The continent pouch operation has become a routine procedure during the last two decades. The introduction of three processes were essential for its development:

- The principle of bowel detubularization to create a low-pressure reservoir in the form of a balloon-shaped sac
- An anti-reflux and continence mechanism
- The use of self-catheterization

A variety of continent reservoirs have been introduced; the majority use ileal segments, ileocaecal segments or the sigmoid colon (7). Following continent urinary diversion, early and late complications have been encountered in 12% and 37% of patients, respectively (8). Late complications include ureteral stricture/obstruction, incontinence, difficulty in catheterization and urinary stones. Metabolic complications are common, but in the majority of cases, and with correct patient selection and education, problems may be minimized with the use of an appropriate bowel segment and early intervention (9). The remaining disadvantage is that a stoma is still necessary.

Bladder reconstruction

Bladder reconstruction or the orthotopic bladder operation has been performed in men for more than a decade, and also, more recently, in women. The reservoir is anastomized to the top of the urethra and the main advantage is that no stoma is necessary. The patient empties the bladder by abdominal straining or clean intermittent catheterization. Disadvantages include nocturnal leakage and problems with voiding requiring intermittent self-catheterization (10). The patient empties the bladder by abdominal straining and usually regains daytime continence while nocturnal leakage remains a problem. Increased post-void residual urine is initially rare, but is reported to affect almost half of the patients after long-term follow-up (11). This is managed by clean intermittent catheterization.

5.9 RECOMMENDATIONS

1. Treatment is recommended at centres with experience in the major types of diversion techniques. These operations should be centralized to departments doing cystectomies on a regular basis.
2. Patients planned for cystectomy should be informed of the possible alternatives, and the final decision has to be based on a consensus between patient and surgeon.

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5.11 Radiotherapy

Definitive radiotherapy with curative intent and the aim of bladder preservation is performed in T1-T4, N0, M0 transitional cell bladder cancer. External beam radiotherapy has not been compared with cystectomy in randomized trials of significant statistical power. Therefore, the decision for or against radiotherapy should be based on prognostic factors and the patient's desire, and will be heavily influenced by the physician's preference. However, the various treatment options have to be discussed with the patient accordingly.

Patients who are suitable for this treatment should have: adequate bladder capacity; normal bladder function; and no recurrent urinary infections, previous inflammation or surgery of the true pelvis with consecutive adhesion (1-3).

External beam radiotherapy

External beam radiotherapy is delivered in 30-40 fractions in doses up to 68 Gy (4,5). Multiple fractions per day may induce a higher local control rate, but these treatment strategies are still investigational (6-8). The same is true for the simultaneous use of systemic chemotherapy and radiotherapy. There is increasing evidence that the addition of cisplatin to radiotherapy leads to a local control rate of up to 80% in T2-T3 tumours (9-12). However, it is unclear whether or not this higher local control rate translates into improved 5-year survival rates. Randomized trials comparing conventional radiotherapy with simultaneous radiochemotherapy are lacking (3).

Brachytherapy

Brachytherapy is an alternative radiotherapeutic approach applied in a few centres throughout Europe. In selected patients with small solitary tumours of less than 5 cm in diameter, loading with iridium, tantalum or caesium after exposing the bladder by cystostomy (with or without partial resection) provides similar results to percutaneous radiotherapy; however, higher local control rates of about 80% are achieved in T2-T3 tumours (13). However, as in other forms of bladder-preserving therapy, local disease recurrence or recurrence elsewhere in the bladder will certainly occur in more than 30% of patients.

Complications

The majority of patients undergoing radical radiation of the true pelvis will experience enteritis, proctitis or 'cystitis', which are usually easily controllable and self-limiting. Late toxic effects of significance (Radiotherapy-Oncology Group grade 3-5), such as radiation cystitis (5%), proctitis (5%) and bowel obstruction (3%), are less prominent in modern series (3,5,11,14). Erectile dysfunction will occur in more than two-thirds of male patients (15). Sexual function in females is not compromised (16).

Prognostic factors

The 5-year survival rate after definitive external beam radiotherapy is reported to be 60-80%, 26-59% and 20-38% for T1, T2 and T3 tumours, respectively. Patients with T4 tumours fixed to the pelvis rarely survive for 5 years without tumour progression (3-5,8,11,17). Favourable prognostic parameters are low T-category, a solitary tumour, lack of upper urinary dilatation and complete TUR of all the visible tumour. Other factors that might positively influence outcome are normal haemoglobin level, low tumour volume (< 5 cm diameter) and lack of concomitant CIS (3-5,14,18). Although the 5-year survival rate is acceptable, local disease recurrence will occur in about 50% of patients (5). A small proportion of these patients can undergo salvage cystectomy, with a favourable long-term outcome in 12-40% (3,11). Although T1 tumours are also treated with radiotherapy, these tumours are usually treated using either complete TUR and additional intravesical immunotherapy or immediate cystectomy with excellent results (4).

5.12 RECOMMENDATIONS

1. External beam radiotherapy can be performed with curative intent in T2-T3, N0, M0 TCC of the urinary bladder.
2. Patients have to be informed that there are no randomized trials comparing radical cystectomy and definitive external beam radiotherapy. However, those patients with T2, solitary, completely resected tumours and a normal upper urinary tract have the highest chance of cure and therefore are most suited for external beam radiotherapy.
3. Brachytherapy should only be applied in selected patients with solitary tumours less than 5 cm in diameter and at centres with significant experience.
4. Lifelong follow-up is required using cystoscopy, exfoliative urinary cytology and other investigations to detect disease dissemination, as in patients who undergo cystectomy.
5. Recurrent Tis and Ta TCC can be treated by intravesical immunochemotherapy (Tis) or TUR plus adjuvant intravesical therapy. Patients with muscle-invasive tumours should undergo radical cystectomy whenever possible.

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5.14 Chemotherapy

Following cystectomy for muscle-invasive bladder carcinoma, up to 50% of patients may develop metastases. This most often occurs within 2 years (1). Most patients relapse at distant sites; one-fourth of patients relapse at the pelvis alone. Response rates of 40-70% with cisplatin-containing combination regimens have led to their use for the treatment of locally invasive disease in combination with cystectomy or radiotherapy, either as neo-adjuvant or adjuvant therapy.

Neoadjuvant chemotherapy

Non-randomized studies have clearly established the feasibility and safety of giving neo-adjuvant chemotherapy. Overall response rates of 60-70% with CR rates around 30%, have been frequently reported (2). These trials have demonstrated that neo-adjuvant chemotherapy can produce tumour 'downstaging'. It has been shown that inoperable cases may become operable after neo-adjuvant chemotherapy (3,4).

Randomized trials have not yet proven a survival benefit with neo-adjuvant chemotherapy (4). However, response to chemotherapy is an important predictor of survival. The 5-year survival rate is 75% in patients who had downstaging of the primary tumour to pT0 or superficial disease versus only 20% in patients who had residual muscle-infiltrating disease (> pT2) (5,6).

Neoadjuvant chemotherapy and bladder preservation

Selected patients with invasive bladder tumours after neo-adjuvant chemotherapy may preserve their bladders, although the approach is highly controversial (7,8). Bladder preservation may be possible with an integrated approach using chemotherapy and radiotherapy (9-14). This combination is capable of producing 5-year survival rates of between 42% and 63%, with organ preservation in approximately 40% of patients.

Prognostic factors for local curability were small tumour size, absence of hydronephrosis, papillary histology, visible complete TUR and a complete response to induction chemotherapy. These results need to be confirmed by randomized trials.

Adjuvant chemotherapy

Several trials with combination chemotherapy appeared to show an advantage in comparison to no treatment (15-19), yet the results are controversial because of small sample size, confusing analyses and methodology (20). The results of a large multicentre trial are imperative to provide convincing data.

Decisions concerning individual patients must be made after careful examination of the histological specimen and knowledge of the known relapse rates per pathological stage. Studies have not clearly proven any advantage for adjuvant therapy based upon muscle infiltration alone (pT2). For patients with extravesical extension (pT3), additional therapy may be useful. For patients with nodal metastases (pN+) and direct extension into the adjacent viscera (pT4), there is a suggestion of improved survival with adjuvant chemotherapy (2). The results of randomized trials addressing this important issue are imperative.

Metastatic disease

Two prospective randomized trials have proven the superiority of M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) over single-agent chemotherapy (21,22). Unfortunately, the use of cisplatin-based combination chemotherapy is associated with significant toxicity and produces long-term survival in only approximately 15-20% of patients. The median survival duration is only 13 months, and long-term survival is attained in approximately 15% of patients with metastases in visceral sites and 30% of those with nodal disease. Other therapeutic options and strategies are clearly needed.

The study of the EORTC is the only randomized trial to compare an every 2-weekly schedule of high dose M-VAC to standard M-VAC (24). A statistically significant difference in terms of CR rate and progression-free survival in favour of high dose M-VAC was observed. Although no difference in median survival was seen, an increase in 2-year survival was observed. However, this may have been due to the small number of patients in tails of the curves.

Novel chemotherapeutic agents such as gemcitabine and the taxanes are among the most interesting therapeutic options currently available (24, 25). In an international trial, M-VAC was compared to gemcitabine and cisplatin (GC) (26). Overall survival was similar on both arms, as was time to progressive disease, time to treatment failure, and response rate.

GC appears to have a reduced toxicity profile compared to M-VAC, and is therefore highly interesting. This study is not statistically powered to reveal equivalence in terms of survival to M-VAC, nor has GC been compared to high dose M-VAC.

The combination of gemcitabine and taxol has been shown to be highly effective in patients who have failed prior M-VAC (27). When cisplatin, gemcitabine and taxol were given to untreated patients, high overall response rates were observed (28).

Prognostic factors

The reported prognostic factors predictive of poor response to chemotherapy include elevated alkaline phosphatase level, age greater than 60 years and performance status (29). More recently, significant interest has developed in molecular markers such as p53, Rb and p21 to help optimize therapy and predict chemosensitivity (30).

5.15 RECOMMENDATIONS

1. Cisplatin-containing combination chemotherapy has resulted in complete remissions in 40-70%, with cure in selected cases.
2. No survival benefit has been proven with neo-adjuvant chemotherapy before cystectomy or radiotherapy.
3. Neo-adjuvant chemotherapy in combination with radiotherapy or other treatment for bladder preservation is an investigational approach at present.
4. Currently, no convincing data are available on the benefits of adjuvant chemotherapy. The treatment decision must be made according to the histological specimen, pathological state and known relapse rate based on these data. For pT3 tumours, additional therapy may be useful; for pN+ and pT4 this is less clear.
5. M-VAC is currently the gold standard of chemotherapy for metastatic disease. The median survival time is 12-30 months and long-term survival can be obtained in around 15% of patients. The outcome for patients with nodal disease is even better. Newer agents under development - gemcitabine and taxanes - may replace M-VAC.
6. Low alkaline phosphatase level, age younger than 60 years, good performance status, minimal nodal disease and no weight loss are good prognostic factors for the outcome of chemotherapy and should, therefore, be taken into account when chemotherapy is planned.

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6. FOLLOW-UP

6.1 Follow-up after TUR in superficial bladder cancer

Cystoscopy
Cystoscopy remains the gold standard of follow-up after TUR, with flexible cystoscopy being more comfortable for patients.

First cystoscopy at 3 months in all cases. Incomplete resection, implantation at traumatized sites in the bladder or rapid growth of epithelial malignancy are responsible for the higher recurrence rate of SBC after TUR at 3 months (1). Therefore early cystoscopy is advisable in all cases of SBC. In high-grade lesions (T1, G2 and G3), a second resection at the site of the TUR is advised at earlier than 3 months. In this type of tumour, up to 35% of positive biopsies are found at repeat TUR at 4-6 weeks after the first resection (2,3). The possibility of rapid evolution to an invasive tumour is a strong argument in defence of this attitude. The exact value of this early repeat TUR on the outcome of these tumours in comparison with 3-month cystoscopy control is not yet established.

Frequency of later cystoscopies. This should be adapted to the prognostic factors of the tumour (4). In all studies performed on SBC, the number of disease recurrences is highest in the first 2 years of follow-up. Subsequently, the number of positive cystoscopies becomes less frequent. In low-risk tumours (single, primary, Ta G1 < 3 cm diameter) with no recurrence at 3 months, a follow-up cystoscopy can be delayed until 9 months later and then carried out yearly for up to 5 years because of the very low recurrence rate (5).

In the case of disease recurrence, the histological findings are the same as those of the primary TUR in over 95% of cases.

In patients with high-risk tumours, cystoscopy every 3 months during the first 2 years remains the most commonly adapted follow-up schedule. Cystoscopy should then follow every 4 months in the third year, every 6 months thereafter for up to 5 years and then yearly. The schedule of follow-up in the intermediate group lies between that of the high- and low-risk groups according to the prognostic factors mentioned above. With any disease recurrence, the schedule of cystoscopies is restarted from the beginning.

How long should the cystoscopies be continued? The Kaplan-Meier curves of cancer recurrence rates all demonstrate a continuous line downwards with time without plateau formation. Recurrences continue to appear during follow-up for up to 10-12 years (5-7). Patients with regular recurrences will continue to have them until death or cystectomy. Patients with recurrences during the first 4 years after TUR continue to have lifelong recurrences (6).

From the available data, it seems advisable to stop follow-up in single Ta G1 tumours in the absence of

recurrence over 5 years. In all other cases, yearly follow-up is advisable for up to 10 years, with lifelong follow-up for the high-risk group (7).

Ultrasonography
In order to avoid cystoscopy, ultrasonography has been used in the follow-up of papillary SBC in some centres (8). Although ultrasonography can detect SBC of a few millimetres in diameter, its reliability in comparison to cystoscopy is not sufficiently established.

Cytology
Cytological samples often fail to demonstrate abnormalities in low-grade SBC (9). The main purpose of cytological examination of urine is the detection or follow-up of an aggressive SBC, such as CIS. A negative cytology result does not exclude the presence of a papillary lesion in the bladder and therefore has little place in the follow-up of low-grade tumours. Evolution to a higher grade of tumour can be detected by cytology and, therefore, it is still used by several urologists in follow-up. The use of new tumour markers is not yet established in the follow-up of SBC (10).

IVP
The development of an upper urinary tract tumour during follow-up of SBC is very rare, and therefore IVP should not be carried out routinely (6,11). Higher numbers of urinary tract tumours can be expected in selected patient groups, such as heavy smokers, industrial workers and those with high-risk tumours, or in the presence of vesico-ureteral reflux. The highest frequency can be expected in Tis, and therefore IVP should be carried out when cytology remains positive during follow-up (12).

Random biopsies of normal-looking mucosa on recurrence
The usefulness of random biopsies in normal-looking epithelium is questionable and can even be hazardous, as it provokes sites of tumour cell implantation (13). It is sufficient to take biopsies of visual urothelial abnormalities only (14). However, patients with a positive cytology but no visual abnormality still need random biopsy to detect Tis. In this case, a TUR biopsy of the prostatic urethra should be included. In Tis of the bladder, a prostate biopsy remains necessary (15).

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6.3 Follow-up after radiotherapy

Lifelong follow-up with cystoscopy and exfoliative urinary cytology is essential after radiotherapy. As muscle-invasive tumours are usually involved, additional investigations for systemic disease, as in patients undergoing cystectomy, should be performed. Superficial tumour recurrence may be controlled by TUR, and additional intravesical chemo- or immunotherapy may be beneficial (1). Invasive recurrence should be treated by cystectomy whenever possible.

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6.5 Follow-up after radical cystectomy

Risk of tumour progression after radical cystectomy

The risk of tumour progression after radical cystectomy strongly depends on the histopathological tumour stage. The risk of tumour progression increases stepwise, from 5% in patients undergoing cystectomy for pT1 G3 tumours (1,2) to almost 100% in patients with pN2 disease (3,4).

Progression risk is highest within the first 24 months following cystectomy, declines from months 24 to 36 and is relatively low after month 36 (3). Tumour progression may occur locally in the true pelvis, in regional or juxtaregional lymph nodes or as distant metastases. Furthermore, urothelial remnants in the upper urinary tract and/or urethra need to be checked for intraluminal tumour recurrences. The total risk of intraluminal recurrences may range from 5-15% with about 50% of cases occurring within 12 months. The risk of new intraluminal tumour formation does not decrease with time (5-7).

Therapeutic consequences of follow-up investigations (role of salvage therapy)

The role of salvage treatment for tumour progression after radical cystectomy has not been evaluated prospectively. However it is known from case reports that secondary surgery with or without adjuvant treatment can prolong disease-free survival time for a minority of patients with pelvic relapses. The same holds true for systemic chemotherapy in patients with distant metastases (8-10).

Furthermore, no prospective data are available for salvage treatment comparing asymptomatic with symptomatic tumour relapse. However, it is evident that patients with symptomatic tumour relapse are often characterized by a reduced general condition and by a poor Karnowsky index (11). As it is well known that a reduced Karnowsky index is a predictor of a poor outcome after salvage treatment, it seems likely that efforts aiming at early detection of tumour progression may lead to an improved success rate for salvage therapy.

Follow-up of which anatomical sites?

After cystectomy patients are at risk of tumour progression or relapse locally (bladder fossa) and systemically (lymph node and distant metastases), as well as intraluminally (upper tract, urethra).

Local pelvic and retroperitoneal relapses. Of all cases with relapse, 15-20% are found in the true pelvis and another 10-15% in the pelvic or retroperitoneal lymph nodes. CT scans of the abdomen and the true pelvis may thus lead to the early detection of up to 35% of all cases with disease progression.

Distant metastases. Distant metastases can occur in any organ: the lung followed by the bone are the most common sites. Again, the risk is highest in the first 2 years, declines in year 3 and is relatively low after year 3. More than 50% of all patients with tumour progression have distant metastases. Consequently, regular chest X-rays, bone scans and abdominal echography (liver, kidney) may lead to early detection of distant metastases in 50% of all patients.

Intraluminal recurrences. The most probable site of intraluminal disease recurrence is the male urethra if it is not prophylactically removed at the time of cystectomy. The incidence of a urethral recurrence is 5-13%. Some contemporary series report a lower risk of urethral recurrence compared with historical series (12). This remains to be confirmed in long-term results. Due to the low incidence of urethral tumours, the necessity of regular controls is a matter of debate. Examination of the urethra for disease recurrence is possible by endoscopy and/or wash-out cytology. As the risk of urethral disease recurrence does not decrease with time, lifelong control is necessary if urethral control is regarded as useful in the individual case.

Upper urinary tract intraluminal recurrences. The cost-benefit of regular intravenous pyelograms is limited by the low frequency of upper urinary tract tumours and may therefore be partially replaced by ultrasound and urinary cytology (13). The highest incidence is found in the highest T and G grade tumours.

6.7 RECOMMENDATIONS

1. Histopathological tumour stage defines the risk of tumour progression; locally advanced primary tumours and especially lymph node metastases predict a high risk of tumour progression. The higher the risk of progression, the higher the potential benefit of regular follow-up.
2. Patients surviving for more than 36 months after cystectomy have a relatively low risk of future tumour progression. The potential benefit of regular follow-up investigations is therefore highest in the first 24 months.
3. Therapeutic efficacy of salvage treatment: there is growing evidence that new chemotherapeutic substances will significantly improve the curative potential of systemic chemotherapy.
4. Mandatory investigations are those that are necessary to document a well-functioning urinary diversion. Follow-up investigations aimed at the early detection of tumour progression or tumour recurrence are defined as optional, and should be performed on the basis of the individual risk profile of the patient and on the basis of the therapeutic consequences.

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6.8 Follow-up after urinary diversion

The follow-up of patients with urinary diversion after cystectomy can be separated into issues related to the surgery itself, metabolic problems associated with the type and extent of bowel segment used, metabolic problems associated with urine storage, infection and the development of secondary cancers. Less common bowel segments and their related problems will not be considered.

Consequences of surgery

Reflux and ureteric stenosis are common problems associated with any kind of urinary diversion (1-9) (Table 3). The quality of the ureters, as well as the anti-reflux technique, are of importance in this respect (10-12). These problems may occur immediately, but can also develop later on. Specific problems of ileum conduits are elongation and stricture formation, as well as stoma stenosis and skin infections (13-16). Pouches using different continence mechanisms have complications typically related to the type of operation performed. Revision is needed even in experienced hands in about 10% of cases. Stone formation within the pouch is related to staples, and also other factors mentioned below (17).

The published results of ileum pouch surgery derive from one series and should therefore be considered with some caution (7). In orthotopic bladder substitution, the anastomosis to the urethra is a problem site for stenosis (7-15%). Moreover, incontinence (5-20%) or failure to void (females: 30%) may be encountered (4,18-20). The proportion of patients with night-time incontinence can be as high as 30% (4,20).

Table 3: Incidence of reflux and ureteral stenosis associated with urinary diversion

Incidence (%)	Reflux(%)	Ureteral stenosis (%)
Ileum conduit	100	10
Colon conduit	5	6
Ureterosigmoidostomy	5	5
Pouch: Ileum Mixed ileum/colon	 0 0-7	 2 8
Orthotopic bladder (ileum)	0-3	25

Metabolic alterations related to bowel segment

Different parts of the bowel have specific functions (20,21). Accordingly, the metabolic problems that occur depend on the extent and the type of bowel segment used for creating the urinary diversion. Removing the terminal ileum will result, in the long term (3-5 years), in a vitamin B12 deficiency, leading to anaemia and

peripheral irreversible neuropathy (19,22,23). The timing of the occurrence of the deficiency depends on the amount of stored vitamin B12. The resection of more than 50-60 cm of bowel may result in bile and fat metabolism disorders. An increased number of gallstones may be encountered (24). Moreover, stools may become fatty and lose. Chronic diarrhoea is twice as frequent in patients with ileocaecal resections compared with ileal resection (25). Oxalate stone formation can also be increased (21). The problems mentioned here are also relevant for operations including the caecum and smaller parts of the ileum.

Metabolic alterations related to urine storage

The reabsorption of urine electrolytes from continent diversions is well known (10,18,13). This reabsorption can only be balanced by adequate renal function. The reabsorption of sodium is more prominent in ileum segments, whereas chloride is reabsorped more in colon segments (26,27). Characteristically, hyperchloraemic acidosis is more often encountered in patients with ureterosigmoidostomy and continent pouches using the caecum (28-32). However, up to 50% of pure ileal reservoirs show mild acidosis due to ammonia reabsorption (33).

Apart from increased reabsorption of electrolytes the kidneys have to deal with a significantly higher fluid load. It is uncertain whether or not increased workload results in loss of renal function, but this may be suspected from previous clinical studies of patients with single kidneys. A recent investigation revealed a similar loss of renal function irrespective of the type of urinary diversion (34). Urinary stones may occur more frequently as a result of hyperchloraemic acidosis and in association with recurrent urinary tract infections (2,33,35). All continent types of urinary diversion are associated with an increased loss of calcium, magnesium and phosphate. Although disorders of calcium reabsorption are known to occur, no significant defects in bony mineralization have yet been noted (36,37).

Urinary tract infection

Bacteria are usually found in urine from ileal conduits (6,38). Very little is known about the true incidence of urinary tract infections in patients with continent pouches and orthotopic bladder substitution. Moreover, the relevance of bacterial colonization within continent reservoirs is unknown (39,40). Apart from being of importance for stone formation and pyelonephritis, in the case of reflux, systemic as well as local effects can be speculated (2). The incidence of stones within the continent pouch is as high as 34% after 5 years and is associated with infection as well as metabolic disorders (41,42). In terms of the latter, the production of nitrosamines may be associated with tumour development (43,44).

Secondary cancers

Secondary cancers may develop because of the underlying disease in the upper urinary tract and urethra, but may also be due to unknown mechanisms within the bowel segment used for urinary diversion. In particular, tumours develop at anastomosic sites between the ureter and bowel (17,45-47). The median latency for tumour development is about 25 years, but tumours have been detected as early as 5 years after surgery (35). Tumour risk is increased by at least 400-fold compared with the normal population.

The excretion of nitrosamines and the continued exposure to carcinogens that may have initiated the original cancer can lead to secondary cancers (43). Patients with an increased risk of developing colon cancer may be especially prone to develop such tumours. Finally, it is very likely that the bowel segment used is of importance, indicating a higher risk for colon cancer compared with ileum segments (45,48-52).

6.9 RECOMMENDATIONS

1. The upper urinary tract has to be investigated by sonography to detect upper urinary tract dilatation and stone formation. The stoma has to be evaluated for stenosis. Reflux and residual urine (bladder substitution) should be excluded in patients with recurrent urinary tract infections.
2. Vitamin B12 baseline determination at time of surgery: follow-up examination is dependent on the initial level.
3. Renal function, electrolyte level and acid-base status: should be assessed on a regular basis.
4. Sonography and plain film should be carried out every 2 years to detect stones in the upper urinary tract as well as in the continent reservoir.
5. Endoscopy should be started 5 years after surgery.

A summary of the follow-up scheme is shown in Table 4.

Table 4: Follow-up scheme after urinary diversion

Year 1: at 3-4 monthly intervals
- Ultrasound of the kidney and reservoir
- Electrolytes and creatinine levels
- Base excess

Years 2-3: at 6 monthly intervals
- Ultrasound of the kidneys and reservoir
- Plain film
- Electrolytes and creatinine levels
- Base excess

Year 4: at yearly intervals
- Ultrasound of the kidneys and reservoir
- Plain film
- Electrolytes and creatinine levels
- Base excess
- Vitamin B12 level

Year 5 and thereafter: at yearly intervals
- Ultrasound of the kidneys and reservoir
- Plain film
- Electrolytes and creatinine level
- Base excess
- Vitamin B12 level
- Coloscopy in patients with ureterosigmoidostomy

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7. ABBREVIATIONS USED IN THE TEXT

BCG:	bacillus Calmette-Guérin
CIS:	carcinoma *in situ*
CT:	computed tomography
EORTC:	European Organization for Research and Treatment of Cancer
GC:	gemcitabine and cisplatin
IVP:	intravenous pyelography
MRC:	Medical Research Council
M-VAC	methotrexate, vinblastine, doxorubicin and cisplatin
NMP22®	nuclear matrix protein
SBC:	superficial bladder cancer
TCC:	transitional cell carcinoma
TNM:	tumour, node, metastasis
TUR:	transurethral resection

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