



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), 9000 in France (2), 2000 in Sweden (3) 8000 in Spain (4) and 1120 in Belgium (5). Approximately 75 to 85 % of patients present with disease confined to the mucosa (stage Ta-Tis) or submucosa (stage T1). The other 15 to 25 % have muscle invasion or nodal disease (stages T2-4, N+) at presentation (1). The management of superficial bladder cancer has become more complex, with urologic opinion differing with regard to initial investigation, treatment and follow-up.

2. CLASSIFICATION

The 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, T2 b outer half). The World Health Organisation (WHO) histological classification is generally applied throughout most of the world (Table 2). 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 histopathologic 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 lamina propria are classified as stage T1. Because Ta and T1 can be removed by transurethral resection, they are grouped under the heading 'superficial bladder cancer' 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 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 defining dysplasias and CIS. There is also important inter observer variability in classifying stage T1 vs TA tumours and grading tumours (11-14).

As a consequence our group strongly recommends that the urologist review 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 in this region (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 to take an occupational history of patients with bladder cancer (18).

Another prominent risk factor is cigarette smoking. Smoking leads to higher mortality from bladder cancer in the 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 (16). Patients with initial grade III tumours were significantly more likely to be heavy smokers than those with less aggressive disease (17).

4. DIAGNOSIS

Early detection and symptoms

Early symptom recognition in bladder tumour 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 with 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 the positive predictive value of microscopic haematuria in asymptomatic patients 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.

Physical examination

Physical examination including digital rectal examination and bimanual pelvic palpation is recommended when facing haematuria. 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-existent pathology (27)

Imaging

Intravenous pyelography

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 (29). The necessity to perform routine IVP at initial diagnosis is now questioned because of the low incidence of important findings (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 more pertinent in detecting bladder tumours (32,30).

Computed tomography

Computed tomography (CT) scan 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 extension of the disease is reduced by artifactual 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 evaluation of lymph node enlargement, but does not provide reliable information on the microscopic aspects of disease. Thus, the 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 routine bone scan before total cystectomy in infiltrative tumours is questionable except in the presence of increased alkaline phosphatase or in patients symptomatic from their bones (34).

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 a positive urinary cytology may indicate a source anywhere in the urinary tract, from the calyx, through the ureters, into the bladder and urethra. Moreover, a negative voided urinary cytology does not necessarily exclude the presence of a bladder tumour, which can co-exist with 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 are the reasons for the research on more reliable tests on urine to detect urothelial malignancies.

New tests to replace cytology

The bladder tumour antigen test (BTA) has been the most extensively studied new marker for bladder tumours in recent years (38-40), but nevertheless its place remains unclear in the diagnosis and follow-up of bladder tumours (41,42). DNA flow cytometry add little to urine cytology (43). Karyometry is another possibility in quantifying cytology (44,45). NMP22 was used by several investigators (44,46)

Immunostaining of Lewis antigen in cells from voided urine was found useful by others (47,48). Fibrin degradation products have also been tested (49). The value of all of these tests is still insufficiently validated in diagnosis and follow-up of bladder tumours.

Cystoscopy and TUR

The diagnosis of bladder cancer ultimately depends on cystoscopic examination of the bladder and pathologic evaluation of the resected lesion. Cystoscopy may initially be performed without anaesthesia in assessing a patient for bladder cancer. If a bladder cancer has been visualized on 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 a mass is palpable in the bladder and, if so, whether it is fixed to the pelvic wall (50). Bimanual examination may be performed both before and after TUR. The presence of a palpable mass after resection implies that there is extravesical tumour. It may be of particular interest to follow the results of precystectomy irradiation (50). TUR of the bladder tumour should be done so as to maximize the preservation of architectural detail and the relation of the tumour to the various layers of the bladder wall. It is primarily the extent to which the tumour involves the various layers of the bladder wall that has traditionally been used for staging bladder cancer and determining prognosis. For pathologic evaluation, the more superficial component of the tumour should be resected separately from its deeper component. Use of cautery current should be minimized to preserve pathologic detail and avoid cautery artifact.

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 (51). Random biopsies of normal mucosa are indicated in the presence of positive cytology, even in the absence of tumour, or in any non papillary tumour. Random biopsies in patients with solitary papillary lesions are contraindicated because of the absence of additional information (52) and because it may be noxious, as lesions to the mucosa can provoke implantation of tumor cells (36). Prostatic urethra biopsies by TUR are indicated for suspicion of TIS of the bladder in view of the high frequency of involvement of the prostatic urethra (53).

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
 - biopsies of all suspected areas
 - random biopsies in presence of positive cytology, large or non papillary tumourbiopsy 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 present or alkaline phosphatase elevated

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Table 1: TNM classification 1997

Urinary Bladder	
Ta Tis T1	Noninvasive papillary In situ: “flat tumour” Subepithelial connective tissue
T2 T2a T2b	Muscularis Inner half Outer half
T3 T3a T3b	Beyond muscularis Microscopically Extravesical mass
T4a T4b	Prostate, uterus, vagina Pelvic wall, abdominal wall
N1 N2 N3	Single =2cm Single >2 to 5 cm, multiple =5 cm >5 cm

Table 2: Histological classification WHO Genève 1974

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

5.1 TREATMENT

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

- Ta-1 are superficial bladder tumours. Treatment will be directed toward the prevention of recurrence and progression.
- T1G3 has a high tendency to progression. The place of early cystectomy still is a matter of debate.
- TIS is a potential highly malignant disease which still can be treated in the majority of the cases with bladder instillations of BCG. A cystectomy is necessary when this fails to cure the disease after two cycles of 6 to 8 weekly instillations.
- T2 or higher tumours are infiltrating tumours and cystectomy will be necessary in the majority of the cases. Bladder preservation can be an option in selected cases.
- N+ and metastatic diseases needs additional therapeutic approaches.

Treatment of Ta-1 lesions

The therapeutic regimen will take into account the risk of recurrence and progression (prognostic factors of the tumours), the side-effects and the cost effectiveness. The recurrence rate of superficial bladder cancer (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 recurrence and progression can be predicted on the basis of clinical and pathological data, which become available at the initial transurethral resection and diagnostic workup 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 recurrence they are, in descending value:

1. The 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, anaplasia grade and the T-category are of utmost importance. Tumours at the bladder neck have a worse prognosis (9).

Based on the prognostic factors, SBC can be divided into the following risk groups:

- Low risk tumours: single, Ta, G1, ≤ 3 cm
- High risk tumours: T1, G3, multifocal or highly recurrent, CIS (TIS)
- Intermediate: all other tumours, Ta-1, G1-2, multifocal, > 3 cm.

One single chemotherapeutic instillation immediately after TUR in all papillary SBC

One single instillation with epirubicin or mytomyacin C within 6 h of TUR is able to reduce 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 which needs 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-1, G1 smaller than 3 cm and papillary tumours need no further treatment, as recurrence rate in this group is very low (< 0.2/ year after one single instillation immediately after TUR).

4 to 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-1, G1-2, 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, it is advocated to continue with monthly instillations after the first induction course. Maintenance therapy longer than 6 months did not improve the reduction in 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 longer than 6 months are worthwhile, if no recurrence is noticed.

Treatment of recurrence

On recurrence, the initial instillation schedule is restarted. In highly recurrent or multiple recurrence it is advocated to change to BCG therapy 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 was found to be superior. The ones most frequently used ones are mitomycin C, epirubicin and adriamycin.

The chemotherapeutic agents are dissolved in 30 to 50 ml physiologic solution or water and are kept in the bladder for 1-2 h. The common advocated doses for mitomycin C are 2-40 mg, for epirubicin, 50-80 mg and 50 mg for adriamycin. The patient is encouraged not to drink before the instillation so that the instillation is not diluted too much.

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. Contracted bladder can appear in patients who develop serious chemical cystitis. Allergic skin reaction occurs frequently on the hands and the genital region with mitomycin C. Washing hands and genital region after micturition is useful 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 more effective in high and intermediate risk SBC, but the literature on this is controversial. It is also currently accepted that BCG prevents progression, but this is based on only few studies with a small number of patients (15). This is not confirmed by 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 the same immunological reaction. In papillary T1-a G1-2 lesions, one can reduce the dose of 25% with the same effectiveness as the full dose and less general side-effects. 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 (31). 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 advocated to wait 14 days after TUR of the bladder before starting BCG. For the same reason, BCG is not indicated in low risk groups in which a potential danger of BCG does not counterbalance its advantage.

Lower recurrence rates have been reported after maintenance therapy of up to 3 years. Boosters of BCG were given at 3, 6, 12, 18, 24, 30 and 36 months (17). Whether 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 still may be effective after failure of BCG therapy and *vice versa*. Sequential therapy, chemotherapy followed by BCG is under investigation, but is not yet validated.

Immunomodulating agents

Other immunomodulating agents have also proved successful in prevention of recurrence and as active as chemotherapeutic agents include: interferon, interleukin, Keyhole limpet-cyanin.

Treatment of TIS

The current standard treatment of TIS consists of BCG instillations over a 6-week period. Complete remission is obtained in up to 70% of cases. If cytology and biopsies remains 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 there is early recurrence, cystectomy with urethrectomy is indicated. In 70% of cases, however, it is possible to preserve the bladder.

Treatment of T1G3 bladder tumours

The T1G3 bladder tumours have a high tendency to progression and therefore some experts tend to do early cystectomy with excellent survival. Nevertheless, it has been demonstrated that 50% of patients can conserve their bladder with bladder instillations of chemotherapeutic agents or immunomodulators. Which T1G3 tumour really needs early cystectomy is not clearly defined, but some factors can influence the decision, such as the solid or papillary appearance of the tumour, the high recurrence rate and multiplicity of the tumours and the presence of concomitant TIS.

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5.2 TREATMENT: RADICAL CYSTECTOMY

Background

Generally, radical cystectomy is the gold standard treatment in most countries for muscle invasive bladder tumour. However, the timing of cystectomy in the treatment of bladder tumours varies. Urologists in certain countries, such as the US and Germany, favour early cystectomy, while others, such as the UK (1), appear to use radiotherapy and/or chemotherapy as 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 (2).

Indications

The indication for cystectomy is primarily a patient with muscle-invasive bladder cancer T2-T4a, N0-NX, M0. Other indications are patients with high-risk superficial tumours (T1G3 and BCG resistant Tis) and those with extensive papillary disease that it is not possible to control with conservative measures. Salvage cystectomy is indicated for non-responders to non-surgical therapies or relapse after bladder sparing treatments, as well as non-transitional cell carcinomas, as these tumours generally respond less well to chemotherapy and radiotherapy than TCC. Contraindications for cystectomy are major co-morbidity and patients not willing to accept the surgical risks.

The over-all staging error between clinical and pathological stages was as high as 44 % in one series (3) and has been found to be highest in the T2 category (4). The frequency of regional lymph node metastases depends of the T-stage, from less than 10% in T1 to almost 33% in the T3-4 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 carcinoma in situ, a frozen section of the margin is advisable. The indications for urethrectomy are controversial and have been narrowed presumably because of the advent of bladder substitution. Currently, urethrectomy is recommended if the tumour involves the bladder neck in women (5) and the prostatic urethra in men. Recent reports indicate that the decision may be based on a frozen section of the urethral margin; however, these studies are hampered by short follow-up (6,7). 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 (8).

A radical cystectomy also includes a dissection of the regional lymph nodes, which will give valuable prognostic information. There are some issues regarding this procedure, including the intent, the anatomical extent and the impact on the remaining operative procedure of the lymphadenectomy. Is the intent diagnostic or curative? To consider it as diagnostic has been based on the poor prognosis of patients with positive nodes. There are some reports of a relatively good prognosis with very limited lymph node involvement and this has stimulated the proponents of curative dissection (9). The limited lymph node dissection consists of removing the tissue in the obturator fossa. An extended operation also involves the tissue around the common iliac. The extent is usually guided by whether the intent is diagnostic or curative. The proponents of extended dissection usually advocate the possibilities of cure with this approach and the minor risk of increased morbidity (10). The survival advantage was most pronounced in patients with low stage primary tumours. (11).

The results of the lymph node staging can influence the finalization of the procedure. Some urologists will perform a peroperative frozen section, while others will wait for the definitive results of the pathological examination. Those who favour frozen section will change the rest of the operation if positive nodes are

verified, e.g. cystectomy will not be performed or a simpler type of urinary diversion will be opted for. 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 a 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 on Treatment of Cancer (EORTC) /Medical Research Copuncil (MRC) trial (12) and 2.3% and 1.2% in the Nordic Cystectomy trials I and II, respectively (13). The early morbidity is around 30% (14,15) and is usually transient. Late morbidity is mainly due to the urinary diversion. The risk of impotence is high and age dependent (16).

Survival rates

The 5-year survival rate is usually reported in the range of 40-60% and has not improved significantly in recent times. The use of preoperative radio- or chemotherapy has not changed the outcome. In a recent report, the 5-year survival rates with no preoperative therapy were 75% for stage pT1, 63% for stage pT2, 31% for stage pT3 and 21% for stage pT4 disease (17). Approximately 10% of cystectomy specimens are without tumour (stage p0) due to radical TUR. Whether this confers a survival advantage over that noted from the initiating population is controversial (18,19). Tumor stage and nodal involvement are the only independent predictors of survival (20)

RECOMMENDATIONS

- Radical cystectomy in T2-T4a, N0-NX, M0 and recurring T1G3 and Tis
- No preoperative radio- or chemotherapy
- Limited lymph node dissection
- Preservation of the urethra if margins negative

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5.3 TREATMENT: URINARY DIVERSION AFTER RADICAL CYSTECTOMY

Four options are presently considered after cystectomy: an ileal conduit; a continent pouch; a bladder reconstruction; or ureterosigmoidostomy. The long-term quality of life outcomes among the first three options, which are the major approaches, have recently been studied (1-3). Regardless of 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 most common. No prospectively controlled randomized studies between the major alternative have been performed. Bladder reconstruction seem to have become the first option in many centres.

Contraindications to more complex procedures are debilitating neurological and psychiatric illnesses, short life expectancy and impaired liver or renal function. For continent urinary diversion the patient has to have the motivation and skill to learn self-catheterization. Contraindications to orthotopic bladder substitutes are TCC of the prostatic urethra, wide spread CIS, high dose preoperative irradiation, complex urethral stricture and intolerance to incontinence.

Ileal conduit

The ileal conduit is a reliable 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 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, and the procedure has become a standard option in selected centres (5,6).

Continent pouch

The continent pouch has become a routine procedure during the last two decades. Three developments 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, ileocecal segments, or the sigmoid colon (7). Following continent urinary diversion, early and late complications have been encountered in 12% and 37% of the 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 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 orthotopic bladder 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).

RECOMMENDATIONS

- 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.
- Patients planned for cystectomy should be informed about the possible alternatives and the final decision has to be based on a consensus between patient and operating surgeon.

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5.4 TREATMENT: RADIOTHERAPY

Definitive radiotherapy with curative intent and the aim of bladder preservation is performed in T1 to 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, patients desire and will be heavily influenced by physicians preference. However, the respective 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, 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 to 40 fractions in a 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 cis-platinum to radiotherapy leads to a local control rate of up to 80% in T2,3 tumours (9-12). However, it is unclear whether 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 very few centres throughout Europe. In selected patients with small solitary tumours of less than 5 cm, afterloading 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 T2/3 tumours (13). But as in other forms of bladder preserving therapy, local recurrence or recurrence elsewhere in the bladder will occur in certainly 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 controlable and self-limiting. Late toxic effects of significance (RTOG grade 3 to 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 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% in T1, T2 and T3 tumours, respectively. Patients with T4 tumours fixed to the pelvis rarely survive 5 years without tumour progression (3-5,8,11,17). Favourable prognostic parameters are low T category, solitary tumour, lack of upper urinary dilatation and complete TUR of all visible tumour. Other factors that might positively influence outcome are normal haemoglobin, low extravesical tumour volume (< 5cm diameter) and lack of concomitant in situ cancer (3-5,14,18). Although the 5-year survival rate is acceptable, local 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 by radiotherapy, these tumours are usually treated either by complete TUR and additional intravesical immunotherapy, or with immediate cystectomy with excellent results (4).

RECOMMENDATIONS

- External beam radiotherapy can be performed with curative intention in T2-T3, N0, M0 transitional cell carcinoma of the urinary bladder.
- 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 tumour and normal upper urinary tract are the patients with the highest chance for cure and therefore are most suited for this kind of treatment.
- Brachytherapy should only be applied in selected patients with solitary tumours less than 5 cm and at centres with significant experience.
- Life-long follow-up is required using cystoscopy, exfoliative urinary cytology and other investigations to detect disease dissemination, as in patients who undergo cystectomy.

- 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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5.5 TREATMENT: 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 in distant sites; one-fourth of patients relapse in the pelvis alone. Response rates of 40-70% with cisplatin-containing combination regimens have led to their use for locally invasive disease in combination with cystectomy or radiotherapy, either as neo-adjuvant or adjuvant therapy.

Neo-adjuvant chemotherapy

Non-randomized studies have clearly established the feasibility and safety of giving neo-adjuvant chemotherapy. Overall response rates of 60-70%, with complete response rates in the 30% range, 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).

The MRC and the EORTC have completed the largest randomized neo-adjuvant chemotherapy trial, which involved 976 patients treated with cisplatin-methotrexate-vinblastine followed by cystectomy or radiotherapy versus immediate cystectomy or radiotherapy (4). The median survival for the chemotherapy group was 44 months vs. 37.5 months for the non-chemotherapy group. This difference was not statistically significant.

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

Neo-adjuvant chemotherapy and bladder preservation

Selected patients with invasive bladder tumours after neo-adjuvant chemotherapy may still preserve have their bladders preserved, although the approach is highly controversial. Bladder preservation may be possible with an integrated approach using chemotherapy and radiotherapy (9-15). 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 a difference in favour of chemotherapy (16-20). Yet the results are controversial because of small sample size, confusing analyses and methodology. A large multicentre trial is imperative to provide convincing data. The EORTC-genitourinary (GU) group in collaboration with the GU Global group has planned a study of immediate vs. delayed adjuvant chemotherapy in patients with T3-T4 and/or N+ bladder tumours.

Decisions concerning individual patients must be made after careful examination of the histologic specimen and knowledge of the known relapse rates per pathologic 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). 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. 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.

Increasing the dose intensity of established chemotherapeutic regimens such as M-VAC by adding haematopoietic growth factors may or may not lead to an improvement in overall survival. Novel chemotherapeutic agents such as gemcitabine and the taxanes are among the most interesting therapeutic options currently available (23-26).

Prognostic factors

The reported prognostic factors predictive of poor response to chemotherapy include alkaline phosphatase, age greater than 60 years and performance status (27). Clinical features that predict a poor outcome include: weight loss during the preceding 6 months and the presence of extranodal metastases (27).

More recently, a significant interest has developed in molecular markers, such as p53 Rb and p21, to help optimize therapy and predict chemo-sensitivity (27).

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RECOMMENDATIONS

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

6.1 FOLLOW-UP AFTER TUR IN SUPERFICIAL BLADDER CANCER

Cystoscopy

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

First cystoscopy at 3 months in all cases

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

Frequency of later cystoscopies

This should be adapted to the prognostic factors of the tumour (5). In all studies performed on SBC, the number of 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, TaG1 < 3cm) with no recurrence at 3 months, a follow-up cystoscopy can be delayed until 9 months later and then yearly up to 5 years because of the very low recurrence rate of the tumour (6). In case of recurrence, the histological findings are the same as the primary TUR in over 95% of cases.

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

How long should the cystoscopies be continued?

The Kaplan-Meier curves of recurrence rates all demonstrate a continuous line downwards with time without plateau formation. Recurrences continued to appear during up to 10-12 years of follow-up (6-8). Patients with regular recurrences will continue to do so until death or cystectomy. Patients with recurrences during the first 4 years after TUR continue to have life-long recurrences (7).

From the available data, it seems advisable to stop follow-up in single Ta G1 tumours in the absence of recurrence during 5 years. In all other cases, a yearly follow-up is advisable up to 10 years and for the high risk group, life long (8).

Ultrasonography

In order to avoid cystoscopy, ultrasonography was used in follow-up of papillary SBC in some departments (9). Although it can detect SBC of a few millimeters diameter, its reliability in comparison to cystoscopy is not sufficiently established.

Cytology

Cytological samples can often fail to demonstrate abnormalities in low grade SBC (10). The main purpose of cytology examination of the urine is the detection or follow-up of an aggressive SBC, such as carcinoma in situ. A negative cytology 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 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.

Intravenous urography (IVP)

The development of an upper urinary tract tumour during follow-up of SBC is very rare and therefore intravenous urography should not be done routinely (7,11). Higher numbers of urinary tract tumours can be expected in selected patient groups, such as heavy smokers, industrial explorers and high risk tumours, or in the presence of vesico-ureteral reflux. The highest frequency can be expected in TIS and therefore IVP should be done 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 noxious, as it provokes sites of implantation (13). It is sufficient to take biopsies of visual urothelial abnormalities only (14,15). However, patients with 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 (16).

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6.2 FOLLOW-UP AFTER RADIOTHERAPY

Life-long follow-up with cystoscopy and exfoliative urinary cytology is essential after radiotherapy. Since 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 when ever possible.

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6.3 FOLLOW-UP AFTER RADICAL CYSTECTOMY

Risk of tumour progression after radical cystectomy

The risk of tumour progression after radical cystectomy strongly depends on 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 tract and/or the urethra need to be checked for intraluminal tumour recurrences. The total risk of intraluminal recurrences may range from 5 to 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 a tumour progression after radical cystectomy has not been evaluated prospectively. However, we know from case reports that secondary surgery with or without adjuvant treatment can prolong disease free survival 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. On the other had, it is evident that patents 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 does seem likely that efforts aiming at early detection of tumour progression may lead to an improved success-rate of salvage therapy.

Follow-up of which anatomical sites?

Patients after cystectomy are at risk of tumour progression or relapse locally (bladder fossa), 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 the retroperitoneal lymph nodes. CT scans of the abdomen and the true pelvis may thus lead to an early detection of up to 35% of all cases with 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 in 50% of all patients.

Intraluminal recurrences

The most probable site of intraluminal 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 phenomenon remains to be confirmed by long-term results. Because of the low incidence of urethral tumours, the necessity of regular controls is a

matter of controversial debate. Principally, control of the urethra is possible by endoscopy and/or wash-out cytology. As the risk of urethral recurrence does not decrease with time, life-long control would be necessary if urethral control is regarded as useful in the individual case.

Upper tract intraluminal recurrences

The cost-benefit of regular intravenous pyelograms is limited by the low frequency of upper 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.

RECOMMENDATIONS

- 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.
- Patients surviving for more than 36 months after cystectomy are characterized by a relative low risk of future tumour progression. The potential benefit of regular follow-up investigations is therefore highest in the first 24 months.
- Therapeutic efficacy of salvage treatment: there is growing evidence that new chemotherapeutic substances will significantly improve the curative potential of systemic chemotherapy.
- Mandatory investigations are those which are necessary to document a well functioning urinary diversion. Follow-up investigations aimed at 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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6.4 FOLLOW-UP AFTER URINARY DIVERSION

The follow-up of patients with urinary diversion after cystectomy can be separated into issues related to surgery by itself, metabolic problems associated with the type and extent of bowel segment used, metabolic problems associated with urine storage, infection and development of second 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 1). 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. A specificity of ileum conduits are elongation and stricture formation, as well as stoma stenosis and skin infections (13-16). Pouches using different continence mechanism have typical complications 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 staplers, but also other factors mentioned below (17).

The results in ileum pouch surgery derive from one series and should therefore 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 the failure to void (females: 30%) may be encountered (4,18-20). Night-time incontinence can be as high as 30% (4,20).

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 B-12 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 B-12. The resection more than 50-60 cm of bowel may result in bile and fat metabolism disorders. An increased number of gall stones may be encountered (24). Moreover, stools may become fatty and loose. Chronic diarrhoea is twice as frequent in patients with ileocecal resections compared with ileal resection (25). Also, oxalate stone formation can 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 an adequate renal function. The reabsorption of sodium is more prominent in ileum segments, whereas chloride is reabsorbed more in colon segments (26,27). Characteristically, hyperchloraemic acidosis is more often encountered in ureterosigmoidostomy and continent pouches using the caecum (28-32). However, up to 50% of pure ileal reservoirs show mild acidosis due to ammonium reabsorption (33).

Apart from increased reabsorption of electrolytes the kidneys have to deal with a significantly higher fluid load. It is uncertain whether increased workload results in loss of renal function, but this may be suspected from previous similar 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 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 mineralisation 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 meaning of bacterial colonisation within the continent reservoirs is unknown (39,40). Apart from being of importance for stone formation and pyelonephritis, in the case of reflux, we can speculate on systemic as well as local effects (2). The occurrence of stones within the continent pouch is as high as 34% after 5 years and 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).

Second cancers

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

The excretion of nitrosamines and the continued exposure to carcinogens that which may have been initiated the cancer can lead to second cancers (43). Patients with an increased risk of developing colon cancer may be especially prone to 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).

RECOMMENDATIONS

- The upper urinary tract has to be followed by sonography to detect upper urinary tract dilatation and stone formation. Stoma has to be evaluated for stenosis. Reflux and residual urine (bladder substitution) should be excluded in patients with recurrent urinary tract infections.
- Vitamin B-12 base line determination at time of surgery. Follow-up examination dependent on the initial level.
- Renal function, electrolytes and acid-base determination should be assessed on a regular basis.
- Sonography and plain films to be carried out every two years to detect stones in the upper urinary tract as well as in the continent reservoir.
- Endoscopy started 5 years after surgery.
- A summary of the follow-up scheme is shown in Table 2.

Table 1: Incidence of reflux and urethral stenosis associated with urinary diversion

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

Table 2: Follow-up scheme after urinary diversion

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<p>Year 1: at 3 to 4 monthly intervals</p> <ul style="list-style-type: none">• Ultrasound of the kidney and reservoir• Electrolytes and creatinine• Base excess <p>Years 2-3: at 6 monthly intervals</p> <ul style="list-style-type: none">• Ultrasound of the kidneys and reservoir• Plain film• Electrolytes and creatinine• Base excess <p>Year 4: at yearly intervals</p> <ul style="list-style-type: none">• Ultrasound of the kidneys and reservoir• Plain film• Electrolytes and creatinine• Base excess• Vitamin B-12 <p>Year 5 and thereafter: at yearly intervals</p> <ul style="list-style-type: none">• Ultrasound of the kidneys and reservoir• Plain film• Electrolytes and creatinine• Base excess• Vitamin B-12• Colonoscopy in patients with ureterosigmoidostomy
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