Guidelines on bladder cancer

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Abstract

Objectives: On behalf of the European Association of Urology (EAU) guidelines for diagnosis, therapy and follow-up of bladder cancer patients were established. Criteria for recommendations were evidence based, and included aspects of cost-effectiveness and clinical feasibility.

Method: A systematic literature research using Medline Services was conducted. References were weighted by a panel of experts.

Results: TNM, 1997, classification and WHO grading 1998 are recommended. Recommendations are developed for diagnosis for bladder cancer in general, treatment of superficial and infiltrative bladder cancer, and follow-up after different types of treatment modalities, such as intravesical instillations, radical cystectomy, urinary diversions, radiotherapy and chemotherapy.

CLASSIFICATION OF BLADDER CANCER

The use of the TNM classification 1997 and WHO grading, 1999, is encouraged, as it corresponds best with the clinical outcome of the tumours (1)

More than 90% of bladder cancers are transitional cell carcinoma (TCC); the remainder are squamous cell or adenocarcinoma.
Bladder tumours are considered superficial (Tis-Ta-T1) or infiltrative (T2-T3-T4) based on cystoscopy, transurethral resection (TUR), imaging studies and histopathological findings.

There is also important inter observer variability in classifying stage T1 vs. TA tumours and grading tumours (2).

DIAGNOSIS

Early detection

Early symptom recognition in bladder tumours is a key to better prognosis (6,7). Haematuria is the most common finding in bladder cancer. The degree of haematuria does not correlate with the extent of the disease.

Bladder cancer may also present with voiding irritability.

Imaging

Intravenous pyelography is considered as an important examination to evaluate haematuria but the necessity to perform routinely is now questioned because of the low incidence of important findings obtained (3). Ultrasonography
combined with plain abdominal film was found to be as accurate in the diagnosis of the cause of haematuria as IVP.

Computed tomography 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.

The significance of routine bone scans before total cystectomy in infiltrative tumours is questionable.

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. It remains often negative in low-grade tumours.

Cystoscopy and TUR

A bimanual examination should be performed first to assess whether or not a mass is palpable in the bladder and, if so, whether it is fixed to the pelvic wall. 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.

The more superficial component of the tumour should be resected separately from its deeper component.

Biopsy specimens of the tumour and suspected area should be taken to map the extent of the disease. 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 not indicated because of the absence of additional information (4) and because it may be nocious, as lesions to the mucosa can provoke implantation of tumor cells. 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 (5).

5.1 TREATMENT

- Ta-1 are superficial bladder tumours. Treatment will be directed towards the prevention of recurrence and progression of the disease.
- T1G3 has a high tendency to progression. The role of early cystectomy still is a matter of debate.
- TIS is a potential highly malignant disease that can still be treated in the majority of cases with bladder instillations of BCG. A cystectomy is necessary when this fails to cure the disease after two cycles of 6 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 diseases needs additional therapeutic approaches.

Treatment of Ta and T1 lesions
The therapeutic regimen for a Ta and T1 tumour will take into account the risk of recurrence and progression, side effects and cost effectiveness. The recurrence rate of superficial bladder cancer (SBC), even after adequate treatment, is widely documented (6,7). The risk of progression to invasive cancer is low in the majority of cases, but goes up to 50% in high grade T1 G3 (7,8), which represents around 10% of cases.

The risk of recurrence and progression can be predicted on the basis of clinical and pathological data.

Prognostic factors: for recurrence (in descending importance)(9,10)

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 outmost importance.

Based on the 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 (TIS)
- Intermediate: all other tumours, Ta-1, G1-2, multifocal, > 3 cm diameter.

Immediate instillation after TUR with a chemotherapeutic agent should be encouraged in all cases as it is able to reduce recurrence rate by about 50 % (11,12). In intermediate risk tumours that needs a further instillation, an early instillation can reduce the need for maintenance therapy (13). Low risk tumours need no further treatment.

Tumours with a higher risk of recurrence 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.

The usefulness of repeated instillations with chemotherapeutic agents is not clearly defined.

There is no proof that chemotherapeutic instillations 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.

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

BCG
It has been found more effective in high risk SBC BCG is able to prevent progression.
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 to 25% with the same effectiveness as the full dose and less general side effects (15).

BCG is not indicated in low risk groups in which the potential danger of BCG does not counterbalance its advantage.
Lower recurrence rates have been reported after maintenance therapy of up to 3 years (14). Whether or not this heavy schedule is necessary for all patients is uncertain.

Treatment of TIS
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 remains positive, another cycle may produce an additional 15% complete remission. Maintenance therapy with booster cycles up to 36 months is advocated to prevent recurrence. If cure is not achieved after this second cycle or there is early recurrence, cystectomy with urethrectomy is indicated.

Treatment of T1G3 bladder tumours
The T1G3 bladder tumours have a high tendency to progress and therefore some experts tend to do early cystectomy. Nevertheless, it has been demonstrated that 50% of patients can conserve their bladder with bladder instillations of chemotherapeutic agents or BCG.

5.2 TREATMENT: RADICAL CYSTECTOMY

Radical cystectomy is the standard treatment in most countries for muscle invasive bladder tumour. However, renewed interest in quality-of-life issues has increased interest in bladder preservation treatments. But radiotherapy is still a choice in several countries. Also, performance status and age can influence the choice of therapy, with cystectomy being reserved for younger patients without concomitant disease.

Indications
The indication for cystectomy is a patient with muscle-invasive bladder cancer T2-T4a, N0-NX, M0. Other indications are patients with high-risk superficial tumours and BCG resistant Tis and T1G3 and extensive papillary disease that cannot be controlled with conservative measures.

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. Currently, urethrectomy is recommended if the tumour involves the bladder neck in women and the prostatic urethra in men.
A radical cystectomy also includes a dissection of the regional lymph nodes, which will give valuable prognostic information. No controlled studies exist supporting the curative value of lymph

node dissection (16). Cystoscopy has a mortality from 1 to 4 % and an important early morbidity. Late morbidity is nearly due to the urinary diversion.

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 preoperative radio- or chemotherapy (17,18) has not changed the outcome.

Tumour stage and nodal involvement are the only independent predictors of survival (19).

5.3 URINARY DIVERSION AFTER RADICAL CYSTECTOMY

Four alternatives are used presently after cystectomy, ileal conduit, continent pouch, a bladder reconstruction and ureterosigmoidostomy. The later is only used in selected centers.

The ileal conduit is a reliable option with well-known good results. However after long term follow-up 20% develop stomal complications and 30% of the renal units become dilated (20).

A variety of continent reservoirs have been introduced, the majority of these used either ileal segments, ileocecal segments or the sigmoid colon (21). Following continent urinary diversion early and late complications have been encountered in 12% and 37%of the patients, respectively (22). Late complications seen included ureteral stricture/obstructions, 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 (23).

Orthotopic bladder replacement have been performed in men for more than a decade an in women more recently. The main advantage is that no stoma is necessary. Disadvantages include nocturnal leakage in one third of the patients and problems with voiding requiring self-intermittent catheterization. As it concerns major surgery early and late complications remains frequent, requiring reoperation in about 22% of the patients (24).

Contra-indications 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. 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.

Studies of quality of life outcomes show that 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 (25). Problems with urinary diversion and sexual functioning were identified as most common.

By many experts and several national guidelines it is recommended to centralize continent pouch and bladder replacement operations in centers doing this intervention regularly, because this major surgery requires experience and teamwork.

5.4 RADIOTHERAPY

Definitive radiotherapy with curative intent and the aim of bladder preservation is performed in T1 to T4,N0,M0 transitional cell bladder cancer (26-29).

The decision for or against radiotherapy should be based on prognostic factors, patients desire and will be heavily influenced by the physician’s preference (27,35).

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 (26,27).

External beam radiotherapy is the most common form of radiotherapy. The use of simultaneous chemotherapy to induce high control is investigated.

Brachytherapy is an alternative radiotherapeutic approach in selected patients with small solitary tumours of less than 5 cm in diameter (32).

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 are less prominent in modern series (28,29). Erectile dysfunction will occur in more than two-thirds of male patients (33). Sexual function in females seems not compromised (34).

Prognostic factors
Although the 5-year survival rate is acceptable, local recurrence will occur in about 50% of patients (28). A small proportion of these patients can undergo salvage cystectomy (28,35).

5.5 CHEMOTHERAPY

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 (36-38).

Randomized trials with neo-adjuvant chemotherapy have not yet proven a survival benefit with neo-adjuvant chemotherapy (39). However, response to chemotherapy is an important predictor of survival (40,41).

Neo-adjuvant chemotherapy and bladder preservation
Selected patients with invasive bladder tumours after neo-adjuvant chemotherapy may still have their bladders preserved, although the approach is highly controversial (41,42). Bladder preservation may be possible with an integrated approach using chemotherapy and radiotherapy (43).

Prognostic factors for local curability were small tumour size, absence of hydronephrosis, papillary histology, visible complete TUR and a complete response to induction chemotherapy.

Adjuvant chemotherapy
Several trials with combination chemotherapy appeared to show a difference in favour of chemotherapy. Yet the results are controversial (44).

Metastatic disease
Two prospective randomized trials have proven the superiority of M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin)(45,46). Unfortunately, the use of this 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.

Novel chemotherapeutic agents such as gemcitabine and the taxanes obtain similar overall survival, time to progressive disease, time to treatment failure, and response rate but gemcitabine + Cisplatinum appears to have a reduced toxicity profile compared to M-VAC (47,48).

The combination of gemcitabine and taxol has been shown to be highly effective in patients who have failed prior M-VAC (49). When cisplatin gemcitabine and taxol were given to untreated patients, high overall response rates were observed (50).

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 (51).

6.1 FOLLOW-UP AFTER TUR IN SUPERFICIAL BLADDER CANCER

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. 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 (52).

Frequency of later cystoscopies
This should be adapted to the prognostic factors of the tumour. In low risk tumours 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 (53). In case of recurrence, the histological findings are the same as those of the primary TUR in over 95% of cases.
In patients with high-risk tumours, a 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 3rd year, every 6 months thereafter for up to 5 years and then yearly. The schedule of follow-up in the intermediate group lies between.

With any recurrence, the schedule of cystoscopies is restarted from the beginning.

It seems advisable to stop follow-up in single Ta G1 tumours in the absence of recurrence during 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 (54).

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 (55).

The highest frequency can be expected in Cis and therefore IVP should be carried out when cytology remains positive during follow-up (56,57).

6.2 FOLLOW-UP AFTER RADICAL CYSTECTOMY

The risk of tumour progression after radical cystectomy strongly depends on histopathological tumour stage (58). Progression risk is highest within the first 24 months following cystectomy. 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.

Therapeutic consequences of follow-up investigations (role of salvage therapy)
No prospective data are available for salvage treatment comparing asymptomatic tumour relapse. Patients with symptomatic tumour relapse often are characterized by a reduced general condition (59). A reduced performance status is a predictor of a poor outcome. It does seem likely that

efforts aiming at early detection of tumour progression may lead to an improved success-rate of salvage therapy.

Anatmical sites
Of all cases with relapse, 15-20% are found in the true pelvis, another 10-15% in the pelvic or retroperitoneal lymph nodes. Local recurrences after cystectomy are reported for pT2a, 2b, and pT3 tumour at 6, 18 and 51% respectively (60).

Distant metastases are mainly located in lever (38%), lung (36%) and bone (28%).
More than 50% of all patients with tumour progression have distant metastases.

The most probable site of intraluminal disease recurrence is the male urethra, if it is not prophylactically removed at the time of the cystectomy. The incidence of a urethral recurrence is 5-13% (61). Tumour involving the bladder neck or prostate and those with TIS are at highest risk. Some contemporary series report a lower risk of urethral recurrences as compared to historical series (62).

Upper tract intraluminal recurrences are even less frequent, the cost-benefit of regular intravenous pyelograms are limited by the low frequency of upper tract tumours and may therefore be partially replaced by ultrasound and urinary cytology (63).

Time schedule for follow-up after radical cystectomy and urinary diversion.

Time	Mandatory	Optional
3 m	**US or IVP Blood Chem Ph.Exam**	
6 m	**Blood Chem Ph.Exam**	**CT Ch X-ray Urethra**
12 m	**US or IVP Blood Chem Ph.Exam**	**CT Ch X-ray Urethra**
18 m	**Blood Chem Ph.Exam**	
24 m	**US KUB Blood Chem Ph.Exam**	**CT Ch X-ray Urethra**
36 m	**Blood Chem Ph.Exam**	**CT Ch X-ray Urethra**
48 m	**US KUB Blood Chem Ph.Exam**	
60 m	**Blood Chem Ph.Exam**	**Endoscopy Urethra**
72 m	**US KUB Blood Chem Ph.Exam**	**Endoscopy Urethra**
96 m	**US KUB Blood Chem Ph.Exam**	**Endoscopy Urethra**
120 m	**US KUB Blood Chem Ph.Exam**	**Endoscopy Urethra**

US = ultrasound of the kidneys
KUB = plain abdominal X-ray
Blood Chem = Liver and kidney tests, electrolytes, base excess (also vit. B12 after 4 years)

Ph. Exam = physical examination including DRE
Endoscopy of bladder substitute or reservoir
Urethra = scopy and or wash
Ch X-ray = Chest X-ray

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* For more extensive information consult the EAU Guidelines presented at the XVIth EAU annual congress, Geneva, Switzerland (ISBN 90-806179-3-9)

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