Μη διηθητικός καρκίνος της κύστης: Οι κατευθυντήριες οδηγίες δίνουν τη λύση

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- Σύγκρουση συμφερόντων : καμία

A **medical guideline** is a document with the aim of guiding decisions and criteria regarding diagnosis, management, and treatment in specific areas of healthcare.

In contrast to previous approaches, which were often based on tradition or authority, modern medical guidelines are based on an examination of current evidence within the paradigm of evidence-based medicine.

- They usually include summarized consensus statements on best practice in healthcare. A healthcare provider is obliged to know the medical guidelines of his or her profession, and has to decide whether or not to follow the recommendations of a guideline for an individual treatment.

- Additional objectives of clinical guidelines are to standardize medical care, to raise quality of care, to reduce several kinds of risk (to the patient, to the healthcare provider, to medical insurers and health plans) and to achieve the best balance between cost and medical parameters such as effectiveness, specificity, sensitivity, resolutiveness, etc.

Problems

- Guidelines may have both methodological problems and conflict of interest.
- Guidelines may make recommendations that are stronger than the supporting evidence.

Wikipedia

EAU Guidelines

It must be emphasised that clinical guidelines present the best evidence available but following the recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients - also taking personal values and preferences and individual circumstances of patients into account.

It should be noted that when recommendations are graded, the link between the LE and grade of recommendation (GR) is not directly linear. Availability of RCTs may not necessarily translate into a grade A recommendation where there are methodological limitations or disparity in published results.

Αξιολόγηση και Σύσταση

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials.
1b	Evidence obtained from at least one randomised trial.
2a	Evidence obtained from one well-designed controlled study without randomisation.
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study.
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities.

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency that addressed the specific recommendations, including at least one randomised trial.
B	Based on well-conducted clinical studies, but without randomised clinical trials.
C	Made despite the absence of directly applicable clinical studies of good quality.

Διάγνωση

Ιστορικό

Patient history should be taken and recorded regarding all important information with possible connection to bladder cancer, including risk factors and history of suspect symptoms.	A

Απεικόνιση

Renal and bladder US may be used during initial work-up in patients with haematuria.	C
At the time of initial diagnosis of bladder cancer, CT urography or IVU should be performed only in selected cases (e.g., tumours located in the trigone).	B

Η επίπτωση στο ανώτερο ουροποιητικό είναι 1,8%
Όταν αναπτύσσεται στο τρίγωνο 7,5%

Palou et al J Urol 2005 (LE 2a)

Διάγνωση

Voided urine cytology is advocated to predict high-grade tumour before TUR.	C
Cytology should be performed on fresh urine with adequate fixation. Morning urine is not suitable because of the frequent presence of cytolysis.	C

Ευαισθησία 28-100%
Ειδικότητα 90%
Millan-Rodriguez et al J Urol 2000 (LE2b)
Lokeshwar et al Urology 2005 (LE2b)

Cystoscopy is recommended in all patients with symptoms suggestive of bladder cancer. It cannot be replaced by cytology or any other non-invasive test.	A
Cystoscopy should describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities. A bladder diagram is recommended.	C

Κανένας δείκτης (Urinary marker) δεν είναι ικανός να αντικαταστήσει την κυστεοσκόπηση
Βελτιώνει την ποιότητα της κατά την παρακολούθηση (Microsatellite analysis)

van der Aa et al J Urol 2010 (LE 1b)

TUR

TURB should be performed systematically in individual steps: bimanual palpation under anaesthesia; insertion of the resectoscope, under visual control with inspection of the whole urethra; inspection of the whole urothelial lining of the bladder; biopsy from prostatic urethra (if indicated); cold-cup bladder biopsies (if indicated); resection of the tumour; bimanual palpation after resection; protocol formulation; formulation of order form for pathological evaluation.	C

Perform resection in one piece for small papillary tumours (< 1 cm), including part from the underlying bladder wall.	B
Perform resection in fractions (including muscle tissue) for tumours > 1 cm in diameter.	B

Richtestetter et al BJU Int 2012 (LE 3)

Biopsies should be taken from abnormal-looking urothelium. Biopsies from normal-looking mucosa (trigone, bladder dome, and right, left, anterior and posterior bladder walls) are recommended only when cytology is positive or when exophytic tumour has a non-papillary appearance.	C
Biopsy of the prostatic urethra is recommended for cases of bladder neck tumour, when bladder CIS is present or suspected, when there is positive cytology without evidence of tumour in the bladder, or when abnormalities of the prostatic urethra are visible. If biopsy is not performed during the initial procedure, it should be completed at the time of the second resection.	C
Biopsy of the prostatic urethra should be taken from abnormal areas and from the precollicular area (between 5 and 7 o'clock position) using a resection loop. In primary non-muscle-invasive tumours when stromal invasion is not suspected, the cold-cup biopsy with forceps can be used.	C

Van der Meijden Eur Uro 1999 (LE 2a)
Palou et al Eur Urol 2012 (LE2b)
Mungan et al Eur Urol 2005 (LE 3)

TUR

If equipment is available, fluorescence-guided (PDD) biopsy should be performed instead of random biopsies when bladder CIS or high-grade tumour is suspected (e.g., positive cytology, recurrent tumour with previous history of a high-grade lesion).	B

Μεγαλύτερη ευαισθησία ειδικά στο CIS

Kaush et al Eur Urol 2010 (LE2a)

Μικρότερη ειδικότητα

Draga et al Eur Urol 2010 (LE 3)

A large, multicentre, prospective randomised trial that compared HAL fluorescence-guided TURB with standard TURB reported an absolute reduction of no more than 9% in the recurrence rate within 9 months in the HAL arm. Median time to recurrence improved from 9.4 months in the white light arm to 16.4 months in the HAL arm after mean follow-up of 53 and 55 months, respectively

Grossman et al J Urol 2010 (LE 1b)

The value of fluorescence cystoscopy for improvement of the outcome in relation to progression rate or survival remains to be demonstrated.

TUR

The specimens from different biopsies and resection fractions must be referred to the pathologist in separate containers and labelled separately.	C
TURB protocol must describe all steps of the procedure, as well as extent and completeness of resection.	C
A second TURB is recommended in the following situations:	A
- after incomplete initial TURB; - if there is no muscle in the specimen after initial resection, with exception of Ta G1 tumours and primary CIS; - in all T1 tumours; - in all G3 tumours, except primary CIS.	
A second TURB should be performed 2-6 weeks after initial resection.	C

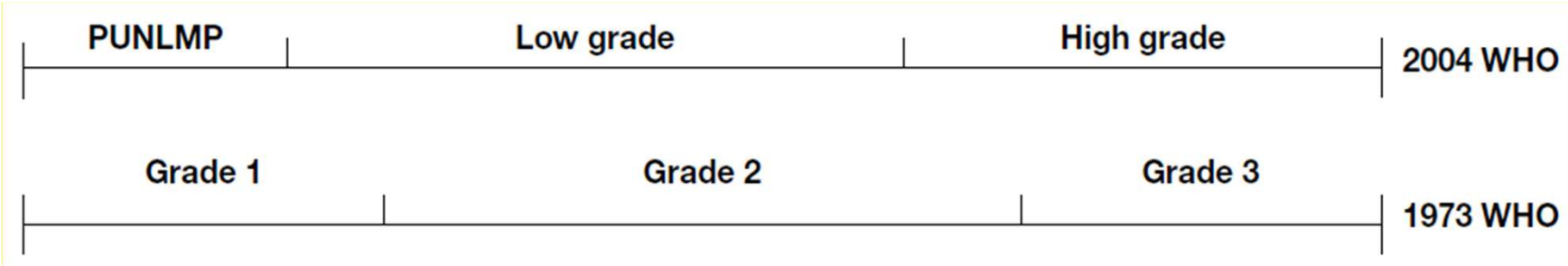
Miladi et al Eur Urol 2003 (LE2a)
Brauers et al J Urol 2001 (LE 2a)

Ιστολογικά χαρακτηριστικά

Depth of tumour invasion is classified according to TNM system.	A
For histological classification, 1973 and 2004 WHO grading systems are used. Until the prognostic role of WHO 2004 is validated by more prospective trials, both classifications should be used.	A
Whenever the terminology NMIBC is used in individual cases, the tumour stage and grade should be mentioned.	A
The pathological report should specify tumour location, tumour grade, depth of tumour invasion, presence of CIS, and whether the detrusor muscle is present in the specimen.	A
The pathological report should specify the presence of LVI or aberrant histology.	C

Lopez-Beltran et al Eur Urol 2004

Σταδιοποίηση



Despite well-defined criteria for the diagnosis of urothelial carcinoma, there is significant variability among pathologists for diagnosis of CIS, for which agreement is achieved in only 70-78% of cases

There is interobserver variability in classification of stage T1 versus Ta tumours and tumour grading in both 1997 and 2004 classifications. The general conformity in staging and grading is between 50 and 60%

Murphy et al J Urol 2002 (LE 2a)
Witjes et al Urology 2006 (LE 2a)

In difficult cases, an additional review by an experienced genitourinary pathologist is recommended.

Πρόβλεψη

Stratify patients into three risk groups according to Table 8.	B

Low-risk tumours	Primary, solitary, Ta, G1 (low grade), < 3 cm, no CIS
Intermediate-risk tumours	All tumours not defined in the two adjacent categories (between the category of low and high risk)
High-risk tumours	Any of the following: • T1 tumour • G3 (high grade) tumour • CIS • Multiple and recurrent and large (> 3 cm) Ta G1G2 tumours (all conditions must be presented in this point)

Application of EORTC risk tables and calculator for individual prediction of the risk of tumour recurrence and progression in different intervals after TURB.	B

Επικουρική θεραπεία

The type of intravesical therapy should be based on the risk groups shown in Tables 8 and 11.	A

Risk category	Definition	Treatment recommendation
Low-risk tumours	Primary, solitary, Ta, G1, < 3 cm, no CIS	One immediate instillation of chemotherapy
Intermediate-risk tumours	All cases between categories of low and high risk	One immediate instillation of chemotherapy followed by further instillations, either chemotherapy for a maximum of 1 year or 1 year full-dose BCG
High-risk tumours	Any of the following: • T1 tumours • G3 tumours • CIS • Multiple and recurrent and large (> 3 cm) Ta G1G2 tumours (all these conditions must be presented)	Intravesical full-dose BCG instillations for 1-3 years or cystectomy (in highest risk tumours)
Subgroup of highest-risk tumours	T1G3 associated with concurrent bladder CIS, multiple and/or large T1G3 and/or recurrent T1G3, T1G3 with CIS in prostatic urethra, micropapillary variant of urothelial carcinoma	Cystectomy should be considered
	BCG refractory tumours	Cystectomy is recommended

Επικουρική θεραπεία

One immediate chemotherapy instillation is recommended in tumours presumed to be at low or intermediate risk.	
In patients with low-risk Ta tumours, one immediate instillation of chemotherapy is recommended as the complete adjuvant treatment.	A
In patients with intermediate-risk Ta T1 tumours, one immediate instillation of chemotherapy should be followed by 1 year full-dose BCG treatment, or by further instillation of chemotherapy for a maximum of 1 year.	A

Mitomycin C = Epirubicin = Doxorubicin

Sylvester et al J Urol 2004 (LE 1a)

One immediate instillation of chemotherapy should be omitted in any case of overt or suspected intra- or extraperitoneal perforation (after extensive TURB, or bleeding requiring bladder irrigation).	C
The optimal schedule of further intravesical chemotherapy instillation and its duration is not defined and should not exceed 1 year.	C
If intravesical chemotherapy is given, it is advised to use the drug at its optimal pH and to maintain the concentration of the drug during instillation by reducing fluid intake.	B
The length of individual instillation should be 1-2 hours.	C

Huncharek et al Anticancer Res 2001 (LE 1a)
Bohle et al Urology 2004 (LE 1a)

Επικουρική θεραπεία

It is still controversial for how long and how frequently chemotherapy instillations should be given. From a systematic review of the literature of RCTs, which compared different schedules of intravesical chemotherapy instillations, one can only conclude that the ideal duration and intensity of the schedule remains undefined because of conflicting data (146). The available evidence does not support any treatment longer than 1 year

Sylvester et al Eur Urol 2008 (LE 3)

Επικουρική θεραπεία

In patients with high-risk tumours, full-dose intravesical BCG for 1-3 years is indicated.	A
In patients with CIS in the epithelial lining of the prostatic urethra, TUR of the prostate followed by intravesical instillation of BCG is an option.	C

Malmstrom et al Eur Uro 2009 (LE 1a)
Sylvester et al Eur Urol 2010 (LE 1a)

Absolute contraindications of BCG intravesical instillation are: during the first 2 weeks after TUR; in patients with macroscopic haematuria; after traumatic catheterization; and in patients with symptomatic urinary tract infection.	C
The management of side effects after BCG intravesical instillation should reflect their type and grade (Table 9).	C

Falkensammer et al Urology 2005 (LE 3)
Rodriguez et al Arch Esp Urol 2008 (LE 3)

BCG

The conflicting results in the outcomes of the studies can be explained by different patient characteristics, duration of follow-up, methodology and statistical power. The majority of studies were however able to show a reduction in the risk of progression in high- and intermediate-risk tumours if BCG was applied including a maintenance schedule.

Επικουρική θεραπεία

In patients at highest risk of tumour progression (Table 11), immediate radical cystectomy should be considered.	C
In BCG refractory tumours, radical cystectomy is indicated.	B

BCG failure	
Whenever a muscle-invasive tumour is detected during follow-up.	
BCG-refractory tumour:	
	1. If high-grade, non-muscle-invasive papillary tumour is present at 3 months (185). Further conservative treatment with BCG is connected with increased risk of progression (122,186) (LE: 3).
	2. If CIS (without concomitant papillary tumour) is present at both 3 and 6 months. In patients with CIS present at 3 months, an additional BCG course can achieve a complete response in > 50% of cases (42) LE: 3).
	3. If high-grade tumour appears during BCG therapy.*
High grade recurrence after BCG. Recurrence of high grade/grade 3 (WHO 2004/1973) tumour after completion of BCG maintenance, despite an initial response (187) (LE: 3).*	
BCG intolerance	
Severe side effects that prevent further BCG instillation before completing induction (170).	

** Patients with low-grade recurrence during or after BCG treatment are not considered as BCG failure.*

Herr et al J Urol 2003 (LE3)
Lerner et al Urol Oncol 2009 (LE 3)

Ριζική κυστεκτομή

Άμεση κυστεκτομή (immediate)

- multiple and/ or large (> 3 cm) T1, high-grade (G3) tumours;
- T1, high-grade (G3) tumours with concurrent CIS;
- recurrent T1, high-grade (G3) tumours;
- T1G3 and CIS in prostatic urethra;
- micropapillary variant of urothelial carcinoma.

Fernandez-Gomez et al J Urol 2009 (LE 3)
Sylvester et al Eur Urol 2006 (LE 3)

Έγκαιρη (early)

Category	Treatment recommendation	GR
BCG refractory tumour	1. Radical cystectomy 2. Bladder-preserving strategies in patients not suitable for cystectomy	B
High-grade recurrence after BCG	1. Radical cystectomy 2. Repeat BCG course 3. Bladder-preserving strategies	C
Non-high-grade recurrence after BCG for primary intermediate-risk tumour	1. Repeat BCG or intravesical chemotherapy 2. Radical cystectomy	C

Raj et al J Urol 2007 (LE 3)
Stein et al J Clin Oncol 2001 (LE 3)

Παρακολούθηση

The follow-up of TaT1 tumours is based on regular cystoscopy.	A
Patients with low-risk Ta tumours should undergo cystoscopy at 3 months. If negative, subsequent cystoscopy is advised 9 months later, and then yearly for 5 years.	C
Patients with high-risk tumours should undergo cystoscopy and urinary cytology at 3 months. If negative, subsequent cystoscopy and cytology should be repeated every 3 months for a period of 2 years, and every 6 months thereafter until 5 years, and then yearly.	C
Patients with intermediate-risk TaT1 tumours should have an in-between follow-up scheme using cystoscopy and cytology, which is adapted according to personal and subjective factors.	C

Oge et al Eur Urol 2000 (LE 2b)
Gofrit et al Eur Urol 2006 (LE 2b)
Soukup et al Eur Urol 2012 (LE 3)

Παρακολούθηση

Regular (yearly) upper tract imaging (CT-IVU or IVU) is recommended for high-risk tumours.	C
Endoscopy under anaesthesia and bladder biopsies should be performed when office cystoscopy shows suspicious findings or if urinary cytology is positive.	B
During follow-up in patients with positive cytology and no visible tumour in the bladder, R-biopsies or biopsies with PDD (if equipment is available) and investigation of extravesical locations (CT urography, prostatic urethra biopsy) are recommended.	B

Millan-Rodriguez et al J Urol 2000 (LE 3)
Van der Aa et al J Urol 2010 (1b)