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REVIEW ARTICLE

Carcinoma in situ of the urinary bladder

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Summary

Urinary bladder cancer ranks 4th among cancers in men and 8th in women. Superficial bladder cancer (stages Tis, Ta and T1) accounts for 75% of bladder cancer cases, whereas carcinoma in situ *(CIS) may appear as an entity of its own, or coexist with another tumor. The diagnosis of CIS is based on urine cytology, cystoscopy and biopsy. Long term follow-up is mandatory due to its high recurrence rate and its invasive potential. Because of this, radical cystectomy has been the gold standard treatment till the mid 1980's. The emergence of intravesical infusion of drugs, especially of BCG, changed the management of CIS altogether. Today, BCG infusion after the initial transurethral resection (TUR) is considered the best treatment, although a consensus regarding the ideal dosing scheme or the maintenance scheduling, has not yet been reached. This, as well as newly developedtherapeutic means, underscore the need for further study on the ideal treatment of CIS of the urinary bladder.*

Key words: BCG, carcinoma in situ, superficial bladder cancer

Introduction - epidemiology

Urinary bladder cancer ranks 4th among cancers in men and 8th in women and represents the 9th most common cause of death related to neoplasms. In the USA 57,000 new cases are diagnosed each year (32.3 new cases per 100,000 Caucasians), and 12,500 die of it. Seventy-five percent of the newly diagnosed cases are superficial (stages Ta, T1 or CIS), 20% are muscle-invasive and 5% have already metastases at the time of diagnosis [1]. Of the CIS cases, 10% exist as an isolated finding and in the rest 90% they co-exist with a papillary or sessile tumor. When isolated, the risk of progression to invasive disease is 20-34% and rises to 42-83% when a CIS coexists with another tumor [2]. Only a small percentage of patients with CIS will never progress to invasive disease [3]. Ridle et al. [4] found that when focal, CIS will progress in 8% of the cases, compared to 78% when it is diffuse.

Bladder cancer is more common in the industrialized countries (USA, Canada, and Europe) while its incidence in Asia and South America is by 70% less. Bladder cancer is almost twice as common in whites as in blacks, but blacks appear to have a higher rate of invasive disease [5]. Men suffer three times as much as women [1].

Risk factors

Bladder cancer is one of the few neoplasms for which many risk factors are well known. The most important are the following:

Professional risk factors

Twenty percent out of all bladder cancer cases can be attributed to exposure to certain chemicals. The latency period is usually quite long (30-50 years). Aniline dyes, aromatic amines and aldehydes are the most com-

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mon agents and workers in the auto industry, dry cleaners, paper industry, leather processing and painters are at higher risk of developing bladder cancer.

Smoking

The risk is increased by four-fold. It is related to the number of cigarettes, the years of smoking and the amount of smoke inhaled. Former smokers have decreased risk compared to active ones.

Age

Bladder cancer may appear at any age but its incidence peaks around the 6th and 7th decades of life. The mean age at diagnosis is 69 in men and 71 in women [1,5].

Sex and race

Relative data is found at the introduction.

Chronic irritating factors

Chronic cystitis (due to chronic indwelling catheter or bladder stones) is associated with increased risk of squamous cell carcinoma of the bladder. This is also true for the cystitis caused by *Schistosoma haematobium.* Some studies have pointed to the possible association of HPV or even other viral infections and bladder cancer but with inconclusive results [5].

Coffee and tea

Both these habits are closely related to smoking and no proof exists that they represent independent risk factors.

Analgesic use

Heavy use (5-15 kg over a 10-year period) of analgesic combinations containing phenacetin has been implicated for bladder cancer.

Artificial sweeteners

In animal studies there is proof of a causative relationship. Such proof does not exist in human studies though.

Radiation

Women who have been exposed to therapeutic irradiation for cervical cancer have a 2-4- fold increased risk.

Cyclophosphamide

The risk is increased up to 9-fold in patients treated with this alkylator.

Tryptophane

The association of trypophane metabolites and bladder cancer is much weaker today than formerly believed.

Heredity

There are no studies suggesting any relevance.

Natural history of CIS

CIS was first described by Melicow in 1952, representing hyperplastic and anaplastic areas in an otherwise healthy-appearing bladder mucosa and emphasizing its invasive potential [6].

CIS is a flat, non-invasive and potentially high-grade neoplasm. The malignant cells infiltrate the full thickness of the mucosa but not beyond it. It is a tumor of unpredictive nature and high progression rate (31-83%). Patients with a history of CIS who progress tend to suffer early metastases (50-75%). It may exist as a focal or diffuse lesion, on its own or co-exist with some other form of bladder cancer. According to Weinstein et al. [7] CIS exists in two forms: an aggressive one, which has the ability to develop into a solid invasive tumor, and a less aggressive one without invasive or metastatic potential. Several prognostic factors have been studied in an attempt to assess the aggressiveness of CIS:

DNA ploidy

Aneuploid CIS tumors have a more aggressive course and aneuploidy is usual in invasive tumors. Flow cytometry has been used for the classification of CIS into 3 categories: a) tumors with one cell line of aneuploidy at diagnosis that remains the same during follow-up; b) tumors with one cell line of aneuploidy at diagnosis but more than one during follow-up; and c) tumors with more than one cell lines of aneuploidy at diagnosis [8]. Tumors in category c are more likely to progress when compared to those in category a (76% and 19%, respectively). Further study is mandatory though, for DNA ploidy to be established as a clinical prognostic tool.

Cytogenetic studies

Mutation of p53 gene in patients with CIS is associated with disease progression [9]. In multivariate analysis p53 expression is the only independent factor associated with progress of disease (p=0.004) and survival (p=0.01).

Other oncogenes or tumor suppressor genes associated with disease progression in CIS patients are the H-ras [10], retinoblastoma gene [11] and nm23 [12], a tumor suppressor gene.

Increased expression of the receptor of epidermal growth factor (EGF) [13], increased production of cathepsin B [14] and of autocrine motility factor [15] have also been studied. Loss of blood group surface antigens (ABO) appears to relate to greater risk of invasion [16].

Certain antigens expressed in superficial bladder tumors, like M344, 19A211 and T138, have been tested for their potential use in CIS patients [13].Further studies are necessary for the clinical application of all the above.

Invasion of Brunn's nests is a bad prognostic sign as local chemotherapeutics cannot reach the lamina propria.

CIS can be found in all areas covered by urothelium: renal pelvis, ureters, bladder and prostatic urethra. The latter may be involved by extension in up to 45% of bladder CIS cases and therefore prostatic urethra biopsies are mandatory [17]. CIS may very rarely involve the seminal vesicles, the ejaculatory duct epithelium, the distal penile urethra and the periurethral glands [5].

Symptoms

Painless hematuria is the most common. Twenty-five percent of CIS patients are asymptomatic and 85% of those have microscopic painless hematuria. Intense irritating symptoms (dysuria, burning on voiding, urgency) are second in frequency and erroneous diagnoses of cystitis, interstitial cystitis or prostatism are easy to occur. Therefore patients with persistent irritating symptoms and no growth in urine culture should have a urine cytology, cystoscopy and biopsy of the suspicious areas [5].

Diagnosis

The most useful diagnostic tools for CIS are cystoscopy and urine cytology.

Cystoscopy

Cystoscopy and biopsy are the most important diagnostic tests. The bladder may appear normal, with reddish, ulcerated or velvet-like areas. Bladder CIS is most usual at the trigone, around the ureteral orifices, the bladder neck, the lateral walls and rarely the anterior wall or the dome [5].

Fluorescence-assisted cystoscopy by intravesical infusion of protoporphyrin IX (5 ALA) is based on the uptake of the substance by the cancerous cells which in turn appear red when seen under blue light, in contrast to the healthy ones that appear blue. This method is very sensitive (95%) in diagnosing superficial bladder cancer and can be very useful in CIS diagnosis and follow up. At present it is considered as an adjunct to cystoscopy [18].

Urine cytology

It is one of the most useful tools in CIS diagnosis. Its sensitivity ranges from 65 to 90% according to the tumor's grade, and can be further increased if it is combined with various tumor markers or fluorescence techniques [19].

Flow cytometry

Bladder washing specimens are used and its sensitivity can be as high as 95%.

Treatment

Bladder CIS can be classified into 3 clinical entities:

1. Asymptomatic focal
2. Symptomatic diffuse
3. Associated with superficial tumors Ta or T1.

Treatment of choice for the first group is intravesical immunochemotherapy.

Patients in the second group should have intravesical infusions and in case of no response one should proceed to radical cystectomy.

Management of patients in the third group depends on the nature of CIS (focal or diffuse).

Treatment of the first group

Focal CIS should be managed with TUR and fulguration of the surrounding area up to 1.0-1.5 cm, followed by intravesical infusion 4 weeks later.

Treatment of the second group

Patients in the second group should have intravesical infusions and in case of no response one should proceed to radical cystectomy.

TUR

The initial management of CIS is fulguration of the visibly involved areas and resection of any co-existing papillary tumor.Because of the non-visible areas as well as the possible great extent of the disease, TUR is very rarely adequate on its own. According to Utz et al., 87% of CIS patients will recur if treated with TUR only, 60% will progress to muscle invasion (can reach 80% with co-existing T1), and 39% will die of the disease in 5 years [20]. It is therefore clear that an adjuvant treatment to TUR is mandatory for CIS patients.

Radical cystectomy

Radical cystectomy has been the most common treatment for CIS of the bladder during the 60's and till the mid 80's. After the introduction of agents for intravesical infusion, it became evident that early cystectomy in these patients was not improving survival [21] and that cystectomy could be offered after an initial failed attempt at intravesical treatment, with the same success rate.

Most urologists agree that at least one course of BCG as the initial management for CIS would not have any impact on survival and that cystectomy may be postponed until objective evidence of disease progression exists [22].

Patients with low-risk CIS, upon failure, may have a second course of instillation with BCG or some other agent, whereas in those with high-risk CIS radical cystectomy should be strongly considered.

Intravesical chemotherapy

Although intravesical chemotherapy has been extensively used over the last years for CIS and superficial bladder tumors (Table 1) [19], results have been somewhat disappointing, since less than 20% of patients treated with it will remain disease-free for 5 years [23].

Historically, thiotepa was the first agent to be used with a long-term tumor-free response rate of less than 15% for patients followed over a period of 5 years. Ever since the following drugs have been tried: mitomycin-C with a respective response rate of 30-60%, doxorubicin with a tumor-free response rate of 25-60%, epirubicin with a tumor-free response rate of 36% for patients followed over a period of 3 years and mitoxantrone with a response rate of 37-47%.

Table 1. Chemotherapeutics for instillation therapy

Year	*Chemotherapeutic agent*
1961	Thiotepa
1965	5-fluorouracil
1966	Methotrexate
1970	Cyclophosphamide
1970	N-Lost
1971	Epodyl
1972	Doxorubicin
1973	Bleomycin
1975	Mitomycin C

Table adapted from Durek et al. [19]

In different studies it has been established that the mean rate of disease progression was not influenced by intravesical chemotherapy as an adjunct to the TUR [24]. Lamm et al. evaluated 3899 patients in 22 randomized studies and found no difference in the recurrence rate at 5 years of follow-up [25]. A possible explanation is that the cytotoxicity of the intravesical agents is only active in the presence of disease and therefore prophylactic chemotherapy is of no value. In addition, a concern exists as to the potential carcinogenic effect of intravesical chemotherapy: surprisingly, more patients receiving intravesical chemotherapy than surgery alone had progressive disease (7.5% and 6.9%, respectively) [25].

Intravesical immunotherapy

Intravesical BCG

The first report of the use of intravesical BCG for the treatment of superficial bladder cancer was by Morales in 1976, with a complete response rate of around 70%. Today, intravesical infusion of BCG is considered by the American Urological Association Clinical Guidelines Panel, the first step in the management of CIS (isolated or co-existing with papillary stage Ta or T1 tumors), in an effort to avoid cystectomy [26]. BCG prophylaxis after TUR or fulguration of superficial bladder cancer significantly decreases recurrence in numerous randomized trials. Pro-

gression of disease appears to be delayed or even decreased in some studies [27]. Nevertheless, data supporting a durable progression-free survival is less apparent due to the lack of long-term data.

Mechanism of action of BCG

BCG remains the most important biologic response modifier in bladder cancer treatment. It acts as a non-specific immunobooster with more than one mechanisms that include both T and B lymphocytes, K (killer) cells and NK (natural killer) cells. Three ways of action have been suggested:

1. The live BCG organism induces an inflammatory response by the macrophages that can be activated without the help of T cells.
2. A delayed type hypersensitivity reaction, in which macrophages phagocytose the BCG particles and thus induce the production of lymphokines by the T cells with further activation of the immune system.
3. A tumor-specific response in which BCG-activated T cells interact with the macrophages that have phagocytosed BCG particles, as well as fractions of tumor cells. In animals BCG has proven ability to suppress tumor growth or even destroy tumors.

Work up of patients prior to BCG administration

1. No growth in urine culture
2. No macroscopic hematuria
3. No irritating symptoms
4. No residual urine
5. PSA measurement

Contraindications to BCG administration

BCG infusions should start no sooner than 2 to 3 weeks after TUR (even 3 to 4 weeks according to some authors). Immunosuppressed patients are excluded, as well as patients with active tuberculosis. Treatment should be delayed in patients with fever, hematuria or any infection necessitating antibiotics.

Therapeutic schemes of BCG

BCG was approved by the FDA as treatment for CIS of the urinary bladder in 1990, after a study showed a disease-free interval of 45% when BCG was used in CIS patients compared to 18% with doxorubicin [28]. In a study population of 1354 CIS patients, Lamm et al. recorded a complete response rate of 72% with BCG [29]. BCG has been shown to statistically improve time to recurrence and disease progression in certain studies [30,26].

The efficacy of the 6-week induction course is proven in many studies [31]. Sarosdy and Lamm studied 120 patients and found a response rate of 79% after a 6-week course, which could rise to 89% if a second course was administered in cases that failed [32]. Nevertheless, the risk of recurrence is always present and different maintenance schemes have been attempted without a consensus having been reached yet.

At present, many urologists, upon failure of the initial 6-week course, will administer a second 6-week course. The efficacy of that is argued by some authors [33]. A maintenance scheme consisting of 6 weekly infusions every 6 months for 2 years after the initial induction course has not shown any benefit [34]. Better results were obtained by using the SWOG maintenance scheme [33] with 3-weekly infusions at the intervals shown in Table 2. During the induction course the maximum concentration of cytokines in urine is observed after the 6th weekly infusion, whereas during maintenance the greatest immune response occurs after the 3rd weekly infusion. Further infusions beyond the 3rd during the maintenance period have adverse effects by suppressing the immune response and by increasing toxicity [35].

According to the SWOG scheme, in case of recurrence during the first follow up at 3 months, there is a choice of a second course 6+3 weeks or radical cystectomy. If the disease persists in any of the next follow ups one should proceed to cystectomy. Nevertheless, 3 different studies contradict the usefulness of maintenance therapy [36].

Also, various immunological and chemotherapeutic regimens have been evaluated specifically in CIS refractory to BCG therapy [37].

Another factor one should always consider when BCG fails is the presence of CIS in the prostatic urethra. CIS of the prostatic urethra occurs in 19-60% of bladder CIS cases and is an important risk factor for BCG failure [38]. Prostatic involvement may occur at different areas (ducts, acini or stroma) [39]. For patients without stroma invasion or extensive acinar involvement, a reasonable approach would be a TUR of the prostatic urethra followed by BCG intravesical infusion and reserve cystoprostatectomy in case of failure. When either of the above two factors exists, one should proceed to immediate cystoprostatectomy. The same is also true for those cases where disease progresses with prostatic stroma invasion after the initial treatment with BCG [39, 40].

Table 2. Therapeutic regimen for the treatment of bladder CIS with BCG

Patient is suitable for therapy	*TUR Exclusion of contraindications 3-4 weeks after TUR*				*Patient not suitable for therapy*
Induction therapy	1st month of treatment	Week	1	•	*No BCG therapy*
6 weekly instillations	*Start of therapy*		2	•	
			3	•	
			4	•	
	2nd month of treatment	Week	5	•	
			6	•	
			7	◦	
			8	◦	
	3rd month of treatment	Week	9	◦	
			10	◦	
			11	◦	
			12	◦	
	First follow-up with cystoscopy ± cytology				
Patient is tumor-free					Patient not tumor-free
Plus 3 weekly instillations	4th month of treatment	Week	13	•	*Surgical therapy indicated**
			14	•	*Restart basic therapy*
			15	•	
			16	◦	
Patient is tumor-free					Patient not tumor-free* *No continuation of BCG therapy*
Maintenance therapy	6th month of treatment	2nd follow-up cystoscopy ± cytology			
		• • •			
1-3 weekly instillations	12th month of treatment	3rd follow-up cystoscopy ± cytology			
		• • •			
	18th month of treatment	4th follow-up cystoscopy ± cytology			
		• • •			
	24th month of treatment	5th follow-up cystoscopy ± cytology			
	30th month of treatment	6th follow-up cystoscopy ± cytology			
	36th month of treatment	7th follow-up cystoscopy ± cytology			
	End of therapy				
					**pT1G3- or pTis- recurrence: cystectomy*

•BCG therapy; °No BCG therapy
Adapted from Lamm et al. [33]

Complications of intravesical BCG

Although generally well tolerated in most cases, 2-6% of patients discontinue BCG treatment due to complications. Quite serious complications may appear though at any time point during treatment with BCG.

Most common complications are:

1. Flu-like syndrome (after the 2nd infusion)
2. Cystitis in 80% of patients (dysuria, frequency)
3. Fever. This is the most common side effect. It rarely rises above 38° C and is usually controlled with antipyretics and fluid replacement. Systemic infection is an ever-existing hazard. When the fever is not controlled for more than 2-3 days the patient should be admitted to the hospital, have BCG discontinued and have antituberculous therapy initiated (usually isoniazide 300 mg/day and rifampicin).
4. Granulomatous prostatitis
5. Pneumonitis, hepatitis
6. Septicemia
7. Small joint arthritis and skin rash [27].

Treatment of BCG-refractory CIS

In an effort to avoid cystectomy in BCG-refractory CIS, various immunologic or chemotherapeutic agents have been tested [37,41,42].

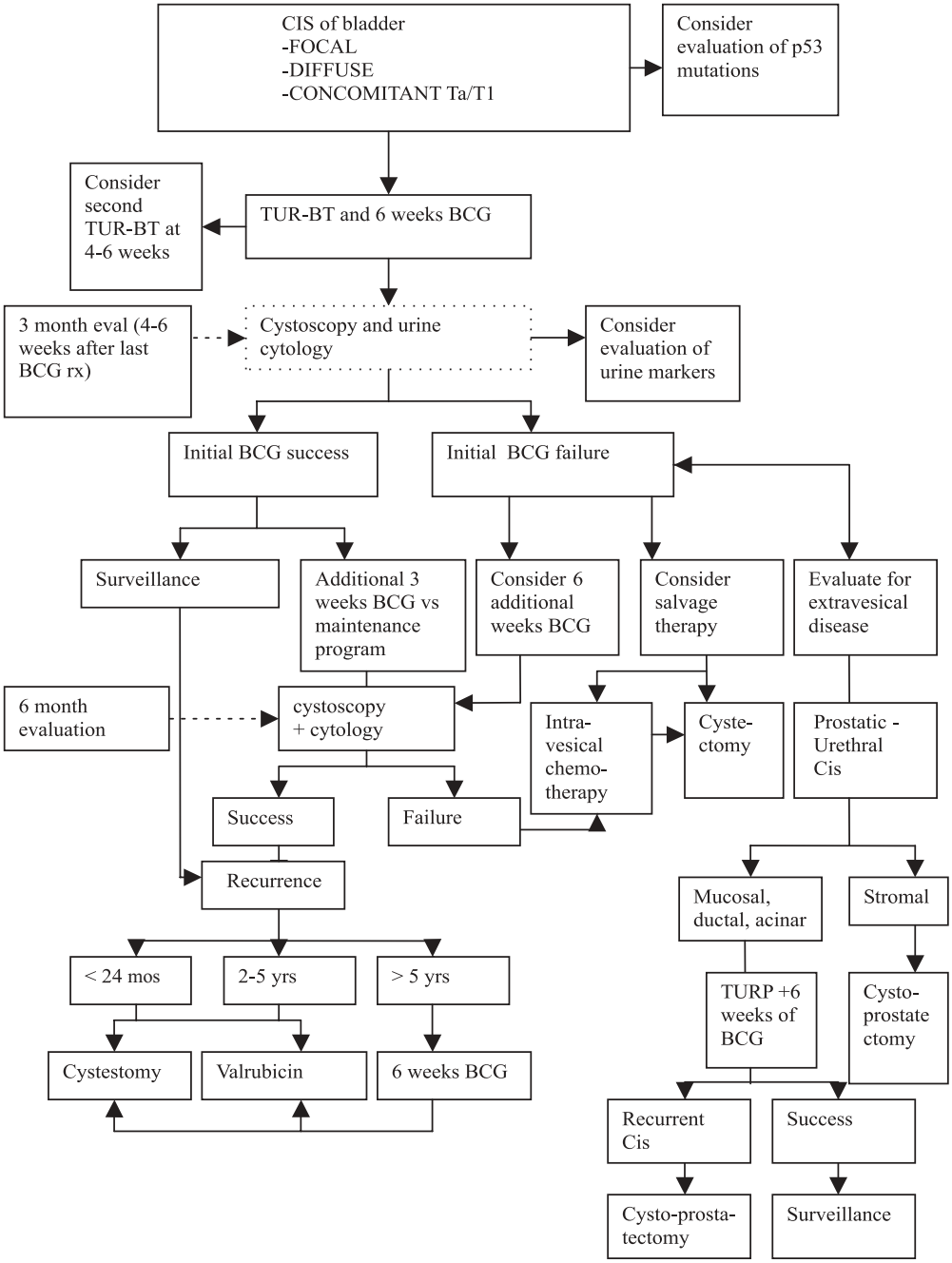

Figure 1. Proposed treatment algorithm for bladder carcinoma *in situ* (CIS) defining treatment choices after initial BCG success or failure and previous transurethral bladder tumor resection (TURB). *add'l*: additional, *chemo*: chemotherapy (from Kim and Steinberg, [48].

Valrubicin

Valrubicin is a new lipid soluble anthracycline, similar to doxorubicin, and is the only FDA-approved agent for BCG-refractory CIS [41]. Valrubicin may be used despite previously failed attempts with other intravesical agents and this does not appear to pose any additional risk to these patients by delaying cystectomy. Cystectomy is mandatory though in case of valrubicin failure.

Bropirimine

Bropirimine taken per os stimulates the immune system and possesses anti-oncogenic properties in bladder cancer and especially CIS [42]. Moreover, there is evidence that it may be effective against BCG-refractory CIS [42]. There is also synergistic action with BCG but further testing is necessary [43]. It has never been FDA-approved due to problems with cardiotoxicity, as well as other side effects (headaches, nausea, weakness) [44].

Interferon a-2b

Interferon a-2b has been used in the treatment of superficial bladder cancer [45]. In a study by Williams et al. [43] the duration of interferon action was relatively short and this along with its high cost render it not suitable for CIS treatment. Its co-administration with BCG though, may be useful since there is proven synergistic action [46]. BCG may also be administered at a lower dosage, thereby decreasing its toxicity on one hand and maintaining or even increasing its efficacy on the other.

Photodynamic therapy (PDT)

During PDT a red laser beam is used to destroy the cancer cells after a photosensitizing agent has been administered intravenously. This agent is incorporated by the cancer cells and leads to their death when the beam is aimed towards them. Nseyo et al. tried this method in 35 patients with refractory CIS. They reported complete response in 52% of the patients with just one course of treatment. Out of these, 58% were able to preserve their bladders. It appears that PDT is a safe and effective method for BCG-refractory CIS and clinical studies are under way to determine whether this method is superior to BCG or chemotherapy [47].

A suggested algorithm for the long-term management of CIS is depicted in Figure 1 [48].

Conclusions

1. Urinary bladder CIS is an unpredictable disease that necessitates long-term and close follow-up.
2. One should be very careful in establishing the diagnosis.
3. Main diagnostic tools are cystoscopy, urine cytology and biopsy.
4. There is universal agreement on the ideal treatment which consists of TUR of the visible lesions followed by 6 weekly intravesical infusions of BCG, 3-4 weeks after TUR.
5. If only TUR is performed, 60% of the patients will progress to muscle invasion and 30% of these will die in 5 years.
6. Prophylactic administration of BCG after TUR decreases both the recurrence and the progression rate and increases the disease-free survival.
7. There is not a universal consensus on the usefulness of maintenance schedules, which are considered by many to prevent recurrences, increase disease-free survival and even overall survival.
8. BCG-refractory CIS is an indication for cystectomy although alternatives do exist that need further testing.
9. Early cystectomy does not appear to add any survival benefit in patients with CIS.

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