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Management of non-muscle infiltrating bladder tumors: update 2014

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ABSTRACT

Bladder cancer is the second urogenital cancer; smoking represents the main risk factor for its occurrence. Urothelial bladder tumors without muscle infiltration are a group of tumors treated with conservative endoscopic resection, often associated with adjuvant instillations of chemotherapy or immunotherapy. The high risk of recurrence leads to a systematic monitoring. Cystoscopy represents the standard of monitoring. Prognosis of this tumor group is heterogeneous. The risk of progression to invasive cancer is highly variable and potentially lethal. Stage and tumor grade are well recognized as prognostic factors. Cystectomy may be considered in high-risk tumors, in case of failure of conservative treatment. The purpose of this article is to analyse through a literature synthesis, prinicipal topics concerning diagnosis, treatment and follow-up of non-infiltrating bladder tumors.

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Introduction

Bladder tumors (BT) are the most common tumors of the urinary tract, representing the second range of urogenital cancers in men (after prostate cancer) [1]. Smoking is the most implicated risk factor, along with other factors such as polycyclic aromatichydrocarbonsand Cyclophosphamide [2]. In East Africa (especially Egypt), chronic Schistosomahaematobiuminfection represent the most common etiology and is often associated with squamous cell histological subtype of carcinoma. Hematuria and signs of bladder irritation are the clinical symptoms most reported [2]. The diagnosis is made by cystoscopy followed by complete transurethral resection of apparent deep lesions to collectmuscularis and analyse local extension. Transitional cell carcinoma is the most predominant histological subtype, found in 90% of cases [1].

Non-muscle infiltrating bladdertumor(NMIBT) until recently were designated as "superficial bladder tumor" (SBT). This surname tends to be abandoned. Indeed, superficial termmeansfavorable prognosis which does not always correspond to reality. Moreover, SBT do not correspond fully to clinicians and pathologists definitions. It is now recommended to use the NMIBT term for tumors without detrusor muscle infiltrationand muscle infiltrating bladder tumors(MIBT) in the case of detrusor muscle infiltration [3].

NMIBT treatment has two principal objectives. Primary, to reduce local recurrence incidence and secondly, to prevent progression to muscle infiltration. Endoscopic resections associated tointravesical chemotherapy orimmunotherapyare currently the most effective conservative treatments and represent treatment reference in most situations. However, a number of patients treated for bladder cancer at high risk of progression, and beyond these treatments developed risk of tumor progression, invasion of muscle bladder, metastasis and death, discussing a problem of cystectomy [4].

Monitoring of NMIBT is based on cystoscopy and urine cytology. No molecular marker, or any imaging technique is not currently allowed to reduce the rate and monitoring arrangement of bladder tumors[5].

Methodology of research

The literature search was performed on the PUBMED using the following keywords: urothelial bladder tumor, chemotherapy, intravesicalMitomycin C, intravesical BCG, transurethral resection, cystectomy. Recommendations of the French Association of Urology (FAU) and theEuropean Association of Urology (EAU)are reported. Meta-analyses and most important phase II trials are also included.

Epidemiology

Bladder cancer is the fourth cancer in order of frequency [6] and is three times more common in men than women. World incidence is estimated at 300.000 new cases/year, most frequently occurring in Egypt (37/100.000/years) [2]. In France, this disease represents the second urological cancer after prostate carcinoma and ranks at the seventh place of all combined cancers (INVSS 2008). Incidence is increasing about 1% per year, butspecific mortality in man seems to decrease [7].

In Morocco, according to the Cancer Registry of Rabat "RECRAB 2005" [8], it occupies the third range in terms of frequency in men, with an estimated incidence of 5.4/100.000 (11 times higher among men than women), and incidence increases markedly with age from 55 years, reaching 120/100 000 after 75 years. It occurs at an average age of 65years (rarely before 40 years) [9], with a sex ratio of 3/1 [10], and is responsible of an estimated mortality of 3% of cancer deaths worldwide.

In Western countries, the transitional cell carcinoma represents more than 90% of bladder cancers [11]. In contrast, the frequency of squamous cell carcinoma is much higher in the Middle East and Egypt due to endemic Schistosomahaematobium infection [12]. At initial diagnosis, 75-85% of tumors are NMIBT.

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Sixty to 70% of lesions recur in the first year, while and 10 to 20% progress to invasive and / or metastatic tumors.

Risk factors:

Tobacco:

Association between smoking and bladder cancer has been described by LILIENFILED and COLL in 1956 [13]. Many epidemiological studies have shown a strong correlation between smoking and the development of bladder cancer [14].Although smoking association to bladder tumors is not strong as for airways cancers, it is estimated that smoking is involved in 25-60% of bladder cancers in industrialized and developed countries [15]. The risk seems to vary depending on the type of tobacco consumed; it is higher for black tobacco smokers thanblondtobacco smokers, and is also low for pipe and cigar smokers [16]. The precise mechanism of bladder carcinogenesis tobacco induced remains to be determined; it seems nevertheless associated with some chemicals in the smoke; polycyclic aromatic hydrocarbons, aromatic amines, unsaturated aldehydes and oxygen free radicals.

Industrial carcinogenicity:

The first cases of blabber tumorscaused by textile dyestuffs are cited since 1995 by Rehn among German workers [13] .We suspect more than 200 substances, essentially drift of hydrocarbons and alanine,used in the business of dyeing, rubber and metallurgy.All these occupational poisonings are responsible for 18-34% ofbladder tumors.These tumors appear after a latency of up to 40-50 yearsfrom the end of exposure, this period is even shorter than the exposure was higher. Exposure during 2 years in a high risk industry may suffice for BT occurrence [17].

Urinary schistosomiasis :

The role of schistosomiasis in carcinogenesis of bladder tumor was evoked since 1911 by FERGUSON, who found a big frequency of bladder cancer especially squamous cell carcinoma in Egyptians affected by Schistosomahaematobium[18].

This histological type represents only 3-7% ofbladder tumors. It is much more common in schistosomahaematobium endemic countries. Indeed, in Egypt,schistosomiasis is a public health problem and squamous cell carcinoma was found with a frequency of 40 to 70%. It is also the same in South Africa (70%) and Mozambique (59%). This contrasts with its rarity in occident where it represents only 1.6 to 7% of all bladder cancers [19].

Although relationship between schistosomiasis and squamous cell carcinoma development seems obvious, the pathogenic mechanism is still poorly understood. Cancerization appears after a long evolution of parasitic bladder. The mechanism would be at the level of neoplastic transformation of inflammatory lesions caused by the presence of parasitic eggs. The chronic bacterial infection often associated with this infection bladder act as an initiator of the tumor [18]. A synergistic effect between smoking andschistosomiasiswas also discussed [20].

Other factors :

Other factors have been implicated (21), but to a lesser degree in the genesis of BT:

• Infection and chronic irritation.

• Some drugs with urinary excretion, such as Cyclophosphamide which multiply the risk by 9 with a latency of 6-13 years.

• Pelvic irradiation for cervical cancer seems to increase the risk by 57 of bladder cancer.

• Coffee is incriminated, but without absolute evidence. A high-fat diet is also a contributory factor.

• Some authors have shown a high frequency of HLA A9, B5 and CW9 in persons with transitional tumor.

• The role and presence of oncogenic virus are also discussed.

TNM 2010 CLASSIFICATION OF UROTHELIAL BLADDER CARCINOMA [22] (Fig1)

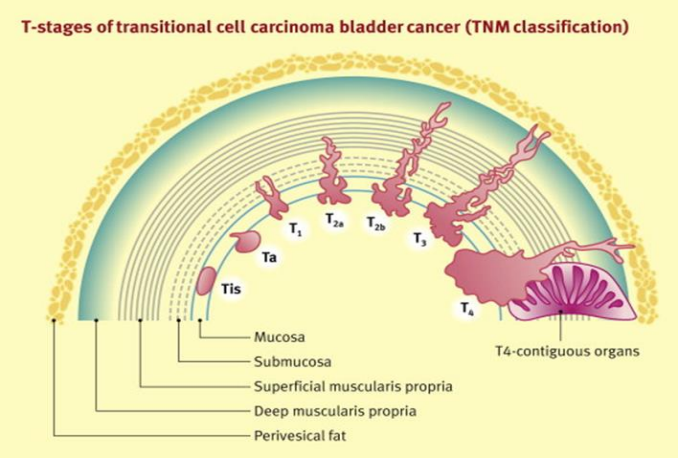

Fig 1. Staging of bladder tumors

T: Primary tumor

. **Tx** Primary tumorcan not be assessed

. **T0** Primary tumor not found

. **Ta** Non invasive papillarycarcinoma

. **Tis**Carcinoma in situ "plan" (CIS)

. **T1**Tumorinvades lamina propria

. **T2** Tumor invades muscularis

- T2a Tumor invades superficial muscle (inner half)
- T2b Tumor invades deep muscle (outer half)

. **T3**Tumor invades perivesical tissue

- T3a Microscopically.
- T3b Macroscopically (extravesical mass).

.**T4** Tumor invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall.

- T4a prostate, uterus or vagina
- T4b Pelvic or abdominal wall

N Regional Lymph Nodes

.**Nx**Lymph nodes can not be assessed

. **N0** No regional lymph node metastasis

. **N1** lymph node metastasis only <2 cm

. **N2** lymph node metastasis only> 2 cm and <5 cm or multiple lymph node metastases <5 cm

. **N3** Metastasis (s) lymph node (s)> 5 cm

M Distant metastasis

. **Mx** metastasis can not be assessed

. **M0** No distant metastasis

. **M1** Distant metastasis

Anatomopahology

Macroscopy:

In 75-85% of cases,bladder tumorshave an expansion of exophytic papillary form more or less compact. These tumors may be sessile or pedunculated. Sometimes, they line the entire bladder mucosa carrying out an aspect of papillomatosis. More rarely, it is budding or ulcerative tumors with a broad base implantation. These tumors are usually very infiltrated and multifocal in 25% of cases [23].

Histological types:

• Urothelial carcinoma: It represents more than 90% of bladder tumors. It consists of urothelial cells arranged in bays in lobules or infiltrating massifs accompanied by a fibrous stroma reaction. It has signs of anaplasia and atypical cytonuclear. These tumors are classified from grade I to grade III according to the degree of cell differentiation [24].

• Variants of transitional cell carcinomas: These are tumors in which the transitional cell carcinoma contains foci of squamous

elements orglandular. These tumors are generally behaved as high-grade tumors usually invasive [20].

• Squamous cell carcinoma: Squamous cell carcinoma accounts for 4-6% of bladder tumors observed in Western countries. This cancer is common throughout East Africa and the Nile Valley, where it represents 66-77% of bladder tumors observed. This tumor may be ulcerated or budding. Macroscopically, it is well or moderately differentiated, often with leucoplasias on the surrounding flat mucosa. This tumor has generally poor prognosis mainly because of delayed diagnosis. Indeed, it is observed at extravesical stage in 76-100% of cases [25].

• Adenocarcinoma: It represents 2% of bladder tumors and is composed of cells that are organized into glands or tubules, with or without mucus-secreting. Traditionally, the primary adenocarcinoma is derived of the urachus, or the bladder. Criteria that suspect primary adenocarcinoma are as follows: it is often located at the base and side walls of the bladder, characterized by the co-existence of cystitis cystica and glandular cystitis within the tumor and the observation of sharp transition between normal urothelium and adenocarcinoma [26].

• Small cell carcinoma: It represents 0.5% of bladder tumors. This is a single and budding tumor, predominantly at the dome. It is pT3 or pT4 at the time of diagnosis[27].

• Sarcomas: Leiomyosarcoma is the most common in adults. It consists of a spindle cell proliferation, atypical organized in crossed beams. On the other hand,the rhabdomyosarcoma is more common in children, especially located at the trigon and bladder neck. It consists of striated muscle cells with variable maturation [28].

• Malignant lymphoma: It is exceptional and is most often MALT lymphoma associated to an excellent prognosis [29].

• Primary malignant melanoma: Melanoma are discovered much more exceptional in the bladder into the urethra. Bladder location is usually discovered late, considering its metastatic potential. Prognosis is very poor, despite oncological treatment combining interferon and cytostatic drugs [30].

• Secondary tumors: Bladder may be the seat of invasion by contiguity of a tumor such as prostate or the cervix. Pulmonary, gastrointestinal or renal metastases have been described [31].

Histological grading:

Diagnosis of NMIBT requires consideration of the entire product of resection. Grade cell is a fundamental criterion in the subsequent management. Indeed, it is based on the assessment of architectural abnormalities (thickness of the urothelium, cell polarity) and cytological (nuclear abnormalities, mitosis) of the urothelium related to the tumor aggressiveness and prognosis. The reference for current grading of urothelial tumors is the 2004 WHO classification [7], but many urologists and pathologists using the 1973 WHO classification. The latter shall increase the proportion of high-grade carcinomas compared to the 1973 WHO classification. Thus, a tumor can be classified as "grade 2 in 1973 WHO classification" and "high grade in 2004 WHO classification" (Table 1) [22.32]. The two classifications separate tumors in 3 grades of aggressiveness not strictly equivalent.

In practice, the 2004 WHO classification seems more in line with bladder tumor markers. It has a better reproducibility than the 1973 WHO classification and explicitly describes different "variants" of infiltrating urothelial tumors. These variants may modify the quotas in diagnosis and therapy [33].

Estimated risk of recurrence and progression of nmibt:

NMITB are characterized byvariable evolution influencing prognosis. They have commonly high risk of recurrence after endoscopic resection (estimated at 70%). It represents the mainly risk of progression to MIBT, and are well classified asNMIBT withlow, intermediate or high risk (Table2)[7]. Progression is characterized by recurrence at higher stage. Progression prevention is essential in term of survival, which is severely compromised if the case of muscle infiltrated, despite late cystectomy. Hence the importance of the research to define prognostic factors that will adjust the monitoring and treatment of NMITB [34].

Using six major clinico-pathological parameters (grade, stage, tumor size, previous rate of recurrence, presence of concomitant CIS and number of tumors), it is possible to calculate the probability of recurrence and progression of a NMIBT according to the risk tables developed by the European Organisation for Research and Treatment of Cancer(EORTC) (www.eortc.be / tools / bladdercalculator) [7]. Thus, it is conventional to differentiate according to the risk of recurrence and progression.

Table 1: Correspondence between 1973 WHO classification (still sometimes used) and 2004 WHO classification

1773 WHO classification	2004 WHO classification
G1 carcinoma	Tumor of low malignant potential. Low-grade carcinoma.
G2 carcinoma	Low-grade carcinoma. High grade carcinoma.
G3 carcinoma	High grade carcinoma.

Diagnosis:

• Clinical circumstances:

Clinical circumstances of discovery are variable. Painless and terminal macroscopic hematuria are the most common clinical signs (85% of cases), its importance is independent of tumor stage or grade [2.22]and it can be very abundant causing full bladder retention. Irritative signs [2.22] are present in 20% of cases. In the absence of urinary tract infection, these symptoms should suspected bladder carcinoma in situ [35]. In addition, diagnosis can be made in the case of urinary tract obstruction or bone pain (lumbar spineor pelvic).

Rarely, clinical examination may be contributory in patients, finding a suprapubic mass in the case of large tumor. It is most often normal for a superficial bladder tumor.Digital rectal examinationresearches mainly pelvic shielding (if locoregionalinvasion of trigone blabber or prostate) in the case of advanced infiltration of bladder muscle [12].

• Biology:

Urinary cytology is a microscopic examination of the urinary sediment. Itis a simple, fast and inexpensivetechnique that uses fresh urine after excluding urinary tract infection. Urine cytology informs about the presence of tumor cells exfoliated in the bladder. When this test is positive and shows cytology in favor of a high-grade tumor, its specificity imposes exploration of the entire urinary tract looking for tumor site [36]. Cytology alone has default sensitivity for the detection of low-grade tumors. Additional techniques have been proposed, as cell labeling with antibodies, protein or enzyme search in urine, molecular or cytogenetic biology [37]. These techniques significantly increase the detection rate of low-grade tumors [38], but through a significant increase in the technical review, duration and cost. For this reason, despite cytology imperfection, it represents the reference for detection and monitoring of bladder tumors particularly high-grade tumors [39].

Urinary molecular markers are evaluated by many studies (BPTA, Track, NMP22, AccuDx, uCyt + Urovision). Variable tests are available, based on the detection of soluble markers or markers associated with cells. Most of these tests have better sensitivity compared to urinary cytology for detection of such bladder tumor, but specificity is lower. Thus, their utility for therapeutic decision during monitoring, and for prognosis

evaluation remain unspecified. The research concerning molecular markers are still under, to avoid unnecessary cystoscopy. The International Consensus Panel on Bladder Tumor Markers suggests combining Cytology and these different urinary tests to improve sensitivity. However, no urinary test can be reached to date for use in clinical practice [7].

Table 2: Classification of non-invasive tumors according to their risk of recurrence and progression

low risk	**Single Ta, low-grade or LMP *(grade 1) and diameter <3 cm and absence of tumor recurrence**
Intermediate risk	- Ta low grade LMP* (WHO 73) multifocal and / or recurrent - T1 low grade (grade 1-2)
High risk	- Ta high grade (grade 2/3 and 3) - T1 high-grade (grade 2/3 and 3) or recurrent T1 - CIS

LMP *: Low Malignancy Potential

• Imaging:

First line examination includessuprapubic and renal ultrasound. Its sensitivity varies between 61 to 84% for polypoid tumors> 5 mm [7]. It is used to specify tumor morphology (endoluminal vegetation) as a mass with an intense echogenicity or medium attached to the wall and protruding into the bladder. It also describes implantation base (sessile or pedunculated), specify location to the trigone and ureteral orifices, and determines size and number of existing lesions. It has an advantage of detection of hydronephrosis. In contrast, it is inefficient to searchtumor infiltration andpelvic lymph nodes [10]. Negative ultrasound does not avoid cystoscopy [7].

Intravenous urography (IVU) may demonstrate hematuria origin, but test sensitivity is low for bladder cancer detection [40].

Results of the helical scanner (CT) are superior to those of IVU for analysis of urinary tract, renal parenchyma and bladder cancer in patients with hematuria [41]. Currently, it is usually reserved for staging, especially for MIBT. Indeed, CT scan represents the gold standard for assessment of impact on the upper urinary tract, appreciates adjacent organs and peri-vesical fat invasion, and searches lymphadenopathy and / or metastasis. Diagnosis ofperivesical fat infiltration has sensitivity at 89% and specificity at 95% before resection. However, when CT scan is done after transurethral resection of bladder (TURB), there is an overestimation of extension due toperi-vesical fat inflammation [7].

Pelvic magnetic resonance imaging (MRI) is useful when extension to adjacent organs is suspected (pT3b stage); diagnostic reliability is estimated at 94% **[**7]. It also allows diagnosis of pelvic wall invasion with bone loss. For lymph nodes evaluation, a literature review between 1980 and 1994 [42] and other work [7] did not show a significant difference between CT scan and MRI with an overall sensitivity of 36% and a specificity of 80-97%. Diagnosis criterionis based exclusively on the size of suspicious lymph nodes.

Given the urinary excretion of FDG (fluoro-deoxy-glucose), PET scan (Positron Emission Tomography) is not efficient for the diagnosis of bladder cancer or for the accurate assessment of the loco-regional extension. Potential indications include the detection of distant metastases and the differentiation between a post-treatment fibrous scar andtumoral relapse. Due to lack of sufficient studies, PET scan is not routinely recommended [22].

Bone scintigraphy isindicated if bone symptoms are associated. Suspected lesions are controlled by conventional radiology and possibly bone CT or MRI. A complement biopsy should be considered a last resort if doubt [7].

- **Endoscopic diagnosis:**

Cystoscopic diagnosis is realized by a flexible fiberscope under local anesthesia for men and without anesthesia for women. It must be done after checking urine culture to be negative, in absence of hemostasis disorder or prior antibioprophylaxis. It allows to specify the topography, size, number and appearance of the tumor (papillary or solid), describes the mucosal abnormalities (edematous mucosa appearance in the CIS) and mapping of lesions. Itconstitutesclinico-pathological prognostic factors that predict the risk of progression of bladder lesions. When patient is referred with an ultrasound strongly suggesting bladder tumor, cystoscopic diagnosisbefore TURBis optional [43].

• TURB:

Visual appearance can be misleading at cystoscopy and bladder tumor diagnosis cannot be made until final pathologic analysis of resection material. This analysis confirms tumor and specifyurothelial or non-urothelialorigin of carcinoma.It can also provide details needed for tumor management, as well as T stage and grade. But exact staging (T stage) requiresa deep resection carrying different strata including bladder muscularis [34].

First step of TURB isexploratory examination which specifies tumor number, size, mucosa bladder appearance and topography especially to prostatic urethra and ureteral orifices. Tumor resectionshould be, if possible, deep and complete. Indeed, a macroscopically complete TURB is always the firsttherapeutic step of NMIBT [44.45]. In tumors with low risk of recurrence and progression (typically single tumor, small size, stage Ta and low-grade), the TURB can be the only active treatment combined with endoscopic surveillance. However,intermediate or high risk tumors requireintravesical instillations based on BCG or Mitomycin, to reduce the risk of recurrence and possibility of progression [34].

The use of fluorescence cystoscopy (FC) in bladder exploration before TURB significantly improves the diagnosis of CIS and appears to reduce the risk of tumoral relapse compared to white light (WL) [46] (Table 3).

Table 3: Comparison of the detection rate of CIS with WL and FC

STUDY	Detection rate of CIS by WL (%)	Detection rate of CIS by FC (%)
PC B201 study [47]	5	49
PC B301 study [48]	58	97
PC B303 study [49]	68	95

This technique enhances visual contrast between benign and malignant cells by the interaction of specific light on a photosensitizing agent that has a specific affinity for tumor cells. It is based on the use of an exogenous molecule (photo sensitizer) that accumulate preferentially in neoplastic cells and emit fluorescence on the red band after excitation in violet (380-470 nm), and which facilitates the visualization of the tumor. To date, three photosensitizing agents are available, two prodrugs (5-aminolevulinic acid or 5-ALA and hexaminolevulinate (HAL)) and a natural substance(hypericin) [46].

The first publication on cystoscopy with 5-ALA was made in 1992. For over a decade, publications have demonstrated the undeniable superiority of FC to detect tumors compared with WL cystoscopy [50]. The majority of published studies concerned the 5-ALA, but currently,comparative studies between HAL versus LB and HAL versus 5-ALA are insufficient [46]. However, the first evaluation studies of HAL (Hexvix ®) showed its superiority compared to WL cystoscopy (Table 4). One study showed the superiority of the HAL compared to 5-ALA. Indeed, the disease-

free survival at eight years was 82% for HAL, 80% for 5-ALA and 67% for WL cystoscopy.

Table 4: Detection of bladder tumors by HAL cystoscopy

PC B201 study [47]	73	96
PC B301 study [48]	78	93
PC B303 study [49]	77	99
PC B302 study [52]	79	93

WL cystoscopy can diagnoses20% of papillary tumors and 23% of additional CIS compared to LB cystoscopy alone, with 17% of patients undergoing a therapeutic care more complete [50]. European (EAU 2011) [53] and French guidelines (FAU 2010) [22] have different indications for use of FC. For the EAU guidelines, fluorescence should be limited to patients suspected of having a high-grade tumor (positive urinary cytology, history of high-grade tumor). The AFU, meanwhile, recommends the use of FC for the diagnosis of CIS and determines clinical situations in which it is indicated (Table 5). It is a technique with good tolerance and few side effects.

Table 5: Indications for FC (FAU 2010).

Multifocal bladder tumor
Large tumor > 30 mm
Early recurrence
High-grade cytology positive
Monitoring of high-risk lesions (T1, G3, and CIS)

In practice, recommended tests for the diagnosis of NMIBT and MIBT according to the latest recommendations from the FAU 2010 are summarized in Table 6[22].

Prognostic factors:

The wide variety of superficial tumors reflects difficulties of predicting evolution. However, there are two risks that are common to all superficial tumors, regardless to stage and grade; recurrence and progression risks. Overall, in all superficial tumors, recurrence risk is estimated at 60-75% with an increase at 10-20% [22].

Frequency risks depend on multiple histopathologicalfactors. The most important are histologicalgrade, tumor multifocality, tumor size, presence or absence of vascular or lymphatic invasion, and the presence or absence of CIS [54].Other prognostic factors exist such the time to development of first recurrence after initial treatment and recurrence rate [54].

Table 6: Recommended tests for the diagnosis of NMIBT and MIBT according to the latest recommendations from the FAU 2010

IN PRACTICE TESTS RECOMMENDED FOR THE DIAGNOSIS OF NMIBT ARE:
Urine cytology:
- Cystoscopy with lesion mapping associated with endoscopic resection preceded by a urinalysis.
- Evaluation of upper urinary tract by uroscan if NMIBT is large, multifocal or high grade cell.
IN PRACTICE TESTS RECOMMENDED FOR THE DIAGNOSIS OF MIBT ARE:
Urine cytology:
- Cystoscopy with lesion mapping associated with endoscopic resection preceded by a urinalysis.
- Uroscan systematically.
- Extension assessment by thoracic CT.

Treatment:

NMIBT treatment aims to preserve bladder. Therapeutic options for conservative treatment include transurethral resection and intravesical instillations based on chemotherapy (Mitomycin C (MMC)) and immunotherapy (Bacillus of Chalmette and Guerin (BCG)).

Conservative treatment:

TURB:

Beyond his interest in the diagnosis of bladder tumors, the TURB, as complete as possible, is the first treatment. Performed under regional or general anesthesia, resection should be deep containing-muscle. The randomized biopsies in optically healthy areas are not indicated systematically [55]. They must be carried out in case of suspicion of associated CIS or in case of positive cytology without solid tumor. Biopsies of the prostatic urethra are indicated when suspected CIS or if prostatic urethra is invaded, or to evaluate extension disease before cystoprostatectomy.

Revaluation transurethral resection is highly recommended if high-grade T1 stage, large and/or multifocal tumor. Indeed, several studies have demonstrated an underestimation of initial sampling results observed during the second resection in about 20-30% of cases [56]. This revaluation is carried out 4 to 6 weeks after the initial endoscopic resection [43].

Intravesical instillations:

MMC:

MMC (Ametycine ®) is one of the agents that cause severe necrosis in case of extravasation. Thus, it cannot be used in case of bladder perforation or macroscopic hematuria.

The possible adverse effects are local signs (pollakiuria, dysuria, hematuria, urethritis) and skin reactions (localized palmoplantar and genital erythema, rarely generalized rashes, eczema) [34].

The MMC can be administered according to different schedules:

• Precociouspostoperative instillation (PPI): It aimsto reduce the risk of early recurrence due to the presence of tumor cells released during resection or residual. Many studies have shown the benefit of the PPI in reducing the risk of recurrence of 12-39% [57], for unifocalor multifocal lesions. It is instillatedwithin 24 hours after endoscopic resection, ideally within six hours. The PPI is not indicated in situations where significant systemic passage is possible: bladder perforation, resection of a large tumor (more than 5 cm), and poorly controlled hemostasis [34].

• Continuous treatment with weekly instillations: The effectiveness of MMC depends on its use[56].It is recommended to reduce diuresis 8 hours before instillation and urine alkalinization with sodium bicarbonate serum. Many protocols are described in literature. There is no pattern of optimum weekly instillations actually demonstrated. Currently, treatment is based on 40mg of 6 to 8 weekly instillations, followed or not by monthly instillation. Instillation conditionns are essential because the MMC can be easily inactivated [22]. Current data are not consistent in term of interest concern of treatment maintenance. Some data may still be retained. Combining PPI to weekly instillationof MMC at 40mg,Tolley [58] showed a statistically not significant reduction of 30 to 50% of recurrences. Analysis of 30831 and 30832 EORTC studies by Bouffioux [59] of intermediate risk tumors, demonstrated that an early instillation of MMC dosed at 30 mg or 50 mg of Doxorubicin forat least one hour, reduced the use of maintenance treatment.

Intravesical immunotherapy: BCG

Immunotherapy is not directly cytotoxic to tumor cells unlike chemotherapy. It stimulates host immunity against tumor cells. Currently, immunotherapy agent routinely used is BCG, which is an attenuated form of mycobacterium tuberculosis. In practice, chemotherapy and immunotherapy are used differently. BCG treatment cannot be used immediately after TURB, it must be administered after 15 days after bladder resection. Indeed, maintenance therapy with BCG has been shown to be effective in reducing the frequency of recurrence and tumor progression. A

large meta-analysis of EORTCrandomizing24 trials and including a total of 4863 patients showed that BCG maintenance treatment reduce at 37% the risk of progression compared to control groups (TURB alone, TURB and intravesical chemotherapy, TURB and immunotherapy) [60]. Finally, considering better tolerance of chemotherapy and strong action in low-grade recurrent tumors, BCG is usually reserved for high-grade NMIBT treatment [34].

BCG immunotherapy must be preceded by complete TURB. Endoscopic reassessment (second look) is sometimes desirable, and can be done one month later after the initial resection, and before the introduction of BCG therapy especially in patients with incomplete resection, multifocal tumor, presence of CIS and in the case of tumor located at the dome or the anterior surface of bladder [61]. Indeed, before proposing to patienta conservative treatment whose effectiveness is directly related to the superficial nature of the tumor and the fact that the resection was complete, it is necessary in some cases to eliminate the risk of an under-staging and make a complementary resection of possible residual tumor. Some authors have reported nearly 30% of pT1 tumors initially classified at tumor resection and staged pT2 or greater at cystectomy [62].

BCG therapy is administered according to the following schedule: weekly instillation of a dose of 81mg of Immucyst ® for six weeks, followed by a therapeutic interval of six weeks. Then, a new dose should be administered once a week for one to three weeks. This treatment may be the full treatment. If maintenance treatment is considered, this pattern will be followed by regular instillations over several years. The best assessed schedule of maintenance treatment is the Lamm protocol: one instillation per week for three weeks, administered six months after the start of treatment and every six months up to 36 months [57]. Various tests have suggested that maintenance therapy may improve the results of BCG treatment, but the optimal regimen of maintenance therapy remains to be defined. Only the randomized SWOG trial (South West Oncology Group) has clearly demonstrated the benefit of maintenance therapy in terms of disease-free survival and tumor progression [22]. However, side effects of this maintenance treatment are significant and instillations number should take into account the local and general tolerance. Even if the optimal number of cycles of maintenance is not always possible, patients are encouraged to take at least 3 cycles of maintenance instillations and continue until they well tolerate [63].

For patients with CIS, the EAU recommends BCG induction therapy followed by maintenance treatment for at least one year. Response to BCG therapy should be evaluated definitely after three months of induction therapy. In case of persistence of CIS, it is recommended to continue treatment with six new weekly instillations. If complete response is not obtained after 6 months, total cystectomy is then recommended [61].

Before starting BCG instillation, it is necessary to inform the patient about treatment modalities and to ensure absence of cons-indications: prior bladder area radiotherapy, immunodeficiency, active tuberculosis and history of systemic BCG reaction. There is also necessary to do clinical, biological evaluation and standard imaging of the chest [7].

Before each instillation, it is necessary to do clinical examination and tolerance evaluation of previous instillations. Instillation should not be done in the case of unexplained fever, macroscopic hematuria and untreated urinary tract bacterial infection [7].

After instillations, patients should urinate sitting down.Hyperhydratation for 48 hours after each instillation is recommended [34].

Potential adverse events are numerous, and their severity is variable. More often, they are represented by [7]:

• Allergic reaction: rash, arthralgia.

• Inflammatory reaction: fever, hematuria, pollakuria, dysuria.

• Other uncommon reactions: urinary tract infection, bladder contracture, symptomatic granulomatous prostatitis, epididymo-orchitis, ureteral obstruction, renal abscess.

• Systemic BCG reaction is uncommon, but is considered as severe reaction defined by occurrence of fever greater than or equal to 39.5 ◦ C for at least 12 hours or greater than or equal to 38.5 ◦ C for at least 48 hours and / or visceral infection (lung and liver essentially). Septic shock remains a serious and exceptional adverse event.

Adverse event treatment is based on its severity. Simple bladder irritation requires only symptomatic treatment. If it lasts more than 48 hours, BCG treatment should be discontinued and treatment with antibiotics (quinolones) should be started. If instillation cannot be administered after ten days of treatment or in the case of significant complication of BCG therapy (granulomatous prostatitis ororchitis), antituberculosis treatment should be necessary, and BCG therapy is stopped. If septic shock associated, the patient should be hospitalized in intensive care [7].

Therapeutic indications (Table 7):

After complete TURB and in the absence of cons-indication, PPI of MMC is indicated for superficial tumors measuring greater than 3 cm of diameter [64-66]. PPI increase recurrence-free interval [57, 58]. In absence of instillations,progression risk at 5 years is estimated at 7.1% and specific mortality at 10 years at 4.3%. According to histology subtype, therapeutic management is discussed according to the estimated risk of tumor relapse and/or progression.

Table 7: Support for non-invasive tumors according to their risk of recurrence and progression.

Lowrisk	Simple monitoring
Intermediate risk	Weekly instillations of MMC during 8 consecutive weeks after bladder cicatrization (4-6 weeks) BCG instillations can be discussed as an alternative to MMC instillations or in case of MMC failure.
High risk	Intravesical instillations of BCG (except cons-indications) after bladder cicatrization (4-6 weeks). If BCG instillations are well tolerated, maintenance therapy should be continued. In case of failure treatment with BCG, cystectomy remains the treatment of choice. After TURB, cystectomy can be immediately discussed in multidisciplinary meeting for some forms of poor prognosis for young patients.

Low-riskNMIBT:

Single immediate instillation reduces the risk of recurrence and is considered as standard treatment. No other treatment should be offered to these patients in the absence of tumor recurrence [57].

Intermediate riskNMIBT:

Complete TURB followed by series of PPI and 6-8 weekly instillations of 40 mg of MMC represents standard treatment, but without consensus in term of treatment duration. Recurrence reduction is reported when maintenance therapy continued for at least 1 or 2 years [67]. A meta-analysis of 22 randomized studies

evaluating the role of intravesical chemotherapy in the treatment of intermediate risk NMIBT showed no benefit in terms of reduction of progression rate compared to TURB alone [68].

BCG instillations can be discussed to treat this group of bladder tumors. Many prospective studies comparing BCG to MMC concluded that maintenance therapy with BCG delay disease progression to muscle infiltrating [69] and reduce recurrence [70].Data from the EORTC 30911 trial suggests that BCG is superior to chemotherapy for treatment of intermediate risk NMIBT in terms of time tofirst recurrence, specific and overall survival [71].

High-riskNMIBT:

The best treatment is complete endoscopic resection followed by 4-6 weeks of adjuvant intravesical instillation of BCG. In rare cases, cystectomy may be indicated immediately.

BCG immunotherapy must be preceded by complete TURB. Panels of international experts even advise new systematic resection of high-grade pT1 tumors, due to high rate of under-evaluation stage [72].

BCG therapy is mainly based on six weekly instillations followed by 3 weekly instillations after six weeks off therapy. This schedule is considered a reference for the treatment of high-risk NMIBT. It aims to prevent and delay tumor recurrence and infiltration of the bladder muscle and allow control of any associated CIS [73]. If BCG instillations are well tolerated, maintenance treatment is required and must be continued as long possible [22].

Monitoring modalities:

NMIBTrequires systematic endoscopic control. This monitoring aims to detect the earliest possible recurrence and progression. Monitoringrecommendation according toFAU [22] or UAE [72], include cystoscopy and cytology analysis, which represent the gold standard for monitoring of NMIBT.

Constraints and invasive character of this exam have led to actively search other methods. However, at present neither the imaging nor the many urinary markers have not demonstrated their ability to replace cystoscopy in terms of diagnostic performance [34]. Result of the first cystoscopy 3 months after the initial TURB isa very important prognostic factor, both for tumor recurrence and progression risk to muscle infiltration [22,74].

Table 8 summarizes timing and monitoring duration of NMIBT according to the latest recommendations of the FAU [22].

Table 8: Monitoring procedures of non-infiltrating tumors according to recurrence and progression risks

Low-risk	**Cystoscopy: in the 3rd, 6th, 12th month and annually for 10 years (for ever if persistence of tobacco abuse)**
Intermediate risk	Cystoscopy: in the 3rd, 6th, 12th month and annually for 15 years (life if persistence of tobacco abuse) Urine cytology: recommended, coupled to cystoscopy Uro-CT scan: every two years and if positive cytology or symptoms of lesion of the upper urinary tract
High risk	Cystoscopy at : 3, 6, 9, 12 months and then every 6 months the second year, then annually for life Urine cytology: 3rd, 6th, 9th, 12th month, then every 6 months the second year, then annually for life Uro-CT scan: every 2 years or if positive cytology or symptoms for lesion of the upper urinary tract

High grade NMIBT, can cystectomy be avoided in case of BCGfailure ?

According to the UAE recommendations, relapsed NMIBT after complete TURB and intravesical BCG instillations requires early cystectomy [72]. For the FAU, cystectomy should also be considered within two years of evolution, but a second chemotherapy with BCG is possible [22]. BCG failure includes different situations [5]:

• Patients refractory to BCG therapy, for which persistence or recurrence was observed at 3 months justify new cycle of treatment and for whom no remission was observed 6 months after treatment starting.

• Patients resistant to BCG, recurring on the same (or less) tumor stage and tumor grade three months later. For these patients, second induction therapy for 6 weeks of BCG provides complete response in 35% of cases.

• Patients with recurrent disease after BCG therapy despite to initial remission at 6 months:Early (6-12 months), intermediate (12-24 months) or late recurrences (> 24 months).

• Patients non tolerating BCG therapy, for whom recurrence was observed after insufficient duration of treatment with BCG, given an early discontinuation (severe side effects).

According to Herr, a total time of treatment and follow-up of at least 6 months is required to identify the early failure of BCG therapy. Patients who relapse on the same (or less) tumor stage and grade at three months should not be considered at failure as a second induction therapy of 6 weeks of BCG will allow to get a response in 35% of cases (patients resistant to BCG) [75]. Instead, appearance of more pejorative lesion on stage and/or grade cell or the presence of CIS at the waning of treatment should be considered a failure and must discuss rapid realization of cystectomy (BCG refractory patients). On the other hand, whenlate recurrence at the same risk-group occur after 2 years, it is possible to propose new instillations of BCG therapy [22].

Intravesical instillation of Gemcitabine appears to be an effective alternative to early cystectomy. Indeed, if instillations of BCG are significantly more effective than Gemcitabine in terms of disease-free survival in first-line treatment of high-risk NIMBT [76], intravesical chemotherapy with Gemcitabine appears to be interesting in salvage treatment for patients with BCG failure as suggested by two recent studies. In a prospective, multicenter, randomized, phase II study, Di Lorenzo *et al.* compared Gemcitabine to BCG in 80 patients with high-risk NIMBT in failure treatment to BCG [77]. In this study, recurrence rate was significantly lower (52.5% *vs* 87.5%, p=0.002) with better disease-free survival at 2 years (19% *vs* 2%, p<0.008). There was no significant difference in terms of progression-free survival between two groups. In the randomized phase III study,Addeo*et al*. compared Gemcitabine *vs* MMC in 120 patients with G1-G3, pTa-pT1 tumors that failed to BCG or Epirubicin. Disease-free survival was significantly better in the Gemcitabine group (72% *vs* 61%, p = 0.0021) [78].

In patients intolerant to BCG therapy, a third dose of BCG instillations have showed the same effectiveness in preventing tumor recurrence and reducing progression risk with less toxicity. The authors recommended standard dose for patients at high risk or with a multifocal tumor, and dose reduction for patients with intermediate-risk tumors and for maintenance therapy [22]. Prescription of Ofloxacin 6 hours after instillation of BCG appears to significantly reduce serious adverse events [22].

Conclusion:

Urothelial bladder tumors without muscle infiltration represent a group of tumors that have commonly following characteristics:

• First line of treatment is conservative; endoscopic resection is often associated with adjuvant instillations of chemotherapy or immunotherapy.

• A high risk of recurrence, which requires systematic monitoring. The standard arrangement of monitoring is cystoscopy.

Prognosis of this tumor group is heterogeneous. Progression risk to invasive cancer is highly variable. Recognized prognostic factors are essentially represented by stage and tumor grade. Cystectomy may be considered in high-risk tumors and in case of failure of conservative treatment.

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