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STUDY PROTOCOLS

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**PROTOCOL HSRBT N. 101-1**

**COMPARATIVE STUDY OF INTRAVESICAL MITOMYCIN C INSTILLATION  
OR MITOMYCIN C AND LOCAL HYPERTHERMIA FOR PROPHYLAXIS OF  
RECURRENCES OF SUPERFICIAL TRANSITIONAL BLADDER TUMORS.**

A PROSPECTIVE RANDOMIZED TRIAL

## **PROSPECTIVE MULTICENTRIC STUDY.**

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## 1. BACKGROUND AND INTRODUCTION

The expected incidence of bladder cancer in the U.S. is 45.000 new cases per year, 70% - 80% of them being superficial (stage Ta, T1, CIS) (1,2,).

Transitional cell carcinoma of the bladder, stage Ta, and T1 is known to recur in about 75% of cases and the risk to develop an aggressive infiltrating lesion vary - the number of tumors present at the entry on study.

Considering prognostic factors it seems logical not to treat patients after tumor eradication with intravesical therapy if they belong to the low risk group (such as Ta , GI, first episode of disease, monofocal).

The literature reports 58% superficial transitional cell carcinoma of the bladder (STCCB) recurrent patients after TUR alone and 38% -42% recurrent patients after TUR and intravesical chemoprophylaxis after a minimum 2 years follow-up (5,6,7).

This recurrence rate does not seem to be strongly related to the cytostatic agents used (41% for Thiotepa , 43% for Mitomycin C, 40% for Adriamicin).

However, considering only the high-risk recurrence patients the prophylactic effect of most chemotherapeutic drugs clinically tested, is very limited (8,9). Recently, many prospective controlled studies showed that for high risk recurrent group patients there is not a significant reduction in the overall recurrence rate comparing intravesical chemotherapeutic agents and BCG (10,11).

As for as prophylaxis of progression is concerned, the intravesical chemotherapy is even less effective. Out of 1612 patients enrolled for randomized studies, 7.24% in control group and 7.27% in treated group respectively present with a progression for stage (12). Further, at present many multicentric controlled studies (13,14) showed that intravesical chemotherapy and immunotherapy alone are unable to eradicate most STCCB.

For some time, both in vitro and in vivo investigations have showed a synergism or an additive effect between hyperthermia in the 42°C - 45°C temperature range, and many cytostatic drugs, including alkylating agents (15,16,17,18).

Physically, STCCB facilitate easy application of local combined approach with hyperthermia and chemotherapy. Since the mid seventies local endovesical hyperthermia (LHT) has almost exclusively induced using hot water irrigations of the bladder (alone or in combination with drugs for both STCCB ablation and prophylaxis reporting controversial clinical results (19,20,21,22)).

Recently a new system (model SB-TS 101) to deliver endovesical hyperthermia simultaneously with cytostatic instillation was designed and built by the Projecting and Development Unit of the S. Raffaele Hospital in Milan. This system is presently patent pending.

This system consists of a special transurethral catheter carrying a 915 MHz microwave applicator which heats the bladder walls and the intravesical cytostatic solution by direct irradiation.

The safety of this technical approach has already been tested in a clinical pilot study for STCCB ablation (23,24).

The following protocol has been devised in order to evaluate and compare the effectiveness and the safety of the association of local hyperthermia and topical chemotherapy versus intravesical chemotherapy alone for prophylaxis of recurrence in selected groups of patients suffering from superficial TCCB.

Among these are those who underwent tumor eradication at the first episode of disease, those with intermediate risk for recurrence and progression, those who are at high recurrence risk, those who failed standard treatments. Patients with a primary, solitary, low stage, low grade tumor are excluded from this protocol.

It is our hope that we shall increase the number of responder patients, a result that will have to be demonstrated by lowering the rate of recurrences and progression.

Details regarding the rationale and the background for hyperthermia and chemotherapy as combined treatment modalities in experimental and human cancers are extensively discussed in the Helsinki Committee Application.

## **2. PURPOSE OF THE STUDY**

The purpose of this study is to compare the effect of intravesical instillation of Mitomycin C compared to intravesical instillation of Mitomycin C plus local Hyperthermia after complete eradication of superficial transitional bladder tumors with respect to:

- 2.1 Effectiveness of the treatments by evaluation of:
  - 2.1.1 Duration of the disease- free interval
  - 2.1.2 Recurrence rate, including evaluation of the number of recurrent tumors
  - 2.1.3 Progression rate
  - 2.1.4 Local incidence of carcinoma in situ during follow-up
  
- 2.2 Safety of the treatments by evaluation of:
  - 2.2.1 Clinical subjective and objective local side effects
  - 2.2.2 Pathological local side effects
  - 2.2.3 Clinical systemic side effects
  - 2.2.4 Intercurrent events
  
- 2.3. Technical aspects:
  - 2.3.1. Materials
  - 2.3.2. Adaptability of the treatment

### **3. SELECTION OF PATIENTS**

#### **3.1 Pre-Tumor eradication assessment**

To improve stage diagnosis of the patients some examinations must be performed before tumor eradication.

The patients must undergo the following examinations:

- 3.1.1. Physical examination
- 3.1.2. IVP
- 3.1.3. Pelvic and abdominal ultrasounds
- 3.1.4. Chest X-ray
- 3.1.5. Lab (Tab.1)
- 3.1.6. Urine analysis
- 3.1.7. Cytology
- 3.1.8. Pelvic CT or NMR for multifocal and/or high recurrent tumors
- 3.1.9. Bone scan for multifocal and/or high recurrent tumors
- 3.1.10. Uroflowmetry with residual urine volume

#### **3.2. Criteria for inclusion on clinical grounds**

Criteria for Admission:

- 3.2.1. All patients with resected, Ta or T1 Grade G1-G3, papillary transitional cell carcinoma of the bladder. Patients with Ta primary and solitary lesions will be excluded.
- 3.2.2. Complete tumor eradication must be possible.
- 3.2.3. Patients may have been treated with cytostatics in the past. However, candidates who underwent such instillations during the last 3 months before the first session of their treatment is scheduled, will be excluded from the study.
- 3.2.4. Able to be present for his scheduled treatment and follow-up
- 3.2.5. Life expectancy > 24 months
- 3.2.6. Able to understand the characteristics, the aim and the procedure of the study and sign an informed consent
- 3.2.7. **SIGNED AN INFORMED CONSENT FORM WHICH WILL COMPRISE AN INTEGRAL PART OF EACH PATIENT'S FILE.**

### **3.3. Criteria for exclusion on clinical grounds**

- 3.3.1. Ta ; G1, single transitional tumors at first episode of disease
- 3.3.2. T> T1 transitional tumors
- 3.3.3. Other than transitional tumors
- 3.3.4. Transitional tumors of the bladder involving the prostatic urethra
- 3.3.5. Primary transitional tumors of the prostatic urethra
- 3.3.6. Solitary, multifocal or associated carcinoma in situ (CIS) at entry on-study
- 3.3.7. Clinical presence of distant or lymphatic metastasis
- 3.3.8. Performance status WHO > 2
- 3.3.9. Patients who cannot be followed-up properly
- 3.3.10. Presence of another tumor
- 3.3.11. Well known allergy to topical or systemic Mitomycin C administration
- 3.3.12. Previous intravesical instillations within 3 months before the first session of their treatment is scheduled or systemic cancer treatment with immunotherapy, cytotoxic drugs or radiotherapy
- 3.3.13. Untreated urinary tract infection or recurrent severe bacterial cystitis
- 3.3.14. Patients suffering from large BPH (>5.5 cm c.c.o. ; > 6.0 cm c.c)
- 3.3.15. Neurogenic bladder
- 3.3.16. Persistent hematuria not due to known tumor
- 3.3.17. Urethrorragia
- 3.3.18. Urethral strictures or other urethral pathology
- 3.3.19. Patients mentally unable to collaborate

### **3.4 Criteria of ineligibility on pathological grounds**

- 3.4.1. Positive cytology after tumor eradication
- 3.4.2. Residual tumor after tumor eradication
- 3.4.3. Tumors not STCCB in TUR specimens

#### **4. DESIGN OF THE TRIAL**

This study is designed as a randomized study. Its aim is to evaluate the different aspects of combined hyperthermia and chemotherapy treatment or chemotherapy alone as described in chapter 2 of this protocol.

Before entering the study, the patient will undergo complete staging of tumor (chapter 3.1) by TUR of all evident bladder tumors. Being free of tumors, the physician in the participating center will control the patient's eligibility according to the inclusion criteria as listed in chapter 3 of this protocol.

If patient evaluation enables him to be enrolled in the study, the physician will see to obtain the informed consent signed. Afterwards, the center will get in contact with the randomization center to obtain instructions about treatment.

The randomization procedure (chapter 6), will blindly enroll the patient into one of two following groups:

Group A: Intravesical Chemotherapy + Local Hyperthermia (chapter 7.1.)

Group B: Intravesical Chemotherapy alone (chapter 7.2.)

Follow-up will start at the end of the inductive part of the treatment.

Patients will be followed-up in a routine manner by physical examination, lab test, cytology, cystoscopy, cold biopsies and additional investigations according to chapter 9. As long as the patient remains tumor-free after prophylactic treatment, no adjuvant treatment, either local or systemic, is to be given.

Treated patient of both groups will be followed-up for at least 2 years.

If recurrence is observed, appropriate notes will be taken and the patient will go out of protocol to be treated traditionally.

## **5. PATIENTS' EVALUATION**

The evaluation of the patients will be done at three timings: before treatment, during treatment and after treatment.

### **5.1. PRETREATMENT EVALUATION (AFTER TUMOR ERADICATION)**

- 5.1.1. Medical history
- 5.1.2. Physical examination
- 5.1.3. Blood exams (Tab. 1)
- 5.1.4. Urine analysis (Tab. 3)
- 5.1.5. Urinary cytology
- 5.1.6. Cystoscopy and cold biopsies of any areas suspected for residual tumor
- 5.1.7. Chart with the map of previous tumors and TUR
- 5.1.8. Uroflowmetry with residual volume
- 5.1.9. Subjective questionnaire (Tab. 5)
- 5.1.10. Additional investigations (not mandatory) (Tab.4)
- 5.1.11. Check list of inclusion and exclusion criteria (including the pathological results of the TUR)

### **5.2. IN TREATMENT EVALUATION**

- 5.2.1. During all treatment period, notes and remarks regarding all physician's and/or patient's observations, complaints etc. will be filled in appropriate form
- 5.2.2. Only for patients in Group A (Hyperthermia + Mitomycin C): special blood exams will be taken three times (Tab. 2): at the end of the first operative session, the morning after the first session and 1 hour after the last session of the inductive cycle.
- 5.2.3. Flexible cystoscopy, although not mandatory, is suggested immediately before starting the 5<sup>th</sup> operative session in group A (Hyperthermia+ Mitomycin C) patients.
- 5.2.4. Seven to ten days after the 8<sup>th</sup> operative session, a cystoscopy will be performed. Cold cup biopsies will be taken only on suspect areas.
- 5.2.5. Additional investigations (Tab. 4) (not mandatory)

### **5.3. POST- TREATMENT EVALUATION**

See Follow- up in Chapter 9

## **6. RANDOMIZATION PROCEDURE**

Randomization can be done from 9 a.m. to 4 p.m. from Monday to Friday, by calling the Secretary of the project at ++39+2+26432782. A specially designated randomization form will be completed by the investigator at the clinical center with the following information and faxed to the same telephone number. (Refer to Form no. 2):

- 6.1 Caller's name
- 6.1 Institution number
- 6.2 Protocol number
- 6.3 Name of responsible physician
- 6.4 Patient's full identification
- 6.5 Patient's birthdate
- 6.6 Performance status (0,1,2)
- 6.7 Stage and grade of the resected tumor
- 6.8 Total number of recurrences

Prof. Gallus (study stacionian) will pre- prepare a numbered list of treatments in randomized order, for each participating clinical center, e.g., the first four randomized patients (1,2,3,4,) for Milan center may be MMC, MMC, MMC+Synergo, MMC. Separate, numbered, randomized treatments for each center will be maintained by the secretary in closed, enumerated envelopes. The envelopes will not be opened until a randomization form from a specific clinical center has been received. Upon receipt of a randomization form, the secretary will open the next consecutive, enumerated envelope and attach the content (specified treatment group) to the randomization form. The randomization form with the specified treatment group will be sent to the clinical center by fax (or personal delivery in HSR). The randomization form will be maintained in the patient's hospital file.

## 7. TREATMENT

Total number of sessions: **12**

Duration of each session: **60 min (40-75)**

Frequency of sessions: **one per week for 2 months (inductive cycle)+  
one per month for 4 months (maintenance cycle)**

The treatment will be started within 20- 40 days after tumor eradication.

The patients will be treated according to these schedules of administration:

**Group A.** **ICT:** 40mg of Mitomycin C dissolved in 100 cc of bidistilled water  
(divided in two portions of 20mg in 50 cc)  
**plus simultaneous**

**LHT:** 42°C ± 2

**Group B.** **ICT:** 40 mg of Mitomycin C dissolved in 100 cc of bidistilled water  
(divided in two portions of 20 mg in 50 cc)

In group A, a medium temperature value at bladder surface within 40°C and 44°C for at least 40 min/session will be necessary to consider the session successful.

The weekly sessions will be scheduled in a way that at least 72 hours will elapse between two successive treatment sessions. This is in order to reduce thermotolerance phenomenon.

### Treatment procedure

7.1.

**Group A:** Patient in semilithotomy position. The session starts emptying the bladder from the residual urinary volume using a 10 Fr Nelaton catheter. Through the same catheter the first preparation of Mitomycin C solution at the dosage of 20 mg in 50 ml of bidistilled water, is inserted. This Mitomycin C solution should be previously heated in a range 43-45°C. Local anesthesia along the urethra with urethral gel is performed and the operative 18/20 Fr catheter is inserted into the bladder via transurethra and the balloon inflated with 15 ml of saline. The three bladder thermocouples are spread out to contact the bladder walls and/or the cytostatic solution. Leaving the catheter at its natural, moderate detraction, hyperthermia can be delivered and all parameters controlled by means the computerized unit of SB-TS 101 System.

After 30 min. of the operative session, the hyperthermia source is stopped, the bladder is completely emptied and the second solution of heated Mitomycin C at the same dosage of 20 mg in 50 ml of bidistilled water, is inserted via the operative catheter and the microwaves reactivated. This operation should take 3-4 min.

After 60 min of the operative session, the microwaves source is stopped, the bladder is completely emptied and the operative catheter removed.

During the operative session, the activity of the cooling system and the power of the microwaves source should be controlled in order to keep temperatures in the range considered successful for at least 40 min.

If during the first 2 sessions the patient complains intensively about cystitic symptoms, it would be convenient to treat him, before starting the remaining sessions, with anticholinergic drugs or analgesics.

7.2.

**Group B:** Patient lies on own back. First the bladder is emptied from the residual urine volume, then the first solution of Mitomycin C at the dosage of 20 mg in 50 ml of bidistilled water is instilled into the bladder by means of a 10 Fr Nelaton catheter. After 30 min of the operative session, the bladder is newly emptied and the second portion of Mitomycin C solution at the same dosage ( 20 mg in 50 cc of bidistilled water) instilled into the bladder via a Nelaton 10 Fr catheter. After 60 min of the operative session patient can void his bladder spontaneously.

## **8. TREATMENT SUSPENSION OR DELAY**

The treatment sessions will be interrupted or postponed in case of:

- 8.1. Patient's intolerance of the procedure
- 8.2. Severe bleedings
- 8.3. Severe urethritis
- 8.4. Severe bladder spasms
- 8.5. Systemic Mitomycin C allergy
- 8.6. At physician's discretion
- 8.7. For group A, if the treatment session suspension happens after more than 30 effective heating minutes, the session will be accounted as suspended successfully.
- 8.8. The treatment is accounted successfully if no more than 1 session was suspended unsuccessfully.
- 8.9. To be accounted as successful a session should not be postponed more than 15 days from the scheduled data.
- 8.10. Treatment suspension or delay might also be considered in case of side effects. Possible local side effects could be urethral inflammation, extensive necrosis of epithelium or necrosis of epithelium in undesired locations.

## **9. FOLLOW- UP**

### **9.1. Group A (Hyperthermia + Mitomycin C) and Group B (Mitomycin C alone)**

- 9.1. The following exams will be assessed 7- 10 days after the last session of the inductive cycle and then quarterly.
  - 9.1.1 Physical examination
  - 9.1.2. Blood exams
  - 9.1.3. Questionnaire
  - 9.1.4. Cystoscopy and biopsies of every suspicious lesion. (Mapping and photos are optional during cystoscopy performed quarterly).
  - 9.1.5. Cytology
  - 9.1.6. Uroflowmetry with residual volume (only quarterly).

### **9.2. The following exams will be assessed at fixed time**

- 9.2.1 I.V.P. after 1 year
- 9.2.2 Abdomino- pelvic US after 1 year
- 9.2.3 Bone scan after 2 years
- 9.2.4 Rx Chest after 2 years

## **10. CRITERIA FOR THE FOLLOW- UP EVALUATION**

- 10.1 The Interim statistical evaluation will be drawn when overall 80 patients will complete 1 year follow-up.  
Following statistical considerations will be drawn every 6 months.  
Definitive statistical evaluations will be reported when all patients will complete 2 years follow- up.

The disease - free patients in protocol will be maintained in clinical follow- up (according to Chapter 9) for at least 2 years.

- 10.2 Recurrent patients go out of protocol at the time of the first relapse.
- 10.3 The recurrence rate, the progression rate and the local incidence of CIS in both group of patients will be evaluated the first time at the Interim, then every 6 months taking into account all accumulated data obtained that far.
- 10.4 Every intercurrent events, complaints or chronic complications related to the treatment will be carefully registered (Free- Form)

## **11. NUMBER OF PATIENTS AND STATISTICAL CONSIDERATIONS**

We can comprehensively assume (considering the heterogeneous population enrolled in this study: single and multifocal tumors, first episode and recurrent tumors, previous and non previous chemoprophylactic treatment), for patients treated with chemotherapy alone, a two years recurrence-rate of 40%.

A sample size of 158 patients (79 per group) will allow to detect a reduction of the recurrence- rate in the treated group with added hyperthermia of 50% with a power of 80%.

The tolerated risk of type 1 error is set at 5% (in a two- tail test)

The Interim statistical report (see 10.1), will define the following development of the study:

- suspension of the study in case of statistical significant higher recurrence-rate in Group A (Hyperthermia plus Chemotherapy) compared to group B (Chemotherapy alone) or vice versa will be attested.
- prolongation of the study till 2 year follow- up or longer, according to Interim report results, in any other case.

## **12. END POINTS**

To compare:

- 12.1 the disease- free interval
- 12.2 the recurrence rate
- 12.3 the progression of stage and grade
- 12.4 the occurrence of CIS
- 12.5 the occurrence of urethelial cell carcinoma in the upper tract or in the prostatic urethra
- 12.6 the occurrence of distant metastasis (according to Consensus Conference in bladder cancer, Niijima '86) between the two treatment arms

## **13. TOXICITY**

### **13.1 Mitomycin C**

Previous studies (2,3) have shown that systemic toxicity is unlikely. For this reason blood counts are necessary only prior to treatment.

Urine analysis must be performed at every control visit.

Complaints of chemical cystitis are reported on the forms. If severe chemical cystitis is encountered it is allowed to postpone the next instillation for 1 week. However, if symptoms do not improve after 1 week or if symptoms recur with the same severity after the next instillation, the patients stops treatment. If the patient stops treatment because of toxicity, he is followed for recurrence and the other end points given in Chapter 12.

### **13.2 Hyperthermia + Mitomycin C**

Previous studies ( 23,24) have shown that systemic toxicity is unlikely. However local and systemic side effects of combined administration are not still tested in large series of patients.

The blood counts and blood special tests are necessary before and after treatment according to chapter 5.

The Mitomycin C tissue and blood-absorption rate, when the drug is administered simultaneously with hyperthermia, is unknown at the present.

The chemical instability of Mitomycin C can induce pharmacological and biological changes in different condition (relating to pH, Temperature, etc.) and its determination in human tissues and blood samples can be very difficult.

Complaints of chemical cystitis are reported on the forms.

In case of severe chemical cystitis it is allowed to postpone the next session for a maximum of 15 days.

However, if symptoms do not improve after 15 days or if symptoms recur with the same severity after the next session, the patient stops treatment and is followed for recurrence and other end points given in chapter 12.

When severe local or systemic toxicity appears, it is recommended to contact the study coordinator.

#### **14. FORMS**

- A) Form attesting that experimental clinical trial using hyperthermia and chemotherapy in combination has been approved by the Ethic Committee of the S.Raffaele Hospital in Milan.
- B) Randomization form is used for patient's randomization by fax.
- C) Form to describe side effects, complaints, chemical cystitis symptoms and intercurrent events during treatment and follow- up.
- D) Flow chart.

#### **15. ETHICS**

It is the responsibility of participants to ensure that this protocol will be approved by Local and/or National Ethics Committees. The treatments at each center will be initiated following the Local and/or National Ethic Committees approval. Participants have to obtain informed and/or written consent from patients according to laws in force in respective countries.

## 16. ADMINISTRATIVE RESPONSIBILITIES

Data processing and statistical aspects:

All forms and all questions concerning data management or statistics should be addressed to:

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## 18. APPENDIX I

### TNM CLINICAL AND HISTOPATHOLOGICAL CLASSIFICATION

#### BLADDER (ICD-0188)

Classified 1974, Confirmed 1978 (Approved by CNC, DSK, ICPR, JJC)

#### RULES FOR CLASSIFICATION

The classification applies only to epithelial tumors. Papilloma is excluded such cases should be listed under the category 'GO'.

Papillary non invasive carcinoma should be listed under the category Ta.

There should be histological or cytological verification of the disease. Any unconfirmed cases must be reported separately.

The following are the minimum requirements for assessment of the T,N, and M categories. If these can not be met the symbol TX, NX, MX will be used.

**T categories:** Clinical examination, urography, cystoscopy, bimanual examination under anesthesia and biopsy or transurethral resection of the tumor prior to definitive treatment.

**N categories:** Clinical examination and radiography including lymphography and urography.

**M categories:** Clinical examination and radiography. In the more advanced primary tumors or when clinical suspicion warrants radiography or isotope studies are recommended.

#### REGIONAL AND JUXTA - REGIONAL LYMPHNODES

The regional lymphnodes are the pelvic nodes below the bifurcation of the common iliac arteries.

The juxta-regional lymphnodes are the inguinal nodes, the common iliac nodes and the para-aortic nodes.

#### TNM POST- SURGICAL HISTOPATHOLOGICAL CLASSIFICATION

pT Primary tumor

pTis Pre invasive carcinoma (Carcinoma in Situ CIS)

pTa Papillary non- invasive carcinoma

pT0 No evidence of tumor found on histological examination of specimen

pT1 Tumor not extending beyond the lamina propria

pT2 Tumor with invasion of superficial muscle(not more than half way through muscle coat)

pT3 Tumor with invasion of deep muscle (more than half way through muscle coat) or with invasion of perivesical tissue  
pT4 Tumor with invasion of prostate or their extravescical structures  
pTX The extent of invasion can not be assessed

## **G - HISTOPATHOLOGICAL GRADING**

'GO' Papilloma, i.e. no evidence of anaplasia  
G1 High degree of differentiation  
G2 Medium degree of differentiation  
G3 Low degree of differentiation or undifferentiated  
GX Grade can not be assessed

## **L - INVASION OF LYMPHATICS**

L0 No lymphatic invasion  
L1 Evidence of invasion of superficial lymphatics  
L2 Evidence of invasion of deep lymphatics  
LX Lymphatic invasion can not be assessed

pN -Regional and juxta- regional lymphnodes  
The pN categories correspond to the N categories

pM- Distant metastasis  
The pM categories correspond to the M categories

## **STAGE GROUPING**

No stage- grouping is at present recommended

## **TNM PRE-TREATMENT CLINICAL CLASSIFICATION**

### **Primary tumor**

Tis Pre- invasive carcinoma (CIS)  
Ta Papillary non-invasive carcinoma  
T0 No evidence of primary tumor  
T1 On bimanual examination a freely mobile mass may be felt: this should not be felt after tumor eradication of the lesion and/or  
Microscopically, the tumor does not invade beyond the lamina propria  
T2 On bimanual examination there is induration or a nodular mass is palpable in the bladder wall which persists after tumor eradicaion of the exophitic portion of the lesion and/or there is microscopic invasion of the deep muscle or of extension through the bladder wall.  
T3a Invasion of the deep muscle

T3b Invasion through the bladder wall

T4 Tumor fixed or extending to neighbouring structures and/or

There is microscopic evidence of such involvement

T4a Tumor infiltrating the prostate, uterus or vagina

T4b Tumor fixed to the pelvic wall and/or abdominal wall

TX The minimum requirements to assess the primary tumor can not be met

### **N- Regional and Juxta regional lymphnodes**

N0 No evidence of regional lymphnode involvement

N1 Evidence of involvement of a single homolateral regional lymphnode

N2 Evidence of involvement of contralateral or bilateral or multiple regional lymphnodes

N3 Evidence of involvement of fixed regional lymphnodes

N4 Evidence of involvement of juxta- regional lymphnodes

NX The minimum requirements to assess the regional and/or juxta- regional lymphnodes can not be met.

### **M- Distant metastasis**

M0 No evidence of distant metastasis

M1 Evidence of distant metastasis

MX The minimum requirements to assess the presence of distant metastasis can not be met.

## **19. APPENDIX II**

### **TESTS AND TABLES FOR PATIENT'S EVALUATION**

#### **TAB. 1 - BLOOD EXAMS**

Azothemia (Urea)  
Creatinine  
Glicemia (Glucose)  
Blood cell count  
Alkaline phosphatase  
VES  
Quick Time  
P.T.T  
LDH  
SGOT, SGPT  
CPK

#### **TAB. 2 - SPECIAL BLOOD EXAMS**

IgG, IgM, IgA  
Mitomycin C levels in serum (whenever is possible)

#### **TAB. 3 - URINALYSIS**

Complete urine examination  
Culture

#### **TAB. 4 - ADDITIONAL INVESTIGATIONS**

Flow Cytometry  
Immunohistochemical tests

**TAB. 5 - QUESTIONNAIRE (SUBJECTIVE SYMPTOMATOLOGY)**

	<b>Score</b>
1) <b>DAYTIME FREQUENCY</b> : > 1/hour	4
1 /2-3 hours	3
1 /3-4 hours	2
1 /5 or more hours	1
2) <b>NOCTURIA</b> : > 2 awakes / night	3
1 or 2 awakes / night	2
no awakes	1
3) <b>PAIN, BURNING OR DISTURBANCE DURING MICTURITION:</b>	
Every time	4
Often	3
Rarely	2
Never	1
4) <b>URGE INCONTINENCE:</b> Often	3
Rarely	2
Never	1
5) <b>STRESS INCONTINENCE:</b> Often	3
Rarely	2
Never	1
6) <b>URETHRORRAGIA:</b> Often	3
Rarely	2
Never	1
7) <b>SOVRAPUBIC, PERINEAL OR PELVIC PAIN :</b>	
Often	3
Rarely	2
Never	1

## **20. APPENDIX III**

### **WHO PERFORMANCE STATUS**

**GRADE 0:** Able to carry out all normal activity without restriction.

**GRADE 1:** Restricted in physically strenuous activity but ambulatory and able to carry out light work.

**GRADE 2:** Ambulatory and capable of all self care but unable to carry out any work; up and about more than 50% of waking hours.

**GRADE 3:** Capable of only limited self care, confined to bed or chair for more than 50% of waking hours.

**GRADE 4:** Completely disabled; cannot carry on any self care; totally confined to bed or chair.