



**Ministry of education
and science of
the Kyrgyz Republic**

IMMUNOTHERAPY OF EARLY- STAGE CANCER BLADDER WITH BCG

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The main goal of the report

- to demonstrate capability of immunotherapy of cancer bladder in the case of **administration of BCG**, live attenuated vaccine.
- We want to show how application of virulence factors of live infectious agent of Mycobacteria tuberculosis helps to kill cancer cells

INTRODUCTION

BLADDER CANCER IS THE SIXTH MOST COMMON CANCER IN THE UNITED STATES AFTER LUNG CANCER, PROSTATE CANCER, BREAST CANCER, COLON CANCER, AND MELANOMA. IT IS THE FOURTH MOST COMMON CANCER IN MEN AND THE TWELFTH MOST COMMON CANCER IN WOMEN. OF THE ROUGHLY 81,000 NEW CASES ANNUALLY, ABOUT 62,000 ARE IN MEN AND ABOUT 19,000 ARE IN WOMEN. OF THE ROUGHLY 17,000 ANNUAL DEATHS, MORE THAN 12,000 ARE IN MEN AND FEWER THAN 5,000 ARE IN WOMEN. THE REASONS FOR THIS DISPARITY BETWEEN THE SEXES ARE NOT WELL UNDERSTOOD

BLADDER CANCER IS A DISEASE IN WHICH MALIGNANT (CANCER) CELLS FORM IN THE TISSUES OF THE BLADDER.

THERE ARE THREE TYPES OF BLADDER CANCER THAT BEGIN IN CELLS IN THE LINING OF THE BLADDER.

THESE CANCERS ARE NAMED FOR THE TYPE OF CELLS THAT BECOME MALIGNANT (CANCEROUS):

TRANSITIONAL CELL CARCINOMA

SQUAMOUS CELL CARCINOMA

ADENOCARCINOMA

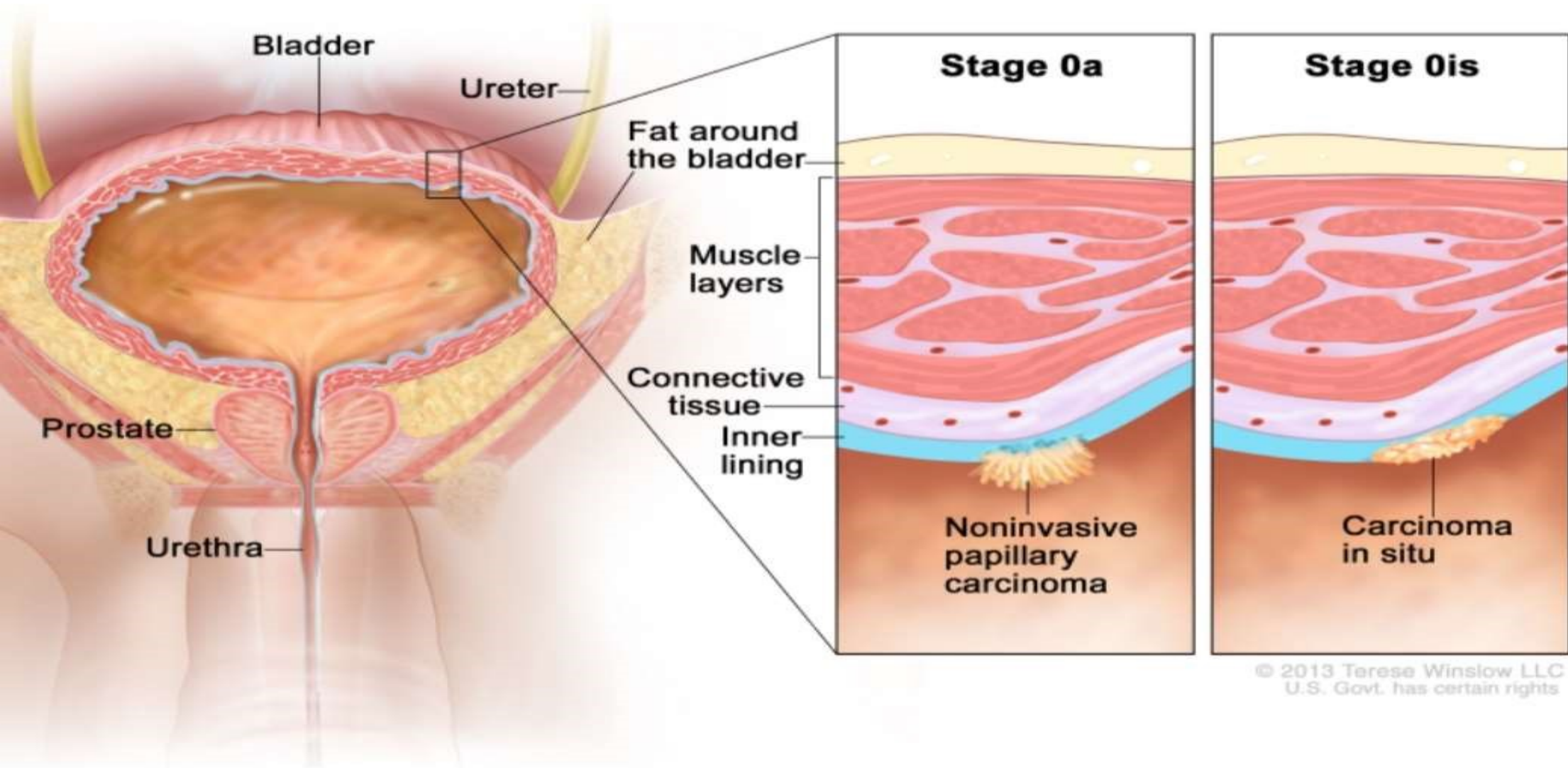
- THE FOLLOWING STAGES ARE USED FOR BLADDER CANCER:
 - ✓ STAGE 0 (NONINVASIVE PAPILLARY CARCINOMA AND CARCINOMA IN SITU)
 - ✓ STAGE I
 - ✓ STAGE II
 - ✓ STAGE III
 - ✓ STAGE IV

BLADDER CANCER CAN RECUR (COME BACK) AFTER IT HAS BEEN TREATED. THE CLINICAL STAGING OF CARCINOMA OF THE BLADDER IS DETERMINED BY THE DEPTH OF INVASION OF THE BLADDER WALL BY THE TUMOR. ACCORDING TO TNM CLASSIFICATION

STAGE 0 NONINVASIVE PAPILLARY CARCINOMA: NO LYMPH NODE METASTASIS, NO DISTANT METASTASIS ABNORMAL CELLS ARE FOUND IN TISSUE LINING THE INSIDE OF THE BLADDER. THESE ABNORMAL CELLS MAY BECOME CANCER AND SPREAD INTO NEARBY NORMAL TISSUE.

STAGE 0 IS CARCINOMA IN SITU, WHICH IS A FLAT TUMOR ON THE TISSUE LINING THE INSIDE OF THE BLADDER. NO LYMPH NODE METASTASIS, NO DISTANT METASTASIS.

Stage 0 Bladder Cancer





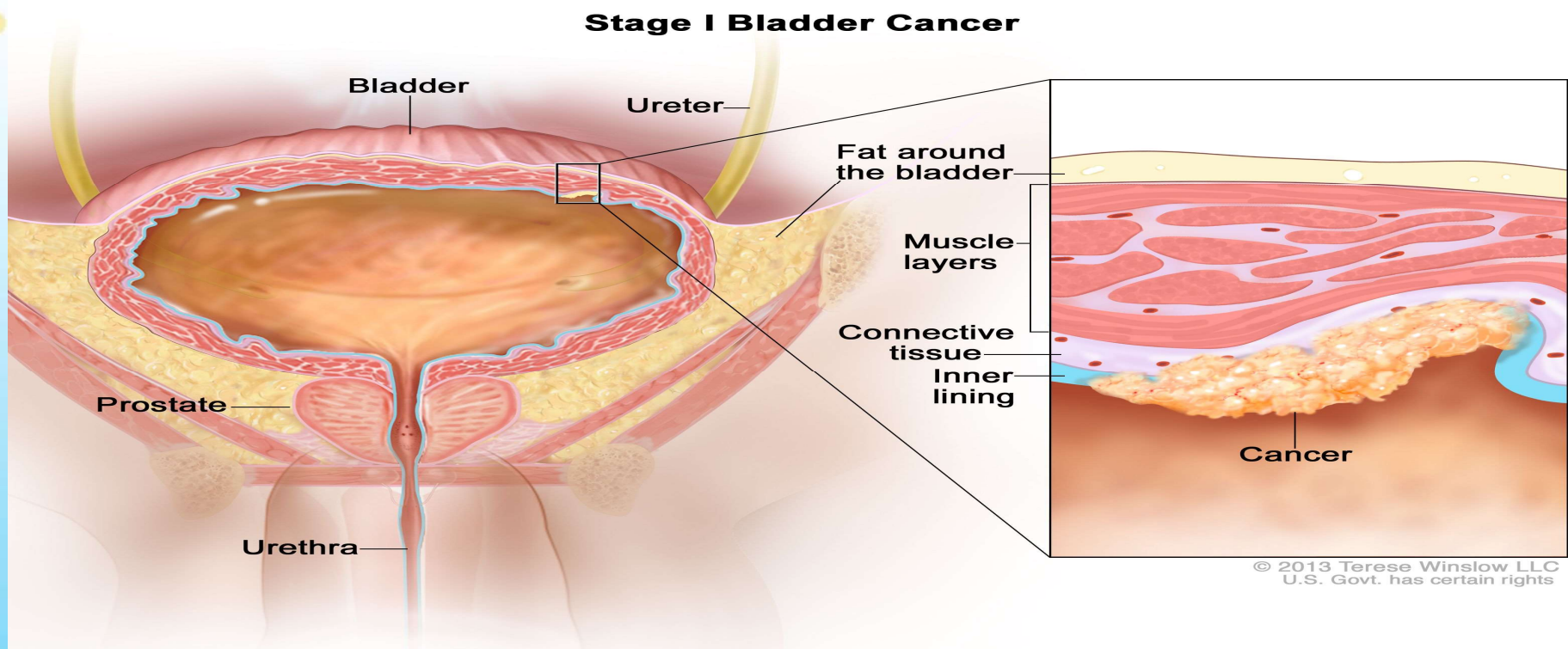
The classic appearance of carcinoma in situ as a flat, velvety patch. Using special staining techniques, it has been shown that significant areas of carcinoma in situ are easily overlooked by conventional cystoscopy. .

- **STAGE T1, N0, M0:**

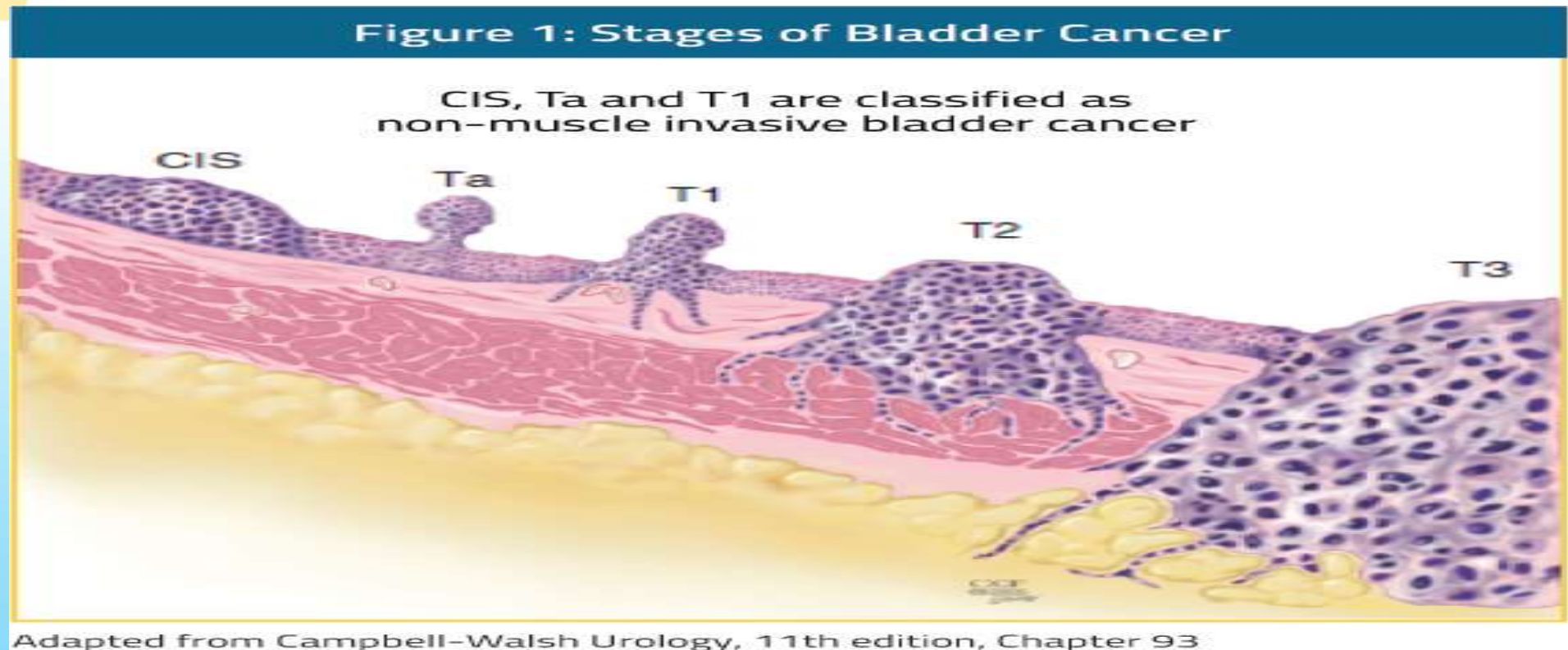
T1 = TUMOR INVADES LAMINA PROPRIA (SUBEPITHELIAL CONNECTIVE TISSUE).

N0 = NO LYMPH NODE METASTASIS

M0 = NO DISTANT METASTASIS.

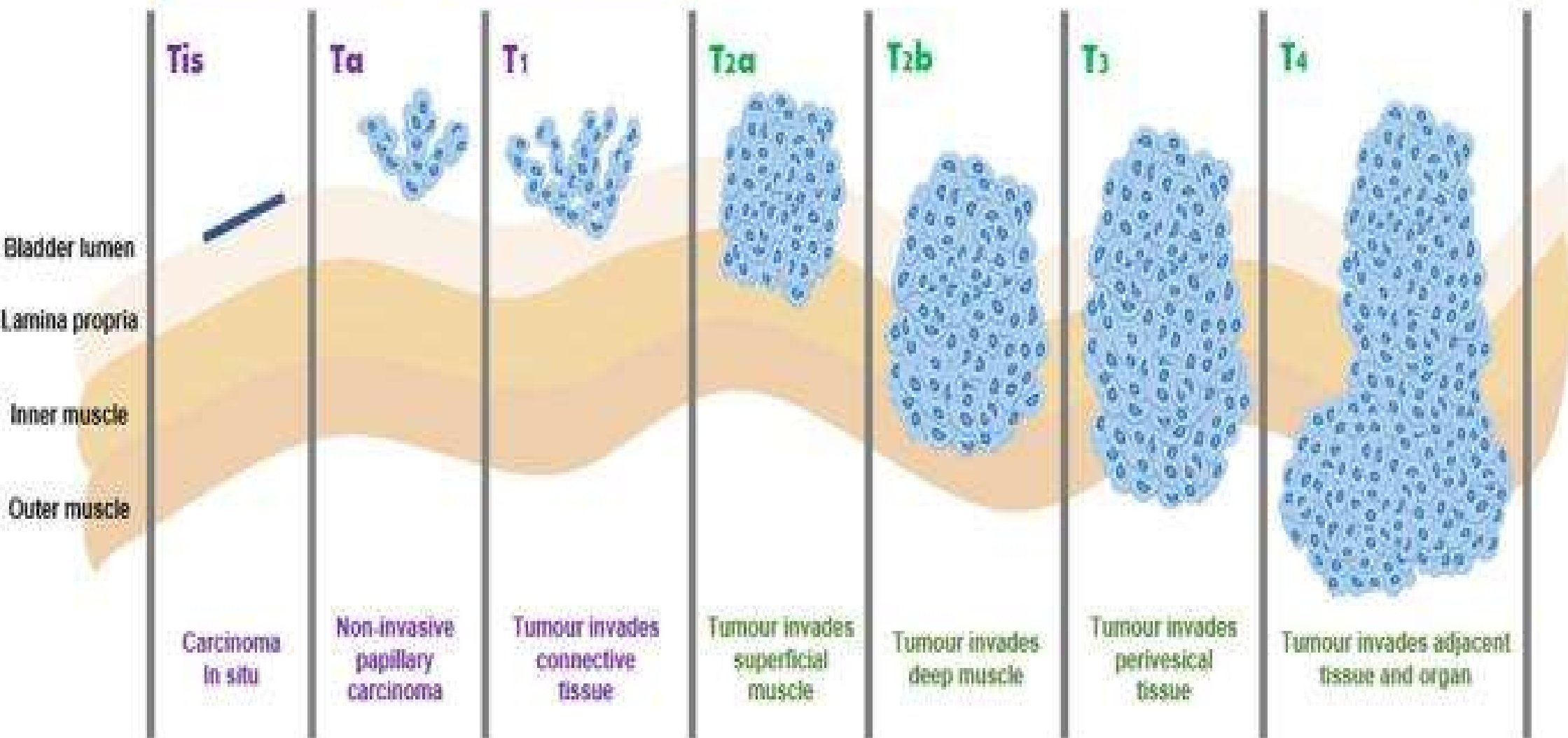


- 75 % OF **BLADDER CANCER** ARE NON-MUSCULAR INVASIVE BLADDER CANCER (NMIBC), NAMELY SUPERFICIAL BLADDER CANCER – STAGES: **STAGE 0- TA, N0, M0, STAGE 0IS- TIS, N0, M0, STAGE T1, N0, M0**



Non-muscle invasive (NMIBC)

Muscle invasive (MIBC)



CLINICAL SYMPTOMS OF NIMBC

- BLOOD IN THE URINE (SLIGHTLY RUSTY TO BRIGHT RED IN COLOR).
- FREQUENT URINATION.
- PAIN DURING URINATION.
- LOWER BACK PAIN.

BCG

THE VACCINE AGAINST TUBERCULOSIS CONTAINS A LIVE, ATTENUATED STRAIN OF MYCOBACTERIUM BOVIS CALLED BACILLUS CALMETTE GUÉRIN (BCG), WAS ORIGINALLY DEVELOPED IN 1921 FROM MYCOBACTERIUM BOVIS WHICH IS COMMONLY FOUND IN CATTLE. BCG USED TO PREVENT TUBERCULOSIS (TB) IN PEOPLE WHO ARE AT A HIGH RISK OF TB OR WHERE TB IS COMMON, IS RECOMMENDED FOR CHILDREN AT HIGH RISK FOR EXPOSURE TO ACTIVE TUBERCULOSIS. THE VACCINE IS GIVEN BY INTRADERMAL ROUTE OF ADMINISTRATION.

IT IS ON THE WORLD HEALTH ORGANIZATION'S LIST OF ESSENTIAL MEDICINES.

OVER 40 YEAR'S DEVELOPMENT HAS ATTESTED BCG TO A VITALLY IMPORTANT TREATMENT FOR NMIBC SINCE MORALES'S FIRST REPORT OF BCG'S SUCCESS IN TREATING BLADDER CANCER IN 1976.



BCG- MECHANISM OF IMMUNOTHERAPY

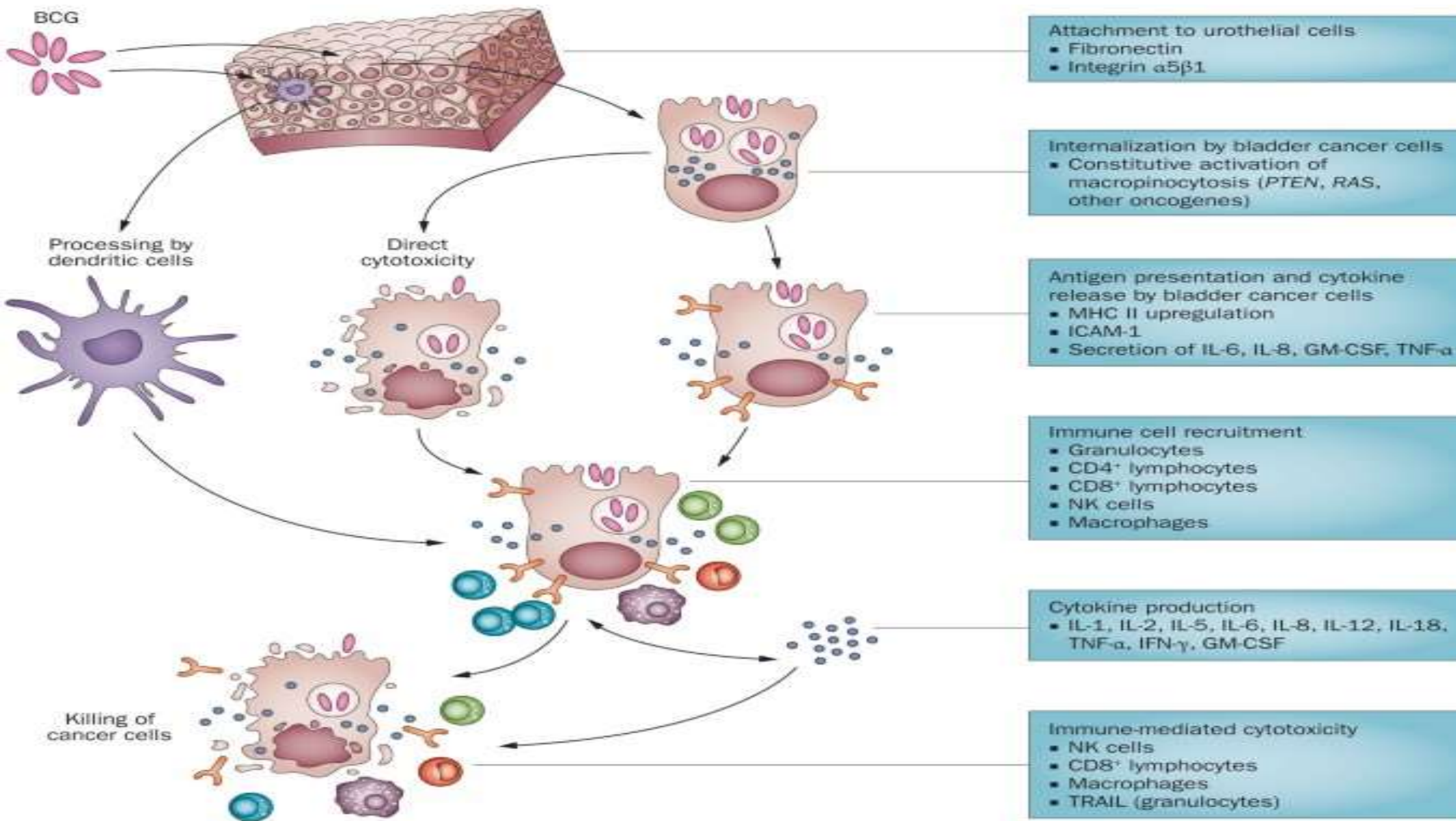
- THE PRELIMINARY KNOWLEDGE OF BCG WORKS ON BLADDER CANCER BELIEVED THAT BCG,
- **ACTIVATES THE INNATE IMMUNITY AND ACQUIRED IMMUNITY OF BLADDER.** RELEVANT RESEARCHES STARTED FOCUSING ON THE VARIOUS SIGNALING PATHWAYS FOR BCG ACTIVATING THE IMMUNE SYSTEM. THE FINDINGS REVEALED THAT BCG NOT ONLY WORKS ON BLADDER CANCER BY ACTIVATING THE IMMUNE SYSTEM, BUT ALSO,
- **DIRECTLY REACTS TO THE TUMOR CELLS, CAUSING APOPTOSIS, NECROCYTOSIS**
- IMMUNE SYSTEM CELL SUBSETS THAT HAVE POTENTIAL ROLES IN BCG THERAPY INCLUDE **CD4+** AND **CD8+** LYMPHOCYTES, **NATURAL KILLER CELLS, GRANULOCYTES, MACROPHAGES, AND DENDRITIC CELLS.** BLADDER CANCER CELLS ARE KILLED THROUGH **DIRECT CYTOTOXICITY** BY THESE CELLS, ACTION OF **PERFORIN AND GRANZYMES.**

BCG- MECHANISM OF IMMUNOTHERAPY

- **BY SECRETION OF SOLUBLE FACTORS SUCH AS TRAIL (TUMOR NECROSIS FACTOR-RELATED APOPTOSIS-INDUCING LIGAND) BY THE DIRECT ACTION OF BCG BY THE INHIBITION OF CELL PROLIFERATION.**
- **OXIDATIVE STRESS.** BLADDER CANCER CELLS INTERNALIZE BCG, WHICH WILL INDUCE INDUCIBLE NITRIC OXIDE SYNTHASE (**INOS**) TO PRODUCE NITRIC OXIDE (**NO**). THE CYTOTOXIC EFFECT OF THE HIGH DOSE OF NO ON UROTHELIAL CARCINOMA CELLS HAS BEEN REPORTED FOR A LONG TIME. BESIDES, THE ACTIVE BCG CAN STIMULATE THE PRODUCTION OF REACTIVE OXYGEN SPECIES (**ROS**) SUCH AS HYDROGEN PEROXIDE (**H₂O₂**), AND **H₂O₂** CAN FURTHER PRODUCE **NO**. THE PRODUCTION OF THESE SUBSTANCES WILL INTERACT WITH EACH OTHER TO PRODUCE STRONG OXIDANTS, LEADING TO OXIDATIVE STRESS RESPONSE IN TUMOR CELLS. IN TURN, THE OXIDATIVE STRESS RESPONSE CAN CAUSE MORE PRODUCTION OF **ROS** AND **NOS**. THIS REACTION EVENTUALLY LEADS TO THE DAMAGE OF DNA AND PROTEINS IN CELLS OR CAUSES A SERIES OF EFFECTS SUCH AS CELL APOPTOSIS AND AUTOPHAGY

BCG- MECHANISM OF IMMUNOTHERAPY

- BCG SERVES AS A **PATHOGEN-ASSOCIATED MOLECULE PATTERN (PAMP)** TO ACTIVATE THE **PATTERN RECOGNITION RECEPTOR (PRR)** ON THE SURFACE OF VARIOUS CELLS, INCLUDING BLADDER TUMOR CELLS AND ANTIGEN-PRESENTING CELLS (APC) OF MACROPHAGES, DENDRITIC CELLS, AND OTHERS.
- THE PRESENCE OF MOST CYTOKINES- **IL-6 AND IL-8** OCCURRED AFTER THE INSTILLATION OF BCG. THE PRESENCE OF CYTOKINES ACTIVATES THOSE EFFECTOR CELLS SUCH AS CD8+ CYTOTOXIC T-CELLS (CTLs), MACROPHAGES, NEUTROPHILS, NATURAL KILLER (NK) CELLS, AND OTHERS. THESE IMMUNE CELLS, ON THE ONE HAND, CAN CONTINUE TO RELEASE CYTOKINES, PROMOTING IMMUNE CASCADE REACTION; ON THE OTHER HAND, THEY CAN KILL TUMOR CELLS IN THEIR WAY.



BCG – TREATMENT

INDICATIONS FOR BCG TREATMENT:

- BCG TREATMENT IS **INTRAVESICAL IMMUNOTHERAPY**, IT IS NOT INTRAVESICAL CHEMOTHERAPY. IMMUNOTHERAPY AND CHEMOTHERAPY DRUGS ARE GIVEN THE SAME WAY, THESE TWO TREATMENTS USE DIFFERENT TYPES OF DRUGS. WHILE CHEMOTHERAPY DRUGS ATTACK CANCER CELLS DIRECTLY, **IMMUNOTHERAPY DRUGS STIMULATE THE POWER OF IMMUNE SYSTEM.**
- **BCG TREATMENT IS USED TO ADDRESS EARLY-STAGE BLADDER CANCER.** THIS INCLUDES BLADDER CANCERS THAT HAVEN'T INVADDED YOUR BLADDER WALL MUSCLE, SUCH AS CARCINOMA IN SITU (IN ITS ORIGINAL LOCATION) BLADDER CANCERS AND **NON-MUSCLE INVASIVE BLADDER CANCERS (NMIBCS).** BCG TREATMENT ISN'T EFFECTIVE AGAINST BLADDER CANCER THAT HAS METASTASIZED (SPREAD TO OTHER PARTS OF THE BODY).
- BCG TREATMENT IS USUALLY GIVEN AFTER TURBT(TRANSURETHRAL RESECTION OF BLADDER TUMOR), WHICH IS A BLADDER SURGERY TO REMOVE ANY VISIBLE CANCER.

BCG TREATMENT

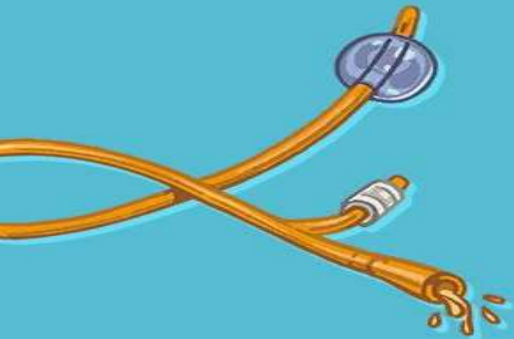
- INTRAVESICAL BCG IS THE TREATMENT OF CHOICE FOR REDUCING THE RISK OF CANCER PROGRESSION AND IS MAINLY USED FOR CANCERS WITH AN INTERMEDIATE OR HIGH RISK OF PROGRESSING **TECHNIQUE**.
- BCG IS IN A LIQUID SOLUTION THAT IS PUT INTO THE BLADDER WITH A CATHETER, UNDER LOCAL ANESTHESIA. THE PERSON THEN HOLDS THE SOLUTION IN THE BLADDER FOR TWO HOURS BEFORE URINATING. THE TREATMENT IS USUALLY GIVEN ONCE PER WEEK FOR SIX WEEKS, STARTING APPROXIMATELY TWO TO THREE WEEKS AFTER THE LAST TURBT.
- **BENEFITS OF INTRAVESICAL BACILLUS CALMETTE-GUERIN (BCG) —** INTRAVESICAL BCG, IN COMBINATION WITH TURBT, IS THE MOST EFFECTIVE TREATMENT FOR HIGH-RISK NON-MUSCLE INVASIVE BLADDER CANCER.
- **BCG THERAPY CAN DELAY TUMOR GROWTH TO A MORE ADVANCED STAGE AND DECREASE THE NEED FOR SURGICAL REMOVAL OF THE BLADDER AT A LATER TIME.**

How BCG Therapy Is Performed

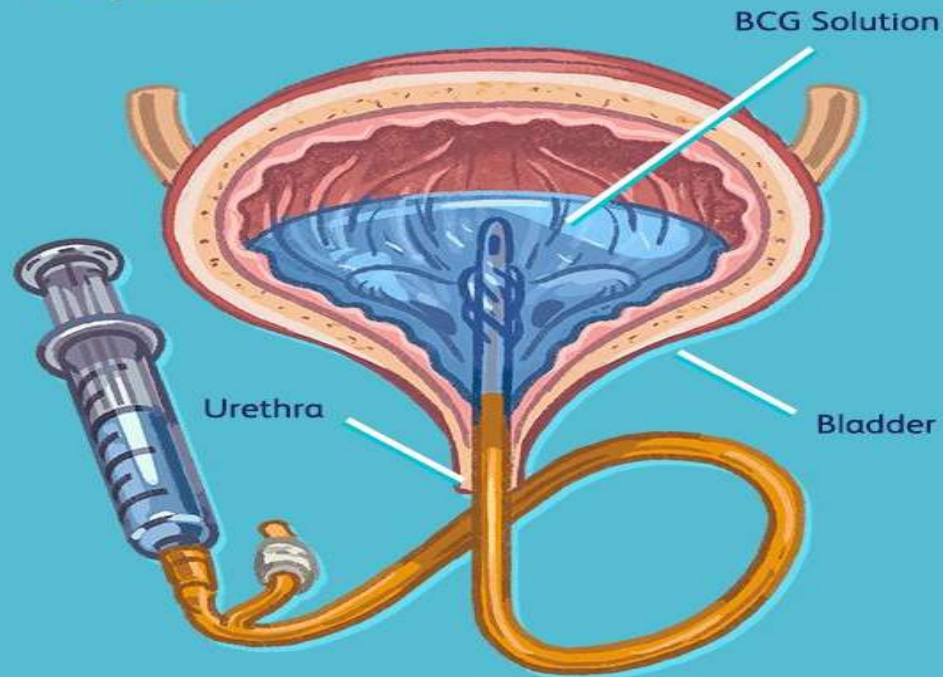
the procedure, limit fluid intake and empty your bladder



few hours, the catheter is clamped, the fluid drains, and the catheter is removed



2 A urinary catheter is inserted through the urethra, and the solution containing BCG is injected

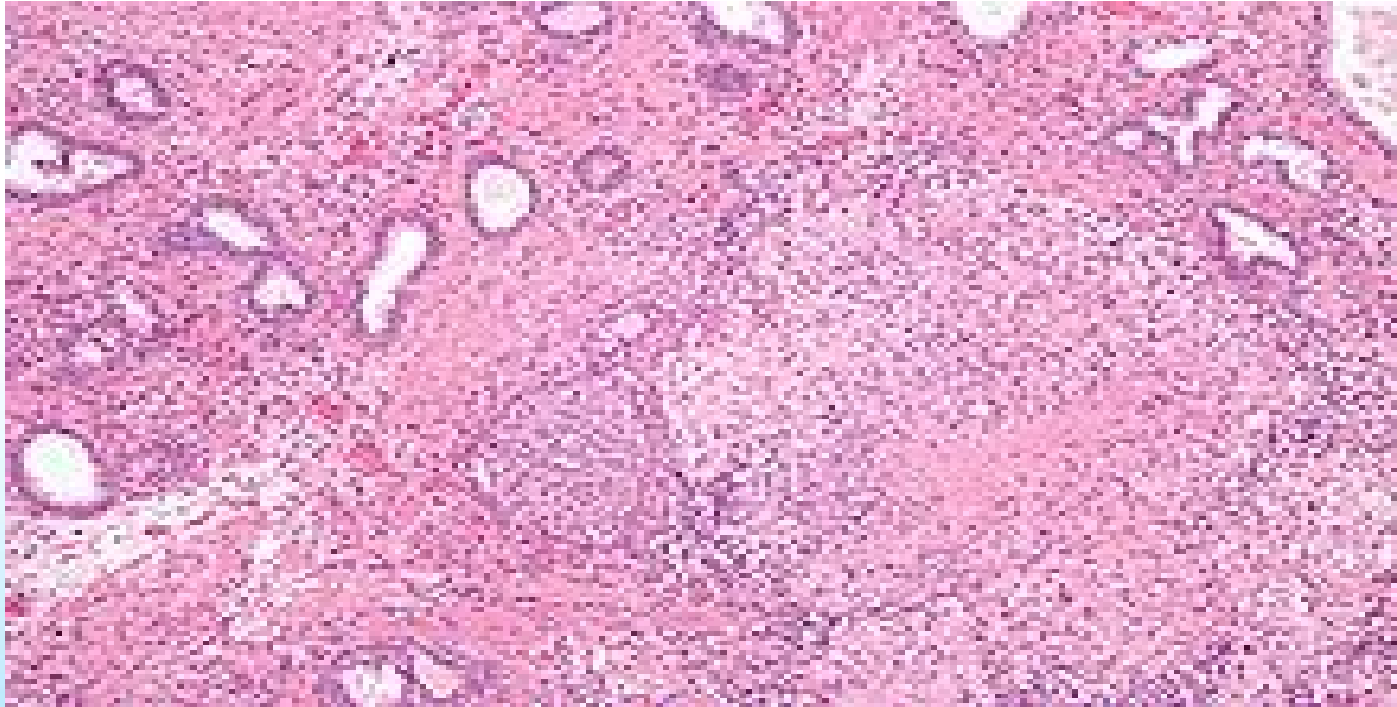


3 The catheter is clamped to help the BCG remain inside the bladder



5 Repeat the procedure around once a week for 6 weeks





- MICROGRAPH SHOWING GRANULOMATOUS INFLAMMATION OF BLADDER NECK TISSUE DUE TO BACILLUS CALMETTE–GUÉRIN USED TO TREAT BLADDER CANCER, H&E STAIN

BCG TREATMENT

- **SIDE EFFECTS OF BACILLUS CALMETTE-GUERIN (BCG) THERAPY, THE ADVERSE REACTION BCG THERAPY,**
- MOST PEOPLE WHO ARE TREATED WITH INTRAVESICAL BCG HAVE SOME SIDE EFFECTS; THE MOST COMMON OF THESE INCLUDE;
- **THE NEED TO URINATE FREQUENTLY,**
- **PAIN WITH URINATION,**
- **FEVER,**
- **BLOOD IN THE URINE,**
- **BODY ACHES**
- **MUSCLE PAIN, JOINT PAIN**
- **TIREDNESS**

THESE SYMPTOMS USUALLY BEGIN WITHIN TWO TO FOUR HOURS OF TREATMENT AND RESOLVE WITHIN 48 HOURS

COMPLICATIONS OF BCG THERAPY

- **LOCAL COMPLICATIONS** RESULT FROM BCG-CONTAMINATED URINE AND **AFFECT THE GENITOURINARY SYSTEM. SYSTEMIC COMPLICATIONS** ARE THE RESULT OF **BCG DISSEMINATION** IN THE BLOODSTREAM, AND THEY MAY BE MUSCULOSKELETAL, VASCULAR, PULMONARY, OR HEPATIC OR INVOLVE OTHER ORGAN SYSTEMS:
- URINARY TRACT INFECTIONS.
- INFLAMMATION OF TESTICLES.
- URETERAL OBSTRUCTION.
- BLADDER CONTRACTURE
- NECROSIS (CELL DEATH).
- BCG SEPSIS
- NEUTROPENIA
- BCG-INDUCED HYPERSENSITIVITY PNEUMONITIS
- HEPATITIS.
- BECAUSE THE IMAGING FINDINGS OF BCG-RELATED COMPLICATIONS CAN MIMIC THOSE OF CANCER OR INFECTION BY ANOTHER ORGANISM, KNOWLEDGE OF PRIOR BCG THERAPY AND AWARENESS OF THE POTENTIAL RELATED COMPLICATIONS ARE ESSENTIAL FOR MAKING THE CORRECT DIAGNOSIS PROSPECTIVELY AND GUIDING APPROPRIATE TREATMENT WITHOUT DELAY.

CONCLUSION AND PROSPECT

- NOWADAYS, IMMUNOLOGICAL THERAPY HAS RECEIVED INCREASING ATTENTION.
- **BCG REMAINS THE GOLD-STANDARD TREATMENT FOR HIGH-RISK NMIBC PATIENTS BCG STARTED THE EARLIEST AND HAS DEVELOPED INTO THE MOST MATURE IMMUNOTHERAPY FOR BLADDER CANCER.** HOWEVER, BCG TREATMENT HAS EXPOSED MANY PROBLEMS, SUCH AS BCG-INTOLERANT, BCG-REFRACTORY, BCG-RELAPSE, AND OTHER SEVERE ADVERSE REACTIONS, WHICH HAVE LED TO SIGNIFICANT INTEREST IN THE MECHANISM OF BCG THERAPY.

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Thank You