Tumori Uroteliali

Vincenzo Pagliarulo
Sezione di Urologia e Andrologia (DETO)
Università di Bari
vincenzo.pagliarulo@uniba.it

Epidemiologia

Incidenza: 26.000 casi ogni anno in Italia

3-5% di tutti i decessi per tumori

7% di tutti i tumori

70% dei tumori del tratto urinario

Età: più alta tra 50 e 70 anni

4-5 volte più frequente nei maschi

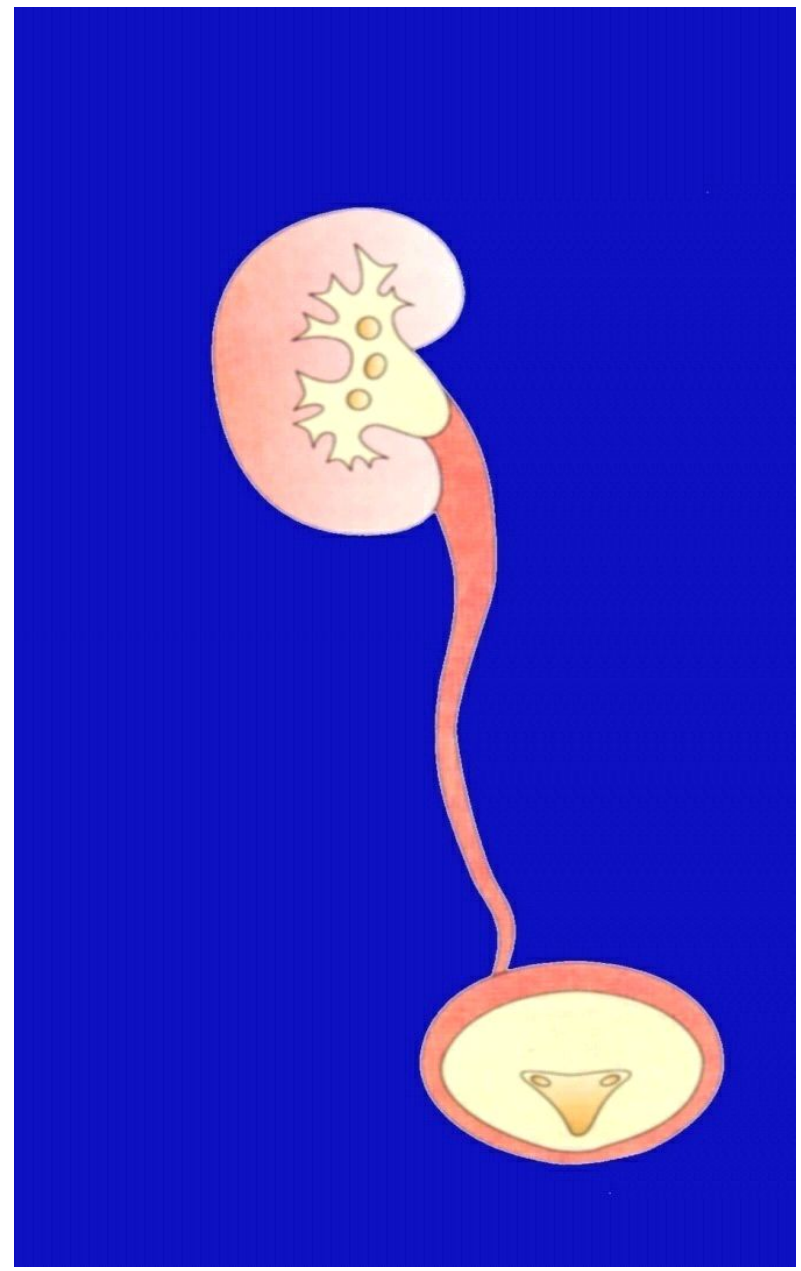
Distribuzione

Upper tract

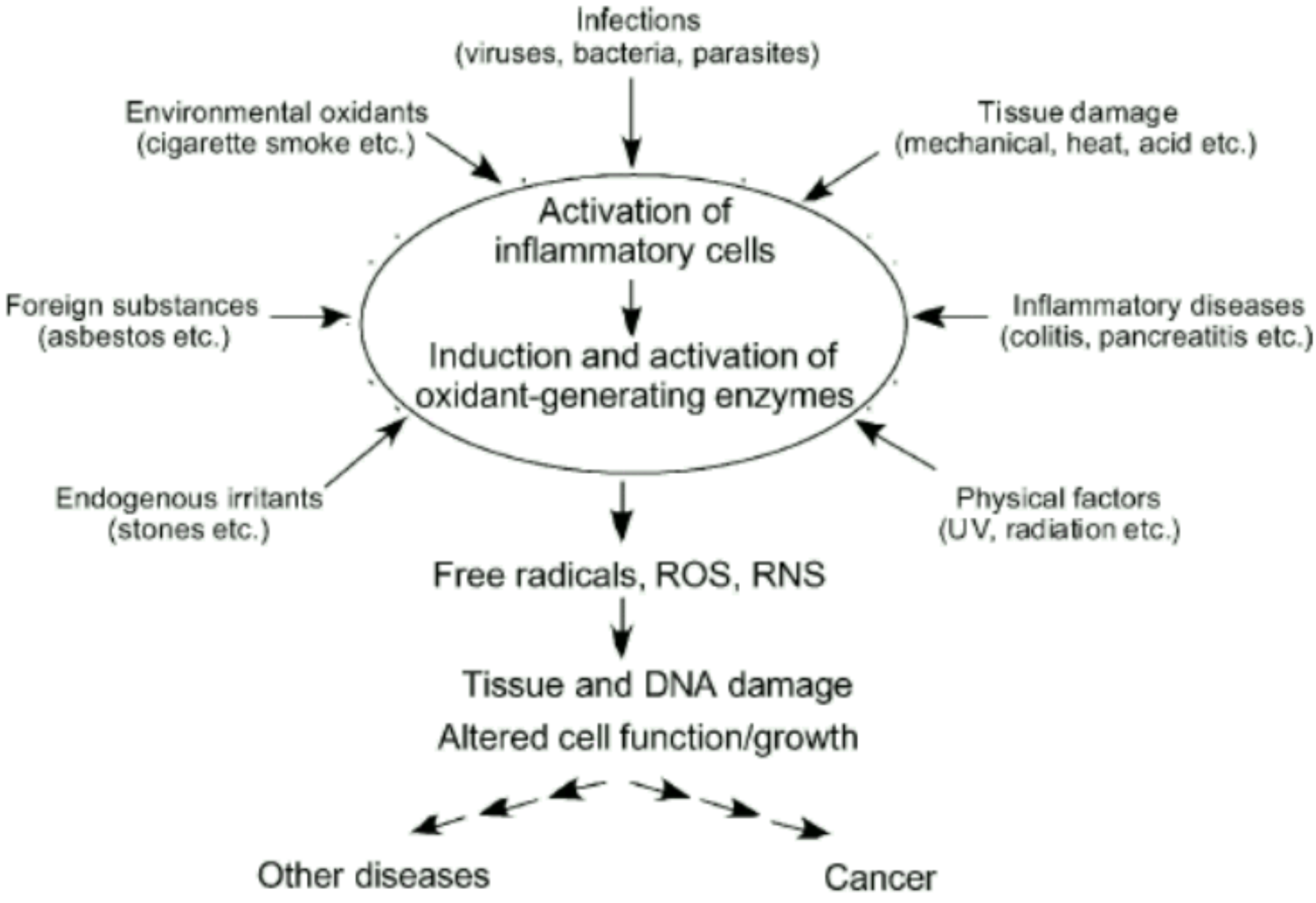
- Renal pelvis 5%
- Ureter 2%

Lower tract

- Bladder 90%
- Urethra 3%



Urothelium needs to be surveilled at any district, regardless of the primary location.


Infections
(viruses, bacteria, parasites)
Environmental oxidants
(cigarette smoke etc.)
Tissue damage
(mechanical, heat, acid etc.)
Activation of
inflammatory cells
Foreign substances
(asbestos etc.)
Inflammatory diseases
(colitis, pancreatitis etc.)
Induction and activation of
oxidant-generating enzymes
Endogenous irritants
(stones etc.)
Physical factors
(UV, radiation etc.)
Free radicals, ROS, RNS
Tissue and DNA damage
Altered cell function/growth
Other diseases
Cancer

Risk Factors

- Sigarette smoke: 33% of urothelial cancers are correlated to sigarette smoking. Specifically, the smoking increases 6,5 the risk to develop upper tract cancers and 4 times the risk to develop bladder cancer. Smoking interruption will lower the risk over time. Cancerogens: nitrosamine, policyclic aromatictic hydrocarbons and b-naftilamina.

- Other tobaccos: if not inhaled the risk is only slightly increased.

- Exposure to othe xenobiotics: b-naftilamina used to cause cancer in 100% of the population working for the extraction of this substance. Other substances: benzidine, halogenated solvents. Professional categories at risk: painters, personnel working with gas (distillation, attendants), coiffeurs.

- Radiotherapy: the risk is 2-4 times increased in women treated for cervix cancer.

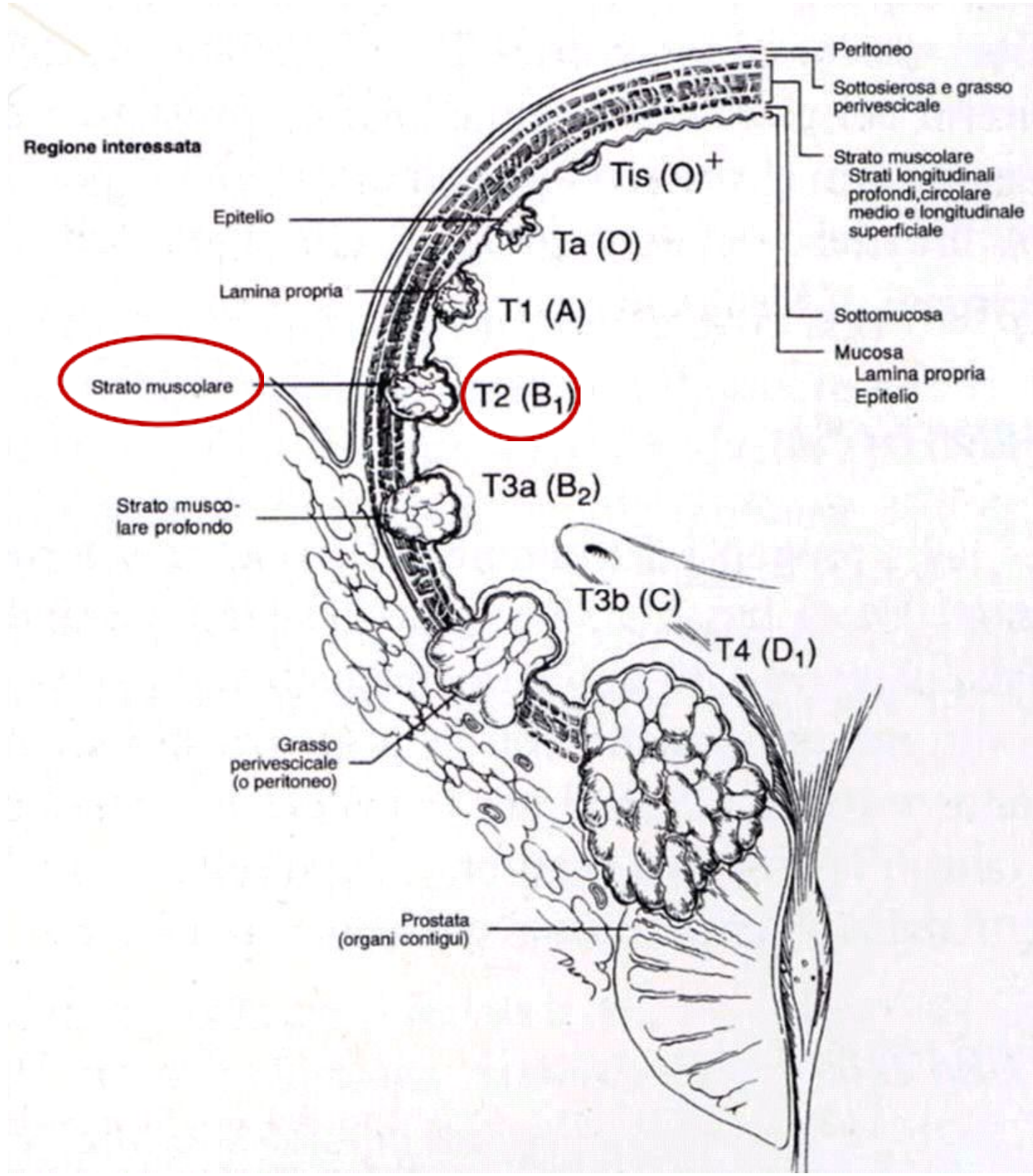
- Genetic predisposition: NAT 2 slow, GSTM 1 null.

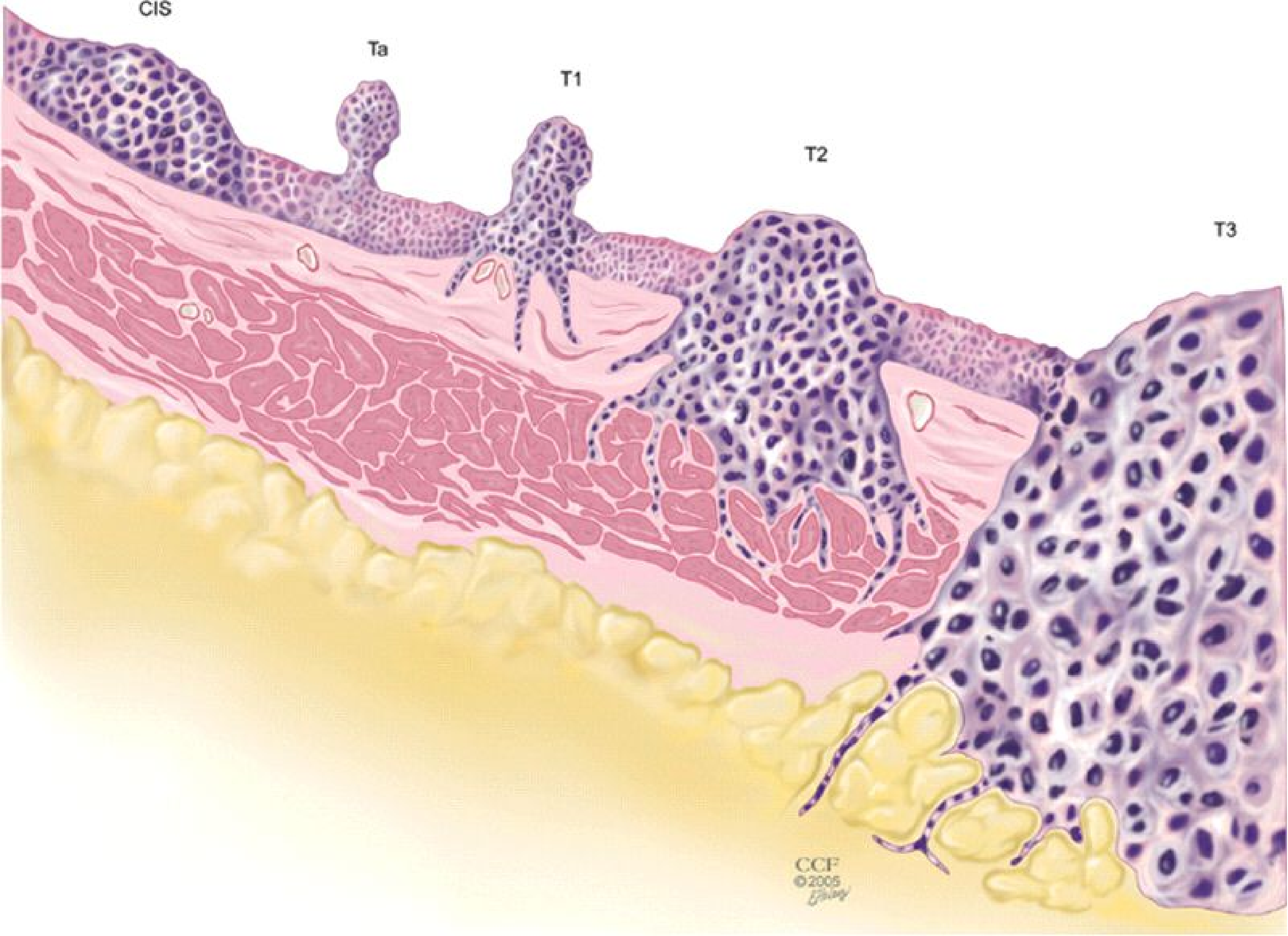
- HPV, infections and chronic inflammation: undemonstrated.

Staging

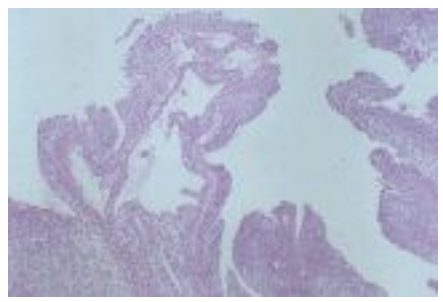
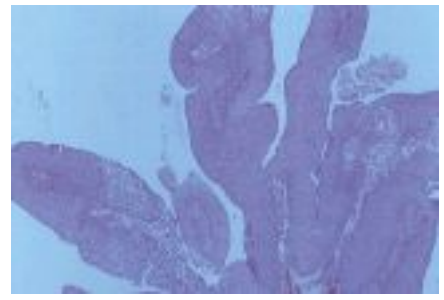
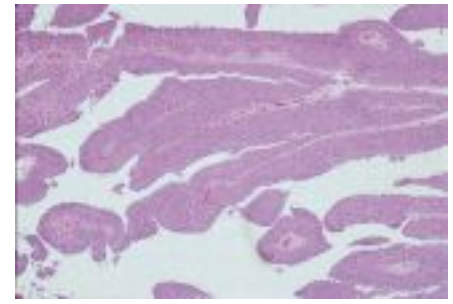
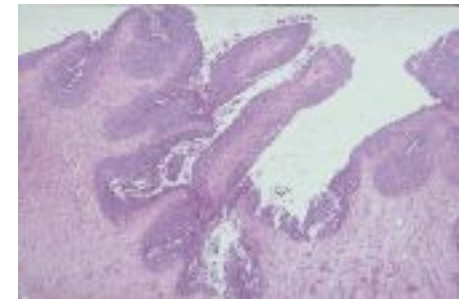
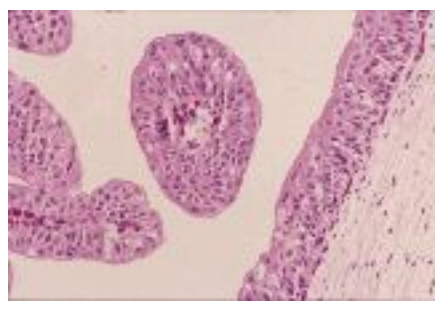
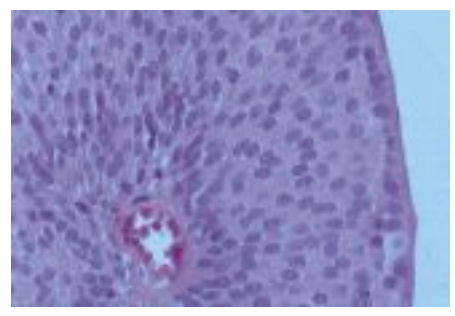
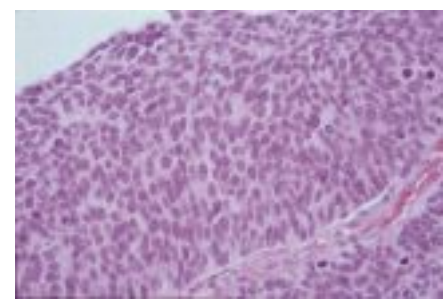
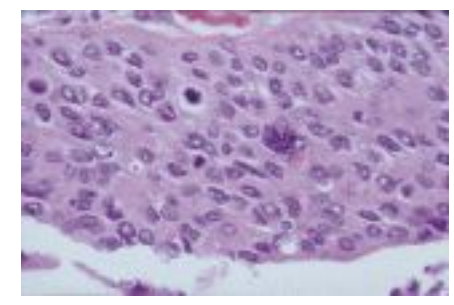
Non muscle-invasive (superficial)

Muscle-invasive



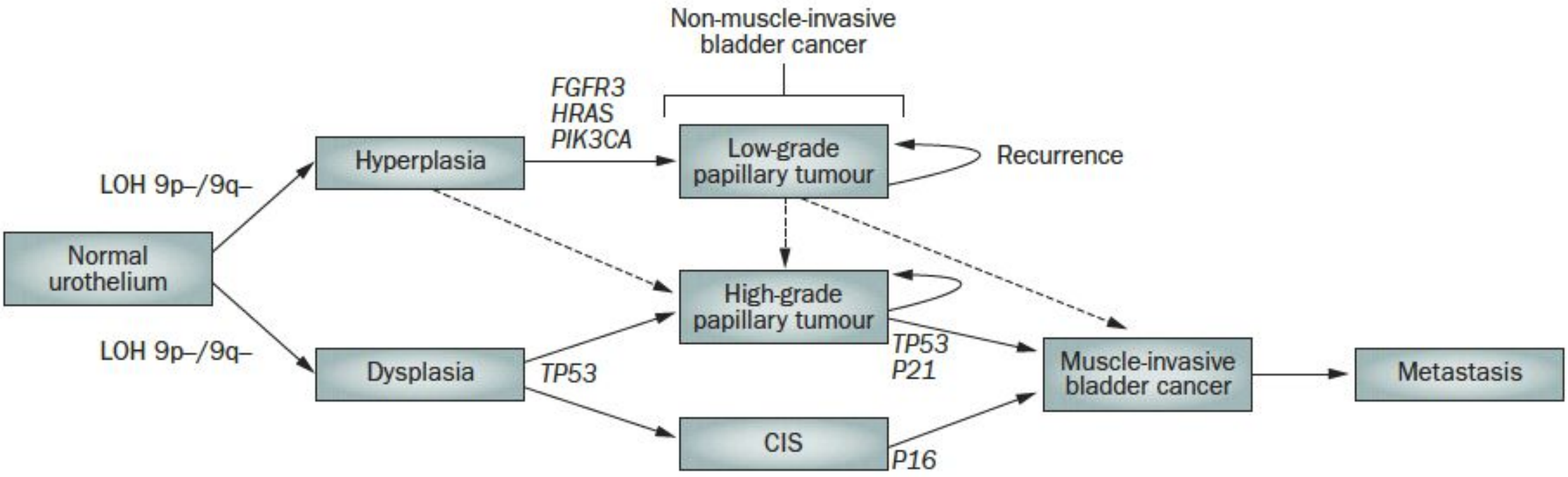


Grading

GRADE	Papilloma	Grade 1/LMP	Grade 2/low grade	Grade 3,4/high grade
	• Normal urothelial cytology	• Normal urothelial cytology	• Mild-mod. urothelial atypia • Increased N/C ratio • Mild-mod. nuclear pleomorphism	• Mod.-marked urothelial atypia • Increased N/C ratio • Mod.-marked nuclear pleomorphism
	• Cellular polarity maintained • No/rare mitoses • Intact umbrella cell layer • 7-8 cell layers	• Cellular polarity maintained • No/rare mitoses • ± umbrella cell layer • >8 cell layers • Increased cellular density	• Loss of cellular polarity • Infrequent mitoses • Variable loss of umbrella cell layer • Variable cell layer thickness	• Loss of cellular polarity • High mitoses, esp. in upper layers • Loss of umbrella cell layer • Variable cell layer thickness • Discohesion, presence of necrosis
Low Power				
High Power				

Invasiveness

Carcinogenic routes



DIAGNOSI

Presentazione Clinica

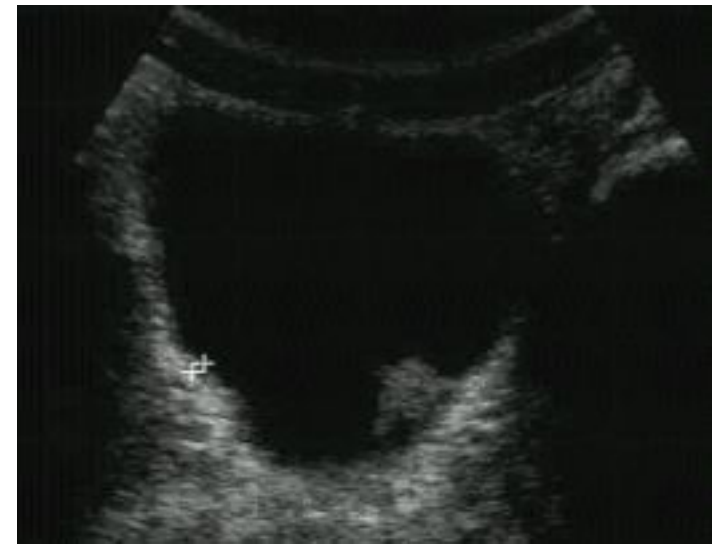
- Macroematuria monosintomatica (37-62%)
- Disturbi del basso tratto urinario (urgency-frequency)
- Dolore al fianco (neoplasia che infiltra il meato ureterale)

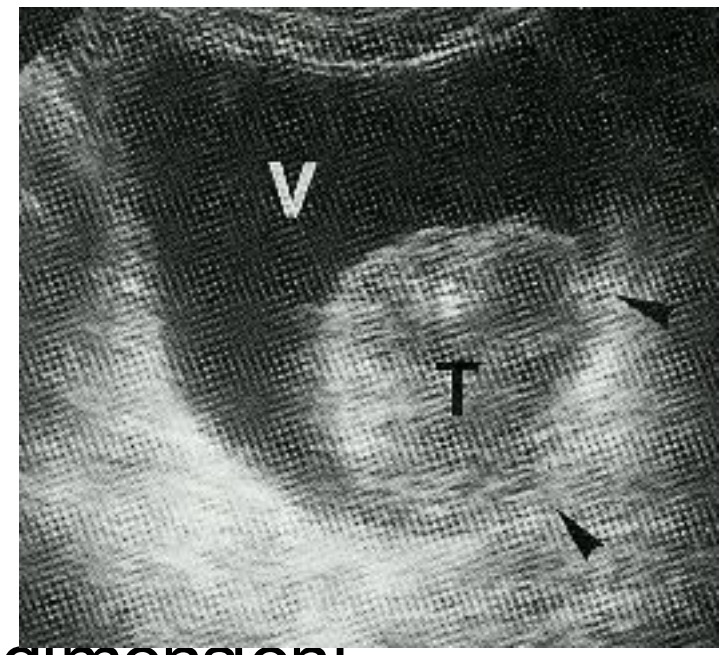
30 % di tutti i pazienti sono asintomatici

Imaging

- Ecografia
- Urethrocistoscopia
- Rx urografia
- TC
- RMN

ECOGRAFIA

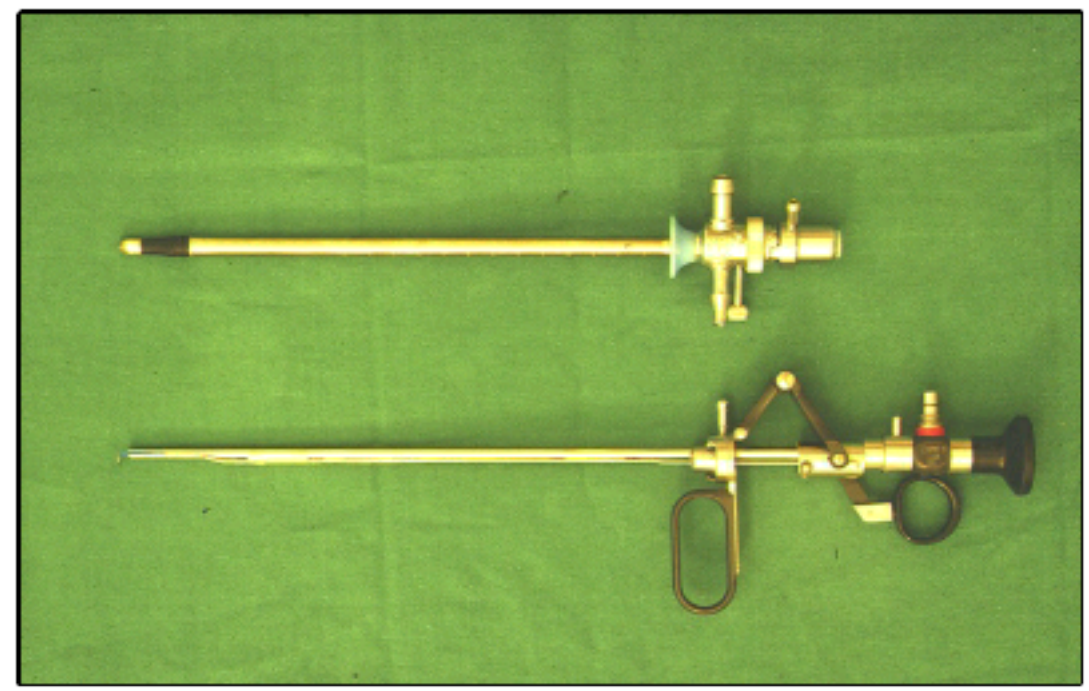


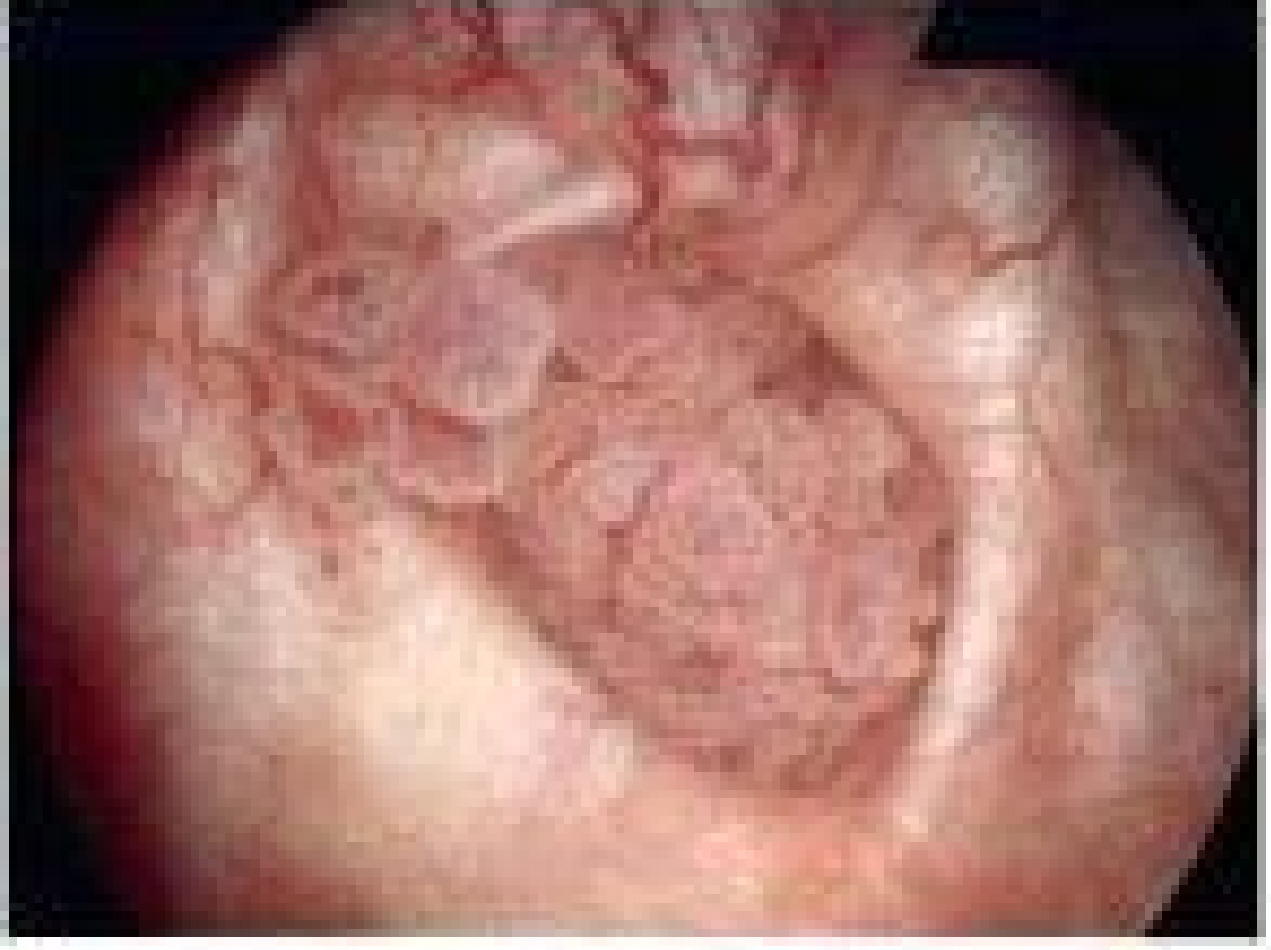


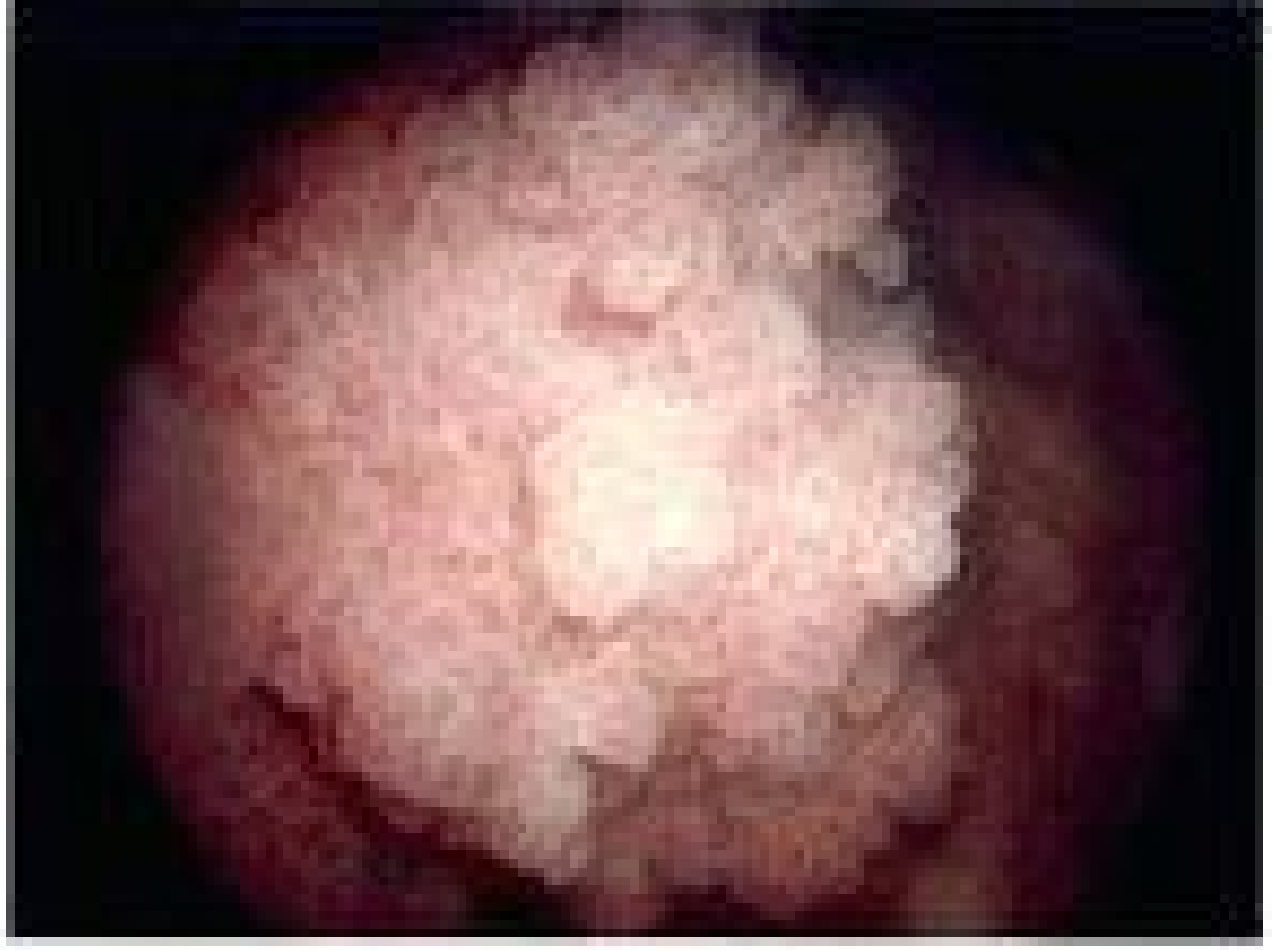
- Non invasiva
- Facile da eseguire
- Economica
- Bassa specificità (coaguli, prostata)
- Bassa sensibilità (in relazione a BMI, sede e dimensioni della neoformazione)

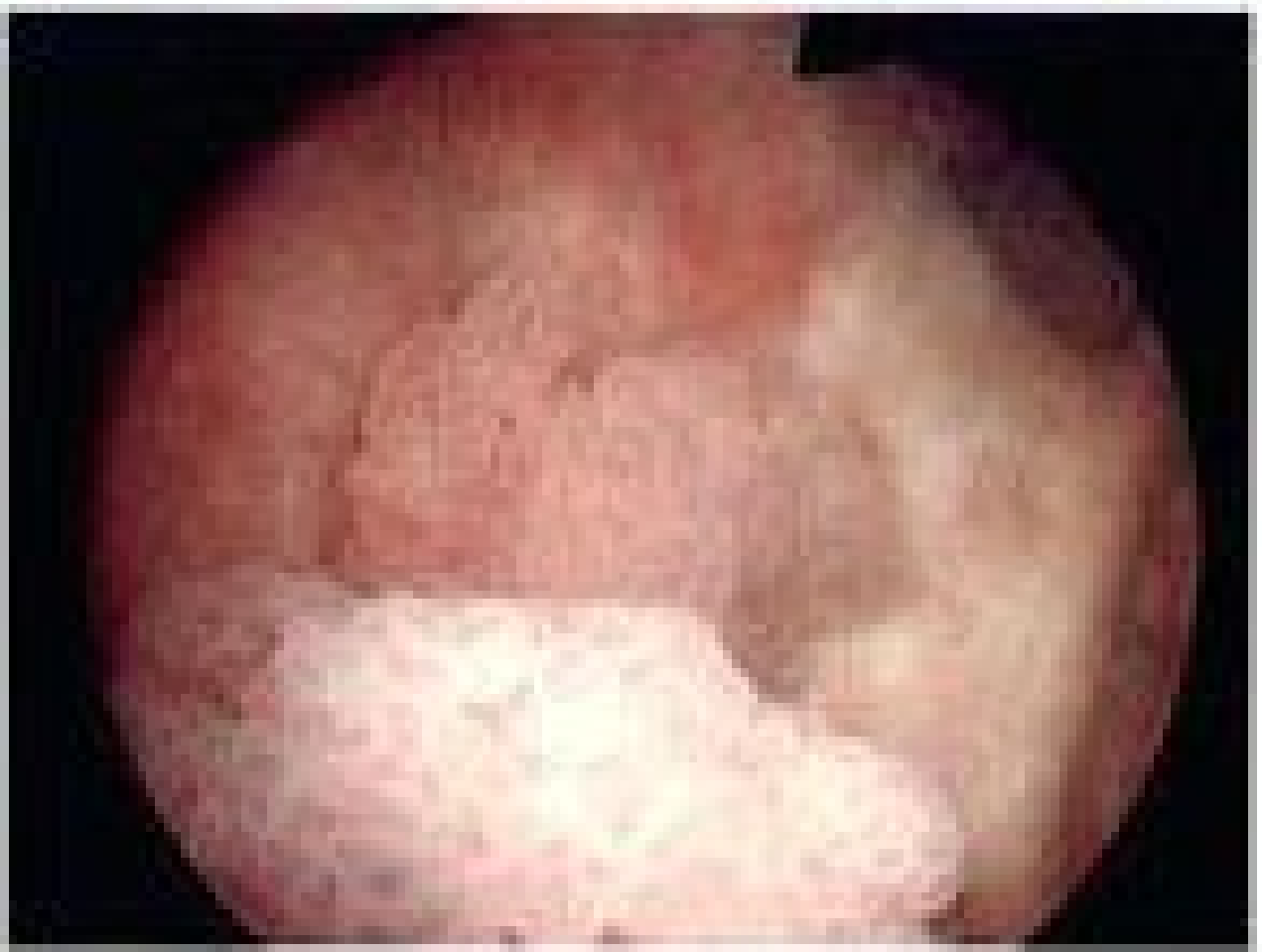
Urethrocistoscopia

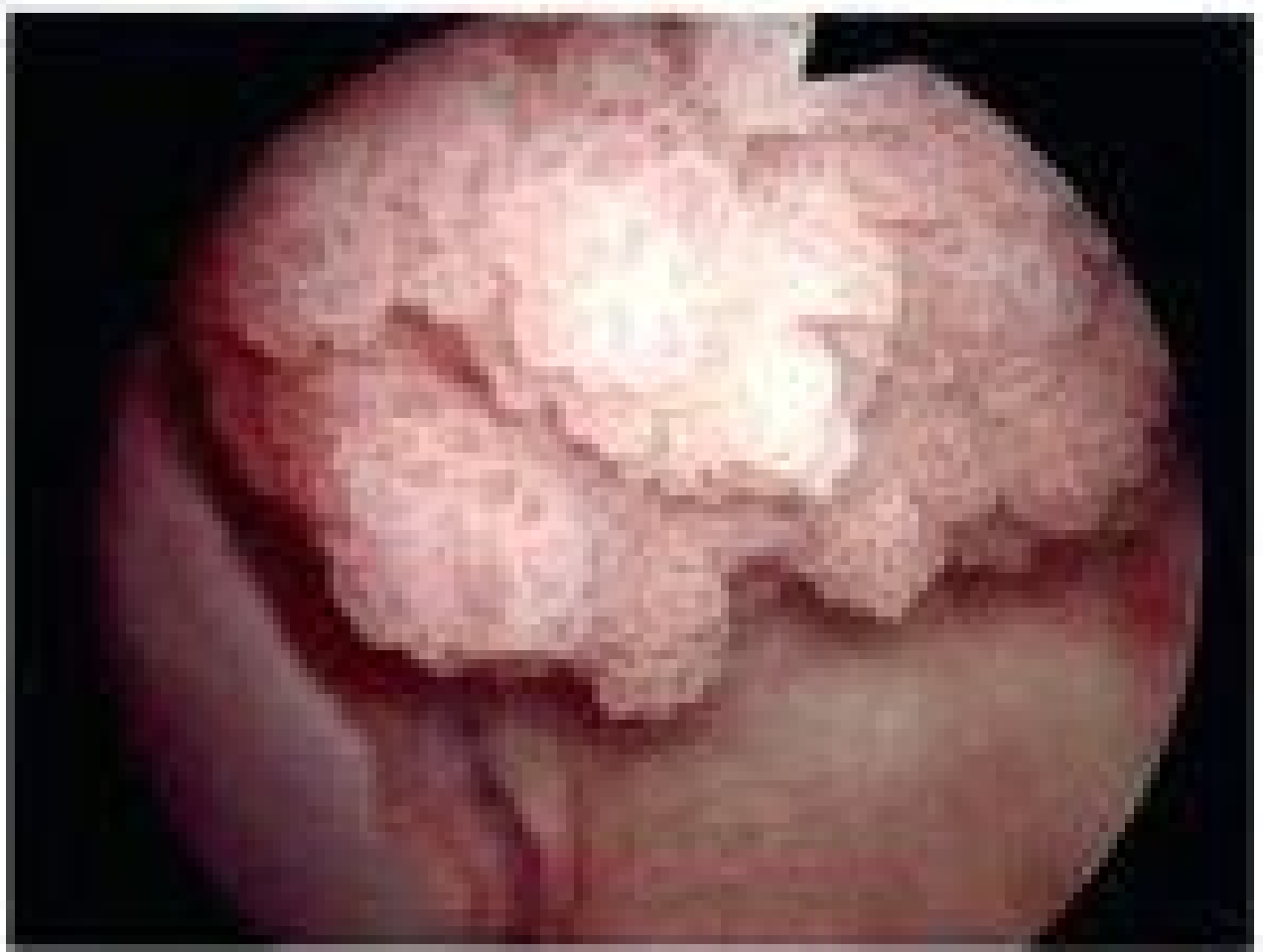
- Gold standard (diagnostic accuracy approximates 100%)
- Invasiva
- Limitazioni: CIS











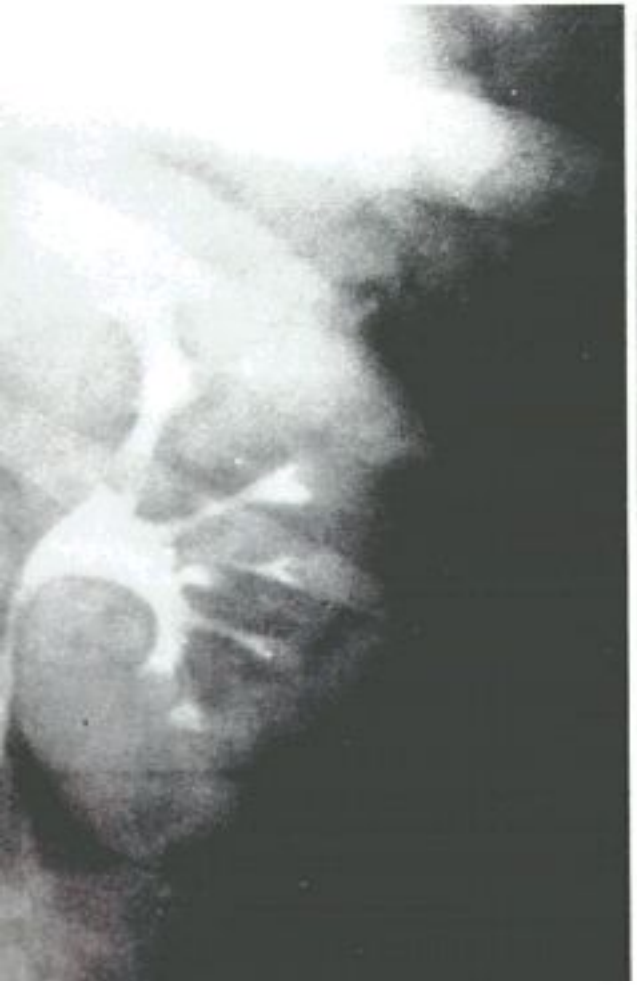
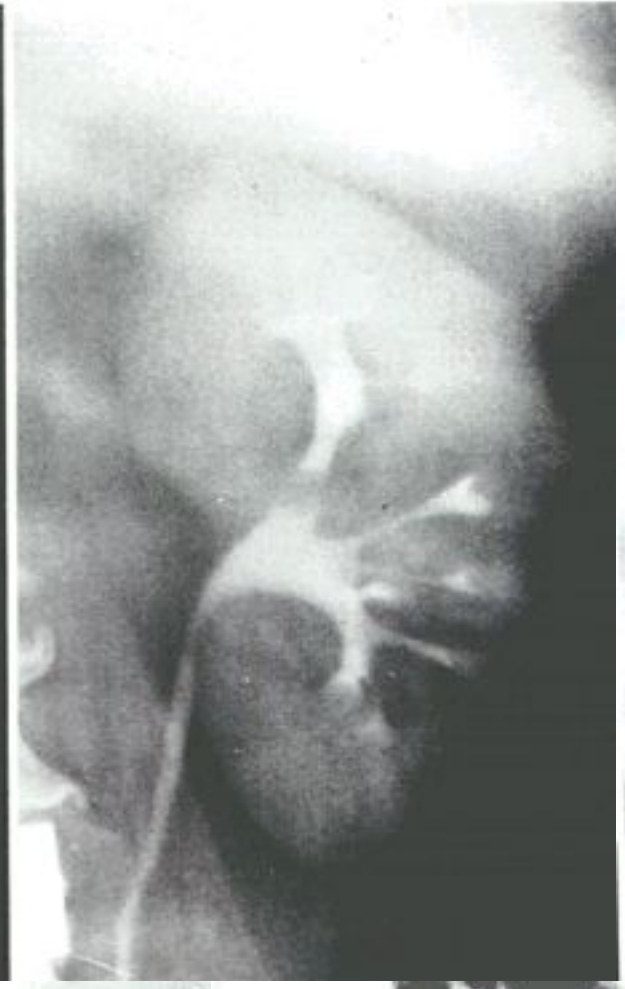
Indicazioni alla cistoscopia

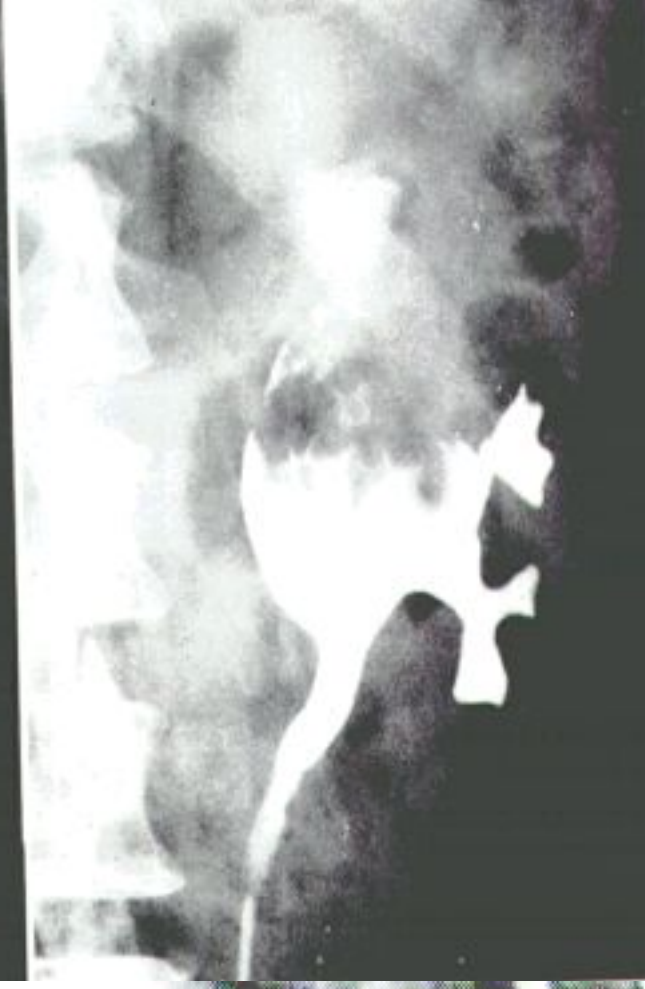
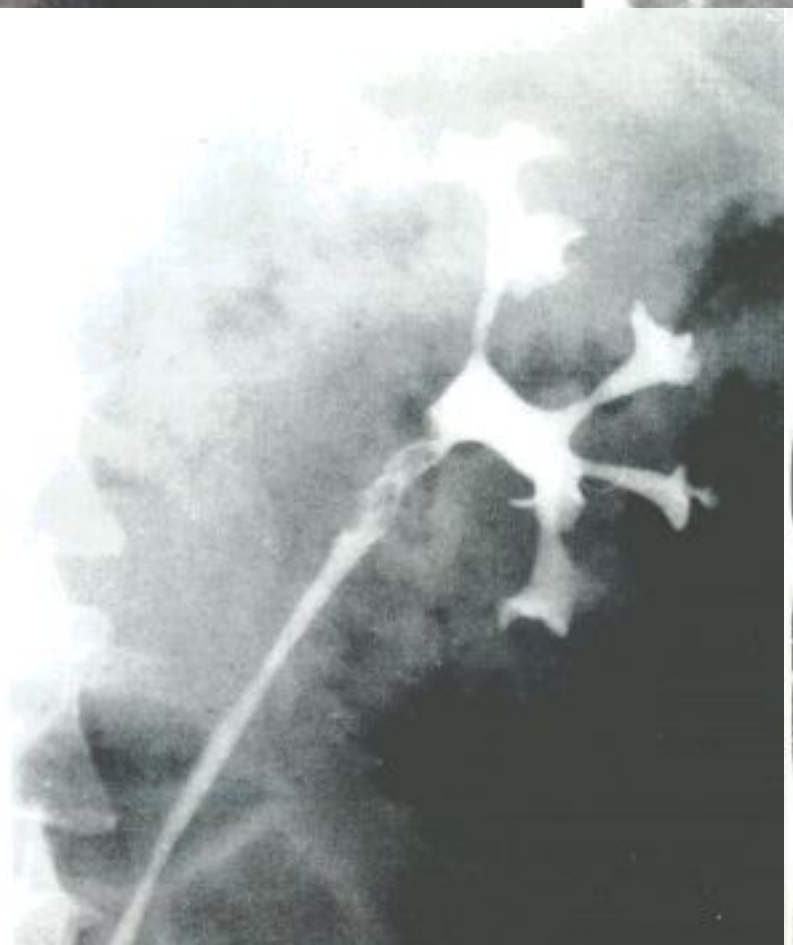
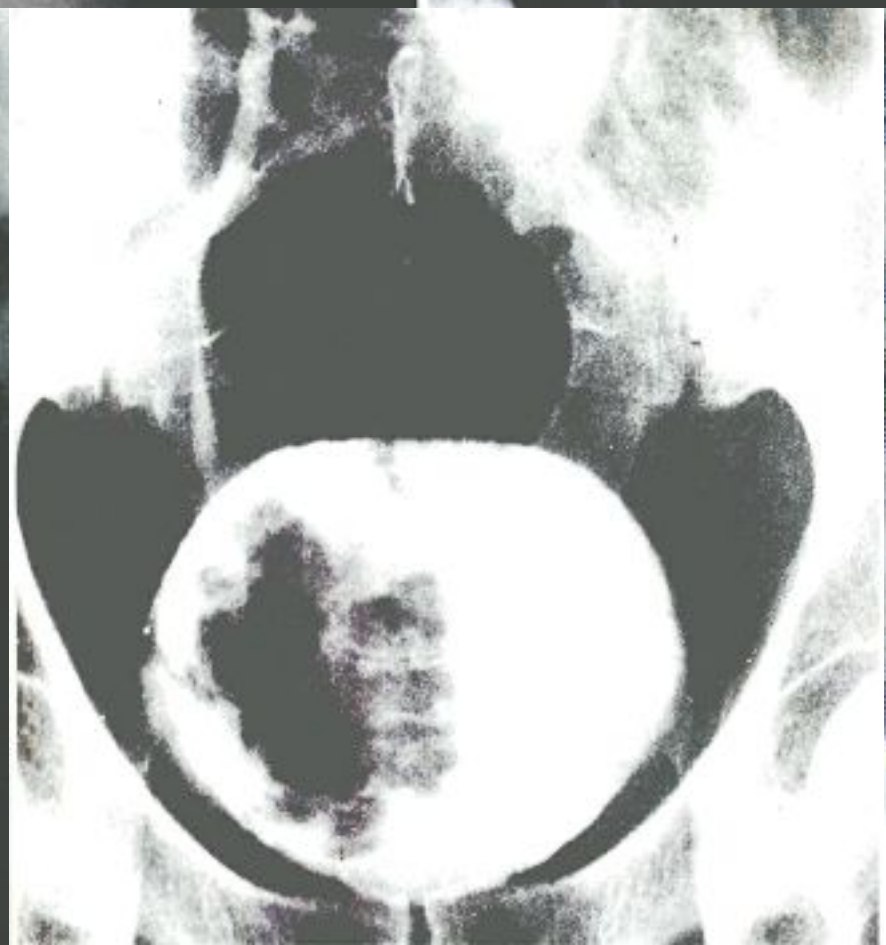
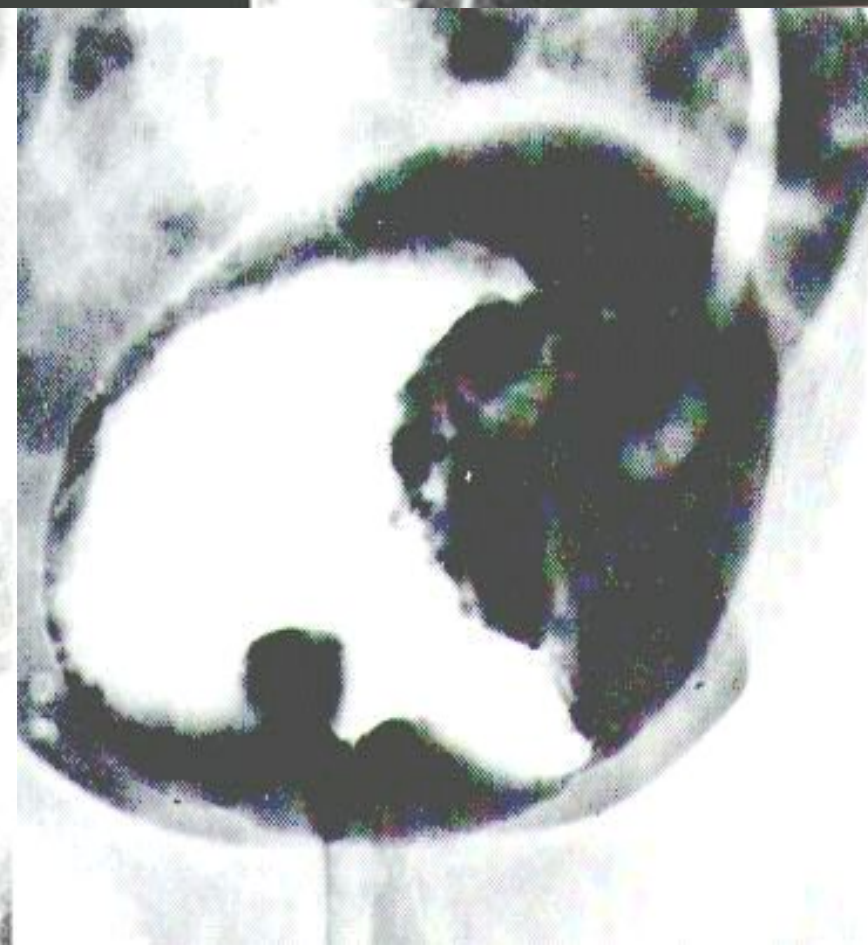
- Macroematuria
- Microematuria in pazienti con fattori di rischio
- Imaging sospetto
- Quadro clinico sospetto

“Non c’e correlazione tra l’entita della ematuria e la malattia sottesa”

Urografia

- Low sensitivity
- Bladder cancer is shown as indirect images (filling gap)
- Useful to study the upper urinary tract
- Useless for clinical staging

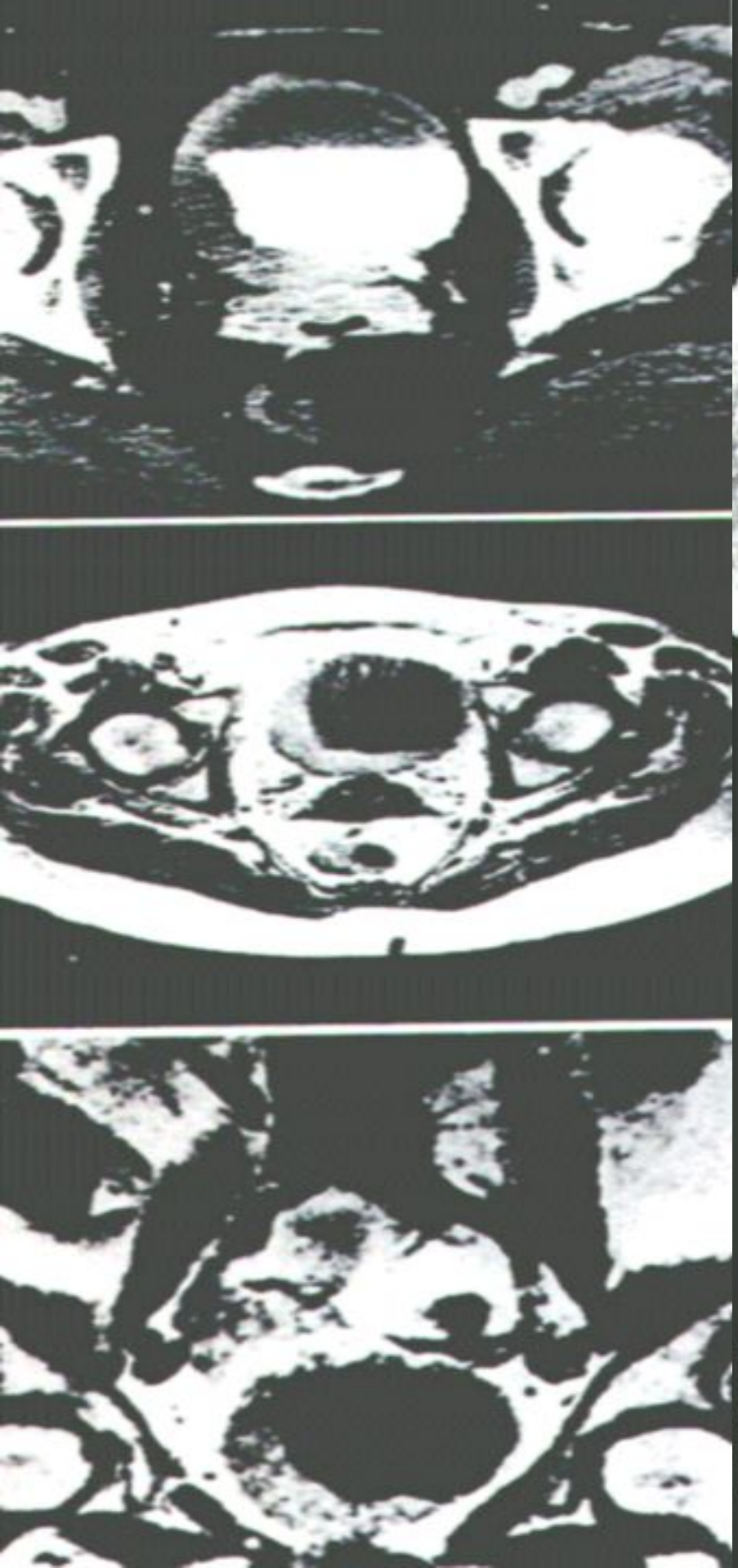
T.C. – R.M.N.

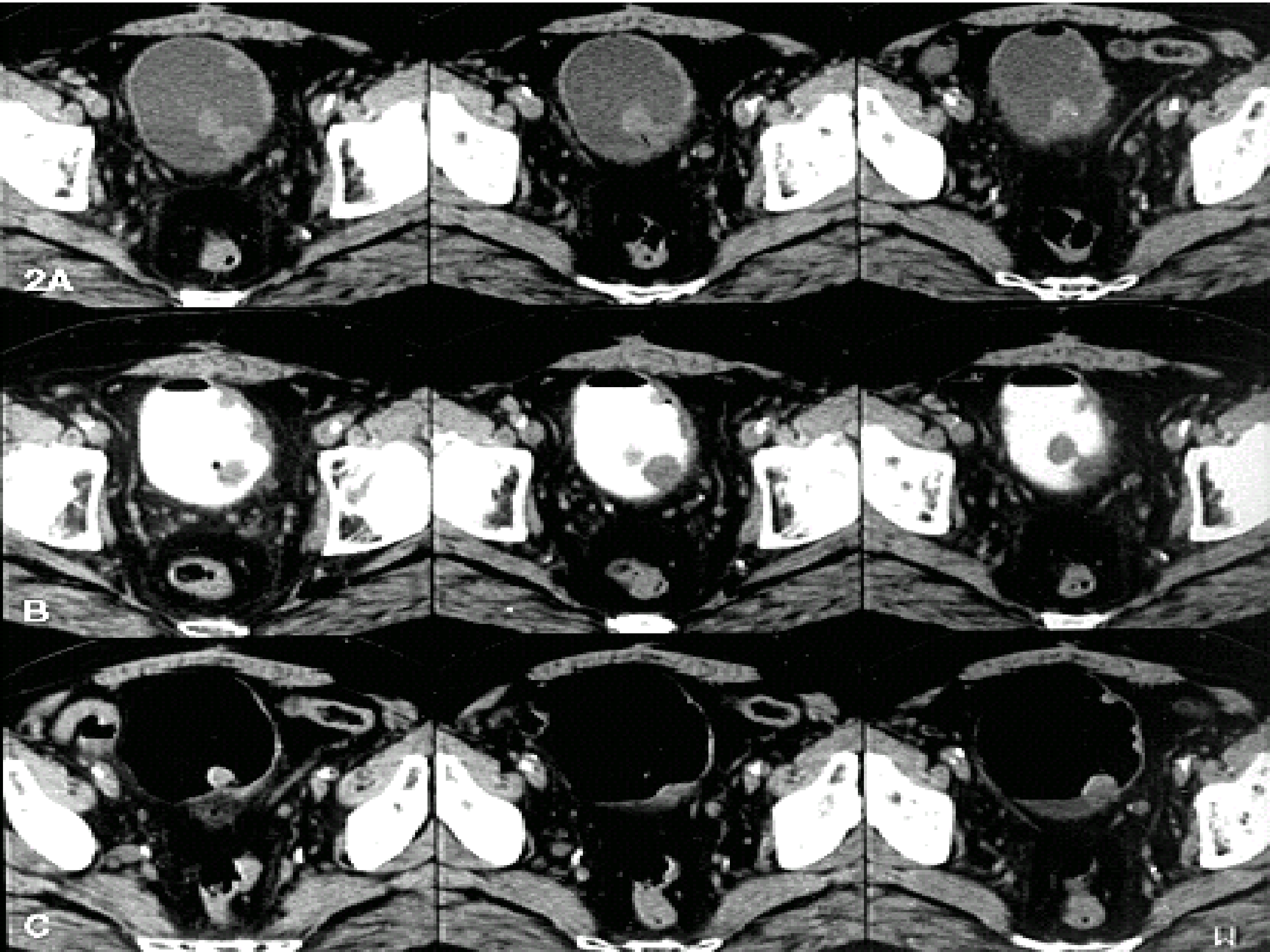
Useful for staging: help for the distinction between organ confined and non confined disease.

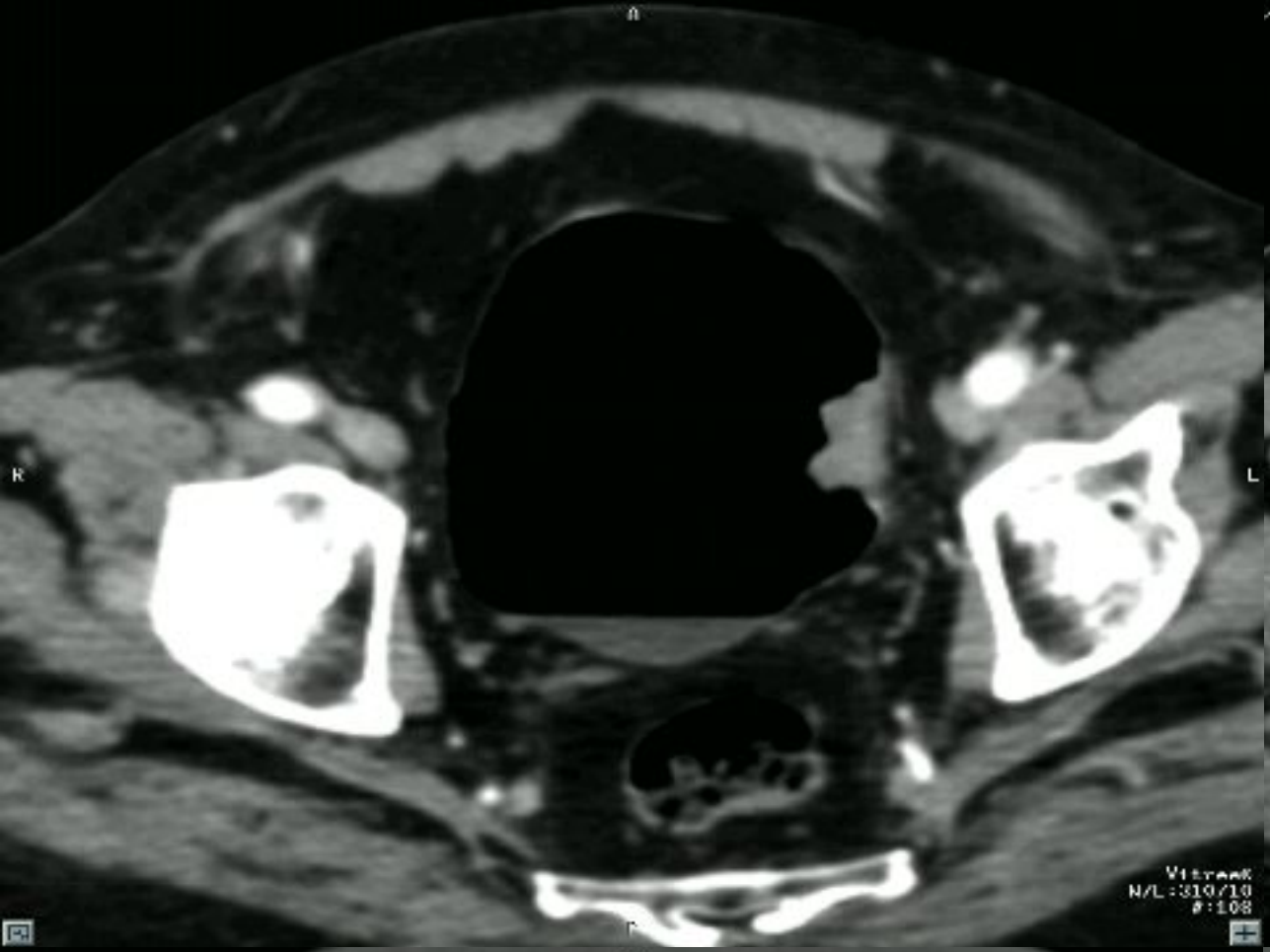
Lymph node information.

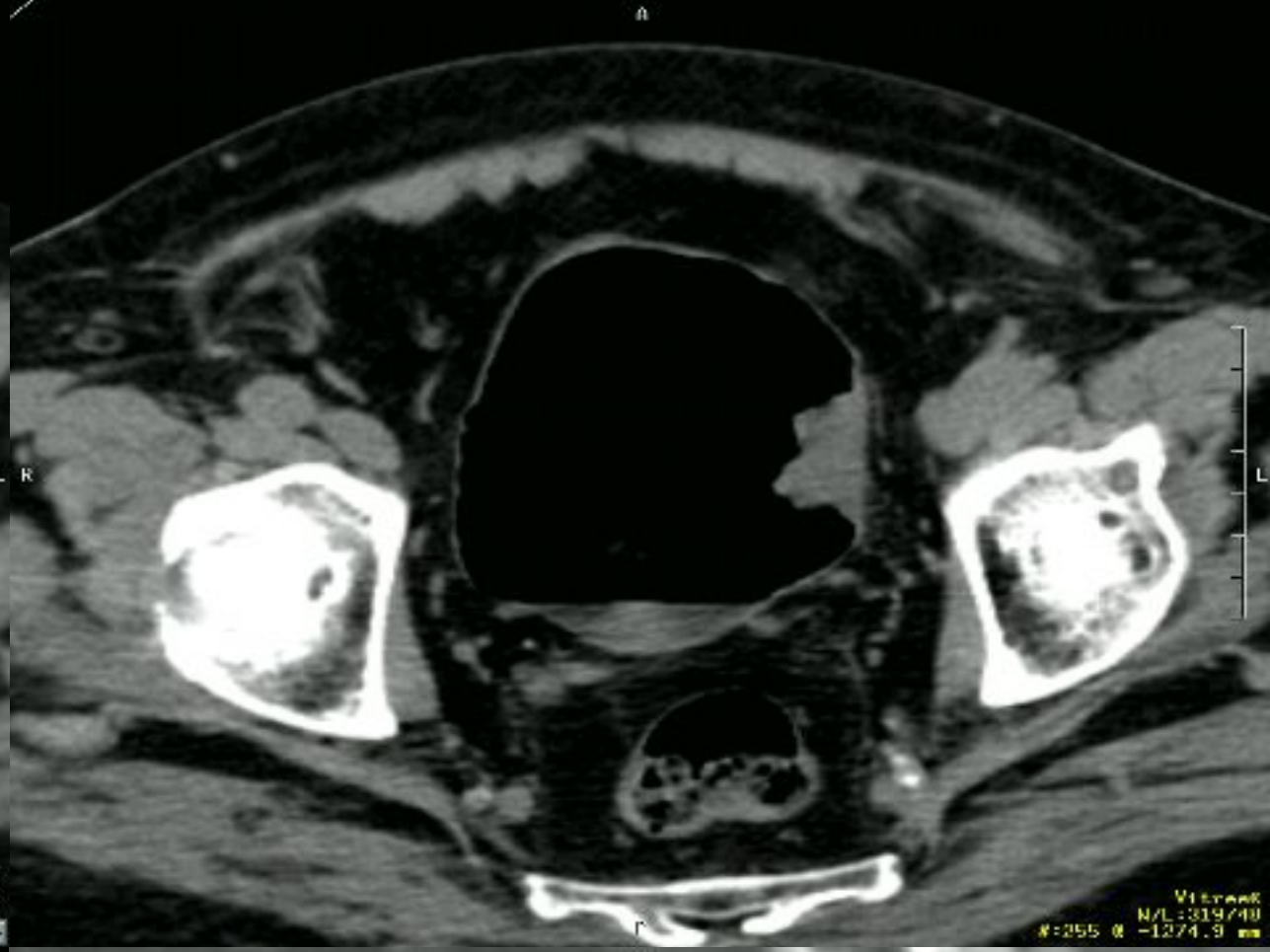
Metastatic spread.

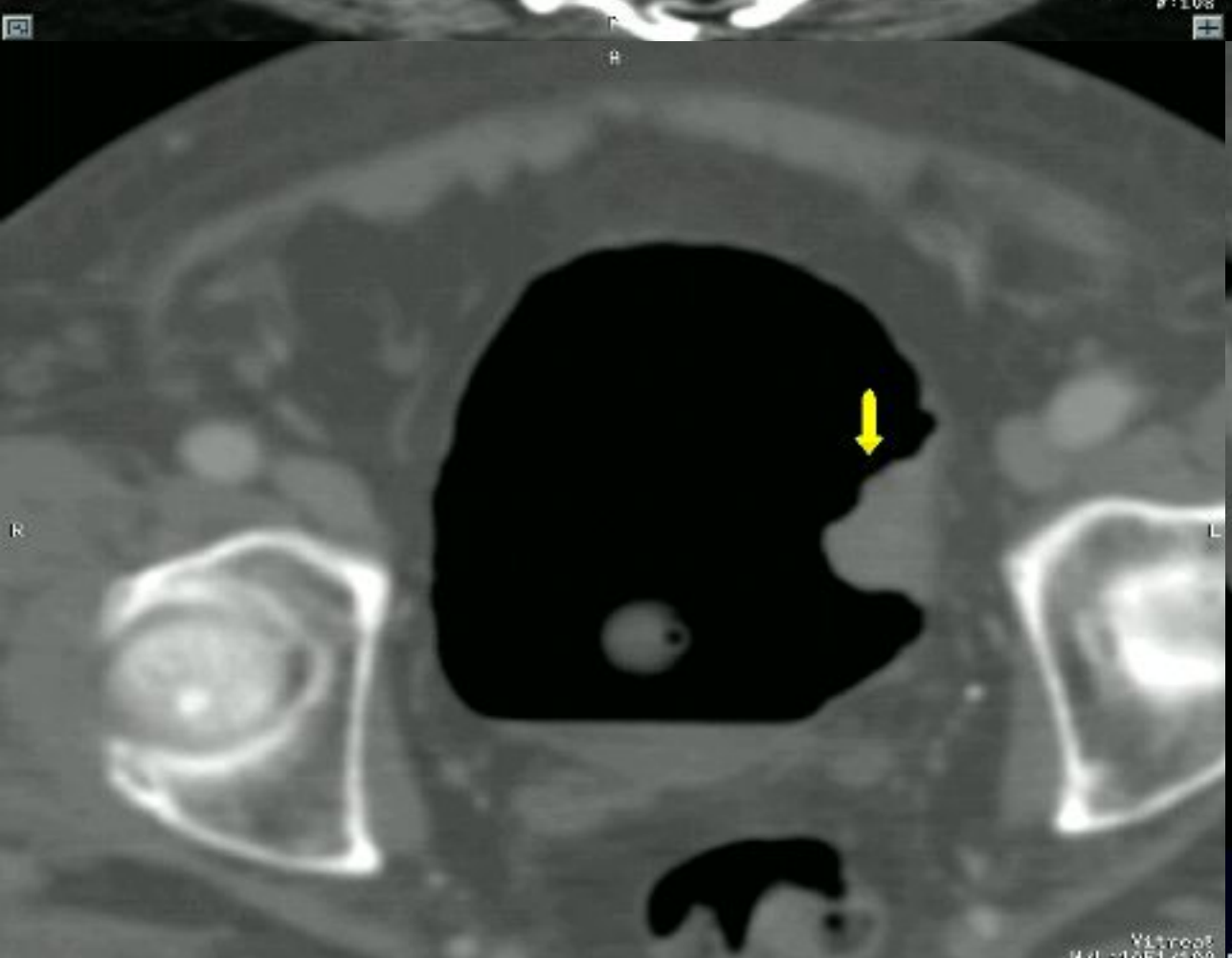
Both are unable to clearly separate between Ta T1 T2 T3a. Diagnostic accuracy: T.C. 40-85%; M.R.I. 50-90%.

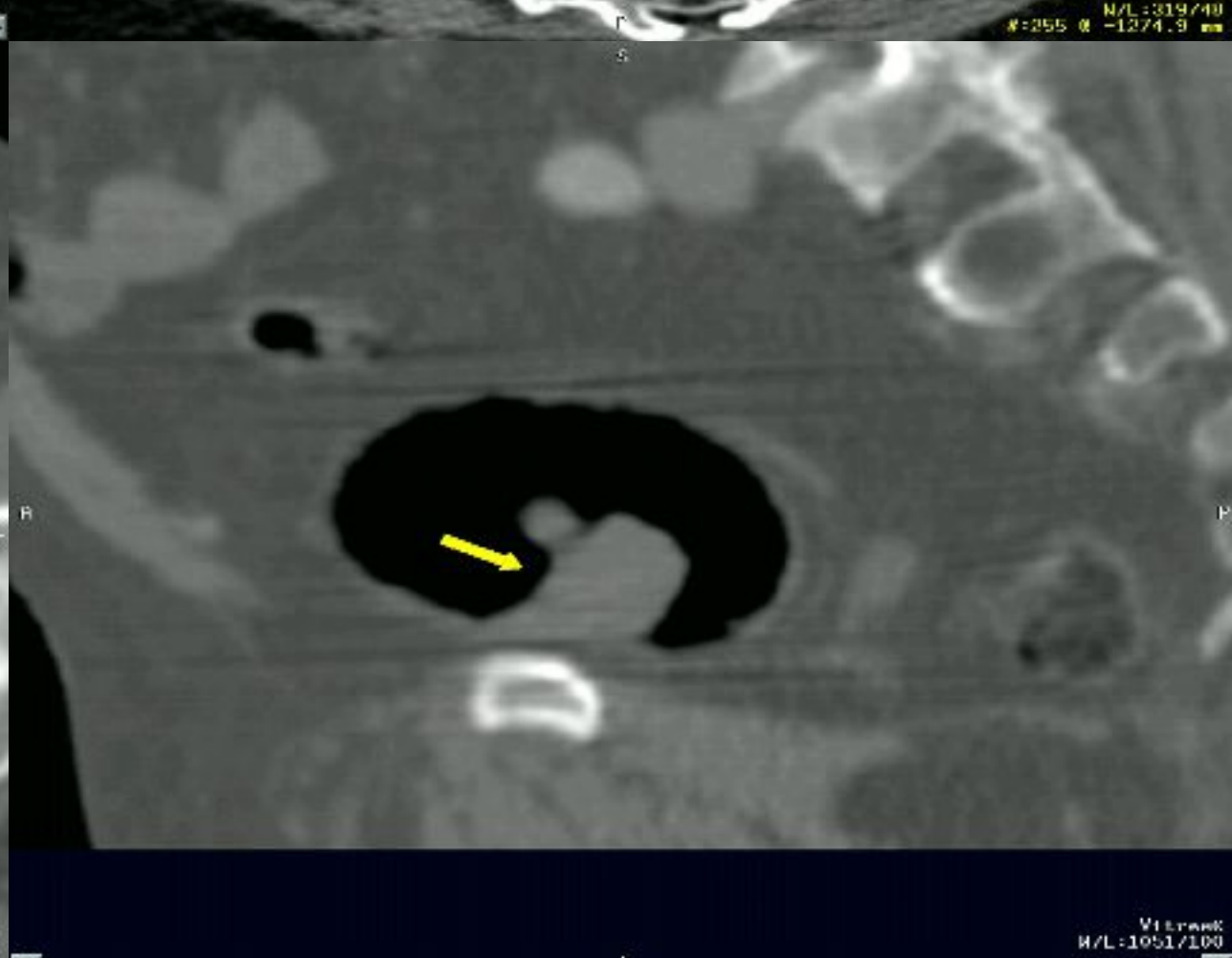


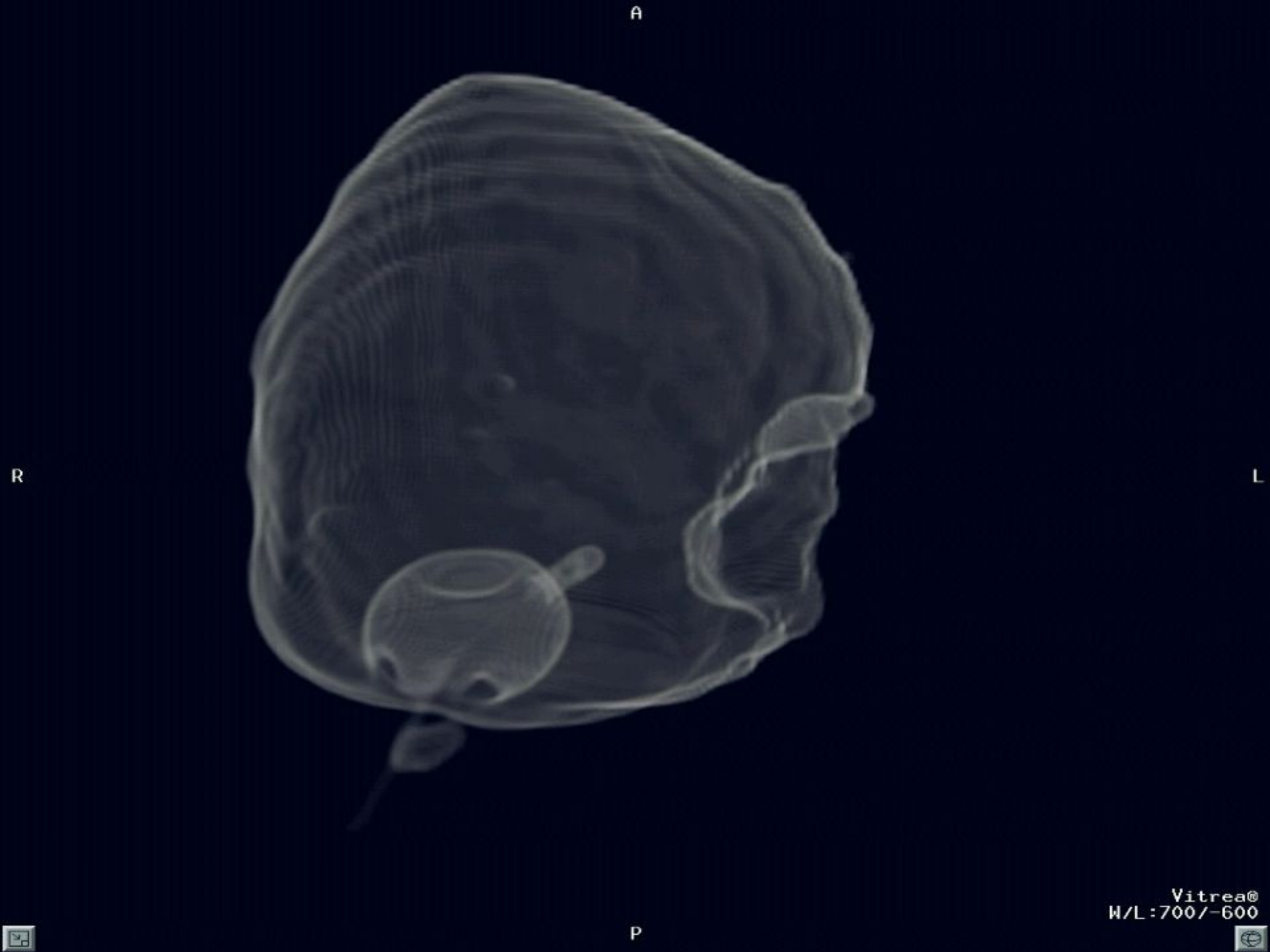

2A
B
C


A
R
L
P
VitreaK
W/L:319/10
#:108


A
R
L
P
VitreaK
W/L:319/40
#:255 @ -1274.9 mm


R
L
P
VitreaK


R
P
VitreaK
W/L:1051/100


A
R
L
P
Vitrea®
W/L:700/-600

Analisi di laboratorio

- Ematuria microscopica
- Citologia urinaria
- Marcatori urinari e molecolari

Microscopic hematuria

Stick urinario

A pseudo-peroxidation reaction will shift the colour of the filter so to form small spots which will aggregate depending on the amount of blood present in the sample. If positive will require a confermation through microscopy.

Esame microscopico del sedimento

Hematuria is confirmed by the presence of 3 or more RBC x field in the sediment of centrifuged urine after observation by means of optic MS at high resolution. Should be repeated if positive.

Citologia Urinaria

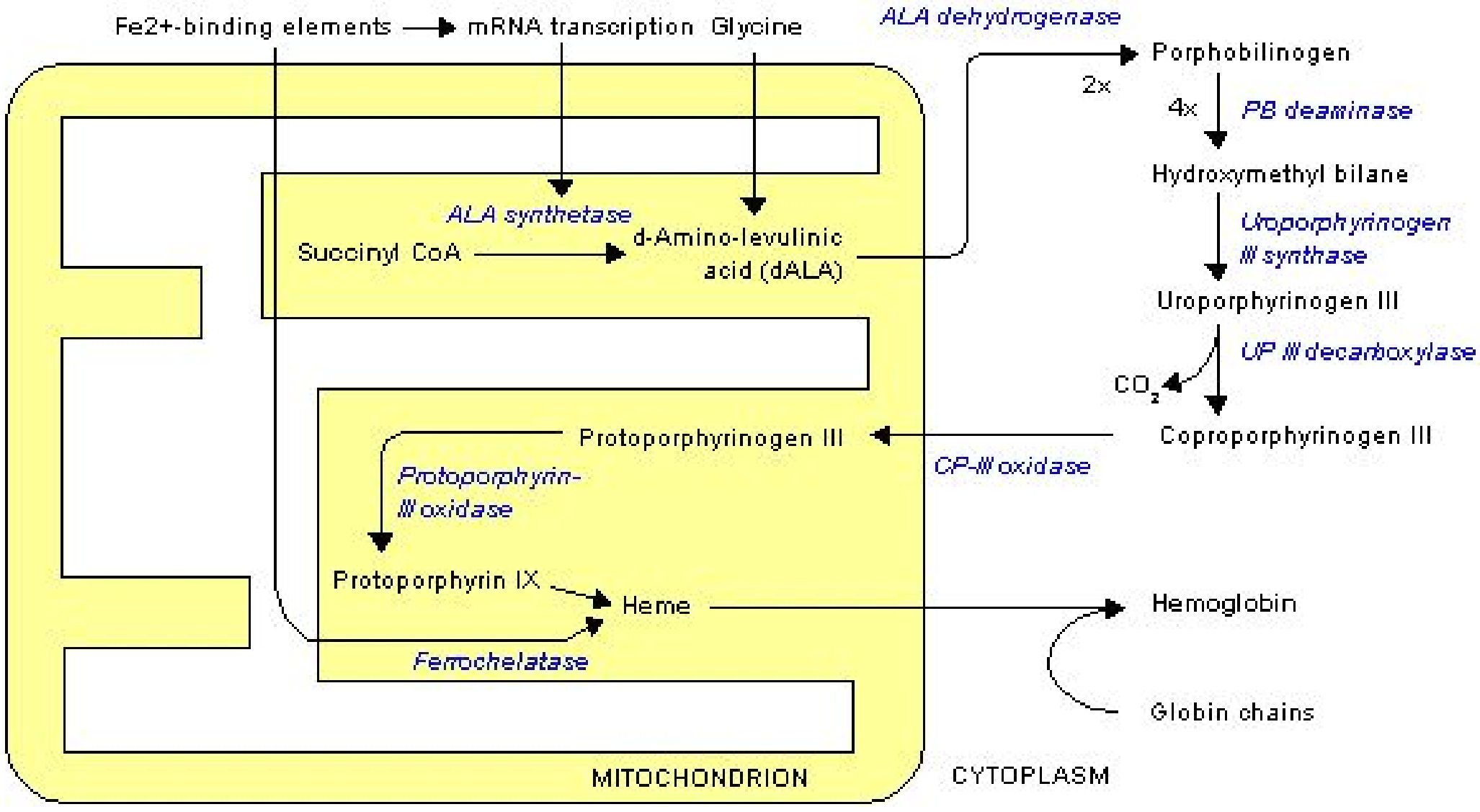
- Deve essere ripetuta per tre giorni consecutivi
- Alta specificità (>95%) e bassa sensibilità (30-50%)
- Riproducibilità interosservatore molto bassa

Urinary and molecular markers

- NMP-22 (nuclear mytotic protein, highly expressed in cells with high mytotic index): low specificity (40%) and sensitivity (65%)
- uCyt+ fluorescence immunology: sensitivity increases to 87% if combined to cytology
- FISH (in sity hybridation): specific as cytology, higher sensitivity

None of these exams is a substitute to cystoscopy

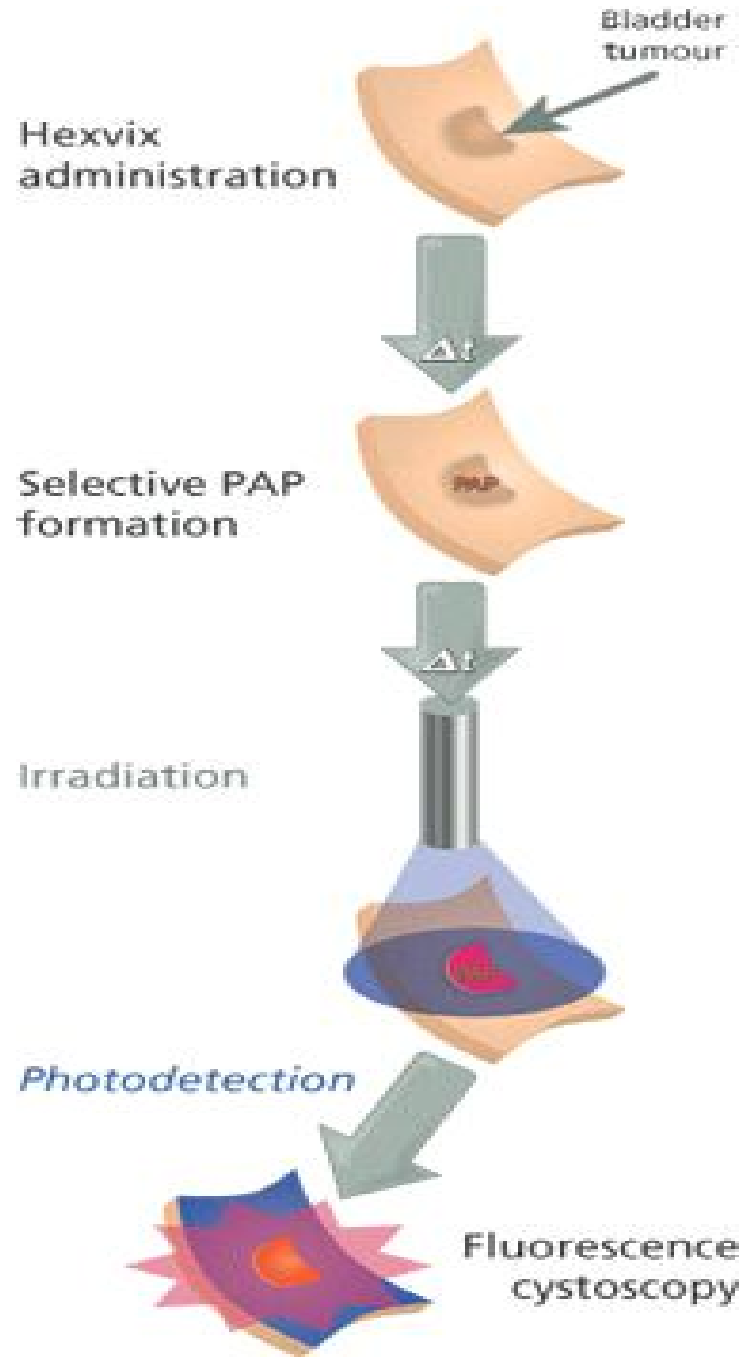
PDD: photodynamic diagnosis



In cancer cells the activity of Ferrochelatase is lower and Protoporphirin IX, which is fluorescent, will accumulate

PDD: technique

- ✓ Instillation of a photosensitizer into the bladder by means of a catheter.
- ✓ The chromophore will be absorbed selectively by cancer cells.
- ✓ After irradiation with a blue light, cancer cells will be detected because will produce a red fluorescence.

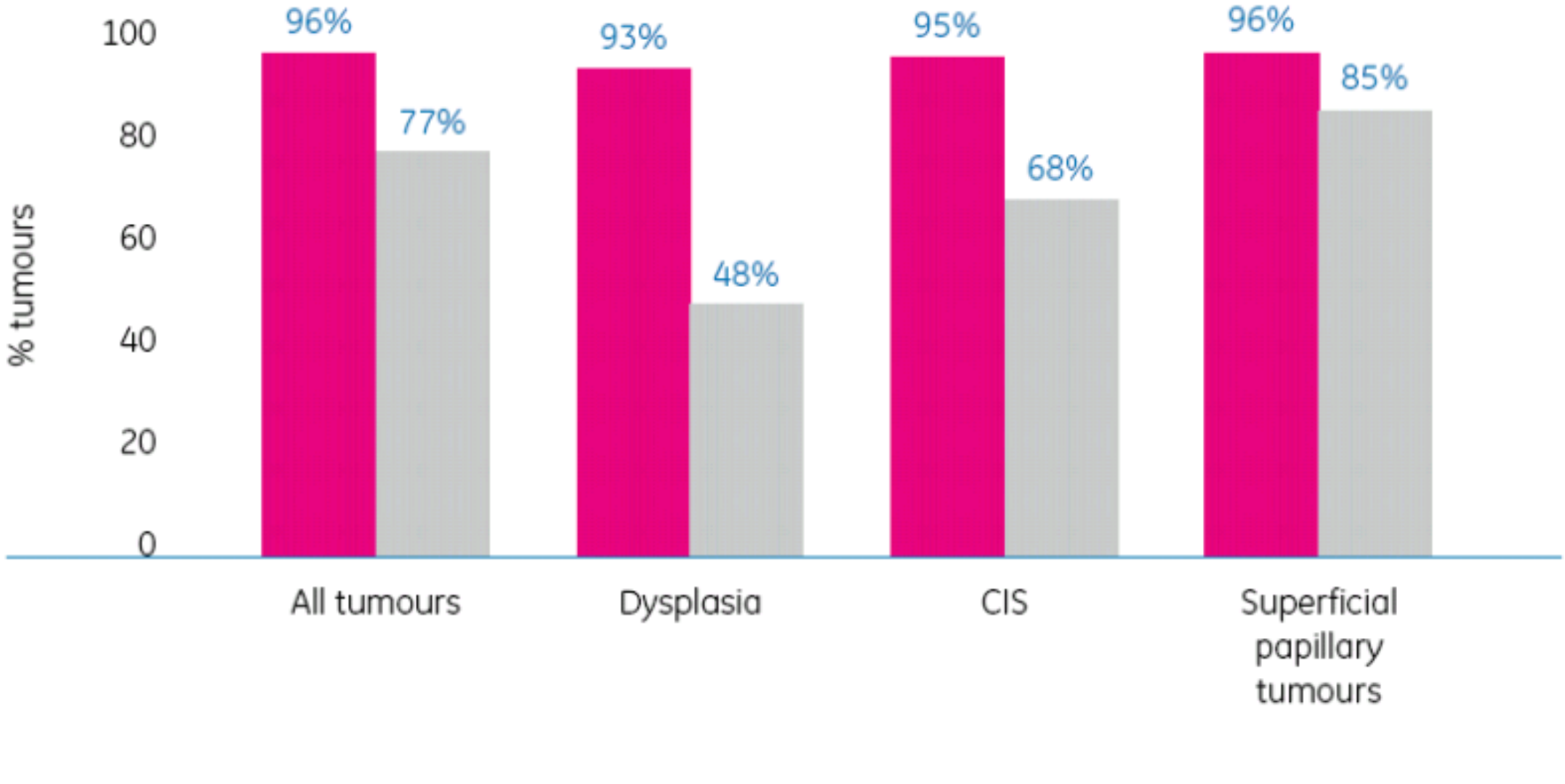


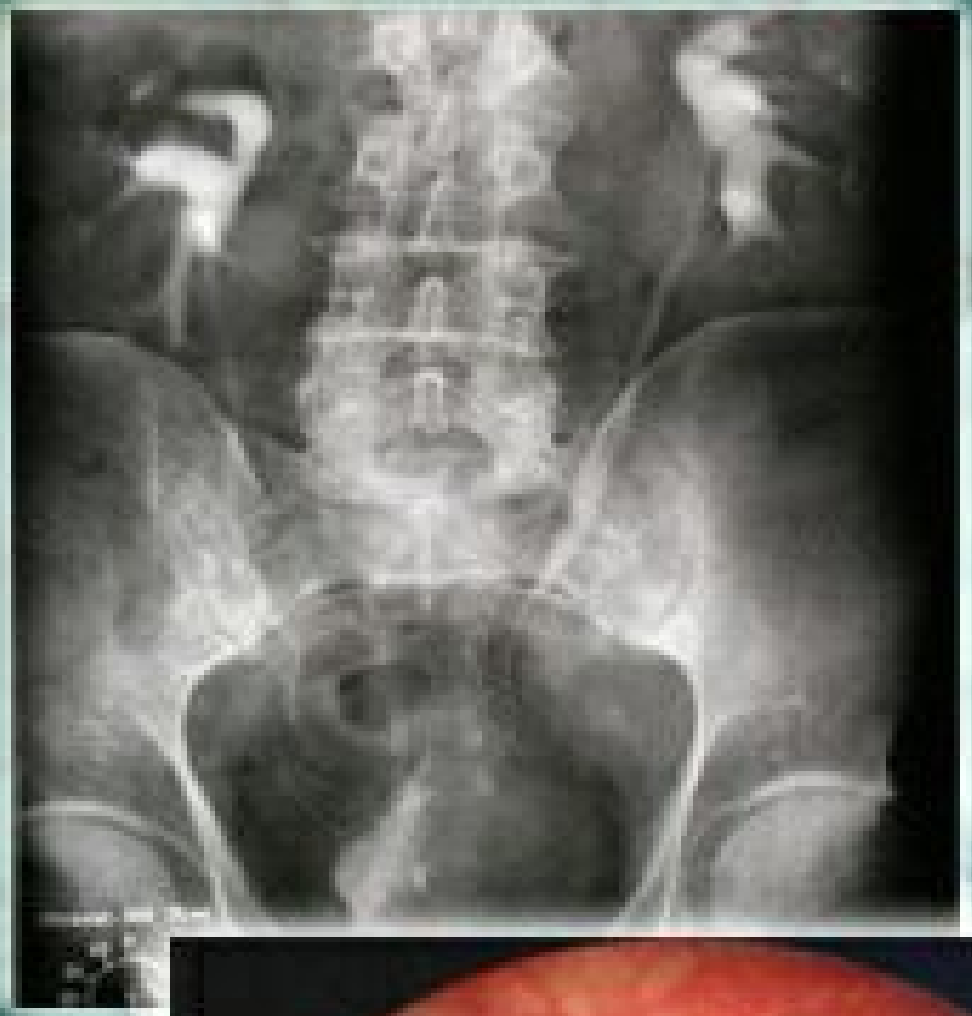
0022-5347/05/1743-0862/0
THE JOURNAL OF UROLOGY®

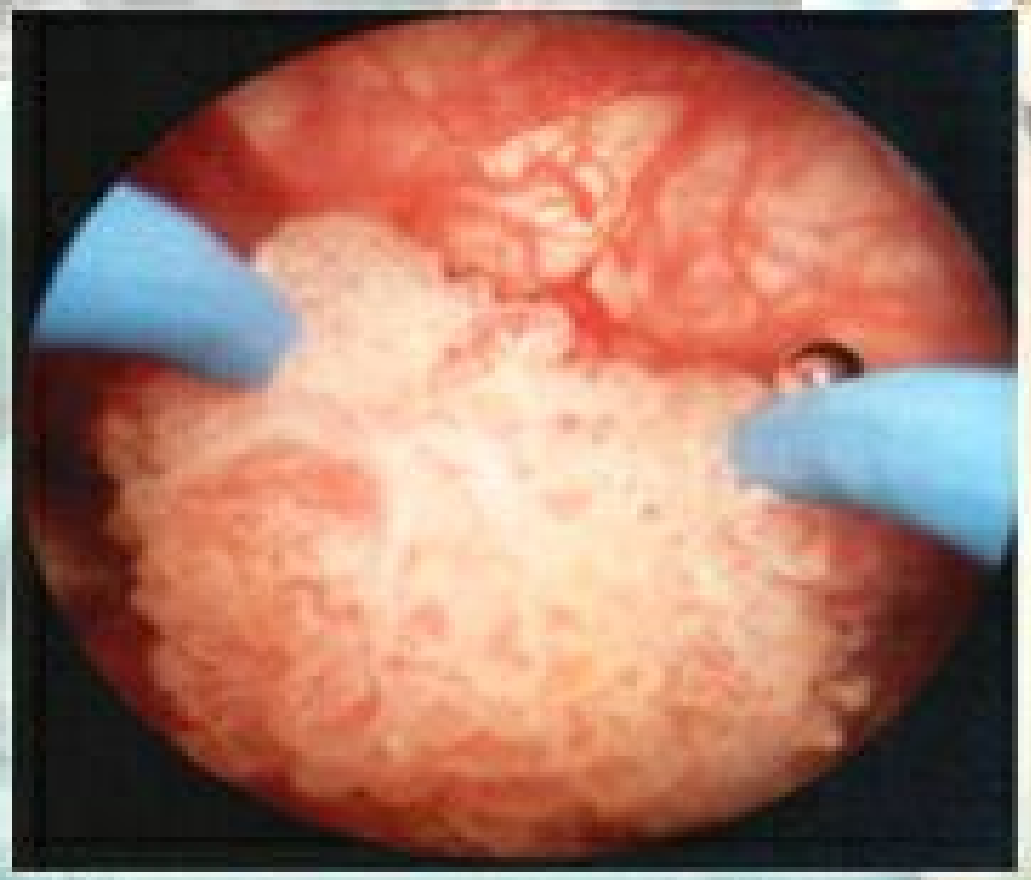
Vol. 174, 862–866, September 2005
Printed in U.S.A.
DOI: 10.1097/01.ju.0000169257.19841.2a

IMPROVED DETECTION AND TREATMENT OF BLADDER CANCER USING HEXAMINOLEVULINATE IMAGING: A PROSPECTIVE, PHASE III MULTICENTER STUDY

DIETER JOCHAM,* FRED WITJES, SIGRID WAGNER, BRAM ZEYLEMAKER, JEROEN VAN MOORSELAAR, MARC-OLIVER GRIMM, ROLF MUSCHTER, GRALF POPKEN, FRANK KÖNIG, RUTH KNÜCHEL AND KARL-HEINZ KURTH







Work out terapeutico

Diagnosi di neoformazione uroteliale

↓

T.U.R.

↓

Nessun trattamento

↓

Terapia endovescicale

- MMC
- Epirubicin
- BCG

↓

Cistectomia radicale e completamento dello staging

Fattori Predittivi

Recidiva e progressione

- 3 Stage
- 3 Grade
- 3 Tumor size
- 3 N° of lesions at diagnosis
- 3 Early recurrence at follow-up
- 3 cis

Sopravvivenza

- 3 Stage

The EORTC tables

Factor	Score	
	Recurrence	Progression
Number of tumors		
Single	0	0
2–7	3	3
≥8	6	3
Tumor size		
<3 cm	0	0
≥3 cm	3	3
Prior recurrence rate		
Primary	0	0
≤1 per year	2	2
>1 per year	4	2
T classification		
Ta	0	0
T1	1	4
Carcinoma in situ		
No	0	0
Yes	1	6
Grade		
G1	0	0
G2	1	0
G3	2	5
Total score	0–17	0–23

Recurrence and Progression Risk

Total EORTC score	Probabilities (95% CI)	
	At 1 year (%)	At 5 years (%)
Recurrence		
0	15 (10–19)	31 (24–37)
1–4	24 (21–26)	46 (42–49)
5–9	38 (35–41)	62 (58–65)
10–17	61 (55–67)	78 (73–84)
Progression		
0	0.2 (0–0.7)	0.8 (0–1.7)
2–6	1.0 (0.4–1.6)	6 (5–8)
7–13	5 (4–7)	17 (14–20)
14–23	17 (10–24)	45 (35–55)

*According to total EORTC bladder cancer risk score. Reprinted from Sylvester, R. J. *et al.* Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur. Urol.* **49**, 466–477 (2006), with permission from Elsevier. Abbreviation: EORTC, European Organization for Research and Treatment of Cancer.

Follow-up

Basso Rischio

- Cystoscopy at 3 months,
- If negative the next at 9 months
- If negative once a year for the next 5 years

Rischio Intermedio

- Cystoscopy every 3 months for 2 years, every 6 months the third year, yearly thereafter.
- Contrast enhanced imaging within the first year after TUR

Alto Rischio

- Cystoscopy every 3 months for 2 years, every 4 months the third year, every 6 months the fourth and fifth years and yearly thereafter.
- Cytology at every cystocopic check
- Contrast enhanced imaging once a year.

Della totalità dei pazienti con malattia muscolo invasiva, il 67-92 % avranno stadio ≥ T2 già al momento della presentazione

Kay and Lange, 1982,
Hopkins et al, 1983,
Vaidya et al, 2001,
Messing, 2001

Cistectomia Radicale

Indicazioni

Bladder cancer:

- High risk non muscle invasive disease characterized by:
  - Carcinoma in situ
  - Early recurrence
  - No responce to intravesical treatment
- Muscle invasive disease (T2)

Other indication (simple cystectomy)

- Neurogenic bladder
- Interstitial cystitis

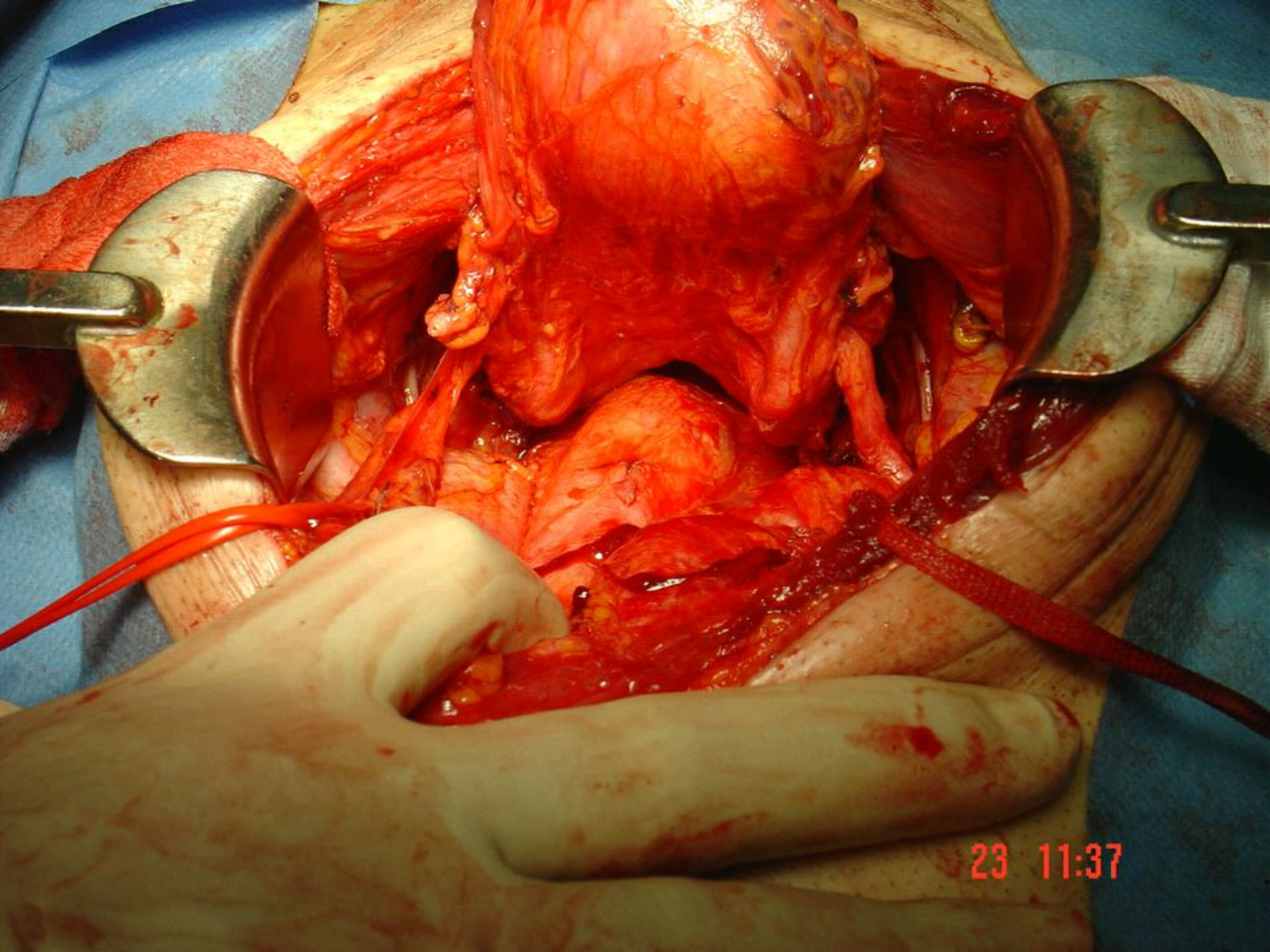
Steps chirurgici

Bladder removal

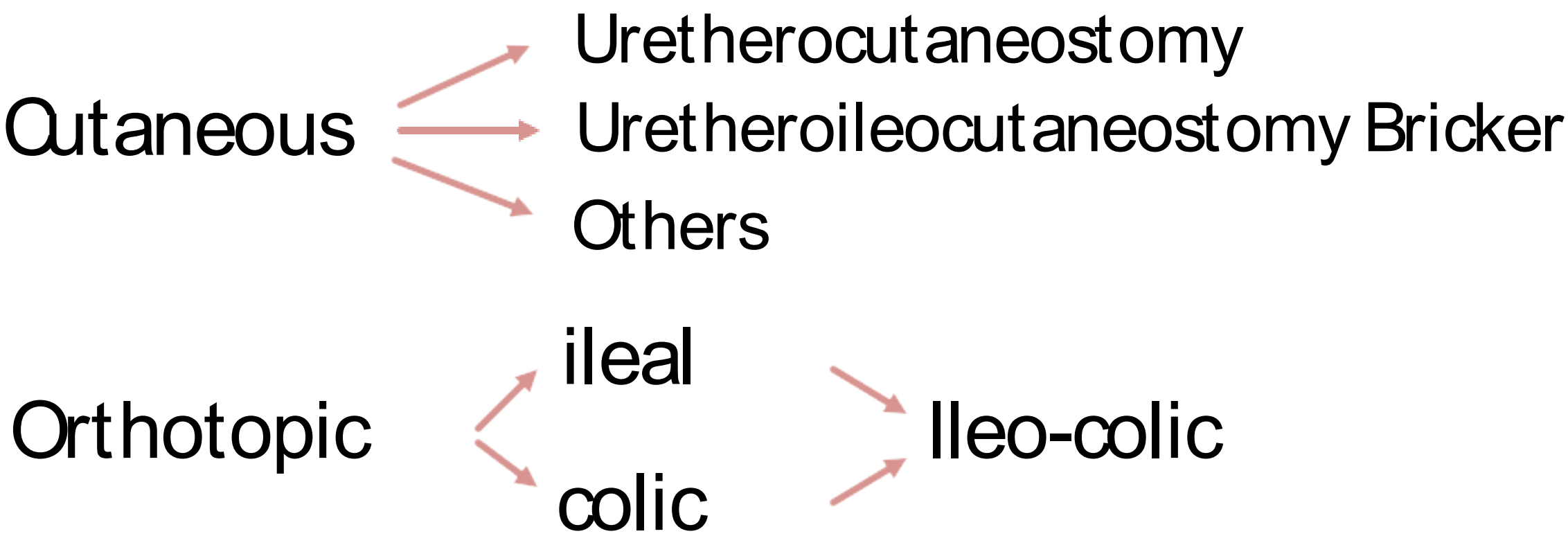
- Male: removal of bladder, prostate with seminal vesicles, extended pelvic lymph node dissection
- Female: anterior exenteratio and extended pelvic lymph node dissection

Reconstructive phase

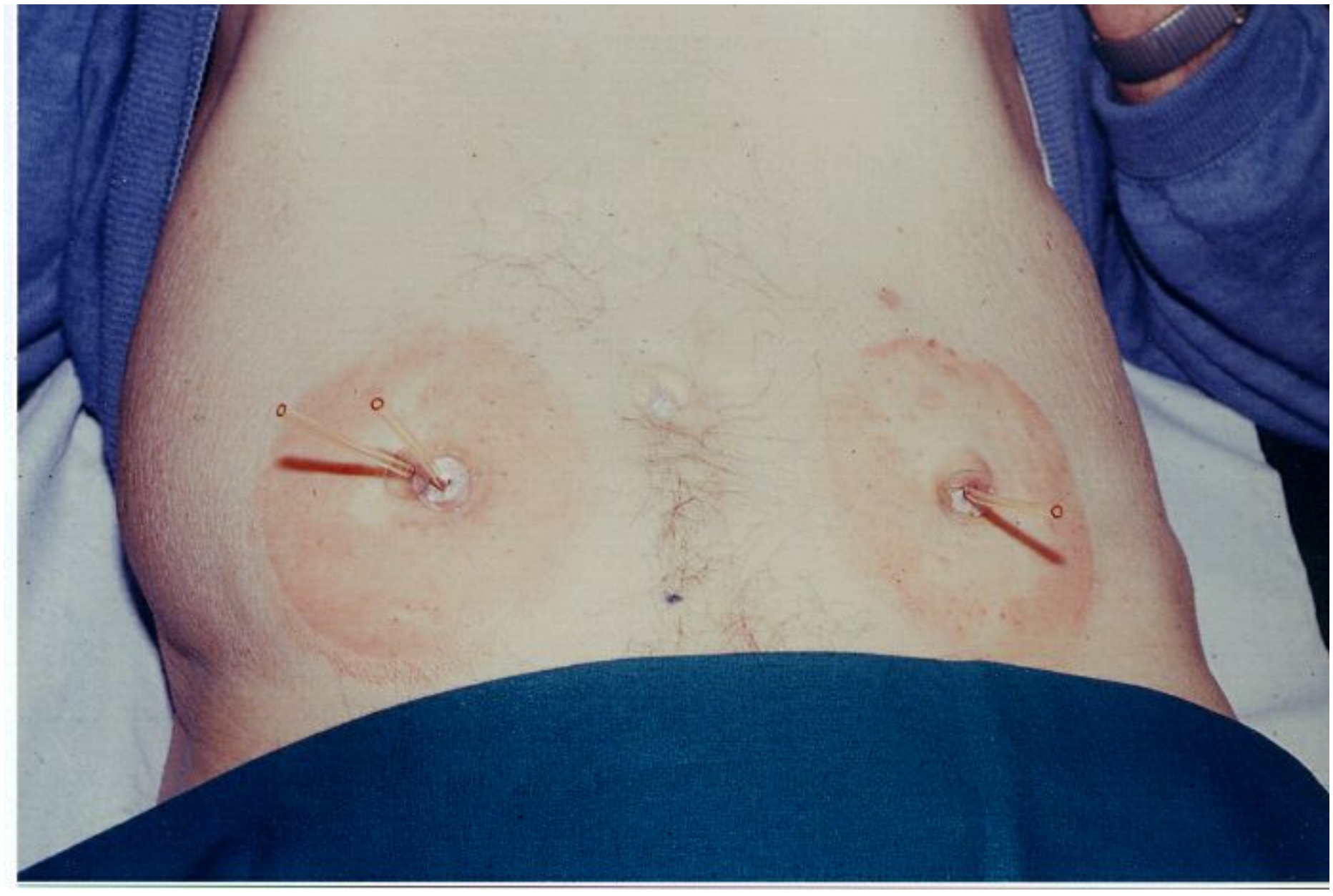
- Urinary diversion


23 11:37

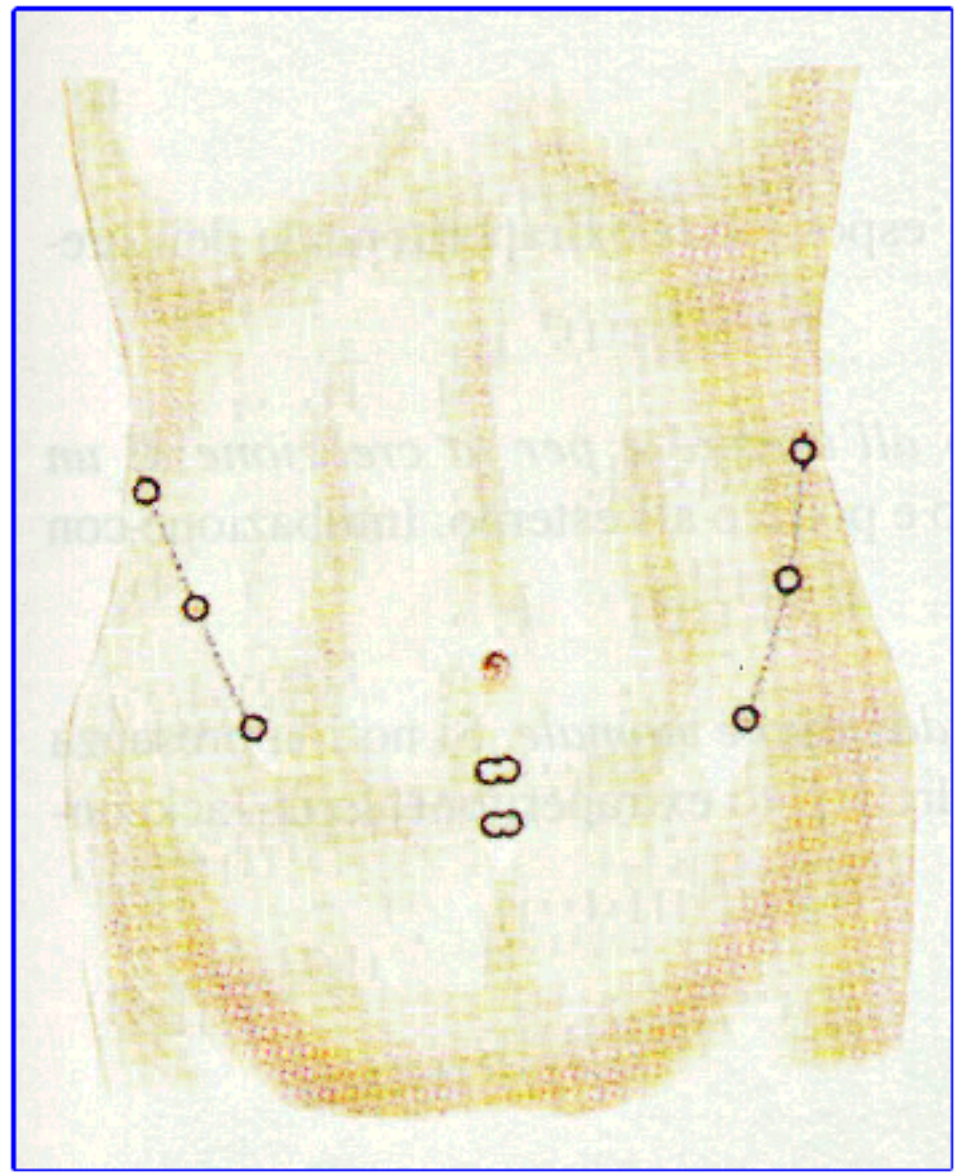
Tipi di derivazioni urinarie



Ureterocutaneostomia



Ureterocutaneostomia

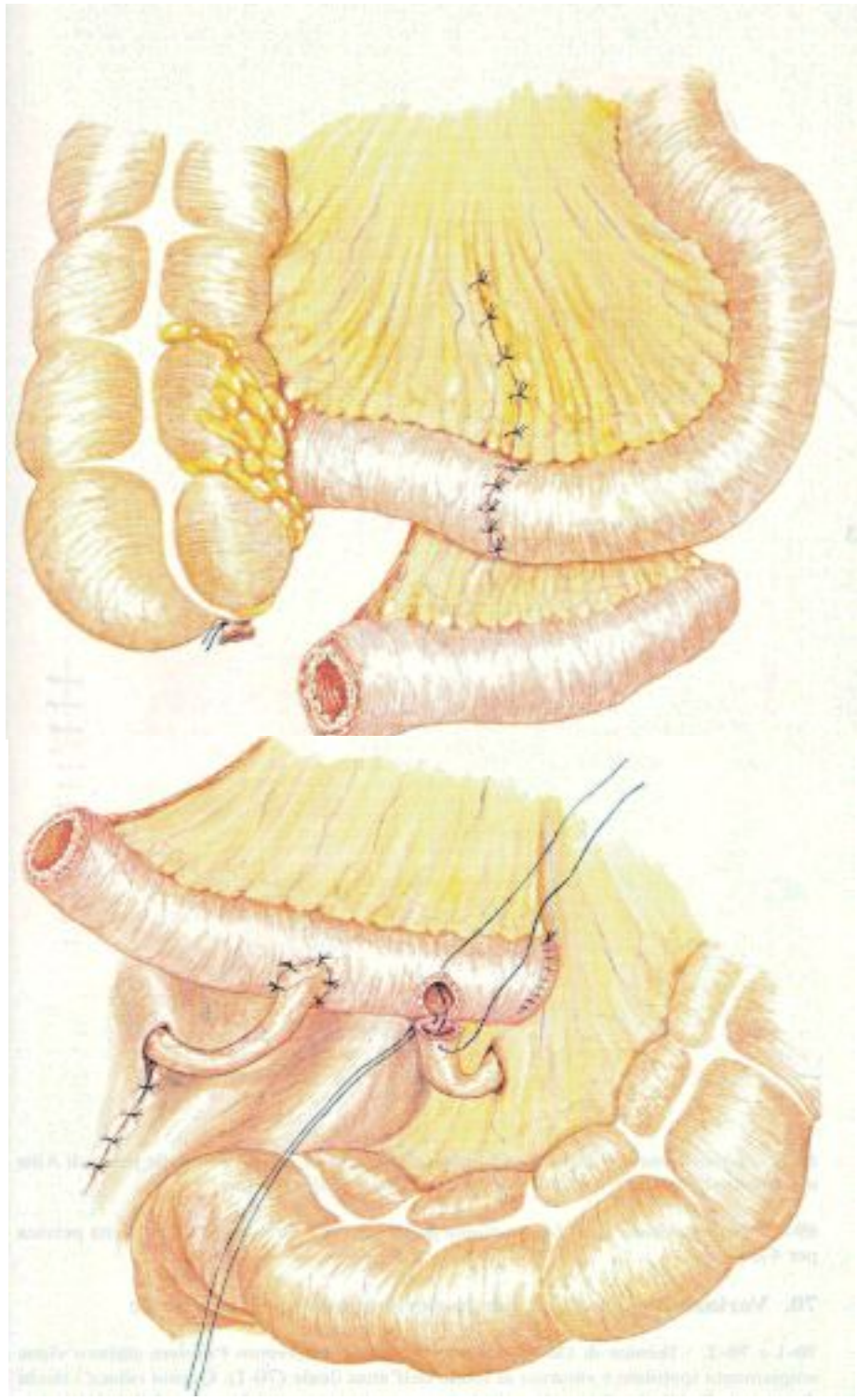


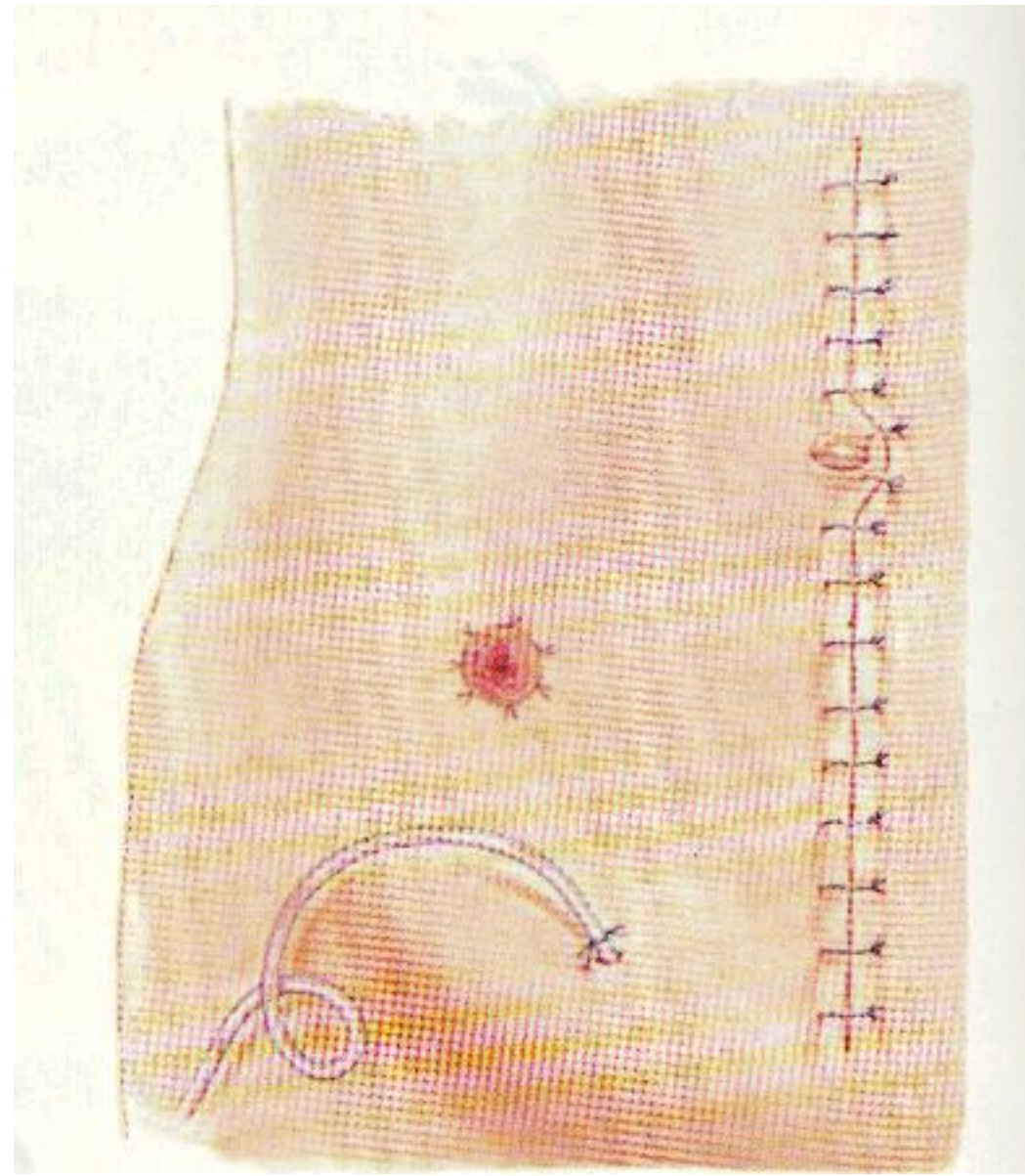
Ureterocutaneostomia

- ALTERAZIONE DELLO SCHEMA CORPOREO
- PROGRESSIVA DEGENERAZIONE DELLA FUNZIONALITA' RENALE
- IRRITAZIONE CUTANEA PERISTOMALE
- ERNIA PERISTOMALE

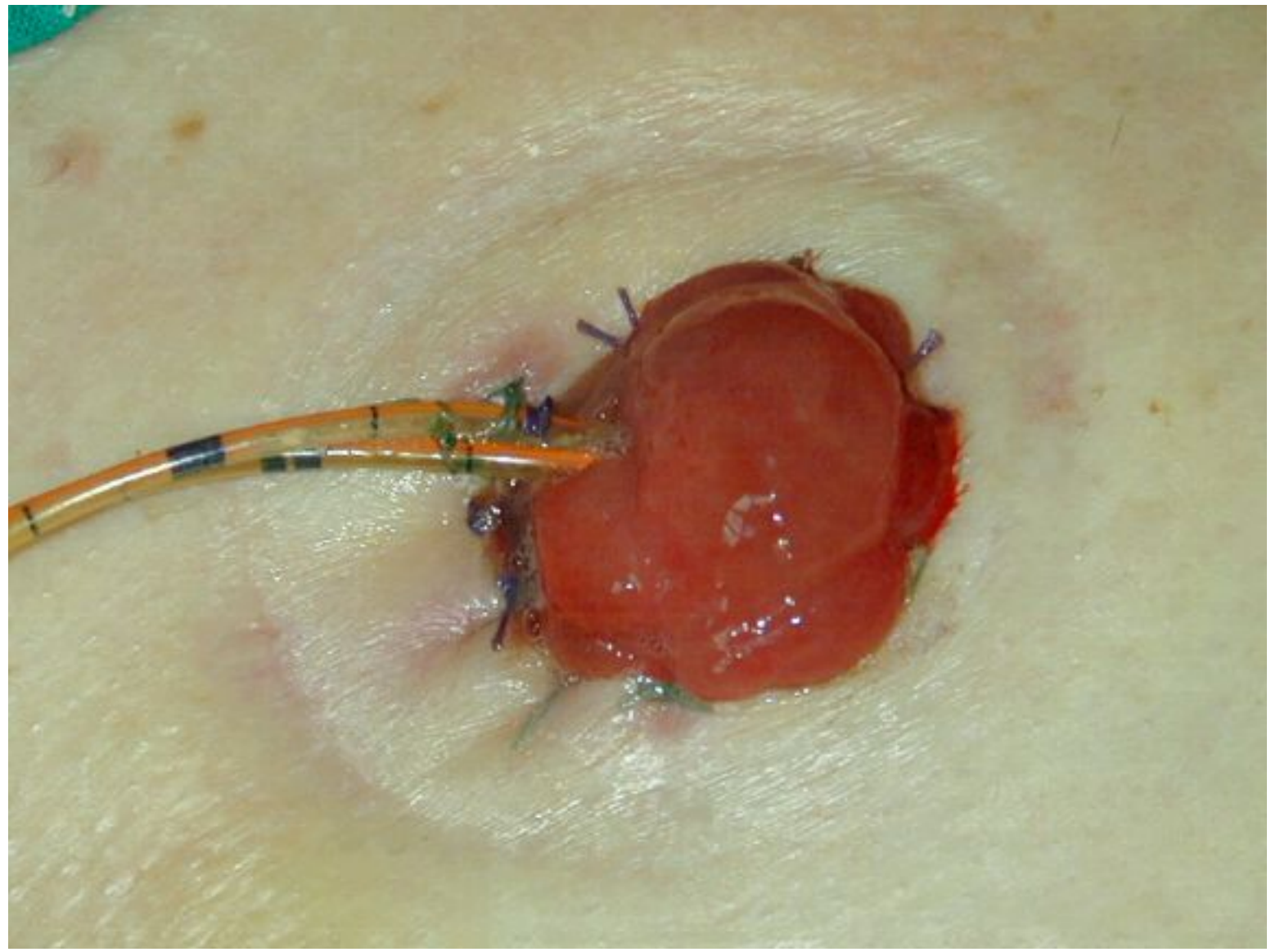
PZ. CON ELEVATO RISCHIO PERIOPERATORIO
BASSA ASPETTATIVA DI VITA

Uretero-ileo-cutaneostomia





Uretero-ileo-cutaneostomia



Uretero-ileo-cutaneostomia

- Rischio di degenerazione della funzionalita' renale
- Alterazione dello schema corporeo
- Ernia peristomale

PZ. CON ELEVATO RISCHIO PERIOPERATORIO
BASSA ASPETTATIVA DI VITA
COUNSELLING

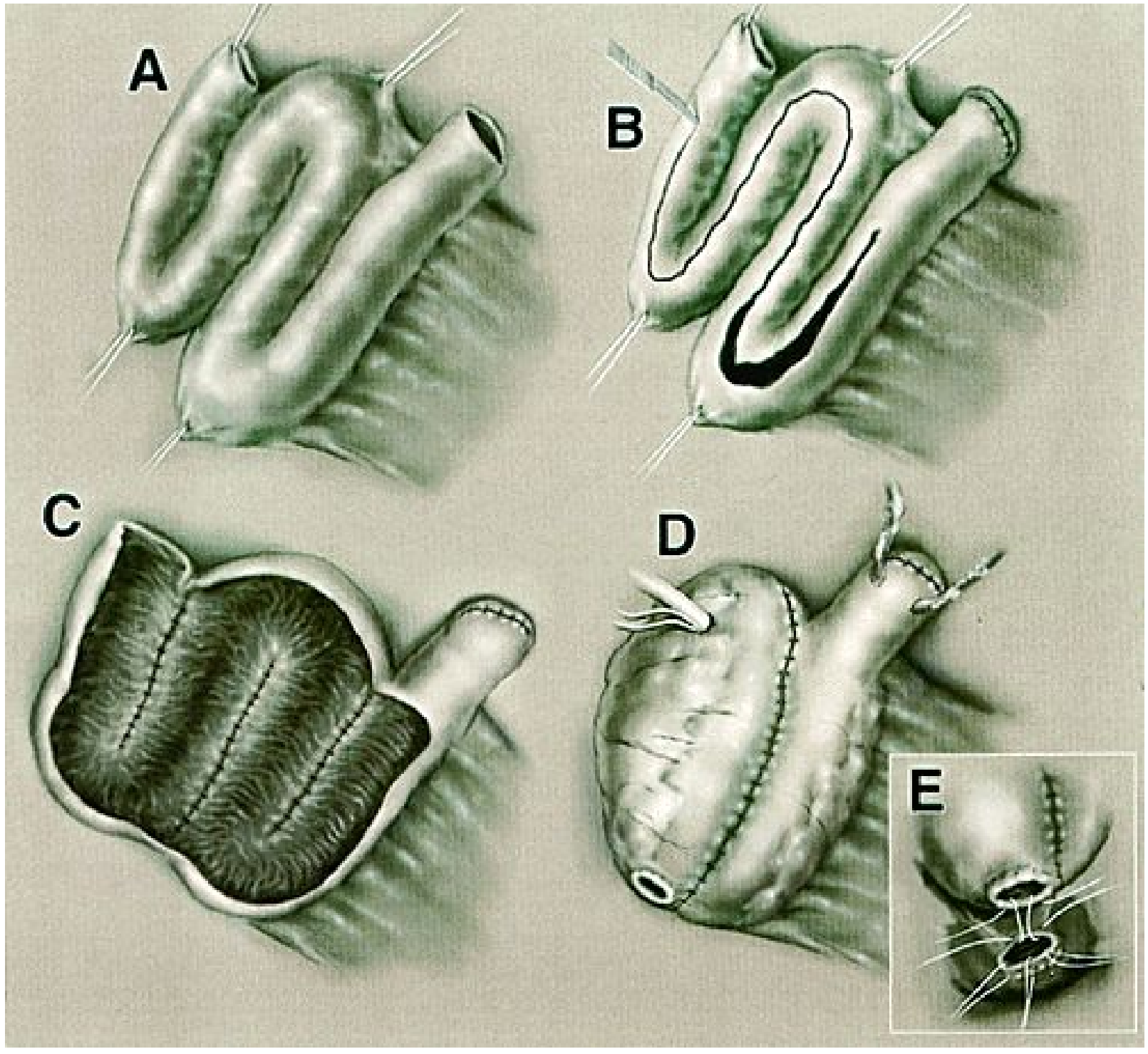
Neo vescica

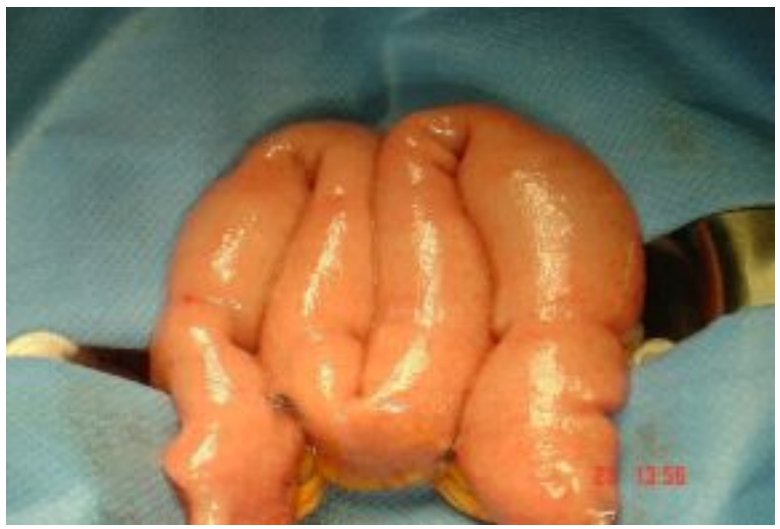
Accettata socialmente

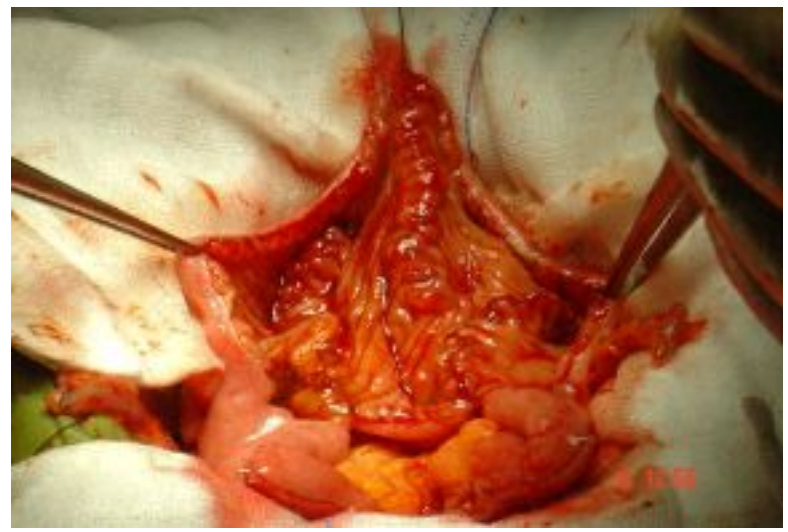
Identificare i pz in cui la neovescica non è la soluzione ideale

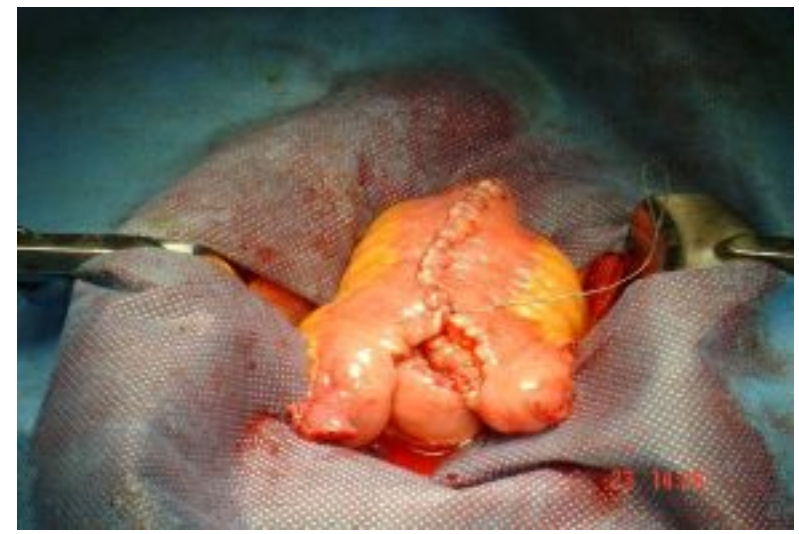
61% dei pz da noi operati riceve una neovescica

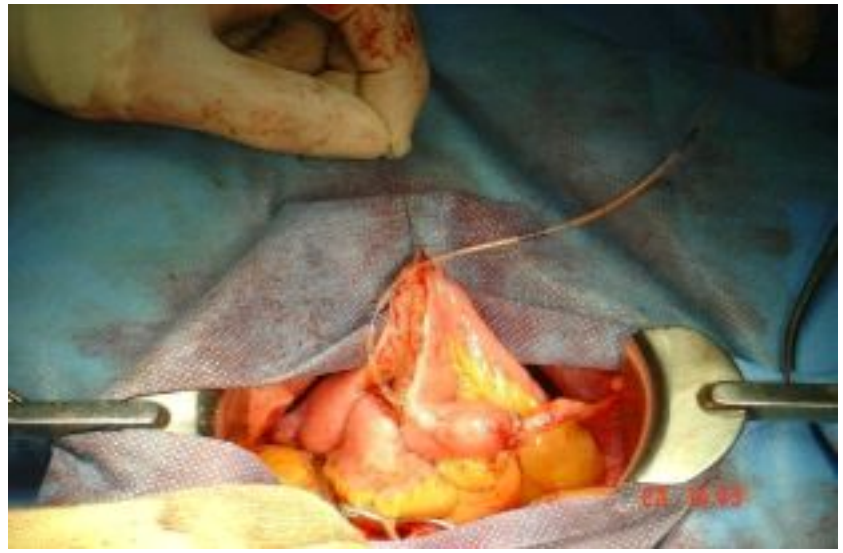
Neo vescica

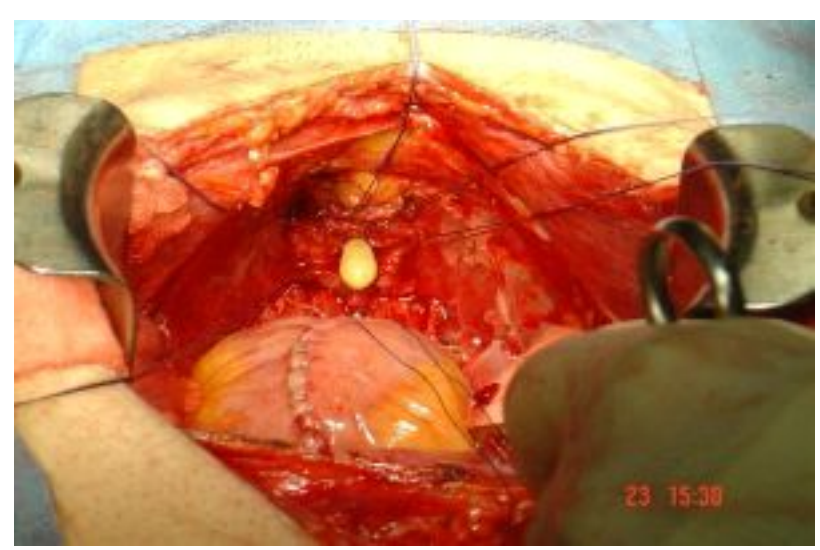











23 15:30

Neo vescica

PROS

MINZIONE PER URETRAM
CONTINENZA URINARIA
PROTEZIONE DELLE ALTE VIE URINARIE

CONS

TUMORE URETRALE
IBD/ NEOPLASIE INTESTINALI
IR (CREATININEMIA > 2 mg/ dl)

Complicanze

Legate alla sostituzione ileale di vescica
(nel caso di derivazione ileale)

Non legate alla sostituzione ileale di vescica

Precoci o tardive

Complicanze precoci legate alla sostituzione ileale di vescica

- Ostruzione completa di vescica a causa di muchi
- Stenosi delle anastomosi uretero-ileali
- Pielonefrite acuta
- Sanguinamento prolungato nella sostituzione ileale di vescica
- Fistole urinarie:
    - Dalla anastomosi ileo-uretrale
    - Dalla anastomosi ileo-ureterale

Complicanze tardive non legate alla sostituzione ileale di vescica

- Disfunzione erettile
- Ascesso tardivo
- Laparocele
- Aderenze intestinali
- Volvolo intestinale
- Uropionefrosi

Complicanze tardive legate alla sostituzione ileale di vescica

- Incontinenza (7-43%)
- Stenosi uretero-ileale
- Reflusso vescico-ureterale
- Stenosi uretro-ileale
- Litiasi vescicale, litiasi renale secondaria
- Fistola neovescica-ileale
- Fistola urinaria cutanea
- Ritenzione, residuo post-minzionale
- Plicatura della parete della neovescica, sinechie endoluminali
- Acidosi metabolica importante
- Pielonefrite acuta
- Insufficienza renale cronica

Sopravvivenza a 5 anni

- *83-92% pT0-T1*
- *75-85% pT2*
- *62% pT3*
- *45-50% pT4*
- *25-35% N+*

Stein et al, JClin Oncol 2001

Chemioterapia adjuvante - indicazioni

pT3/ pT4 o N+

- progression rate del 27% in pz trattati vs 82% dei pz non trattati

- sopravvivenza a 5 aa del 59% in pz trattati vs 13% dei pz non trattati

Herr et al, J urol 2001
Sternberg, 2007

Chemioterapia adjuvante - indicazioni

Malattia metastatica (M+)

sopravvivenza media a 5 aa del 17 %

Sternberg, 2007