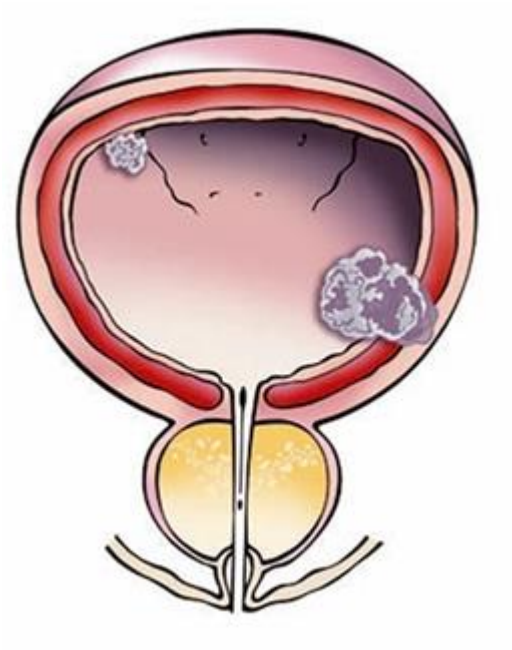
Bladder Cancer



Prof. L. Da Pozzo

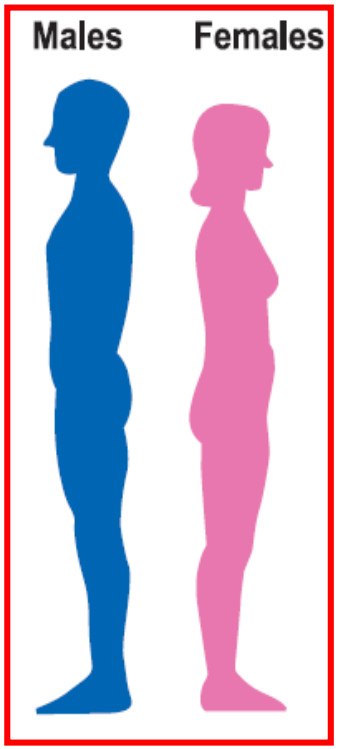
UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA

Ospedale di Bergamo

Sistema Socio Sanitario
Regione Lombardia
ASST Papa Giovanni XXIII

Cancer Statistics Incidence
Bladder Cancer

1. Prostate 19%
2. Lung 14%
3. Colon 9%
4. **Bladder 7%**
5. Melanoma 6%
6. Kidney 5%



1. Breast 28%
2. Lung 14%
3. Colon 9%
4. Uterus 7%
5. Thyroid 5%
6. NH-Lymphoma 4%
7. Kidney 3%

Jemal et al. CA Cancer J Clin 2018 60(5):277-300

EPIDEMIOLOGY

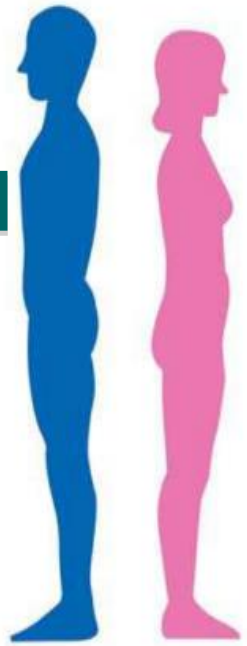
- Fourth malignancy by incidence in males.
- The global mortality rate (per 100,000 people / year) is 3.2 deaths for men and 0.9 for women.
- It represents the eighth most common cause of cancer death in humans.
- There is a male: female ratio of approximately 4: 1, thus a white: black ratio of approximately 2: 1
- Bladder cancer incidence and mortality is decreasing in some registries in response to the decreased impact of known risk factors.

Wade J. Sexton, et al. Cancer Control 2010

EPIDEMIOLOGY

Estimated New Cases

Males			Females		
Prostate	164,690	19%	Breast	266,120	30%
Lung & bronchus	121,680	14%	Lung & bronchus	112,350	13%
Colon & rectum	75,610	9%	Colon & rectum	64,640	7%
Urinary bladder	62,380	7%	Uterine corpus	63,230	7%
Melanoma of the skin	55,150	6%	Thyroid	40,900	5%
Kidney & renal pelvis	42,680	5%	Melanoma of the skin	36,120	4%
Non-Hodgkin lymphoma	41,730	5%	Non-Hodgkin lymphoma	32,950	4%
Oral cavity & pharynx	37,160	4%	Pancreas	26,240	3%
Leukemia	35,030	4%	Leukemia	25,270	3%
Liver & intrahepatic bile duct	30,610	4%	Kidney & renal pelvis	22,660	3%
All Sites	**856,370**	**100%**	**All Sites**	**878,980**	**100%**

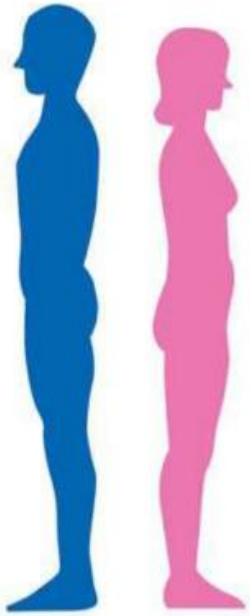


Siegel et al. CA Cancer J Clin 2018

EPIDEMIOLOGY

Estimated Deaths

Males			Females		
Lung & bronchus	83,550	26%	Lung & bronchus	70,500	25%
Prostate	29,430	9%	Breast	40,920	14%
Colon & rectum	27,390	8%	Colon & rectum	23,240	8%
Pancreas	23,020	7%	Pancreas	21,310	7%
Liver & intrahepatic bile duct	20,540	6%	Ovary	14,070	5%
Leukemia	14,270	4%	Uterine corpus	11,350	4%
Esophagus	12,850	4%	Leukemia	10,100	4%
Urinary bladder	12,520	4%	Liver & intrahepatic bile duct	9,660	3%
Non-Hodgkin lymphoma	11,510	4%	Non-Hodgkin lymphoma	8,400	3%
Kidney & renal pelvis	10,010	3%	Brain & other nervous system	7,340	3%
All Sites	**323,630**	**100%**	**All Sites**	**286,010**	**100%**



Siegel et al. CA Cancer J Clin 2018

EPIDEMIOLOGY

	Common Types of Cancer	Estimated New Cases 2018	Estimated Deaths 2018
1.	Breast Cancer (Female)	266,120	40,920
2.	Lung and Bronchus Cancer	234,030	154,050
3.	Prostate Cancer	164,690	29,430
4.	Colorectal Cancer	140,250	50,630
5.	Melanoma of the Skin	91,270	9,320
6.	**Bladder Cancer**	**81,190**	**17,240**
7.	Non-Hodgkin Lymphoma	74,680	19,910
8.	Kidney and Renal Pelvis Cancer	65,340	14,970
9.	Uterine Cancer	63,230	11,350
10.	Leukemia	60,300	24,370

Bladder cancer represents 4.7% of all new cancer cases in the U.S.

https://www.cancer.gov/types/bladder/hp

EPIDEMIOLOGY

Estimated New Cases in 2018	81,190
% of All New Cancer Cases	4.7%

Estimated Deaths in 2018	17,240
% of All Cancer Deaths	2.8%

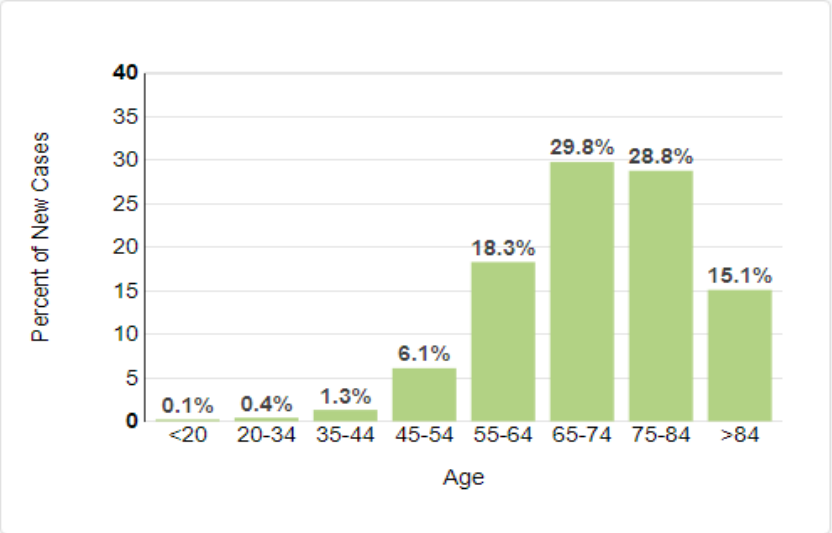
Percent Surviving 5 Years

76.8%

2008-2014

https://www.cancer.gov/types/bladder/hp

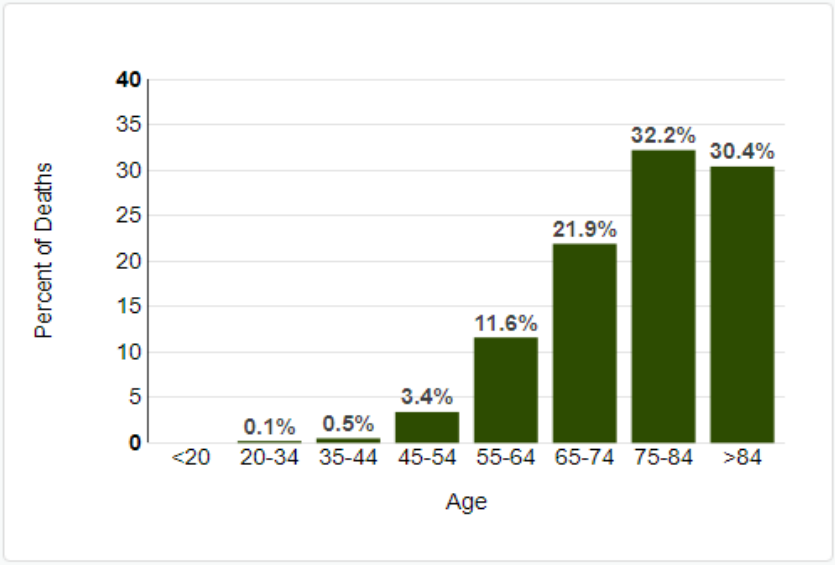
EPIDEMIOLOGY



Bladder cancer is most frequently diagnosed in patients between 65 and 74 years of age

Median Age At Diagnosis

72



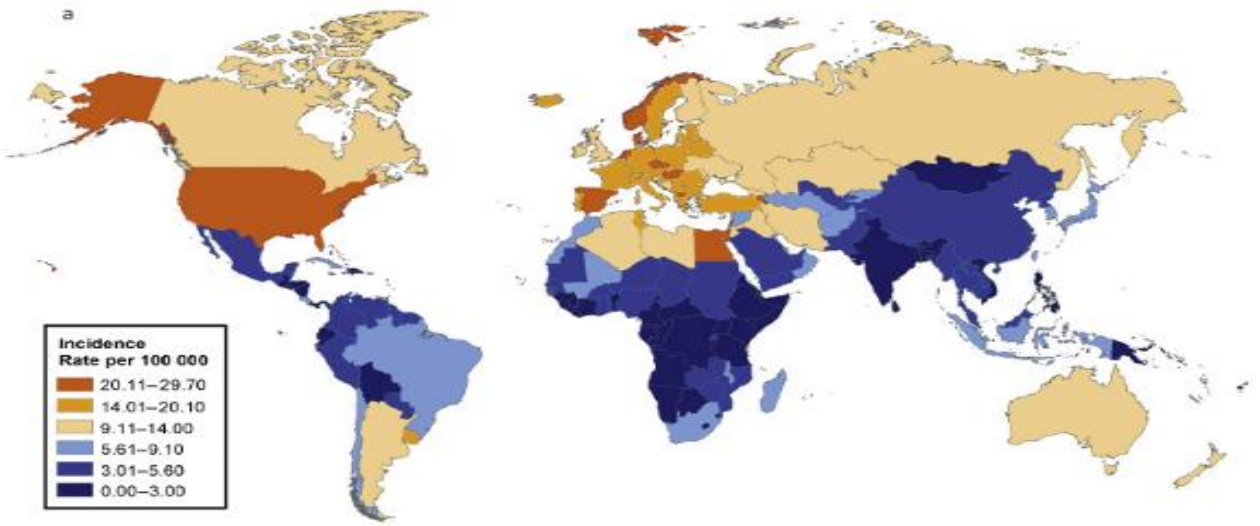
The mortality rate from bladder cancer is highest in patients between 75 and 84 years of age

Median Age At Death

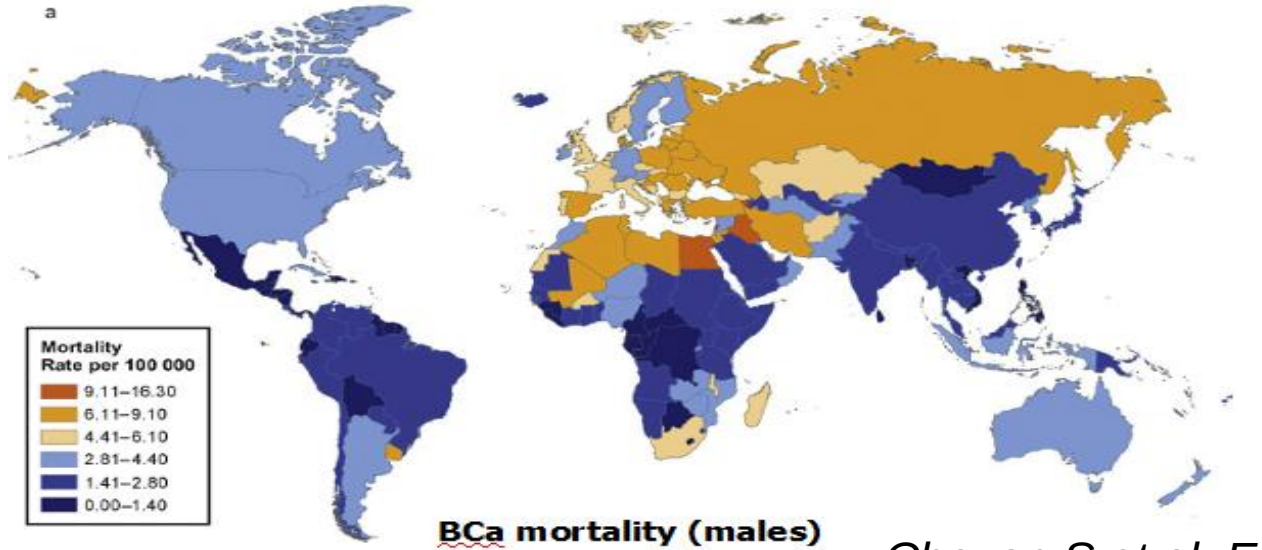
79

https://www.cancer.gov/types/bladder/hp

EPIDEMIOLOGY



BCa incidence (males)



BCa mortality (males)

Chavan S et al. Eur Urol 2014

Gender and Bladder Cancer: A Collaborative Review of Etiology, Biology, and Outcomes

Jakub Dobruch[a,*], *Siamak Daneshmand*[b], *Margit Fisch*[c], *Yair Lotan*[d], *Aidan P. Noon*[e], *Matthew J. Resnick*[f], *Shahrokh F. Shariat*[g], *Alexandre R. Zlotta*[e], *Stephen A. Boorjian*[h]

EUROPEAN UROLOGY 69 (2016) 300–310

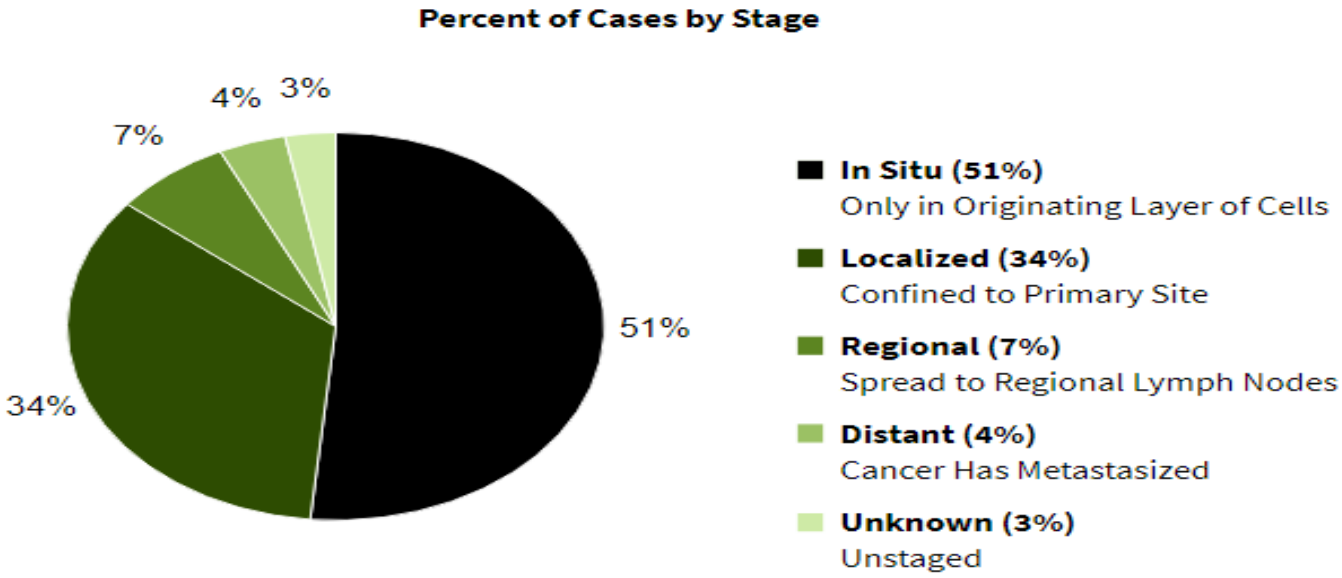
While the incidence of bladder cancer is 3 to 4 times higher in men, women are more often diagnosed in a more advanced stage of the disease.

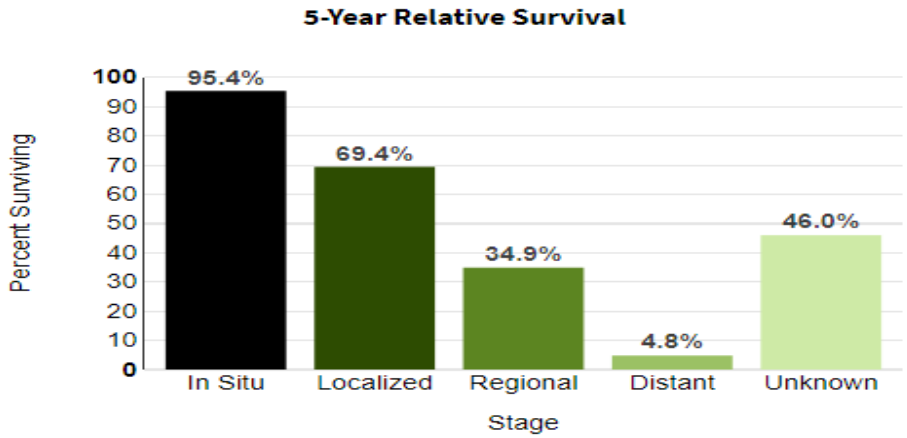
There are no significant gender differences in the clinical presentation of the disease (hematuria, LUTS)

However, symptomatic treatments in the absence of in-depth diagnostics are more frequent in women than in men (47% VS 19%) in the year preceding the diagnosis of bladder cancer ($p < 0.05$)

There are consistent but not unambiguous data suggesting higher bladder cancer mortality in women

EPIDEMIOLOGY





https://www.cancer.gov/types/bladder/hp

RISK FACTORS

Tobacco smoke is the most important risk factor for bladder cancer.
It is the cause of about 50% of all cases.

Family history and genetic factors appear to play a limited role in the risk of developing bladder cancer

Occupational risk factors (aromatic amines, polycyclic aromatic hydrocarbons, and chlorinated hydrocarbons are the second most important risk factor, causing approximately 10% of all bladder cancers)

Schistosomiasis

Environmental pollution

Previous Radiotherapy - Previous Chemotherapy

Tobacco

Smoking is the most important risk factor and is the cause of 50% of cancers !!

Smokers have a 4 times higher risk of developing bladder cancer than non-smokers.

The risk is higher in smokers than in former smokers

Burger et al. Eur Urol 2013

Tobacco

- **There is a pathophysiological link between tobacco smoke and bladder cancer**
- **Tobacco smoke contains aromatic amines, such as b-naphthylamine and polycyclic aromatic hydrocarbons known to be among the causes of bladder cancer**
- **These substances are excreted by the kidney and have a carcinogenic effect on the entire urinary system**
- **Some suggest that smoking cessation improves bladder cancer outcome.**
- **Environmental exposure to smoke could be a risk factor for bladder cancer**
- **The effects of environmental exposure are generally more pronounced in women, particularly in women who have never smoked**

Burger et al. Eur Urol 2013

Occupational Risk

- **Occupational exposure to aromatic amines (benzidine, 4-aminobiphenyl, 2-naphthylamine, 4 chloro-o-toluidine), polycyclic aromatic hydrocarbons and chlorinated hydrocarbons constitute the second most important risk factor for bladder cancer.**
- **It has been suggested that up to 20% of all bladder cancers are related to such exposure, mainly in industrial processes related to the production of paint, dyes, metals and petroleum products.**

Burger et al. Eur Urol 2013

Schistosomiasi

Schistosomiasis is the second most common parasitic infection after malaria, with 600 million people exposed to the infection in Africa, South America, Asia and the Caribbean
Schistosoma haematobium and Bilharzia infections strongly correlated with the development of bladder squamous cell Ca

The nature of this close relationship is not completely resolved (irritation from parasite eggs?)

Histology

Table 1. — Bladder Tumor Histologies

Malignant
- Transitional cell carcinoma (TCC)
- Pure TCC
- TCC with mixed features (squamous or glandular differentiation)
- Micropapillary
- Nested
- Lymphoepithelioma-like
- Squamous cell carcinoma
- Adenocarcinoma (primary bladder)
- Small cell carcinoma
- Carcinosarcoma (mixed epithelial and mesenchymal elements)
- Sarcomatoid (epithelial elements only)

Premalignant
- Leukoplakia (precursor for squamous cell carcinoma)
- Cystitis glandularis (precursor for adenocarcinoma)

Benign
- Squamous metaplasia
- Nephrogenic adenoma
- Cystitis cystica and follicularis
- Pseudosarcoma
- Malacoplakia

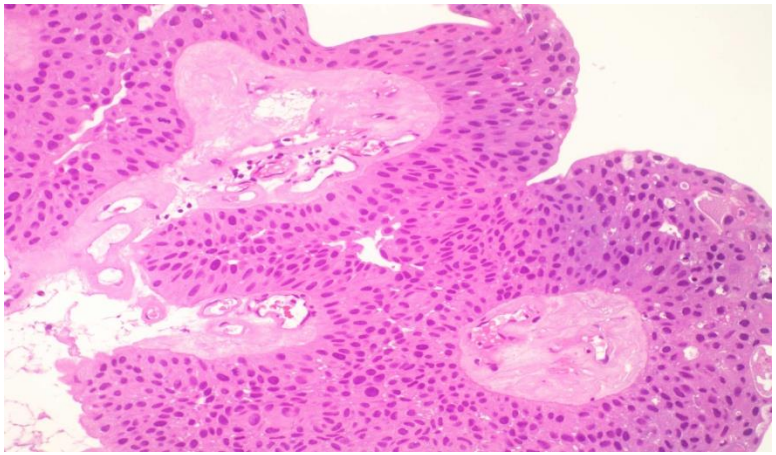
90%

5%

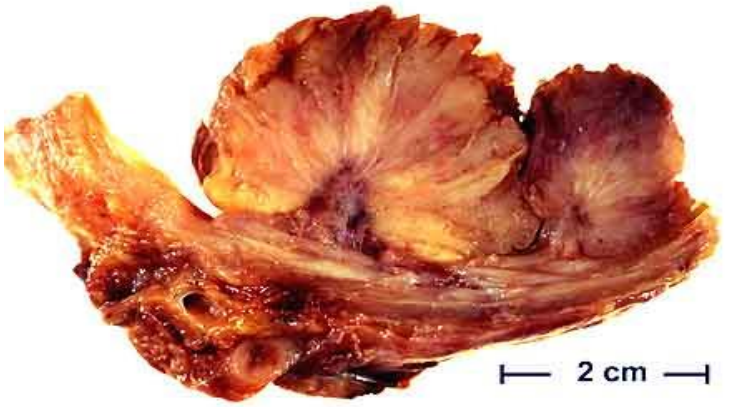
1-2%

Wade J. Sexton, et Al. Cancer Control 2010

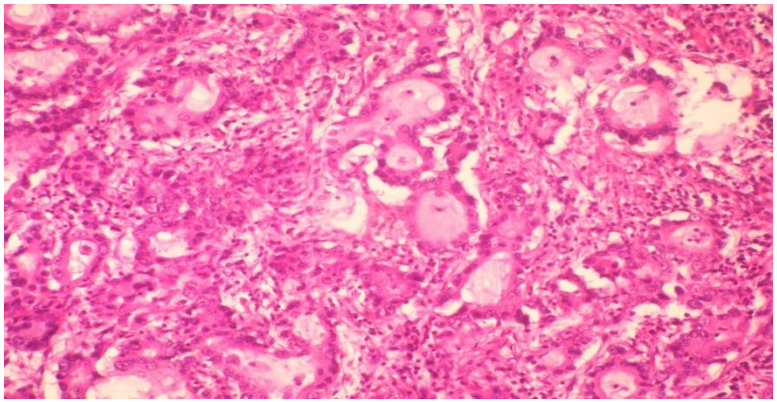
Typical Histology



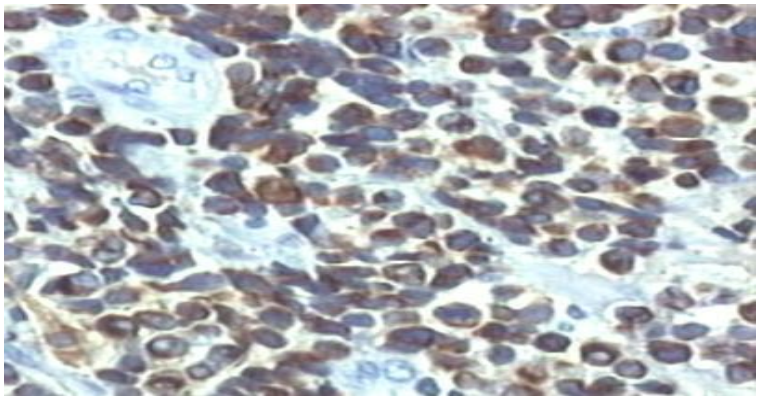
Urotelial carcinoma



Squamos cell carcinoma



Adenocarcinoma

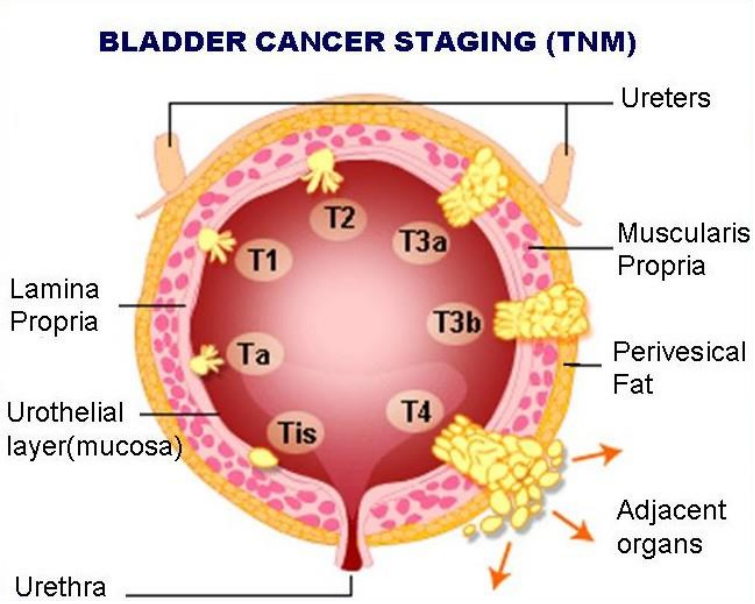


Small cell carcinoma

TNM

Table 4.1: 2017 TNM classification of urinary bladder cancer

T - Primary tumour		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
Ta	Non-invasive papillary carcinoma	
Tis	Carcinoma *in situ*: 'flat tumour'	
T1	Tumour invades subepithelial connective tissue	
T2	Tumour invades muscle	
	T2a	Tumour invades superficial muscle (inner half)
	T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue	
	T3a	Microscopically
	T3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall	
	T4a	Tumour invades prostate stroma, seminal vesicles, uterus or vagina
	T4b	Tumour invades pelvic wall or abdominal wall
N – Regional lymph nodes		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
N3	Metastasis in common iliac lymph node(s)	
M - Distant metastasis		
M0	No distant metastasis	
	M1a	Non-regional lymph nodes
	M1b	Other distant metastases

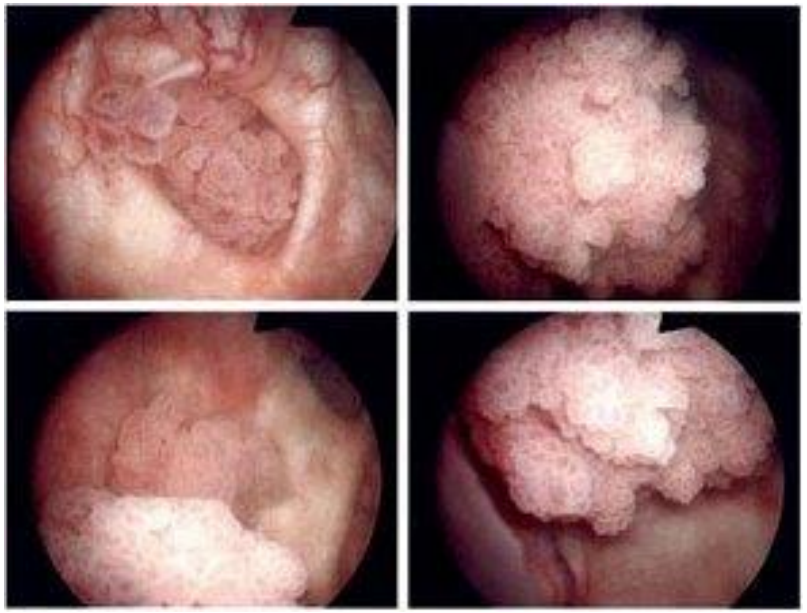


EAU Guidelines on
Non-muscle-invasive
Bladder Cancer
(TaT1 and CIS)

Non-Muscle Invasive Bladder cancer

About 75% of all bladder cancers

15-20% progress to muscle invasive bladder cancer



EAU Guidelines on
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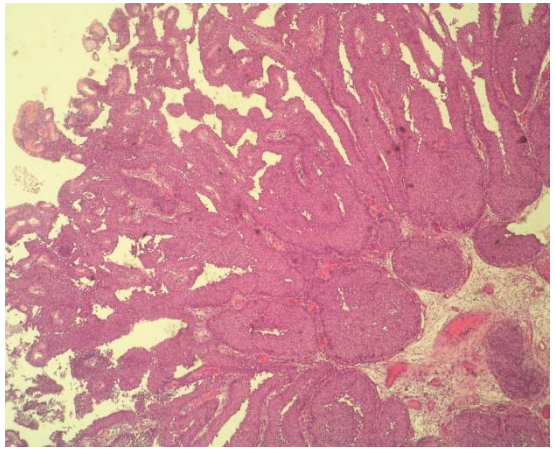
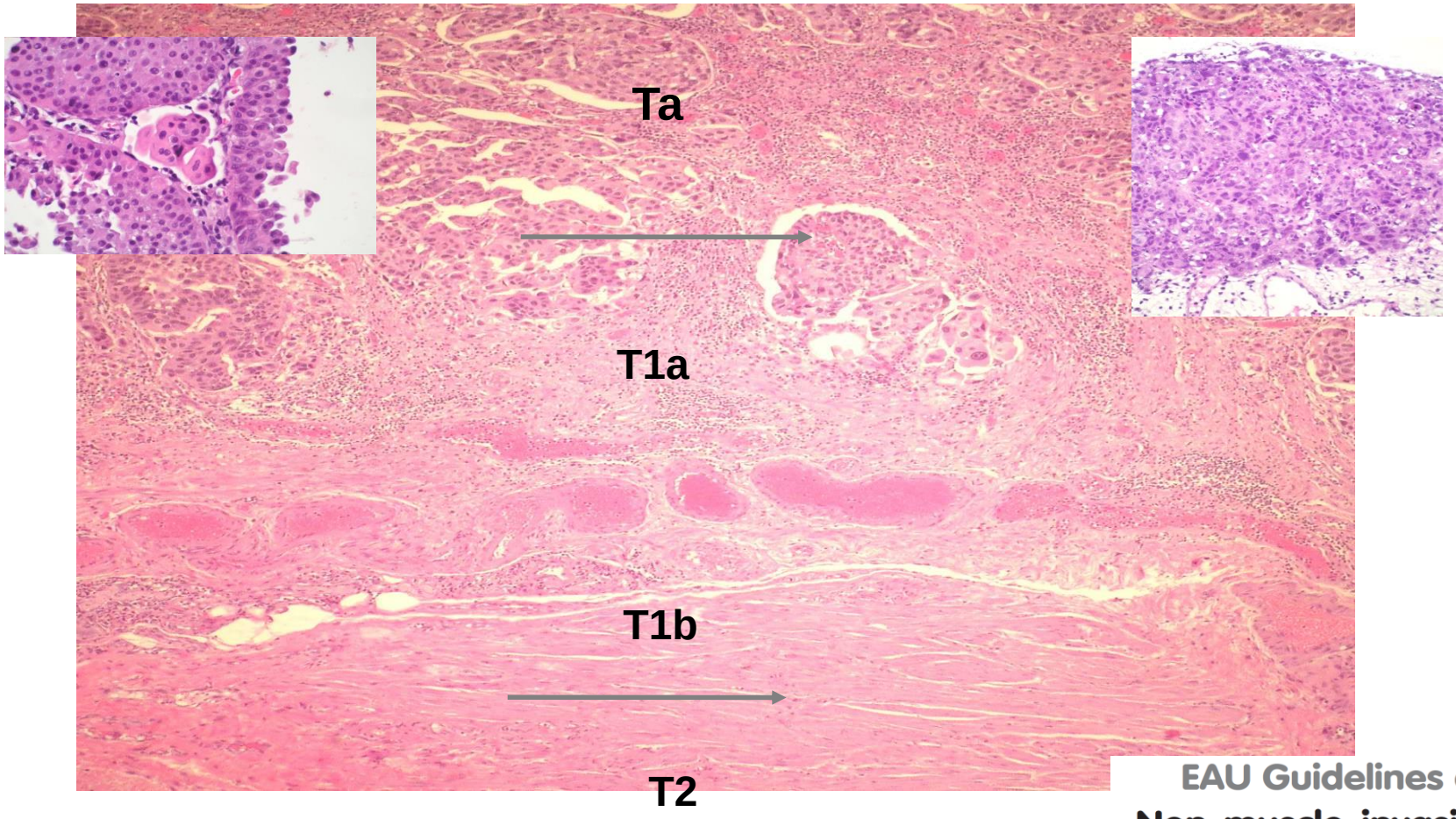
(TaT1 and CIS)



Non-Muscle Invasive Bladder cancer



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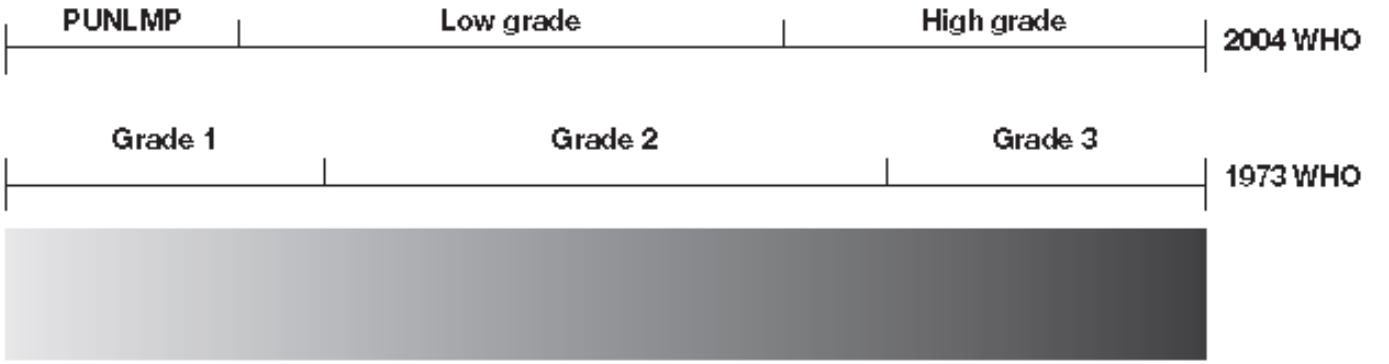
Bladder Cancer
(TaT1 and CIS)

NEW ISUP1998/WHO2004 GRADING SYSTEM CLASSIFICATION



Histologic Spectrum of urothelial carcinoma [UC]

**1973 WHO Grade 1 carcinomas have been reassigned to papillary urothelial neoplasm of low malignant potential (PUNLMP) and low-grade (LG) carcinomas in the 2004 WHO classification, and Grade 2 carcinomas to LG and high-grade (HG) carcinomas. All 1973 WHO Grade 3 carcinomas have been reassigned to HG carcinomas (Reproduced with permission from Elsevier).*

EAU Guidelines on
Non-muscle-invasive Bladder Cancer (TaT1 and CIS)

Holgman S. et al J Urol 2001
Samaratunga H et al Urology 2002

WHO 2004 GRADING SYSTEM CLASSIFICATION

The new WHO classification of 2004 WHO includes 3 categories: PUNLMP, low grade urothelial carcinoma, high urothelial carcinoma.

PUNLMP is defined as a lesion that has no cytological features of malignancy but shows normal urothelial cells in a papillary configuration.

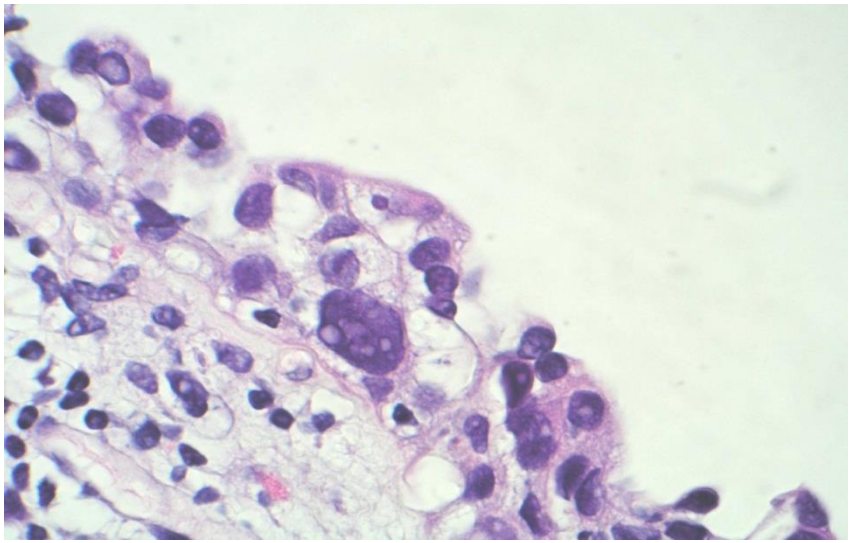
Although the risk of progression is negligible, it is not completely benign and can recur.

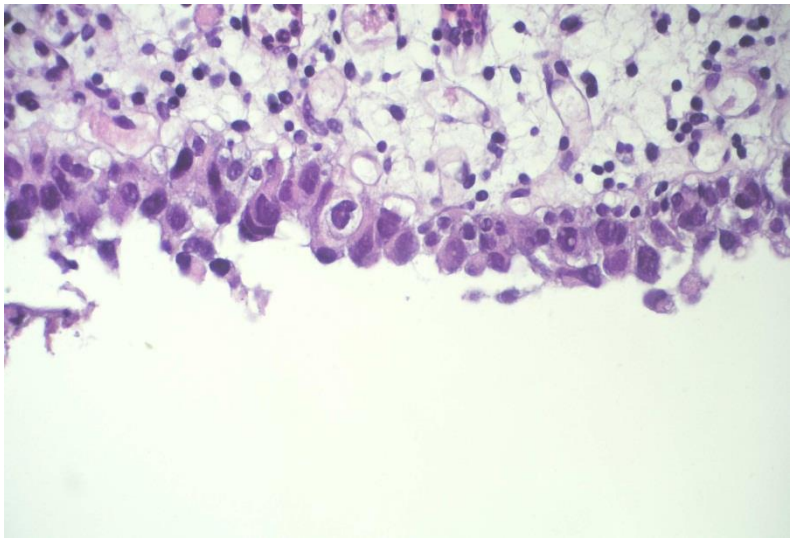
EAU Guidelines on
Non-muscle-invasive
Bladder Cancer
(TaT1 and CIS)

Holgman S. et al J Urol 2001
Samaratunga H et al Urology 2002

Carcinoma in situ

- Carcinoma in situ (CIS) is a flat, high-grade, non-invasive urothelial carcinoma. It can be overlooked on cystoscopy or mistaken for an inflammatory lesion. It is often multifocal.
- In the absence of treatment, approximately 54% of patients with CIS progress to a muscle-invasive disease

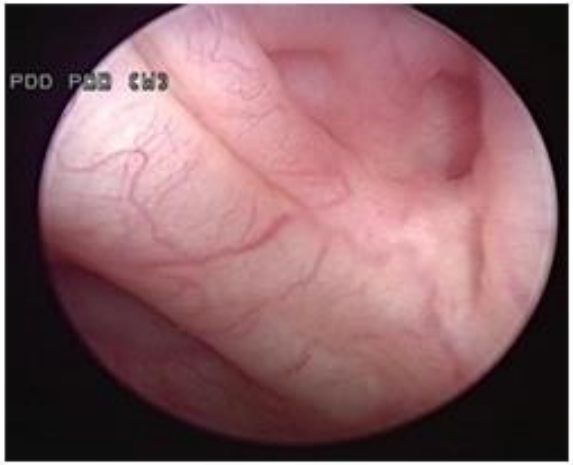




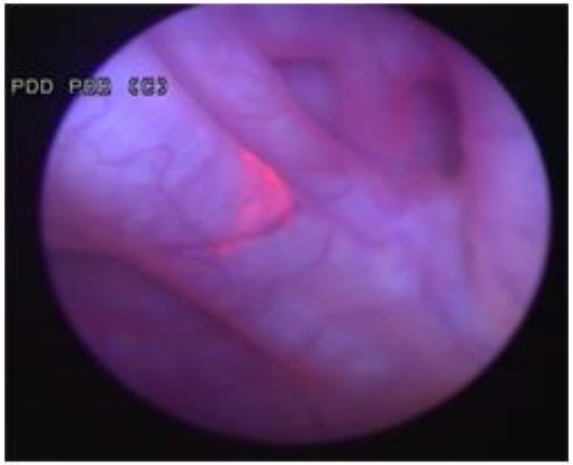
Carcinoma in situ

De novo CIS constitutes less than 3% of all urothelial neoplasms

Synchronous or metachronous CIS during urothelial carcinoma follow-up accounts for 45% and 90% of all bladder cancers



Normal (white light) cystoscopy image of bladder



Same image with blue light cystoscopy showing tumor in pink

© Ashish Kamat, MD

EAU Guidelines on
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Bladder Cancer
(TaT1 and CIS)

Diagnosis

- Symptoms:

  Monosymptomatic hematuria (85% of cases)

  LUTS especially of the filling phase: more typical of locally advanced neoplasm
- Imaging
- Urinary cytology
- Urine molecular tests
- Cystoscopy/Transurethral resection

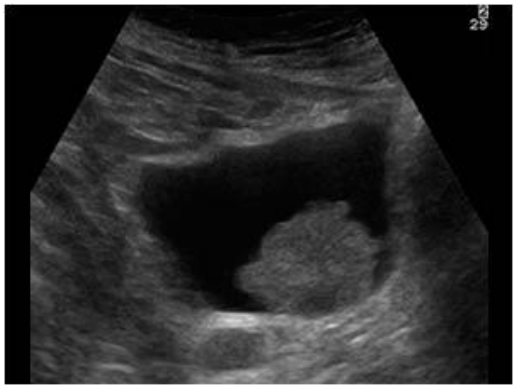
EAU Guidelines 2021
Babjuk et al. Eur Urol 2013;64:639-53

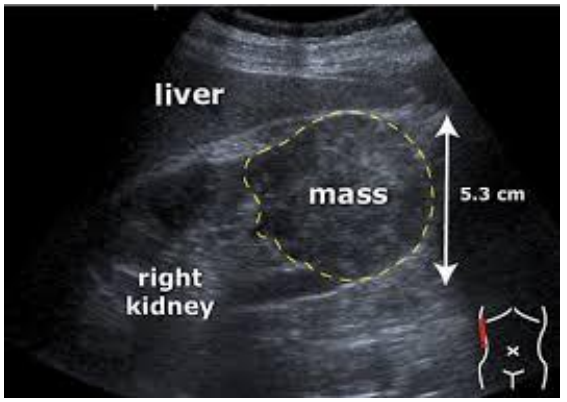
Bladder Cancer - Symptoms

MACROSCOPIC HAEMATURIA

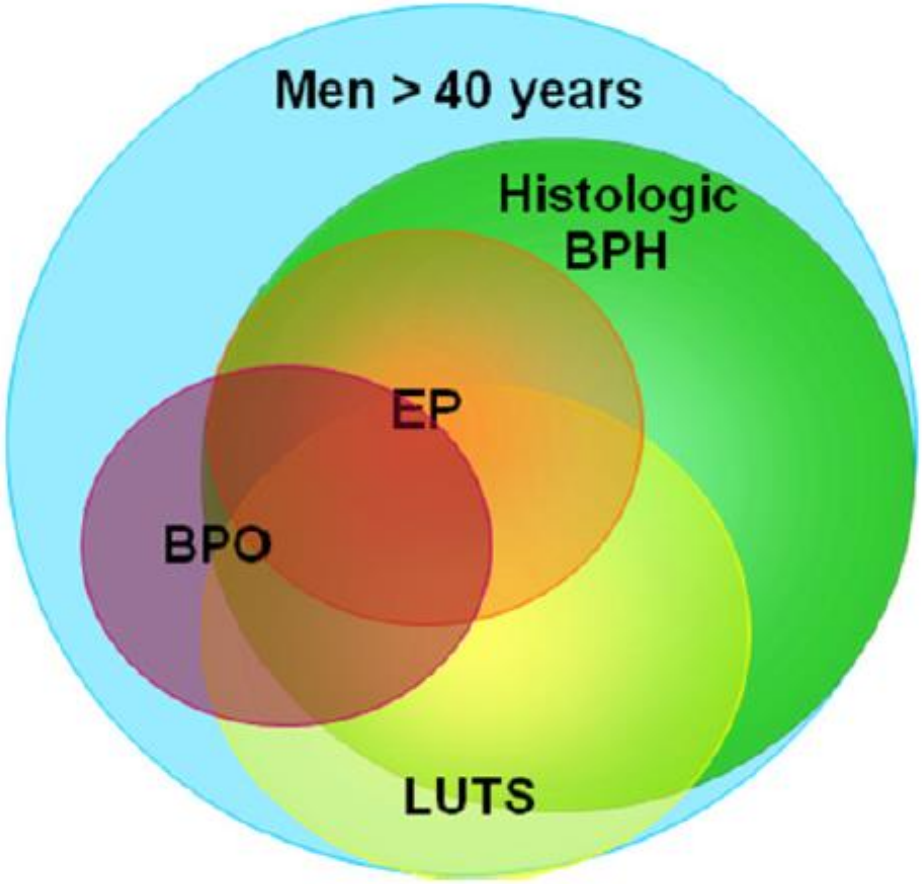
- ✓ Presence of blood in urine is **NOT** a peculiar symptoms of BPH.

- ✓ Urinary tract **US** ust be performed in all patients with hematuria





Bladder cancer - LUTS



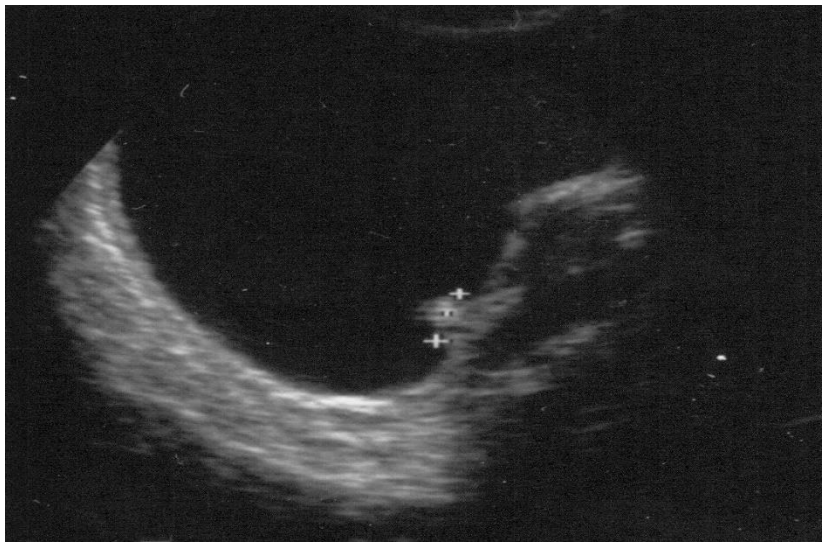
Roehrborn CG. Med Clin North Am. 2011, 95(1): 87-100

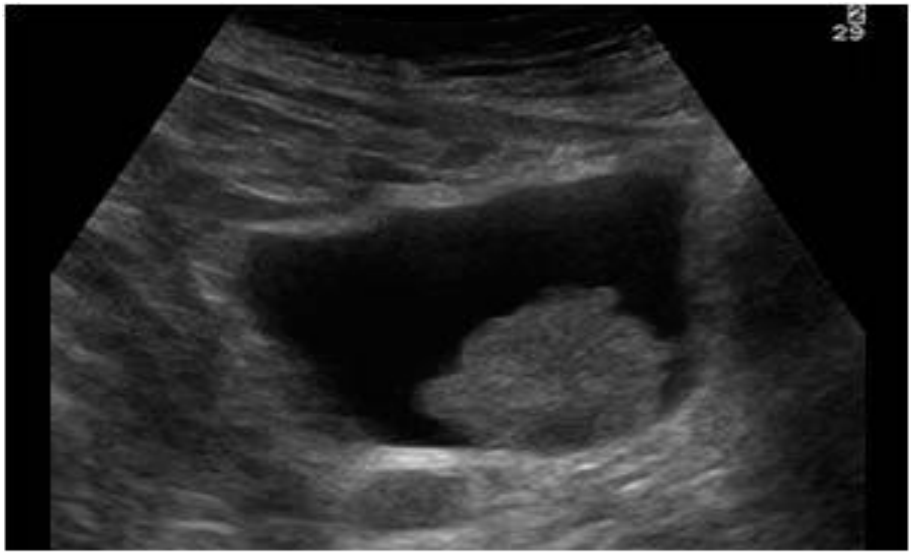
LUTS: Lower urinary Tract Symptoms

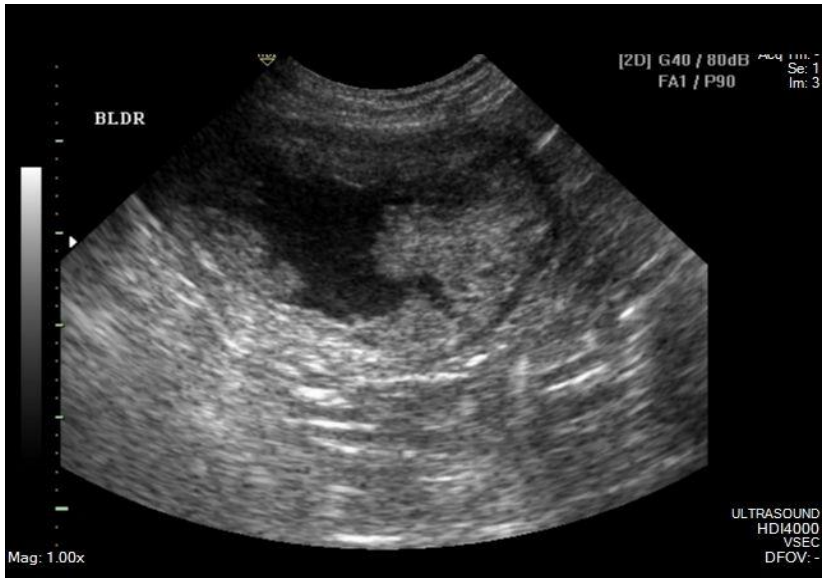
FILLING OR STORAGE SYMPTOMS (IRRITATIVE)

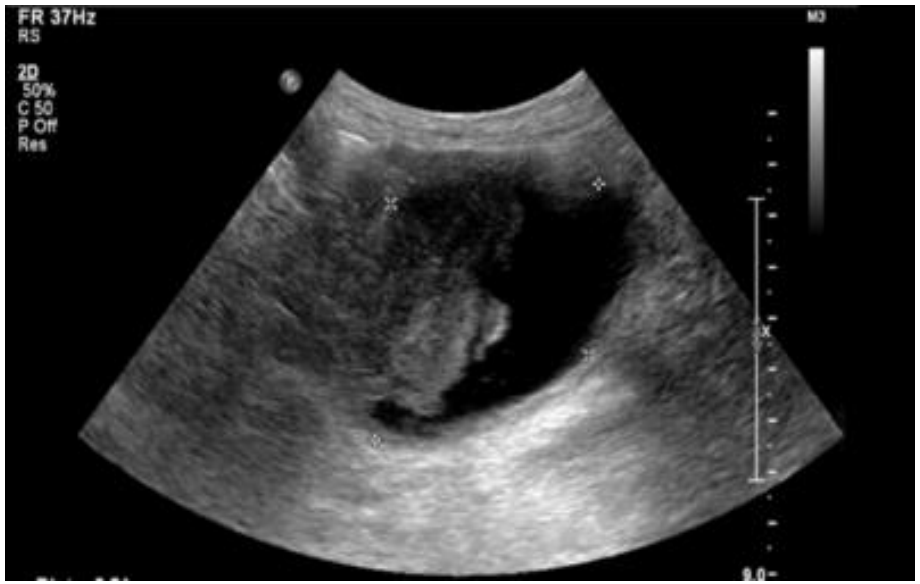
- ✓ **Pollakiuria** : frequent daytime urination
- ✓ **Nicturia**: frequent night time urination
- ✓ **Urgency**: urgent necessity to urinate
- ✓ **Urge incontinence**: urinary incontinence secondary to urgency

Imaging: Abdominal US









Imaging: Abdominal US

Ultrasound of the abdomen allows the characterization of renal masses, the detection of any hydronephrosis and the visualization of intraluminal neoformation in the bladder

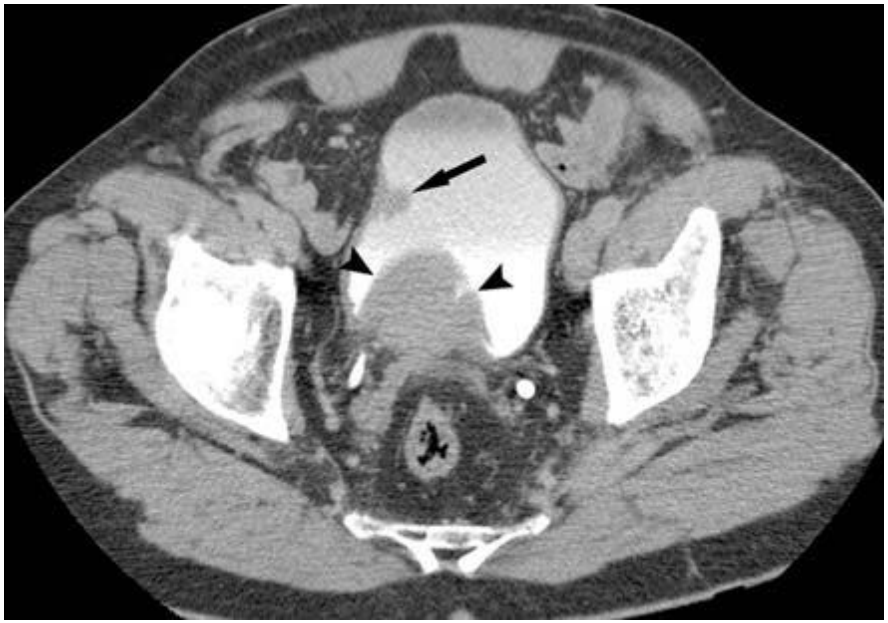
Ultrasound therefore represents a useful tool for the diagnosis of bladder cancer in patients with hematuria; however, it does not exclude the presence of a tumor of the upper excretory route.

CIS cannot be diagnosed with imaging methods.

EAU Guidelines on
Non-muscle-invasive
Bladder Cancer
(TaT1 and CIS)

Imaging: Uro-CT

- A Ct scan is the Gold Standard for bladder neoplasms, infiltrating and non



EAU Guidelines on
Non-muscle-invasive
Bladder Cancer
(TaT1 and CIS)

Urinary Cytology

The search for neoplastic cells exfoliated in the urine by spontaneous urination or bladder washing is a test that has a high sensitivity in high-grade neoplasms (84%), but low sensitivity in low-grade neoplasms (16%)

Sensitivity of cytology for the diagnosis of CIS is 28-100%

A positive urinary cytology can indicate the presence of a neoplasm at any level of the urinary tract; a negative cytology does not exclude the presence of neoplasm

Urinary Cytology

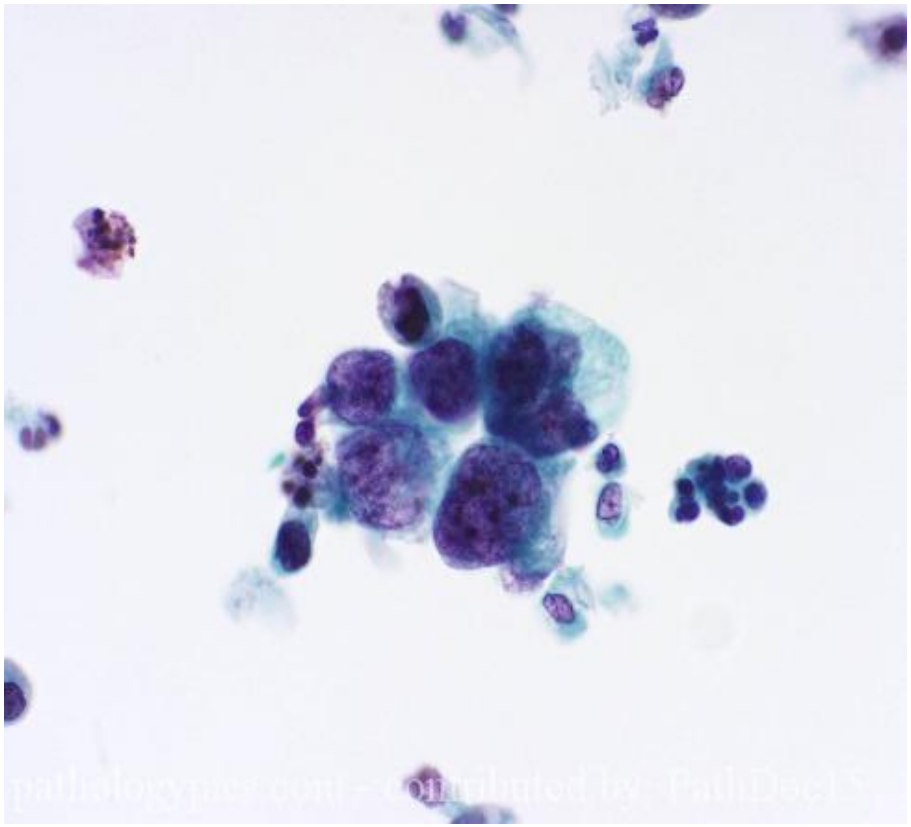
Elevata sensibilità e specificità

Possibili falsi negativi
- Tumori di basso grado

Possibili falsi positivi
- Calcolosi urinaria
- Corpi estranei
- Derivazioni "intestinali"

Risposte dubbie
- Radioterapia
- Terapia endocavitaria

Campioni non analizzabili
- Infezione
- Flogosi



EAU Guidelines on
Non-muscle-invasive
Bladder Cancer
(TaT1 and CIS)

Test molecolari delle urine

Table 5.1: Summary of more established urinary markers

Markers (or test specifications)	Overall sensitivity (%)	Overall specificity (%)	Sensitivity for high-grade tumours (%)	Point-of-care test	LE
UroVysion (FISH)*	30-86	63-95	66-70	No	2b
Microsatellite analysis	58-92	73-100	90-92	No	1b
Immunocyt/uCyt +*	52-100	63-79	62-92	No	2a
Nuclear matrix Protein 22*	47-100	55-98	75-92	Yes	2a
BTA stat*	29-83	56-86	62-91	Yes	3
BTA TRAK*	53-91	28-83	74-77	No	3
Cytokeratins	12-88	73-95	33-100	No	3

BTA = bladder tumour antigen.

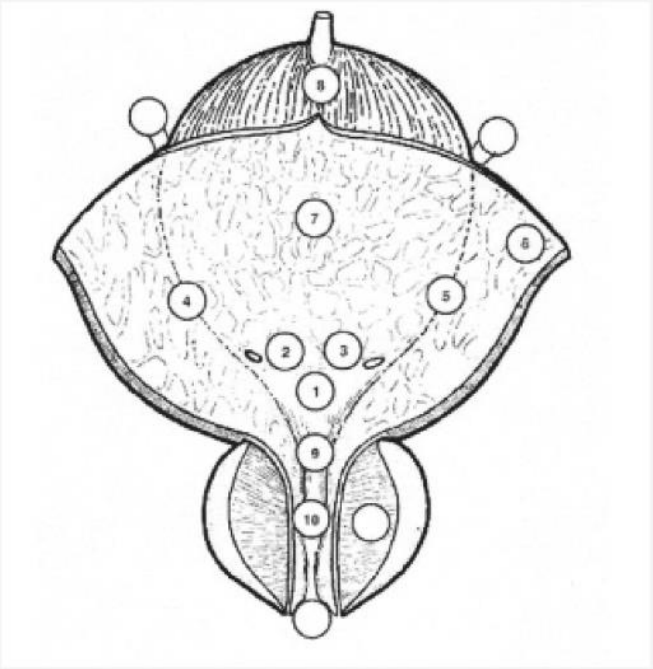
** FDA approved.*

None of these markers are currently accepted for diagnosis and follow-up in clinical practice

Cistoscopy

- The diagnosis of bladder cancer depends on cystoscopy and histological examination of the resected tissue.
- Usually cystoscopy is performed on an outpatient basis with a flexible instrument.
- An accurate description of the findings is recommended, including a description of the site, appearance, size and number of neoplasms.
- The use of a bladder diagram is recommended.

Figure 5.1: Bladder diagram



1 = Trigone	6 = Anterior wall
2 = Right ureteral orifice	7 = Posterior wall
3 = Left ureteral orifice	8 = Dome
4 = Right wall	9 = Neck
5 = Left wall	10 – Posterior urethra

5.9.Summary of evidence – primary asssessment of NMIBC

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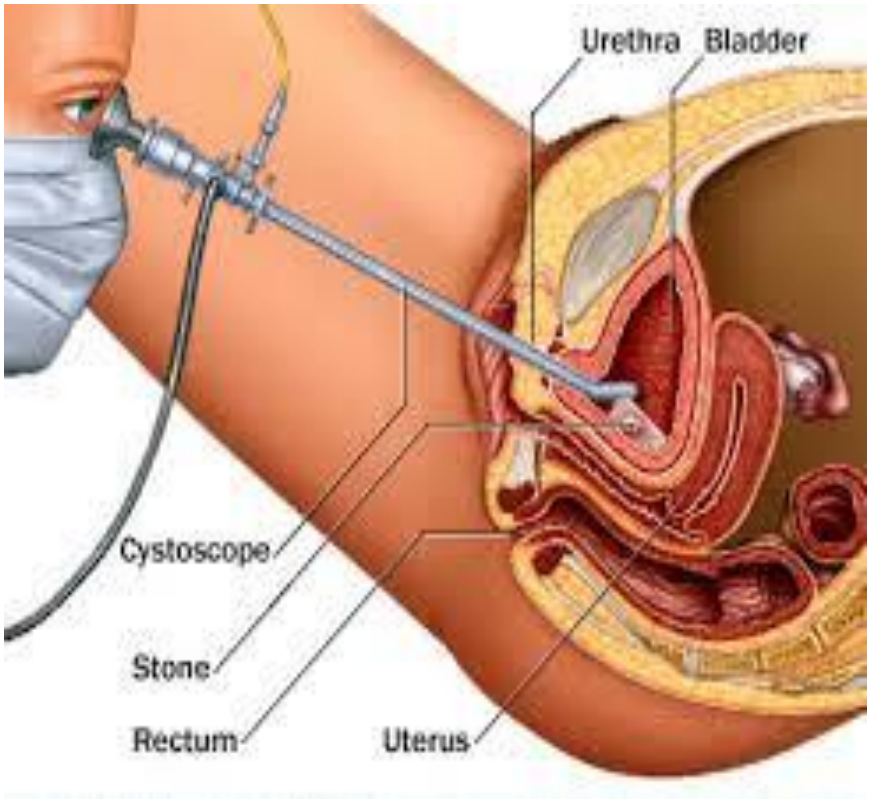
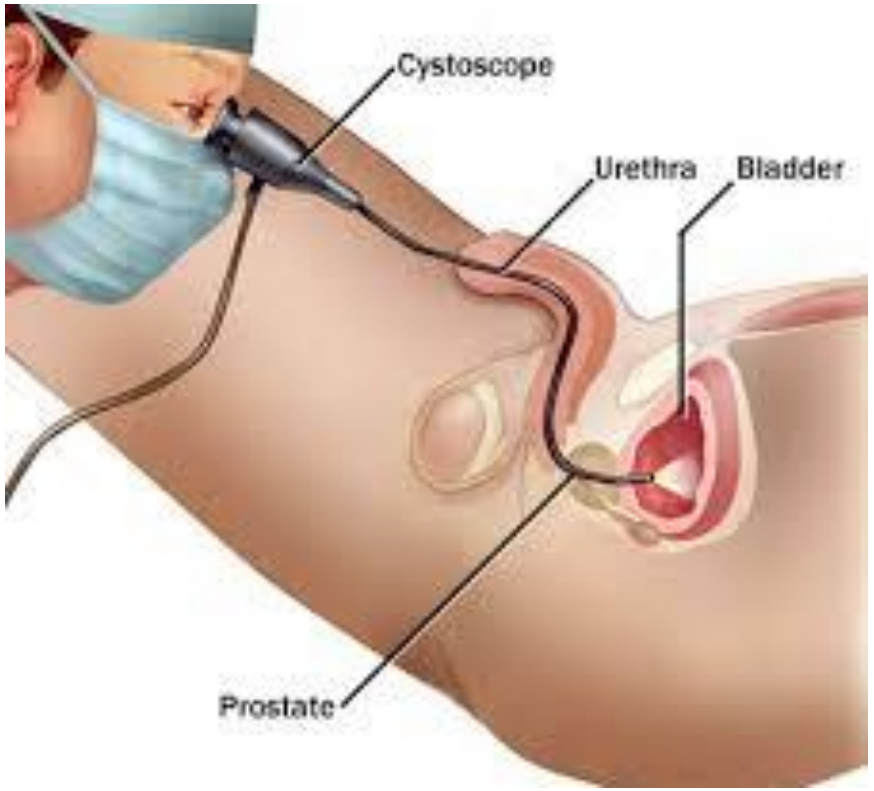
Non-muscle-invasive
Bladder Cancer
(TaT1 and CIS)

Cistoscopy





EAU Guidelines 2018
Babjuk et al. Eur Urol 2013;64:639-53

Cistoscopia

Recommendations	Strength rating
Take a patient history, focusing on urinary tract symptoms and haematuria.	Strong
Renal and bladder ultrasound and/or computed tomography-intravenous urography (CT-IVU) may be used during the initial work-up in patients with haematuria.	Weak
Once a bladder tumour has been detected, perform a computed tomography urography in selected cases (e.g., tumours located in the trigone, multiple- or high-risk tumours).	Strong
Perform cystoscopy in patients with symptoms suggestive of bladder cancer or during surveillance. It cannot be replaced by cytology or by any other non-invasive test.	Strong
In men, use a flexible cystoscope, if available.	Strong
Describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities during cystoscopy. Use a bladder diagram (Figure 5.1).	Strong
Use voided urine cytology as an adjunct to cystoscopy to detect high-grade tumour.	Strong
Perform cytology on fresh urine or urine with adequate fixation. Morning urine is not suitable because of the frequent presence of cytolysis.	Strong
Use the Paris system for cytology reporting.	Strong
Repeat urine cytology in patients with initial cytology results suspicious for high-grade urothelial carcinoma.	Weak

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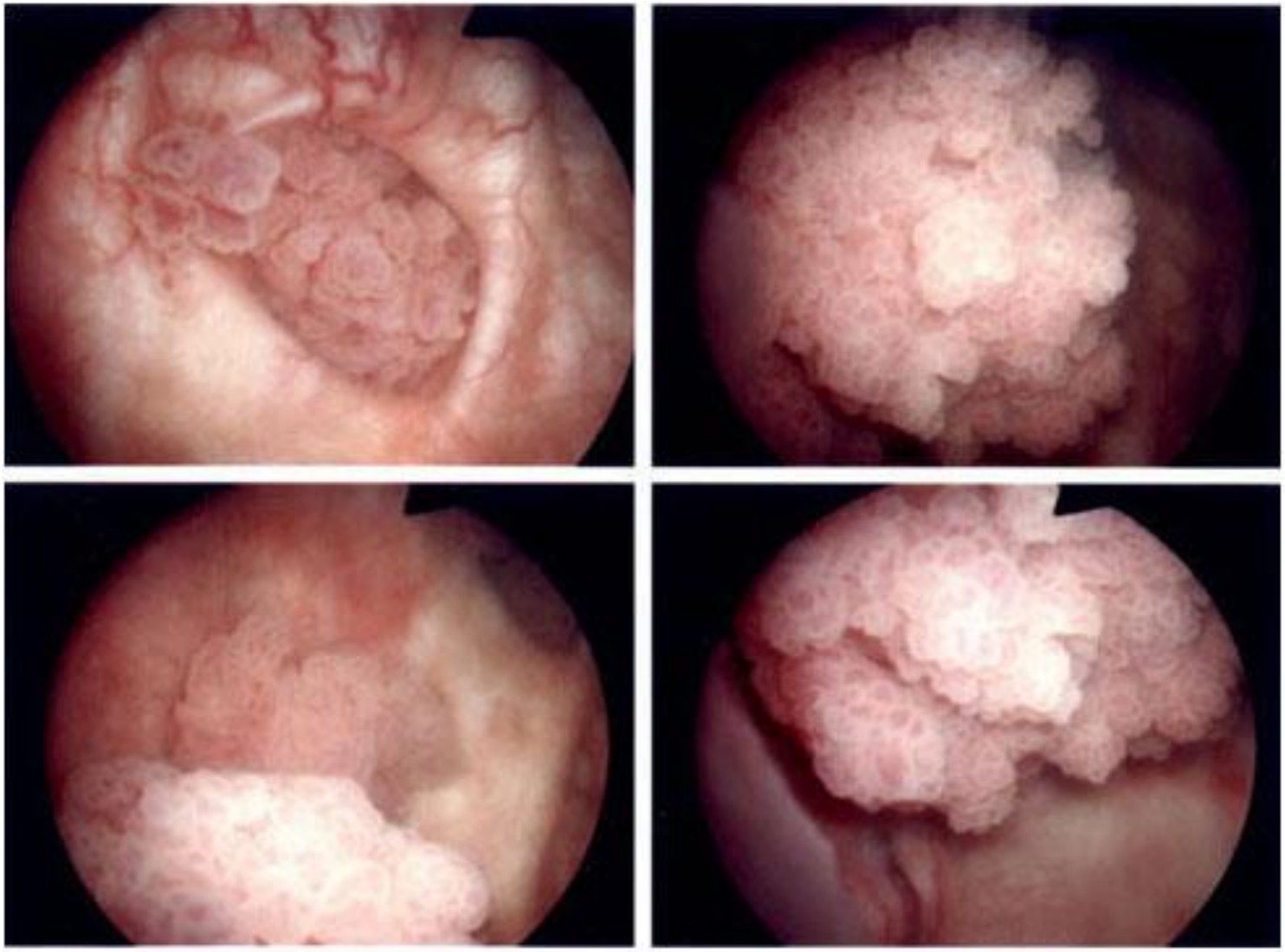
Non-muscle-invasive
Bladder Cancer
(TaT1 and CIS)

Cistoscopy



Cistoscopia in fluorescenza

Photodynamic diagnosis (PDD) is performed

using ultraviolet light after intravesical

instillation of 5-aminolevulanic acid (ALA) or

hexaminolevulanic acid (HAL)

Fluorescence-guided biopsy and resection

are more sensitive for diagnosing

malignancies, especially CIS

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Non-muscle-invasive
Bladder Cancer
(TaT1 and CIS)

Cystoscopy in PDD diagnoses more bladder neoplasms than in white light, particularly more high-risk neoplasms.

Furthermore, TURBT in PDD makes resection more complete and increases disease-free survival rates

Sensibillty

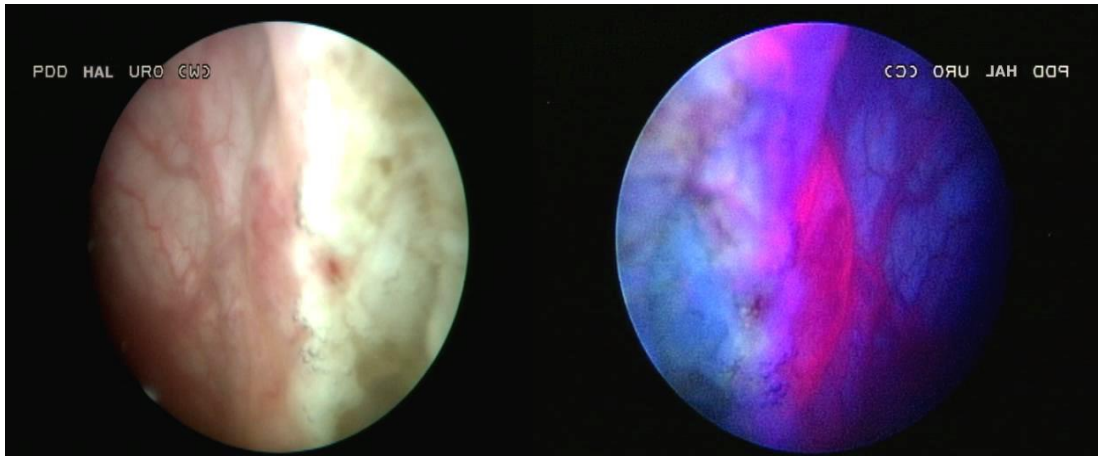
Mowatt G, et al. Int J Technol Assess Health Care. 2011

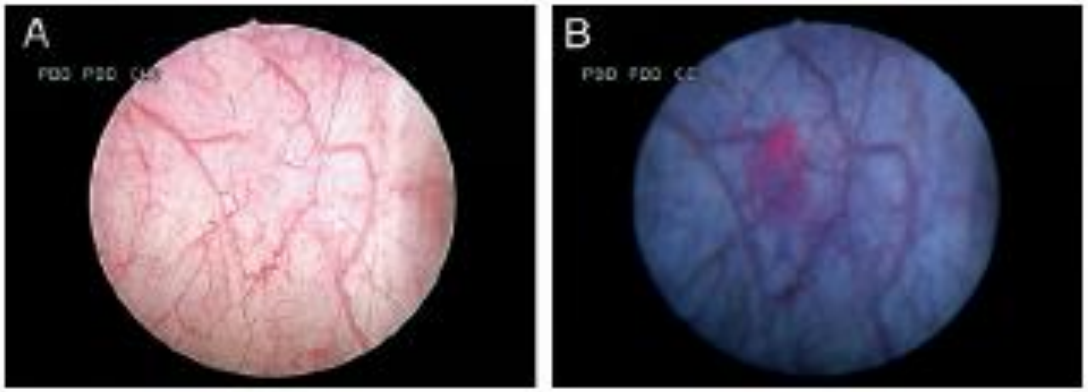
Photodynamic diagnosis has a lower specificity than that in white light (63% vs. 81%).
False positives may be due to inflammation or a recent TURB-T or the results of instillation with BCG.

Specificity

Draga,et al. Eur Urol, 2010
Ray, E.R., et al. BJU Int, 2010.

Fluorescence Cistoscopy





Ta grade 2 TCC on bladder floor under white light illumination (*A*) and using HAL fluorescence cystoscopy (*B*). Lesion was only visible under blue light.

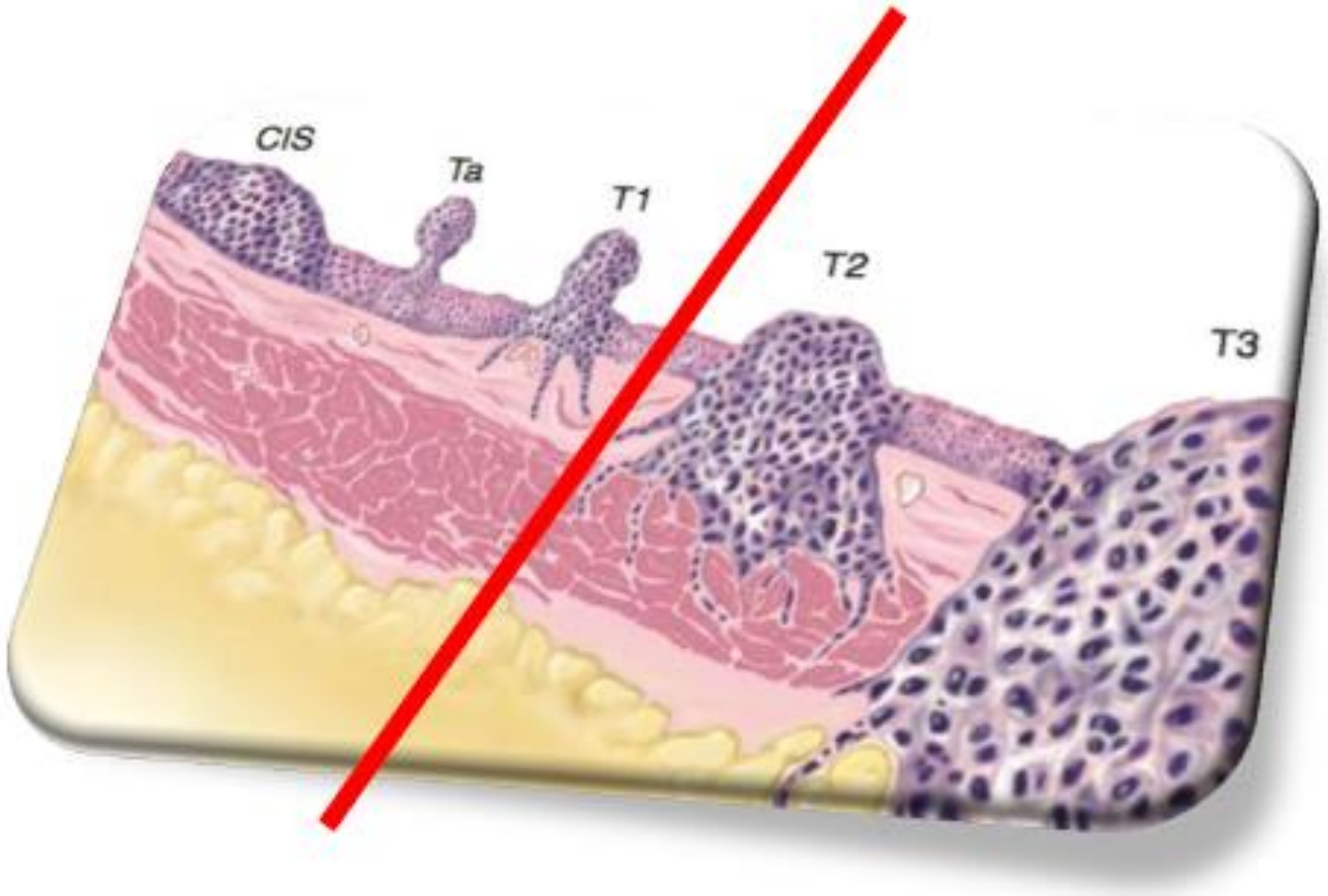
- A meta-analysis reports in the PDD arm an increase in cancer diagnoses of all risk groups and a reduction in the risk of recurrence at 12 months <10%

Burger et al 2013

- PDD is recommended in the suspicion of high-grade malignancy (patients with positive cytology or with a history of high-grade malignancy)

Therapy

NON MUSCLE INVASIVE



NMIBC: therapy

Transurethral resection of bladder tumour (TURB-T)

Adjuvant intravesical instillation (chemotherapy or Bacillus of Calmette-Guerin (BCG)

Radical cystectomy (if disease progression or BCG failure)

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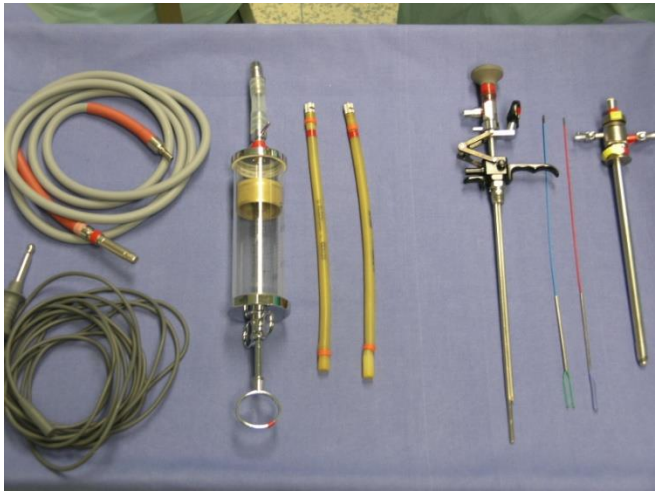
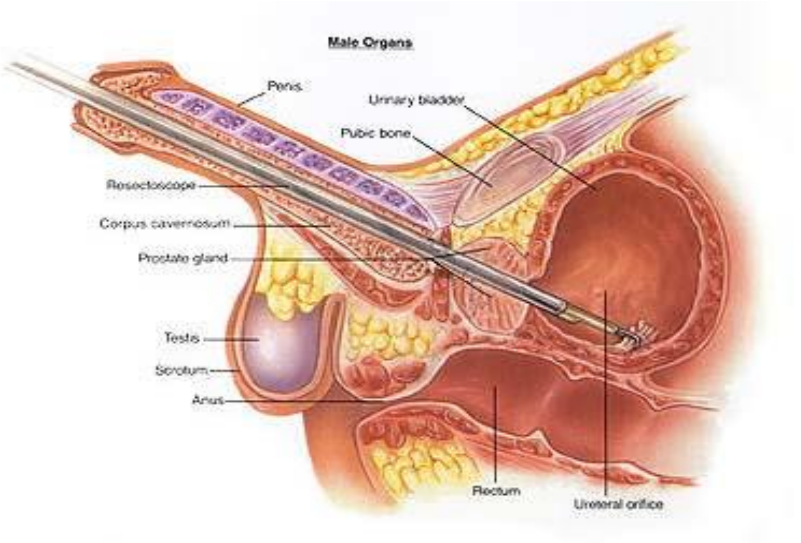
Bladder Cancer
(TaT1 and CIS)

TURB

The goal of TURB in Ta, T1 neoplasms is to obtain a correct diagnosis and remove all visible lesions.





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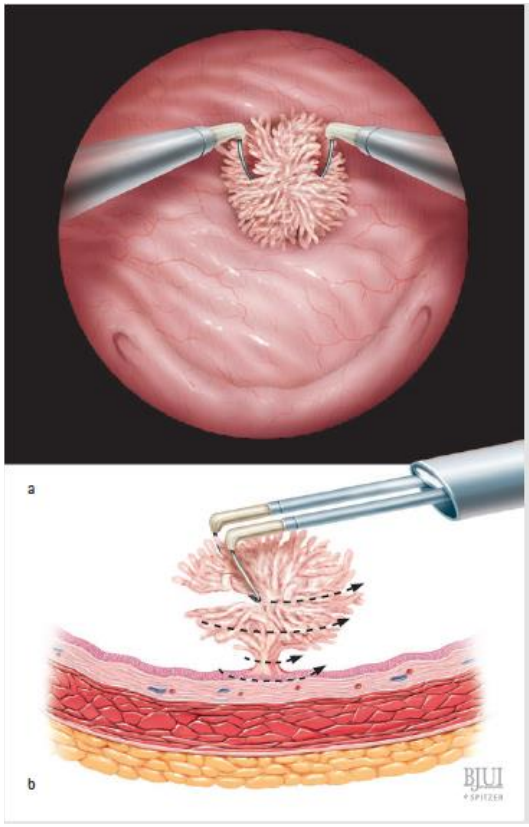
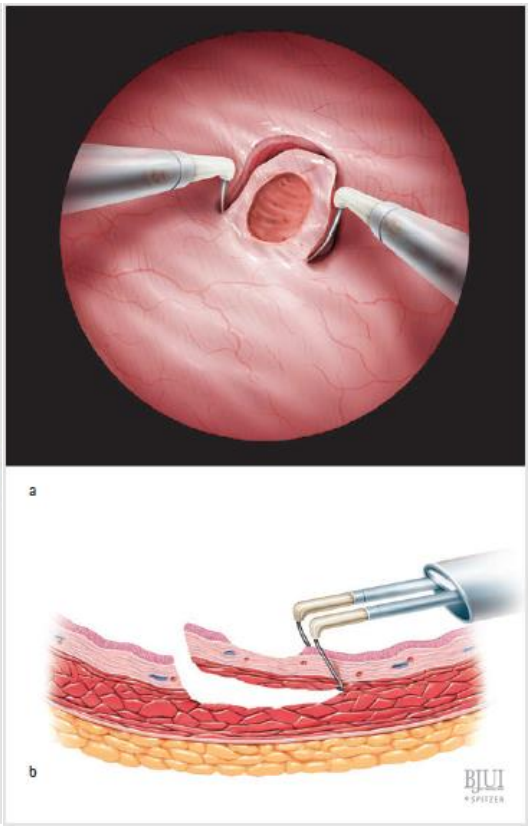
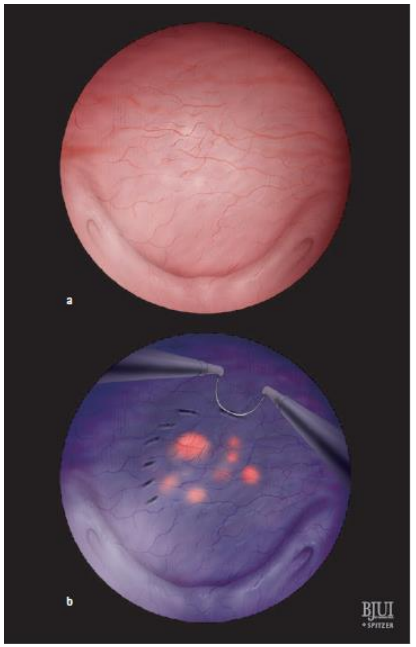
Bladder Cancer
(TaT1 and CIS)

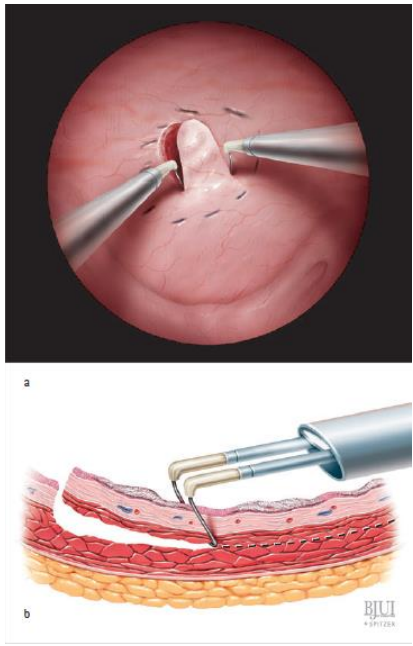
TURB





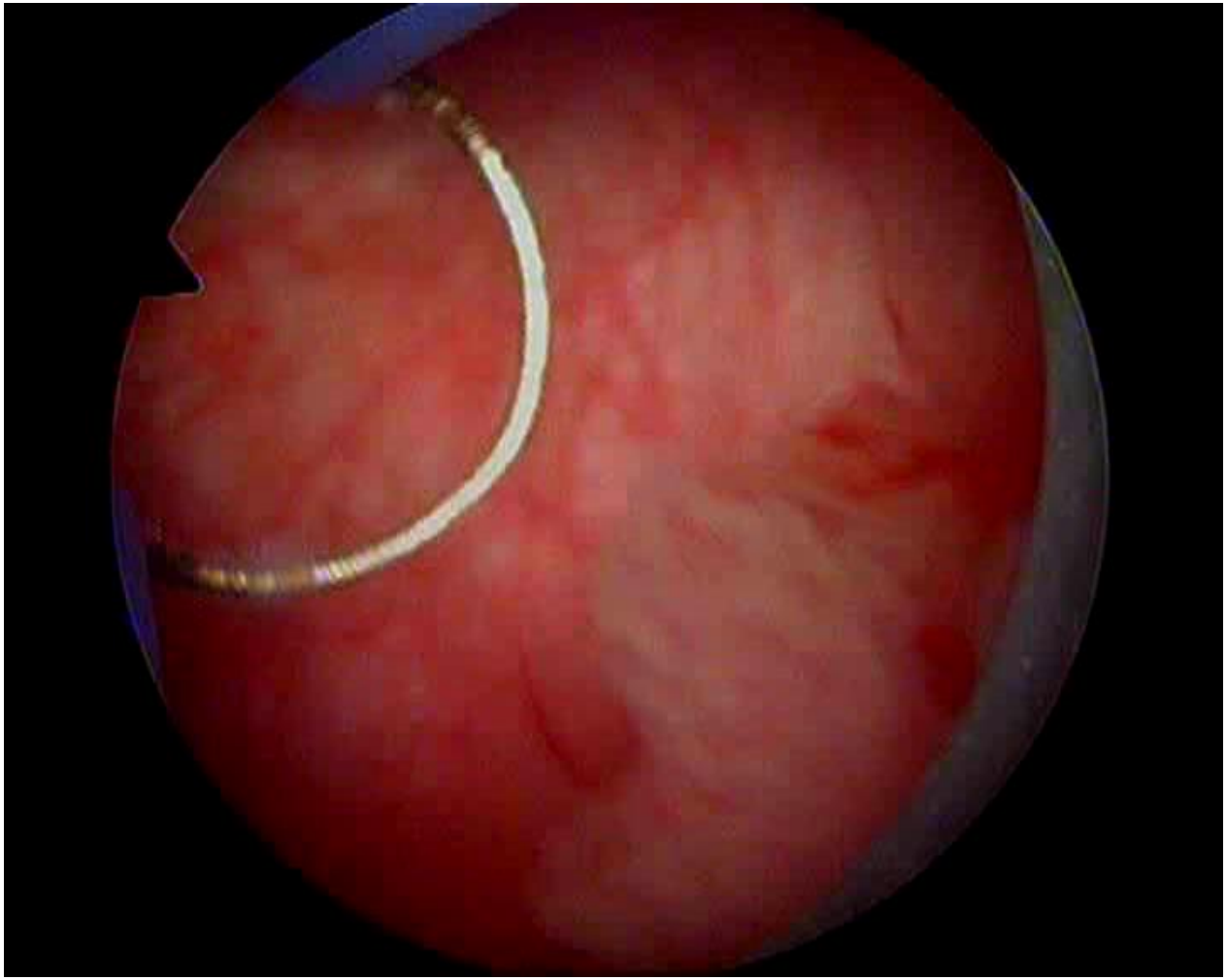
Papillary Lesion





CIS

TURB



NMIBC: EAU recomendations

Performance of individual steps	
Perform *en-bloc* resection or resection in fractions (exophytic part of the tumour, the underlying bladder wall and the edges of the resection area). The presence of detrusor muscle in the specimen is required in all cases except for TaG1/LG tumours.	Strong
Avoid cauterisation as much as possible during TURB to avoid tissue deterioration.	Strong
Take biopsies from abnormal-looking urothelium. Biopsies from normal-looking mucosa (trigone, bladder dome, and right, left, anterior and posterior bladder wall) are recommended when cytology is positive or when high-risk exophytic tumour is expected (non-papillary appearance). If equipment is available, perform fluorescence-guided (PDD) biopsies.	Strong
Take biopsy of the prostatic urethra in cases of bladder neck tumour, when bladder carcinoma *in situ* is present or suspected, when there is positive cytology without evidence of tumour in the bladder, or when abnormalities of the prostatic urethra are visible. If biopsy is not performed during the initial procedure, it should be completed at the time of the second resection.	Strong
Take the biopsy from abnormal areas in the prostatic urethra and from the precollicular area (between the 5 and 7 o'clock position) using a resection loop. In primary non-muscle-invasive tumours when stromal invasion is not suspected, cold-cup biopsy with forceps can be used.	Weak
Use methods to improve tumour visualization (FC, NBI) during TURB, if available.	Weak
Refer the specimens from different biopsies and resection fractions to the pathologist in separately labelled containers.	Weak
The TURB protocol must describe tumour appearance, all steps of the procedure, as well as the extent and completeness of resection.	Strong
In patients with positive cytology, but negative cystoscopy, exclude an upper tract urothelial carcinoma, CIS in the bladder (random biopsies or PDD-guided biopsies) and tumour in the prostatic urethra (prostatic urethra biopsy).	Strong
Perform a second TURB in the following situations: • after incomplete initial TURB, or in case of doubt about completeness of a TURB); • if there is no muscle in the specimen after initial resection, with the exception of TaLG/G1 tumours and primary CIS; • in T1 tumours.	Strong

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Non-muscle-invasive
Bladder Cancer
(TaT1 and CIS)

Second resection (RE-TUR)

The significant risk of residual tumor after a first TURB with Ta, T1 histological examination has been demonstrated by several (LE: 2a):

Persistence of disease after the first resection was observed in 33-55% of patients with T1 bladder neoplasm and in 41.4% of patients with TaG3 bladder neoplasm

The neoplasm is often underdiagnosed after the first resection

The probability that a muscle-infiltrating disease is found from the second resection of an initially T1 neoplasm varies from 4 to 25%

The probability is 45% if there was no muscle tissue in the sample

NMIBC: recidiva e progressione

- I pazienti con malattia Ta, T1 possono essere classificati in classi di rischio secondo **fattori prognostici**

- Per predire il rischio di recidiva e progressione a breve e a lungo termine l'EORTC Genito-Urinary cancer Group ha sviluppato dei sistemi di scoring e delle tabelle di rischio.

EORTC scoring system

Il sistema EORTC scoring è basato su

- Numero di tumori
- Dimensioni
- Prima recidiva
- Categoria T
- Presenza di CIS
- Grado della neoplasia

EAU Guidelines on
Non-muscle-invasive
Bladder Cancer
(TaT1 and CIS)

Table 6.1: Weighting used to calculate disease recurrence and progression scores

Factor	Recurrence	Progression
Number of tumours		
Single	0	0
2-7	3	3
> 8	6	3
Tumour diameter		
< 3 cm	0	0
> 3	3	3
Prior recurrence rate		
Primary	0	0
< 1 recurrence/year	2	2
> 1 recurrence/year	4	2
Category		
Ta	0	0
T1	1	4
Concurrent CIS		
No	0	0
Yes	1	6
Grade		
G1	0	0
G2	1	0
G3	2	5
Total Score	**0-17**	**0-23**

Table 6.2: Probability of recurrence and disease progression according to total score

Recurrence score	Probability of recurrence at 1 year		Probability of recurrence at 5 years	
	%	(95% CI)	%	(95% CI)
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 score	Probability of progression at 1 year		Probability of progression at 5 years	
	%	(95% CI)	%	(95% CI)
0	0.2	(0-0.7)	0.8	(0-1.7)
2-6	1	(0.4-1.6)	6	(5-8)
7-13	5	(4-7)	17	(14-20)
14-23	17	(10-24)	45	(35-55)

NB: Electronic calculators for Tables 6.1 and 6.2, which have been updated for the iPhone, iPad and Android phones and tablets, are available at http://www.eortc.be/tools/bladdercalculator/.

Per facilitare il trattamento è importante classificare i pazienti in classi di rischio.

EAU Guidelines on
Non-muscle-invasive
Bladder Cancer
(TaT1 and CIS)

NMIBC: reccomandations following TURBT

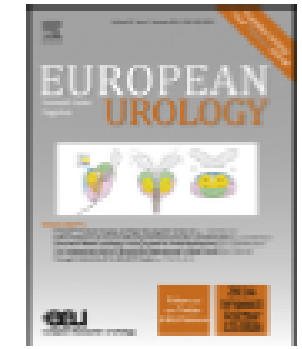
7.6. Treatment recommendations in Ta, T1 tumours and CIS according to risk stratification

Risk category	Definition	Treatment recommendation
Low-risk tumours	Primary, solitary, Ta, G1/PUNLMP, LG, < 3 cm, no CIS	One immediate instillation of intravesical chemotherapy after TURB.
Intermediate-risk tumours	All cases between categories of low and high risk	In patients with previous low recurrence rate (less than or equal to one recurrence per year) and expected EORTC recurrence score < 5, one immediate instillation of intravesical chemotherapy after TURB. In all patients either 1-year full-dose BCG treatment (induction plus 3-weekly instillations at 3,6 and 12 months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of 1 year.
High-risk tumours	Any of the following: • T1 tumours; • HG/G3 tumours; • CIS; • Multiple and recurrent and large (> 3 cm) Ta G1G2 tumours (all these conditions must be presented).	Intravesical full-dose BCG instillations for 1-3 years or cystectomy (in highest-risk tumours - *see below*).
	Subgroup of highest-risk tumours	
	T1G3/HG associated with concurrent bladder CIS, multiple and/or large T1G3/HG and/or recurrent T1G3/HG,T1G3/HG with CIS in the prostatic urethra, unusual histology of urothelial carcinoma, LVI (see Sections 4.6 and 6.2).	Radical cystectomy should be considered, in those who refuse intravesical full-dose BCG instillations for 1-3 years.
	BCG failures.	Radical cystectomy is recommended.

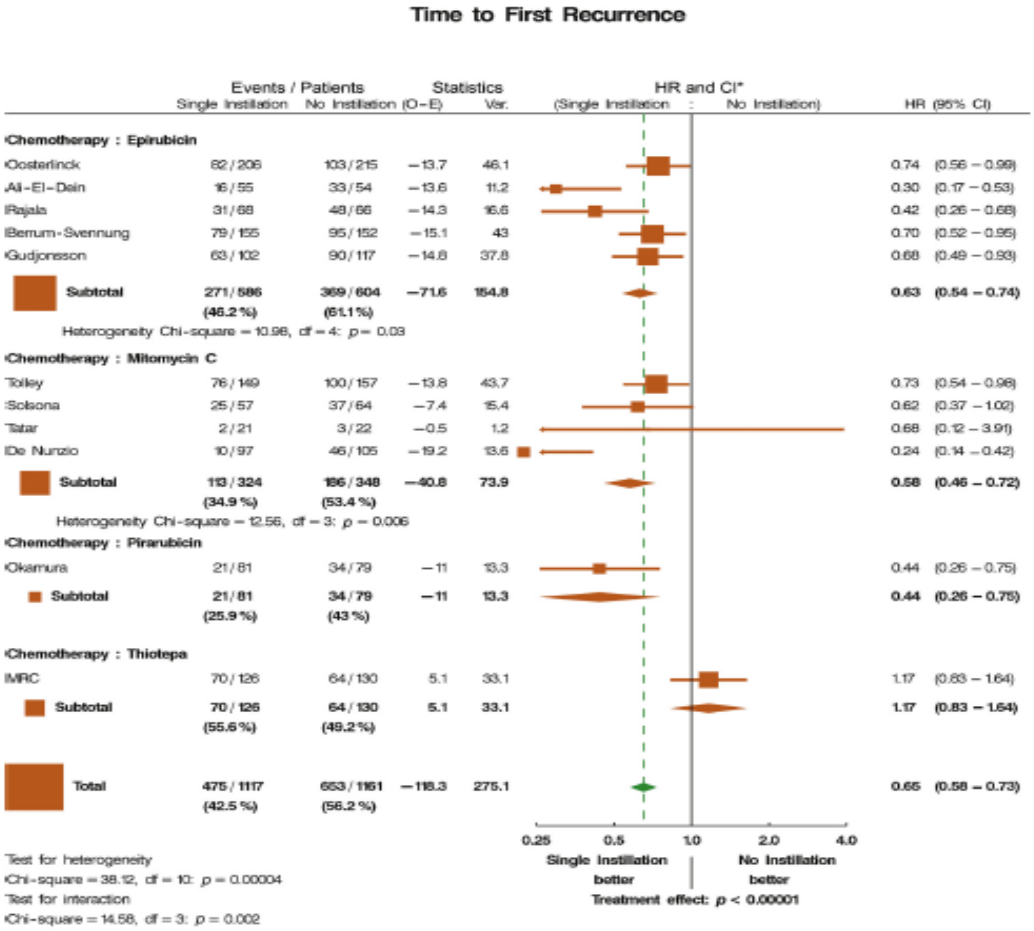
BCG=bacillus Calmette-Guérin; CIS=carcinoma in situ; HG=high-grade; LG=low-grade; LVI=lymphovascular invasion; TURB=transurethral resection of the bladder.

EAU Guidelines 2016

Systematic Review and Individual Patient Data Meta-analysis of Randomized Trials Comparing a Single Immediate Instillation of Chemotherapy After Transurethral Resection with Transurethral Resection Alone in Patients with Stage pTa–pT1 Urothelial Carcinoma of the Bladder: Which Patients Benefit from the Instillation?



Richard J. Sylvester[a,*], *Willem Oosterlinck*[b], *Sten Holmang*[c], *Matthew R. Sydes*[d], *Alison Birtle*[e], *Sigurdur Gudjonsson*[f], *Cosimo De Nunzio*[g], *Kikuo Okamura*[h], *Eero Kaasinen*[i], *Eduardo Solsona*[j], *Bedeir Ali-El-Dein*[k], *Can Ali Tatar*[l], *Brant A. Inman*[m], *James N'Dow*[n], *Jorg R. Oddens*[o], *Marek Babjuk*[p]



A single postoperative instillation reduces the relative risk of recurrence by 35% and the 5-year risk of recurrence by 14%

It is not effective in patients with

EORTC risk score ≥5.

BCG

It is currently the most effective intravesical therapy for the prophylaxis and treatment of superficial bladder cancer.

Effective in the treatment of residual papillary disease and carcinoma in situ and in the prophylaxis of superficial recurrence.

Mechanism not yet fully known IMMUNOMODULATOR
Stimulates T-Helper lymphocytes, B lymphocytes, macrophages Increased response to cytotoxic T cells Increased production of IL1, IL2, IL6, IFNg, TNFa Triggers immunological response type II (IL4)

76% average complete response
40-43% reduction in the recurrence rate compared to untreated (30-32% vs 73-75%).

BCG significantly reduces the progression, the disease-free interval and the percentage of patients with Cis undergoing Radical Cystectomy.

BCG

Effetti Collaterali

Possono essere GRAVI!!!

Disuria (91%)

Pollachiuria (90%)

Ematuria (46%)

Febbre (24%)

Malessere (18%)

Nausea (8%)

FOLLOW-UP

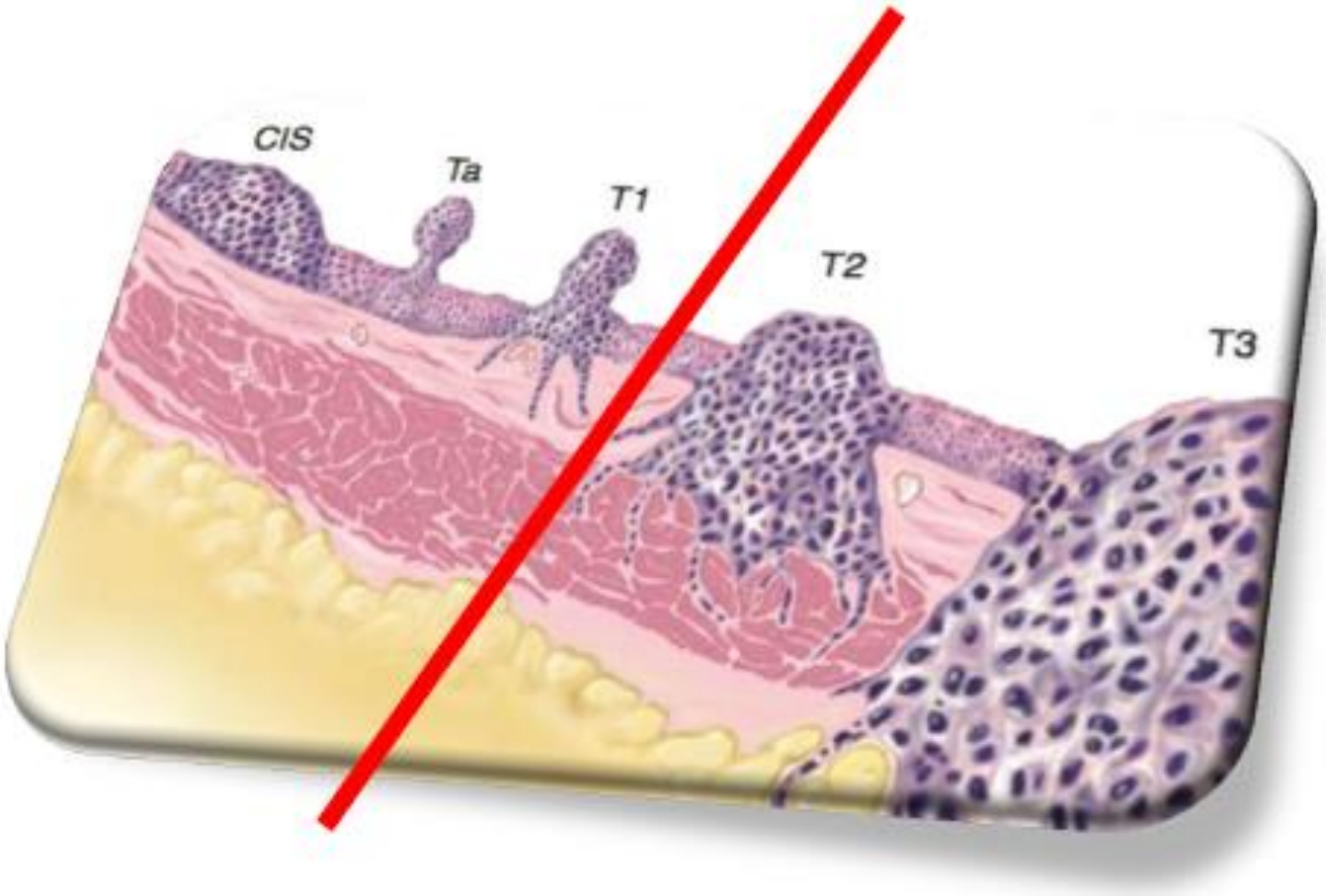
8.1 Summary of evidence and guidelines for follow-up of patients after transurethral resection of the bladder for non-muscle-invasive bladder cancer

Summary of evidence	LE
The first cystoscopy after transurethral resection of the bladder at 3 months is an important prognostic indicator for recurrence and progression.	1a
The risk of upper urinary tract (UUT) recurrence increases in patients with multiple- and high-risk tumours.	3

Recommendations	Strength rating
Base follow-up of TaT1 tumours and carcinoma *in situ* (CIS) on regular cystoscopy.	Strong
Patients with low-risk Ta tumours should undergo cystoscopy at three months. If negative, subsequent cystoscopy is advised nine months later, and then yearly for five years.	Weak
Patients with high-risk tumours should undergo cystoscopy and urinary cytology at three months. If negative, subsequent cystoscopy and cytology should be repeated every three months for a period of two years, and every six months thereafter until five years, and then yearly.	Weak
Patients with intermediate-risk Ta tumours should have an in-between (individualised) follow-up scheme using cystoscopy.	Weak
Regular (yearly) upper tract imaging (computed tomography-intravenous urography [CT-IVU] or IVU) is recommended for high-risk tumours.	Weak
Endoscopy under anaesthesia and bladder biopsies should be performed when office cystoscopy shows suspicious findings or if urinary cytology is positive.	Strong
Consider random (R)-biopsies or photodynamic diagnosis (PDD)-guided biopsies after intravesical treatment (at three or six months) in patients with CIS.	Weak
During follow-up in patients with positive cytology and no visible tumour in the bladder, R-biopsies or PDD-guided biopsies (if equipment is available) and investigation of extravesical locations (CT urography, prostatic urethra biopsy) are recommended.	Strong
In patients initially diagnosed with TaLG/G1-2 bladder cancer, use ultrasound of the bladder during surveillance in case cystoscopy is not possible or refused by the patient.	Weak

Therapy

MUSCLE INVASIVE



Neoplasia vescicale muscolo-invasiva (MIBC): stadiazione

The purpose of the imaging techniques is to show the extent of local invasion by the neoplasm, any involvement of the upper excretory route, any invasion of the lymph node or other distant organs (bones, liver, adrenals, lungs and peritoneum.

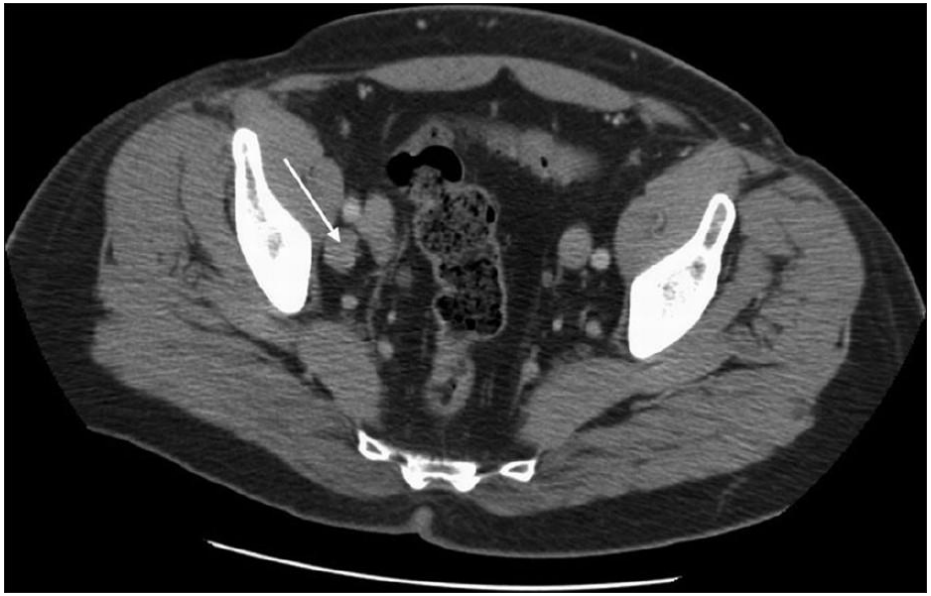
MRI is more accurate in local staging of the tumor

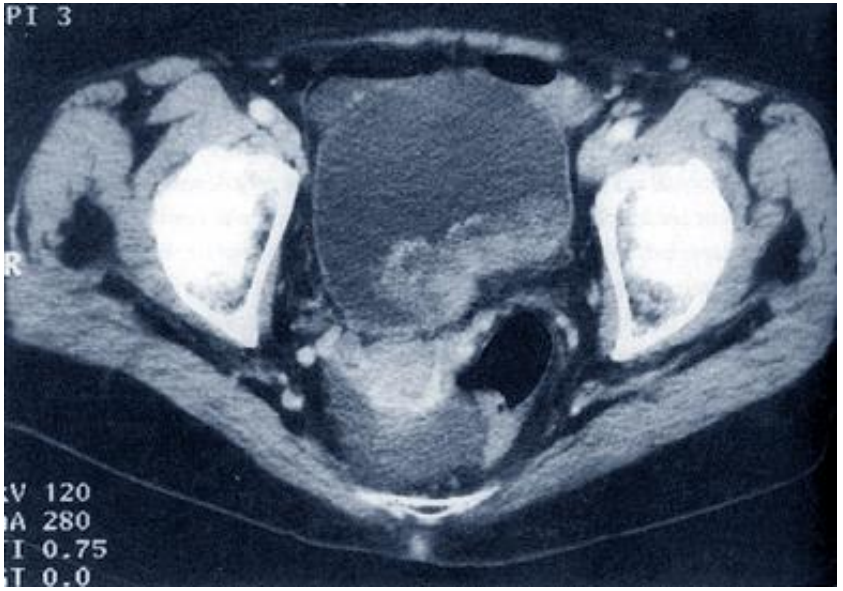
CT is not able to differentiate the stages between Ta and T3a but is useful for demonstrating the invasion of pervesical fat (T3b) and adjacent organs.

There is currently no evidence that supports the use of PET.

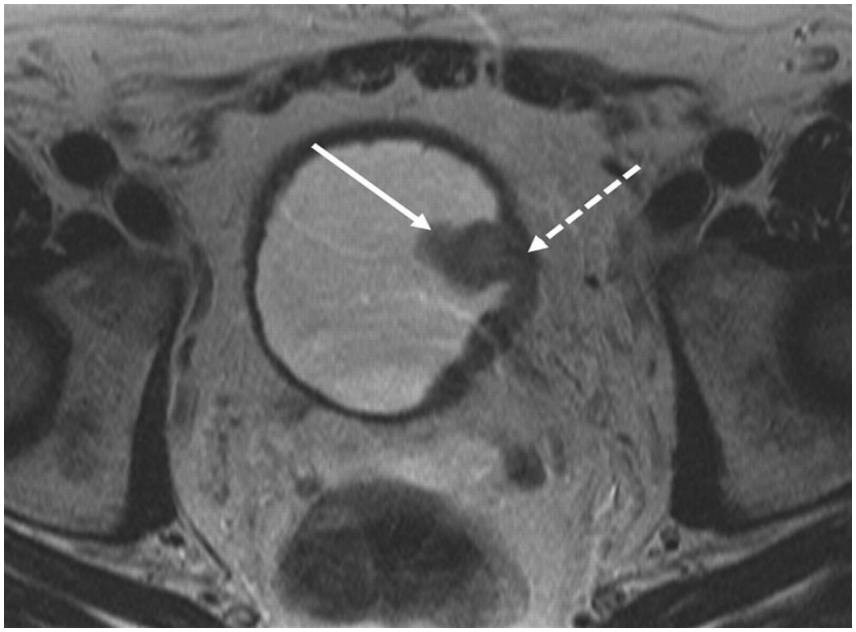
EAU Guidelines on
Muscle-invasive and Metastatic Bladder Cancer

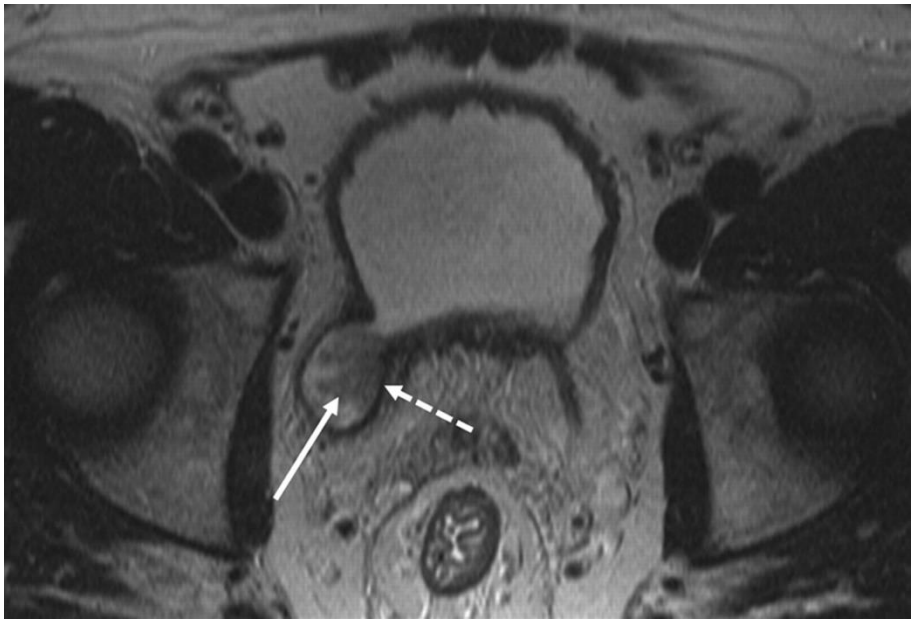
MIBC: staging





Role of MRI





Lymph node staging
CT of the abdomen and MRI

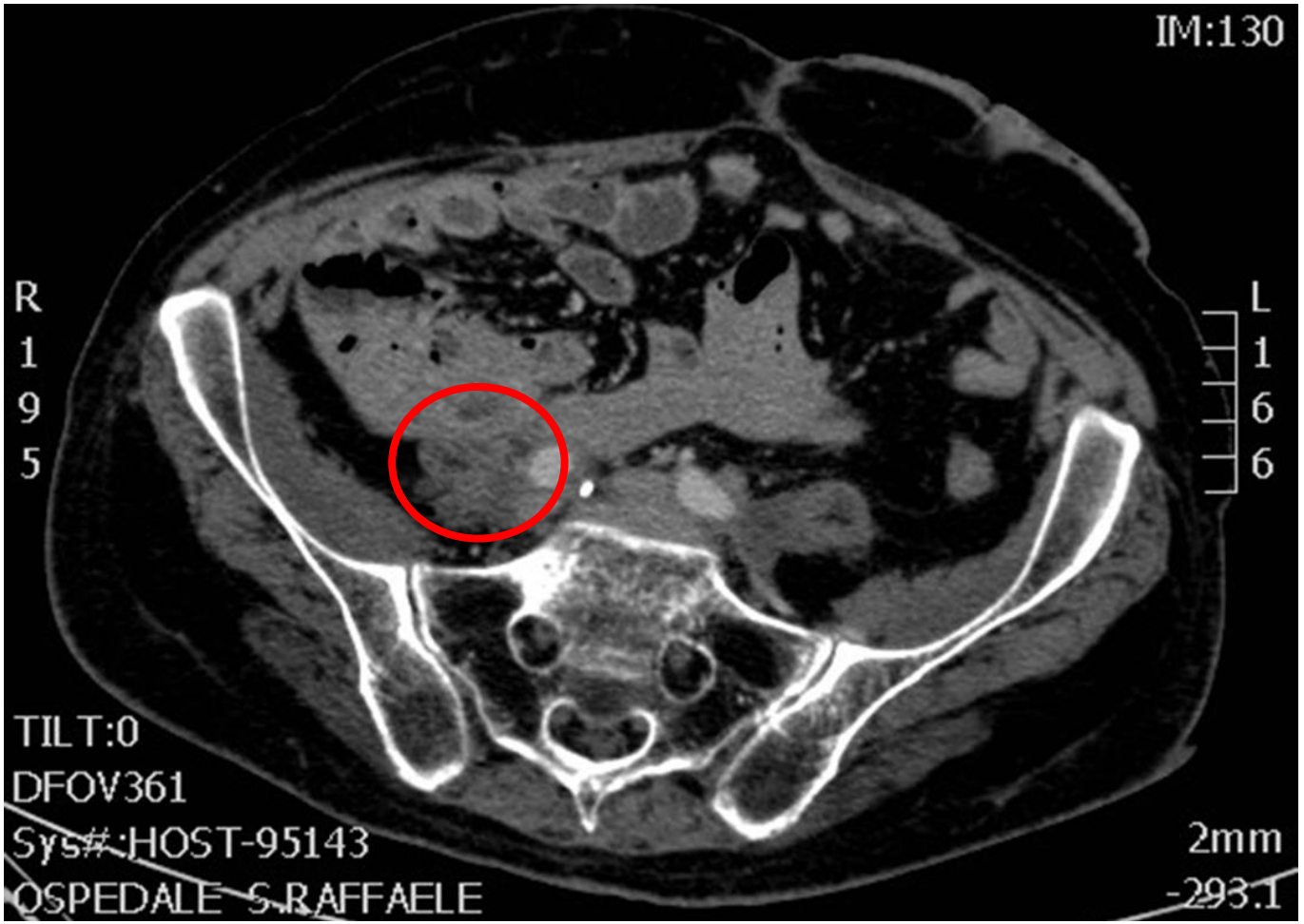
- CT and MRI have **low sensitivity** in detecting lymph node invasion (about 40%).

- This low sensitivity can be explained by the fact that the lymph node invasion is determined solely by dimensional criteria.

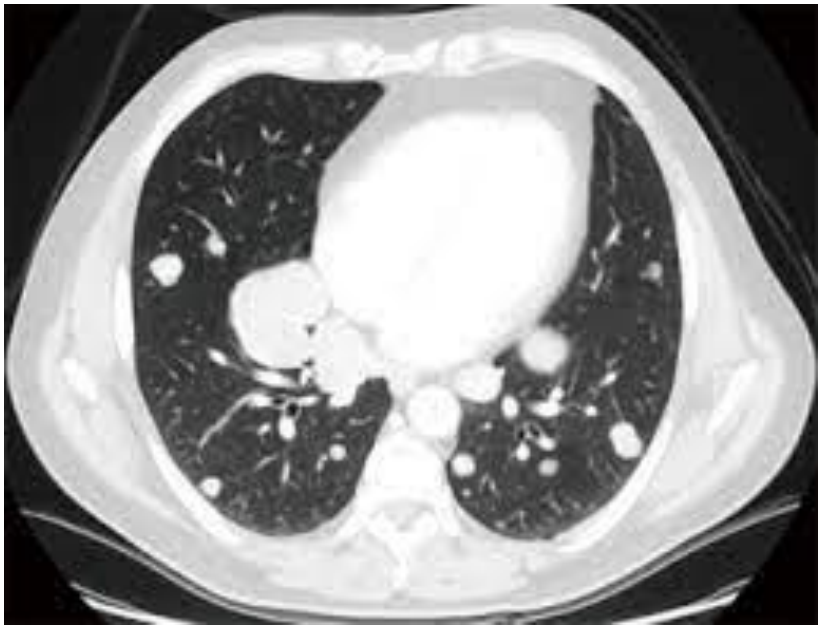
- MRI with DWI sequences can diagnose lymph node metastases in normal-sized lymph nodes, but its negativity does not exclude the presence of lymph node metastases.

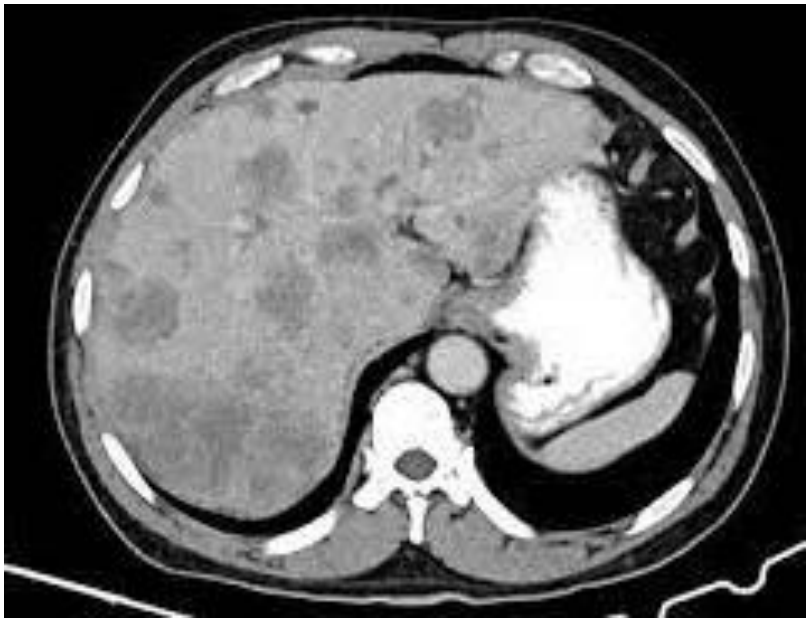
EAU - ESTRO - ESUR - SIOG Guidelines on Prostate Cancer 2018

N-Staging - CT Abdomed

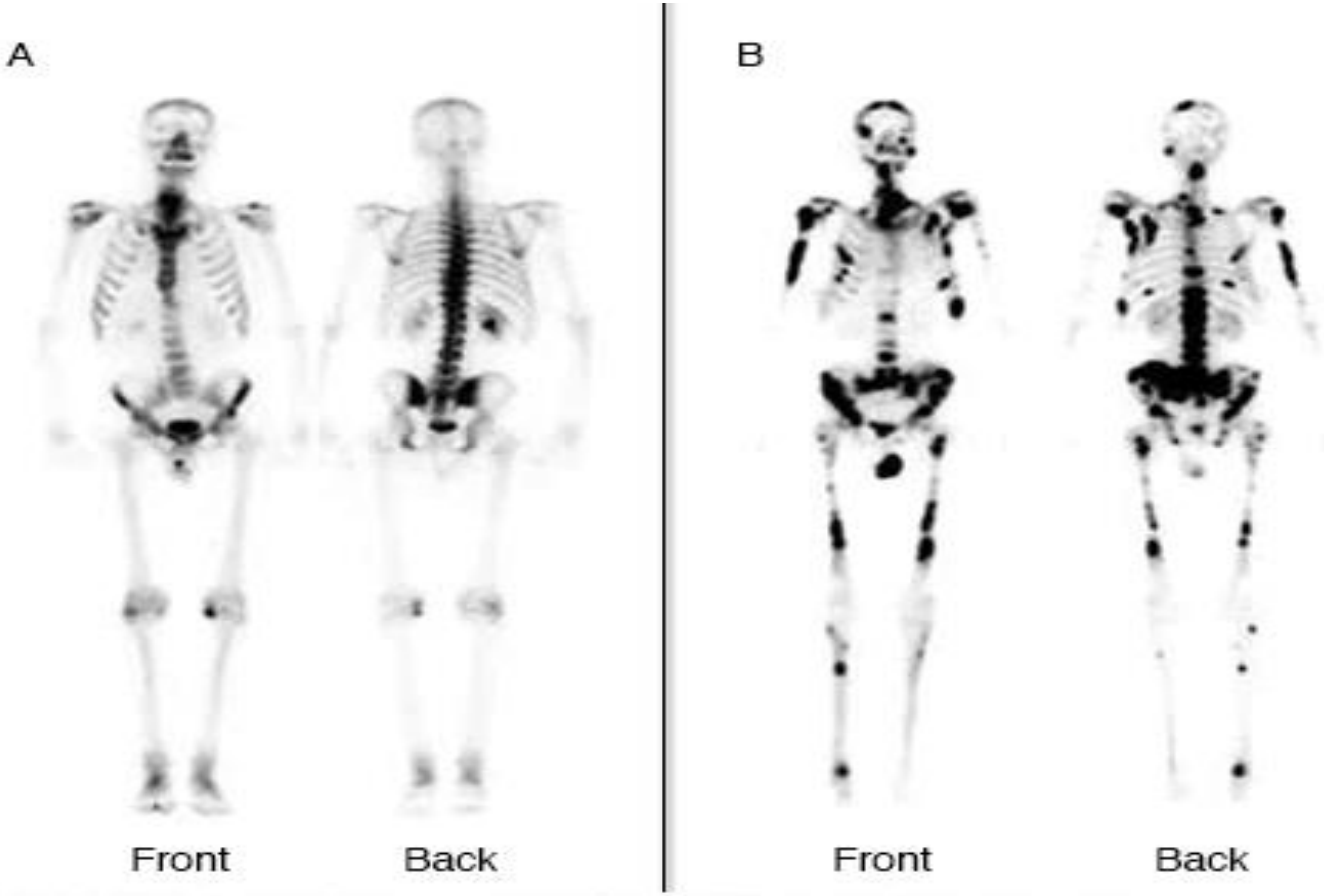


M-Staging
CT Abdomed and Chest

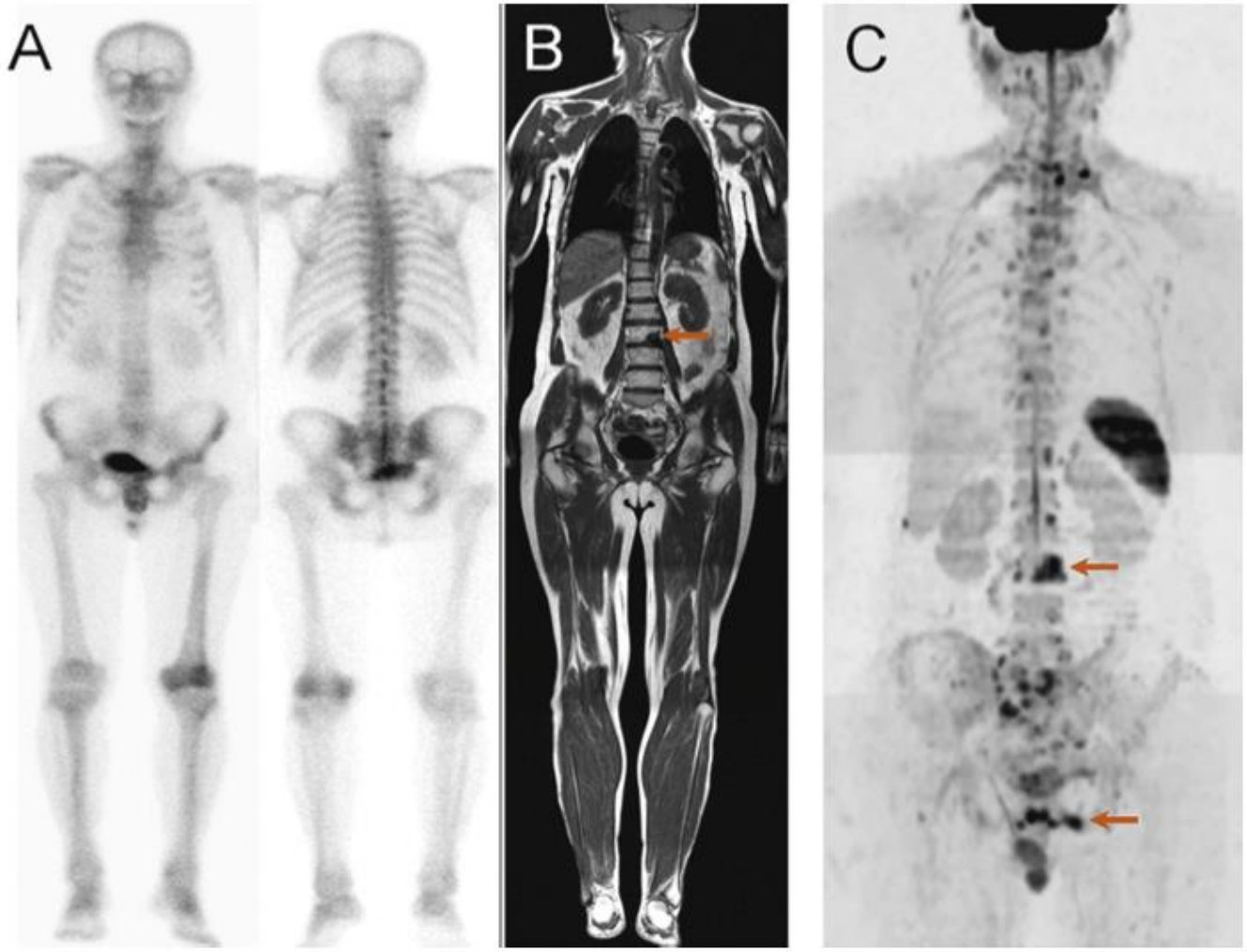




M-Staging Bone Scan



M-Staging FDG PET CT



MIBC: treatment

Radical cystectomy with extended lymphadenectomy is the standard treatment for MBIC

However, this gold standard offers a 5-year survival of 50%. Age and comorbidities should be considered before a patient is referred for radical cystectomy

Neo-adjuvant chemotherapy should be considered in patients with pT2-pT4a disease Non-invasive treatments (trimodal therapy) should be considered only in highly selected patients.

Neoadjuvant Chemotherapy

ADVANTAGES OF NEOADJUVANT CHEMOTHERAPY
Chemotherapy is given in an earlier period of time when the micrometastatic disease is expected to be less prevalent.
The patient is expected to tolerate chemotherapy better before cystectomy

DISADVANTAGES OF NEOADJUVANT CHEMOTHERAPY
The major drawback is the delay in local treatment in patients who are unresponsive or who develop disease progression
A longer interval of 12 weeks between diagnosis of muscle invasive disease and cystectomy is associated with worse outcomes

Neoadjuvant Chemotherapy

Table 82–4.

Randomized Phase III Trials of Neoadjuvant Chemotherapy

STUDY GROUP	NEOADJUVANT ARM	STANDARD ARM	PATIENTS	SURVIVAL
Aust/UK (Wallace et al, 1991)	DDP/RT	RT	255	No difference
Canada/NCI (Coppin et al, 1996)	DDP/RT or preop RT + Cyst	RT or preop RT + Cyst	99	No difference
Spain (CUETO) (Martinez Pineiro et al, 1995)	DDP/Cyst	Cyst	121	No difference
EORTC/MRC (International Collaboration of Trialists, 1999)	CMV/RT or Cyst	RT or Cyst	976	5.5% difference in favor of CMV
SWOG Intergroup (Natale et al, 2001)	M-VAC/Cyst	Cyst	298	Trend in benefit with M-VAC ($P = .06$)
Italy (GUONE) (Bassi et al, 1998)	M-VAC/Cyst	Cyst	206	No difference
Italy (GISTV, 1996)	M-VEC/Cyst	Cyst	171	No difference
Genoa (Orsatti et al, 1995)	DDP/5FU/RT/Cyst	Cyst	104	No difference
Nordic 1 (Malmstrom et al, 1996)	ADM/DDP/RT/Cyst	RT/Cyst	311	No difference, 15% benefit with ADM + DDP in T3-T4a
Nordic 2 (Sherif et al, 2002)	MTX/DDP/Cyst	Cyst	317	No difference
Abol-Enein (1997)	CarboMV/Cyst	Cyst	194	Benefit with CarboMV

ADM, doxorubicin; Carbo, carboplatin; Cyst, cystectomy; DDP or C, cisplatin; E, epirubicin; MTX, methotrexate; RT, radiation therapy; V, vinblastine.

Sternberg et al. Urology. 2007

Conclusions	LE
Neoadjuvant chemotherapy has its limitations regarding patient selection, current development of surgical techniques, and current chemotherapy combinations.	3
Neoadjuvant cisplatin-containing combination chemotherapy improves overall survival (OS) (8% at five years).	1a
Neoadjuvant treatment of responders and especially patients who show complete response (pT0 N0) has a major impact on OS.	2
Currently, no tools are available to select patients who have a higher probability of benefitting from neoadjuvant chemotherapy (NAC). In the future, genetic markers, in a personalised medicine setting, might facilitate the selection of patients for NAC and differentiate responders from non-responders.	

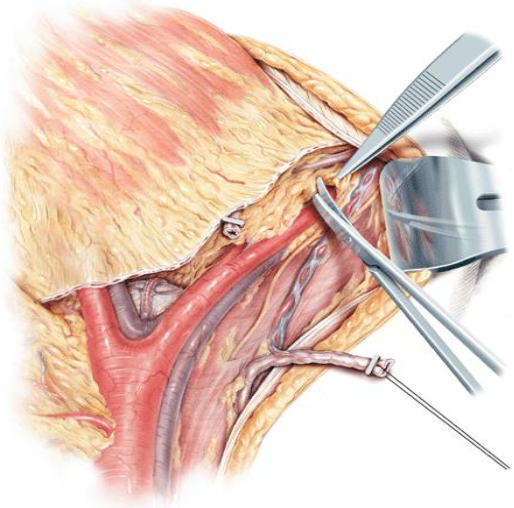
EAU Guidelines on
Muscle-invasive and Metastatic Bladder Cancer

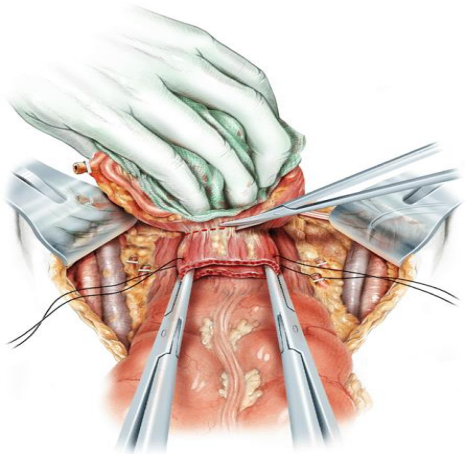
Chemioterapia neoadiuvante

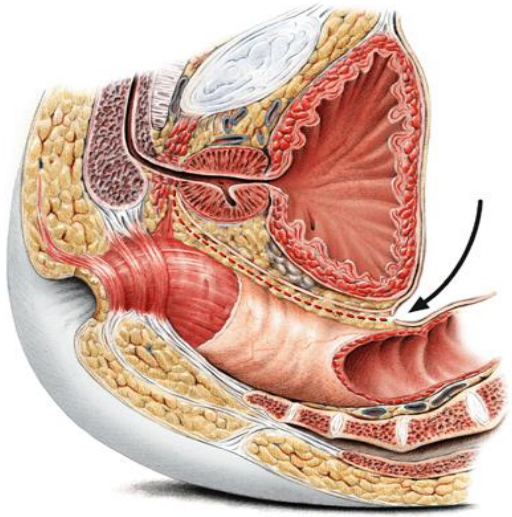
Recommendations	Strength rating
Offer neoadjuvant chemotherapy (NAC) for T2-T4a, cN0M0 bladder cancer. In this case, always use cisplatin-based combination therapy.	Strong
Do not offer NAC to patients who are ineligible for cisplatin-based combination chemotherapy.	Strong

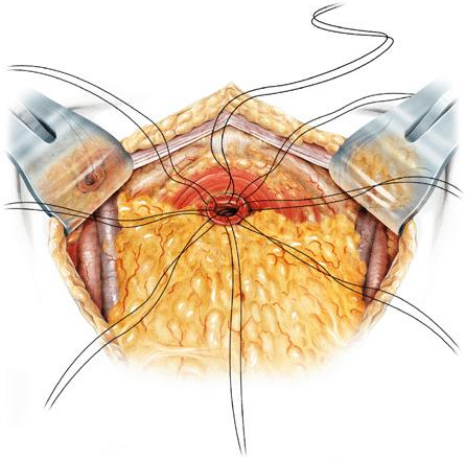
EAU Guidelines on
Muscle-invasive and Metastatic Bladder Cancer

Cistectomia radicale









Radical cystectomy involves the removal of the bladder, soft tissues per bladder, prostate and seminal vesicles in men.

In women, it includes the removal of the bladder, uterus / uterine cervix, ovaries and the anterior wall of the vagina.

In selected cases, preservation of the uterus and vagina or nerve-sparing procedures.

Indications

In accordance with the UAE guidelines it is reasonable to propose an early radical cystectomy to patients with non-muscle invasive disease at higher risk of progression:

T1G3 / high-grade CIS-associated neoplasm;

Multiple or large or recurrent T1G3 neoplasms

T1G3 neoplasms with CIS in the prostatic urethra TURB

Lymphovascular invasion BCG failure.

- > T2

EAU Guidelines on
Non-muscle-invasive
Bladder Cancer
(TaT1 and CIS)

EAU Guidelines on
Muscle-invasive
and Metastatic
Bladder Cancer

lymphadenectomy

Recommendations	Strength rating
Do not delay cystectomy for > 3 months as it increases the risk of progression and cancer-specific mortality.	Strong
Before cystectomy, fully inform the patient about the benefits and potential risks of all possible alternatives. The final decision should be based on a balanced discussion between the patient and the surgeon.	Strong
Do not offer an orthotopic bladder substitute diversion to patients who have a tumour in the urethra or at the level of urethral dissection.	Strong
Pre-operative bowel preparation is not mandatory. "Fast track" measurements may reduce the time of bowel recovery.	Strong
Offer radical cystectomy in T2-T4a, N0M0, and high-risk non-MIBC (as outlined above).	Strong
Perform a lymph node dissection as an integral part of cystectomy.	Strong
Do not preserve the urethra if margins are positive.	Strong

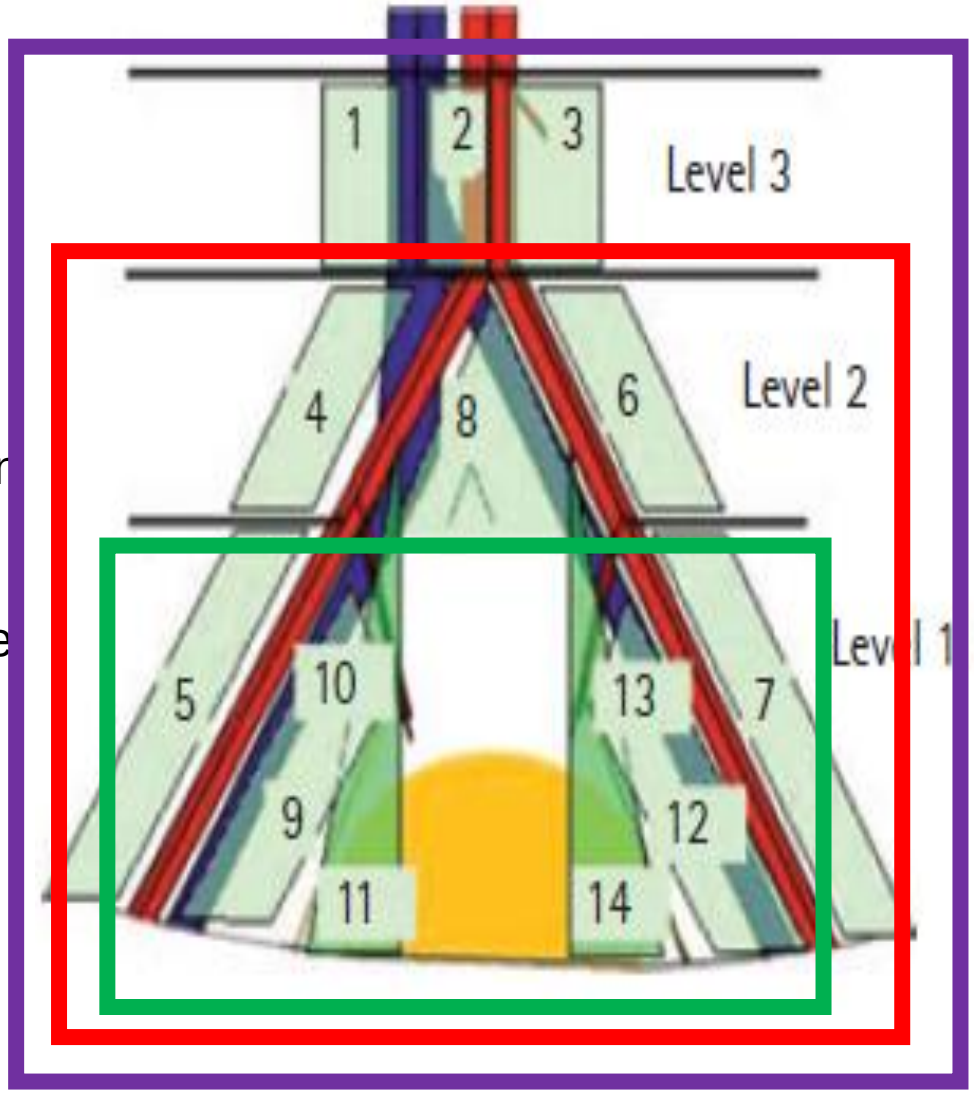
EAU Guidelines on
Muscle-invasive and Metastatic Bladder Cancer

Types of lymphadenectomy

Super-extended lymphadenectomy reaches cranially at the level of the inferior mesenteric artery.

ePLND extends proximally to the common iliac artery up to at least the intersection with the ureter, but more commonly to the aortic bifurcation.

sPLND is anatomically limited to the region under the bifurcation of the common iliac artery and extends from the genitofemoral nerve laterally to the bladder pedicle medially



Wiesner C et al. BJU Int. 2009

Jensen JB et al. Int J Urol. 2012

EUROPEAN UROLOGY 66 (2014) 1065–1077

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Review – Bladder Cancer

The Impact of the Extent of Lymphadenectomy on Oncologic Outcomes in Patients Undergoing Radical Cystectomy for Bladder Cancer: A Systematic Review

Harman M. Bruins[a,], Erik Veskimae[b], Virginia Hernandez[c], Mari Imamura[d], Molly M. Neuberger[e], Philip Dahm[e,f], Fiona Stewart[d], Thomas B. Lam[d], James N'Dow[d], Antoine G. van der Heijden[a], Eva Compérat[g], Nigel C. Cowan[h], Maria De Santis[i], Georgios Gakis[j], Thierry Lebret[k], Maria J. Ribal[l], Amir Sherif[m], J. Alfred Witjes[a]*

In terms of oncological outcomes, each type of lymphadenectomy is better than the absence of lymphadenectomy for patients undergoing

An extended lymphadenectomy could improve outcomes although there is no evidence that a super-extended lymphadenectomy would be of further benefit.

At the state of the art, there is no strong enough evidence to recommend the ideal extension of lymphadenectomy**.**

Urinary Diversions

Types of derivation

Incontinents

Ureterocutaneostomy

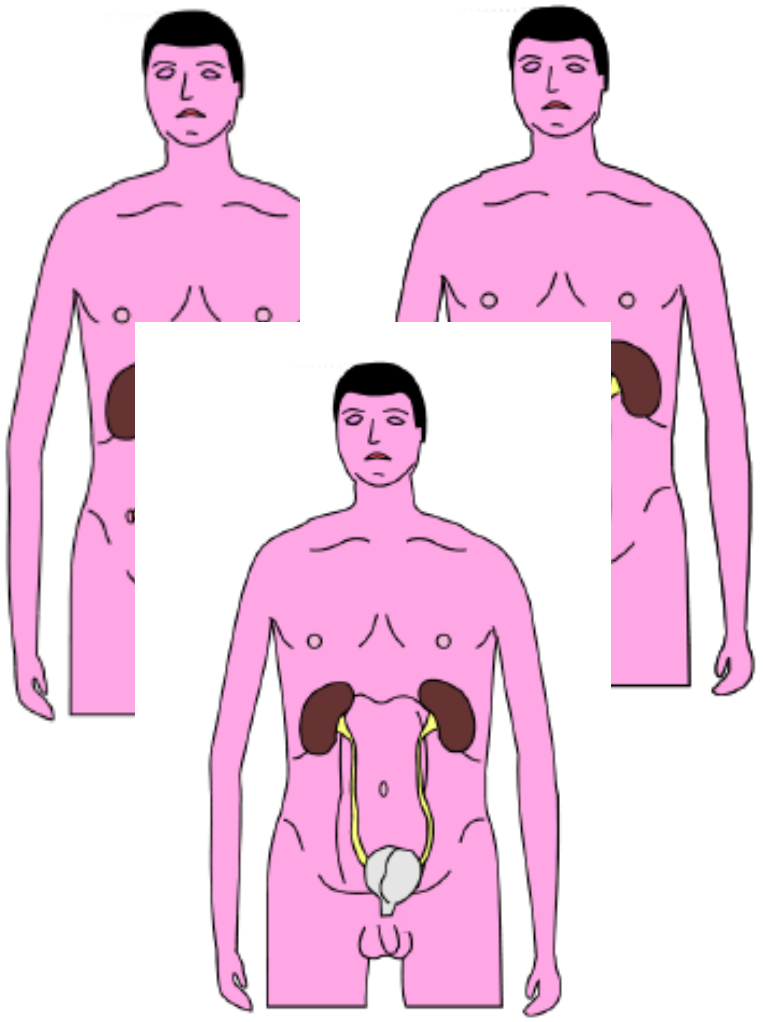
Ureteroileocutaneostomy

Continents

Ureterosigmoidostomy

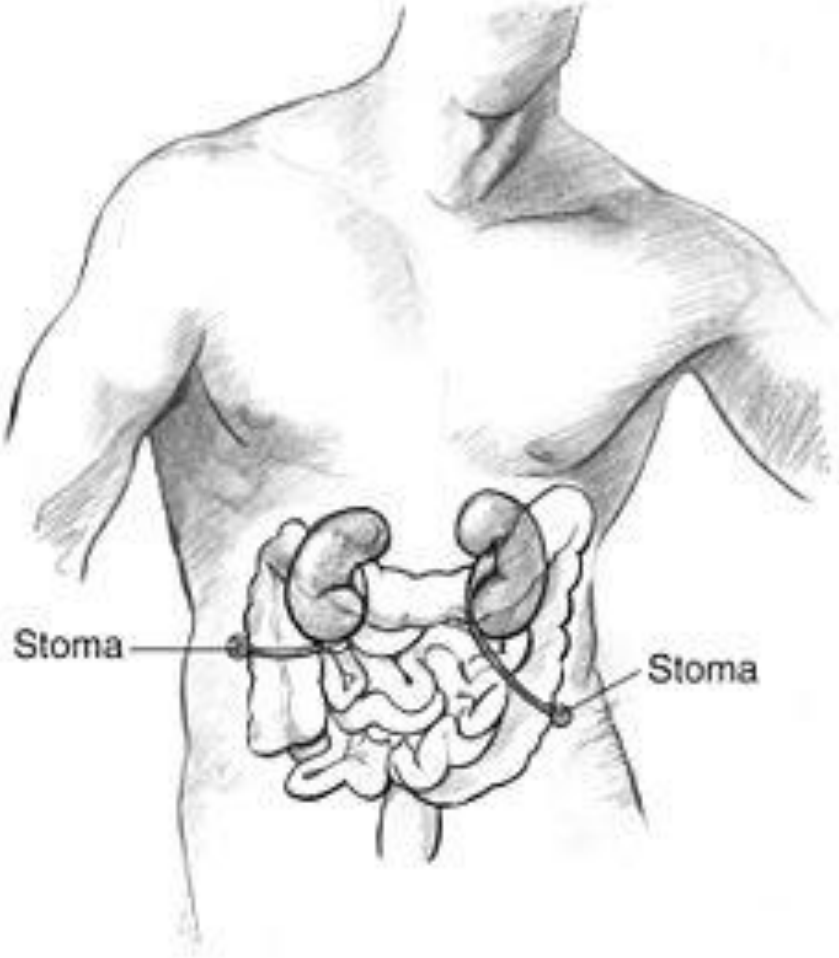
Orthotopic neobladder

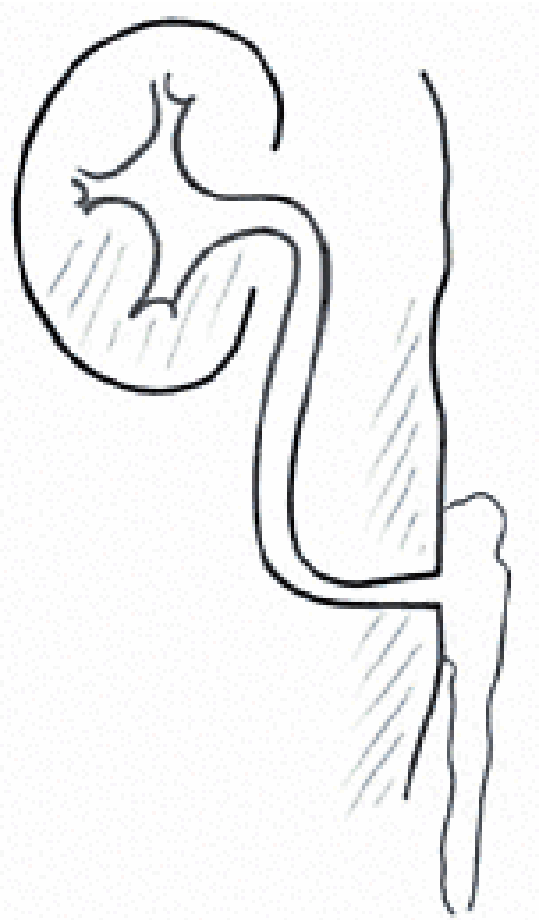
Heterotopic neobladder



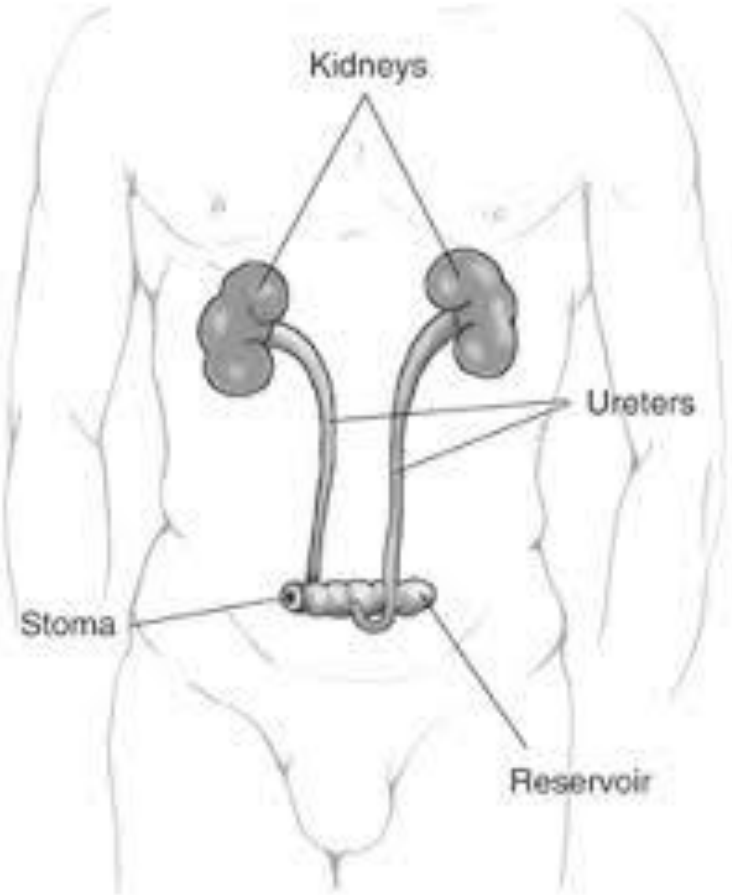
Colombo r E Naspro R et al. Eur Urol Supplem 9(2010) 736 – 744

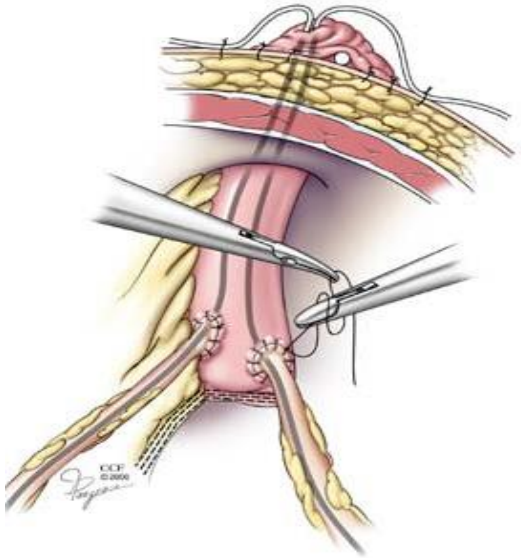
Continent Diversion: Ileal Conduit



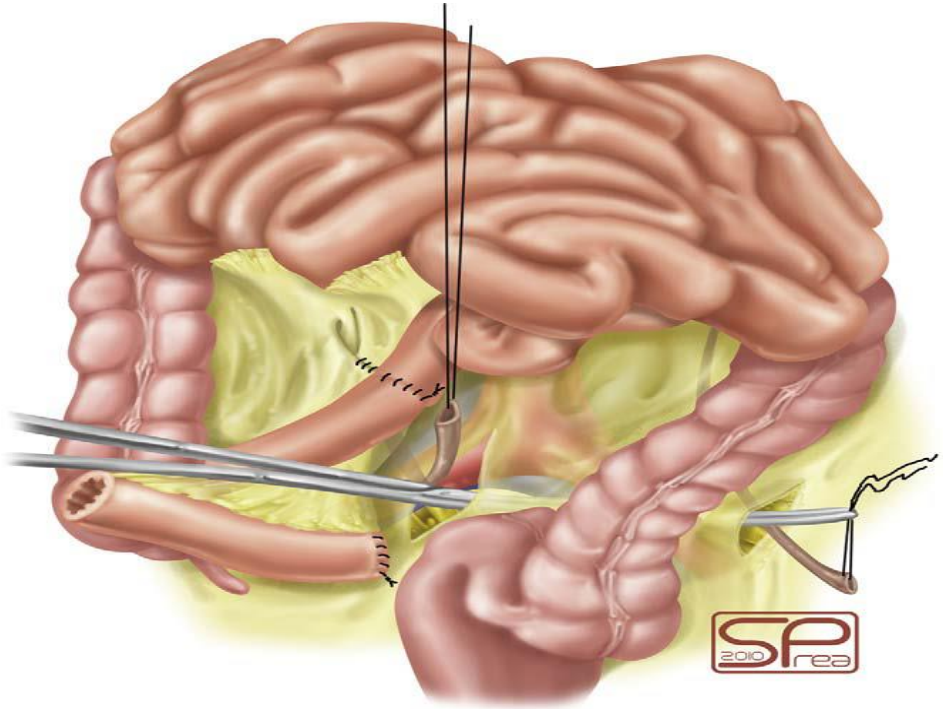


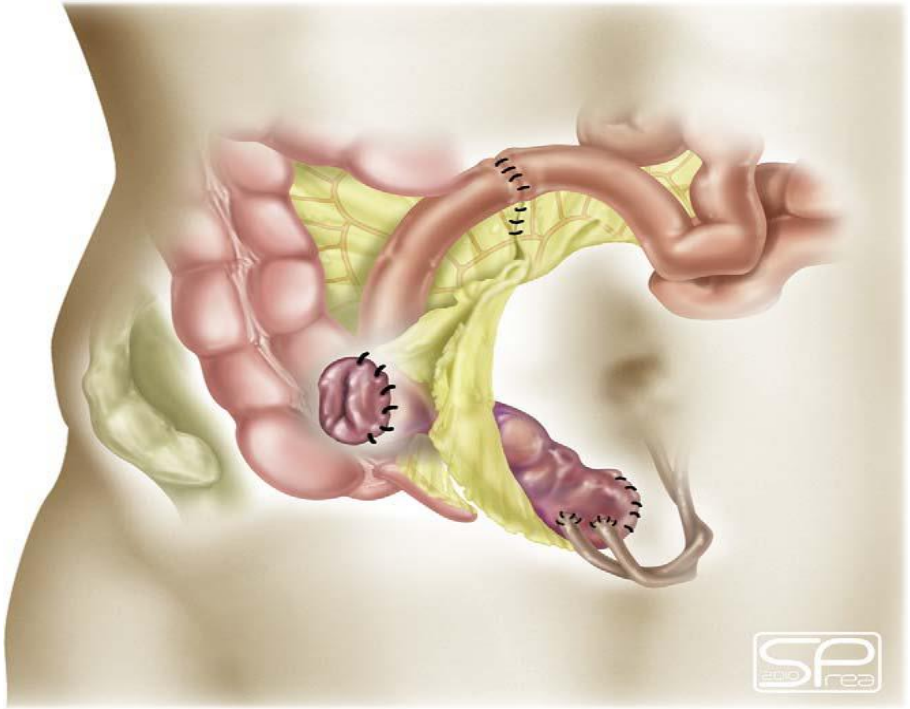
Continent Diversion: Ileal Conduit





Continent Diversion: Ileal Conduit

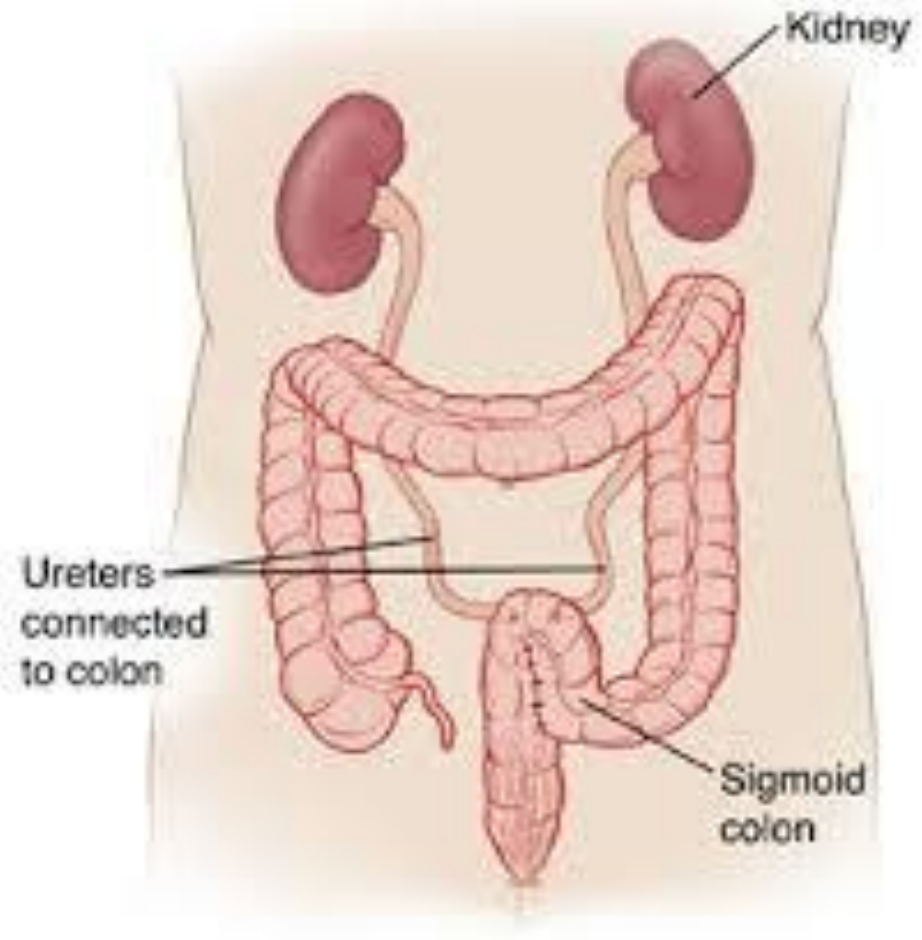




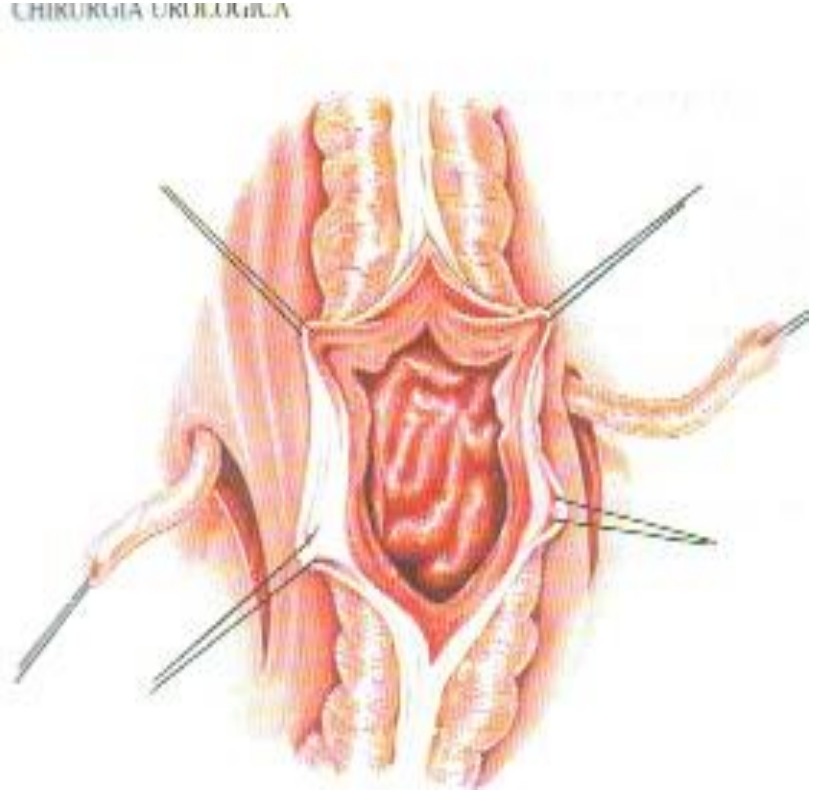
Isolation of the ureters. The left ureter generally requires a more proximally extended isolation. Transposition of the left ureter to the right side of the pelvis through a tunnel prepared at the bases of the sigmoid mesentery in front of the common iliac vessels.

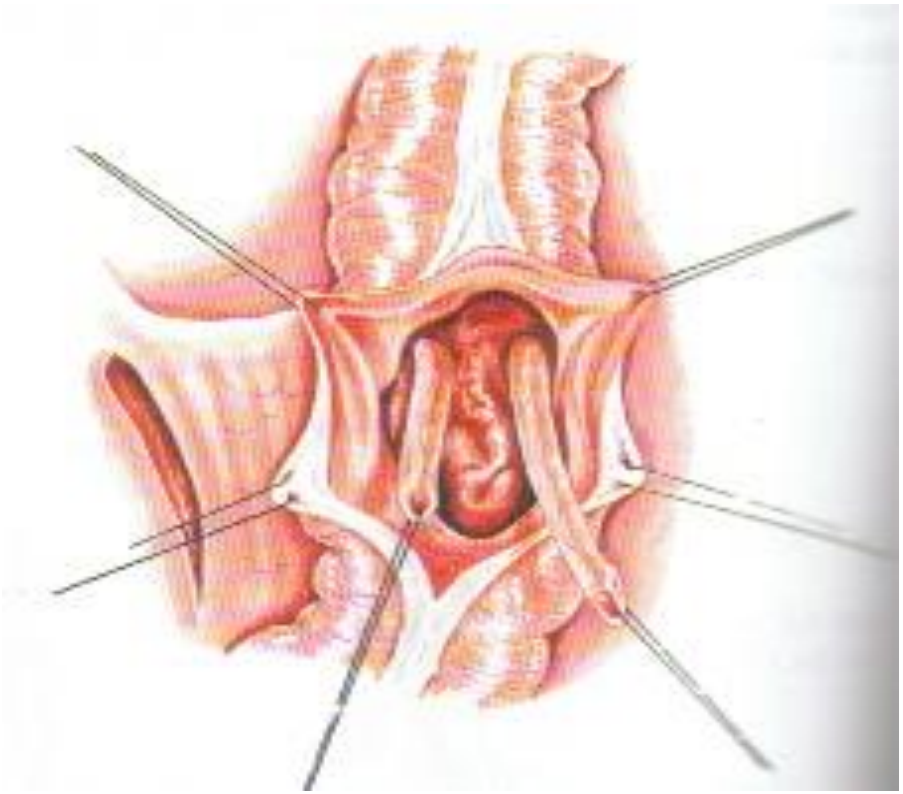
Colombo R and Naspro Ral. Eur Urol Suppl 9(2010) 736 – 744

Continent Divertion: Ureterosigmoidostomy



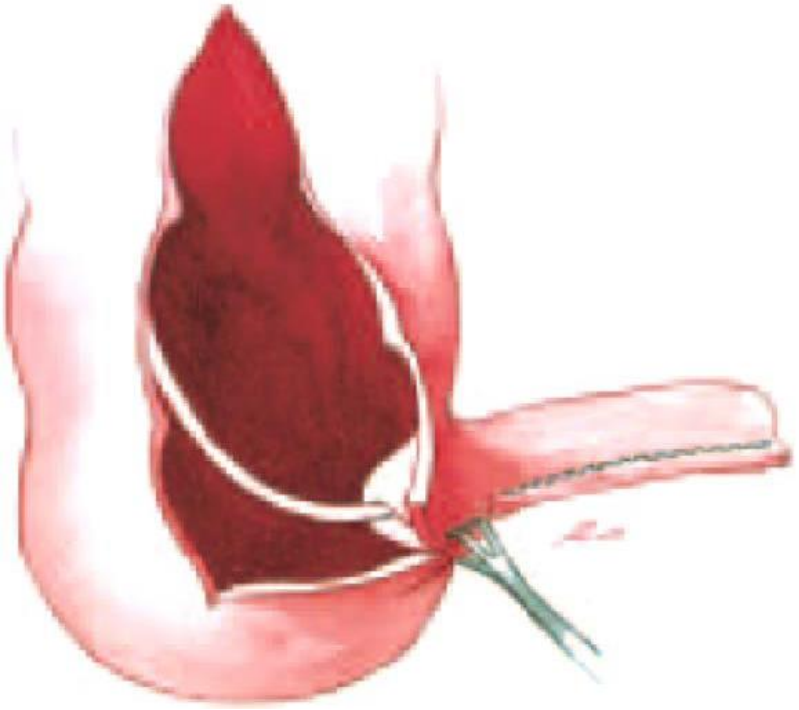
Continent Diversion: Ureterosigmoidostomy



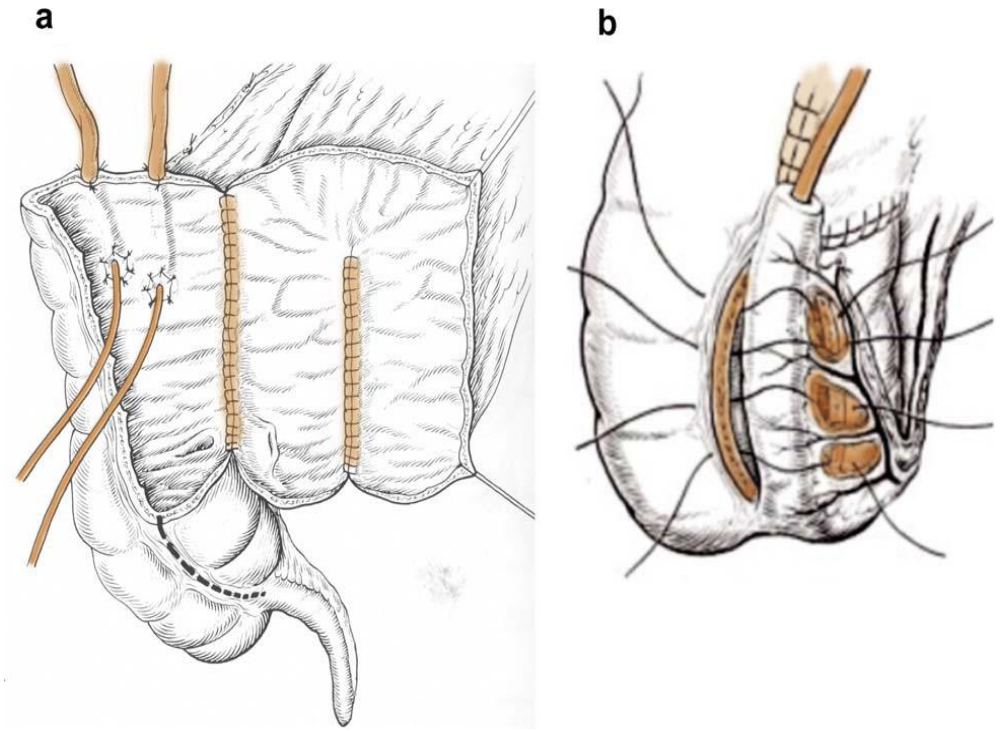


Colombo et al. Eur Urol Supplm 9(2010) 736 – 744

Continent Eterotopic conduit: Indiana Pouch



L'Indiana Pouch è confezionata a partire dal segmento ileocecale con un tratto ileale che viene configurato come tratto efferente

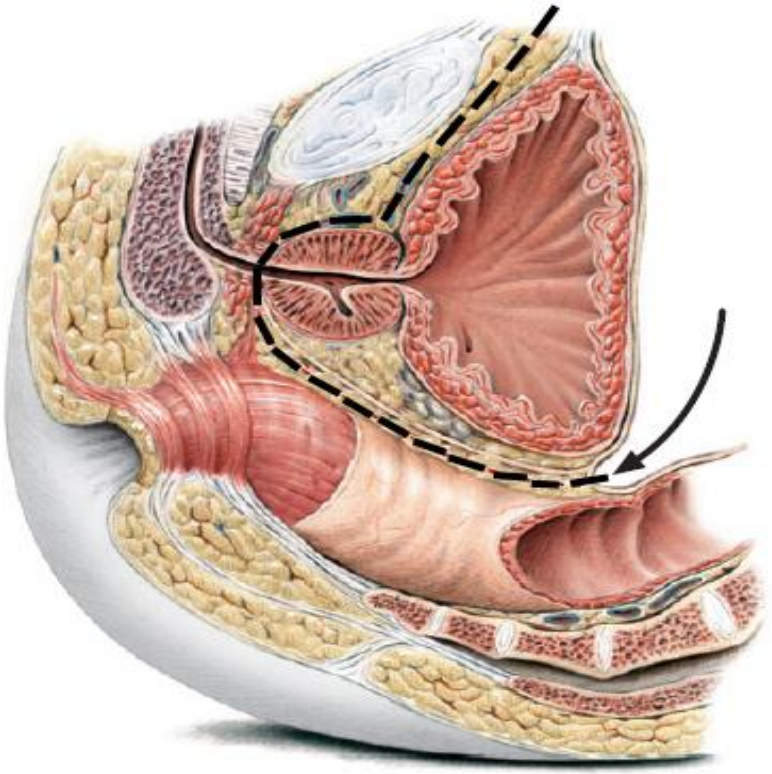


L'appendice vermiforme è usata come stoma nella Mainz I modificata

Colombo et al. Eur Urol Supplm 9(2010) 736 – 744

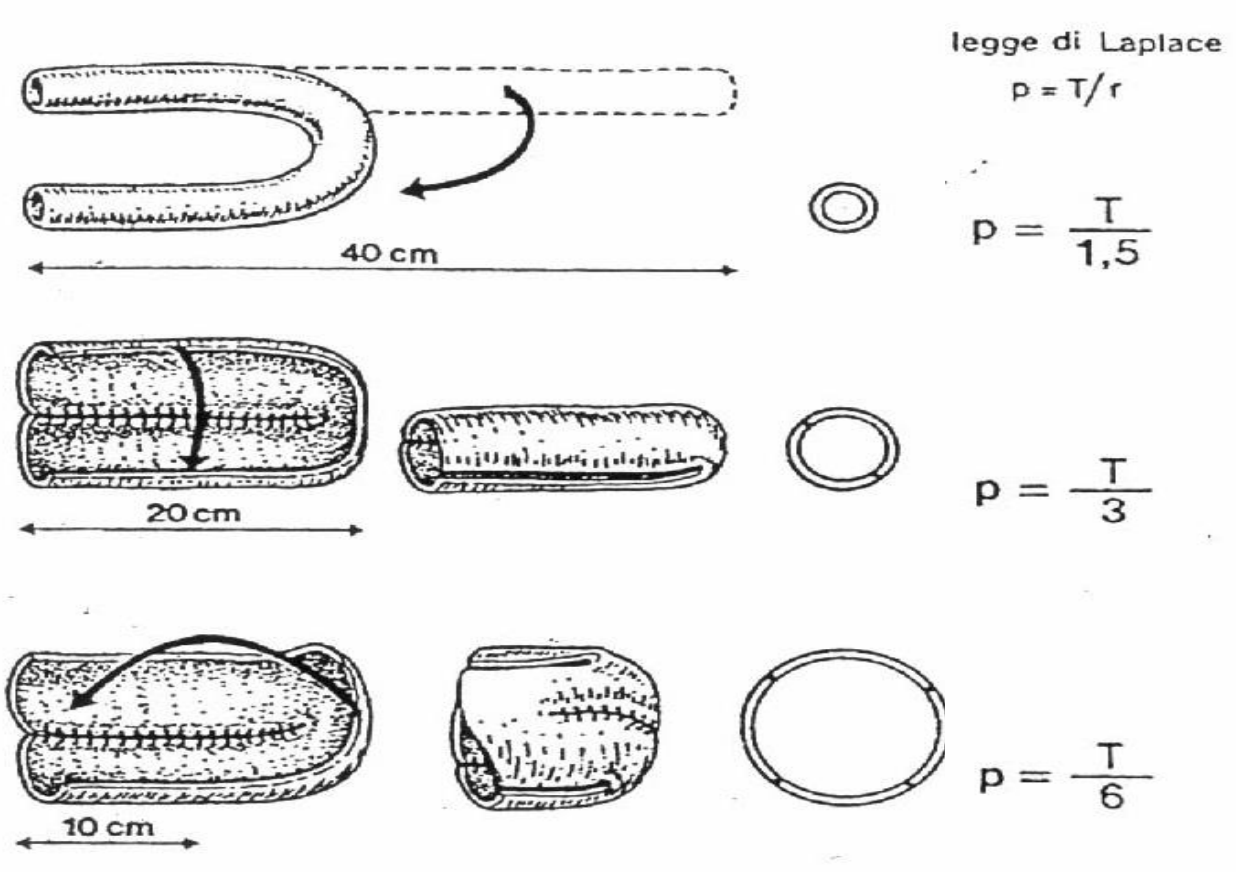
Continent Orthotopic conduit: Neobladder (Studer)

1. PRESERVARE LO SFINTERE URETRALE



Continent Orthotopic conduit: Neobladder (Studer)

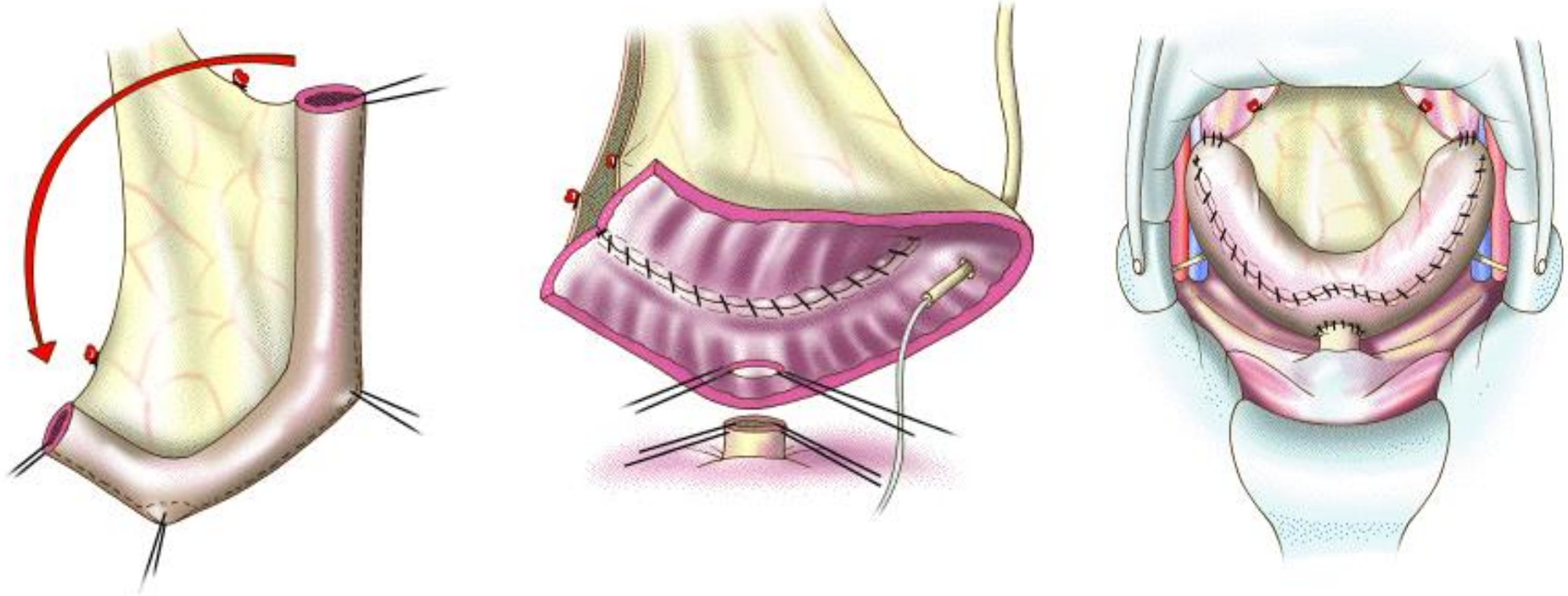
2. DETUBULARIZZATO E RIPIEGATO



Laplace: P = T/r

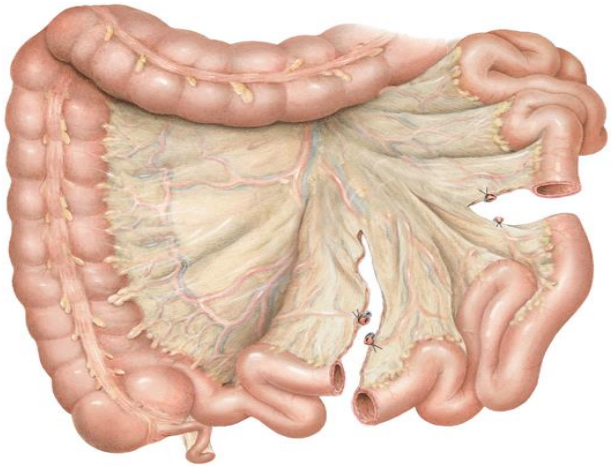
Continent Conduit: Neobladder (Camey III)

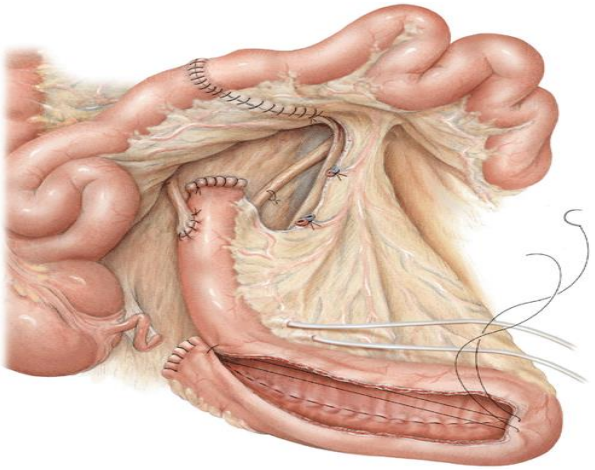
Isolamento di un segmento di ileo terminale (40 cm), che viene detubularizzato .

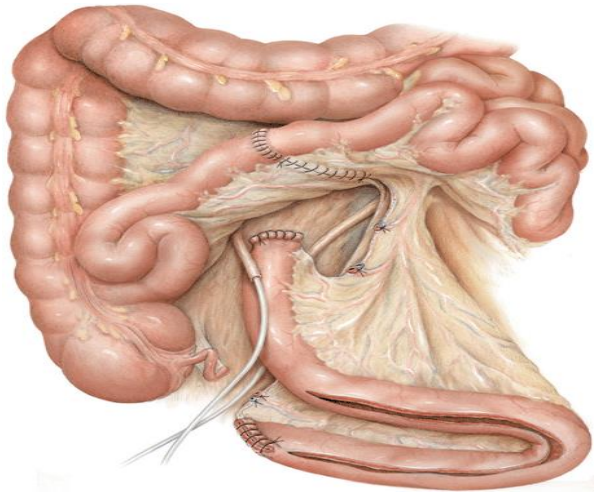


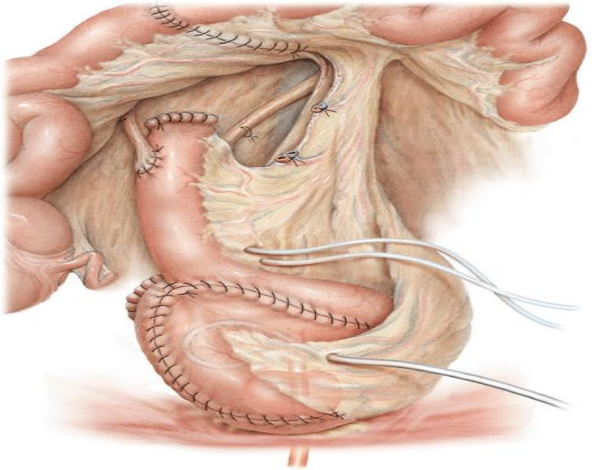
Continent Conduit: Neobladder (Studer)

Isolamento di un segmento di ileo terminale (40 cm), che viene detubularizzato e ripiegato.

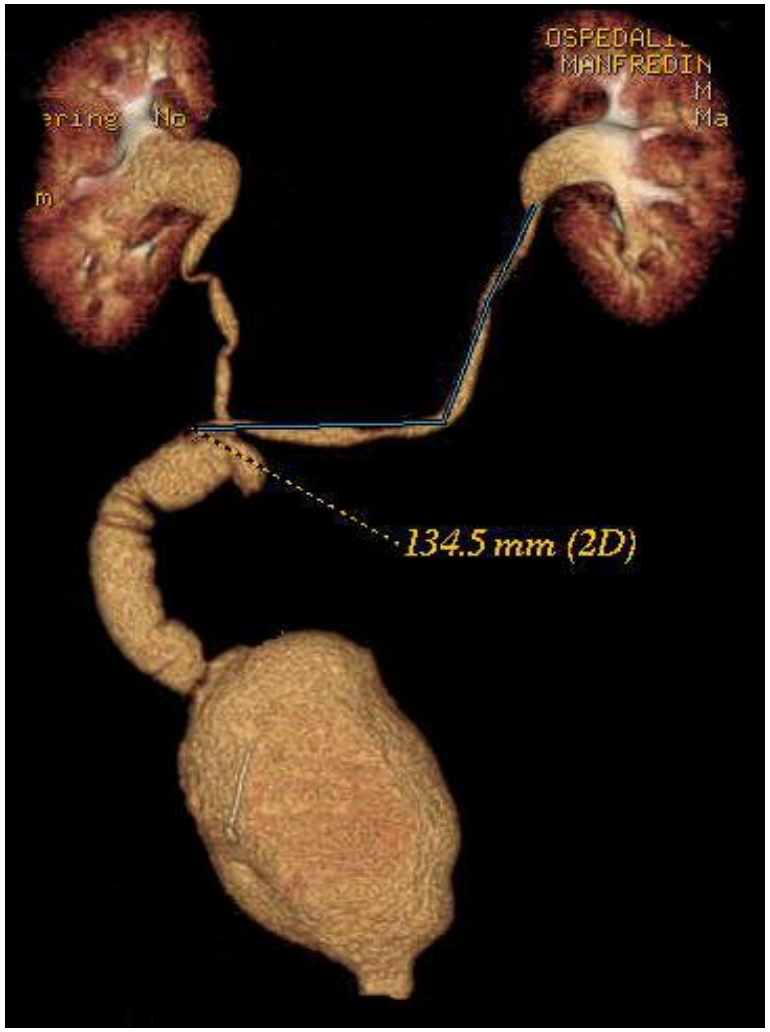


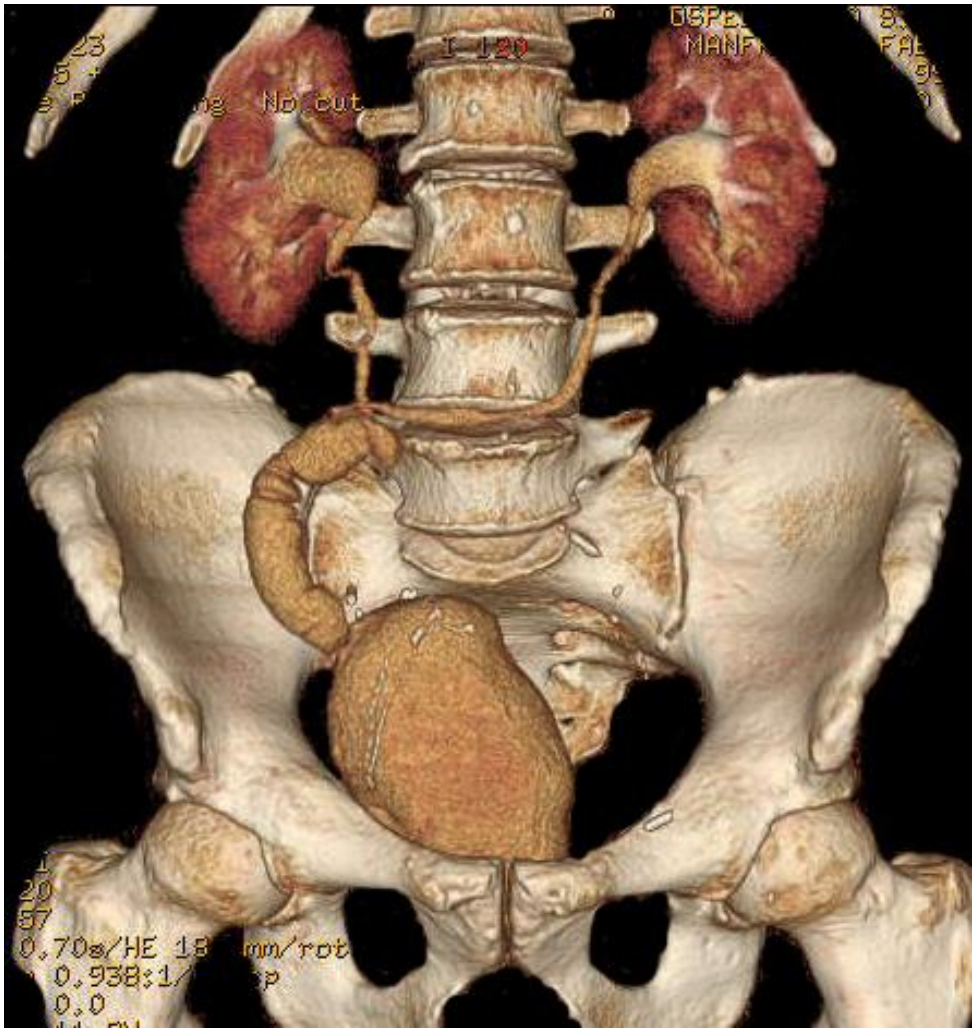




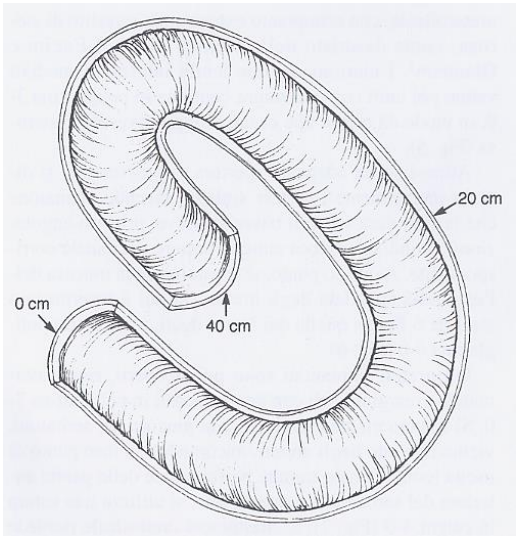


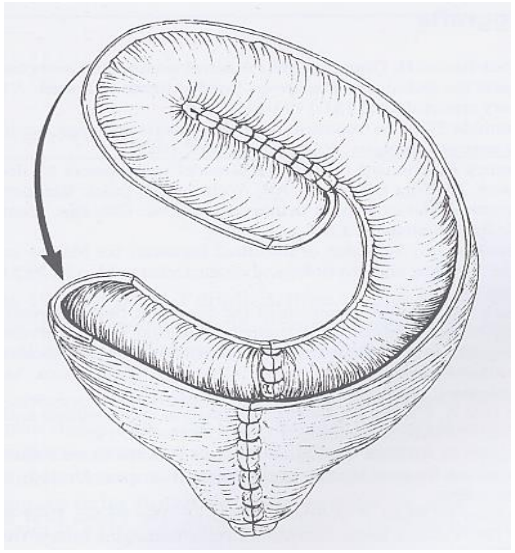
Continent Conduit: Neobladder (Studer)

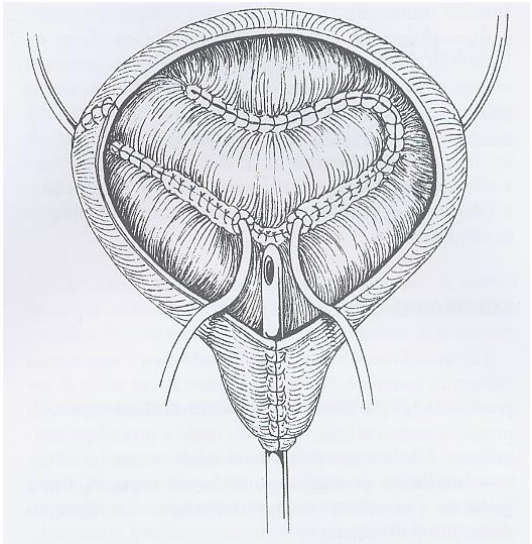


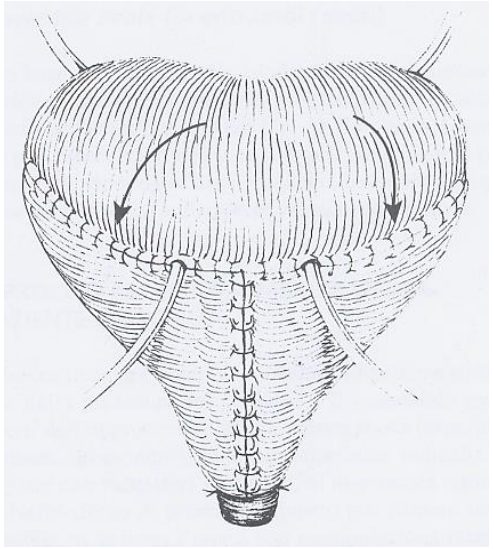


Continent Conduit: Neobladder (VIP)

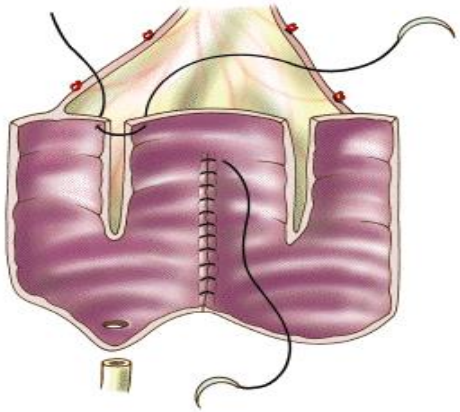


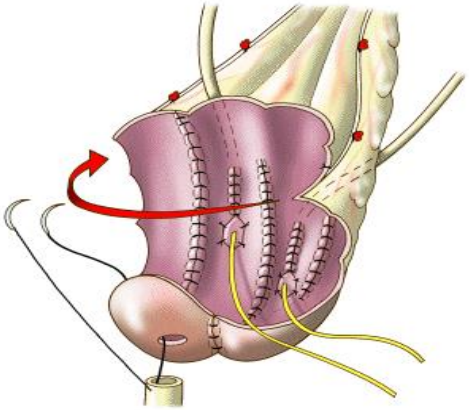


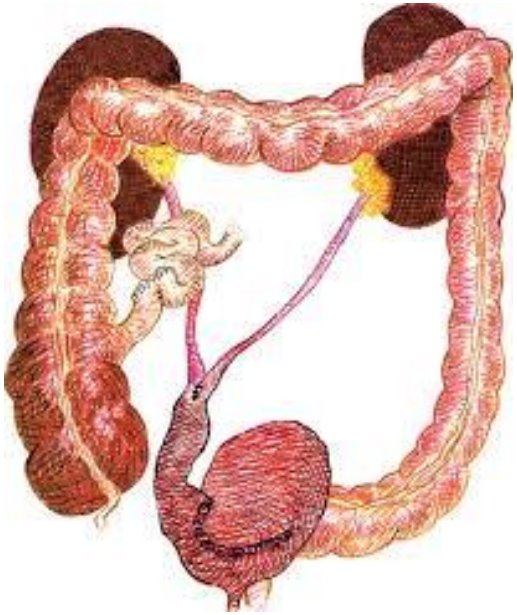


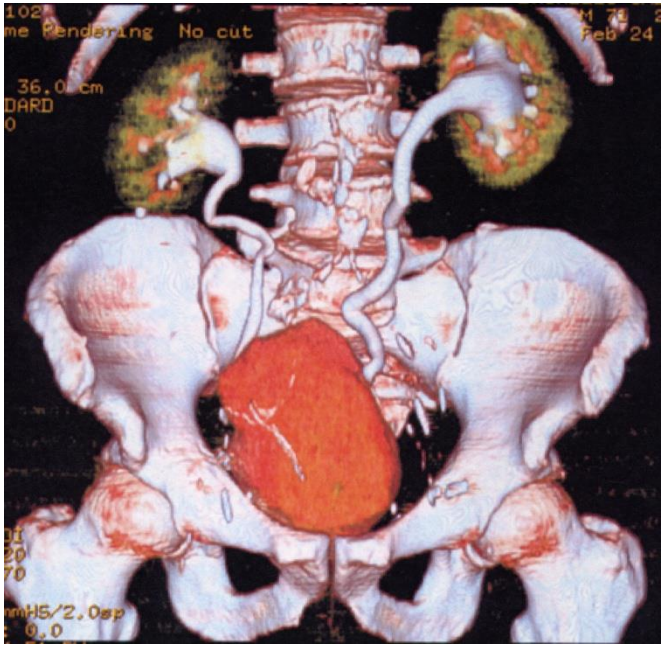


Continent Conduit: Neobladder (HAUTMANN)

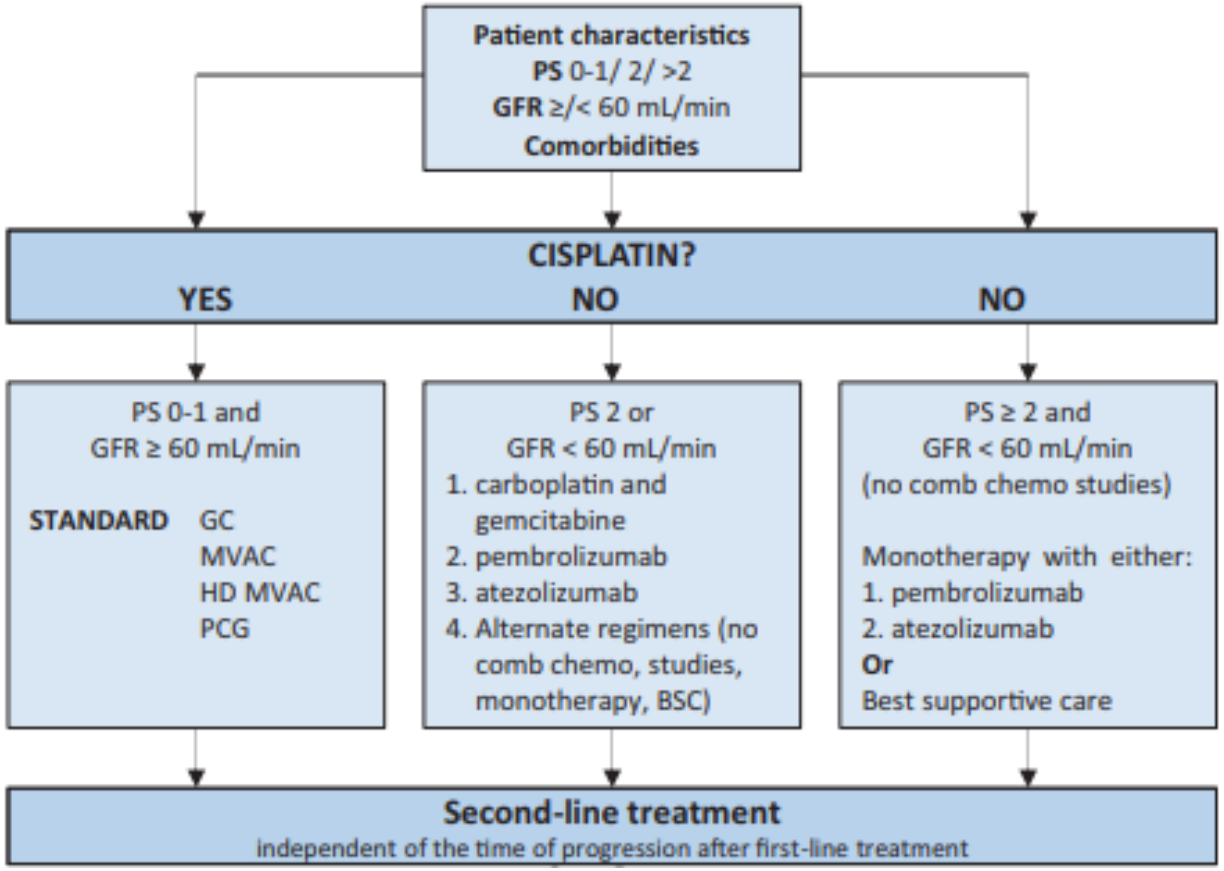






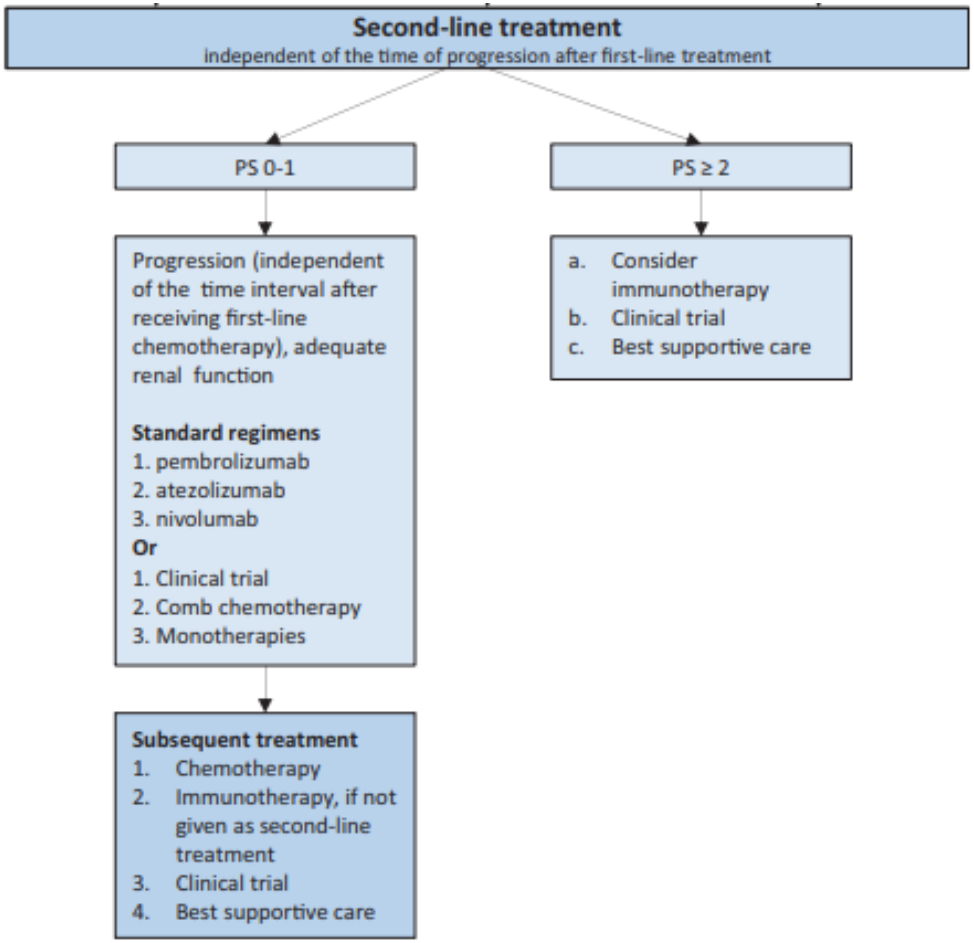


METASTATIC BLADDER CANCER



AU Guidelines on
uscle-invasive
and Metastatic
Bladder Cancer

METASTATIC BLADDER CANCER



EAU Guidelines on
Muscle-invasive and Metastatic Bladder Cancer

FOLLOW-UP

8.3 Time schedule for surveillance

Although, based on low level of evidence, some follow-up schedules have been suggested, guided by the principle that recurrences tend to occur within the first years following initial treatment. A schedule suggested by the EAU Guidelines Panel includes a CT scan (every 6 months) until the third year, followed by annual imaging thereafter [4]. Patients with multifocal disease, NMIBC with CIS or positive ureteral margins are at higher risk of developing UTUC, which can develop late (> three years). In those cases, monitoring of the UUT is mandatory during follow-up. Computed tomography is to be used for imaging of the UUT [561].

Site of recurrence	Summary of evidence	LE	Recommendation	Strength rating
Local recurrence	Poor prognosis. Treatment should be individualised depending on the local extent of tumour.	2b	Offer radiotherapy, chemotherapy and possibly surgery as options for treatment, either alone or in combination.	Strong
Distant recurrence	Poor prognosis.	2b	Offer chemotherapy as the first option, and consider metastasectomy in case of unique metastasis site.	Strong
Upper urinary tract recurrence	Risk factors are multifocal disease (NMIBC/CIS or positive ureteral margins).		See EAU Guidelines on Upper Urinary Tract Urothelial Carcinomas.	Strong
Secondary urethral tumour	Staging and treatment should be done as for primary urethral tumour.	3	See EAU Guidelines on Urethral Carcinoma	Strong

EAU Guidelines on
Muscle-invasive and Metastatic Bladder Cancer