# ΑΜΦΙΣΒΗΤΩΝΤΑΣ ΤΑ ‘GUIDELINES’

## ΔΙΗΘΗΤΙΚΟΣ ΚΑΡΚΙΝΟΣ ΟΥΡΟΔΟΧΟΥ ΚΥΣΤΕΩΣ


**ΙΩΑΝΝΗΣ ΒΑΡΚΑΡΑΚΗΣ**

ΑΝΑΠΛΗΡΩΤΗΣ ΚΑΘΗΓΗΤΗΣ ΟΥΡΟΛΟΓΙΑΣ

ΕΘΝΙΚΟ & ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ

**ΒΑΣΙΛΕΙΟΣ ΤΖΩΡΤΖΗΣ**

ΑΝΑΠΛΗΡΩΤΗΣ ΚΑΘΗΓΗΤΗΣ ΟΥΡΟΛΟΓΙΑΣ

ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ




**Dept. Urology, Athens Medical School, J. Varkarakis**

# Δ Ε Ν Υ Π Α Ρ Χ Ε Ι Σ Υ Γ Κ Ρ Ο Υ Σ Η Σ Υ Μ Φ Ε Ρ Ο Ν Τ Ω Ν

| | |
|---|---|
| 1a | **1** |
| 1b | 2 |
| 2a | 10 |
| 2b | 15 |
| 3 | 22 |
| 4 | 2 |

| | |
|---|---|
| A | **13** |
| B | 24 |
| C | 23 |

**Table 1: Level of evidence*.**

| Level | Type of evidence |
|---|---|
| 1a | Evidence obtained from meta-analysis of randomised trials |
| 1b | Evidence obtained from at least one randomised trial |
| 2a | Evidence obtained from one well-designed controlled study without randomisation |
| 2b | Evidence obtained from at least one other type of well-designed quasi-experimental study |
| 3 | Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports |
| 4 | Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities |

*Modified from Sackett et al. (1).*

**Table 2: Grade of recommendation*.**

| Grade | Nature of recommendations |
|---|---|
| A | Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial |
| B | Based on well-conducted clinical studies, but without randomised clinical trials |
| C | Made despite the absence of directly applicable clinical studies of good quality |

*Modified from Sackett et al. (1).

# ΕΠΙΔΗΜΙΟΛΟΓΙΑ & ΑΙΤΙΟΛΟΓΙΚΟΙ ΠΑΡΑΓΟΝΤΕΣ

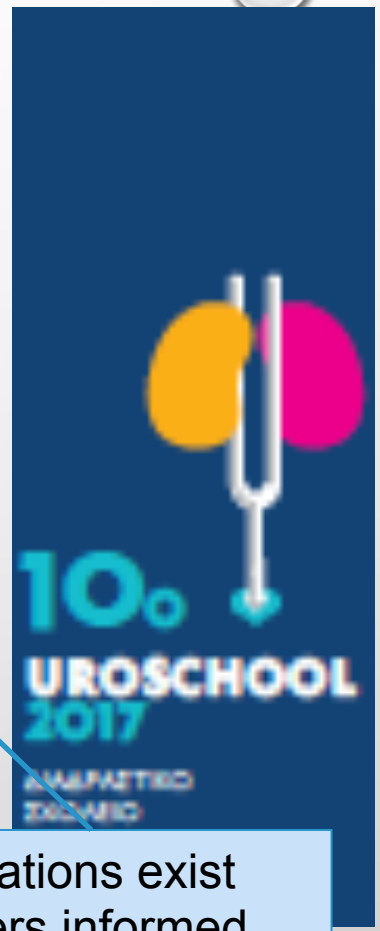
Incidence varies across countries

| Summary of evidence | LE |
|---|---|
| Worldwide, bladder cancer is the 11th most commonly diagnosed cancer. | 2a |
| Several risk factors connected with the risk of BC diagnosis have been identified. | 3 |
| Active and passive tobacco smoking continues to be the main risk factor, while the exposure-related incidence is decreasing. | 2a |
| The increased risk of developing bladder cancer in patients undergoing external-beam radiotherapy (EBRT), brachytherapy (BT), or a combination of EBRT and BT, must be taken into account during patient follow-up. As bladder cancer requires time to develop, patients treated with radiation at a young age are at the greatest risk and should be followed up closely. | 3 |

Long latency time
Young pt more at risk
Long term FU

**Principle preventable risk**: active /passive smoking **GR: B**
Stop smoking
1-4y 40% drop of risk
>25y 60% drop of risk

Regulations exist
Workers informed
Protective measures
**GR: A**




# ΠΑΘΟΛΟΓΟΑΝΑΤΟΜΙΚΗ ΕΚΘΕΣΗ

| Recommendations | GR |
|---|---|
| Record the depth of invasion (categories pT2a & pT2b, pT3a, pT3b or pT4). | A* |
| Margins with special attention paid to the radial margin, prostate, ureter, urethra and peritoneal fat and uterus and vaginal top. | |
| Record the number of lymph nodes and number of positive lymph nodes. | |
| Record lymphatic or blood vessel invasion. | |
| Record the presence of CIS. Morphological **subtypes** | |

TNM 7th edt

After TUR & CHEMO **may be difficult to find the tumor**.
Include entire ulcerated area


# Ιστολογικοί υπότυποι

By definition, urothelial carcinoma with divergent differentiation refers to tumours arising within the urothelial tract, in which some percentage of "usual type" urothelial carcinoma is present along with other morphologies

Urothelial carcinoma has long been known to have a remarkable propensity for divergent differentiation, which is seen most commonly in association with high-grade and locally advanced disease The incidence of divergent differentiation in cystectomy specimens is as high as 33%.

EUROPEAN UROLOGY 70 (2016) 106–119

| Third edition [51]: | Fourth edition [1]: |
|---|---|
| *Invasive urothelial tumours* | *Invasive urothelial tumours* |
| Infiltrating urothelial carcinoma | Infiltrating urothelial carcinoma with divergent differentiation |
| with squamous differentiation | Nested, including large nested |
| with glandular differentiation | Microcystic |
| with trophoblastic differentiation | Micropapillary |
| Nested | Lymphoepithelioma-like |
| Microcystic | Plasmacytoid/signet ring cell/diffuse |
| Micropapillary | Sarcomatoid |
| Lymphoepithelioma-like | Giant cell |
| Lymphoma-like | Poorly differentiated |
| Plasmacytoid | Lipid rich |
| Sarcomatoid | Clear cell |
| Giant cell | Tumours of maüllerian type |
| Undifferentiated | Tumors arising in a bladder diverticulum |

WHO 2016

; however, it is recommended that pathologists report the percentage of divergent histologies in the pathology report.

EUROPEAN UROLOGY 70 (2016)

# Ιστολογικοί υπότυποι

| Disease | Optimal Treatment | Grade of Recommendation |
|---|---|---|
| Squamous cell carcinoma | Radical cystectomy | B |
| Primary adenocarcinoma | Radical cystectomy | B |
| Urachal adenocarcinoma | En bloc excision of urachus and umbilicus with partial cystectomy | B |
| Metastatic adenocarcinoma involving the bladder | Complete resection of involved portion of the bladder; partial cystectomy with negative margins or radical cystectomy | B |
| Small cell carcinoma | Local treatment and chemotherapy | B |
| Bladder sarcoma | Radical cystectomy | C |
| Carcinosarcoma, sarcomatoid tumors | Multimodality therapy | C |
| Paraganglioma and pheochromocytoma | Partial cystectomy with pelvic lymph node dissection; perioperative adrenergic blockade | C |
| Pseudotumor | Transurethral resection or partial cystectomy | C |
| Melanoma, primary, of bladder | Radical cystectomy | C |
| Lymphoma, primary | Local irradiation | C |

**Nonurothelial Cancer of the Bladder**

Hassan Abol-Enein, Bruce R. Kava, and Adrienne J. K. Carmack

UROLOGY 2007.

# Κλινικές πληροφορίες

| | |
|---|---|
| Intravesical immunotherapy (BCG, interferon-α) | Reparative urothelial atypia<br>Denudation of urothelium with frequent ulceration<br>Bladder wall granulomatous inflammation<br>Eosinophilic cystitis (moderate to severe, occasional)<br>Persistence of CIS in von Brunn's nests<br>Lamina propria oedema and mild perivascular inflammation with neutrophils, lymphocytes, dendritic reticulum cells and eosinophils (interferon-α) |
| Mitomycin C | Denudation of the surface epithelium<br>Atypia in the surface umbrella urothelial cells<br>Denuding papillae of persistent papillary neoplasia<br>Less significant abnormalities in the deeper layers of the urothelium<br>Low nuclear/cytoplasmic ratio<br>Associated eosinophilic cystitis (mild to moderate; common)<br>Encrusted cystitis or haemorrhagic cystitis (rare) |
| Cyclophosphamide | Necrosis of urothelium of the bladder and upper urinary tract<br>Atypical form of regeneration<br>Large, bizarre nuclei with coarse chromatin and small to medium sized nucleoli<br>Reactivation of polyomavirus infection<br>Bladder cancer following cyclophosphamide therapy (uncommon)<br>Haemorrhagic cystitis (currently uncommon)<br>Encrusted cystitis (rare) |
| Ketamine | Urothelium diffusely denuded with frequent urothelial ulceration<br>Reactive urothelial changes that can mimic CIS<br>Inflammatory cell infiltration infiltrated predominantly by lymphocytes and a variable number of eosinophils<br>Lamina propria with prominent granulation tissue with congested vessels<br>Varying degrees of bladder wall fibrosis (late stage)<br>Upper urinary tract damage and hydronephrosis<br>High p53 and Ki67 (frequent); normal CK20 |

REVIEW

**Iatrogenic changes in the urinary tract**

Antonio Lopez-Beltran,[1,2] Gladell P Paner,[3] Rodolfo Montironi,[4] Maria R Raspollini[5] & Liang Cheng[6]

REVIEW

# Iatrogenic changes in the urinary tract

Antonio Lopez-Beltran,[1,2] Gladell P Paner,[3] Rodolfo Montironi,[4] Maria R Raspollini[5] & Liang Cheng[6]

| | |
|---|---|
| Neoadjuvant systemic chemotherapy | Urothelium with minor atypia<br>Hyalinization of the wall and fewer foreign body giant cells<br>Frequent lymph node hyalinization<br>Xanthoma (occasional)<br>Persistence of urothelial CIS or NMIBC (frequent)<br>Residual tumour grade: (i) no tumour; (ii) tumour <50%; (iii) tumour >50% |
| Radiation therapy | Denudation of urothelium with frequent ulceration<br>Overall increase in urothelial cell size with normal nuclear to cytoplasmic ratio<br>Acute inflammatory reaction in lamina propria with atypical stromal cells<br>Blood vessels thrombosis and bladder wall fibrosis (late stage)<br>Intensified eosinophilic staining of cytoplasm (common)<br>Pseudocarcinomatous hyperplasia (uncommon); xanthoma (rare) |
| Photodynamic and laser therapy | Coagulation and/or haemorrhagic necrosis<br>Normal tissues range from oedema to coagulation necrosis<br>Well demarcated from non-irradiated tissues<br>Vascular endothelium enlargement<br>Dystrophic calcification (occasional)<br>Spindling artefact of urothelial cells |
| Surgery related alterations | Postsurgical necrobiotic granuloma and nonspecific granulomatous reaction<br>Xanthoma (rare)<br>Postoperative spindle cell nodule<br>Fistula or suture granuloma<br>Recurrent cancer in bladder augmentations and intestinal conduits |
| Gene therapy | Marked cytoplasmic vacuolization of tumour cells (early)<br>Inflammatory infiltrate mainly of B cells and macrophages<br>Apoptosis-mediated tumour necrosis<br>Non-neoplastic tissues unaffected |

Intravesical and systemic therapeutic agents, as well as other therapeutic procedures, including mitomycin C, cyclophosphamide, BCG, platin-based chemotherapy agents, radiotherapy, photodynamic and laser treatment and gene therapy, produce a host of changes and alterations in the urothelium, some of them mimicking carcinoma. The diagnosis of these lesions relies upon haematoxylin and eosin (H&E)-based pathological evaluation, and therefore pathologists must be aware of the altered morphology secondary to therapy.

A conservative approach with repeat cystoscopy and biopsy after the inflammation has resolved is suggested in equivocal cases.

# ΔΙΑΓΝΩΣΗ

**$S_X$**: PAINLESS HEMATURIA

**$PE_X$**: **BIMANUAL** EXAM vs $_PT$

**URINE CYTOLOGY**: CIS / HG (90% SPECIFICITY **LE 2B**)

NO URINE **MARKER**

**CYSTOSCOPY**: **BLADDER DIAGRAM**

- CAN BE OMITTED IF SURE WITH IMAGING

**PDD**

- FOR T1 HG TO EVALUATE FOR **CIS**
- **RE-TUR**

Frozen section @ RCB more accurate

| | |
|---|---|
| Take a biopsy of the prostatic urethra for cases of bladder neck tumour, when bladder CIS 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. | LE 3 |
| Take a biopsy at the time of the second resection, if no biopsy was taken during the initial procedure. | C |

# ΑΠΕΙΚΟΝΙΣΤΙΚΟΣ ΕΛΕΓΧΟΣ - ΣΤΑΔΙΟΠΟΙΗΣΗ

| | |
|---|---|
| Imaging as part of staging in MIBC provides information about prognosis and assists in selection of the most appropriate treatment. | 2b |
| In patients with confirmed MIBC, use CT of the chest, abdomen and pelvis as the optimal form of staging. Include excretory-phase CT urography for complete examination of the upper urinary tract. | B |

## Imaging for Local Staging

**CT**

- Accuracy **55-92%**
- **Cannot** distinguish **pTa - pT3a**
- Useful in detecting **pT3b**

**MRI**

- Accuracy **73-96%**
- **DCE** distinguish tumor from **reaction**/surrounding tissues
- In pt with CRF risk of **Nephrogenic Systemic Fibrosis**

## Imaging for Lymph Nodes

**MRI** and **CT** equivalent

- **Low** sensitivity and specificity
- No micrometastasis
- Postivity when
  - ✓ **Pelvic LN >8mm**
  - ✓ **Abdominal >10mm**

## Imaging of Distant Metastases

MRI and CT equivalent **(GR C)**

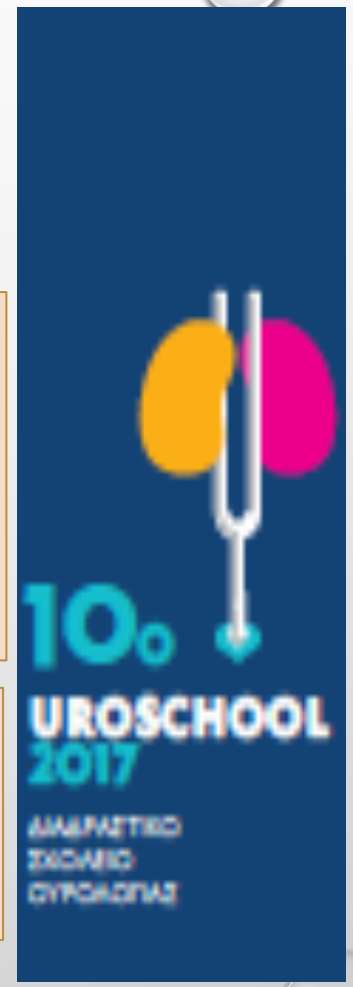
- **CT for lung** (**GR C**)
- **MRI** better SE & SP than bone scan for **bone M+**
- **Imaging bone or brain if Sx**

## Imaging for UUTUC

- Excretory phase CT urography better than MRI **(GR C)**
- Always confirm with biopsy **(GR C)**

**Insufficient data** for use

- DWI
- FDC-PET/CT



# ΠΡΟΓΝΩΣΗ

- TUMOR **STAGE**
- **NODAL** STAGE
- **ALBUMIN** (COMPLICATIONS, OS, RFS)
- TUMOR LOCATION (**TRIGONE**)
- **TUMOR MARKERS** (NOT SUFFICIENT EVIDENCE)
  - BASAL BC CHEMOSENSITIVE (OVEREXPRESSION OF EGFR3)
  - LUMINAL BC CHEMORESISTENT (OVEREXPRESSION OF FGFR3, ERBB3, ERBB2)
- **COMORBIDITY**


# ΧΕΙΡΟΥΡΓΙΚΗ ΝΟΣΗΡΟΤΗΤΑ

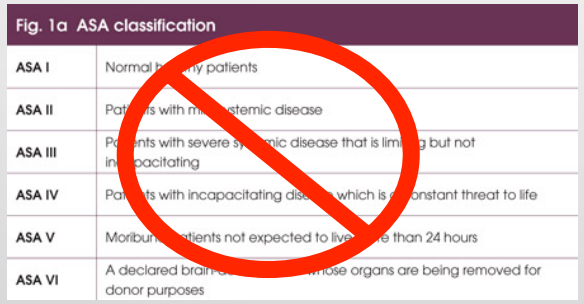
- STAGE
- TYPE OF SURGERY
- TYPE OF DIVERSION
- BOWEL ANASTOMOSIS
- XBRT
- PSHX

- COMORBIDITIES
  - **CHRONOLOGICAL AGE**
  - **BIOLOGICAL AGE**
- **BMI**
- **ALBUMIN** (RFS, OS)
- **FEMALE** (PARASTOMA)

# ΡΟΛΟΣ ΤΗΣ ΣΥΝΟΣΗΡΟΤΗΤΑΣ

| Summary of evidence | LE |
|---|---|
| Chronological age is of limited relevance. | 3 |
| A comorbidity score developed in particular for the assessment of patients diagnosed with BC would be helpful. | 3 |

| Recommendations | GR |
|---|---|
| Base the decision on bladder-sparing or radical cystectomy in elderly/geriatric patients with invasive bladder cancer on tumour stage and comorbidity. | B |
| Assess comorbidity by a validated score, such as the Charlson Comorbidity Index, the ASA score should not be used in this setting (see section 7.4.4.1). | |



| Fig. 1a ASA classification | |
|---|---|
| ASA I | Normal h…y patients |
| ASA II | Pat…s with m…stemic disease |
| ASA III | P…nts with severe s…mic disease that is lim…g but not in…pacitating |
| ASA IV | Pa…ts with incapacitating dis… which is …onstant threat to life |
| ASA V | Moribun…tients not expected to live …e than 24 hours |
| ASA VI | A declared brain-… whose organs are being removed for donor purposes |

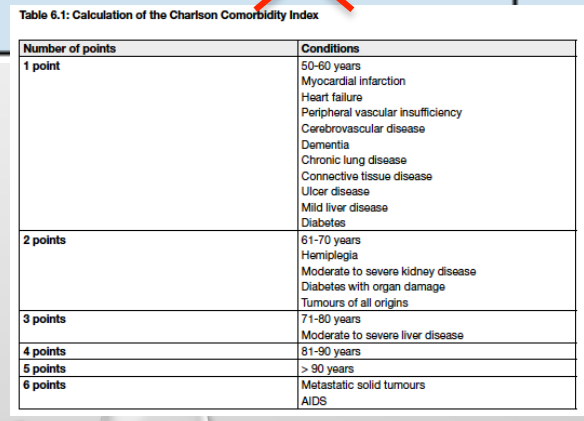
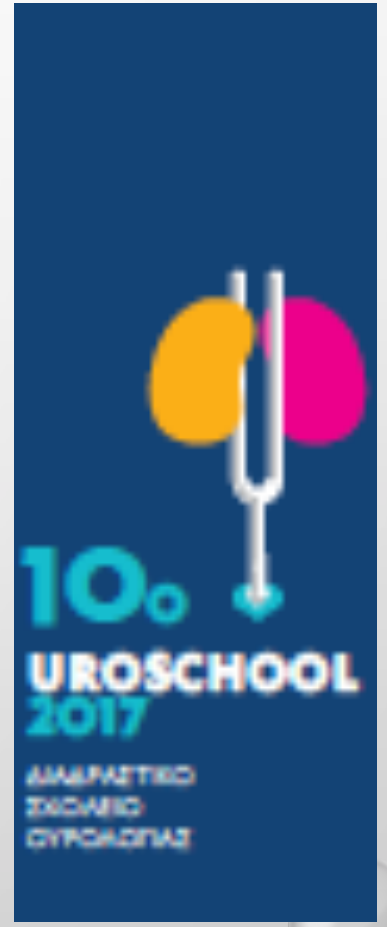


**Table 6.1: Calculation of the Charlson Comorbidity Index**

| Number of points | Conditions |
|---|---|
| 1 point | 50-60 years<br>Myocardial infarction<br>Heart failure<br>Peripheral vascular insufficiency<br>Cerebrovascular disease<br>Dementia<br>Chronic lung disease<br>Connective tissue disease<br>Ulcer disease<br>Mild liver disease<br>Diabetes |
| 2 points | 61-70 years<br>Hemiplegia<br>Moderate to severe kidney disease<br>Diabetes with organ damage<br>Tumours of all origins |
| 3 points | 71-80 years<br>Moderate to severe liver disease |
| 4 points | 81-90 years |
| 5 points | > 90 years |
| 6 points | Metastatic solid tumours<br>AIDS |




# Χρειαζόμαστε άλλες οδηγίες για τις γυναίκες;

- 4$^{H}$ συχνότερη νεοπλασία Άνδρες
- 8$^{H}$ Γυναίκες

| Site | % Localized | | % Regional | | % Distant | |
|---|---|---|---|---|---|---|
| | Male | Female | Male | Female | Male | Female |
| Lung + bronchus | 15.1 | 18.2 | 22.1 | 21.7 | 54.5 | 51.1 |
| Colon + rectum | 40.8 | 38.9 | 35.2 | 36.3 | 18.7 | 18.5 |
| Skin melanoma | 82.4 | 85.8 | 9 | 7.3 | 4.4 | 2.8 |
| Bladder | 72.8 | 67.6 | 14.2 | 15 | 6.6 | 9.5 |
| NonHodgkin lymphoma | 27.6 | 30.4 | 14.3 | 15.1 | 49.2 | 44.5 |
| Kidney + renal pelvis | 60.1 | 63.3 | 17.8 | 15.4 | 17.3 | 15.5 |
| Thyroid | 58.1 | 70.5 | 30.5 | 22.9 | 8.4 | 4.2 |
| Pancreas | 7.4 | 9.1 | 26 | 26.4 | 53.2 | 47.8 |
| Liver | 38.4 | 38.4 | 26 | 22.7 | 18.2 | 17.2 |
| Brain + other nervous system | 74.3 | 71.6 | 15.7 | 16 | 2.2 | 2.3 |

Najari B. J Urol 2013

# Χρειαζόμαστε άλλες οδηγίες για τις γυναίκες;

| Study | Patients (*n*) | | Pathologic stage (%) | | Median | 5-yr CSS (%) | | MVA of CSS association with gender | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | F | M | pT0/pTa/pTis/pT1/pT2/pT3/pT4 | | FU | F | M | | | |
| | | | F | M | (mo) | | | HR | 95% CI | *p* value |
| Kluth et al [7] | 1605 | 6497 | 5.3/4.5/7.4/11.0/25.0/ 37.0/9.5 | 5.6/4.3/8.2/15.0/24.0/ 31.0/12.0 | 41.0 | 72.0 | 76.0 | 1.17 | 1.05–1.30 | 0.004 |
| Messer et al [74] | 890 | 3186 | pT0/1 28.9%; pT2 24.6%; pT3/4 46.6% | pT0/1 32.1%; pT2 23.9%; pT3/4 44.3% | 31.5 | 63.0 | 69.6 | 1.25 | 1.09–1.44 | 0.002 |
| Tilki et al [75] | 50 | 193 | 8.2/7.8/48.1/13.2/11.9/4.9/5.8 | | 37.3 | 64.8 | 92.8 | 2.45 | 1.10–5.48 | 0.029 |
| Tilki et al [76] | 40 | 188 | pT0 after radical cystectomy only | | 48.2 | 87.6 | 94.3 | 4.47 | 1.37–14.6 | 0.013 |
| Soave et al [10] | 119 | 398 | 10.1/2.59/4.2/8.4/23.5/34.5/16.8 | 9.8/4.8/10.6/14.1/17.1/26.6/17.1 | 44.0 | 60.0 | 72 | NP | | |
| Mitra et al [11] | 414 | 414 | pT0/pTa/pTis 20.1%; pT1 14.5%; pT2 23.7%; pT3 35.0%; pT4 6.0% | | 12.2 yr | 60 [a] | 70 [a] | NP [b] | | |
| Tilki et al [79] | 94 | 488 | pT4 cancers only | | 55.0 | 23.8 | 39.8 | 1.67 | 1.22–2.28 | 0.001 |
| May et al [80] | 36 | 192 | pT4a cancers only | | 30.0 [c] | 15.0 | 40.0 | 1.83 | 1.17–2.85 | 0.008 |
| Liberman et al [81] | 1506 | 4119 | pT4 cancers only | | 43.0 | 62.0 | 1.18 | NP | | <0.001 |
| Kaushik et al [82] | 37 | 91 | pT4 cancers only | | 10.5 yr | 17.2 | 31.1 | 1.05 | 0.62–1.77 | 0.87 |
| Otto et al [93] | 507 | 1976 | pT≤1 24.7%; pT2 27.6%; pT3 38.8%; pT4 8.9% | pT≤1 29.5%; pT2 26.8%; pT3 32.6%; pT4 11.1% | 42.0 | 60.0 | 66.0 | 1.26 | 1.05–1.49 | 0.011 |
| May et al [94] | 133 | 388 | pT≤2 42.9%; pT3/4 57.1% | pT≤2 41.0%; pT3/4 59.0% | 59.0 | 53.0 [d] | | 1.35 | NP | 0.048 |

# Γιατί;

- Αναζήτηση βοήθειας από την ασθενή
- Γενικοί ιατροί
- Βιολογικές διαφορές
  - Ιστολογικοί τύποι
  - Οδοί μεταβολισμού καρκινογόνων
  - Ορμόνες (οιστρογόνα)

# Χρειαζόμαστε άλλες οδηγίες για τις γυναίκες;

EUROPEAN UROLOGY 69 (2016) 300–310

**Gender and Bladder Cancer: A Colla... 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]*

*Conclusions:* Numerous potential biologic and epidemiologic factors probably underlie the gender differences observed for bladder cancer incidence, stage at diagnosis, and outcomes. Continued evaluation to define clinical applications for manipulation of the sex steroid pathway and to improve the standardization of hematuria evaluation in women may improve future patient outcomes and reduce these disparities.

# ΡΙΖΙΚΗ ΚΥΣΤΕΚΤΟΜΗ ΣΕ ΜΗ ΔΙΗΘΗΤΙΚΟ CAB

**T1G3** risk of progression @ 5y **45%**
T1G3 **after BCG** risk of progression @5y **19.3%**

With **BCG** effect on progression & recurrence but **NS effect on OS and DSS**

**Under-staging** of Ta-T1 found in RCBx **36-62%**
Re TUR **upstages** T1 tumors in **10-20%**

**CSS worse when NMIBC progresses** to MIBC (compared to de-novo MIBC)

| Recommendations | GR |
|---|---|
| Consider immediate radical treatment in all T1 tumours at high risk of progression (i.e., high grade, multifocality, CIS, and tumour size, as outlined in the EAU guidelines for non-muscle-invasive bladder cancer [2]). | C |
| Offer radical treatment to all T1 patients failing intravesical therapy. | B |

# Ορισμός BCG-REFRACTORY

Radical cystectomy is also strongly recommended in patients with BCG-refractory tumours, defined in the NMIBC guideline as:

- whenever muscle-invasive tumour is detected during follow-up;
- if high-grade, non-muscle-invasive papillary tumour is present at 3 months;

EAU Guidelines

## DEFINING BACILLUS CALMETTE-GUERIN REFRACTORY SUPERFICIAL BLADDER TUMORS

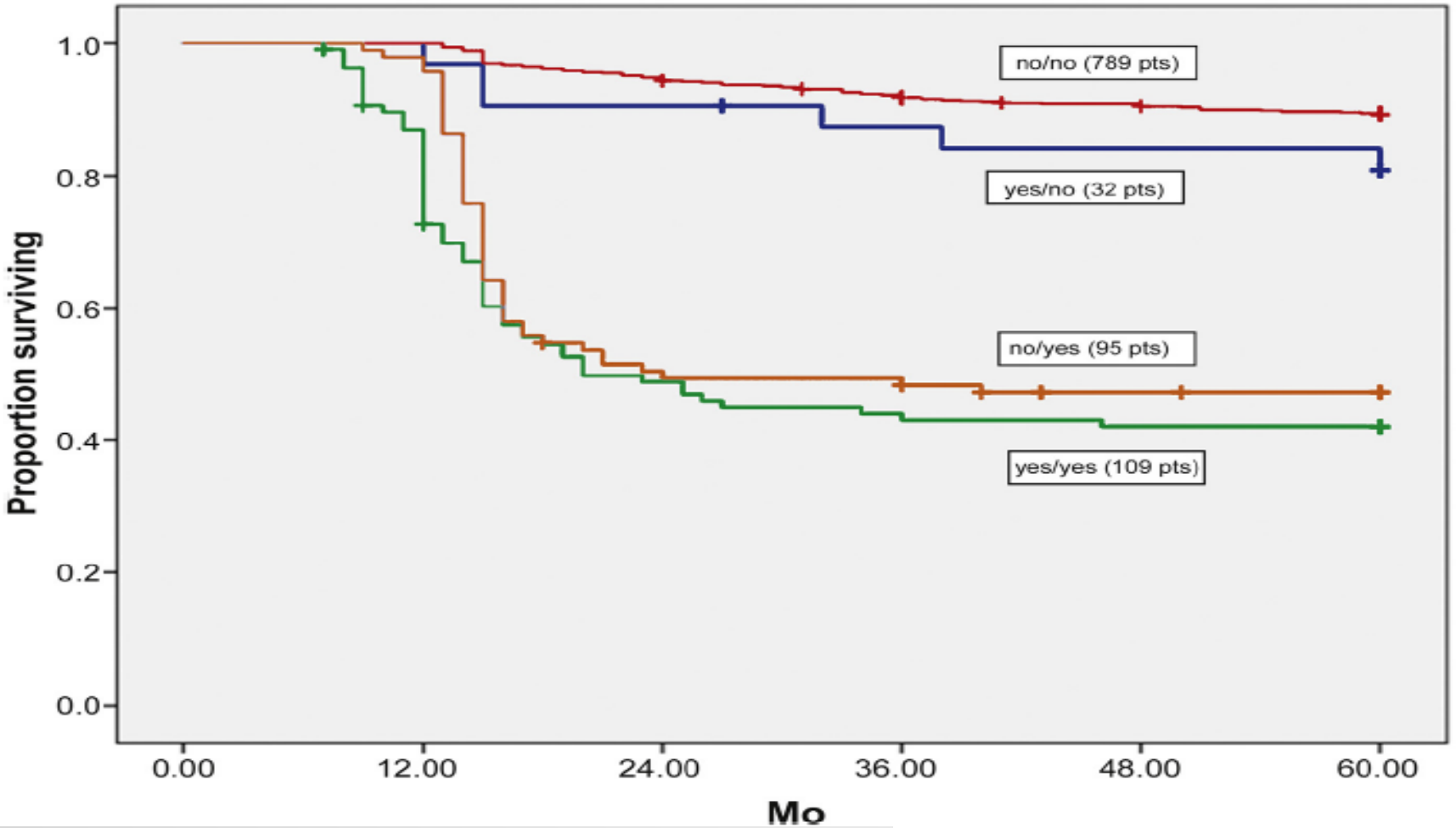
Vol. 169, 1706–1708, May 2003

HARRY W. HERR AND GUIDO DALBAGNI

*From the Department of Urology, Memorial Sloan-Kettering Cancer Center, New York, New York*

Results: Of the 93 cases 57% were negative for tumor at 3 months and 43% had residual tumor resected. At 6 months 80% of the patients were tumor-free and 20% had persistent or recurrent tumor. Maintenance BCG did not decrease tumor recurrence further than induction BCG. Subsequent tumor-free interval during 24 months of followup were best predicted by response to BCG after 6 months.

Conclusions: A minimum treatment and followup time of 6 months is required to identify high risk, superficial bladder tumors as truly BCG refractory.




3 και 6 μήνες μετά TUR-B

**Bacillus Calmette-Guérin Without Maintenance Therapy for High-Risk Non–Muscle-Invasive Bladder Cancer**

*Harry W. Herr* *, *Guido Dalbagni*, *Sherri M. Donat*

*Department of Urology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA*

EUROPEAN UROLOGY 60 (2011) 32–36

We suggest in the context of visibly complete transurethral resection and sufficient exposure to intravesical BCG, that BCG-refractory patients are best identified after 6 mo rather than 3 mo.

# Ορισμός BCG-refractory

The analysis demonstrated that persistent disease at 3 mo after induction BCG disappeared in 23% of patients after a further 3 mo, even without additional BCG. A more important group, however, is the 77% of patients with tumours that still persist at 6 mo, whereby the curves presented show a dramatic 60% 2-yr progression rate. How many of those patients could we render "progression-free" by performing an early radical cystectomy at 3 mo, with potentially better disease-related survival? This is why we should be very cautious in our recommendations.

which could be, as soon as it is published, the key for a potential change in guideline recommendations.

**Reply to Harry Herr's Letter to the Editor re: Marko Babjuk, Andreas Böhle, Maximilian Burger, et al. Carcinoma of the Bladder: Update 2016. Eur Urol.**

# ΝΕΟΕΠΙΚΟΥΡΙΚΗ ΧΜΘ

| Recommendations | GR |
|---|---|
| Offer neoadjuvant chemotherapy for T2-T4a, cN0M0 bladder cancer.<br>In this case, always use cisplatin-based combination therapy. | A |
| Do not offer neoadjuvant chemotherapy to patients who are ineligible for cisplatin-based combination chemotherapy. | A |

**Advantages**

- Earliest time **with lowest tumor burden** of micrometastatic Dx
- **In vivo chemosensitivity**-response (pT0)
- Better **tolerability** before RCx
- No impact on **surgical morbidity**

**Disadvantages**

- **Delay** of RCx in **chemoresistant** (no trials of delay due to NAC)
- **Overtreatment** of pt without micrometastatic
- NAC in patients that can tolerate cisplatin

Currently, no tools are available to select patients who have a higher probability of benefitting from neoadjuvant chemotherapy. In the future, genetic markers, in a personalised medicine setting, might facilitate the selection of patients for neoadjuvant chemotherapy and differentiate responders from non-responders.

# ΝΕΟΕΠΙΚΟΥΡΙΚΗ ΧΜΘ

| Summary of evidence | 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 OS (5-8% at 5 years). | 1a |
| Neoadjuvant treatment of responders and especially patients who show complete response (pT0 N0) has a major impact on OS. | 2 |

3 metanalysis
11 RCTs -**3005**pt
**Old series**

**Updated** largest **RCT** phase 3 with **FU 8 y**
- **16% reduction** of mortality risk
- Improves survival 6% at 10 y

**New chemo**
similar results
No RCTs

# Neoadjuvant Chemotherapy in Invasive Bladder Cancer: Update of a Systematic Review and Meta-Analysis of Individual Patient Data

European Urology 48 (2005) 202–206

Advanced Bladder Cancer (ABC) Meta-analysis Collaboration

***Results:*** Updated results are based on 11 trials, 3005 patients; comprising 98% of all patients from known eligible randomised controlled trials. We found a significant survival benefit associated with platinum-based combination chemotherapy (HR = 0.86, 95% CI 0.77–0.95, $p = 0.003$). This is equivalent to a 5% absolute improvement in survival at 5 years. There was also a significant disease-free survival benefit associated with platinum-based combination chemotherapy (HR = 0.78 95% CI 0.71–0.86, $p < 0.0001$), equivalent to a 9% absolute improvement at 5 years.

***Conclusions:*** These results provide the best available evidence in support of the use of neoadjuvant platinum-based combination chemotherapy.

year survival. The results are convincing, but one may ask if they may be generalised to the whole patients population in the routine treatment of invasive bladder cancer. For this purpose a review of inclusion criteria and patients characteristics has been made in the three major trials of this study [2–4] which represent 1913

International Collaboration of Trialists Lancet 1999
Grossman HB et al New Engl J Med 2003
Sherif A et al Eur Urol 2004

In conclusion this meta-analysis demonstrates very clearly a 5% survival advantage of neoadjuvant cis-platin-based chemotherapy in T2–4a N0 bladder cancer patients before local curative therapy. Nevertheless these results are valid in a selected patients population who have a PS 0/1, a creatinine clearance >50 ml/mn and who are less than 70 years old. The 30 to 40% proportion of patients who are actually older than 70 years, those with PS 3/4 or impaired renal function are unlikely to benefit from this treatment strategy. As they represent more than a third of patients with localised bladder cancer, their treatment requires further specific studies.

**Editorial Comment**

Jean-Pierre Droz, *Lyon, France*

European Urology 48 (2005) 202–206


JAMAICA
TDK
BOLT

# NEOADJUVANT Χημειοθεραπεία

## Low Incidence of Perioperative Chemotherapy for Stage III Bladder Cancer 1998 to 2003: A Report From the National Cancer Data Base

Kevin A. David,*,† Matthew I. Milowsky,* Jamie Ritchey,* Peter R. Carroll‡ and David M. Nanus§,‖

TABLE 2. *Treatment patterns for stage III bladder TCC, 1998–2003*

| | No. Stage III Bladder TCC (%) |
|---|---|
| Surgery of interest + chemotherapy (974): | |
| Surgery + adjuvant chemotherapy | 744 (10.4) |
| Neoadjuvant chemotherapy + surgery | 82 (1.2) |
| Surgery + chemotherapy (nonadjuvant) | 148 (2.1) |

## Treatment of Muscle Invasive Bladder Cancer: Evidence From the National Cancer Database, 2003 to 2007

Ugo Fedeli, Stacey A. Fedewa* and Elizabeth M. Ward

**Results:** The proportion of patients treated with cystectomy (42.9%) and radiation therapy (16.6%) remained stable with time while the incidence of those who received chemotherapy increased from 27.0% in 2003 to 34.5% in 2007 due to an increase in neoadjuvant chemotherapy and chemotherapy without surgery. The

# Πραγματικότητα

**Risk based neoadjuvant chemotherapy in muscle invasive bladder cancer**

**Isuru S. Jayaratna, Neema Navai, Colin P. N. Dinney**

Department of Urology, MD Anderson Cancer Center, Houston, TX 77030, USA

which patients will have the poorest outcomes. These can be roughly divided into those factors that represent locally advanced disease [palpable or fixed mass on examination under anesthesia (EUA)], cross-sectional imaging revealing signs of extravesical extension or local organ involvement, hydronephrosis) and those factors that predict regional/ distant metastasis [lymphovascular invasion (LVI), and variant histology] .

# ΠΡΟΕΓΧΕΙΡΗΤΙΚΗ XBRT

| Summary of evidence | LE |
|---|---|
| No data exist to support that pre-operative radiotherapy for operable MIBC increases survival. | 2a |
| Pre-operative radiotherapy for operable MIBC, using a dose of 45-50 Gy in fractions of 1.8-2 Gy, results in downstaging after 4-6 weeks. | 2 |
| Limited high-quality evidence supports the use of pre-operative radiotherapy to decrease the local recurrence of MIBC after radical cystectomy. | 3 |

| Recommendations | GR |
|---|---|
| Do not offer pre-operative radiotherapy to improve survival. | A |
| Offer pre-operative radiotherapy for operable MIBC since it can result in tumour downstaging after 4-6 weeks. | C |


# PREOPERATIVE RT

Anticancer Res. 1998 May-Jun;18(3B):1931-4.

**Planned preoperative radiation therapy in muscle invasive bladder cancer; results of a meta-analysis.**

Huncharek M[1], Muscat J, Geschwind JF.

**CONCLUSION:** The available clinical trial data do not support a role for routine use of pre-operative radiation therapy in the treatment of muscle invasive bladder cancer. Additional well designed trials are needed to address this issue.

A meta-analysis of the five randomised trials showed an OR for the difference in 5-year survival of 0.71 (95% CI: 0.48-1.06) in favour of pre-operative RT [232]. However, the meta-analysis was potentially biased by the patients in the largest trial who were not given the planned treatment. When the largest trial was excluded, the OR became 0.94 (95% CI: 0.57-1.55), which is not significant.

# PREOPERATIVE RT

Guideline on Muscle-Invasive and Metastatic Bladder Cancer (European Association of Urology Guideline): American Society of Clinical Oncology Clinical Practice Guideline Endorsement

*J Clin Oncol 34:1945-1952. © 2016*

*Matthew I. Milowsky, R. Bryan Rumble, Christopher M. Booth, Timothy Gilligan, Libni J. Eapen, Ralph J. Hauke, Pat Boumansour, and Cheryl T. Lee*

Preoperative radiotherapy for operable MIBC can result in tumor down-staging after 4-6 weeks.

***Not endorsed by ASCO based on the evidence that the EAU reviewed***

# ΡΙΖΙΚΗ ΚΥΣΤΕΚΤΟΜΗ

| | |
|---|---|
| *Radical cystectomy* | |
| Do not delay cystectomy for >3 mo because it increases the risk of progression and cancer-specific mortality. | B |
| 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 patient and surgeon. | B |
| Preoperative bowel preparation is not mandatory. Fast-track measurements may reduce the time of bowel recovery. | C |
| Offer radical cystectomy in T2–T4a, N0M0, and high-risk non-MIBC (as outlined earlier). | A* |

**Indications**

- Pt **fit and willing**
- Localised MIBC (T2-T4a/N0M0)
- Nonresponsive or high risk NMIBC
- After failure of bladder preserving techniques
- **Palliative**

**RCB in the elderly**

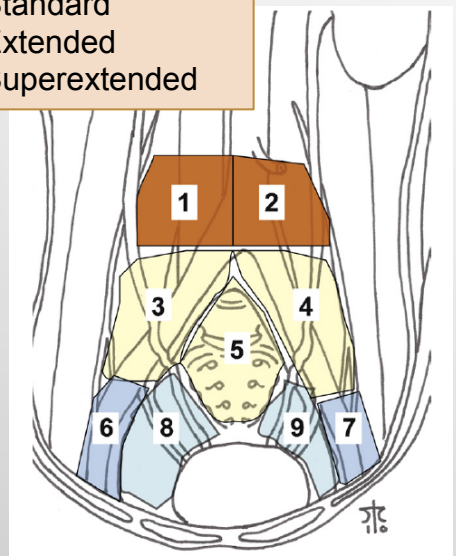
- Greatest risk reduction of disease related and non disease related death
- **Increased perioperative morbidity**
- **Not increased perioperative mortality**
- Usually ileal **conduit**

# ΛΕΜΦΑΔΕΝΙΚΟΣ ΚΑΘΑΡΙΣΜΟΣ

Lymph node dissection must be an integral part of cystectomy. A

**Nodal counts**: inter-individual variability, therefore limited utility as a surrogate for the anatomic extent

- Standard
- Extended
- Superextended




**Extent of LND not established**

- LND > no LND
- Extended / Superextended > limited / standard
- Extended= Superextended

| | |
|---|---|
| There are data to support that an extended LND (vs. a standard or limited LND) improves survival after radical cystectomy. | 3 |

# ΑΝΤΙΜΕΤΩΠΙΣΗ ΤΗΣ ΟΥΡΗΘΡΑΣ

**Risk factors for urethral involvement**
- **Prostatic** tumor involvement (male)
- **Bladder neck** involvement (female)

LE 2 GR B

**Intraoperative frozen section** has high **sensitivity** and specificity for the detection of a malignant urethral margin
LE 2b GR B

Pt with **(+)** final urethral **margin** has **risk** of urethral **recurrence**
LE 3 GR B

**Urethrectomy** should be **considered** in pt with **invasive carcinoma** at the urethral margin and in case of urethral recurrence
LE 3 GR B

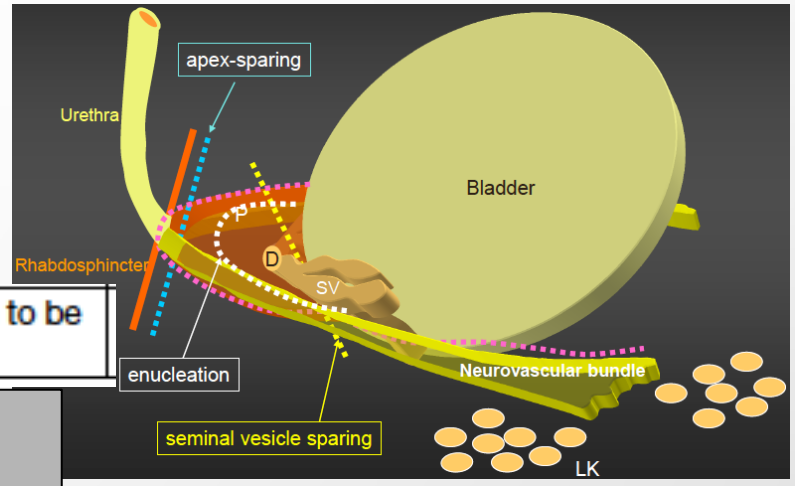
In pt with **noninvasive tumor or in situ** at the urethra **conservative** treatment is an option
LE 3 GR C

Preserve the urethra if margins are negative.

Check the urethra regularly if no bladder substitution is attached. B

# ΤΕΧΝΙΚΕΣ ΔΙΑΤΗΡΗΣΗΣ ΤΗΣ ΣΕΞΟΥΑΛΙΚΟΤΗΤΑΣ ΣΤΟΝ ΑΝΔΡΑ

- **Prostate sparing** Cx (P/SV/NVB)
- **Capsule sparing** Cx-adenoma (SV/NVB)
- **Seminal sparing** Cx (SV, NVB)
- **Nerve sparing** RCx (NVB)




None of the sexual-preserving techniques (prostate/capsule/seminal/nerve sparing) have shown to be superior and no particular technique can be recommended.

- Non oncologic inferiority
- Better sexual outcomes
- Better continence results

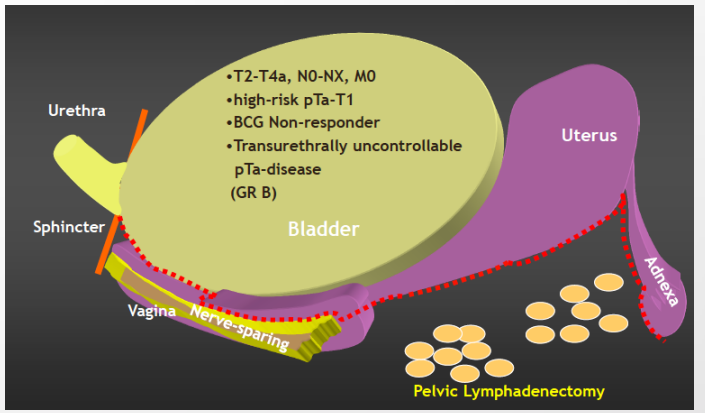
Overall quality of the evidence was moderate - **Careful selection**

| Recommendations | LE | GR |
|---|---|---|
| Offer sexual-preserving techniques to men motivated to preserve their sexual function since the majority will benefit. | 2 | B |
| Select patients based on:<br>- Organ-confined disease;<br>- Absence of any kind of tumour at the level of the prostate, prostatic urethra or bladder neck | 2 | A |
| Do not offer sexual-preserving cystectomy as standard therapy for MIBC. | | C |

# ΤΕΧΝΙΚΕΣ ΔΙΑΤΗΡΗΣΗΣ ΤΗΣ ΣΕΞΟΥΑΛΙΚΟΤΗΤΑΣ ΣΤΗΝ ΓΥΝΑΙΚΑ

| Recommendations | LE | GR |
|---|---|---|
| Offer sexual-preserving techniques to female patients motivated to preserve their sexual function since the majority will benefit. | 3 | C |
| Select patients based on:<br>• Organ-confined disease;<br>• Absence of tumour in bladder neck or urethra. | | C |
| Do not offer pelvic organ-preserving radical cystectomy for female patients as standard therapy for MIBC. | | C |

| Summary of evidence |
|---|
| Data regarding pelvic organ-preserving radical cystectomy for female patients remain immature. |




| | |
|---|---|
| CSS | 70-100% |
| OS | 65-100% |
| **Day Cont** | **70.3%** |
| Night Cont | 67.2% |
| Self Cath | 17.6% |
| **Sex activity** | **86.7%** |
| Sexuality | 80-100% |

# ΕΛΑΧΙΣΤΑ ΕΠΕΜΒΑΤΙΚΗ ΚΥΣΤΕΚΤΟΜΗ

| Summary of evidence | LE |
|---|---|
| RARC provides longer operative time time (1-1.5 hours), major costs; but shorter LOS (1-1.5 days) and less blood loss compared to ORC. | 1 |
| RARC series suffer from a significant stage selection bias as compared to ORC. | 1 |
| Grade 3, 90-day complication rate is lower with RARC. | 2 |
| Most endpoints, if reported, including intermediate term oncological endpoint and QoL are not different between RARC and ORC. | 2 |
| Surgeons experience and institutional volume are considered the key factor for outcome of both RARC and ORC, not the technique. | 2 |
| Recommendations on how to define challenging patients and an experienced RARC surgeon are still under discussion. | 3 |
| The use of neobladder after RARC still seems under-utilised, and functional results of intracorporeally constructed neobladders should be studied. | 4 |

102/105 LE 4
Only 3 LE2b

| | |
|---|---|
| Inform the patients of advantages and disadvantages of ORC and RARC to select the proper procedure. | C |
| Select experienced centres, not specific techniques, both for RARC and ORC. | B |
| Beware of neobladder under-utilisation and outcome after RARC. | C |

# ΕΚΤΡΟΠΗ ΤΩΝ ΟΥΡΩΝ

**Types of diversions**
- **Abdominal wall**
  - Ileal/colonic conduit
  - Ureterocutaneostomy
  - Continent pouches
- **Urethral diversion**
  - Ileal neobladders
- **Rectosigmoid diversions**

**Ureterocutaneostomy**
- Single kidney
- Stomal stenosis
- Ascending UT infection
- Less diversion related complications

**Ileal conduit**
- Early complications 48%
- **Stomal 24%**
- UUT 30%

**Neobladder**
- Early & late complications 22%
- **Incontinence** day time 10%
- Incontinence night time 30%
- Stenosis 18%
- **Metabolic disorders** , B12

**Contraindications for neobladder**
- Psychiatric illness
- Debilitating neurological Dx
- Urethral tumor
- Impaired liver / renal function
- High dose XBRT
- Complex urethral sstricture
- Sphincter incontinence
- Age >80

Oncologic results **NOT DEPENDENT** from type of diversion

**NOT** possible to **RECOMMEND** a particular type of diversion

# ΝΟΣΗΡΟΤΗΤΑ-ΘΝΗΤΟΤΗΤΑ-CSS

| | |
|---|---|
| Perioperative **mortality** @ 30d | 1.2-3.2% |
| Perioperative **mortality** @ 90d | 2.3-8% |
| **Early complications** 90d | 58% |
| **Late** complications | Depends on type of diversion |
| **RFS** @ 5y/10 y | 68%/60% |
| **OS** @ 5y/10y | 66%/43% |

| | **5y RFS** |
|---|---|
| pT1 | 76% |
| pT2 | 74% |
| pT3 | 52% |
| pT4 | 36% |

**Trend analysis**
Increased 5y survival rate for all stages except metastatic DX

| CLAVIEN System | | Morbidity | Management |
|---|---|---|---|
| **Grade I** | Any deviation from the normal post-operative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs such as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside. | **Immediate complications:** | |
| | | Post-operative ileus | Nasogastric intubation (usually removed at J1)<br>Chewing gum<br>Avoid fluid excess and hypovolemia (provoke splanchnic hypoperfusion) |
| | | Post-operative nausea and vomiting | Antiemetic agent (decrease opioids)<br>Nasogastric intubation |
| | | Urinary infection | ATB, no ureteral catheter removal<br>Check the 3 drainages (ureters and neobladdder) |
| | | Ureteral catheter (UC) obstruction | 5cc saline UC injection to avoid the obstruction<br>Increase volume infusion to increase dieresis |
| | | Intra abdominal urine leakage (anastomosis leakage) | Check drainages and watchful waiting |
| | | Anaemia well tolerated | Martial treatment (give iron supplement) |
| | | **Late complications:** | |
| | | Non compressive lymphocele | Watchful waiting |
| | than those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included. | cardiopathy history | |
| | | Pulmonary embolism | Heparinotherapy |
| | | Pyelonephritis | ATB and check kidney drainage (nephrostomy if necessary) |
| | | Confusion or neurological disorder | Neuroleptics and avoid opioids |
| **Grade III** | Requiring surgical, endoscopic or radiological intervention | UC accidentally dislodged | Indwelling leader to raise the UC |
| | | Anastomosis stenosis (7%) | Renal drainage (ureteral catheter or nephrostomy) |
| | | Ureteral reflux | No treatment if asymptomatic |
| **III-a** | Intervention not under general anaesthesia | Compressive lymphocele | Transcutaneous drainage or intra-operative marsupialisation (cf grade III) |
| **III-b** | Intervention under general anaesthesia | Ileal anastomosis leakage | Ileostomy ASAP |
| | | Evisceration | Surgery in emergency |
| | | Compressive lymphocele | Surgery (marsupialisation) |
| **Grade IV** | Life-threatening complication (including CNS complications: brain haemorrhage, ischaemic stroke, subarachnoid bleeding, but excluding transient ischaemic attacks) requiring IC/ICU management. | Rectal necrosis | Colostomy |
| | | Neobladder rupture | Nephrostomy and indwelling catheter/surgery for repairing neobladder |
| | | Severe sepsis | ATB and check all the urinary drainages and CT Scan in emergency |
| **IV-a** | Single organ dysfunction (including dialysis) | Non-obstructive renal failure | Bicarbonate/aetiology treatment |
| **IV-b** | Multi-organ dysfunction | Obstructive pyelonephritis and septicaemia | Nephrostomy and ATB |
| **Grade V** | Death of a patient | | |
| *Suffix 'd'* | *If the patient suffers from a complication at the time of discharge, the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.* | | |

| | |
|---|---|
| Surgical complications of cystectomy and urinary diversion should be reported using a uniform grading system. Currently, the best-adapted, graded system for cystectomy is the Clavien grading system. | 2 |

| Summary of evidence | LE |
|---|---|
| For MIBC, offer radical cystectomy as the curative treatment of choice. | 3 |
| A higher case load reduces morbidity and mortality of cystectomy. | 3 |
| Radical cystectomy includes removal of regional lymph nodes. | 3 |
| There are data to support that extended LND (vs. standard or limited LND) improves survival after radical cystectomy. | 3 |
| Radical cystectomy in both sexes must not include removal of the entire urethra in all cases, which may then serve as the outlet for an orthotopic bladder substitution. The terminal ileum and colon are the intestinal segments of choice for urinary diversion. | 3 |
| The type of urinary diversion does not affect oncological outcome. | 3 |
| Laparoscopic cystectomy and robotic-assisted laparoscopic cystectomy are feasible but still investigational. Current best practice is open radical cystectomy. | 3 |
| In patients aged > 80 years with MIBC, cystectomy is an option. | 3 |
| Surgical outcome is influenced by comorbidity, age, previous treatment for bladder cancer or other pelvic diseases, surgeon and hospital volumes of cystectomy, and type of urinary diversion. | 2 |
| Surgical complications of cystectomy and urinary diversion should be reported using a uniform grading system. Currently, the best-adapted, graded system for cystectomy is the Clavien grading system. | 2 |
| No conclusive evidence exists as to the optimal extent of LND. | 2a |



| Recommendations | GR |
|---|---|
| Do not delay cystectomy for > three months as it increases the risk of progression and cancer-specific mortality. | B |
| Before cystectomy, fully inform the patient about the benefits and potential risks of all possible alternatives, and the final decision should be based on a balanced discussion between patient and surgeon. | B |
| Offer an orthotopic bladder substitute or ileal conduit diversion to male and female patients lacking any contraindications and who have no tumour in the urethra or at the level of urethral dissection. | B |
| Do not offer pre-operative radiotherapy when subsequent cystectomy with urinary diversion is planned. | A |
| Pre-operative bowel preparation is not mandatory. "Fast track" measurements may reduce the time of bowel recovery. | C |
| Offer radical cystectomy in T2-T4a, N0M0, and high-risk non-MIBC (as outlined above). | A* |
| Lymph node dissection must be an integral part of cystectomy. | A |
| Preserve the urethra if margins are negative. | |
| Check the urethra regularly if no bladder substitution is attached. | B |

# ΠΑΡΗΓΟΡΗΤΙΚΗ ΚΥΣΤΕΚΤΟΜΗ

| Recommendations | GR |
|---|---|
| Offer radical cystectomy as a palliative treatment to patients with inoperable locally advanced tumours (T4b). | B |
| In patients with symptoms, palliative cystectomy may be offered. | B |

**Palliative RCx**
- **Recurrence** up to **100%**
- If P-RCx not possible offer **palliative XBRT**

| Supportive Care | |
|---|---|
| **Obstruction of the UUT** | **Bleeding & Pain** |
| Stents | Stop anticoagulants |
| NT | TUR coagulation |
| Diversion | Installation of<br>• 1% **silver nitrate**<br>• 1-2% alum<br>• 2-4% **formalin**-30 min<br>• **Radiation**<br>• **Embolization 90%** |

# ΘΕΡΑΠΕΙΕΣ ΔΙΑΤΗΡΗΣΗΣ ΤΗΣ ΚΥΣΤΕΩΣ ΓΙΑ ΚΛΙΝΙΚΑ ΕΝΤΟΠΙΣΜΕΝΗ ΝΟΣΟ

TURBT

| Recommendation | LE | GR |
|---|---|---|
| Do not offer transurethral resection of bladder tumour alone as a curative treatment option as most patients will not benefit. | 2a | B |

XBRT

| Recommendation | GR |
|---|---|
| Do not offer radiotherapy alone as primary therapy for localised bladder cancer. | B |

CHEMO

| Recommendation | GR |
|---|---|
| Do not offer chemotherapy alone as primary therapy for localised bladder cancer. | A |

**XBRT** (LE3)
- Unfit for RCx
- Stop bleeding

| Summary of evidence | LE |
|---|---|
| With cisplatin-based chemotherapy as primary therapy for locally advanced tumours in highly selected patients, complete and partial local responses have been reported. NOT Durable response | 2b |

# ΔΙΑΤΗΡΗΣΗ ΤΗΣ ΚΥΣΤΕΩΣ : MULTIMODALITY $T_X$

| Summary of evidence | LE |
|---|---|
| In a highly selected patient population, long-term survival rates of multimodality treatment are comparable to those of early cystectomy. | 2b |

| Recommendations | GR |
|---|---|
| Offer surgical intervention or multimodality treatments as primary curative therapeutic approaches since they are more effective than radiotherapy alone. | B |
| Offer multimodality treatment as an alternative in selected, well-informed and compliant patients, especially for whom cystectomy is not an option. | B |

| | |
|---|---|
| **CSS@5y** | **50-80%** |
| OS@5y | 36-74% |
| Salvage Cx | 10-30% |

**STRONG CONTRAINDICATIONS**
- Poor bladder function
- Extensive cis

# ΕΠΙΚΟΥΡΙΚΗ ΧΜΘ

| Recommendation | GR |
|---|---|
| Offer adjuvant cisplatin-based combination chemotherapy to patients with pT3/4 and/or pN+ disease if no neoadjuvant chemotherapy has been given. | C |

**9 trials** with serious differences

- **None better OS**
- All together **trend** towards better OS and DFS
- **DFS benefit more evident in LN+**

**Large RCT (EORTC 30994)**

- **Better DFS but not OS**

# ADJUVANT Χημειοθεραπεία (Μη μεταστατικό)

**Table 1.** Reported Randomized Trials of Adjuvant Therapy for MIBC

| First Author | Eligibility | Regimen | Total Patients Randomly Assigned | Completed Accrual | Improved Survival |
|---|---|---|---|---|---|
| Bono[26] | pT2-T4a | Cisplatin plus methotrexate | 90 | Yes | No |
| Freiha[27] | p3b-4, N0 or N+ | CMV | 55 | No* | No |
| Otto[28] | pT3 | MVEC | 108 | Yes | No |
| Skinner[29] | pT3-4 or N+ | Multiple cisplatin-based combinations | 102 | No* | No |
| Lehmann[30] | pT3-4a and/or pN+ | MVAC or MVEC | 49 | No* | No |
| Studer[31] | Multifocal recurrent pT1 or pT2-T4a | Cisplatin | 91 | Not | No |
| Stadler[32] | pT1/T2 N0M0 | MVAC | 114 | Yes | No |
| Cognetti[33] | pT2 grade 3, N0-2; pT3-4, N0-2, any grade; or pN1-2, any T, any grade | GC | 194 | No | No |
| Paz-Ares[34] | pT3-4 and/or pN+ | PCG | 142 | No | Yes |
| Sternberg[35] | pT3-4 and/or pN+ | GC, MVAC, or DD-MVAC | 284 | No | No |

Abbreviations: CMV, cisplatin, methotrexate, and vinblastine; DD-MVAC, dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; GC, gemcitabine plus cisplatin; MIBC, muscle-invasive bladder cancer; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; MVEC, methotrexate, vinblastine, epirubicin, and cisplatin; PCG, paclitaxel, cisplatin, and gemcitabine.

*Stopped early because interim analysis favored adjuvant chemotherapy.

†Stopped early because interim analysis favored control arm of no adjuvant chemotherapy.

# Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3–pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial

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Interpretation Our data did not show a significant improvement in overall survival with immediate versus deferred chemotherapy after radical cystectomy and bilateral lymphadenectomy for patients with muscle-invasive urothelial carcinoma. However, the trial is limited in power, and it is possible that some subgroups of patients might still benefit from immediate chemotherapy. An updated individual patient data meta-analysis and biomarker research are needed to further elucidate the potential for survival benefit in subgroups of patients.

**Re: Immediate Versus Deferred Chemotherapy After Radical Cystectomy in Patients with pT3-pT4 or N+ M0 Urothelial Carcinoma of the Bladder (EORTC 30994): An Intergroup, Open-label, Randomised Phase 3 Trial**

Sternberg CN, Skoneczna I, Kerst JM, et al

Lancet Oncol 2015;16:76–86

Consequently, NC should remain the preferred strategy at this time. Perhaps it is time for a randomized trial comparing NC and AC.

# Not eligible for cisplatin (unfit)

An international survey among BC experts [448] was the basis for a consensus statement on how to classify patients unfit for cisplatin-based chemotherapy. At least one of the following criteria has to be present: PS > 1; GFR ≤ 60 mL/min; grade ≥ 2 audiometric loss and peripheral neuropathy; and New York Heart Association (NYHA) class III heart failure [449].

More than 50% of patients with urothelial cancer are not eligible for cisplatin-based chemotherapy [450-453].

Renal function assessment in UC is of utmost importance for treatment selection. Calculation of creatinine clearance (CrCl) (24-h urine collection) with current formulae tend to underestimate clearance in patients aged > 65 years compared to measured CrCl [450, 454].

# Πραγματικότητα

## Chemotherapy for Muscle-Invasive Bladder Cancer: Better Late Than Never?

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# ΠΑΡΑΚΟΛΟΥΘΗΣΗ ★

LE low

CT q4mt for 1st year
CT q6mt until 3rd year
CT q12mt thereafter

- 50% M diagnosed **after** Sx
- 50% M diagnosed **before** Sx (benefit?)
  - ***Lung M** diagnosed and treated before Sx improved survival*

| Site of recurrence | Summary of evidence | LE | Recommendations | GR |
|---|---|---|---|---|
| Local recurrence<br>5-15% @24mt | 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. | C |
| Distant recurrence<br>50% @24mt | Poor prognosis. | 2b | Offer chemotherapy as the first option, and consider metastasectomy in case of unique metastasis site. | C |
| Upper urinary tract recurrence<br>1-6% late | Multifocal disease (NMIBC/ CIS or positive ureteral margins. | | See EAU guidelines on Upper Urinary Tract Carcinomas [1]. NUx | |
| Secondary urethral tumour<br>1.5-6% @14-40mt<br>>50% die form M | Staging and treatment should be done as for primary urethral tumour. | 3 | Use local conservative treatment for non-invasive tumour. | C |
| | | | Offer urethrectomy in isolated invasive disease. | B |
| | | | Do not use urethral washes and cytology. | A |

Risk for Urethral recurrence
- Female bladder neck
- Men prostatic inv., RCB for NMIBC

UR REC after orthotopic 1-4%
UR REC after non orthotopic 4-11%
OS after Asx detection>OS after Sx detection

Dept. Urology, Athens Medical School, J. Varkarakis

# ΠΑΡΑΚΟΛΟΥΘΗΣΗ

## LONG TERM FU

**Urinary diversion complications 54% @ 15y**

- B12deficiency
- Metabolic Acidosis
- Renal function deterioration
- Urinary tract infections
- Stenosis U-Int
- Stomal complications
- Bladder continence
- Emptying dysfunction (2/3 women CIC)
- Bone fractures due to chronic MA

# ΠαρακολοΥθηση

Surveillance protocols commonly used are built on observed recurrence patterns from retrospective RC series. Prospective trials demonstrating the effectiveness of follow-up after RC, and particularly its impact on survival, are lacking.

EUROPEAN UROLOGY 58 (2010) 486–494

# Do Patients Benefit from Routine Follow-up to Detect Recurrences After Radical Cystectomy and Ileal Orthotopic Bladder Substitution?

*Gianluca Giannarini*[a], *Thomas M. Kessler*[a], *Harriet C. Thoeny*[b], *Daniel P. Nguyen*[a], *Claudia Meissner*[a], *Urs E. Studer*[a,*]

EUROPEAN UROLOGY 58 (2010) 486–494

| Site of recurrence | Mode of diagnosis of recurrence | |
|---|---|---|
| | Routine follow-up, *n* | Symptoms, *n* |
| Pelvic | 4 | 8 |
| Bone* | 5 | 33 |
| Lung* | 29 | 7 |
| Extrapelvic lymph nodes | 10 | 6 |
| Liver | 4 | 4 |
| Brain | 0 | 4 |
| Penis | 2 | 0 |
| Peritoneal carcinosis | 0 | 1 |
| Muscle (leg) | 0 | 1 |
| Pelvic and distant*† | 3 | 15 |
| Upper urinary tract | 9 | 5 |
| Urethra* | 21 | 3 |
| Total | 87 | 87 |

Patients in whom recurrences after RC and ileal orthotopic bladder substitution are diagnosed by routine follow-up investigations have a slightly higher survival probability than patients with symptomatic recurrences. Regular surveillance is particularly effective in detecting urethral, usually noninvasive recurrences, which can be treated conservatively and are associated with good prognosis. Moreover, the predominance of lung and extrapelvic lymph node metastases in long-term survivors may justify the use of routine cross-sectional imaging. Finally, routine follow-up is associated with no serious recurrence-related complications.

# Oncological Followup After Radical Cystectomy for Bladder Cancer—Is There Any Benefit?

Bjoern G. Volkmer,*,† Rainer Kuefer, Georg C. Bartsch, Jr., Kilian Gust and Richard E. Hautmann

THE JOURNAL OF UROLOGY®
Vol. 181, 1587-1593, April 2009

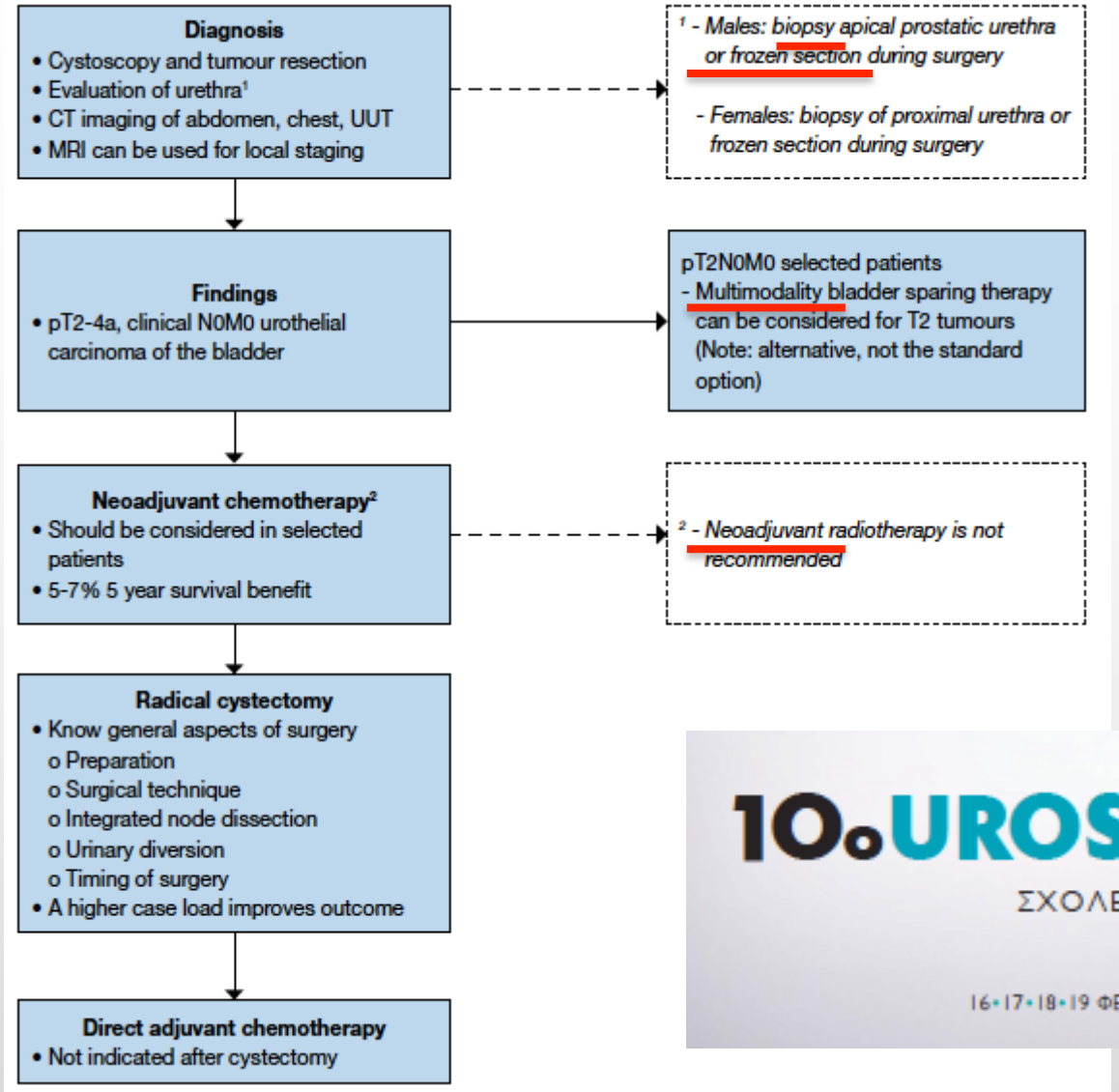
n=1290

| | Symptomatic | Asymptomatic |
|---|---|---|
| No. pts | 290 | 154 |
| Age at cystectomy | 64.0 | 64.7 |
| % Tumor stage: | | |
| Ta/Tis/T1 N0 M0 | 5.2 | 8.4 |
| T2a/T2b N0 M0 | 17.6 | 15.6 |
| T3a–T4b N0 M0 | 29.3 | 25.3 |
| TX N+ M0 | 47.9 | 50.6 |
| % Local recurrence | 45.5 | 35.1 |
| % Metastasis: | | |
| Bone | 30.3 | 22.0 |
| Pulmonary | 15.9 | 22.7 |
| Liver | 19.3 | 14.3 |
| Mos to recurrence | 17.5 | 20 |
| % Chemotherapy/radiotherapy for tumor recurrence/metastasis | 40.0 | 38.3 |

Our data show that improved imaging techniques have a tendency to detect tumor recurrence earlier but this does not cause a survival benefit. The tendency toward slightly better survival in our latest patients, in whom recurrence was diagnosed within the last 8 years, was caused by the introduction of gemcitabine as a chemotherapy agent. As long as we do not have a therapy that can offer patients with metastatic bladder cancer better survival rates than today, tumor recurrence will remain a fatal incident.

Ευχαριστώ


ΙΝΣΤΙΤΟΥΤΟ
ΜΕΛΕΤΗΣ
ΟΥΡΟΛΟΓΙΚΩΝ
ΠΑΘΗΣΕΩΝ
10ο UROSCHOOL 2017
ΣΧΟΛΕΙΟ ΟΥΡΟΛΟΓΙΑΣ
16•17•18•19 ΦΕΒΡΟΥΑΡΙΟΥ - ΠΟΡΤΑΡΙΑ ΠΗΛΙΟ




10ο UROSCHOOL2017

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