New Strategies in the Diagnosis and Treatment of Non Muscle Invasive Bladder Cancer: ESOU Lecture

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Background: Incidence and Costs

- **Bladder cancer (BC)** is one of the most common malignancies in the world: it is **diagnosed in approximately 900,000 men and women each year.** About 20%-25% will die of the disease.

- In **Europe** > 1M TURB performed yearly for BCs. 75% are NMI at first diagnosis while 25% are MI.

- *This burden of therapy and F-UP means that BC is one of the most expensive malignancies to manage in terms of total expenditures.*

- Botteman et al Pharmacoeconomics 2003
  Burger et al Eur Urol 2012
Epidemiology (BC)

- 75-85% of TCC-patients present with the disease confined to the mucosa (pTa, CIS) or submucosa (pT1): NMIBC

- **Risk factors**
  - aromatic amines
  - cigarette smoking

Diagnosis

- An early and correct diagnosis of bladder cancer is of paramount importance for the future treatment plans and outcomes of the patients

- Early diagnosis of BC can prevent major surgery and improve patient survival

- **Conclusion**: Diagnosis of BC is extremely important
Hot Topics in Diagnosis

Imaging
Urinary cytology
Urine molecular markers
Urethro-cystoscopy
Future directions

Imaging

- **US**: improvement in the technical quality of US resulted in improvement in diagnosis of NMIBC.
  - **Sensitivity**: 63-98%
  - **Specificity**: 99%
  - US: strictly dependent from operator experience (rad/urol)

US can detect small bladder tumors (5 mm).
It can be performed in the emergency department (Eco-Fast)
Bladder and UUT can be evaluated

**Drawbacks**: difficult interpretation of the bladder in case of clots, enlarged prostate protruding into the bladder, bladder trabeculation. False positive rate: very low (<3%)
Kidneys can be evaluated for renal masses. NMI UUT Ts detection rate is low depending from the diameter of the T.
Ultrasound: Clinical Case

- **01.18**: US (Eco-Fast) can be performed in the emergency department by urologists
- A lesion of 4 cm in the L trigone was detected

URO-CT

- **Uro-CT**: the gold standard for diagnosis of urothelial tumors
- **Sensitivity**: 88-100%  **Specificity**: 93-100%
- Uro-CT is used primarily to visualize upper urinary tract. The incidence of UUTcc in patients with hematuria is 0.2-0.4%.
  In patients with tumors localized in the trigone the incidence of UUTTcc = 6-7%
  Soloway et al ICBC 2012
Uro-CT In Diagnosis of UUT Tcc

- Uro-CT: the location of the tumor in the UUT has a direct impact on the detection accuracy:
  * Renal Pelvis tumors: sensitivity 78-94%
  * Ureteral tumors: sensitivity 19-54%
  Scolieri et al Urology 2000

mpMRI

- "An Evaluation of morphological and functional MRI sequences in classifying NMIBC and MIBC"
  V Panebianco et al Eur Rad 2017, Eur Urol 2019

- Results:
  A correct evaluation of bladder wall infiltration by MRI is possible in a large number of patients with bladder cancer (>70%)

- Conclusions:
  MRI can diagnose correctly NMIBC vs MIBC.
  The experience of the radiologist plays a major role
  Prospective studies are needed to confirm these results
Urinary cytology

High sensitivity in high-grade tumors
but low sensitivity in low grade tumors (level of evidence 3)

It is useful when a high-grade malignancy or CIS is present

Cytological interpretation is user dependent

The evaluation can be hampered by UTI, stones
or intravesical instillation
Cytology: Conclusions

• Cytology is still the standard marker for the diagnosis and follow-up of NMI Bladder Cancer
• Cyto predictive value if positive = 95%. If negative = 96%
  It is user (pathologist) dependent and this may be the reason why not all the urological centers use it regularly.
• In case of a positive cytology in a patient with a negative cystoscopy we have up to 95% probability of having an urothelial Tcc of the urinary tract

Urine Molecular Markers

The limitation of cytology in low G and the invasiveness of cystoscopy have generated interest in molecular markers

Genetics
  DNA alteration

Epigenetics
  impediment DNA transcription

Genomics
  alteration of quantitative mRNA translation

Proteomics
  alteration at protein level
Urinary Biomarkers in 2019

- Currently there is no consensus regarding the use of urinary biomarkers for diagnosis of BC. Randomized studies are needed to determine the appropriate use of UB in diagnosis and surveillance of Bladder Cancer

- EAU Guidelines 2018:
  NO statement on Urinary Biomarkers

New Biomarker In the Diagnosis of BC

- ADXBLADDER (MCM5 Elisa): is a double-monomoclonal antibody sandwich enzyme-linked immunoassay (ELISA). Both antibodies have high affinity and specificity for the antigen MCM5

- Used in Bladder cancer detection and follow-up. A multicenter study ready......
**ADXBLADDER Test**

- Minichromosome maintenance (MCM) proteins as markers of cancer have been well studied over the last 20 years
- A valuable & highly reliable method of detecting MCM5 in urine
- AxDxBLADDER is built on the biology and location of the MCM proteins in normal and malignant layers vs. malignant atypia/malignant
- In normal urothelium, MCM5 is restricted to the basal proliferative compartment. In urothelial cancer, MCM5 is expressed in all layers, resulting in exfoliation of MCM5-expressing tumor cells in the urines.

**Figure adapted from Current Opinion in Cell Biology, 2007, 19:672–679**

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**ADXBLADDER (MCM5 Elisa):**

- **CLINICAL EXPERIENCE**
  - Used in Bladder cancer detection and follow-up. A multicenter study ready......
  - 575 patients with micro and macro hematuria included
  - Sensibility in NMIBC: LR = 50% IR = 67% HR: 92%
  - Negative predicting value = 97%
Cystoscopy

- **Flexible Urethro-cystoscopy**: can detect more tumours than cystoscopy performed with rigid instruments (standard)

- **Bladder diagram**: the use of bladder diagram at the time of first diagnosis is one of the most important parameter for < 3-RR (Brausi et al J Urol’04)

TUR

- **TUR** with white-light is considered nowadays the gold standard for the diagnosis and treatment of non muscle invasive bladder tumors (NMIBC)
- However TUR must be «ADEQUATE»
  - a. all visible tumors resected
  - b. muscle must be present in the specimen, if not «Tx»
  - c. no bladder perforation
  - d. no bleeding
- **En Block TUR** becoming the standard .... + Adjuvant therapy....
Transurethral Resection - goals

Diagnostic...
- Endoscopic detection
- Pathologic information
- Molecular markers

Therapeutic...
- Oncologic principles
- Prevention of recurrence
- Prevention of progression

PDD
Photodynamic Diagnosis:
Enhances Tcc detection rate and Cis by 20% and 39% respectively
... 39% (CI, 23–57) more CIS positive patients were detected with PDD ...

Impact on progression HAL vs. WL-TUR-BT

551 patients with NMIBC

RANDOMIZED

HAL: 271 Pat.

WL: 280 Pat.

Median F/U: 55 months

T2-T4 progression 8 (3.1%)  p=0.066  16 (6.1%)

Grossman, Stenzl et al., J Urol, 2012
NBI

- The system has integrated NBI and WLC: with the push of a button the NBI mode is activated by the mechanical insertion of a NB filter in front of the WL source

- NBI: Sensitivity: 93-100% Specificity: 61-82% vs WLC: Sensitivity : 57-87% Specificity : 59-86%

NBI Data

- 2 meta-analyses (6 prospective studies)
  - 24% pap. tumour
  - 28% CIS
  - RFS?
CONFOCAL LASER ENDOMICROSCOPY (Cellvizio)

What is Cellvizio®?

• *A unique optical biopsy system*
• Probe-based system, used during endoscopic procedures in the GI, Pulmonary and Urinary Tracts
• Compatible with existing endoscopes
• **Real-time visualization of tissue at the cellular level**
• Makes it possible to access difficult locations in the body such as the bile duct, the ureters or even pancreatic cysts
• Different probe types for different indications and needs
• **Providing real-time visualization of tissues**

Available for cystoscopy and ureteroscopy procedure
**Cellvizio Procedure**

- **Phase II study.** *Objective:* detection of dysplasia and Cis. Results: 73% concordance between screen diagnosis and final pathology diagnosis. *Brausi et al 2017 EAU*

**Case - Suspicious Cis**

- **Normal urothelium:** umbrella cells
- **CIS suspicious area:**
  - Pleomorphic, not cohesive cells with indistinct borders
  - Large irregular blood vessel
- **Post biopsy of suspicious area:** Muscle fibers
Confocal Laser Endomicroscopy (CLE) has been used for the first time for the diagnosis of UUT Tcc by Bonnal et al in a phase II study. The technique was feasible with no side effects (Bonnal et al Urol 2012)

Breda et al (Eau 2016) showed a concordance in diagnosis between OR screen evaluation and final path report of about 75%. They used it to detect suspicious areas of UUT where biopsy were taken
Optical Coherence Tomography (OCT)

- **OCT**: Optimal **depth of penetration (up to 2-3mm)**. The 3 layers of the normal bladder wall (urothelium, lamina propria and muscularis propria) can be clearly distinguished.
- **Technique**: a probe is introduced into the bladder through a cysto channel.

- **Clinical results MIBC**: Sensitivity = 100%, Specificity = 90%
  - NMIBC with PDD: Sensitivity: 97.5% Specificity: 97.9%
  - Cis: Sensitivity: 95.7% Specificity: 92.3% (3-dim OCT)
- Limitation: false pos (inflammatory lesions, instillations)

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**OCT**

- Invasion of the muscularis mucosa can be detected in the bladder and in the Upper Urinary Tract.
RAMAN SPECTROSCOPY

RS measures molecular components of tissue both qualitatively and quantitatively. Using RS a pseudocolor map of examined tissue is created. Tissue areas with similar molecular composition are depicted in the same color. Such images are comparable to histopathology and images of stained tissues. Molecular composition changes if path. transformations occur.

Results: RS provide an objective prediction of the path. diagnosis

Clinical data: Draga et al used a fiber through a working channel of the cystoscope. Sensitivity 85%, Specificity: 79%

Shapiro used RS to detect tumor cells in urine samples

Sensitivity: 96% Specificity: 90%

Future: RS used instead of cytology for diagnosis

SPIES

Virtual-Cystoscopy

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<th></th>
<th>USVC</th>
<th>CTVC</th>
<th>RMVC</th>
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<tr>
<td>SENSIBILITY</td>
<td>77%</td>
<td>93%</td>
<td>90%</td>
</tr>
<tr>
<td>SPECIFICITY</td>
<td>96%</td>
<td>98%</td>
<td>94%</td>
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<td>ODD RATIO</td>
<td>72.472</td>
<td>604.22</td>
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Very near future: genomics

- Fold changes 80 genes
- High throughput and low cost qPCR (>9,000 qPCR reactions, Fluidigm-BioMark)
**BC Treatment: Non Muscle Invasive**

- **TUR** with white-light is considered nowadays the golden standard for the diagnosis and treatment of non muscle invasive bladder tumors (NMIBC)

- However TUR must be «ADEQUATE»
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  d. no bleeding

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**Pathological Reports: Role of Pathologists**

- After an Adequate/complete TUR pathologist should tell:
  - Type of Tumor (TCC, adenoCA, squamous)
  - Stage (Ta-T1- >T1)
  - Grade
  - Vascular invasion
  - Limphatic invasion
  - Perineural invasion
  - CIS
  - P-53, Ki-67, Bc-L2, Ploidy (optional)
Quality of TUR: Variability in 3-RR (EORTC)

SINGLE TUMORS

- 3.4% - 20.6% if no adjuvant treatment
- 0% - 15.4% if adjuvant vesical treatment

MULTIPLE TUMORS

- 16.7% if no adjuvant intravesical treatment
- 7.4% - 45.8% if adjuvant intravesical treatm, (Brausi et al Eur Urol 2002)

Quality of TUR

- This variation between European Institutions, (from 0 to 46%) was not due to the characteristics of the tumor. (mutiplicity, grade, stage, ....)

- After a closer surveillance the surgeon has been showed to be responsible of the “Incomplete TUR” and therefore of the “Left Behind Tumors” (Brausi M et al. Eur Urol 2002).

- No big changes in these 15 years !!!!! Why ????: not enough time dedicated to teaching programs on TURBT (this year at AUA for the first time a corse on TURBT was instituted)
How often is there DM in T1 Specimens?

- Wijkstrom BJU 1998 = 59%
- Cheng Am J Clin Path. 2000 = 34%
- Bernardini J Urol 2001 = 64%
- Herr BJU 2001 = 39%
- Maruniak J Urol 2002 = 51%
- Dalbagni Urol 2002 = 60%
- Brausi (Pers. Com) 2000 = 51%
- Brausi J Urol 2008 = 79%
- Brausi (Pers. Com) 2010 = 85%
- Hermann (pers. Comm.) 2014 = 95%

En-bloc resection

Kramer et al, Minimally Invasive Therapy, 2014
Endoscopic submucosal dissection (ESD)

1. Definition of margins
2. Elevation of the lesion
3. Circumferential incision
4. Dissection

En-Bloc TUR
En-Bloc Resection: *DM present in > 90% (Eur Urol 2018)*

Perfect orientation and embedding possible

En-Bloc Resection
NMIB: Treatment

- Even when a complete/adequate TUR of BC is performed 50-70% of patients will recur and 20-25% progress in time

- In order to reduce or avoid recurrences and Progression adjuvant therapy can be administer to our patients

- Instillation of drugs into the bladder after TUR has become the standard treatment: Chemotherapy, Immunotherapy, Immuno-chemo.... Criteria: according to the patient risk

  - **Low risk:** single LG, **High Risk:** Ta-T1 HG, Cis, recurrent T1, **Intermediate:** all the others

Treatments of NMIBC: Controversies

- **1. The adjuvant treatment in Intermediate Risk patients: Chemotherapy vs BCG**

- **2. BCG Therapy:** Which dose and for how long?

- **3. Side Effects of BCG:** dose reduction with same efficacy?
Objectives

Compare the long-term efficacy of epirubicin and BCG +/- INH with respect to time to

- first recurrence
- progression
- distant metastases
- death (all causes and disease specific)

Take into account risk group:

- **Intermediate risk**: neither T1 nor grade 3
- **High risk**: stage T1 or grade 3
Conclusions

BCG is more effective than Epirubicin with respect to
• Time to first recurrence
• Time to distant metastases
• Time to death (all causes and bladder cancer)

As compared to epirubicin, intermediate risk patients appear to benefit from BCG as much or more than high risk patients.

BCG: How Much, for How Long ? Reduce Dose: is it Still Effective ?

Final Results of an EORTC-GU Cancers Group Randomized Study of Maintenance Bacillus Calmette-Guérin in Intermediate- and High-risk Ta, T1 Papillary Carcinoma of the Urinary Bladder: One-third Dose Versus Full Dose and 1 Year Versus 3 Years of Maintenance

Jorg Oudens①, Maurizio Brausi①, Richard Sylvestre①, Aldo Bono①, Cees van de Beek①, George van Andel①, Paolo Gontero①, Wolfgang Hoelzl①, Levent Turkeri①, Sandrine Marreaud①, Sandra Collette①, Willem Oosterlinck①
Protocol 30962: Statistical Design

- 4 treatments arms: no assumption of interaction

**Primary Objectives:** non inferiority study to determine
* 1/3 dose is not inferior in efficacy to full dose
  1) 1/3 dose vs full dose with 1 year maintenance
  2) 1/3 dose vs Full dose with 3 years maintenance
* short term maintenance (1 year) is not inferior in efficacy to long term maintenance (3 yrs)
  1) 1 year vs 3 years maintenance with 1/3 dose BCG
  2) 1 year vs 3 years maintenance with full dose BCG

**Secondary Objectives:**
Determine if 1/3 dose BCG short term maintenance is associated with less local or systemic side effects

Protocol 30962: Results

- Median and maximum F-up: 7.1 and 13.5 yrs

**Recurrence**  587/1355 pts. (43%): 37.4% with Ta-T1, 6.7% developed Cis

**Progression** > T2: 109 pts. (8%) and 4.9% had distant metastases

**Death rate** : 27% (369/1355)

**Deaths of BC** : 5% (68/1355)

Disease Free Interval: Events at 5 years
**Final Conclusions & Recommendations**

One third dose is not associated with less toxicity and has a higher recurrence rate.

The choice of the duration of BCG maintenance must balance its efficacy with the inconveniences of an extended maintenance schedule.

**Recommendations:**

**Intermediate risk patients:**
- full dose should be given during one year

**High risk patients:**
- full dose should be given during three years

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**NMIBC : Therapy**

- **Adequate TUR** or **En-Block TUR**+ **Adjuvant therapy** according to patient risk:

  - **LOW RISK**: 1single instillation post TUR (6 hours)  
    (Eau Guidelines 2017, IBCG 2015)
  - **INTERMEDIATE RISK**: BCG (1 year) better than chemo (MMC)
  - **HIGH RISK**: BCG Maintenance for 3 years . 
    Sequential BCG + MMC/EMDA (maintenance) even better

- **BCG Toxicity**: can be reduced with counselling , adequate catheters,avoiding bleeding, medical presence,… prophylaxis
Stage

- Substaging pT1  WHO 2016

Ta, Tis, T1, or T2 disease. Accumulating data suggest that substaging T1 disease is clinically relevant, but the specific details on how to do so are yet to be agreed upon [1242,1809,2119,2579]. It is important to be aware of clinical and biological variables that may affect prognosis [81,252,440,842]. Based on the available data, it is recommended to provide an assessment of the depth and/or extent of subepithelial tissue invasion in T1 cases.

ICCR
(International Collaboration on Cancer Reporting)