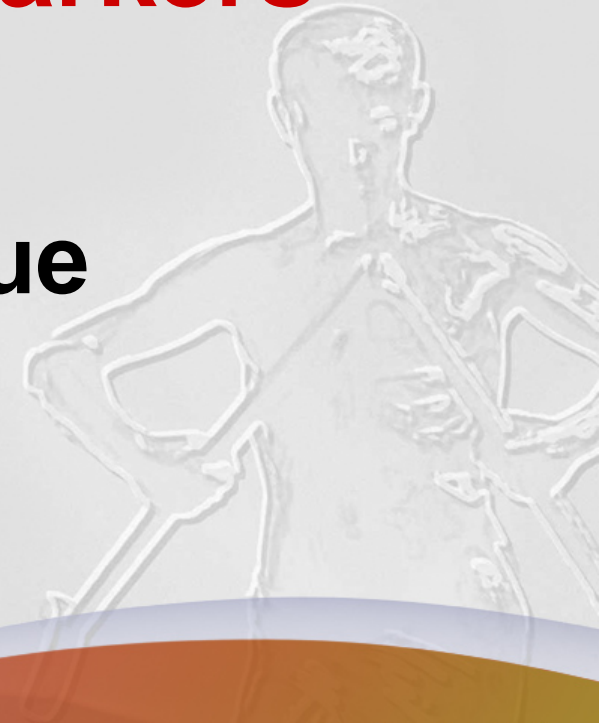


Cytokeratin Tumor Markers

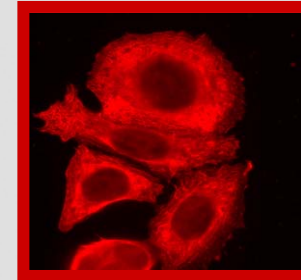
Added Clinical Value

Helena Goike



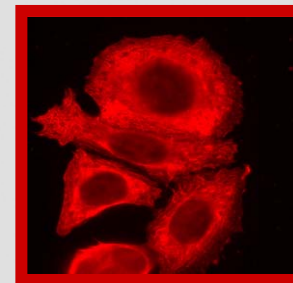
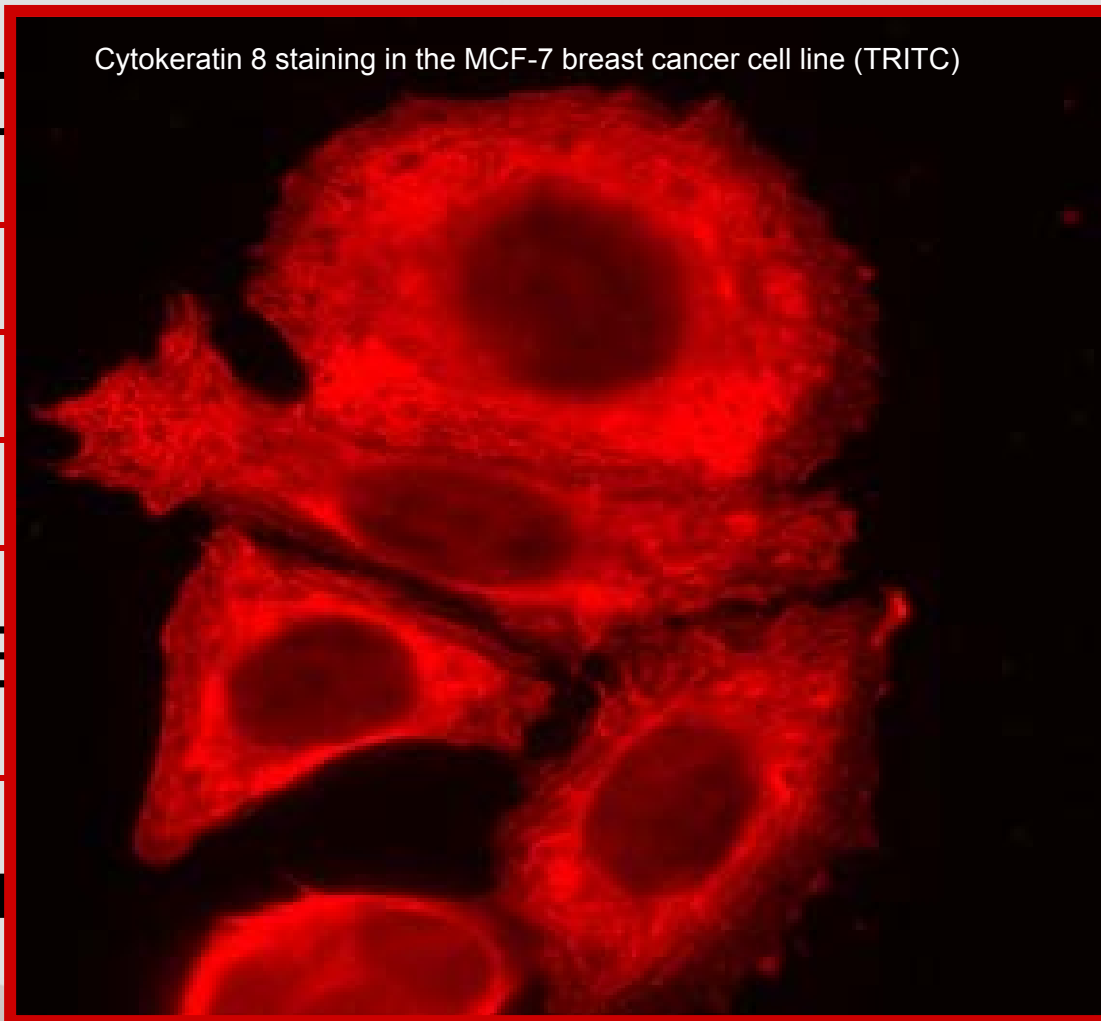
What are cytokeratins?

- Cytoskeletal proteins
 - Intermediate filament proteins
 - Family of more than 20 different proteins
 - Obligate heterodimers
 - Cytokeratins 8, 18 and 19 most abundant
- Epithelial cell specific expression
 - Overexpressed in transformed cells
- Involved in apoptosis



What are cytokeratins?

- C
- E
- I



proteins

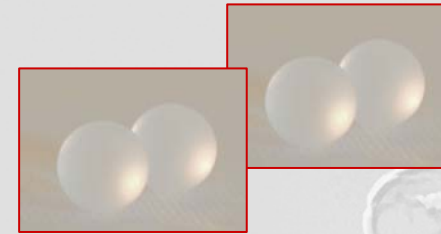
abundant

on

cells

Cytokeratins as Tumor Markers

- Tumor cell activity markers
 - Early and distinct signals
- Management of patients with carcinomas
 - Prognosis, monitoring and follow-up
- Complementary to volume markers – defined combinations
 - Increased sensitivity



Added clinical values

Prediction of possible therapeutic response

Prediction of rapid clinical progression

Optimized therapy based on early response

Motivation to complete therapy courses

Termination of ineffective therapy

– reduced toxicity and society costs

Simplified & sensitive follow up – long lead times

Reduced use of more expensive examinations

prognosis
monitoring
follow up

Cytokeratin Panel – Clinical Use

TPS

Breast, Prostate and
Gastrointestinal cancers

TPAcyk

General epithelial cancers

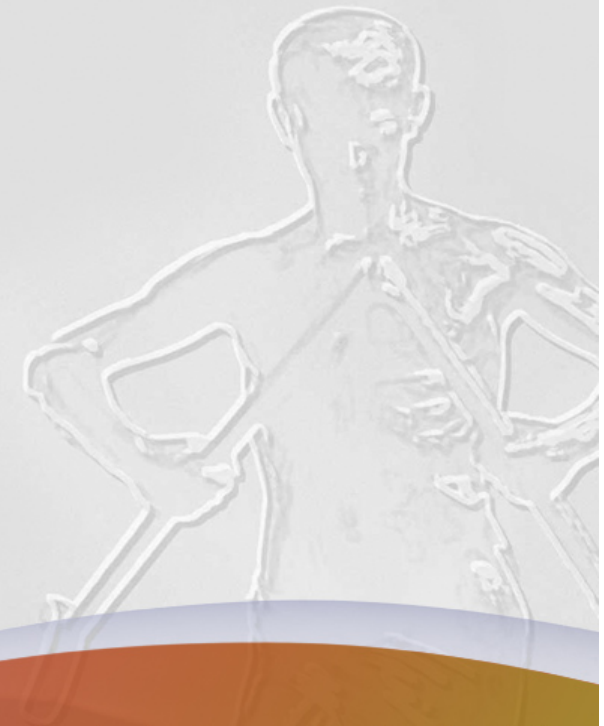
MonoTotal

Non-Small Cell Lung cancer

UBC

Urinary Bladder cancer

MonoTotal[®]



Uživatelské setkání RIA
PIEŠŤANY
2007

MonoTotal[®]

- **Indication(s)**

- Non-Small Cell Lung Cancer
- (*Esophagus cancer*)

♂ 1st ♀ 6th

♂ ♀ ~ 2%

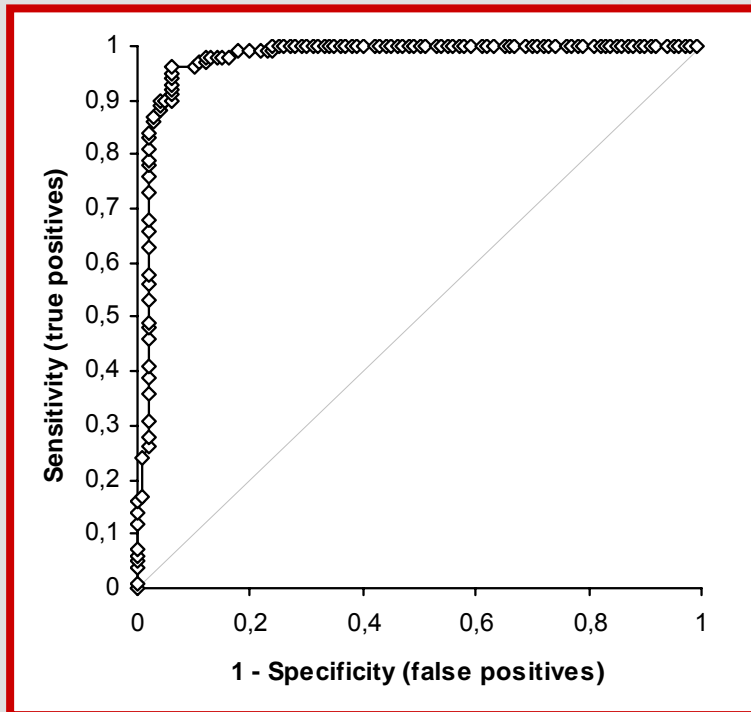
- **Clinical data**

- ~ 6 papers and abstracts

- **Other tests**

- CYFRA 21-1 and TPA
- Correlation >90%

MonoTotal[®] Assay Details



ROC analysis for MonoTotal RIA, with area under the curve = 0.975.

Antigen

CK 8/18/19

Assay format

RIA

Reproducibility

Intra-assay <5%

Inter-assay 5-10%

Measuring range

0 – 6000 U/l

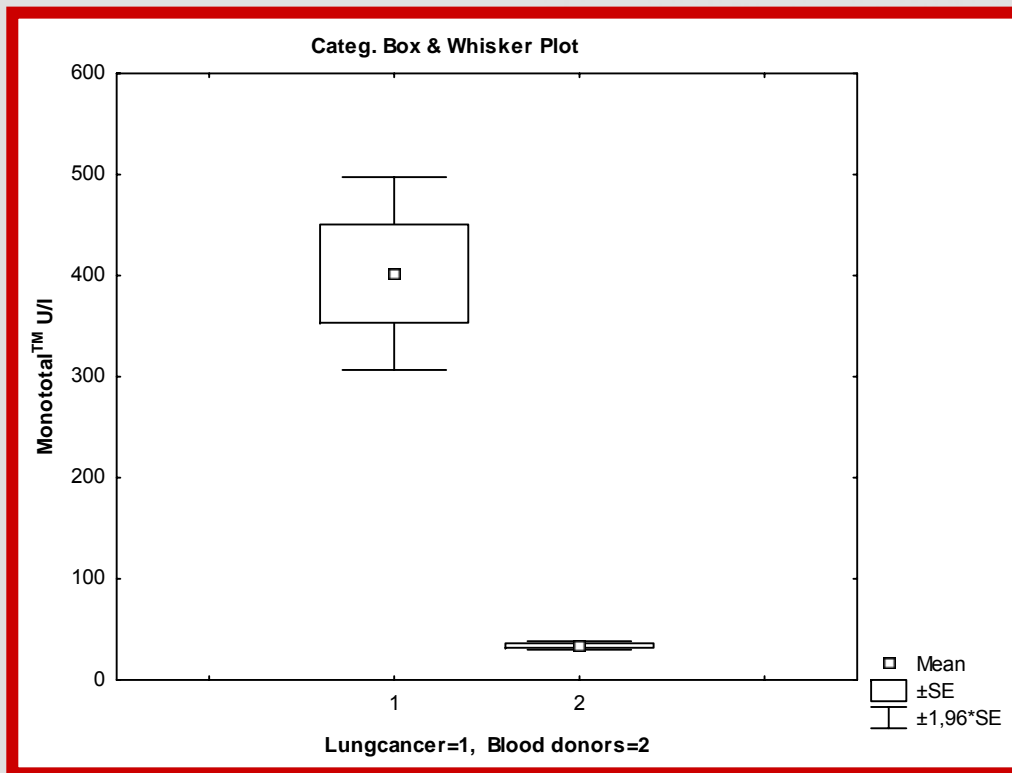
Cut off value

75 U/l

Samples

serum

MonoTotal[®] & NSCLC

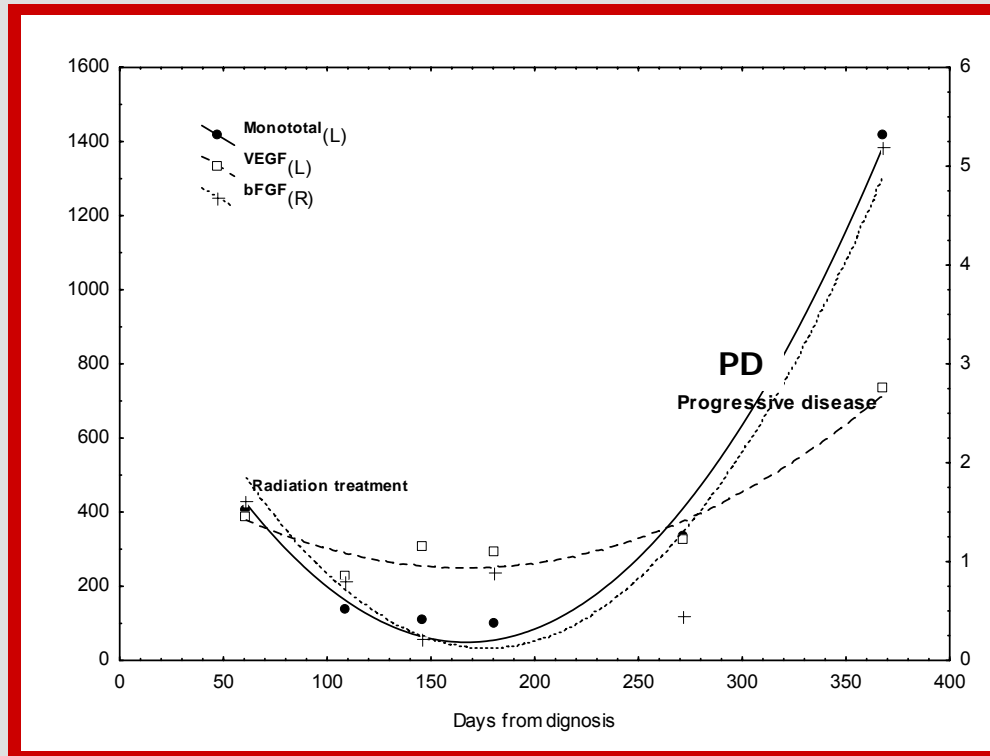


Baseline levels in lung cancer patients (stage III) vs. healthy blood donors

Levels show gradual increase by ~ 600 U/I from baseline to time of death

Eriksson, Neoplasma 2006

MonoTotal[®] & NSCLC



Prognosis

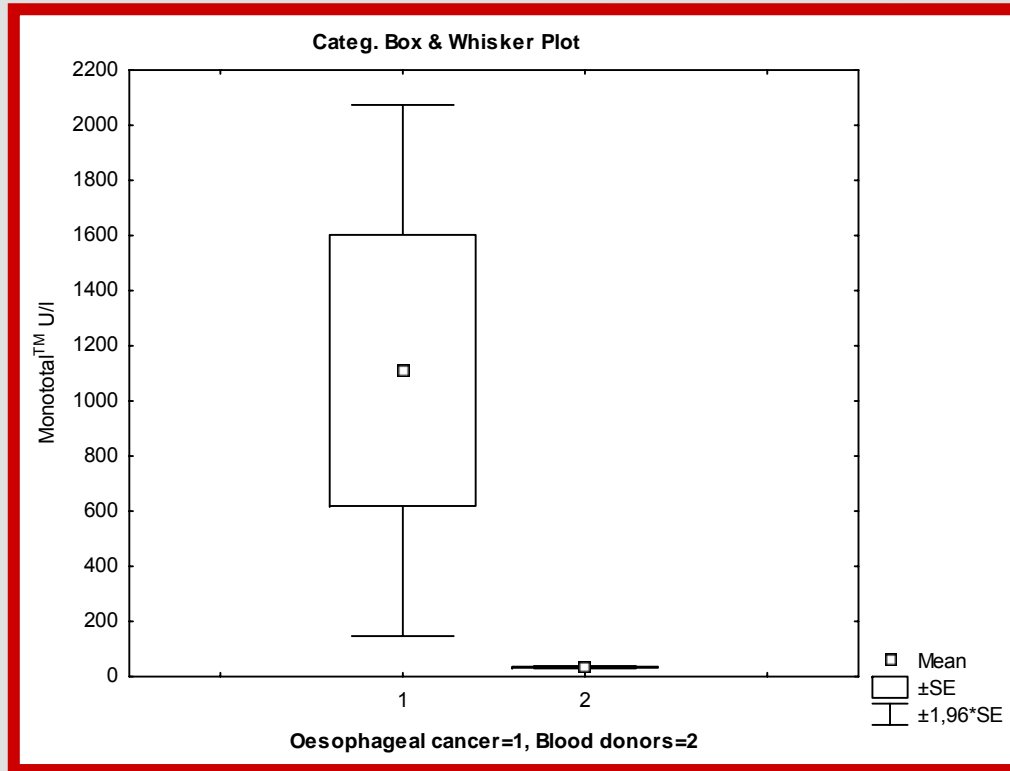
Baseline levels are of prognostic value (survival) in patients with advanced NSCLC (stage III)

Monitoring

Long lead time prior to clinical manifestation during therapy

Eriksson, Neoplasma 2006

MonoTotal[®] & Esophagus cancer

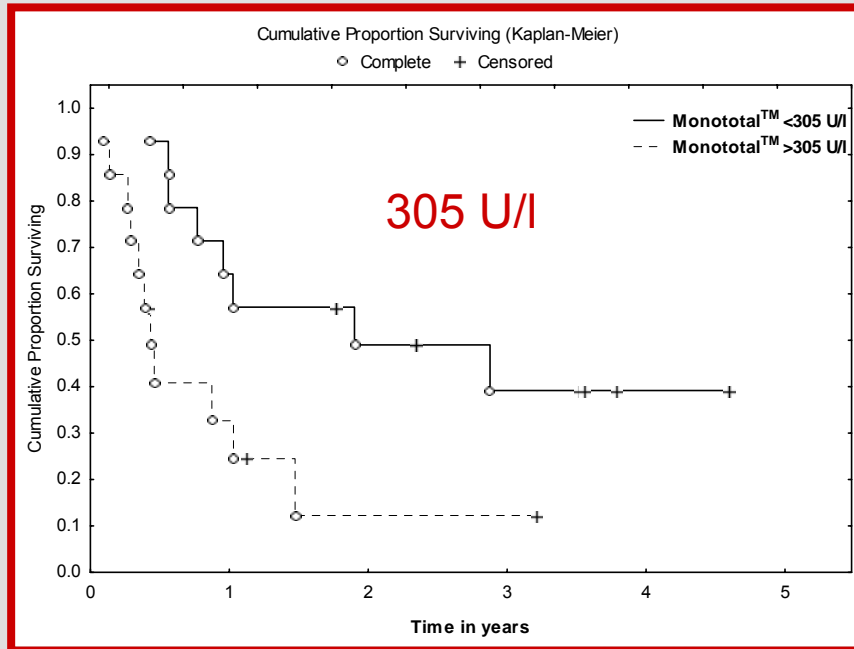


Baseline levels
in esophagus
cancer patients
of all stages vs.
healthy blood
donors

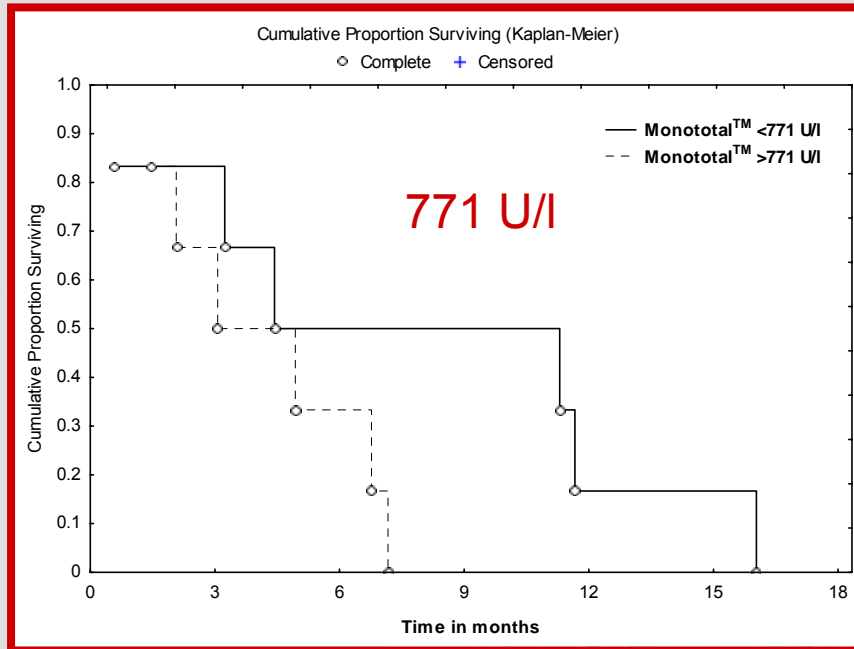
98% of patients
show increased
levels of
MonoTotal

Brattström, Dis Esophagus 2005

Esophagus cancer - survival analysis



Survival analysis for patients with localised disease according to median MonoTotal levels



Survival analysis for patients with metastatic disease according to median MonoTotal levels

Difference in median levels are statistically significant

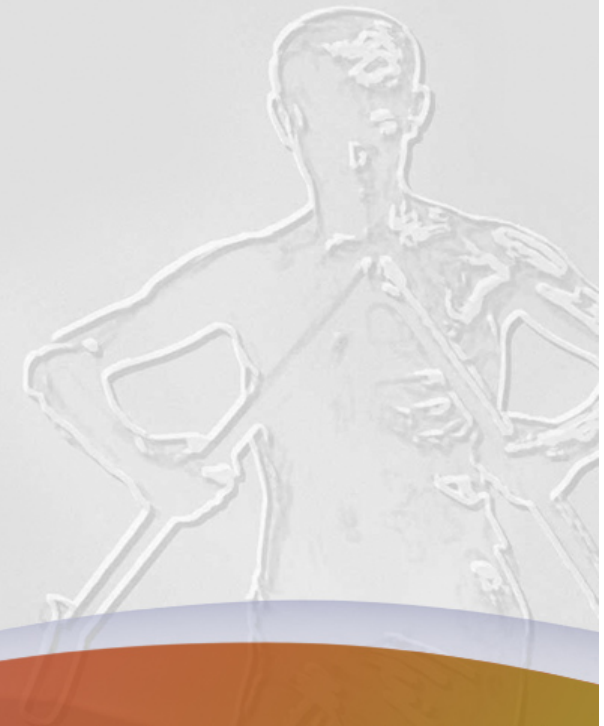
Brattström, Dis Esophagus 2005

MonoTotal[®] Added clinical value

- **Non-Small Cell Lung Cancer**
 - Pre-therapeutic prognostic value (survival) in advanced disease
 - Long lead-times compared to clinical manifestation during therapy monitoring
- **Esophagus cancer**
 - Strong prognostic value (survival) for both localized and metastatic disease



UBC[®]



Uživatelské setkání RIA
PIEŠŤANY
2007

UBC[®] - Urinary Bladder Cancer antigen

- **Indication**

- Urinary Bladder Cancer

♂ 5th ♀ 13th

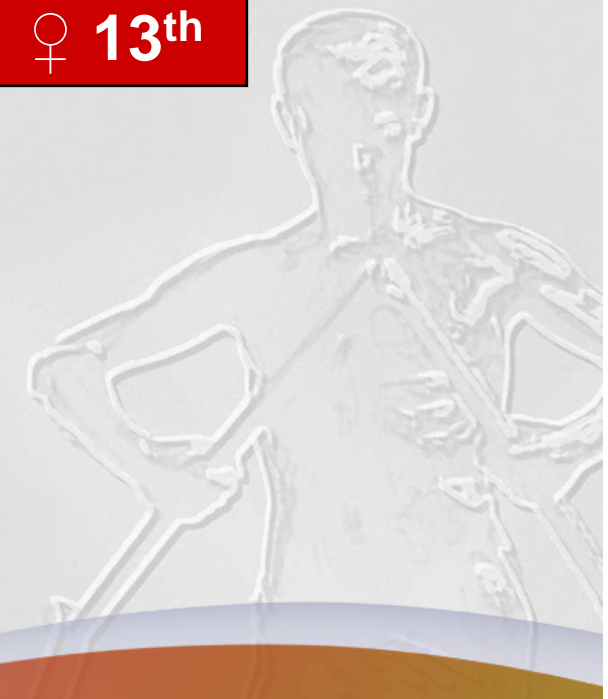
- **Clinical data**

- >30 papers and abstracts

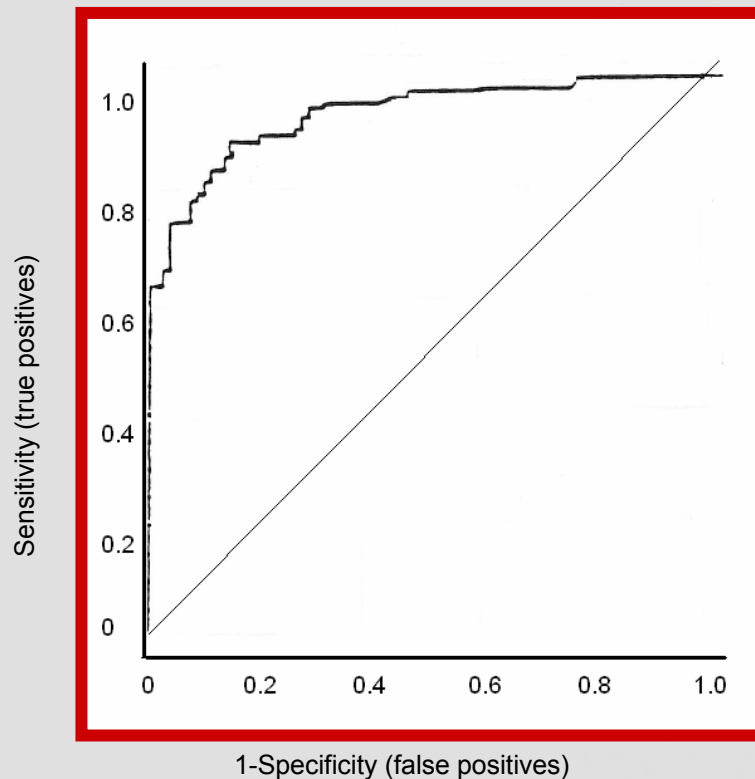
- **Other methods/tests**

- Voided urine cytology

- NMP22 and BTA



UBC[®] Assay Details



ROC analysis for UBC with area under the curve = 0.933.

Antigen

CK 8/18

Assay format

RIA and ELISA

Reproducibility

Intra-assay <5%

Inter-assay 5-10%

Measuring range

0 – 30 µg/l

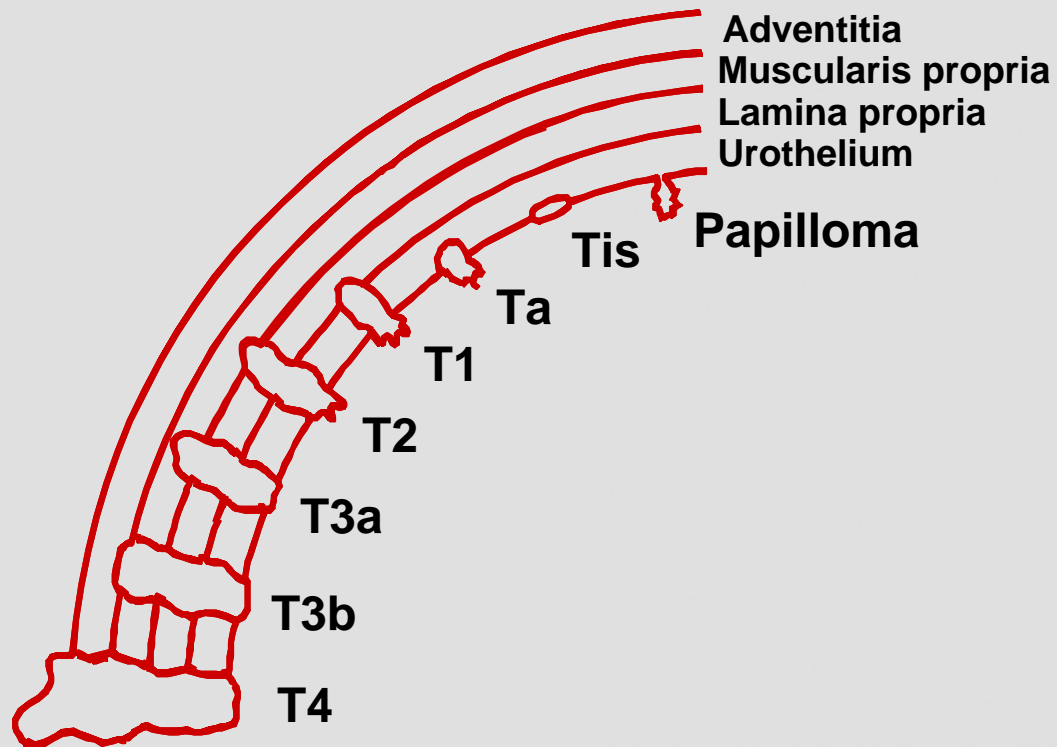
Cut off value

12 µg/l

Samples

urine

Urinary Bladder Cancer

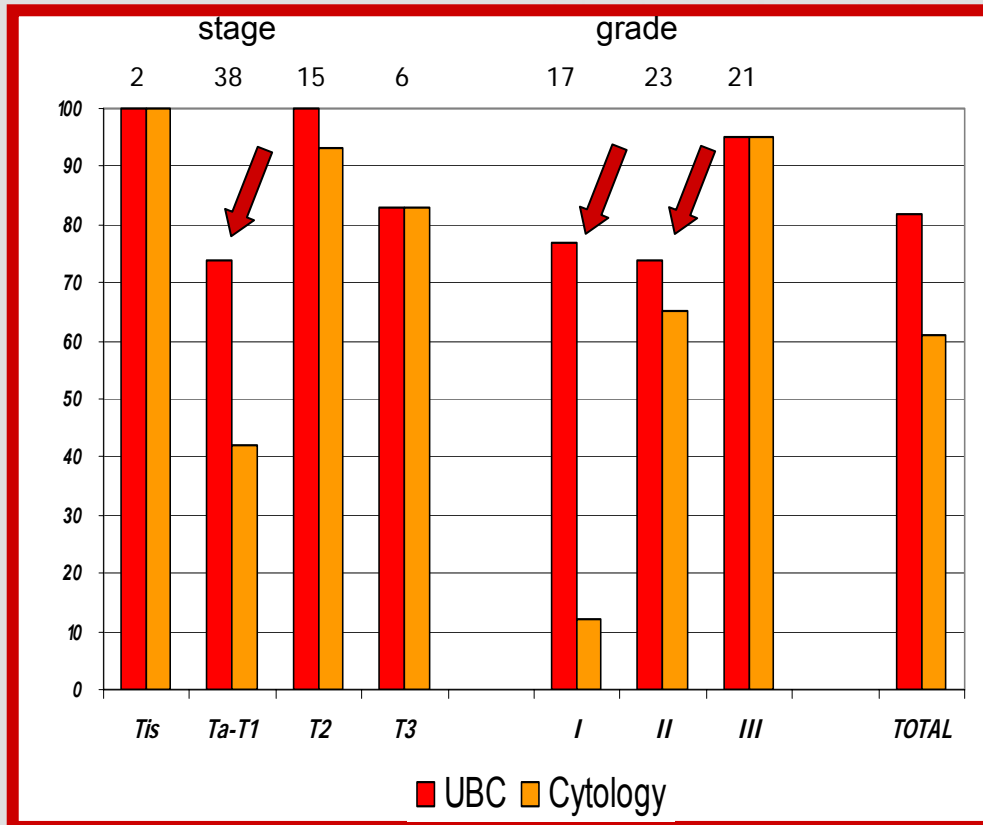


High risk of recurrence and progression – long follow up needed

Routine management; cytology, cystoscopy, and transurethral resection

Tumor markers?

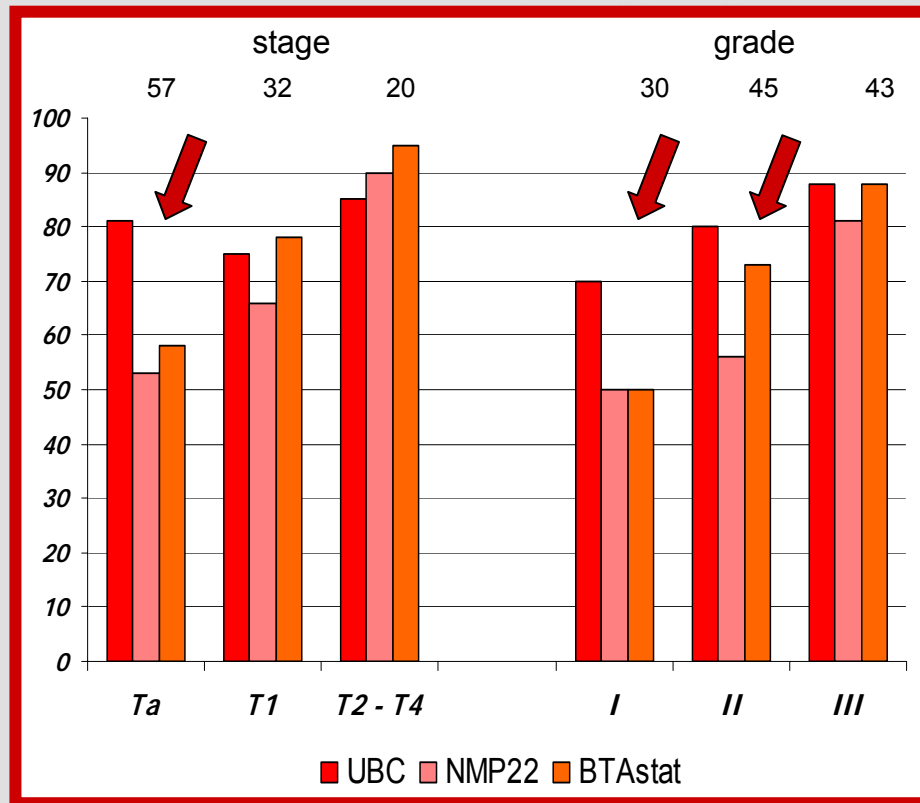
UBC[®] vs. Voided Urine Cytology (VUC)



	<i>Sensitivity</i>
VUC	61%
UBC	82%

Sumi, Clin Chim Acta 2000

UBC[®] vs. BTAst[®] & NMP22

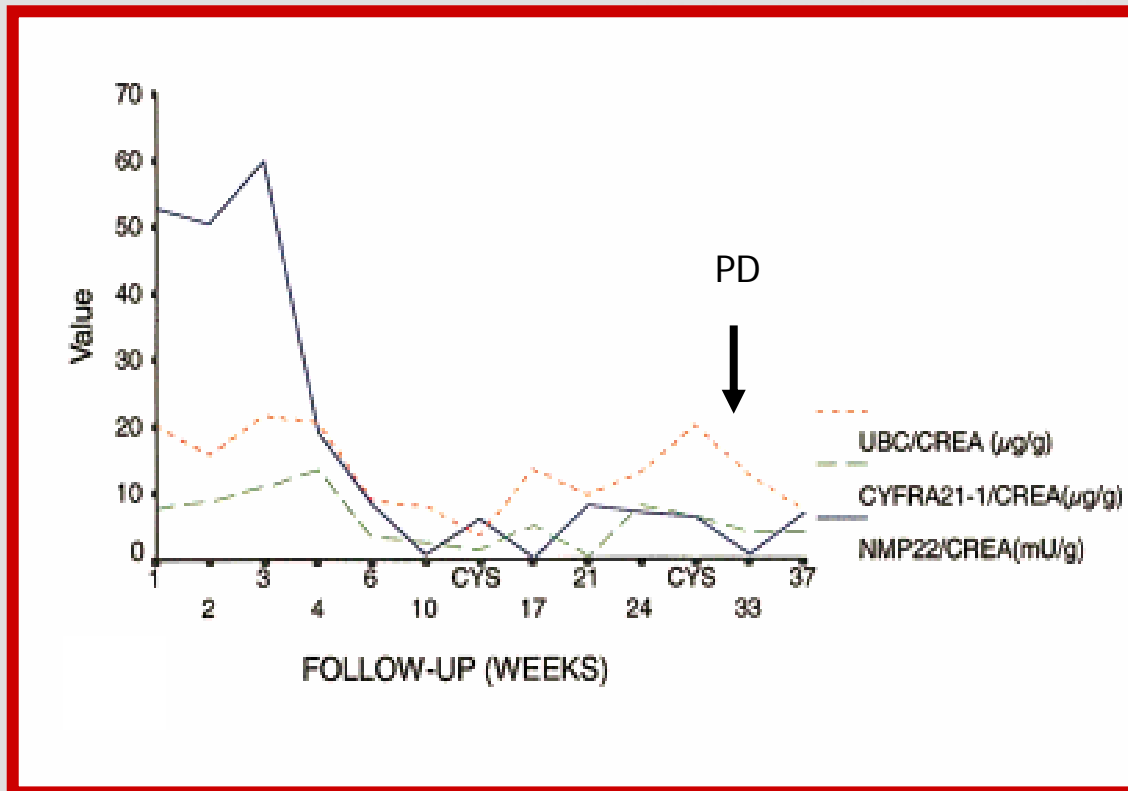


<i>Sensitivity</i>	
BTAst[®]	73%
NMP22	64%
UBC	81%

UBC/BTAstat 92%

Giannopoulos, J Urol 2001

UBC[®] Clinical Use Bladder



Serial UBC could detect recurrent disease earlier than scheduled cystoscopies in;
87% follow-up
67% monitoring

Serial negative results indicated disease free follow-up status in 87%

Patient with resected superficial bladder tumor monitored during therapy. Initial TM decrease after surgery is followed by peaking TM increases during follow-up, reflecting progressive disease as detected at scheduled cystoscopic examination week 25.

Sanchez-Carbayo, Cancer 2001

UBC[®] Added clinical value

- **Serial tumor markers can detect recurrence earlier, easier and more cost-effective than scheduled cystoscopies**
 - Persistent negative tumor marker results strongly indicates a disease free status
- **Methodology comparisons**
 - UBC superior to cytology
 - UBC show better overall performance than BTAstat and NMP22; including higher sensitivity for lower stage/grade tumors
 - Combination UBC & BTAstat yield 92% sensitivity

Cytokeratins & cancer management

Valuable in

- disease prognosis
- therapy monitoring
- patient follow-up



Early & distinct indications of therapy outcome and tumor recurrence

- long lead times to clinical manifestation compared to conventional methods

Recommended tumor marker combinations for proven clinical efficiency

- TPS and CA 15-3 in breast cancer
- TPS and PSA in prostate cancer
- TPS and CA 19-9 in pancreatic cancer
- TPS and CA 125 in ovarian cancer

Recommended tumor markers for proven clinical efficiency

- TPS in gastrointestinal cancers
- TPAcyk in epithelial cancers (general marker)
- UBC in urinary bladder cancer
- MonoTotal in non-small cell lung cancer

Thank you!

