Bladder cancer and Hexvix

PhotoCure Capital Markets Day

Prof Fred Witjes, MD, PhD
Dept Urology, Nijmegen, the Netherlands

Oslo, June 14 2006.

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Subjects

- Natural history (non) invasive bladder cancer
- Diagnosis
- Current treatment
- Market size
- Hexvix®: clinical studies
- Hexvix®: potential clinical use

Or: (non) invasive bladder cancer for a non-urologist in 25 minutes

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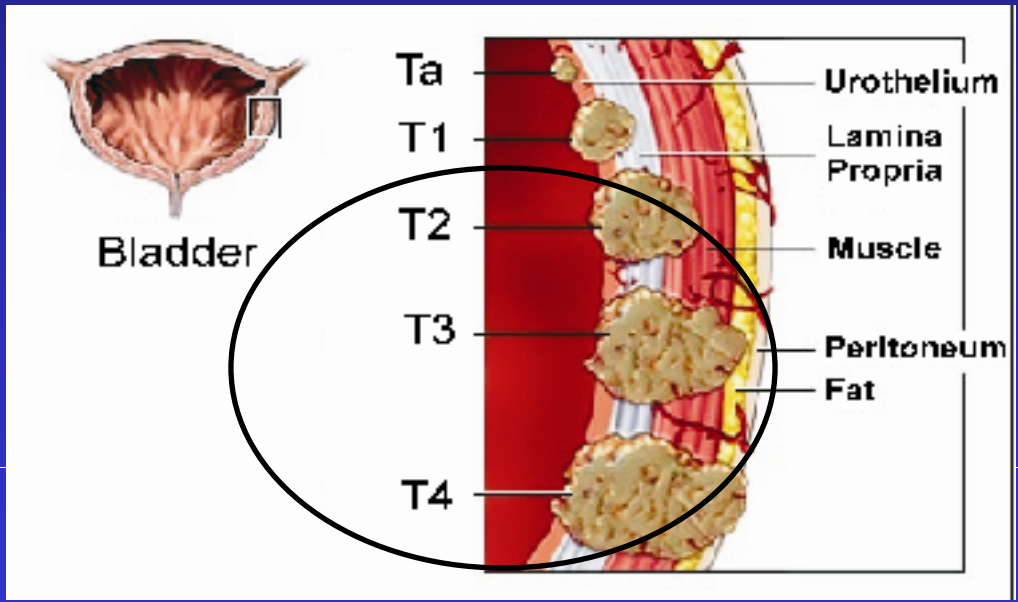
Invasive bladder cancer

- Means that it grows in the whole bladder wall
- Th/ radical surgery +/- systemic chemotherapy
- Straight forward diagnosis and therapy



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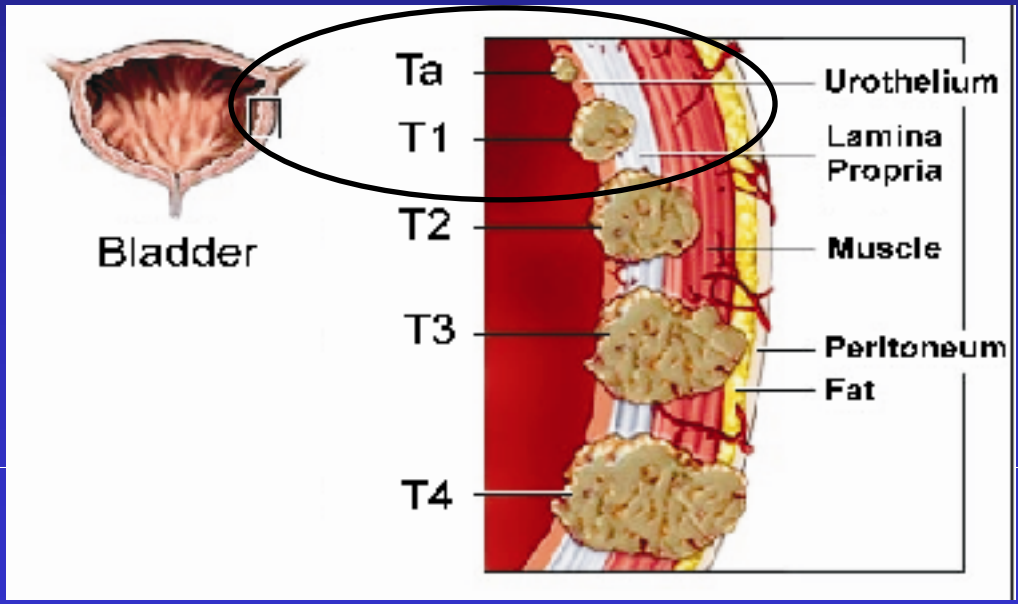
Non invasive bladder cancer

- Only grows in the mucosa of the bladder
- Treatment with resection of only this tumor, followed by bladder instillations with drugs
- Still debate on diagnosis and treatment



Non invasive bladder tumors

- Frequently ***recurs*** after therapy
  - Inconvenient for the patient, but not dangerous
  - A lot of work for the urologist
  - Expensive for community
  - An opportunity for the pharmaceutical Industry
- Can ***progress*** after therapy
  - Potentially life threatening

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Natural history non invasive bladder cancer

- Low risk (±30%)
  - 30% recurrence rate in 2 years
  - No progression to muscle invasive disease
- Intermediate risk (±40-50%)
  - 50-60% recurrence rate
  - <5% progression
- High risk (±20-30%)
  - 70-80% recurrence rate
  - 10-30% progression

Many patients and/or events

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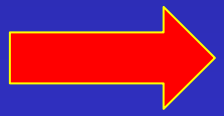
Diagnostic goals in urinary TCC

- Identification of primary or recurrent TCC of the urinary tract
- Screening (early detection of risk groups)

- Tools: cystoscopy and urinary cytology

Summary of cytology

1. Cytology has a high interobserver variability
2. Cytology not the best but simple and specific
3. At best use a marker together with cytology
4. Markers do not yet meet the demands of urologist nor the patient



An opportunity for improvement!!

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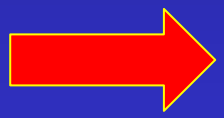
Summary of cystoscopy

1. UCS is invasive and expensive
2. Sensitivity for papillary tumors between 55-95%
3. Sensitivity CIS 30% (lesions) or 70% (patients)



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The official guidelines

(Oosterlinck et al., Eur Urol 2002;41:105-12)

- Low risk tumor
  - TUR
  - 1x chemo with 6 to 24 hours
  - no clinical questions

The official guidelines

(Oosterlinck et al., Eur Urol 2002;41:105-12)

- Intermediate risk tumors
  - TUR
  - a course of 6-10 weekly intravesical instillations with chemotherapy
  - Sometimes intravesical instillations with BCG

→ Still many recurrences (in part due to incomplete resections!!)

The official guidelines

(Oosterlinck et al., Eur Urol 2002;41:105-12)

- High risk tumours
  - TUR followed by 6 weeks intravesical BCG
  - Consider a second TUR to check the completeness of the first resection
  - Often 1-3 years treatment with BCG

  - BCG is toxic
  - Still many recurrences and progression

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Superficial bladder cancer

- It is (usually) not a lethal disease → limited interest of cancer foundations
- It is a frequent disease
  - Rather high incidence
  - High recurrence rate → very high prevalence
  - Prevalence estimates based on recurrence rates, # TUR's and # outpatient coagulations in NL
- Patients are monitored – 4 million cystoscopies are estimated to be performed in the EU/US every year
- In conclusion, it is a significant problem for health care (budgets)

Cancer incidence and prevalence

Tumour	Incidence US 2005	Incidence EU 2004
Bladder ca	63,210	120,000
Bladder ca prevalence (conservative estimate)	180,000	360,000
Colon ca	145,290	376,400
Lung ca	172,570	381,500
Prostate ca	232,090	237,800
Breast ca	211,240	370,100

Health economics bladder cancer

(Botteman et al., Pharmacoeconomics 2003)

- Bladder cancer fifth most expensive cancer
- Per patient cost from diagnosis until death highest of all cancer, k$ 96-187 (2001 values)
  - Current diagnostics not cost effective (markers?)
  - Current therapies not cost effective
  - Current frequent follow up not cost effective
  - No new developments
  - This is studied “marginally”
  - No awareness

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EAU 2005, #639, Ragavan et al., UK

- All new patients 2001-2002

	# pts	Total miljon £	£ per patient	Research miljon £
Prostate	15,099	92.74	7,294	20.56
Bladder	7,703	55.39	8,349	4.62

→ Need for re-evaluation of future research money

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Technique Hexvix PDD

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Technique Hexvix

- 85 mg Hexvix powder, sterile, refrigerator stored
- 52 mL phosphate buffered saline solvent (pH=6)
- 50 mL of 8mM solution of Hexvix
- Soluton is stable during 24 hours when stored at 2-8ºC

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Instillation time frame

- Hexvix is installed into the bladder by means of a normal catheter
- The patient is asked to retain the fluid for 60 minutes
- Following bladder evacuation the cystoscopy should start within 30 minutes

The procedure

- Special light system (that can provide both white and blue light)
- Special optics
- Special light cable

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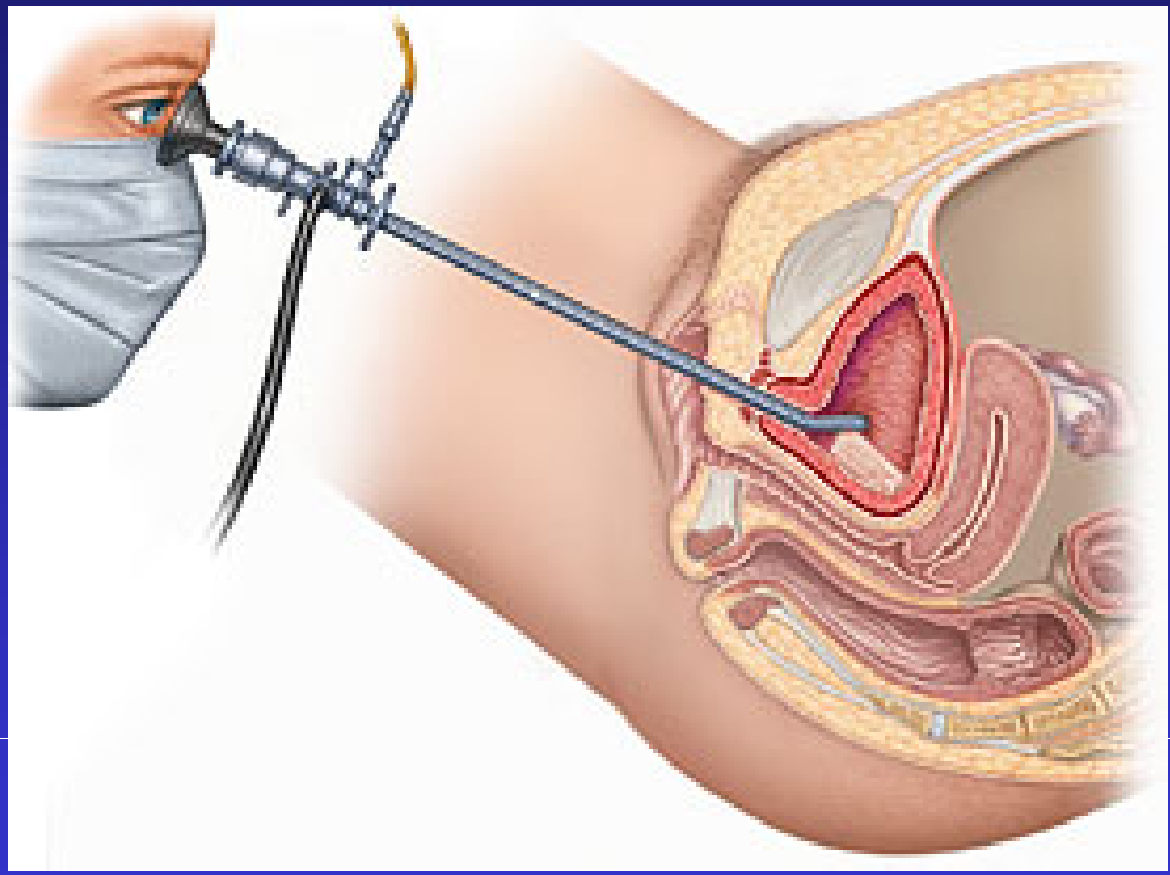
Urethro-cystoscopy



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Conclusion: technique Hexvix PDD is easy

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The theoretical advantages of Hexvix®

- New photo-sensitizers, e.g. hexyl aminolevulinate (Hexvix)
  - Instillation time approximately 1 hour
  - Better imaging and contrast
  - Less photobleaching

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The PDD studies with Hexvix

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Hexvix clinical program

PC B301	286 pts	19 centers	EU	Tumor detection (CIS)	Completed
PC B302	311 pts	18 centers	US/CAN	Tumor detection (CIS)	Completed
PC B303	162 pts	10 centers	EU	Patient management	Completed
PC B305	610 pts	26 centers	US/CAN/ EU	Tumor detection (Ta/T1)/ Recurrence	Ongoing

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Main objectives

PC B301 and PC B302:

- Improved detection of patients with CIS
- Population: Patients with increased risk of having CIS

PC B303:

- Improved patient treatment
- Population: Patients with known or suspected bladder cancer

<u>Document Hexvix as an adjunct to white light cytoscopy</u>

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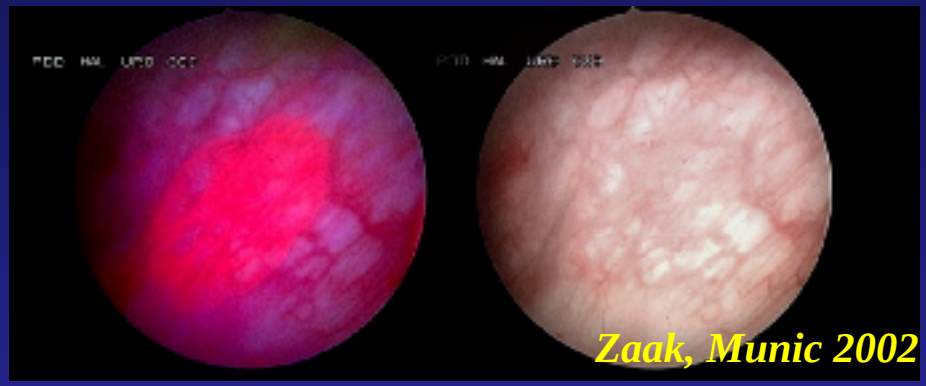
PC B301/302/303 results

CIS patients detected with Hexvix only



Study #	# pts included	# CIS patients	Detected with H only
301	211	79 (37%)	17 (22%)
302	196	53 (27%)	9 (17%)
303	146	29 (20%)	4 (14%)
Total	553	161(29%)	30 (19%)

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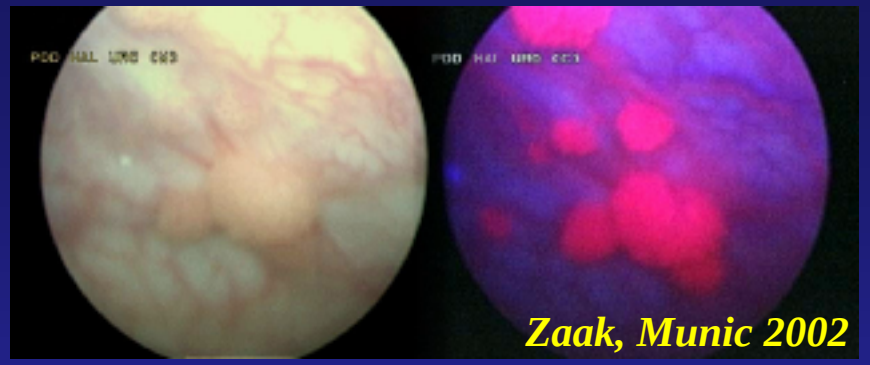
PC B301/302/303 results

Patients with more Ta/T1 lesions detected with Hexvix



Study	pts included	pts with Ta/T1	pts with more Ta/T1
301	211	155 (73%)	38 (25%)
302	196	116 (59%)	34 (29%)
303	146	74 (51%)	15 (20%)
Total	553	345 (62%)	87 (25%)

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PC B301/302/303 results

Overall lesion detection rate:

Study	Hexvix	Standard
301	97%	77%
302	93%	79%
303	96%	77%

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Also with Hexvix there is a significant higher detection rate of flat and papillary tumours

Procedure is quick

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Change in pt management (303)

(Jocham et al, J Urol 2005)

- Multicenter study, 146 pts
- 50 ml Hexvix
- independent urologist reviewer

⇨ 38/146 (24.4%) additional detection

⇨ Sens: 96% vs. 79%

⇨ 25/146 (17%) change of intra- or postop. management

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Safety

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Safety conclusions

- In all, Hexvix appears safe in an older patient population with subsequent co-morbidity
- Side effects predominantly due to procedure, co-morbidity etc
- Side effects seldom considered as related to the study drug (Hexvix), and if yes not severe and reversible

Hexvix so far

- Procedure is quick and safe
- With Hexvix there is a safe and significant higher detection rate of flat and papillary tumours
- Flexible fluorescence cystoscopy is feasible
- False positive detection rate is acceptable
- There is better patient management

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Future perspectives

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Benefit for the patient

- Recurrence rate is lower with Hexvix PDD than after white light procedures
- With Hexvix better patient management is achieved (study 303)
- Hexvix has advantages over 5-ALA (not approved)
    - Instillation time approx. 1 hour
    - Better imaging and contrast
    - Less photobleaching

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Benefit for the patient

So, although the reduction in recurrence rate after Hexvix remains to be proven (study 305), my expectations are very high

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Take home messages PDD with Hexvix

- Higher sensitivity, especially in flat leasions
- Safe
- Good and quick imaging

- Significant reduction of residual tumour
- Clear change of patient management

- ~~Reduction of the recurrence rate (yet to be proven)~~

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Indications Hexvix PDD

1. Every TURT
2. Cytology +, endoscopy – (flexible!)
3. Follow up high risk tumours (CIS, flexible!)
4. Follow up intermediate risk tumours <2 years (flexible!)
5. Not in follow up low risk patients, seldomly in invasive tumours

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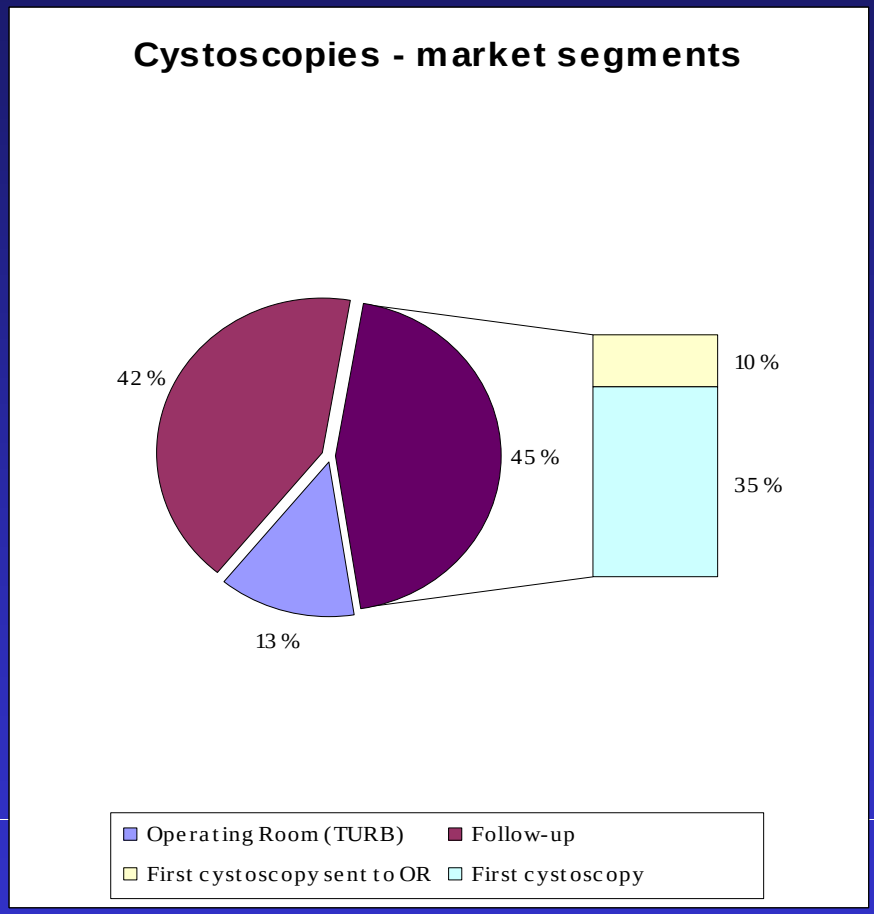
Hexvix Market



- Assumptions:
  - Avg. 1.5 cystoscopies/year for patients with bladder cancer
  - App.15% of first cystoscopy patiens are sent to the Operating Room (OR)
  - Many patients undergo screening for bladder cancer due to hematuria
  - Normally only patients with positive cystos/cytology goes to the OR
- 4 mill cystoscopies yearly in US/EU

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Thank you for your attention

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