

# Overview of Diagnosis and Management of Non-Muscle Invasive Bladder Cancer

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- Clinical trials
  - Endo, FKD, JBL, Roche/Genentech, Viventia
- Advisory Board
  - Ferring, Nucleix, OncoGeneX, Sitka, Taris
- Consultant
  - Biocancell, Telesta, Theracoat, Vaxiion

- Bladder cancer statistics
- Staging and grading NMIBC
- Risk stratification and treatment according to risk strata
- Outcomes: recurrence vs. progression
- Differences in population, disease management, US vs. Canada vs. Poland
- Current state of the art for peri-op chemo

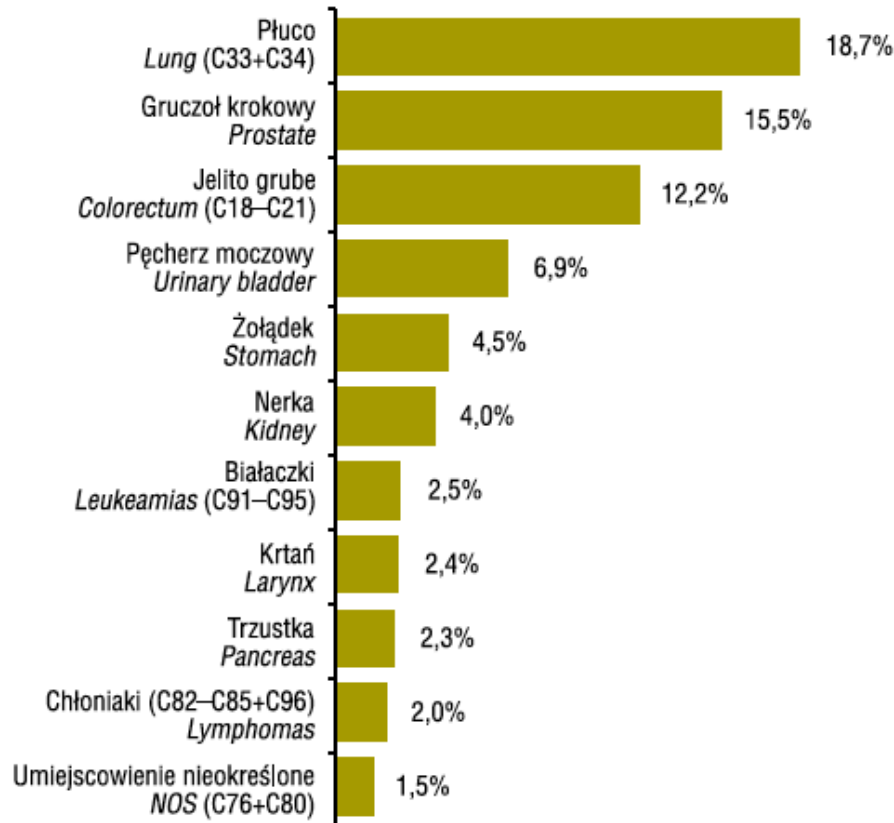
- 76,960 new cases<sup>1</sup>
- 16,390 deaths<sup>1</sup>
  - 77.5% 5 year survival (2006-2012)
- 89% of U.S. patients  $\geq$  55 years old
- 4th most common cancer in men
  - Prostate, lung, colorectal more common
- 10th most common solid tumor cancer in women
- U.S. Prevalence 587,246 (SEER, 2013)
  - Lifetime risk 2.4%
- Cost per patient: Most expensive cancer from diagnosis to death

<sup>1</sup> Siegel, R et al Ca Cancer J Clin 66:7, 2016

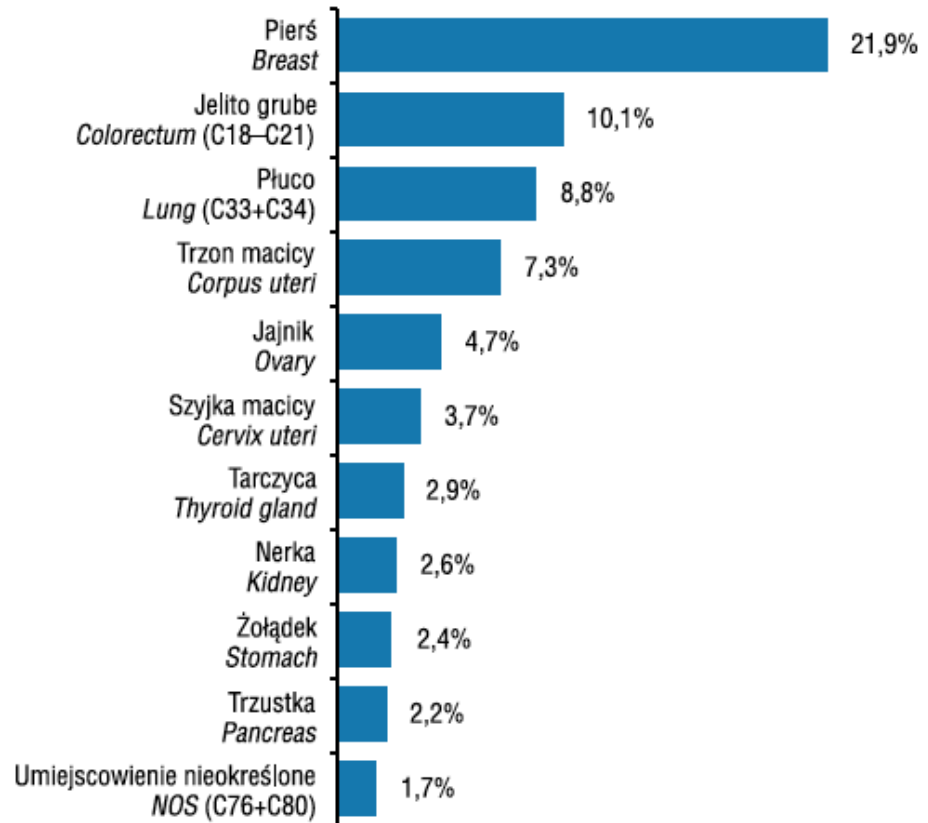
# Are There Geographic Differences

- Poland – follow EAU guidelines

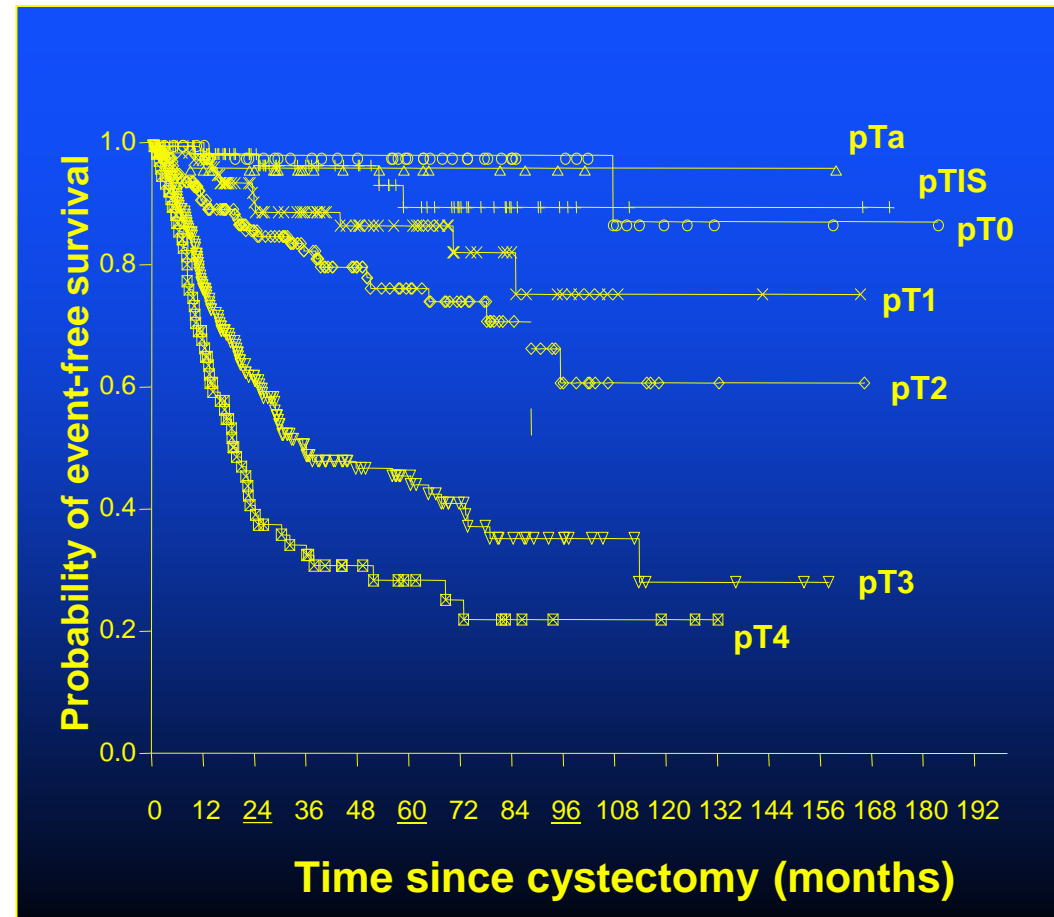
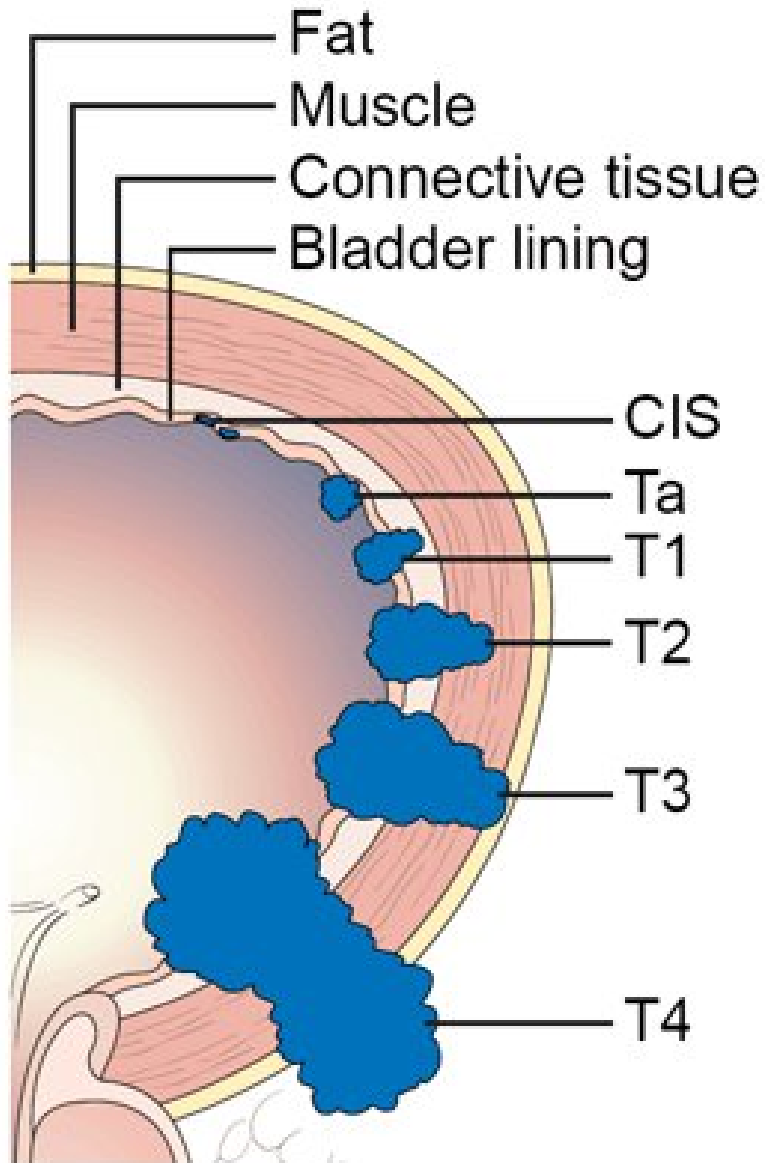
**Figure 6.5.** The structure of registered cancer incidence, males, Poland 2013



**Figure 6.6.** The structure of registered cancer incidence, females, Poland 2013



# Clinical and Pathologic Tumor Staging



Shariat, et al, J Urol 176:2414, 2006

- WHO 1973
  - G1 – well differentiated
  - G2 – Moderately differentiated
  - G3 – Poorly differentiated
- WHO/ISUP 1998
  - Low grade
  - High grade
- WHO 2004
  - Identical to WHO/ISUP 1998

# Relationship of 1973 WHO to 2004 WHO/ISUP

## WHO 1973

## WHO 2004

Papilloma

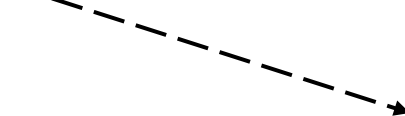


Papilloma

Grade 1



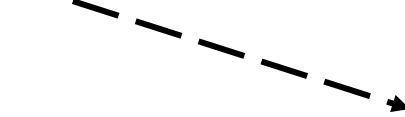
PUNLMP



Grade 2



Low grade



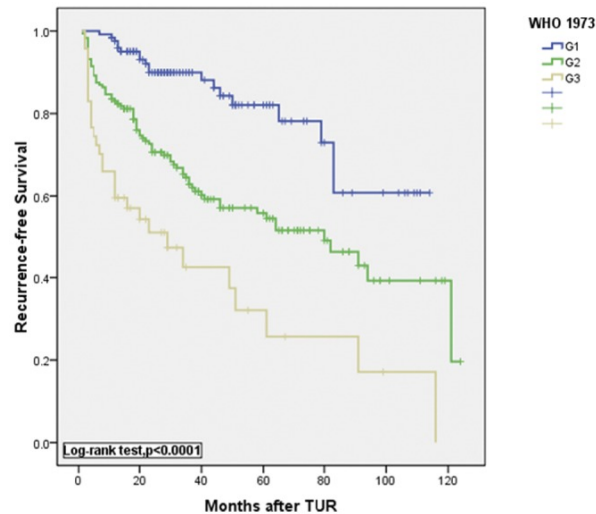
Grade 3



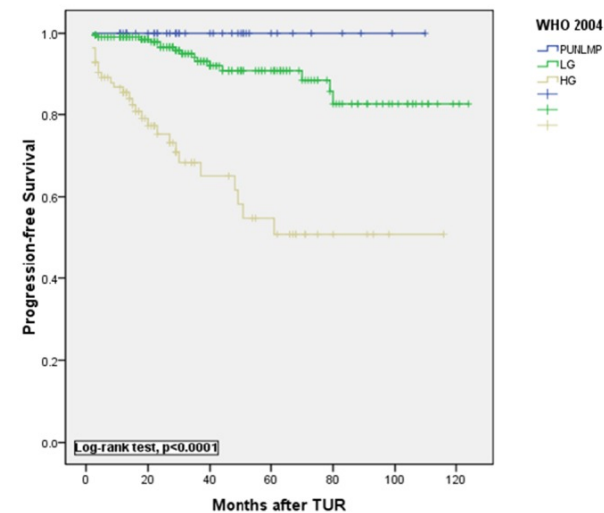
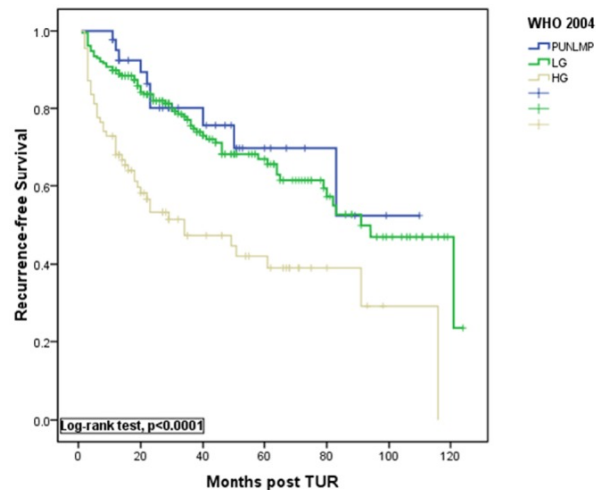
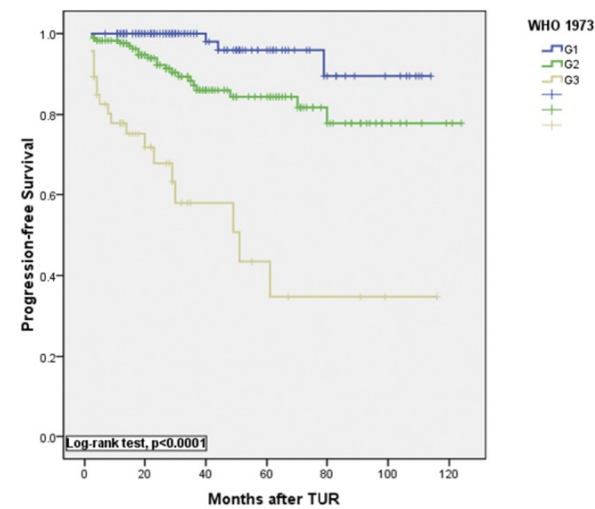
High grade



## Recurrence



## Progression



- Accurate determination of stage and grade
  - Surgical quality – TURBT and bladder biopsies
  - *Strongly* recommend re-review and 2<sup>nd</sup> TUR for T1G3
- Variant histology: micropapillary
- Focality – single vs. multiple
- Presence of CIS
- Status at 3 month follow-up
- Tumor size

- **Low** – Ta low grade solitary, primary,  $\leq 3\text{cm}$  - 50% patients
- **Intermediate** - Multifocal, recurrent Ta, low grade,  $\leq 3\text{cm}$  - 35% patients
- **High** - CIS, any high grade (Ta or T1); multifocal **and** recurrent **and**  $>3\text{cm}$  TaLG – 15%
- **Very high** - Multiple and/or large ( $>3\text{ cm}$ )  
T1HG, T1HG + CIS  $\pm$  P urethra, micropapillary

- **Low** – TaLG solitary, primary,  $\leq 3\text{cm}$ ; PUNLMP
- **Intermediate** – TaLG  $> 3\text{cm}$ ; Recurrence , 1 year; multifocal, recurrent Ta, low grade,  $\leq 3\text{cm}$ ; High grade Ta HG  $\leq 3\text{cm}$ ; T1 LG
- **High** – T1 HG; any recurrent TaHG; Ta HG  $> 3\text{cm}$  or multifocal; CIS; any recurrence after BCG; any variant histology or LVI; any high grade cancer in prostatic urethra

# Risk Stratification

## Recurrence and Progression Risk

| <u>Risk group</u> | Recurrence(%) |            | Progression(%) |            |
|-------------------|---------------|------------|----------------|------------|
|                   | <u>1yr</u>    | <u>5yr</u> | <u>1yr</u>     | <u>5yr</u> |
| Low               | 15            | 31         | 0.2            | 0.8        |
| Intermediate      | 24-38         | 46-62      | 1-5            | 6-17       |
| High              | 61            | 78         | 17             | 45         |

NB. Based largely on randomized trials of intravesical chemotherapy

- **Low** – peri-operative chemotherapy only
- **Intermediate** – peri –op plus induction chemotherapy  $\pm$  maintenance
- **High** – peri-op plus induction BCG plus maintenance
  - Assess response with cysto, cytology, and biopsy (for CIS)
- **Very high** – consider primary cystectomy

# Intravesical Immunotherapy and Chemotherapy

## Immunomodulatory agents

Bacillus Calmette-Guérin (BCG)

***Approved for Ta, T1HG and CIS***

Interferons

## Chemotherapeutic Agents

Thiotepa

***Approved for superficial papillary***

Mitomycin C

Doxorubicin, epirubicin, valrubicin

***Val approved for BCG refractory CIS***

Gemcitabine

## Mechanism of Action

Inflammatory host response;

release of cytokines

May be combined with interferons

Lymphocyte activation; cytokine  
release; phagocyte stimulation

Antiproliferative actions

Antiangiogenic

Alkylating agent; cross-links nucleic  
acids

Antibiotic; inhibits DNA synthesis

Intercalating agents; inhibits DNA  
synthesis

Deoxycytidine analog; inhibits DNA  
synthesis

- Peri-operative single dose chemotherapy
  - TaLG only (AUA, NCCN, EAU)
  - All patients with NMIBC (CUA, NICE)
- Induction intravesical chemotherapy +/- 1 year maint
  - Intermediate risk
  - Induction alone (AUA, NCCN, NICE)
  - Induction + maint (EAU, CUA)
- Induction BCG + maintenance 3 yr
  - All high risk patients
- Radical cystectomy
  - Option for highest risk patients and BCG unresponsive



## Special Report

Urology 83:262, 2014

### **Clinical Trial Design for the Development of New Therapies for Nonmuscle-invasive Bladder Cancer: Report of a Food and Drug Administration and American Urological Association Public Workshop**

Jonathan P. Jarow, Seth P. Lerner, Paul G. Klu  
Dean Bajorin, Sam Chang, Colin P. N. Dinney,  
Michael O'Donnell, Diane Zipursky Quale, Mai  
Bhadrasain Vikram

Bladder Cancer 1 (2015) 29–30  
DOI 10.3233/BLC-159002  
IOS Press

Short Communication

3/30/2015

10/26/2015

Clarification of Bladder Cancer Disease  
States Following Treatment of Patients  
with Intravesical BCG



Bl Cancer. 2015; 1(2): 133–136.

Published online 2015 Oct 26. doi: [10.3233/BLC-150016](https://doi.org/10.3233/BLC-150016)

PMCID: PMC4832566

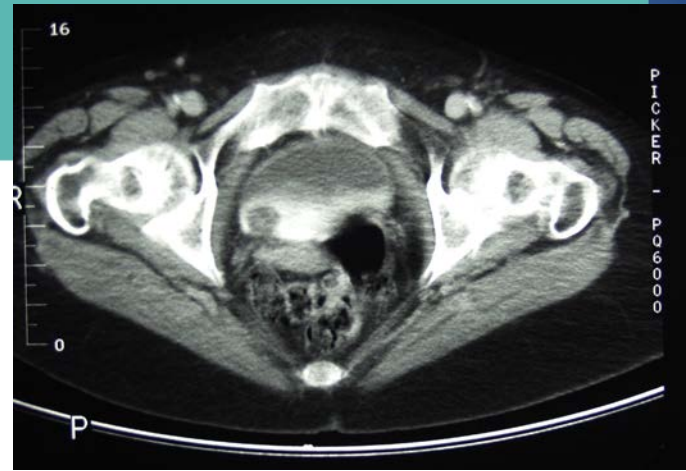
NIHMSID: [NIHMS776513](https://www.ncbi.nlm.nih.gov/pmc/articles/NIHMS776513/)

### **Development of Systemic and Topical Drugs to Treat Non-muscle Invasive Bladder Cancer**

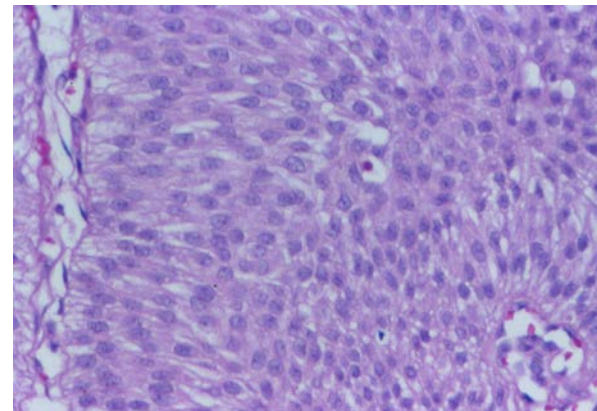
Jonathan Jarow,<sup>a</sup> V. Ellen Maher,<sup>b,\*</sup> Shenghui Tang,<sup>c</sup> Amna Ibrahim,<sup>b</sup> Geoffrey Kim,<sup>b</sup> Rajeshwari Sridhara,<sup>c</sup> and Richard Pazdur<sup>b</sup>

# Case

- 60 -year-old woman
- Gross painless hematuria x 6 months
- Multiple courses of antibiotics



Solitary LG Ta tumor  
Low risk disease



# Post-TUR Drug Options

## Options:

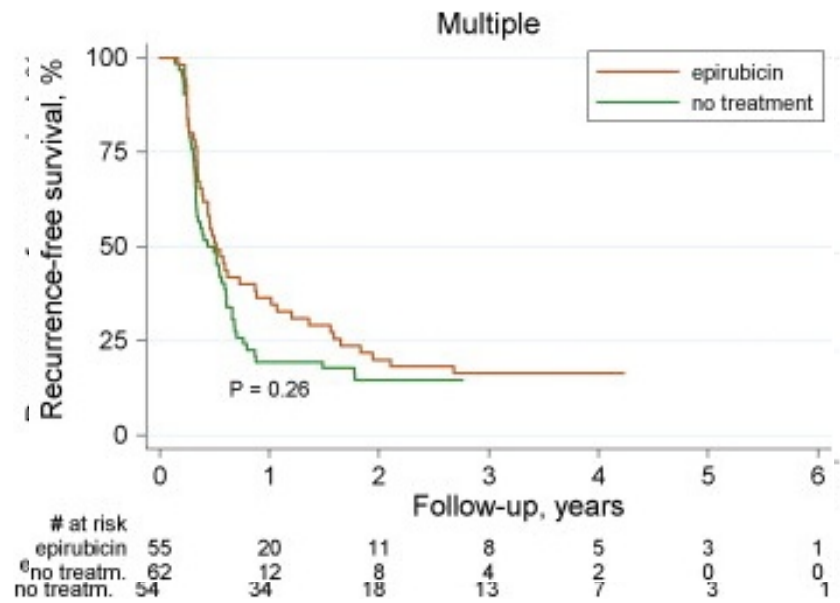
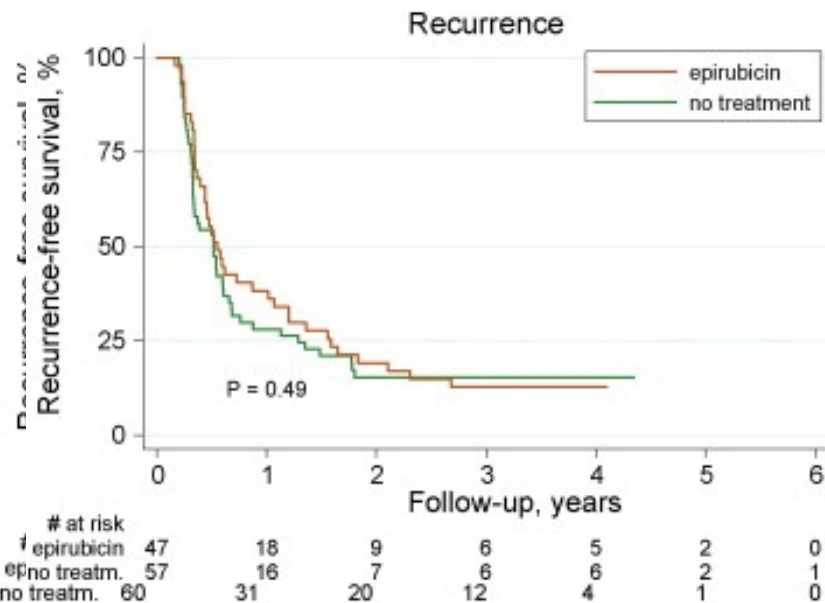
|             |  |
|-------------|--|
| Mitomycin C | 30-40 mg in 20-50cc                          |
| Doxorubicin | 40-50 mg in 50cc                             |
| Epirubicin  | 80 mg in 50cc                                |
| Gemcitabine | 2gms in 100cc (SWOG 0337<br>report due 2016) |

- Retain x 1-2 hours
- Options:
  - Treat in OR or PAR
  - Ideal to treat within first 6-24 hours post-TUR
- ***DO NOT DO in face of possible perforation***
- ***NEVER use BCG post-TUR***

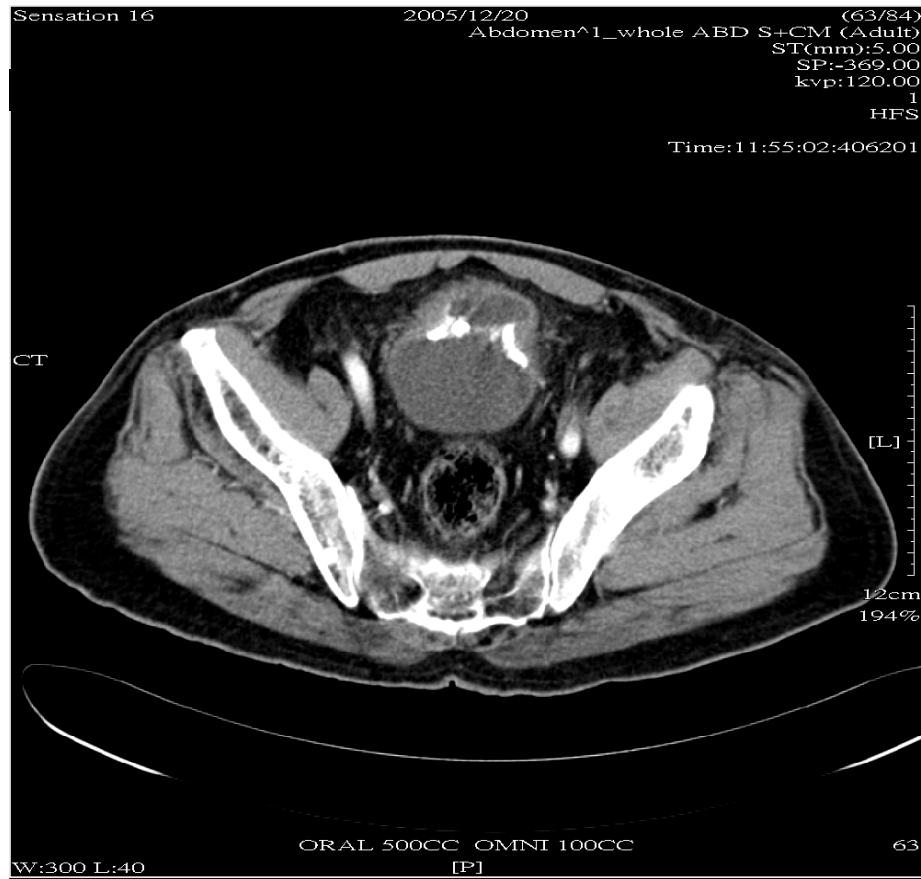
# Post-TUR Epirubicin

214 patients epirubicin vs. no instillation

Most helpful for lowest risk tumors:



# Rare Toxicities



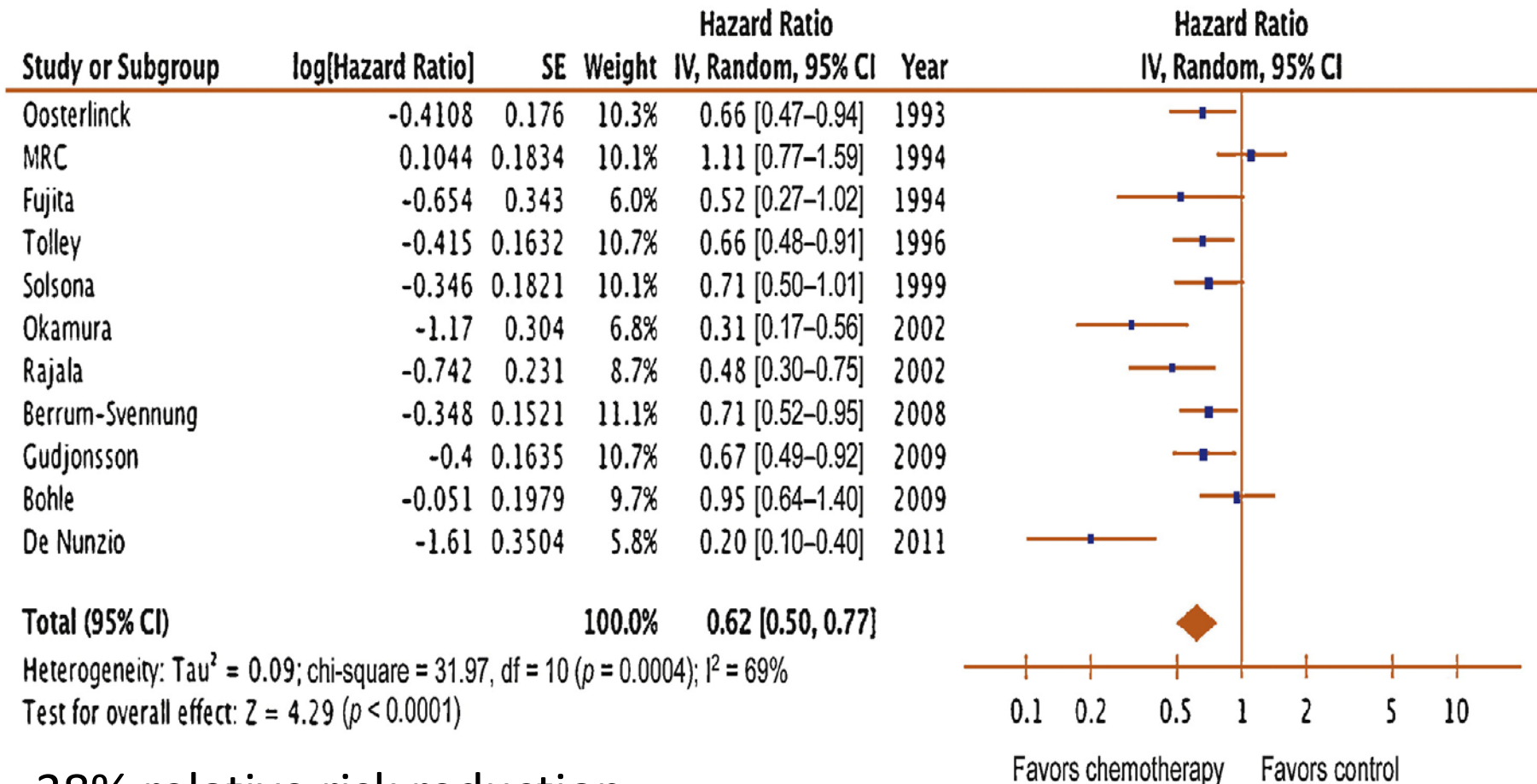
Dystrophic calcification of the bladder following Mitomycin C



Ulcer in buccal mucosa following cutaneous Gemcitabine absorption



# Post-TUR Chemotherapy – Systematic Review

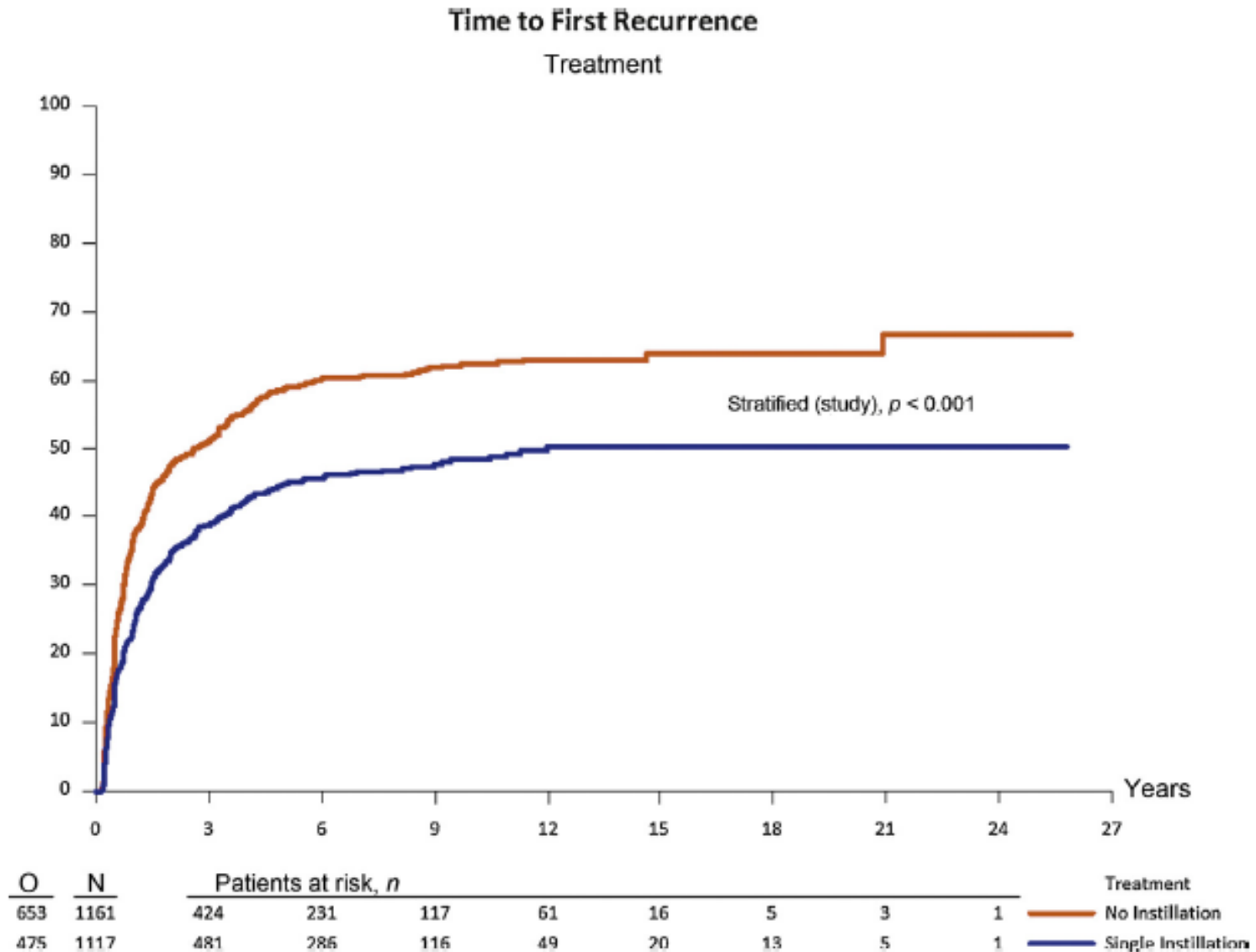


38% relative risk reduction

Previous meta analysis –11% absolute risk reduction for recurrence  
 (Sylvester, R et al, J Urol 171:2186, 2004) Perlis, et al Eur Urol 64:421, 2013

- Individual patient data 11 of 13 trials
- N = 2278
- Relative risk reduction for recurrence 35%
  - HR 0.65 ( 0.58-0.74;  $p < 0.001$ )
- 5-year recurrence probability reduced from 58.8% to 44.8%
- No benefit in patients with  $> 1$  recurrence/year or EORTC risk score  $\geq 5$
- No benefit for risk of progression or death

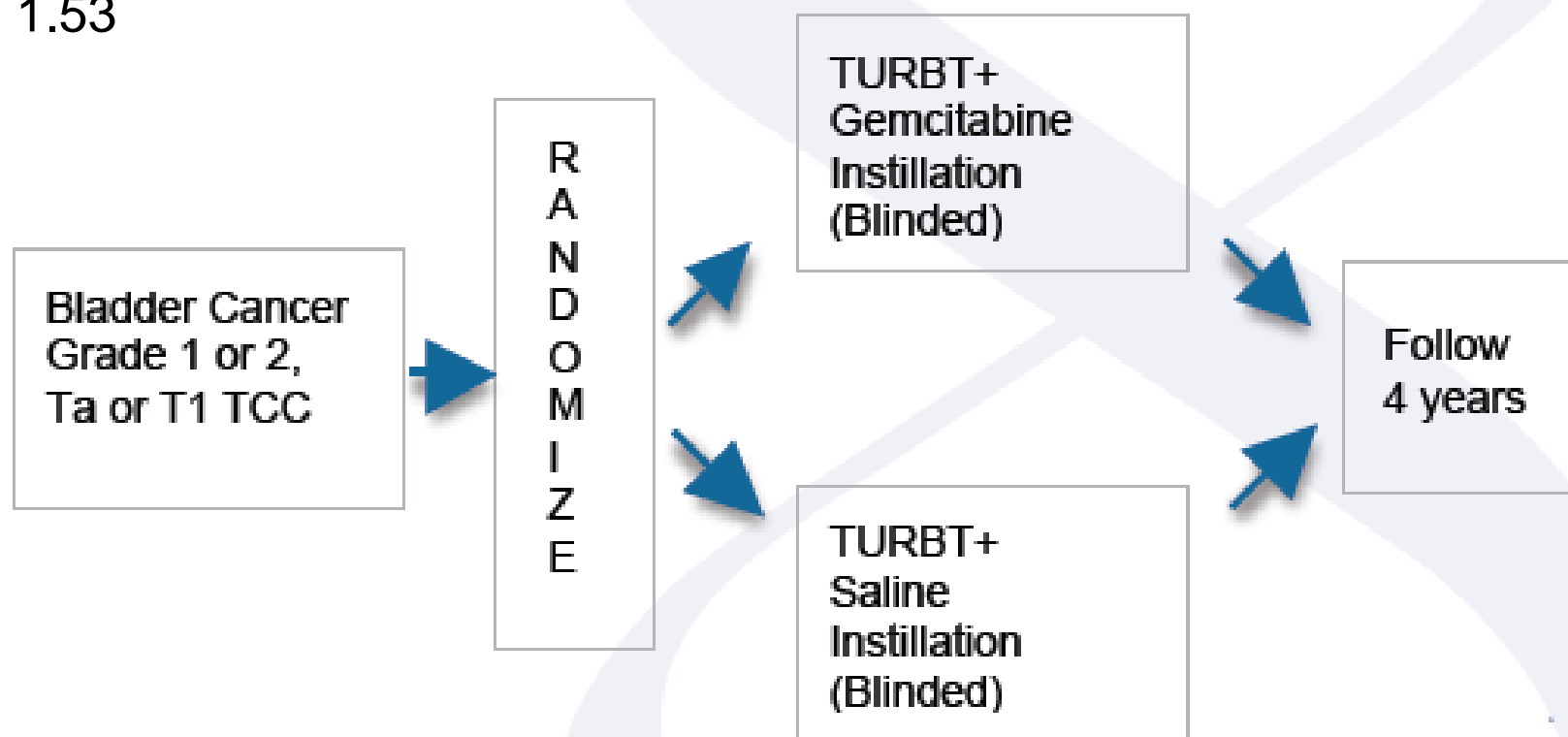
# Post-TUR Chemotherapy - Meta-analysis





- Est 2-yr RR in control arm 60%
- Powered to detect 45% RR in Gem arm
- HR 1.53

### S0337 Schema



**Primary objective:** Determine efficacy after transurethral bladder resection (TURBT) of single intravesical gemcitabine instillation versus saline instillation in preventing recurrence of completely resected Grade 1 or 2, Ta or T1 transitional cell cancer (TCC) of the bladder at two years

- Survey of 259 US urologists<sup>1</sup>
  - 61% participated
  - 1010 eligible patients
  - 17% received peri-op instillation
  - 66% of urologists never used
- Judicious use <sup>2</sup>
  - Prospective quality improvement collaborative
  - 2794 patients over 22 months/5 practice sites
  - Ideal use 38% to 35% after intervention
  - Judicious use 83 to 86% (appropriate use and non-use)

<sup>1</sup> Cookson, et al J Urol 187:1571, 2012

<sup>2</sup> Barocas, et al J Urol 190:2011-6, 2013

- 324 urologists surveyed (France, Germany, Italy, Spain, UK)
  - 55% participated
  - 954 TURBT in 771 patients
  - 43% received peri-op CTx
  - Factors associated with utilization
    - Country (UK highest, France lowest), fellowship trained, higher risk for recurrence, lower risk of progression, higher volume NMIBC treated

- Similar issues regarding low utilization as US
- Cost MMC 6 x Epirubicin so some centers using Epi preferentially
- Logistic constraints in high throughput operating room and managing cytotoxic ctx
- Small TaLG tumors often managed with office fulguration
- Most care provided by community urologists
  - Centralized care to academic center only in one region in Quebec

- Low and intermediate risk most appropriate
  - Solitary and multifocal and/or recurrent TaLG
  - Small volume TaHG
  - Safety proven but rare severe toxicities with MMC
- Utilization varies but increased from early reports
- Geographic variation in utilization within US, Canada and Europe
- But, guidelines consistent in recommending use