# Radiation-based strategies in bladder conserving treatment for muscle invasive bladder cancer

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# Bladder cancer …. another very difficult management problem

**70-80% present with non-invasive disease:**

- **long intervals to progression, providing many opportunities …..**
  - **to under-treat**
  - **to over-treat**

# A difficult management problem (cont'd)

**Ultimately more than half of those diagnosed develop muscle invasive cancers…..**

**In these people the issues are:**

- **the "best" treatment is a very formidable undertaking**
- **metastases are frequent**
- **many patients have serious co-morbidities and/or are elderly**

# Worldwide …..

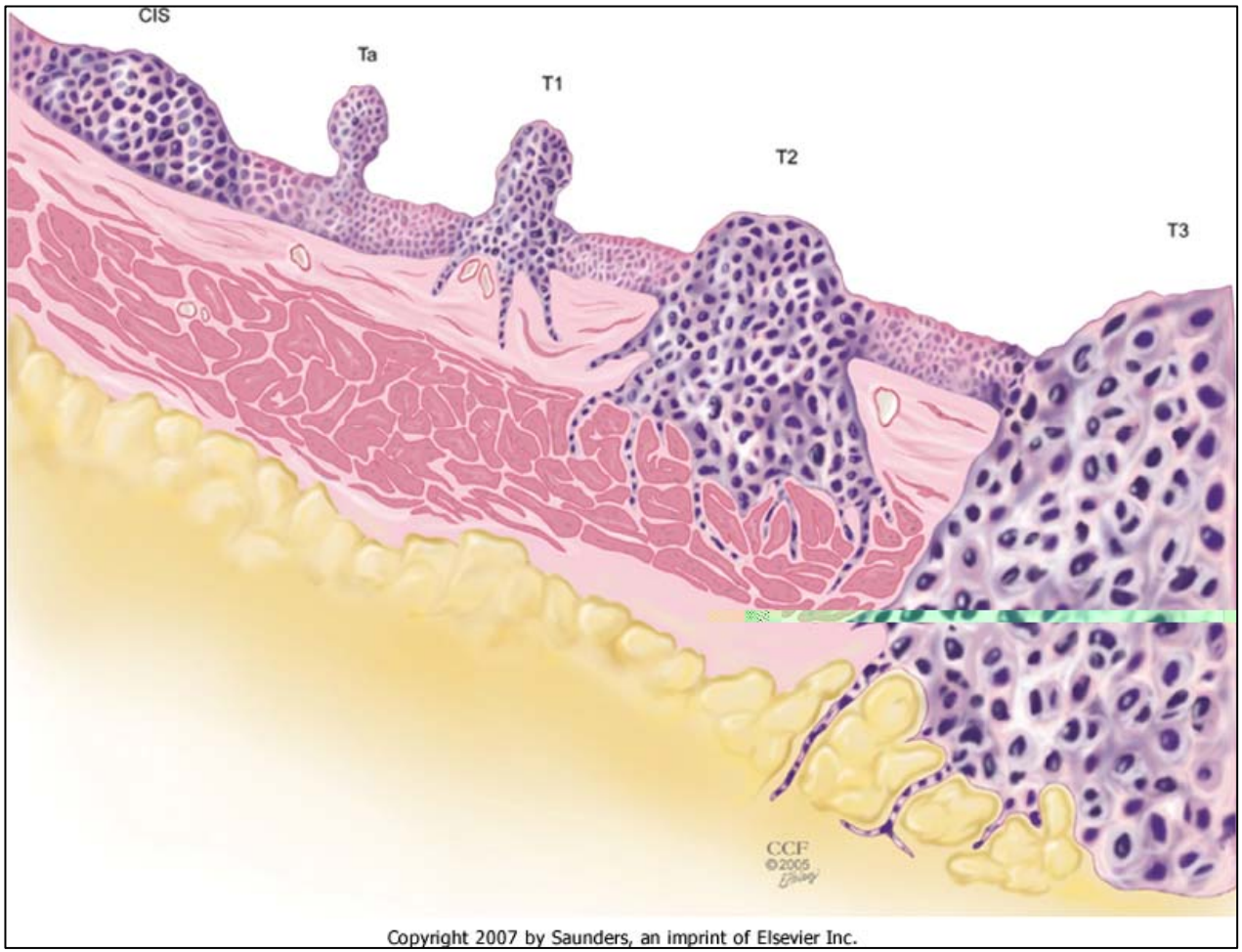
**Approx. 357,000 new cases/annum**

**Approx. 145,000 deaths**

- **9th most common cancer**
- **13th most common cause of death**
- **Male 4 : 1 Female**

**Approximately 40% die as a result of bladder cancer**

# Let's remind ourselves of the staging system



# Muscle invasive cancer: Long term survival by stage after "optimal" treatment [1, 2, 3]

| | pT2 | pT3a | pT3b | pT4 |
|---|---|---|---|---|
| % developing metastases | 36 | 45 | 69 | 70 |
| % survival ≥ 5 years | | | | |
| Cystectomy | ~70(63-89) | ~50(31-62) | | ~35(21-50) |
| Radiation alone | 40-45 | 15-40 | | 2-12 |
| Chemo-radiation | 70-75 | 50-55 | | 25 |

- **These are the best ranges of results recorded**
- **5 year survival for T2 bladder cancer is 38.5% according to the US National Cancer database**

# Outlook is not good even when treatment is optimal, which raises the questions:

- **How many are fit enough to receive optimal therapy?**
- **How many can access it?**
- **What happens to those who do not receive optimal therapy?**

**Case selection factors can have a very important impact on reported results**

# The need to cure the 70% of patients presenting with *non* muscle invasive cancer is very obvious

- **Approx. half develop recurrences after TURBT**
- **Recurrence can be reduced by 40% using adjuvant intra-vesical therapies including BCG and/or cytotoxic instillations [4, 5]**
- **But how many actually receive intra-vesical therapies?**
- **Can intra-vesical therapies be improved?**
- **How frequently is muscle invasion missed while intra-vesical therapies for recurrences continue?**

**Prevention of muscle-invasion is enormously important ….. but once again selection factors are operative**

# Could urinary bio-markers help?

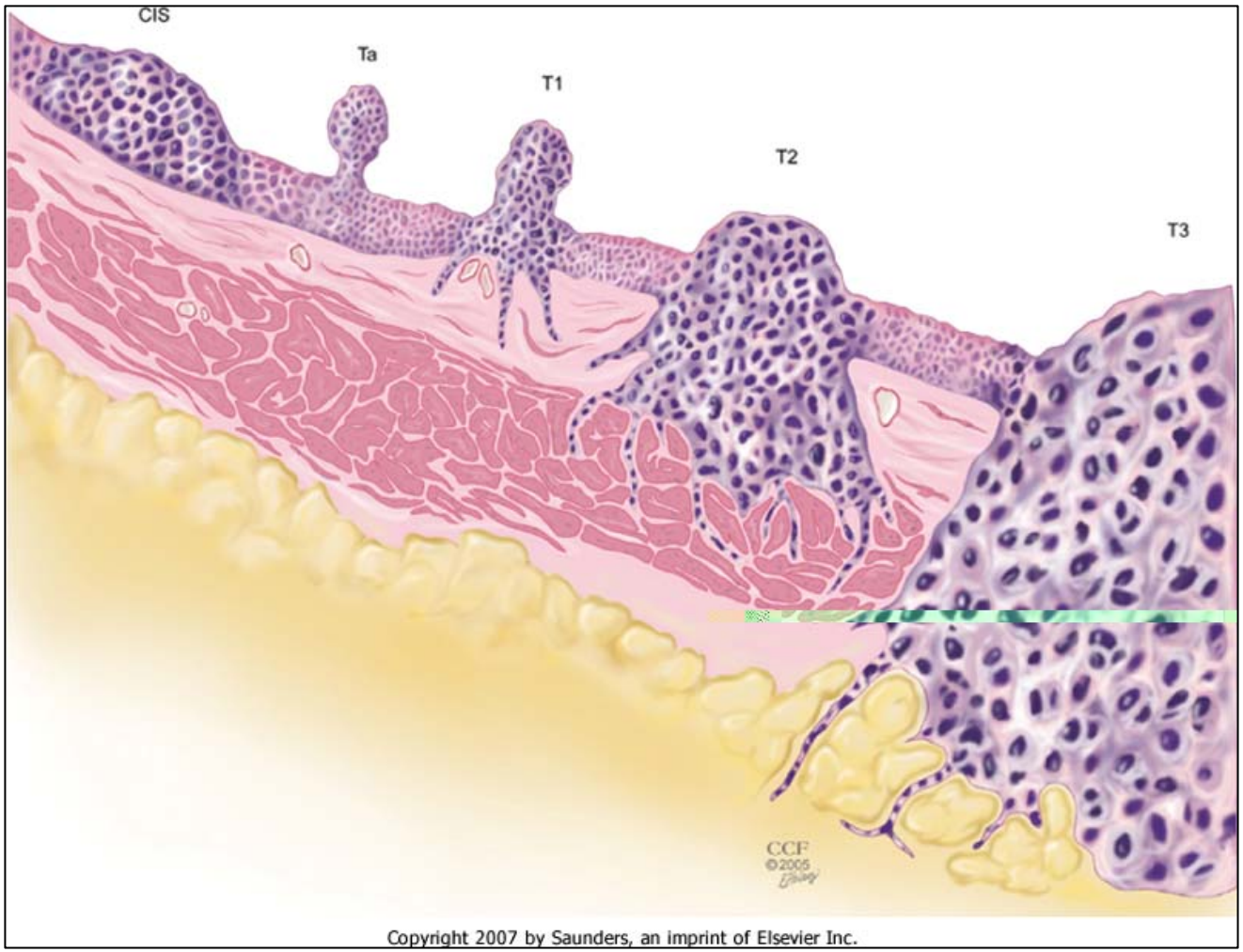
- **In predicting recurrence?**
- **In signalling early muscle invasion?**

**Telomerase, Nuclear Matrix protein 22, and NMP22 Bladder Chek®, Survivin, Bikunin, BTA Trak® and Stat®, ImmunoCyt®, and Uro-vision® present options [6, 7]**

# Important considerations for optimal radiation based strategies…..

- **Has TURBT been complete?**
- **How big is the bladder at each treatment session?**
- **Are the lymph nodes to be treated?**
- **What are the options when chemotherapy cannot be given?**

# How feasible is complete TURBT?



# Can we ensure that our radiation fields cover the bladder each day?

- **Bladder volumes are now easy to measure ….. so self catheterisation when needed is now an option**
- **A set of differently sized radiation volumes can be derived for each patient, to be used as required**
- **Presently there is no good way to insert radio-opaque fiducial markers**

# Incidence of lymph node metastases is 20-25% when pelvic CT is negative

**There is good reason to irradiate the pelvic lymph nodes ….. but will the eradication of pelvic lymph node metastases contribute to cure?**

# Options available when chemotherapy cannot be given?

- **Split course accelerated radiotherapy did *not* improve outcome [8]**
- **Nor did treatment in hyperbaric oxygen [9]**
- **However carbogen breathing / oral nicotinamide may be more promising [10, 11]**

# The recent carbogen/nicotinamide trial [10]

- T1 high grade, T2,3 any grade, T4a(prostate)
- RT 55Gy 20Fx 4 weeks or 64Gy 32Fx 6.5 weeks
- Carbogen 2% $CO_2$ and 98% oxygen to allow better oxygen diffusion (85% toleration)
- Nicotinamide 40-60mg/kg 1-2 hours before RT to reduce capillary shutdown and increase perfusion (70% toleration)
- Accrual 333 between 2000 and 2006

# Early results from this trial [11].....

## 3 year data:

| | RT alone | RT CN | p | HR |
|---|---|---|---|---|
| LRFS | 46% | 59% | 0.04 | - |
| CSS | 56% | 68% | 0.10 | 0.87 |
| OS | 63% | 74% | 0.04 | 0.86 |

**No difference in bowel or urinary toxicity ….. but bowel frequency greater after RTCN**

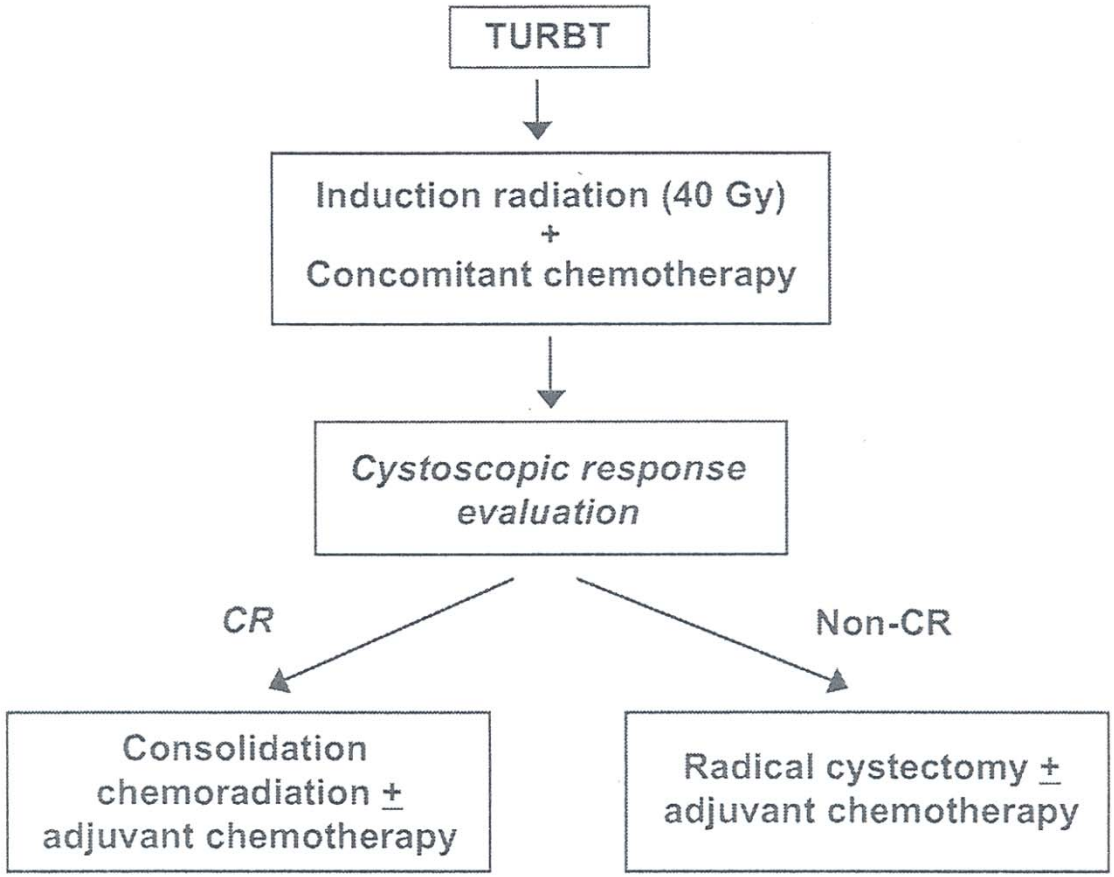
# Combinations of radiation and chemotherapy

- **Concomitant chemo-radiation is the most widely used option**
- **The use of neo-adjuvant chemotherapy has support from randomised trials**
- **Adjuvant chemotherapy may yet find a role**

# Experiences of a large single institution and three multi-centre groups

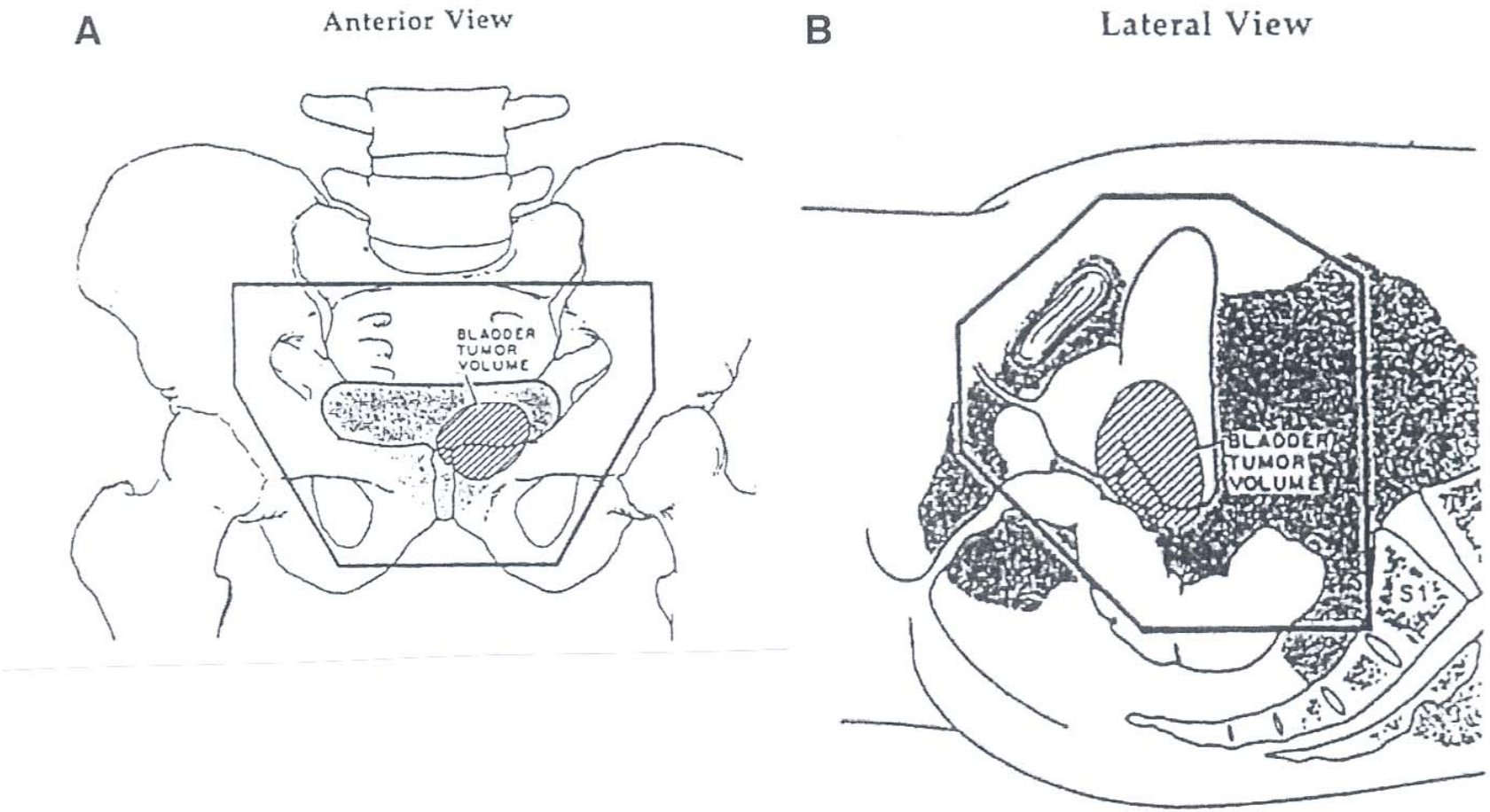
- **Massachusetts General Hospital [MGH] (Shipley and Zietman, Boston, USA)**
- **RTOG (USA)**
- **Erlangen, Lubeck and Halle (Germany)**
- **TROG (Australia and New Zealand)**

# The MGH experience [12, 13, 14].....



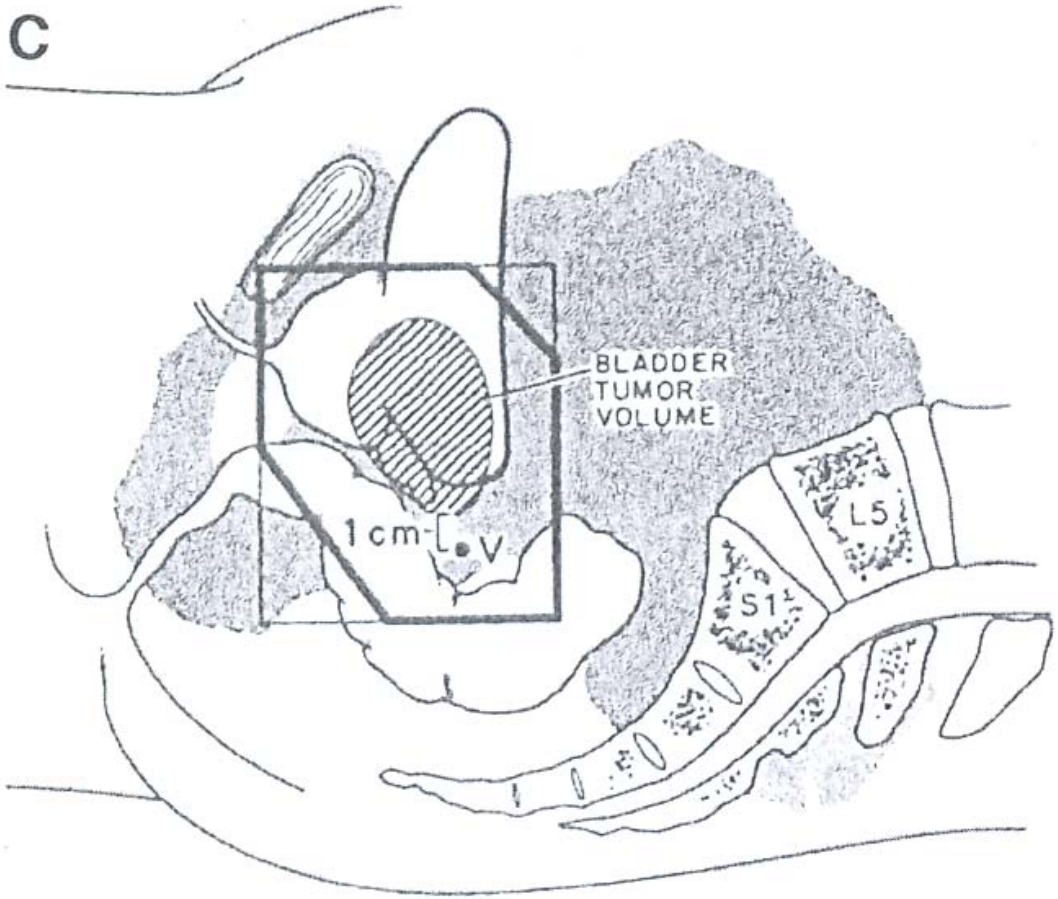

**Close inter-disciplinary collaboration is emphasised**

# The MGH experience…..



# The MGH experience…..

## Partial bladder boost



# The MGH selection criteria

- Absence of hydronephrosis
- Absent pelvic lymph node involvement (MR, CT and sometimes biopsy)
- Adequate renal function
- Normal FBC, electrolytes, LFTs
- Medically fit for cystectomy

# Key findings in 190 patients [13].....

- **Using concurrent weekly cisplatin (20mgs/m² i.v.)**
- **53% had complete TURBT**
- 

| | All cases | T2 | T3, 4a |
|---|---|---|---|
| 10 yr CSS | 59% | 66% | 52% |
| 10 yr CSS (with bladder) | 45% | 50% | 34% |
| 10 yr CSS (in 34% requiring cystectomy) | 44% | - | - |

- **32 patients had superficial recurrences with 10 ultimately requiring cystectomy**

# Key findings (cont'd)

**Visibly incomplete TURBT reduced:**

- **CR rate (NS)**
- **OS and CSS rates (NS)**
- **CSS with bladder by ⅓ (p=0.03)**

**and increased:**

- **Immediate cystectomy by 2x**
- **Salvage cystectomy by ⅓**

# The RTOG experience

## 6 prospective protocols over 20 years

- **85-12 (n=42)** — Daily RT/concurrent CDDP (CTRT) 5 year survival 52%, 42% with an intact bladder [15]
- **88-02 (n=91)** — Found that neo-adjuvant CT (NACT) with MCV (MTX, CDDP, VLB) was tolerable [16]
- **89-03 (n=123)** — A RCT to test NACT, failed to accrue due to poor tolerance of NACT. Survival at 5 years very similar in the two arms [17]

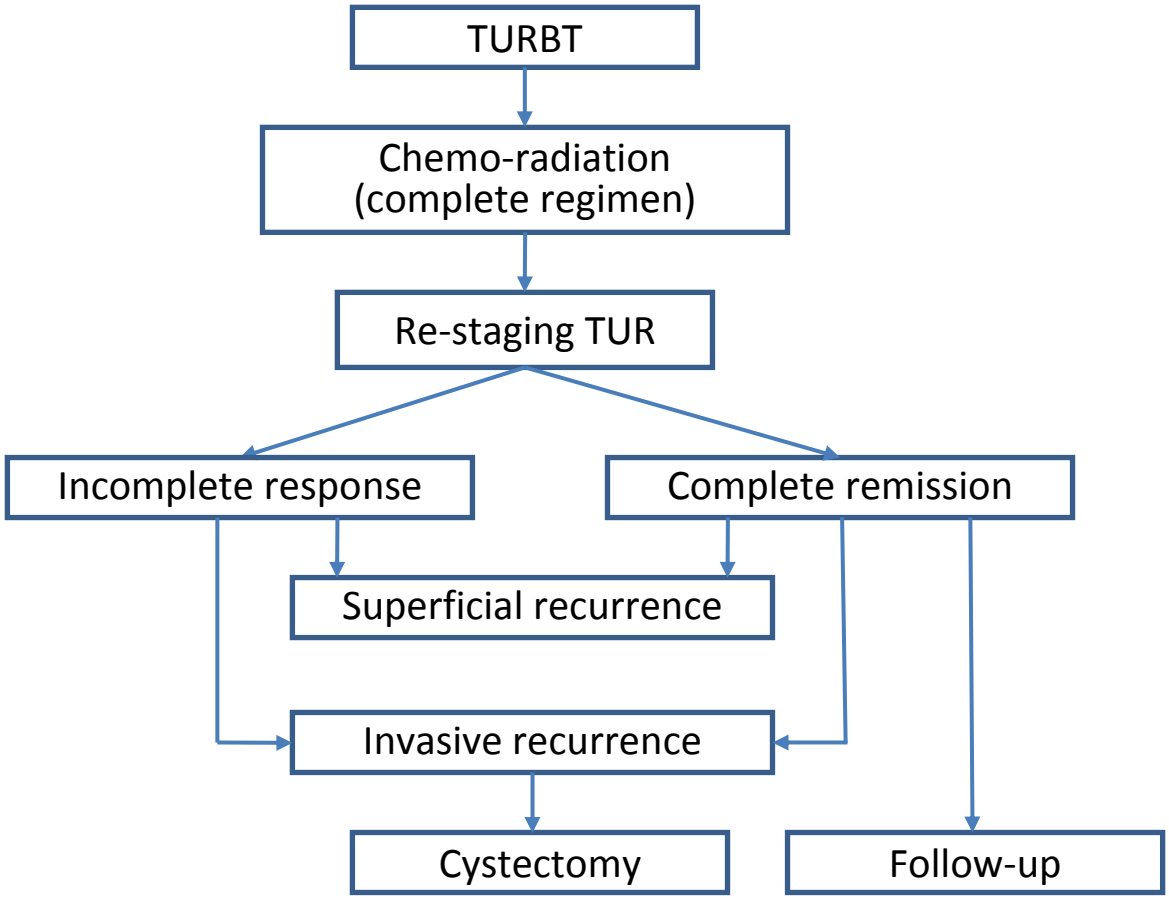
# The RTOG experience (cont'd)

- **95-06 (n=34)** — BD fractionation x 6/concurrent CDDP / 5FUx6
  3 year survival 83%, 66% with bladder [18]
- **97-06 (n=52)** — BD fractionation daily / concurrent CDDP followed by adjuvant MCV x 3
  3 year survival 61%, 48% with bladder
  77% had grade 3/4 toxicity during MCV [19]
- **99-06 (n=50)** — Split course BD fractionation / weekly CDDP and Paclitaxel followed by adjuvant GS (Gemcitabine, CDDP)
  2 year survival 79%, 69% with bladder, 74% with grade 3/4 toxicity during GS [20]

# Key findings

- **The use of neo-adjuvant and adjuvant chemotherapy has contributed more to toxicity than efficacy**
- **Unorthodox fractionation did not increase efficacy**
- **Tumour bio-marker studies found that p21, pRB and p16 are not prognostic**
- **However Her-2 over-expression is associated with reduced response, and EGFR with improved CSS**
- **This has lead RTOG 05-24 testing Trastuzumab**

# The German experience [21, 22, 23]




**Inter-disciplinary collaboration "Teamwork is not optional"**

# The German experience (cont'd)

| Period | Sample Size | TURBT combined with | pCR (%) | 5-year OS (%) | 5-year OS with bladder (%) |
|---|---|---|---|---|---|
| 1982-85 | 126 | Radiotherapy | 61 | 40 | 37 |
| 1985-93 | 95 | Radiotherapy + carboplatin | 66 | 45 | 40 |
| 1985-93 | 145 | Radiotherapy + cisplatin | 82 | 62 | 47 |
| 1993-06 | 112 | Radiotherapy + 5-fluorouracil/cisplatin | 88 | 74 | 61 |
| 2005-08 | 38 | Radiotherapy + 5-fluorouracil/cisplatin + regional deep hyperthermia | 95 | 80* | 82* |

* At 3 years of follow-up

# Key findings …

- **Importance of complete TURBT**

  **10 year survival**

  - **50% for complete TURBT (R0)**
  - **33% for microscopic residual (R1)**
  - **18% for macroscopic residual (R2)**

- **Possibility that CDDP is more effective than CBDCA and that a combination with 5FU may be the most effective**

# The TROG experience [24].....

- **97-01 (n=70)** — **63Gy 35Fx 7 weeks / 7x CDDP 35mg/m$^2$ weekly**
  **31/70 required CDDP dose reductions**

- **99-06 (n=43)** — **64Gy 32Fx 6.4 weeks / 6x CDDP 35mg/m$^2$ weekly**
  **7/43 required CDDP dose reductions**

# The TROG experience (cont'd)

- **79 (70%) had CR at 6 month cystoscopy**
  - **11/79 had invasive recurrence**
  - **18/79 had superficial recurrence**
  - **15 had salvage cystectomies**
  - **69/113 (61%) retained functional bladders**
- **At 5 years**
  - **CSS was 50%**
  - **LRFS was 45%**

# Experience from randomised controlled trials .....

| Trial | Sample Size | Treatments compared | Outcome |
|---|---|---|---|
| NCIC CTG [25] | 99 | Pre-op or definitive RT<br>(40Gy 20Fx) or (60Gy 30 Fx)<br>vs<br>Pre-op or definitive CTRT<br>3 x CDDP 100mg/$m^2$ / $2^{nd}$ weekly | 5 year pelvic progression free: 40 vs 59% (p=0.04) |
| TROG 02.03 [24] | 68 | 64Gy 32 Fx 6.4 weeks<br>vs<br>64Gy 32 Fx 6.4 weeks<br>(6 X CDDP 35mg/$m^2$ /weekly) | |
| UKCCR [2] | | Standard volume or whole bladder RT<br>(64Gy 32Fx or 55Gy 20Fx)<br>vs<br>The same RT plus Mito C 12mg/$m^2$<br>Days 1 and 22<br>5 FU 500mg/$m^2$ /day<br>Days 1-5 and Days 22-26 | |

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