Should all patients be offered chemo-radiotherapy?

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No!

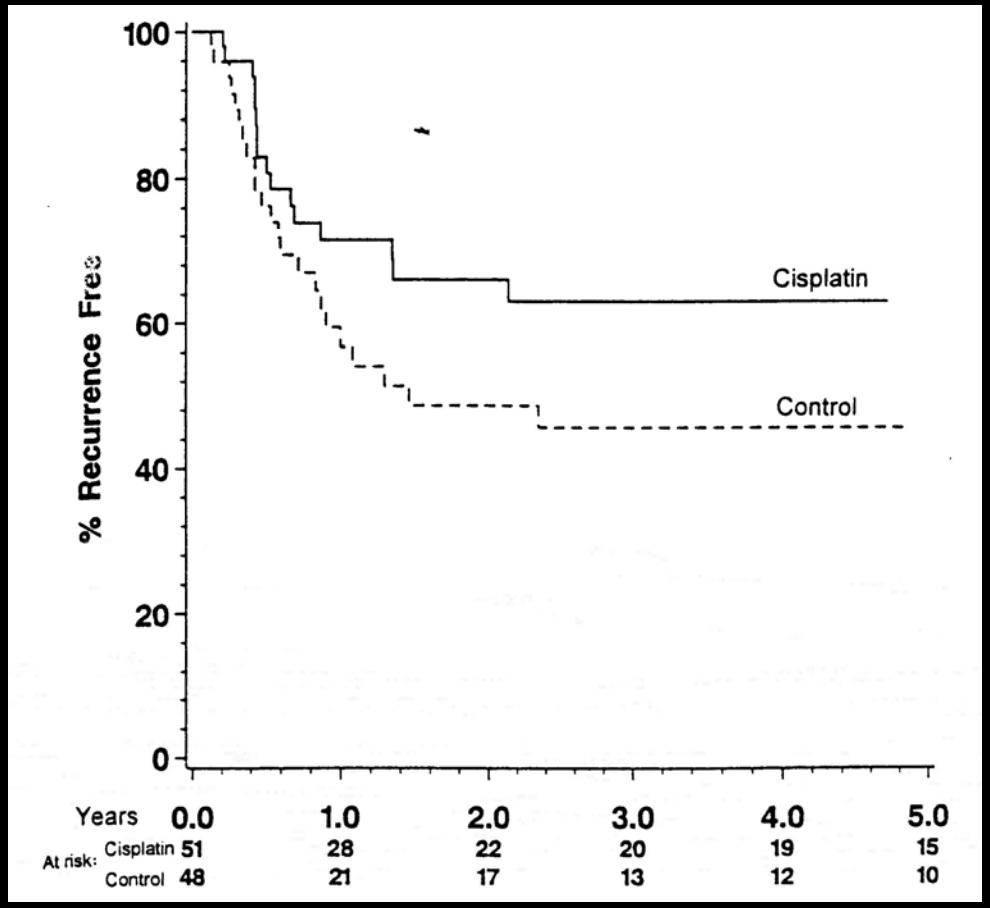
Introduction

- Overview of bladder preservation
- Survival with bladder cancer and patterns of care
- How can we select patients?

Synchronous Chemo-radiotherapy

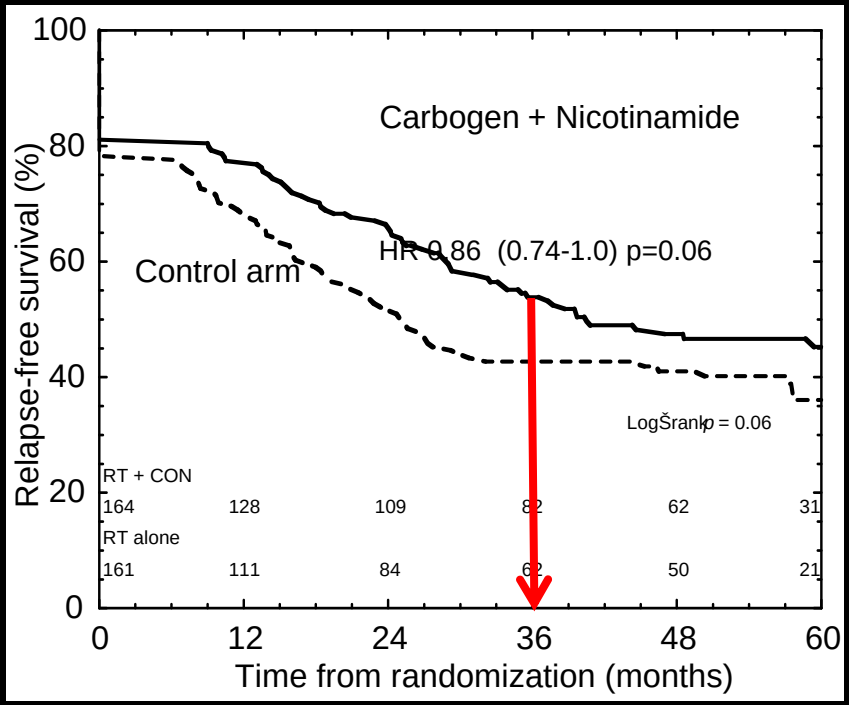
- Numerous phase I/II studies showing feasibility and safety
- Three phase III studies
  - RT vs RT + Cisplatinum (NCIC)
  - RT vs RT + nicotinamide/carbogen (BCON)
  - RT vs RT + 5FU/MMC (BC2001)

Cisplatinum and RT +/- surgery

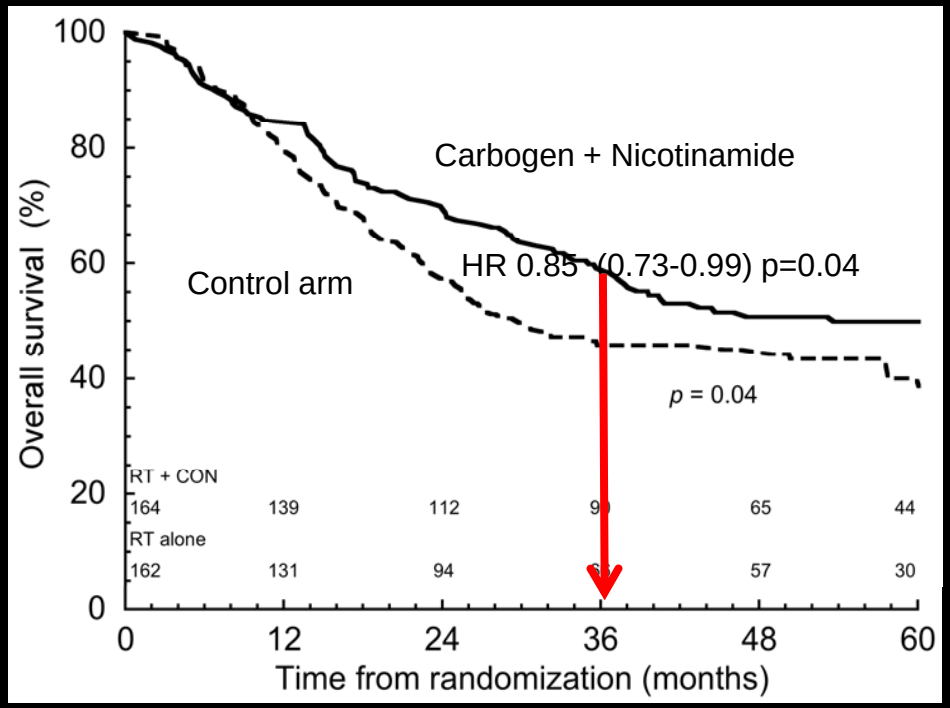


- Coppin et al, J. Clin Onc. 14:2901-2907

BCON Results

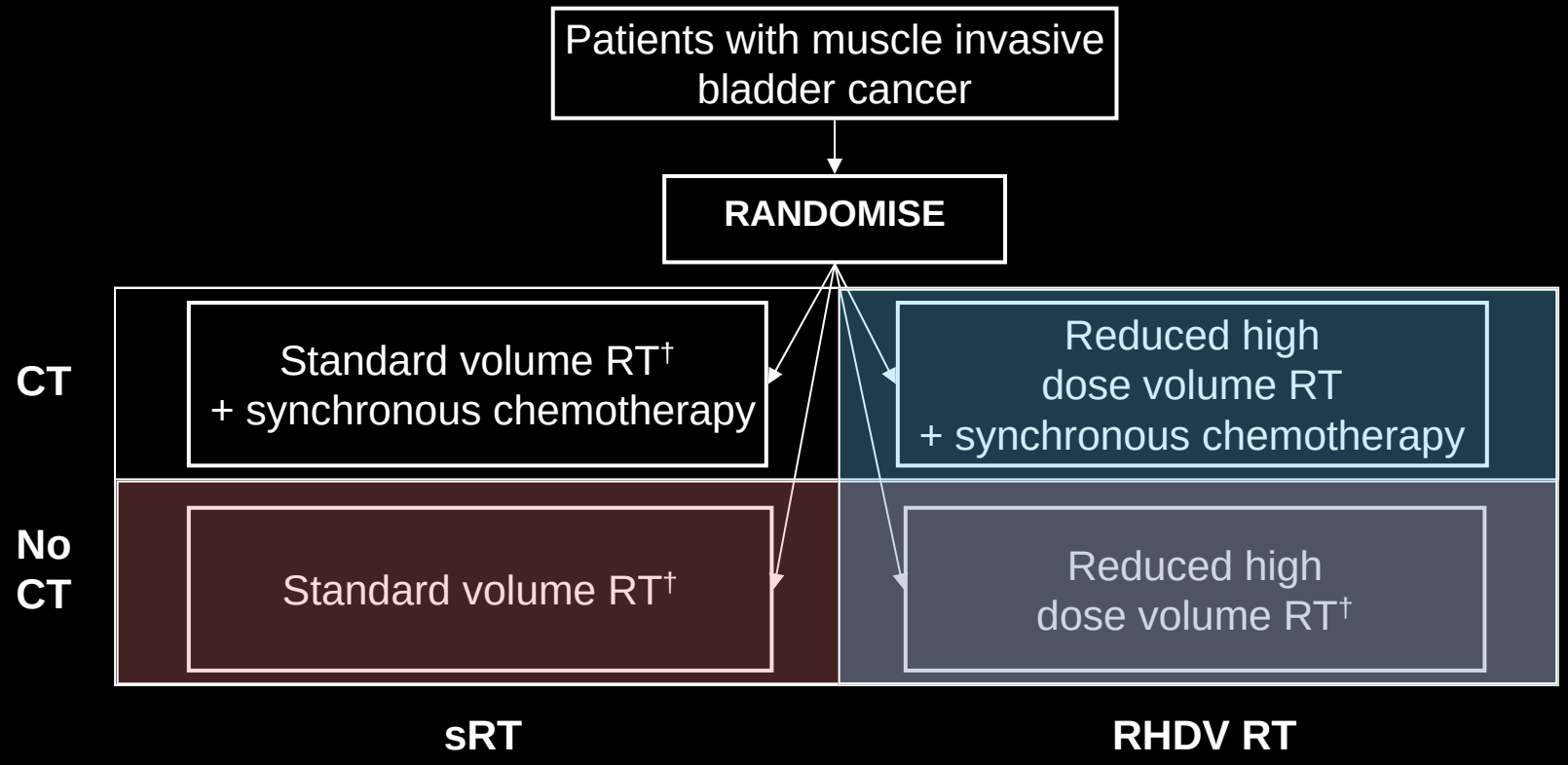


Relapse free survival



Overall survival

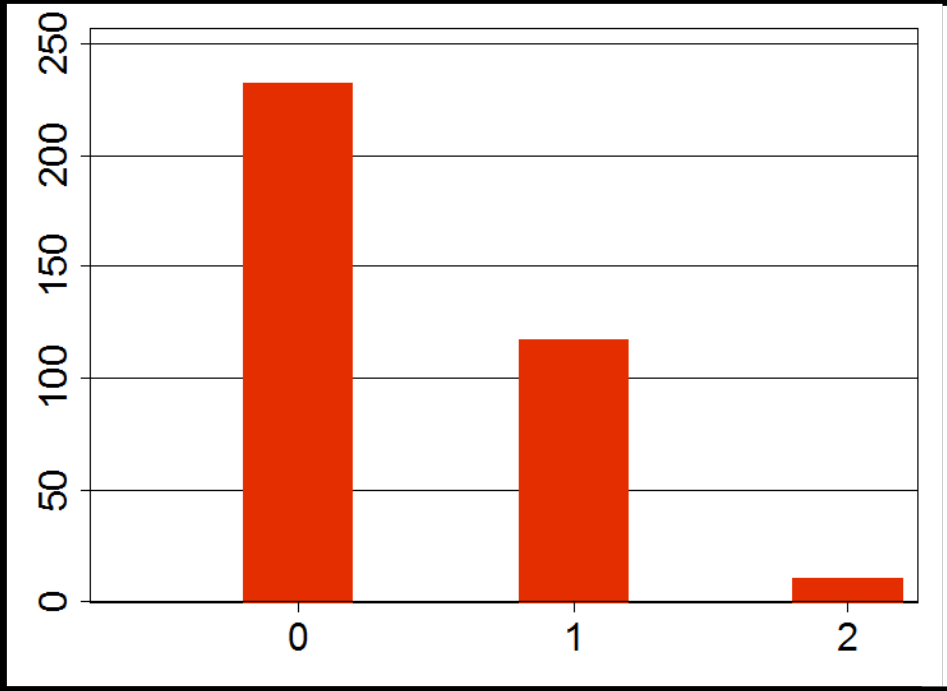
BC2001: Trial design



Pragmatic design: Centres could offer double or either single randomisation
Patients ineligible for one randomisation could participate in other

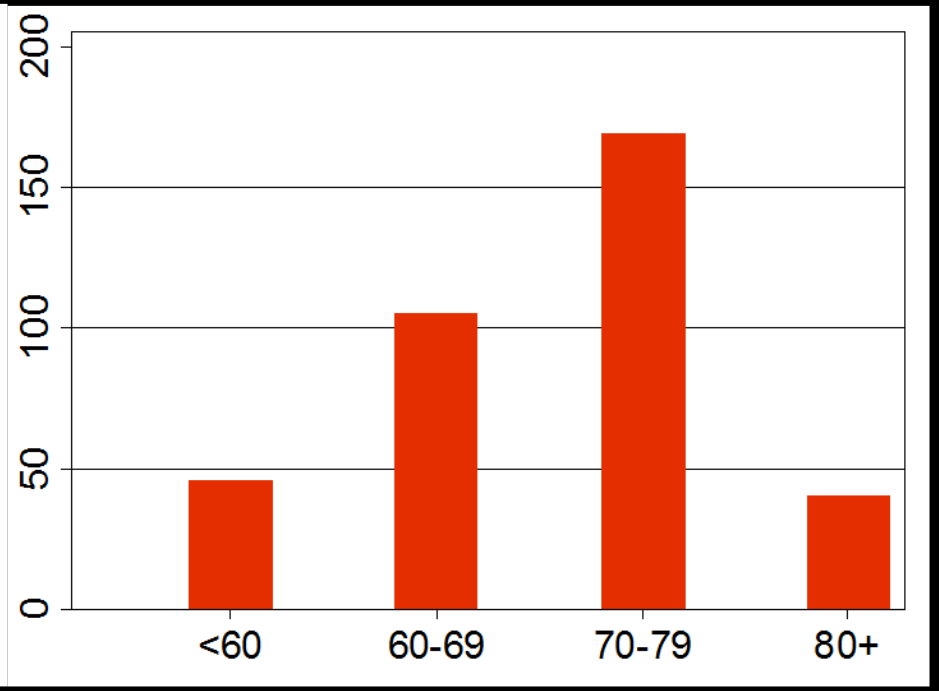
Patient demographics

Performance status



Male = 289/360 (80%)

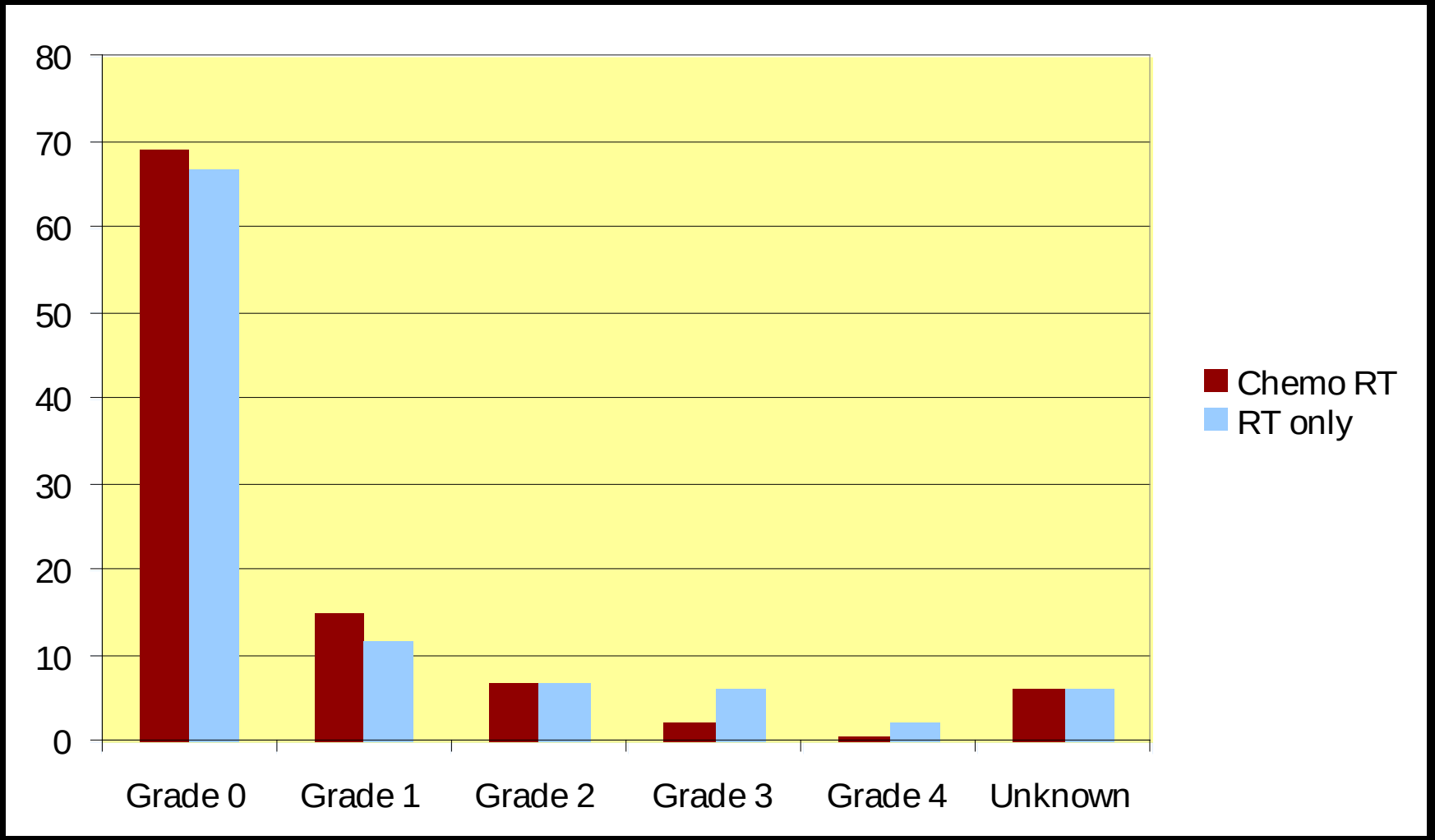
Age at randomisation



- Mean (SD) 70.5 (8.2) years
- Median (IQR) 71.9 (64.1 - 76.2) years
- Older than patients in previously published trials including SWOG 8710[1](median 63 y) and BA06[2] (median 64 y)

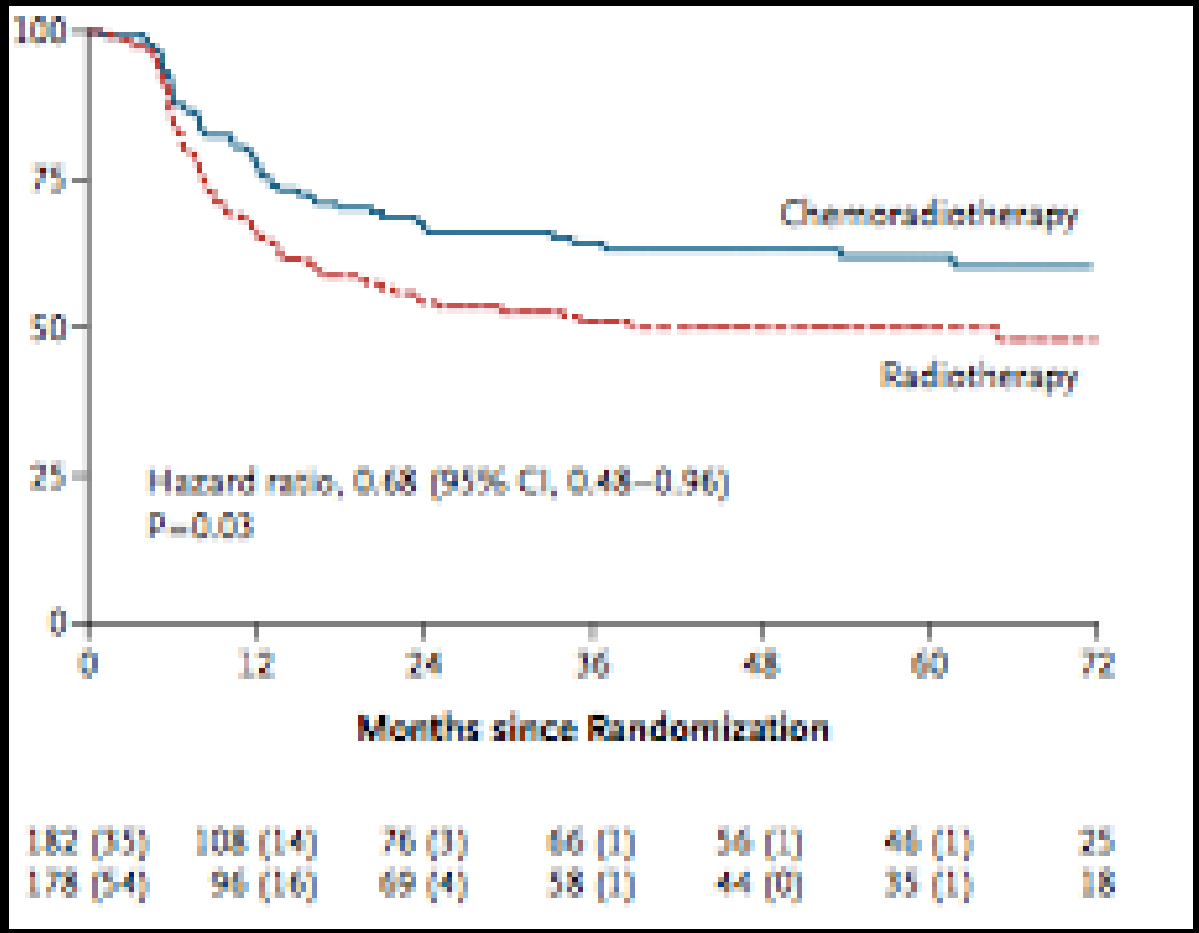
1. Grossman et al NEJM 2003 Volume 349:859-866
2. Lancet 1999; 354: 533-40

RTOG 6 month toxicity outcomes



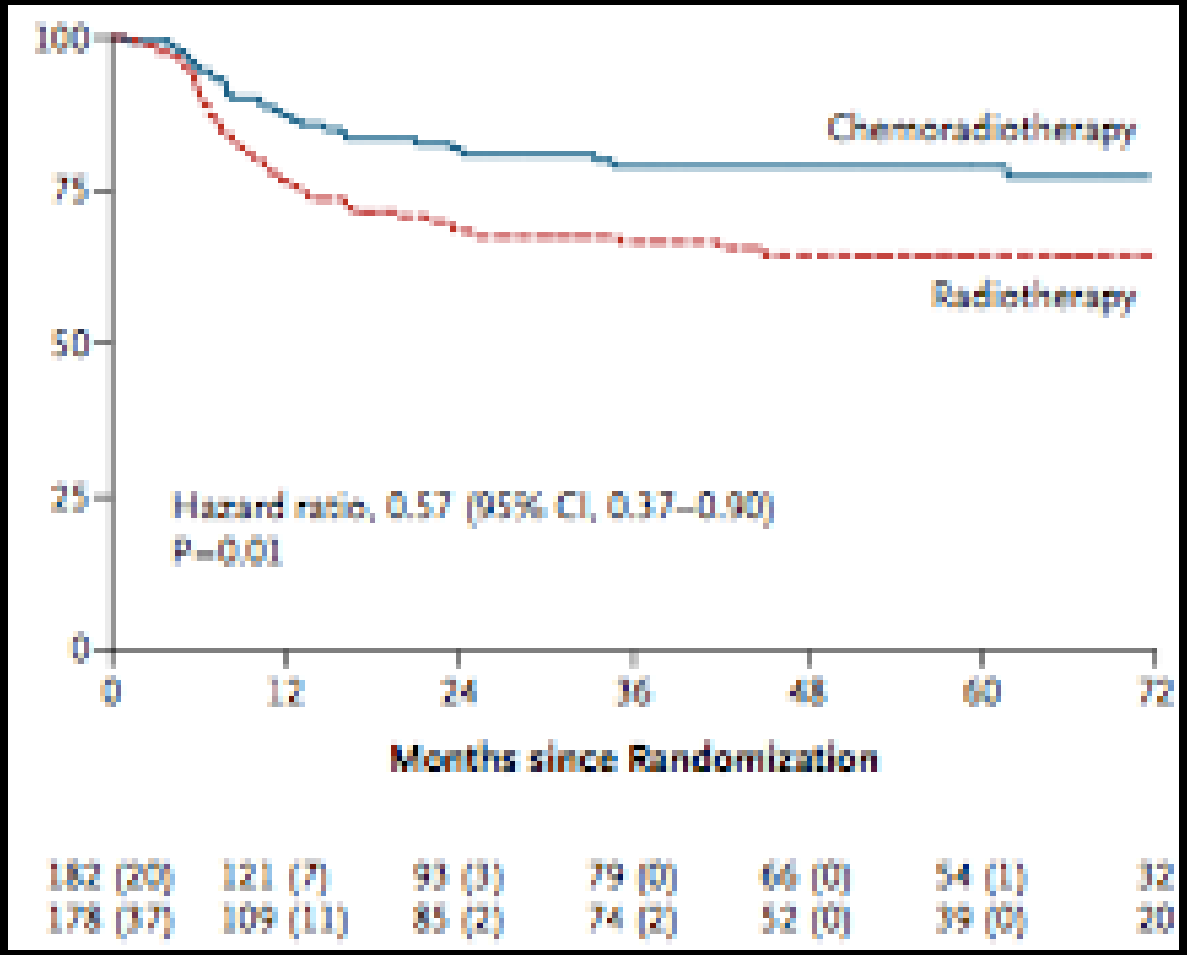
n= 291, 145 RT only, 146 chemo-radiotherapy

Loco-Regional Disease Free Survival



James et al, NEJM, 2012 366:1477-88

Invasive loco-regional disease free survival

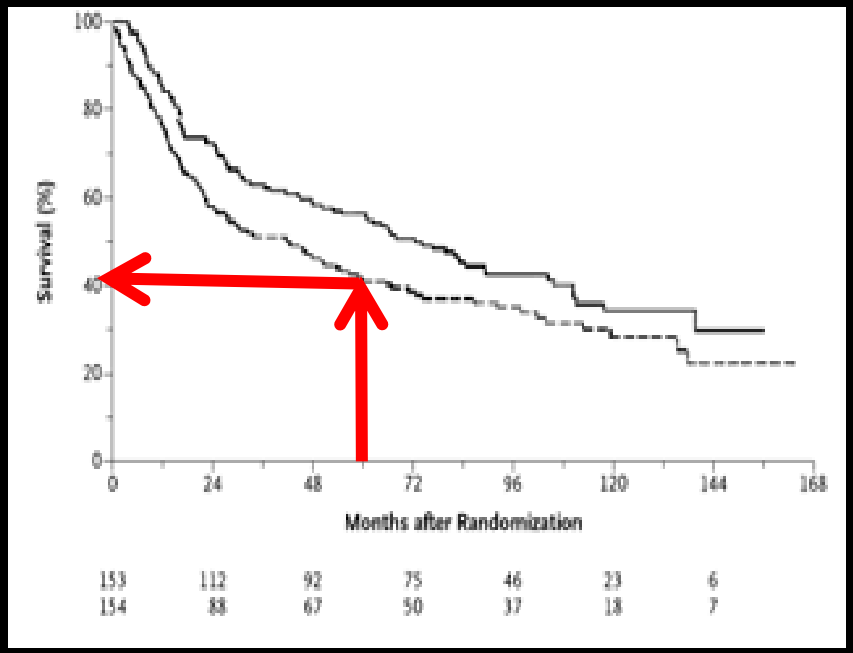


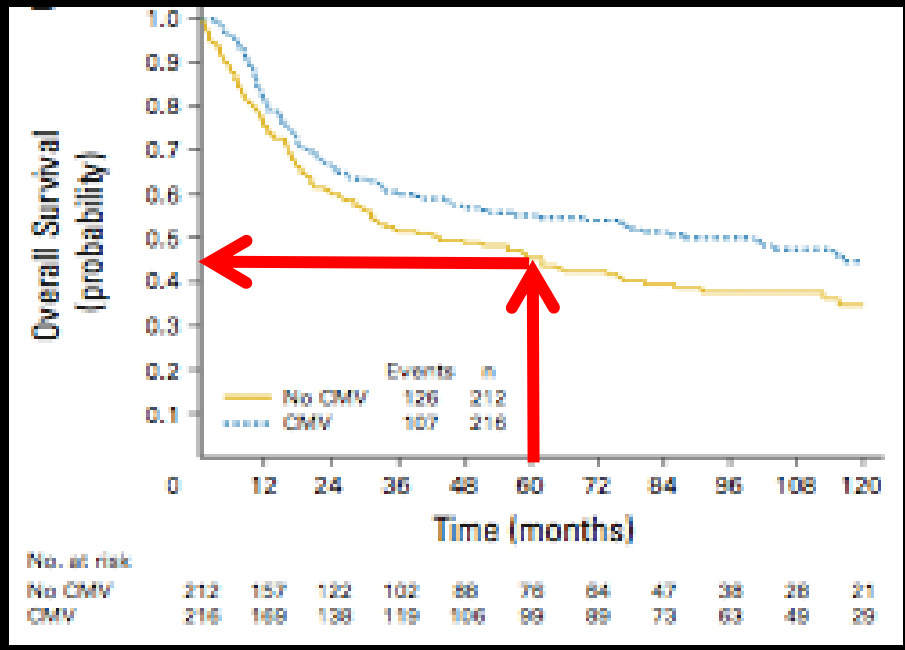
James et al, NEJM, 2012 366:1477-88

Bladder cancer is a systemic disease

- No plateau in survival curves
  - Patients die from metastases
- Treatment needs to address local control and distant metastases
- Local control
  - Surgery or RT
- Metastases
  - Systemic chemotherapy

Survival after radical treatment





Surgery +/- MVAC chemotherapy

Surgery or RT +/- CMV chemotherapy

Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. New England Journal of Medicine 2003;349:859-66.
Griffiths G, Hall R, Sylvester R, Raghavan D, Parmar MK. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. J Clin Oncol 2011;29:2171-7.

Patterns of care vary worldwide

- UK RT: cystectomy 3:1

  Munro N et al. Int J Radiat Oncol Biol Phys. 2010
- Sweden RT: cystectomy 1:4

  Jahnson S et al. Scand J Urol Nephrol. 2009
- USA
  - Surgery widely available
  - RT availability varies by age, sex and address
  - Overall round 11% receive RT (SEER)

    Konety BR et al. J Urol. 2003

Survival surgery vs radiotherapy

- Stein et al: 1054 cystectomy patients 5- and 10-YS 60% and 43%
- Rödel et al: 415 RT patients 5- and 10-YS 51% and 31%
- However, cystectomy series:
  - included 213 T0, Ta, Tis patients
  - excluded 112 inoperable patients
- If comparison is restricted to operable muscle-invasive disease, 5-YS:
- radical cystectomy 47%
- Conservative therapy 45%

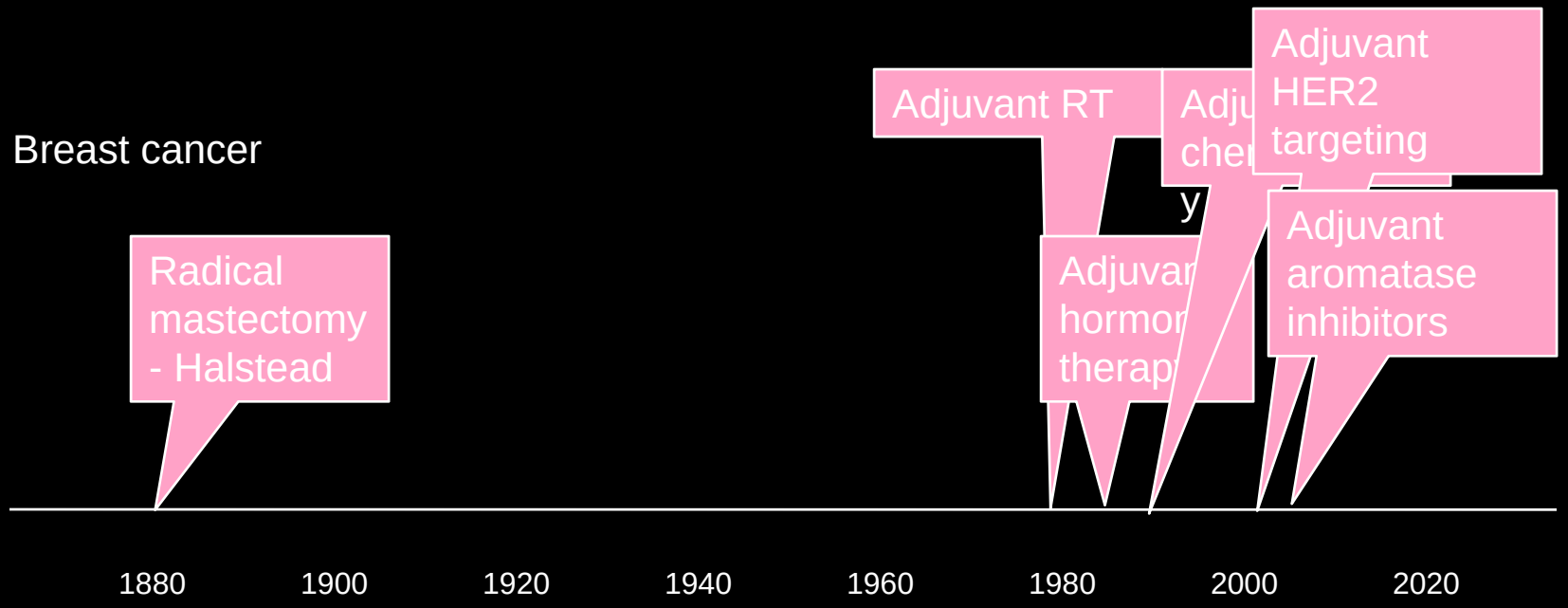
Rödel C, et al: J Clin Oncol 20: 3061-3071, 2002

Stein JP et al *JCO* Feb 1 2001: 666-675

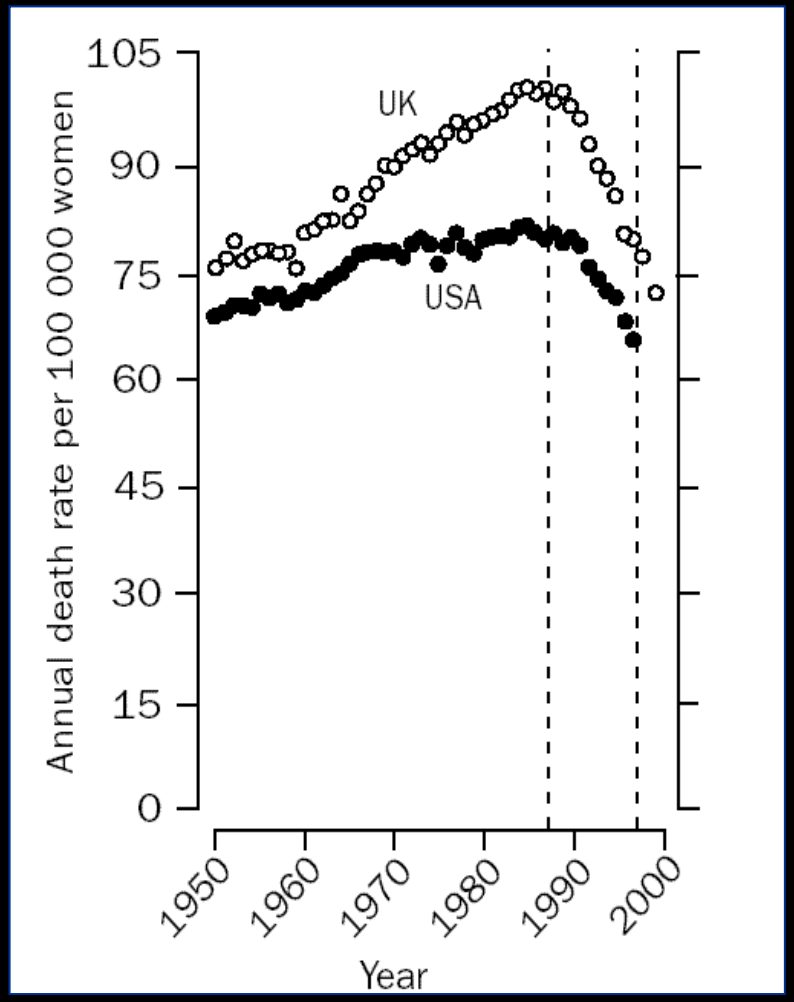
Conclusion: surgery vs. RT

- Patterns of care very variable
- Long term survival rates comparable with surgery or RT
- No compelling evidence for superiority of surgery
- Bladder cancer is a systemic disease – improvements will depend on systemic therapy

Radical therapy timelines



Mortality Rate From Breast Cancer US and the UK



Is surgery better than radiotherapy for local control?

- It doesn’t matter

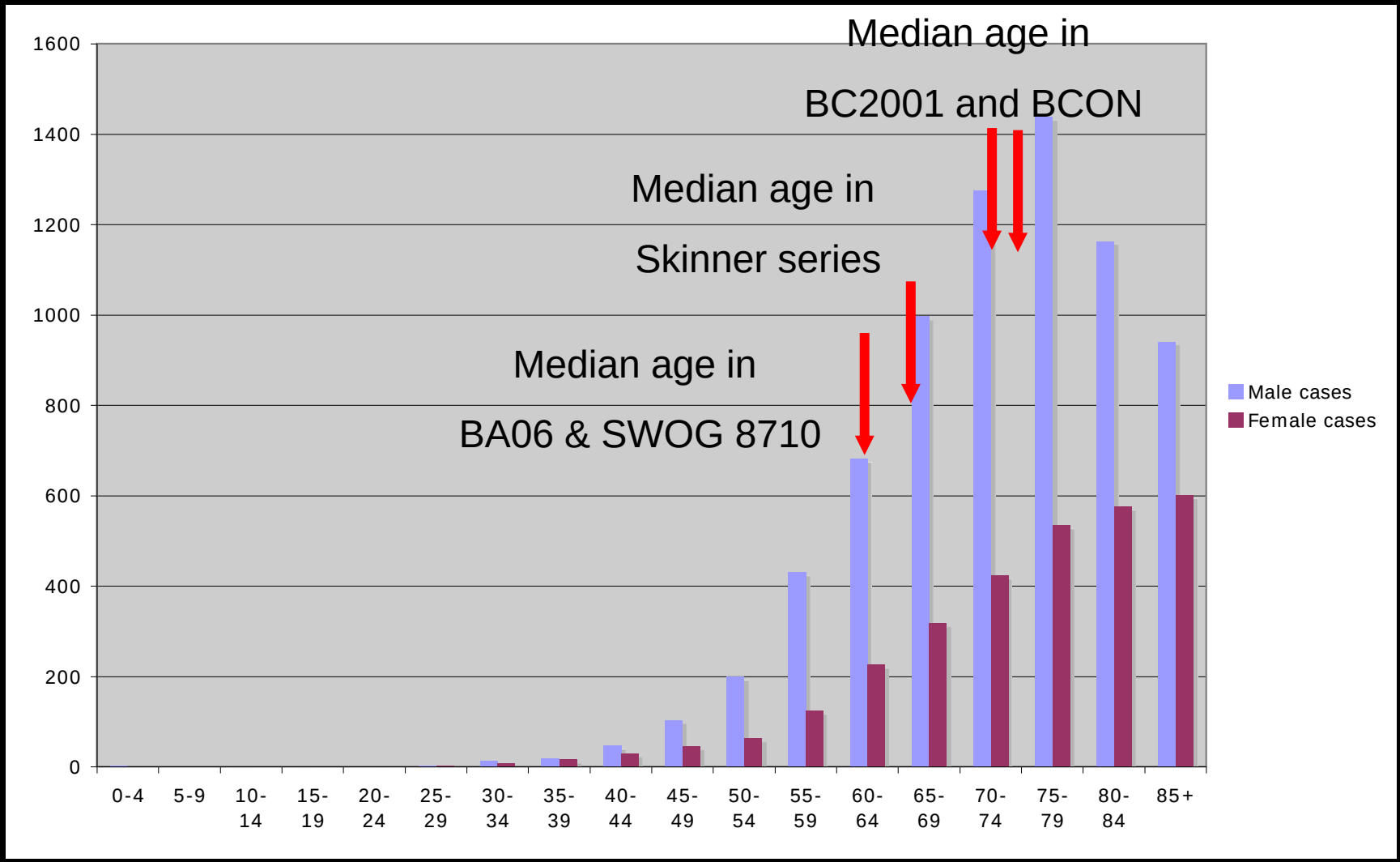
Patients unsuitable for (chemo)RT

- Poor bladder function
- Highly symptomatic bladders
- Extensive CIS
- Prior pelvic RT
- Inflammatory bowel disease
- Certain genetic disorders

Patients unsuitable for surgery

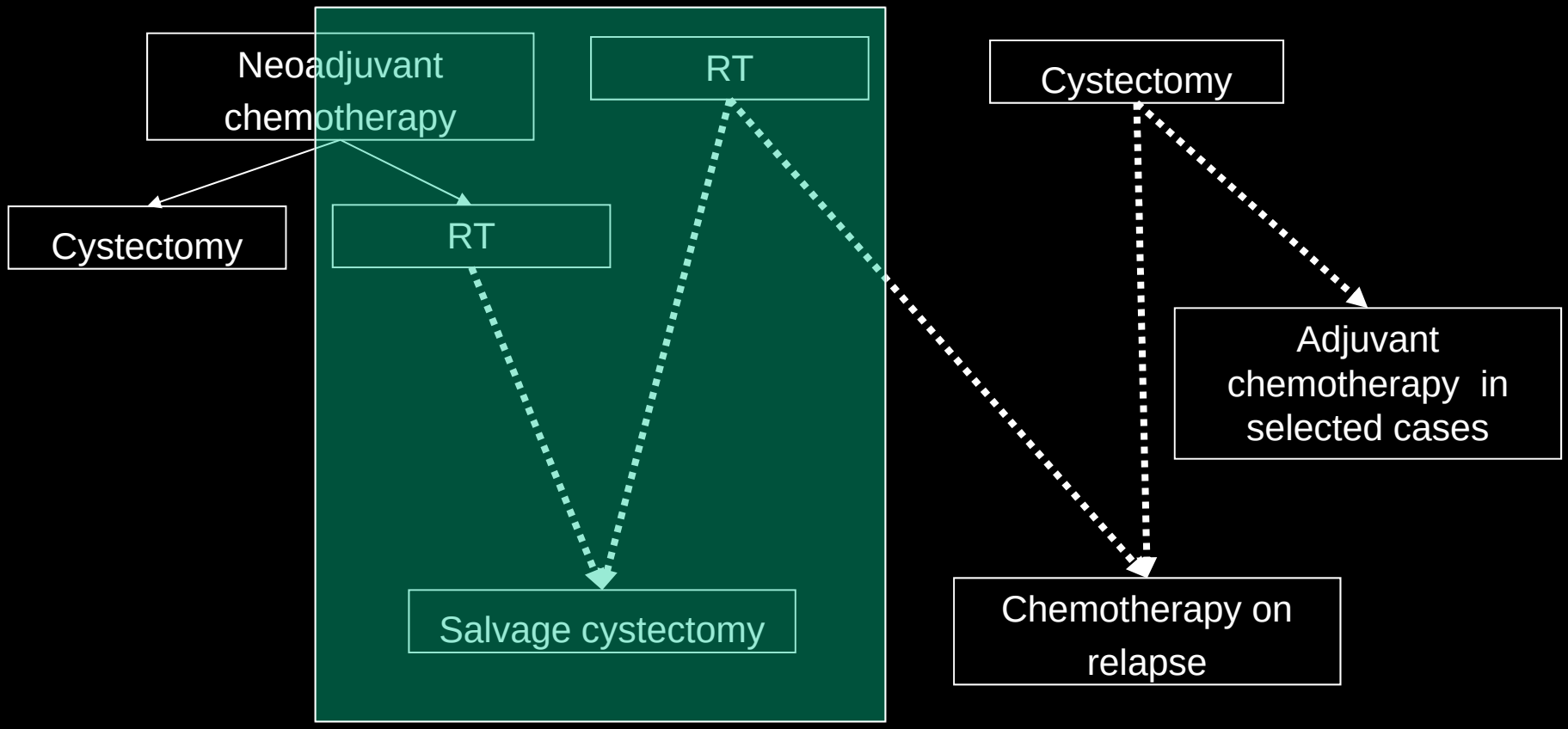
- Elderly
- Severe cardiovascular or chest problems
- Obese
- Diabetes
- Patients reluctant or unable to cope with stoma
- etc

Age at diagnosis

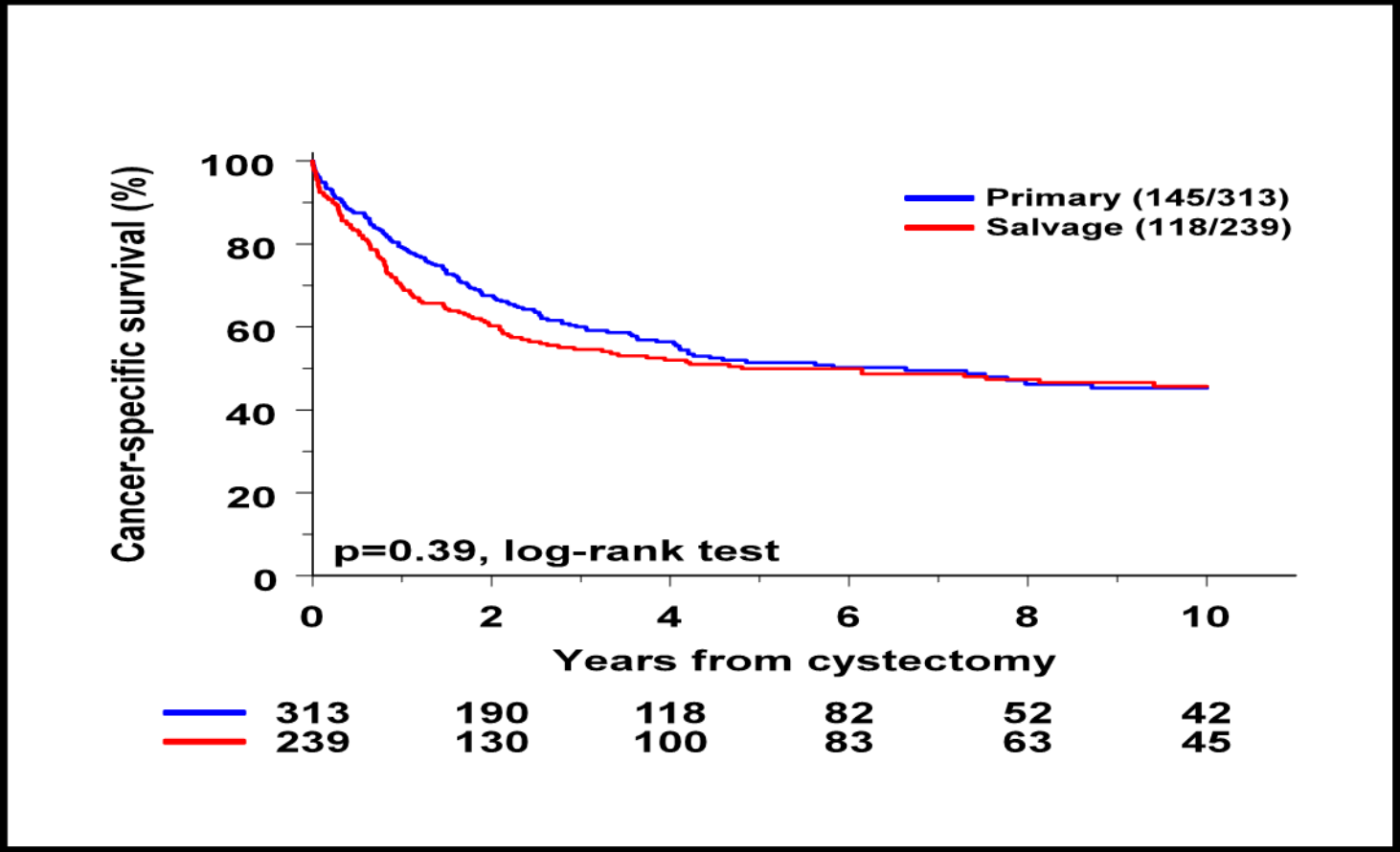


Is initial RT with salvage surgery safe and feasible?

Treatment approaches – muscle invasive disease



Primary vs Salvage Cystectomy

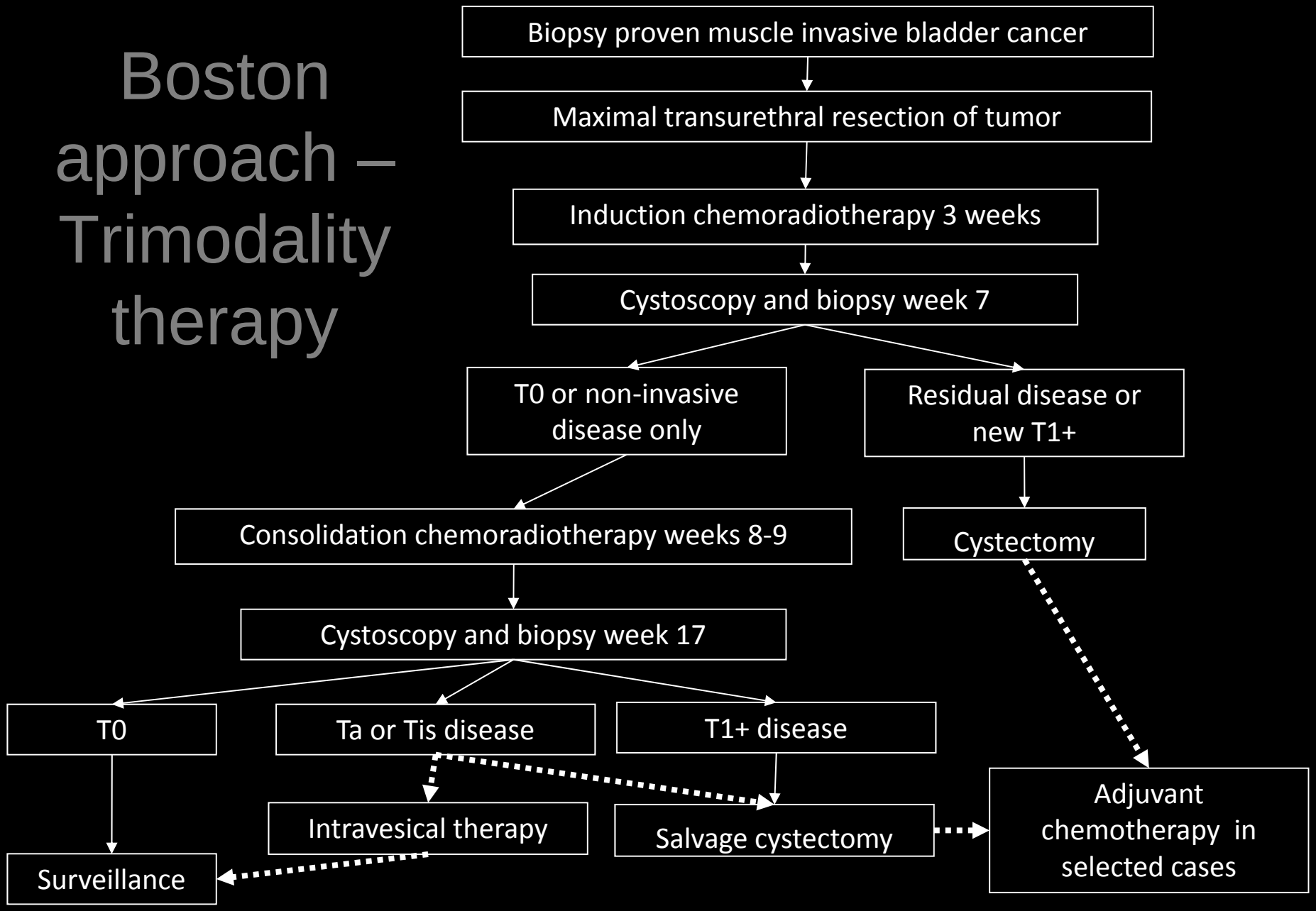


Addla et al. The Journal of Urology Vol. 181, Issue 4, Supplement, Page 633

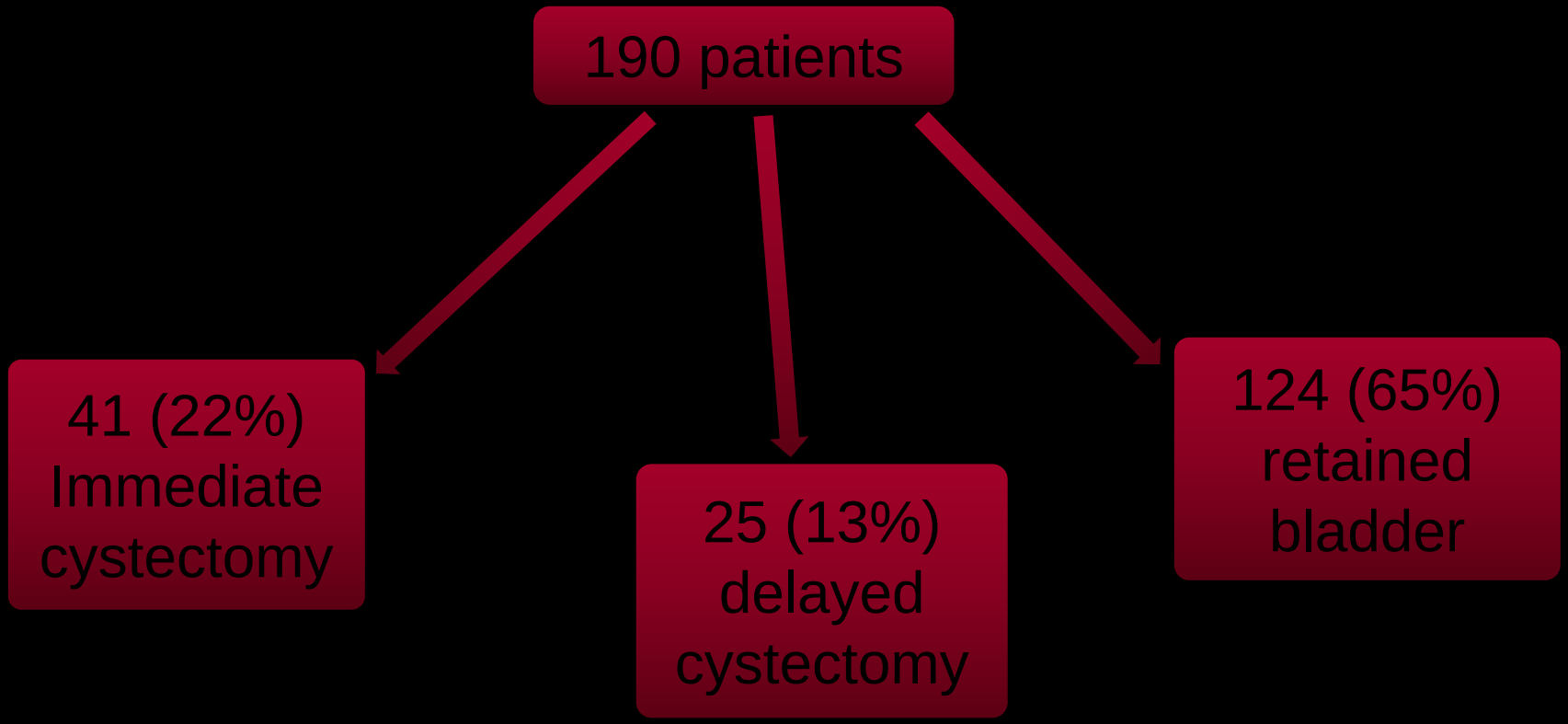
Can we select patients for bladder preservation

- By response to initial therapy
- By using biological markers

Boston approach – Trimodality therapy



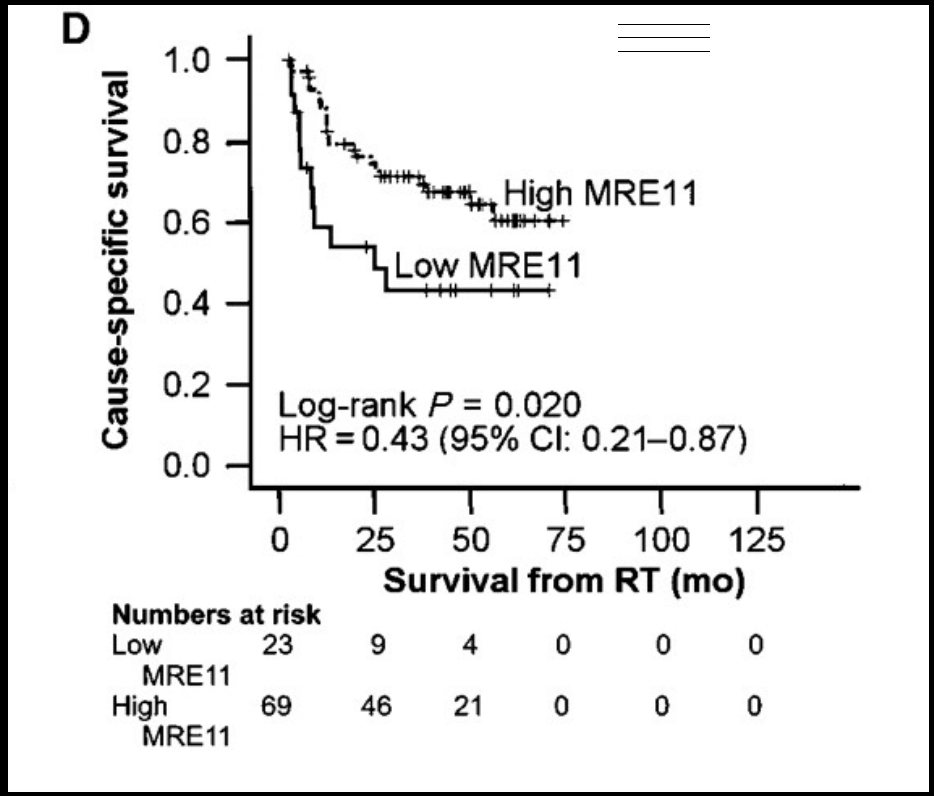
Results – Boston approach



Kaufman et al. Proc ASCO 2001 Abstract 683

MRE11

- DNA damage signalling protein
- Predictive of outcome following RT
  - 43.0% vs 71.2%, p=0.02
- Not predictive of outcome with surgery



Choudhury A, Nelson LD, Chilka S, Johnston C, Elliot F, Lowery J, Akhtar N, Bentley J, Knowles MA, Taylor C, Churchman M, Harnden P, Bristow RG, Bishop DT, Kiltie AE (2010) MRE11 expression is predictive of cause-specific survival following radical radiotherapy for muscle invasive bladder cancer. Cancer Research 15:7017-7026.

Conclusions

- Radio-sensitising agents substantially improve local control
- Risk of metastasis independent of primary therapy
- Salvage cystectomy has similar survival to primary cystectomy
- Time to re-evaluate the role of bladder preservation?