Chemo-radiotherapy in muscle invasive bladder cancer

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Overview

- Evidence base for cystectomy vs bladder preservation
- Chemo-radiotherapy vs radiotherapy alone
- Future directions:
  - Technical developments in radiotherapy
  - Trials

Cystectomy – " Gold standard"

Should be best way of treating majority of patients with a disease

Should give demonstrably better outcomes than alternatives

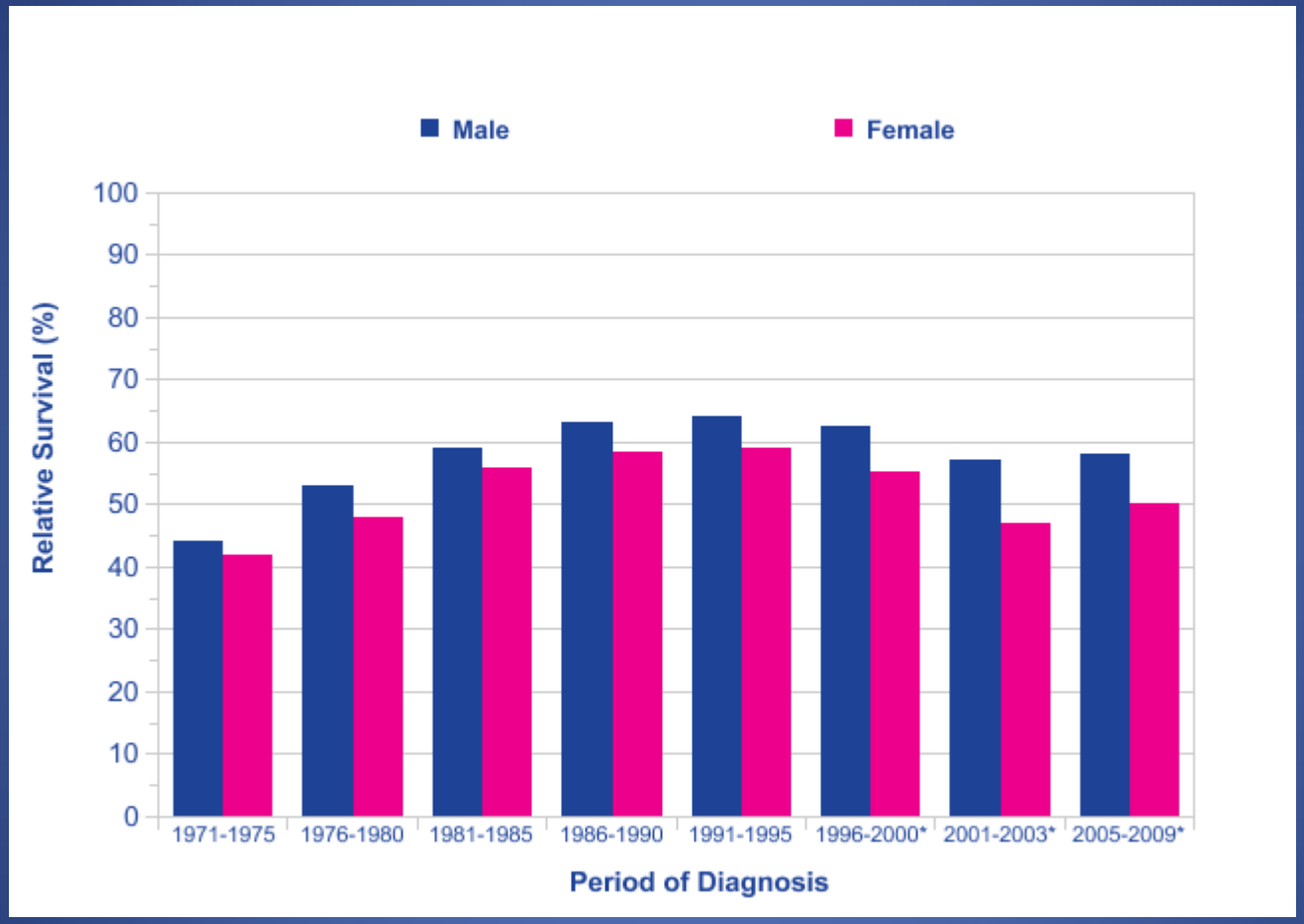
Should have solid evidence base to underpin its use

Fact

Bladder cancer outcomes have not significantly improved for 30 years

Zehnder P, Studer UE, Skinner EC, Thalmann GN, Miranda G, Roth B, Cai J, Birkhauser FD, Mitra AP, Burkhard FC, Dorin RP, Daneshmand S, Skinner DG, Gill IS. Unaltered oncological outcomes of radical cystectomy with extended lymphadenectomy over three decades. BJU Int 2013;112:E51-8

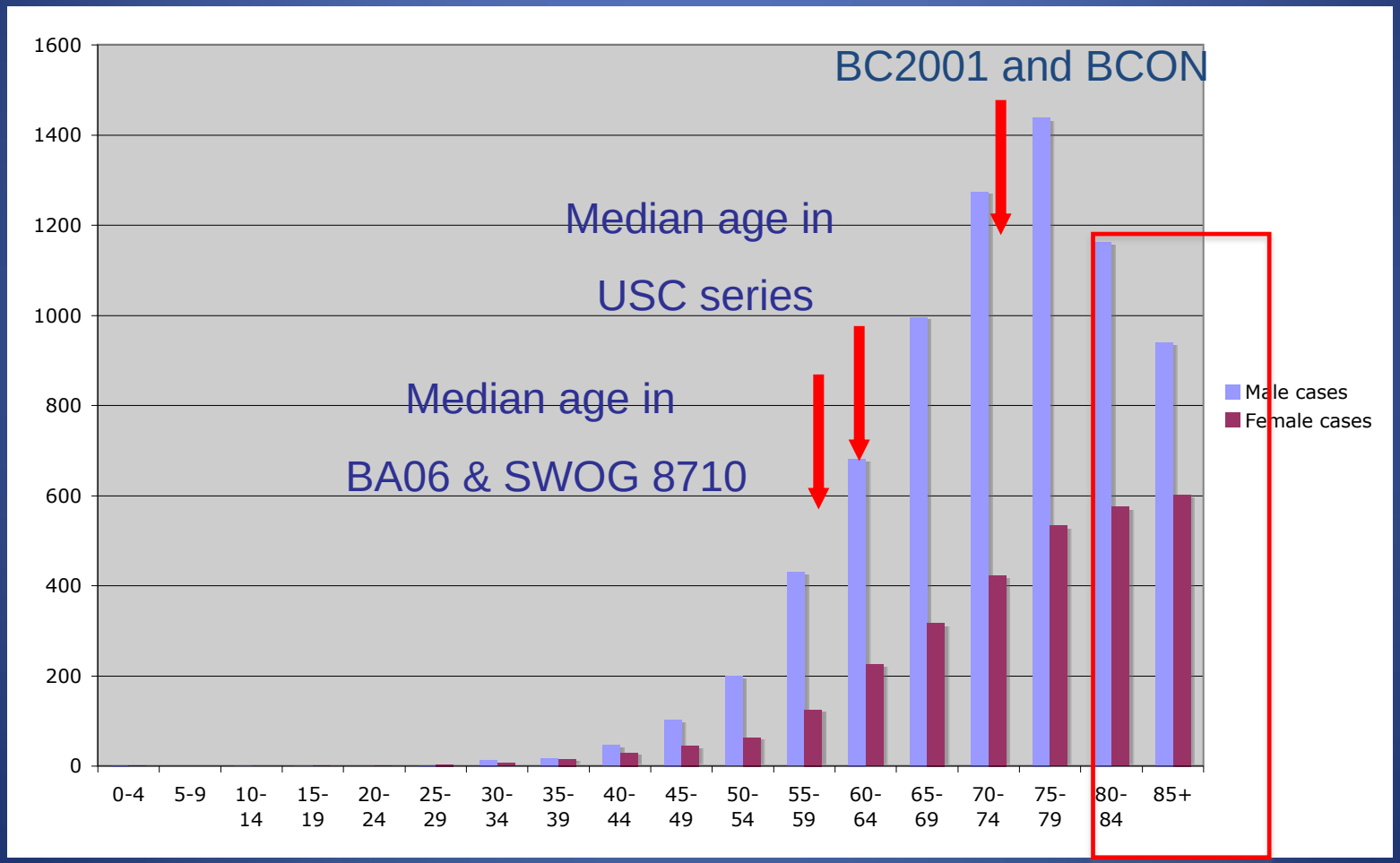
Age standardised 5 year survival rates in UK



Prepared by Cancer Research UK - http://info.cancerresearchuk.org/cancerstats/

The best way of treating majority of patients?

Age at diagnosis



Age distribution of cystectomy series – UK data

- Median age: 68
- Interquartile (midspread) range: 62-74
- Aged > 80y: 6%
- Incident cases >80y: approx 20%
- Cystectomy as primary treatment >80 years: 7%

Is survival better with surgery?

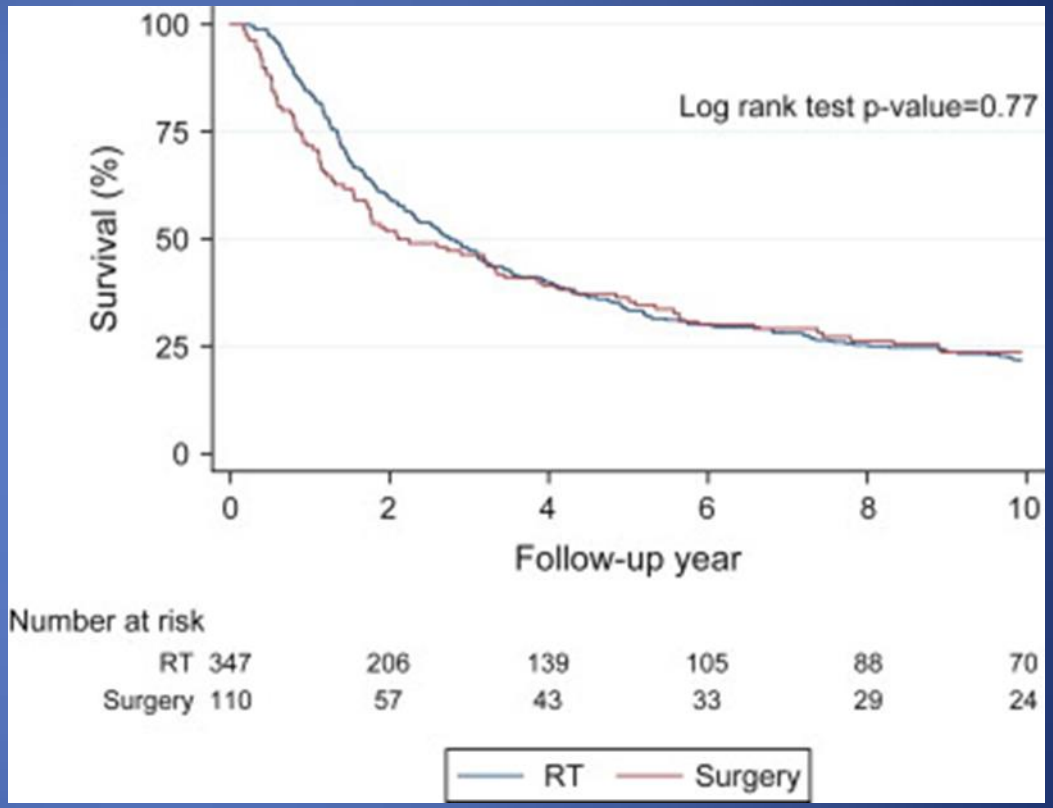
- Should give demonstrably better outcomes than alternatives
- Should have solid evidence base to underpin its use

Survival from UK cancer registry

453 UK patients, 1993-6

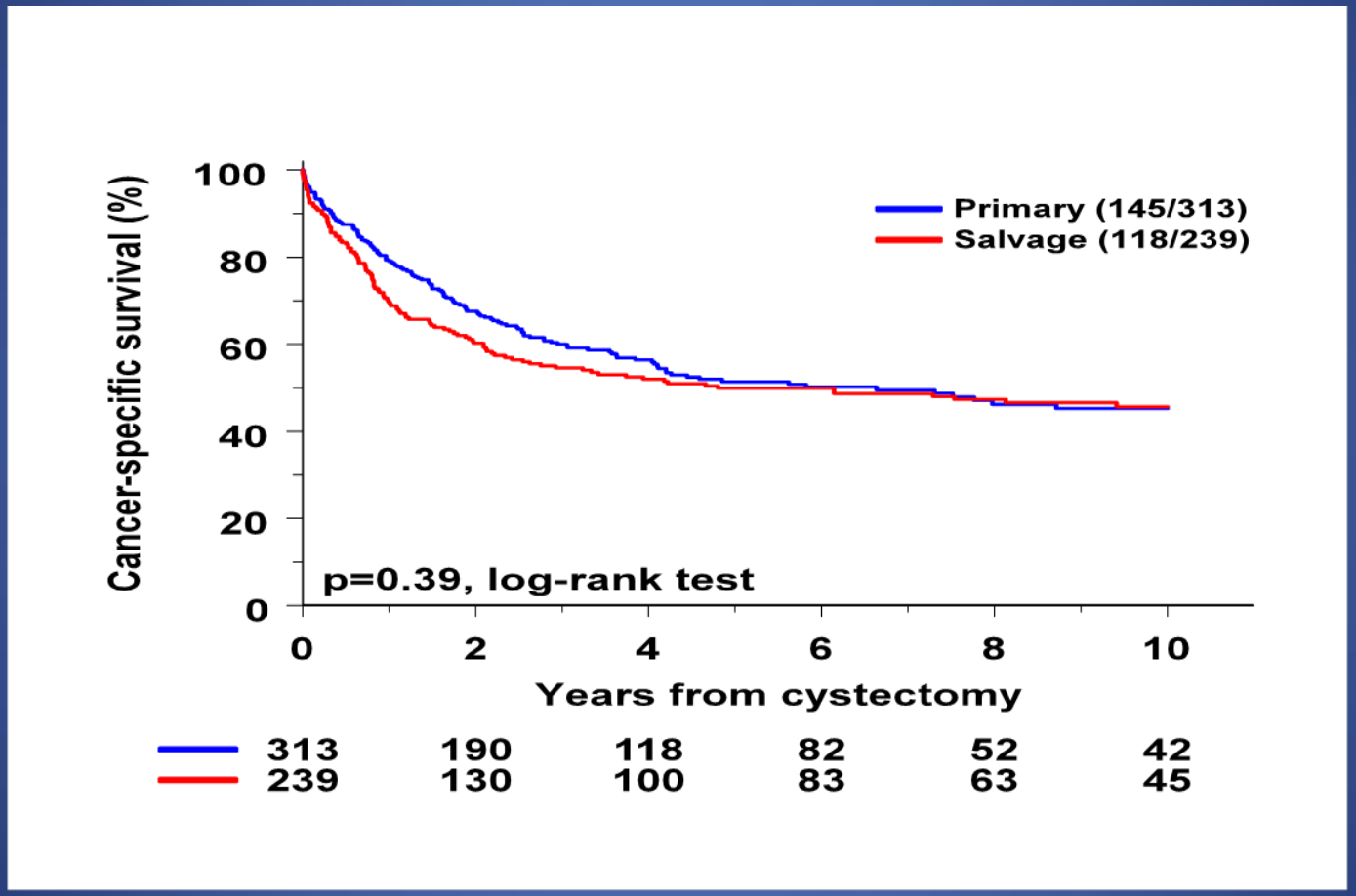
Ratio RT : Cystectomy 3:1

10 year survival:
RT 22% Surgery 24%



Munro NP, Sundaram SK, Weston PM, et al. A 10-year retrospective review of a nonrandomized cohort of 458 patients undergoing radical radiotherapy or cystectomy in Yorkshire, UK. Int J Radiat Oncol Biol Phys 2010;77:119-24.

Primary vs Salvage Cystectomy



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

Are complication rates higher with Salvage Cystectomy?

Complication	1970–2005		
	Salvage cystectomy, % (No.)	Primary cystectomy, % (No.)	*p* value
Wound infection	5 (21)	3.8 (16)	0.47
Haemorrhage	1.7 (7)	0.5 (2)	0.17
Anastomotic bowel leak	1.4 (6)	1.1 (5)	0.98
Wound dehiscence	4.8 (20)	4.2 (18)	0.83
Urinary leak	3.8 (16)	4 (17)	0.89

* More than 30 d postoperative; there was no statistically significant difference in either of the groups (χ^2 test).

No

Differential complication rates following Radical Cystectomy in the irradiated and non-irradiated pelvis. Vijay AC et al Eur Urol 57 (2010) 1058-1063

Canadian Cancer Registry – bladder cancer

- Variations in the use of cystectomy vs. radical radiotherapy were not associated with difference in survival
- Survival differences related to tumour related factors

The management and outcome of bladder carcinoma in Ontario1982-1994. Hayter CR, Paszat LF, Groome PA, et al: Cancer 89: 142-151, 2000

Survival Cystectomy vs Radical Radiotherapy

- Stein *et al*: 1054 Cystectomy patients 5 &10ys 60% and 43%
- Rödel *et al*: 415 RT patients 5 &10ys 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, 5ys survival:

Radical Cystectomy 47%
Conservative therapy 45%

Stein JP et al *JCO* Feb 1 2001: 666-675
Rödel C, et al: J Clin Oncol 20: 3061-3071, 2002

Is survival better with surgery?

No

Choice of Treatment

- Surgery and radiotherapy data relate to different segments of the population
- Neoadjuvant therapy data also mainly relate to younger patients
- Hence age/fitness is important factor in treatment decisions

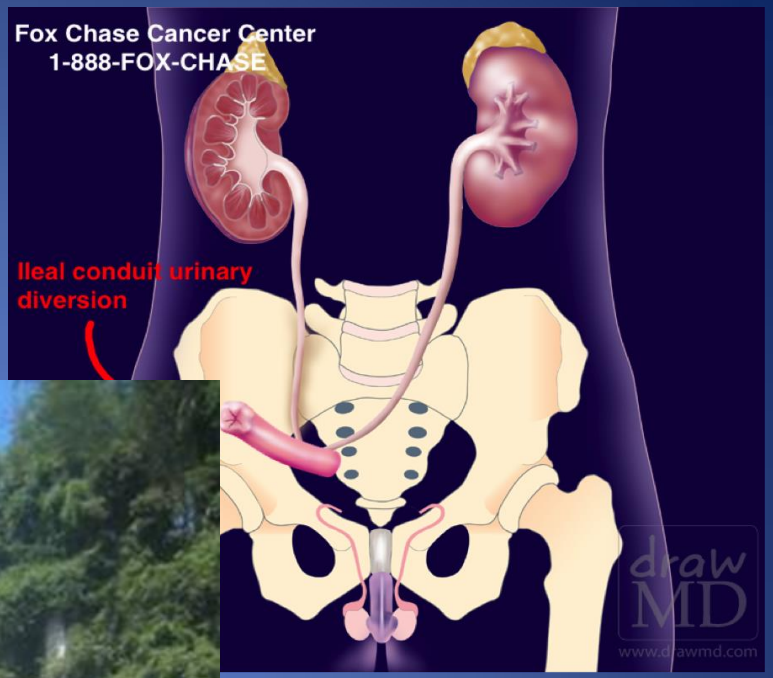
Patients unsuitable for surgery

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

Patients unsuitable for (Chemo) Radiotherapy

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

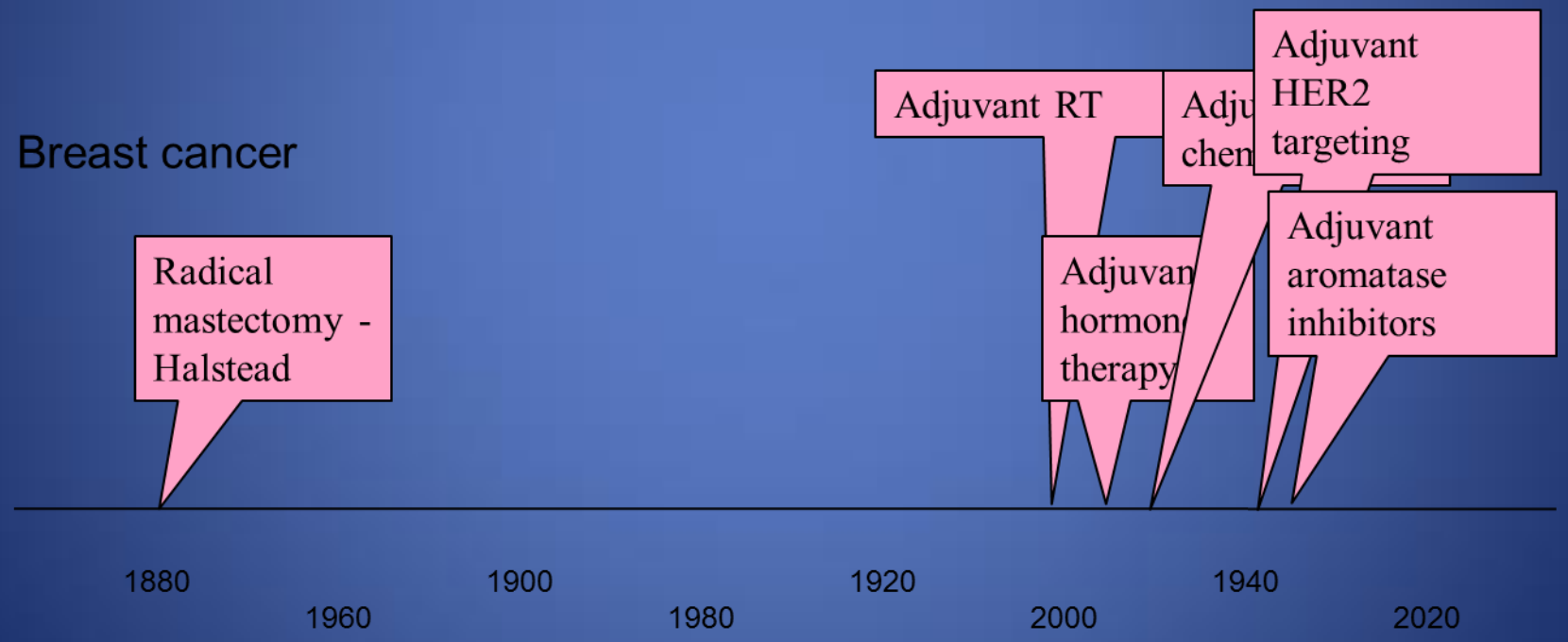
Bladder preservation


Fox Chase Cancer Center
1-888-FOX-CHASE
Ileal conduit urinary diversion
draw MD
www.drawmd.com

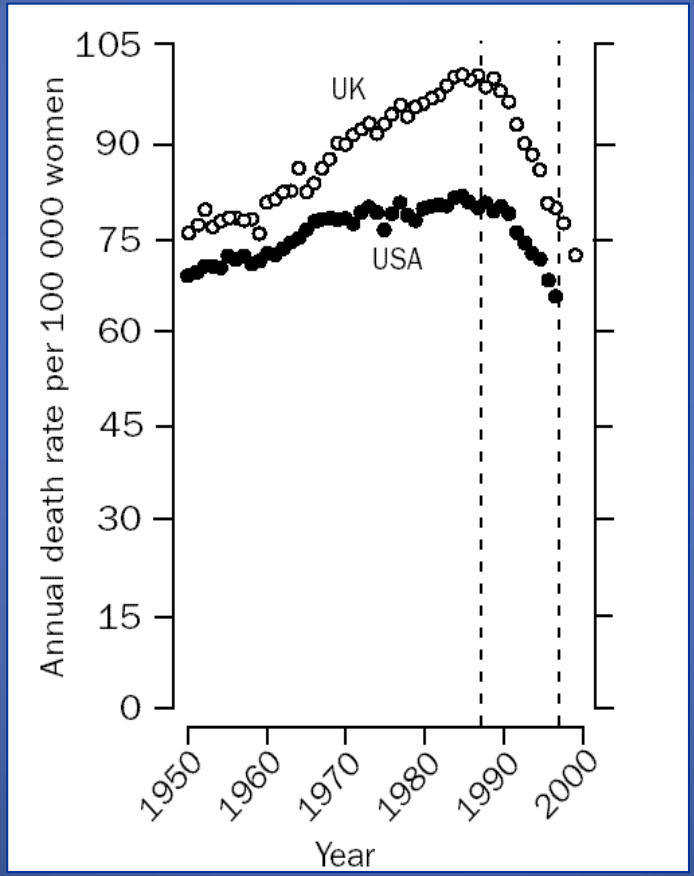
Bladder cancer is systemic disease

- No plateau in survival curves
- Patients die with metastatic disease
- Treatment needs to address both local control and systemic disease
- Most important factor for future study is how to improve systemic control

Breast cancer therapy timelines



Mortality Rates From Breast Cancer US and the UK

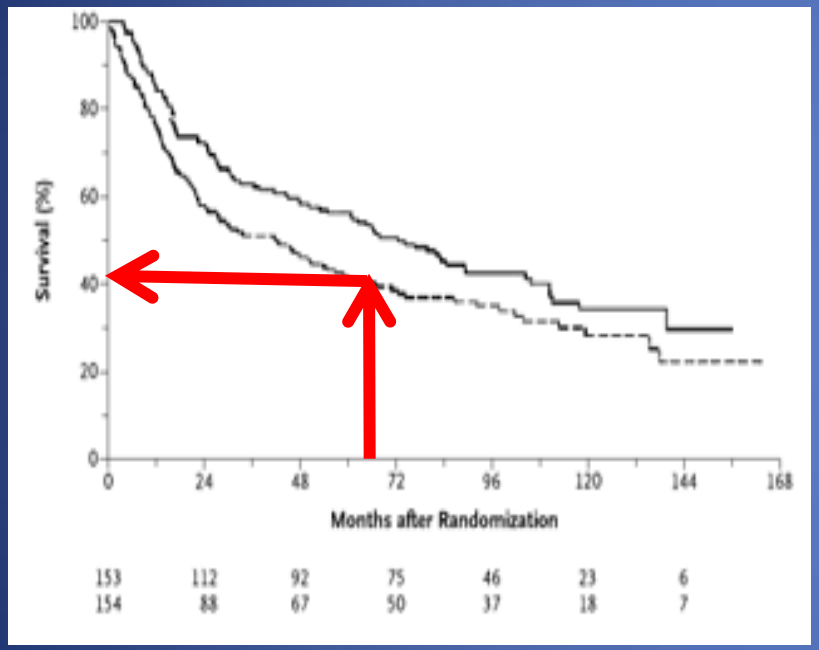


Organ preservation revisited

	Anal cancer	Bladder cancer
Key study	ACT 1	BC2001
Treatment	5FU/MMC Radiotherapy 60Gy/31f	5FU/MMC Radiotherapy 64Gy/32f
Loco regional failure	~29%	33% (18%)
Overall survival	58%	50%
Salvage/alternative treatment	Abdomino-perineal resection/colostomy	Cysto/prostatectomy Ileostomy
Ref	Northover et al 2010 BJC 102 p1123-8	James et al 2012 NEJM 2012;3661477-88.

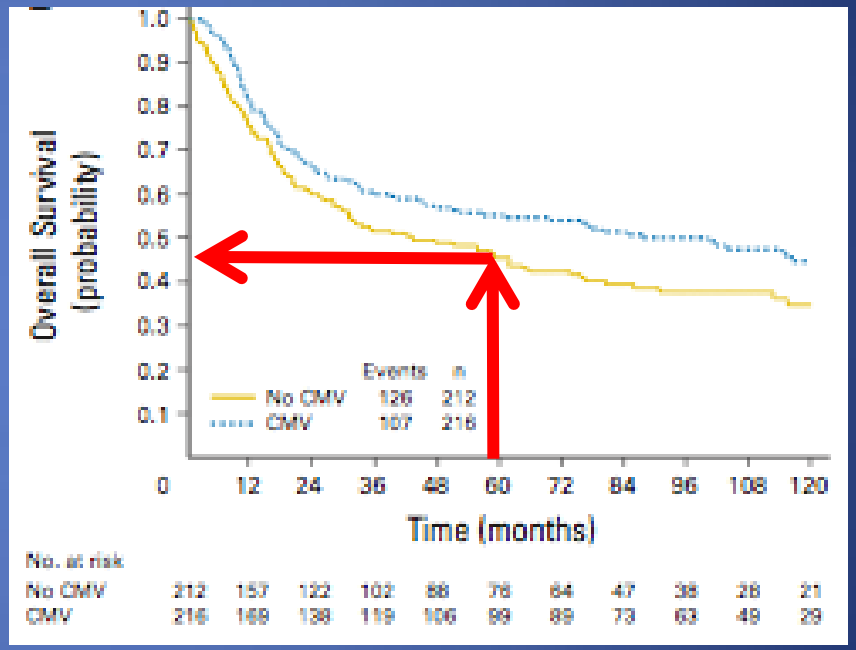
Neoadjuvant Chemotherapy

US Intergroup Trial



Surgery +/- MVAC chemotherapy

BA06 EORTC 30894

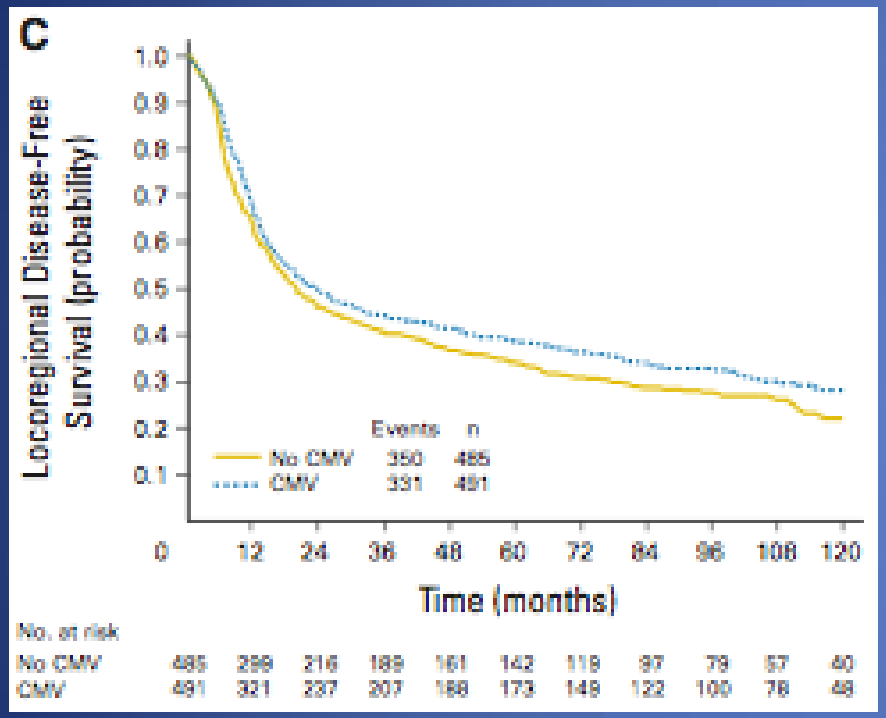


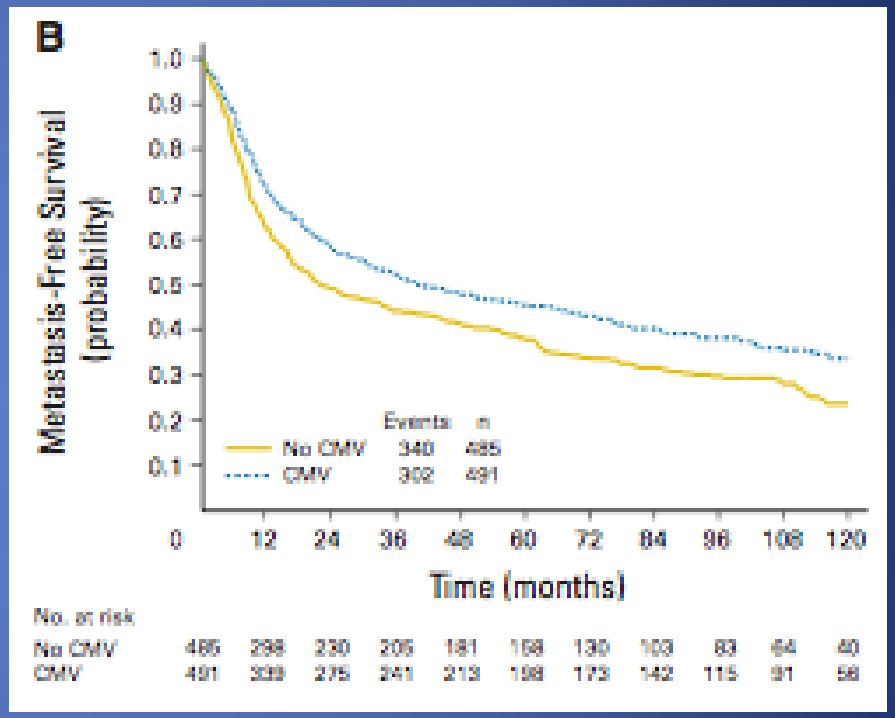
Surgery or RT +/- CMV chemotherapy

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.

MRC/EORTC Trial - Loco-regional and metastatic control





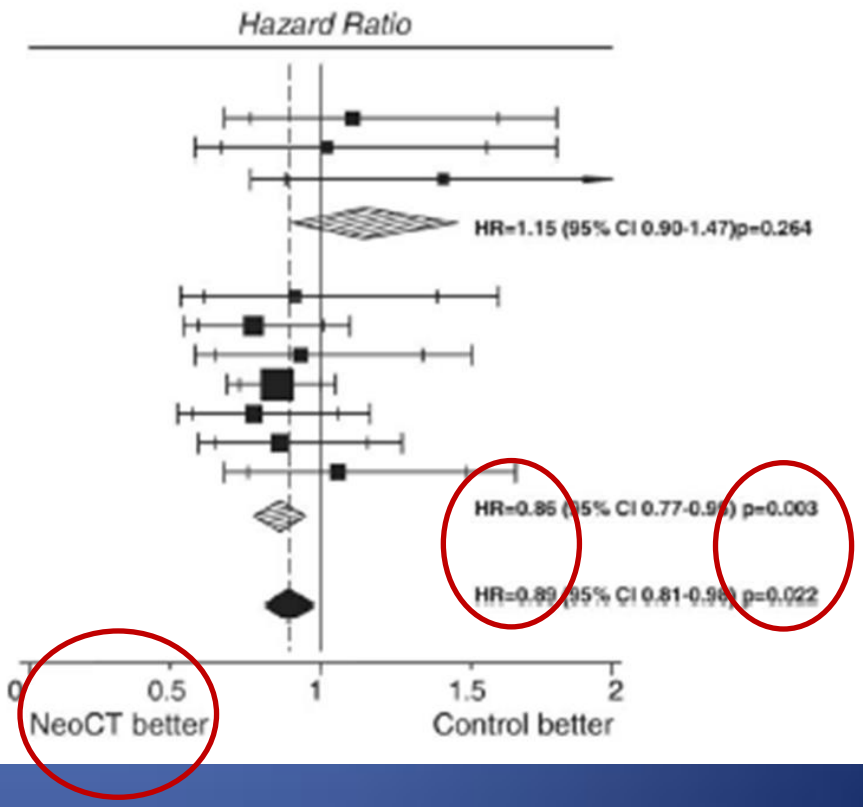
Locoregional control

Metastatic control

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.

Neoadjuvant Chemotherapy – meta analysis

	(no. events/no. entered) CT	Control	O-E	Variance
Single agent platinum				
Wallace [2]	59/83	50/76	2.74	27.18
Martinez-Pineiro [3]	43/62	38/59	0.33	20.11
Raghavan [2]	34/41	37/55	5.85	16.51
Sub-total	136/186	125/190	8.92	63.80
Platinum-based combinations				
Cortesi unpublished	43/82	41/71	-1.87	20.84
Grossman [9]	98/158	108/159	-13.61	51.00
Bassi [5]	53/102	60/104	-1.95	28.13
MRC/EORTC [6]	275/491	301/485	-23.69	143.61
Malmström [8]	68/151	84/160	-9.97	37.94
Sherif [8]	79/158	90/159	-6.37	42.18
Sengeløv [7]	70/78	60/75	1.79	31.96
Sub-total	686/1220	744/1213	-55.67	355.65
Total	822/1406	869/1403	-46.75	419.45

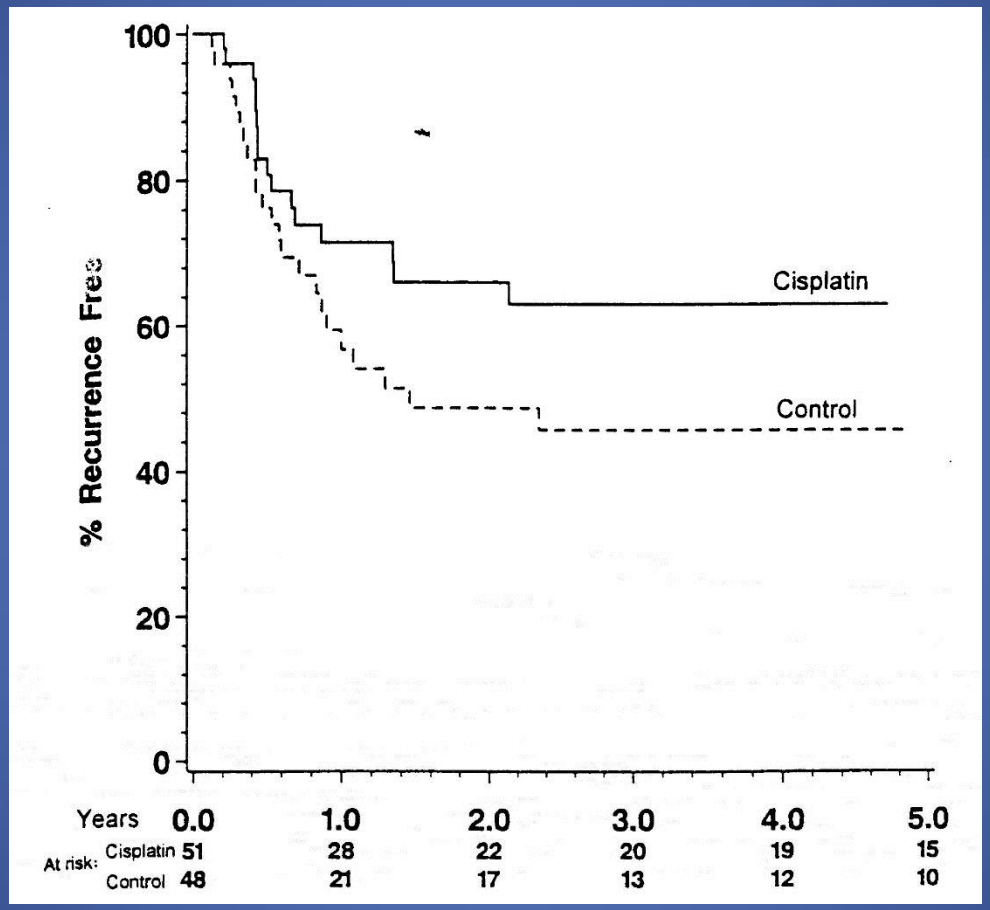


ABC MAC 2003 Lancet 361 p1927-1934
ABC MAC 2005 Eur Urol 48:202-206

Synchronous Chemo-Radiotherapy

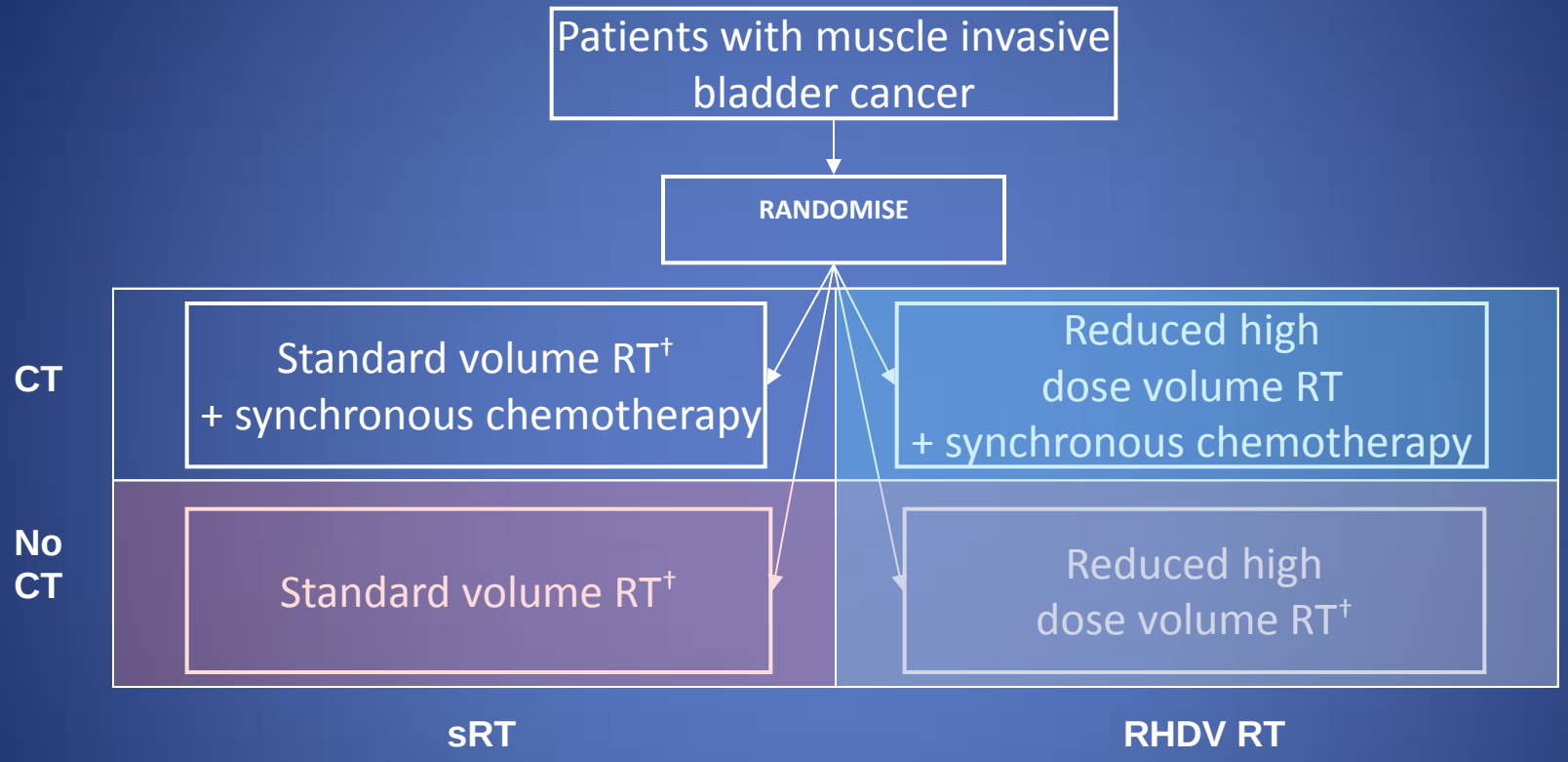
- Numerous phase I/II studies showing feasibility and safety
- Three phase III studies
  - RT vs RT + Cisplatinum (NCIC)
  - RT vs RT + 5FU/MMC (BC2001)
  - RT vs RT + nicotinamide/carbogen (BCON)

Cisplatin and RT +/- surgery



Coppin CM, Gospodarowicz MK, James K, et al. Improved local control of invasive bladder cancer by concurrent cisplatin and preoperative or definitive radiation. Journal of Clinical Oncology 1996;14:2901-7

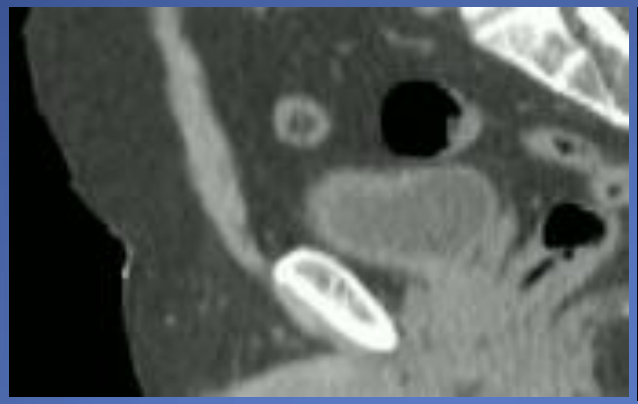
BC2001: Trial design



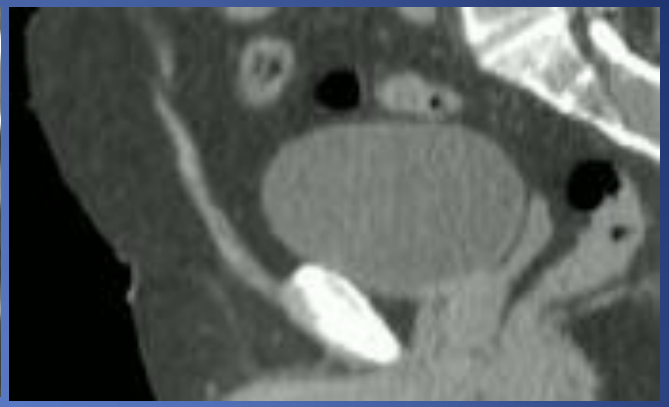
Pragmatic design: Centres could offer double or either single randomisation

- Bladder radiotherapy challenges

Deformable

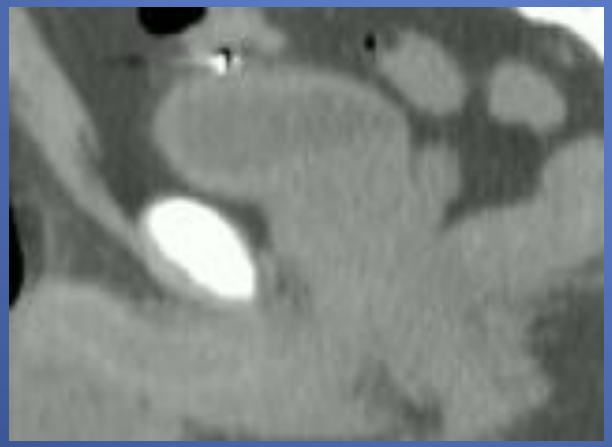


Empty bladder

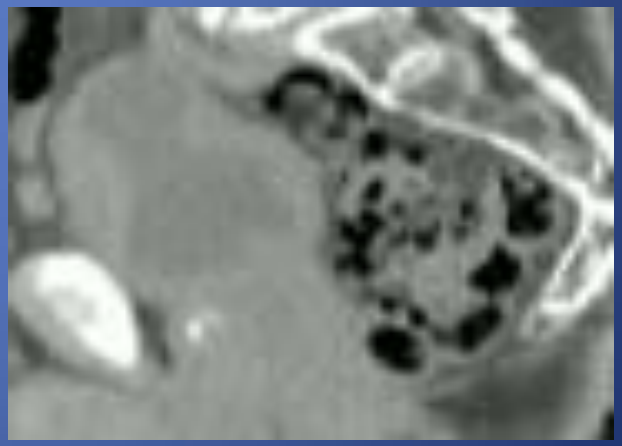


'Empty' bladder

Mobile

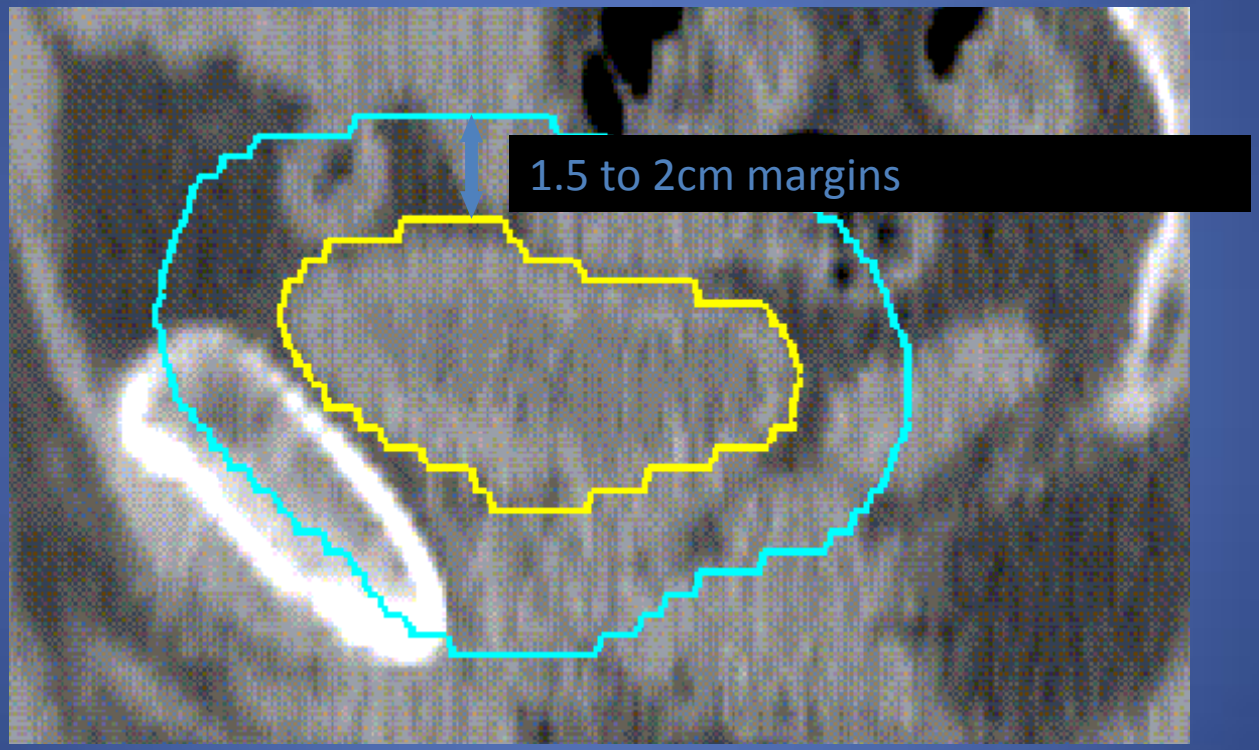


Empty rectum

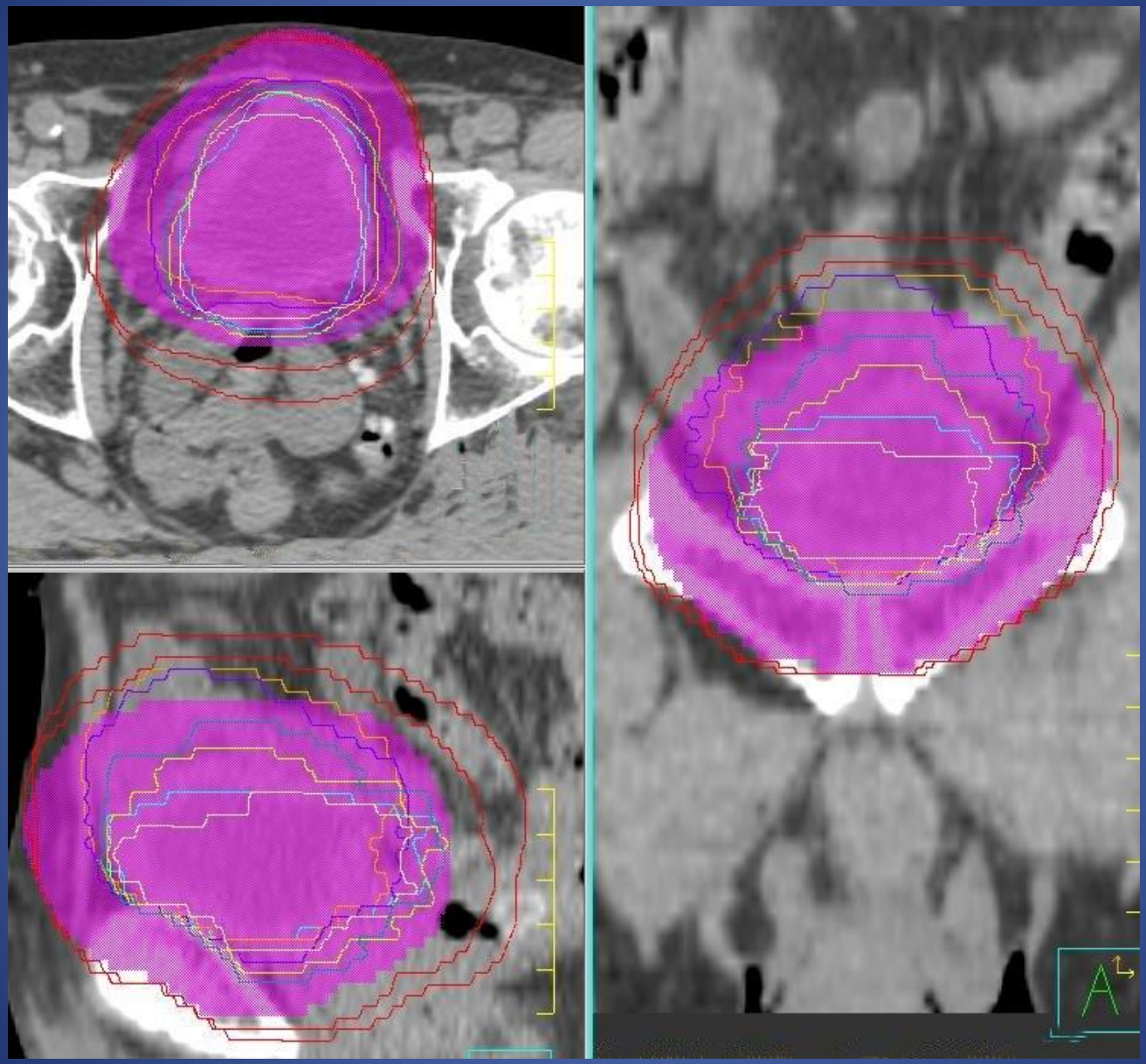


Full rectum

Conventional Radiotherapy-Empty Bladder

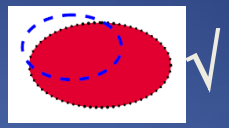


Courtesy of Fiona McDonald

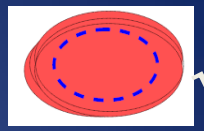

A

Cone beam CT

Systematic error

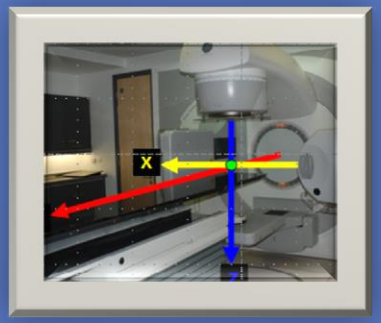


Random error

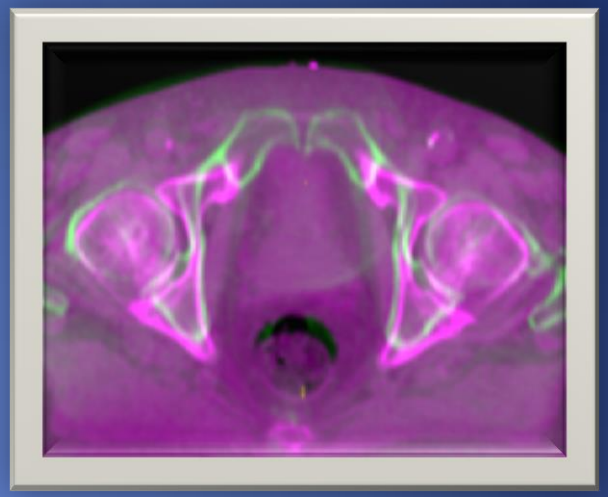


Planning CT

On-line correction strategy

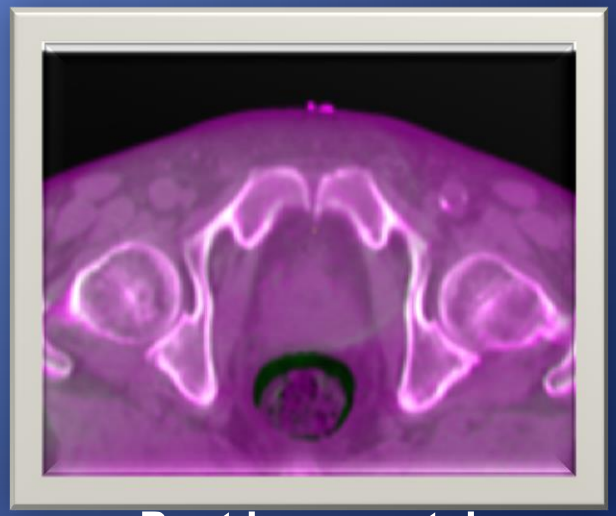


3 planes of couch adjustability



Pre bone match

Cone beam CT



Post bone match

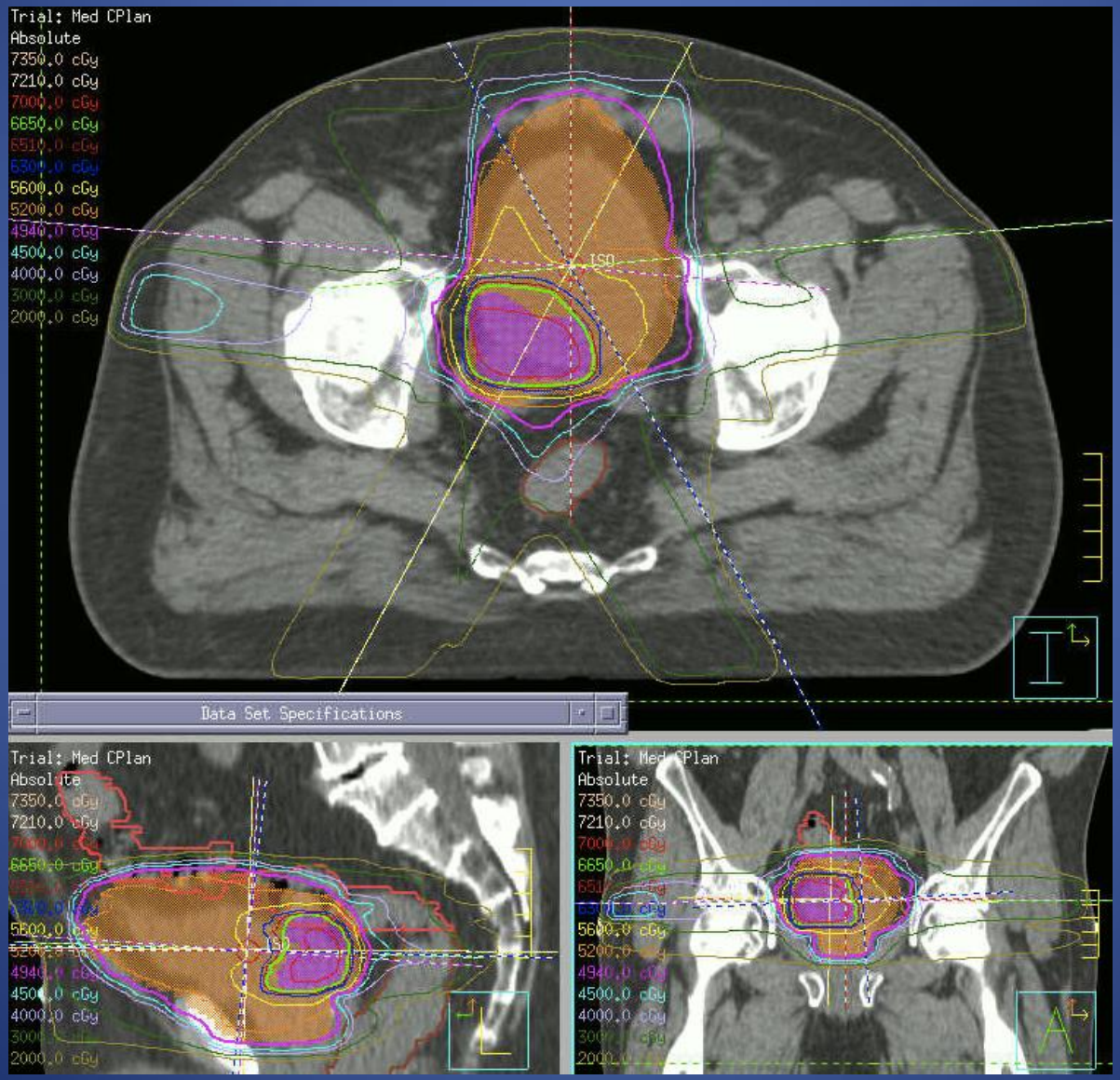
CTV coverage according to margin and set up technique

Foroudi et al 2012 Clin Oncol 24 673-681

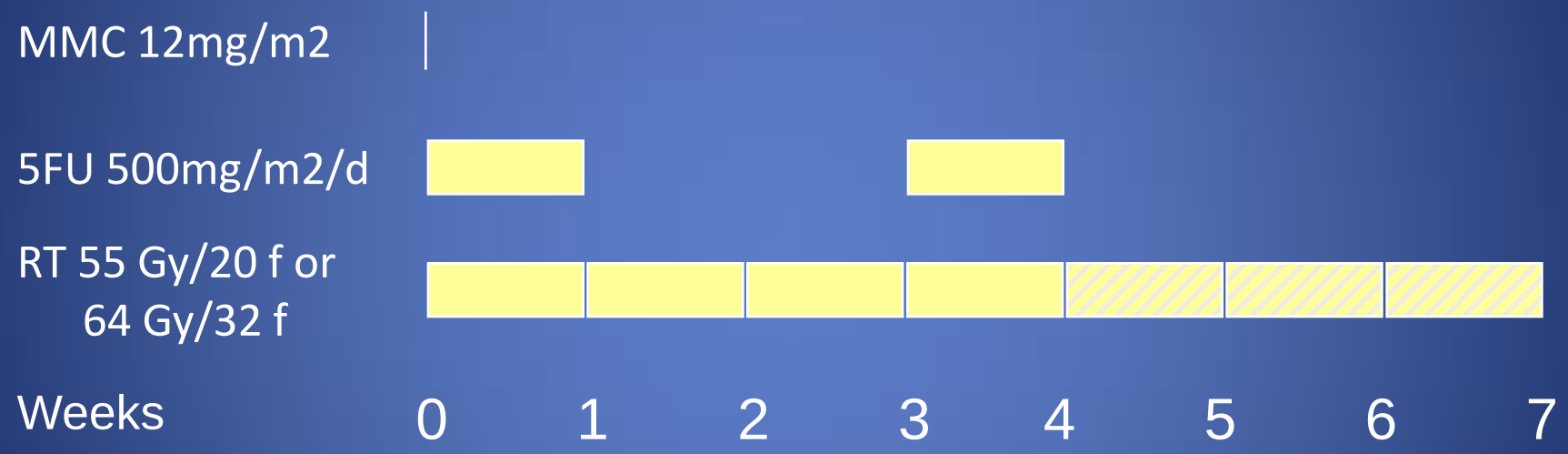
	CTV+0.5	CTV+1.0	CTV+1.5	CTV+2.0	CTV+2.5
Skin	0	19	56	**93**	**96**
Bone	0	41	63	**89**	**96**
Soft tissue	52	**89**	**96**	**100**	**100**

Retrospective analysis of 30 patients having daily CBCT set up by skin, bone or soft tissue match

Concomitant boost (partial bladder)



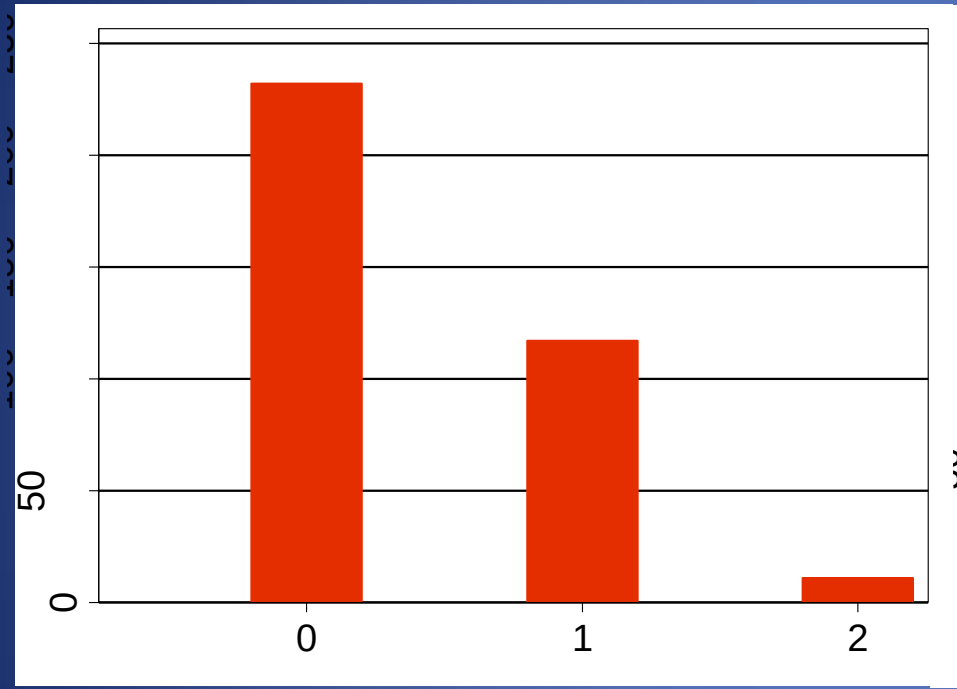
Chemotherapy regimen



Target volume tumour + bladder + 1.5-2cm
Chemotherapy via peripherally inserted central line as outpatient therapy

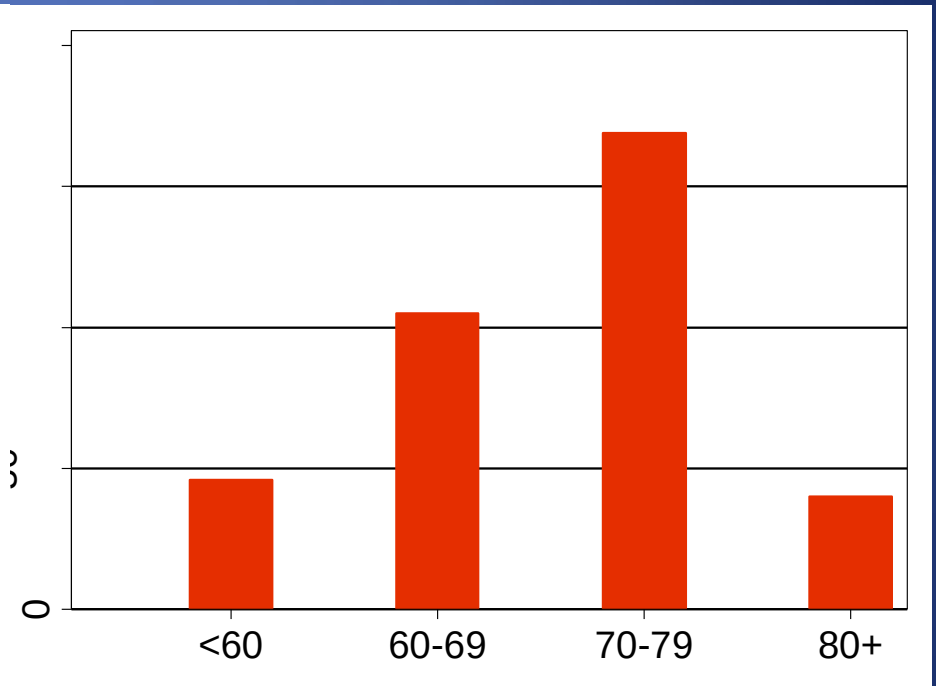
Patient demographics

Performance status



Male = 289/360 (80%)

Age at randomisation



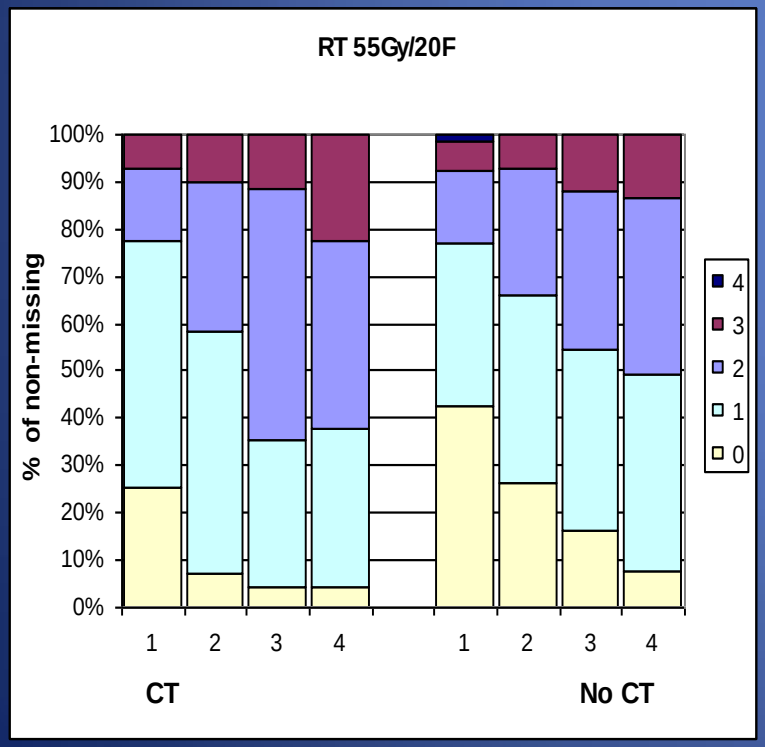
- Mean (SD) 70.5 (8.2) years
- Median (IQR) 71.9 (64.1 - 76.2) years
- Older than patients in previously published trials including SWOG 8710[1](median 63 y) and BA06[2] (median 64 y)

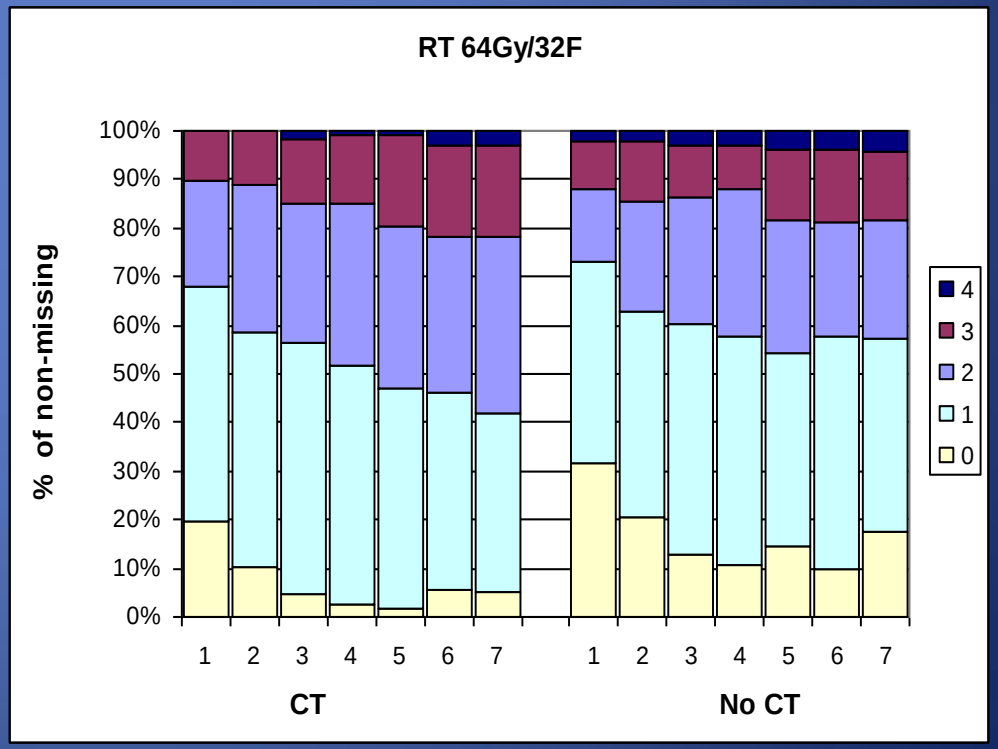
1. Grossman et al NEJM 2003 Volume 349:859-866
2. Lancet 1999; 354: 533-40

Acute toxicity

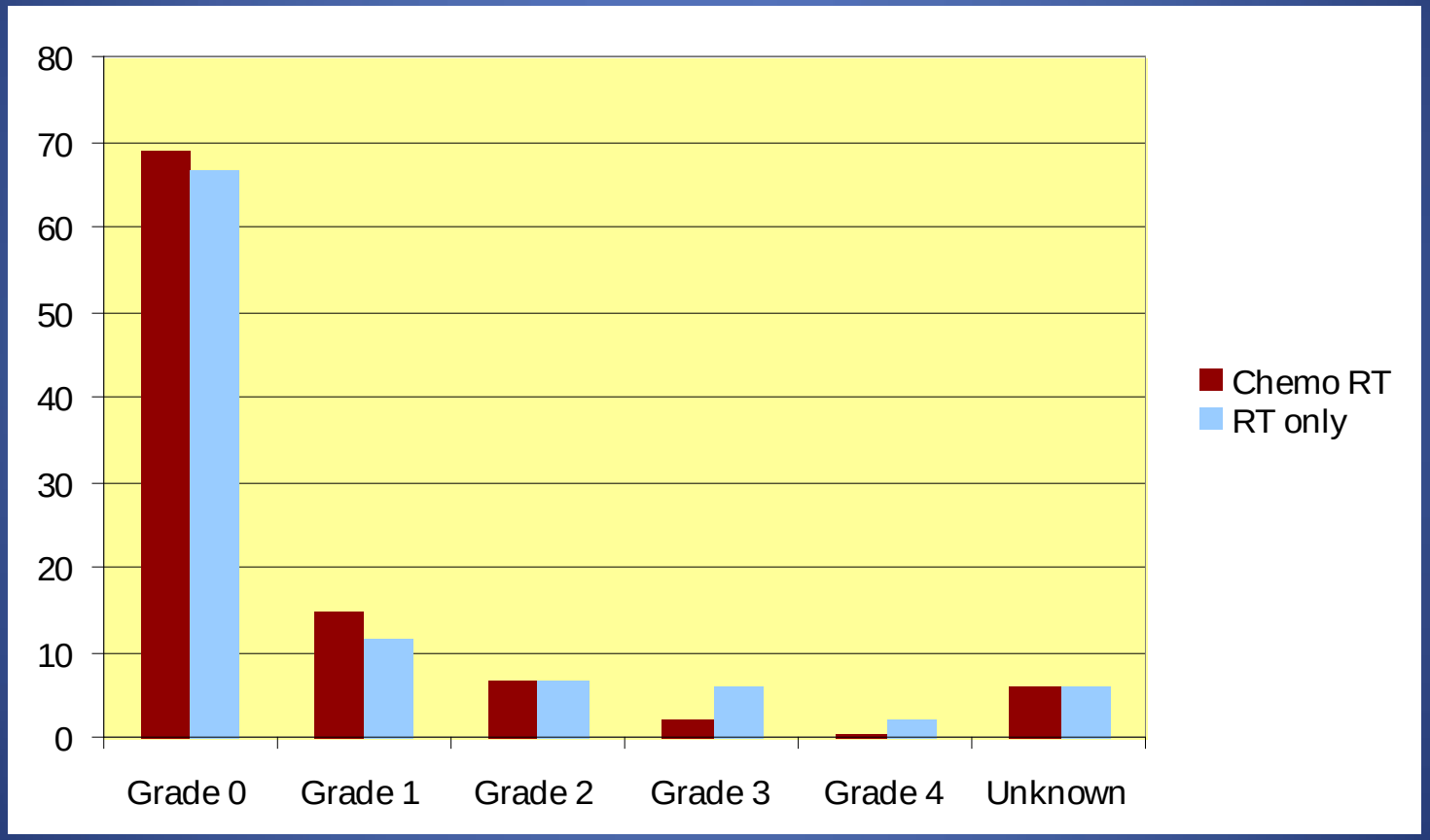
- Proportions with a grade 3/4 at any time on treatment:
- 62/179 (34.6%) CT vs. 49/172 (28.5%) No CT (% of pts with data)
- Stratified Chi-square test p=0.19

Worst grade of on-treatment toxicity by week



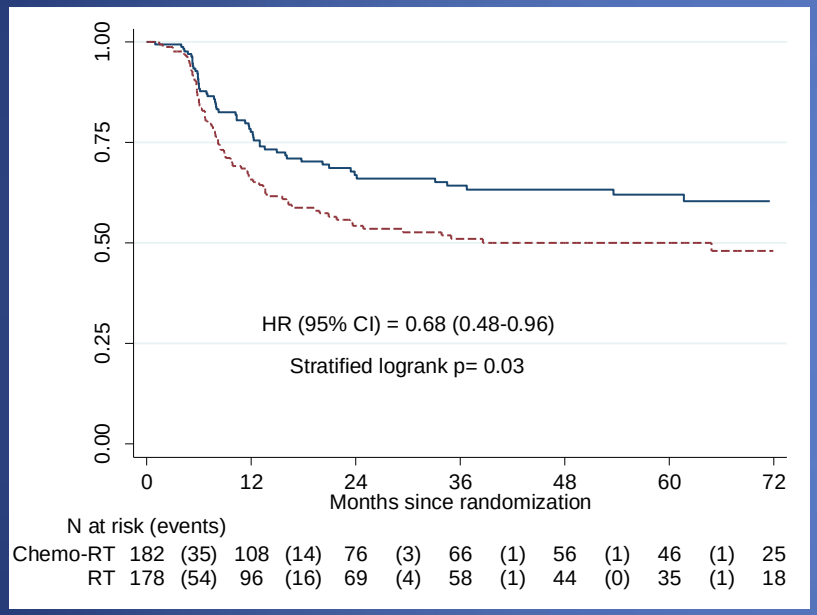


RTOG 6 month toxicity outcomes

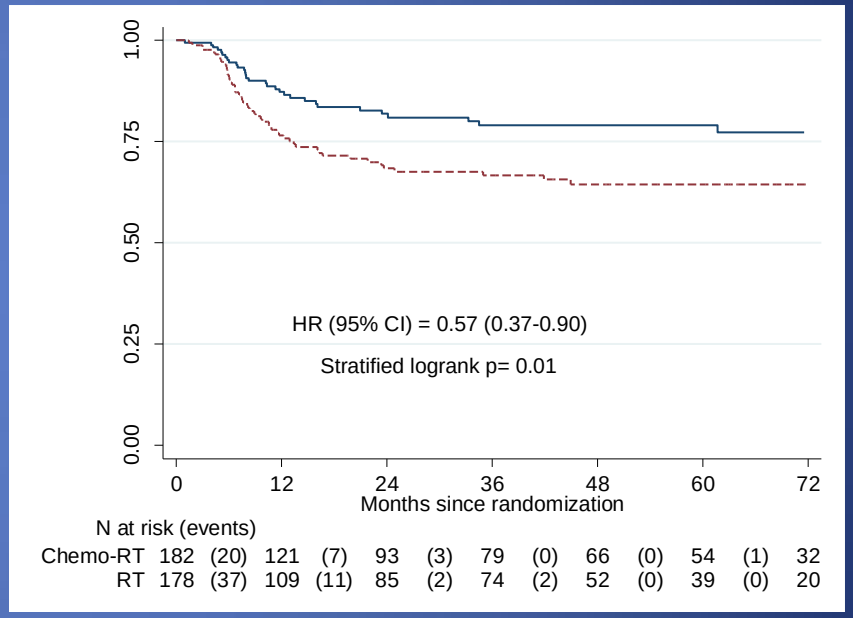


n= 291, 145 RT only, 146 chemo-radiotherapy

Loco-regional disease free survival in chemotherapy randomisation



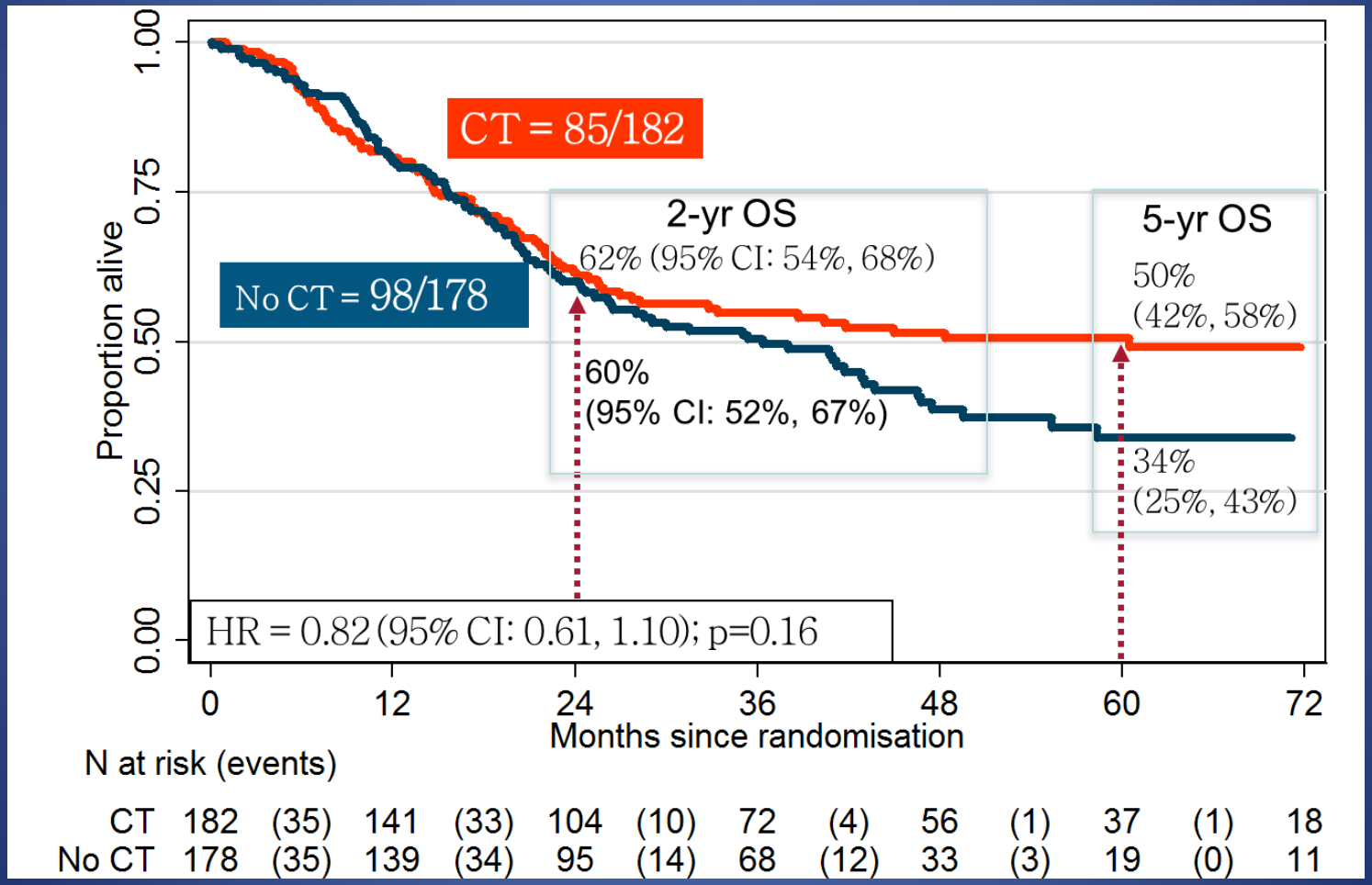
Loco-regional control
(invasive and non-invasive)



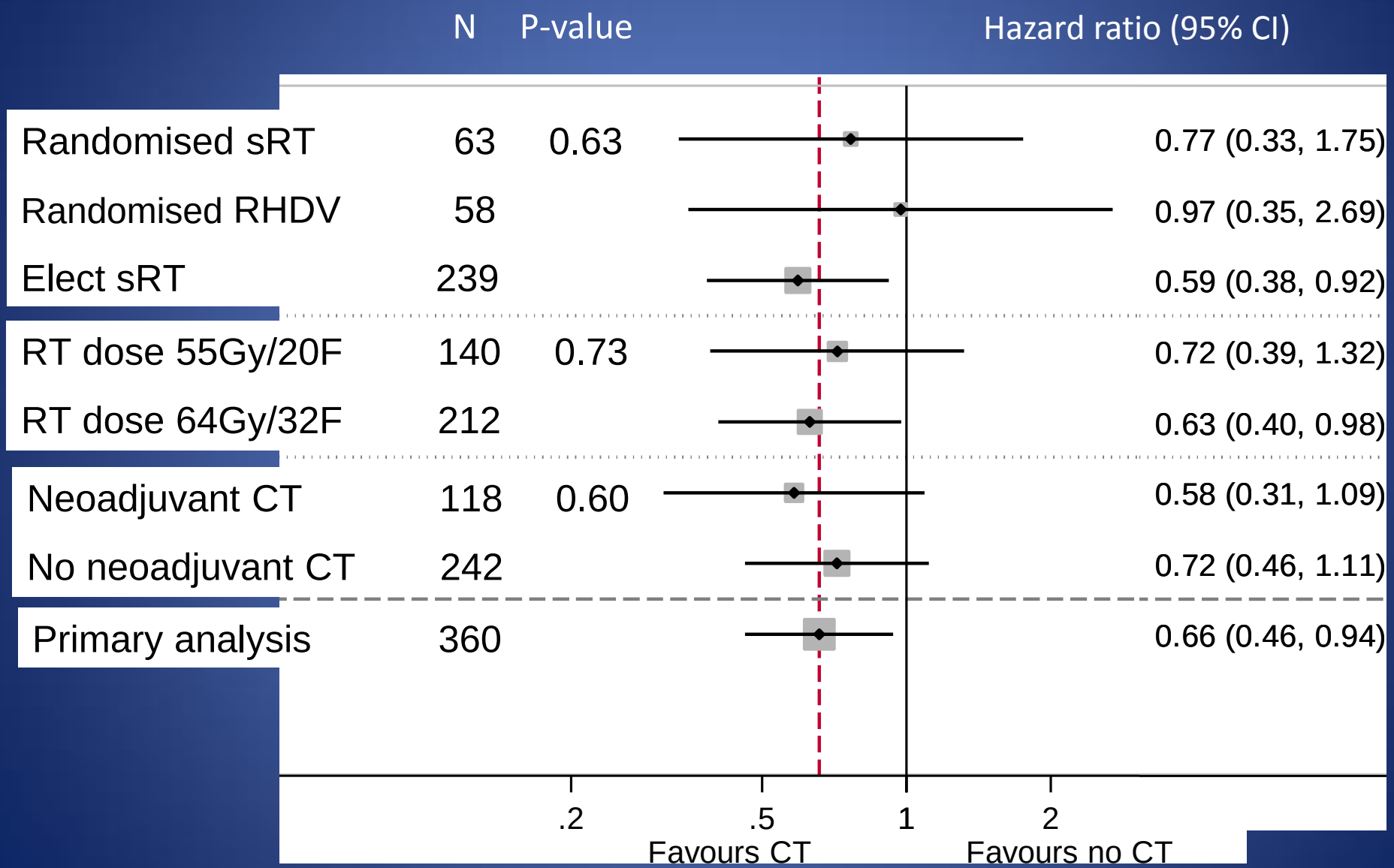
Invasive loco-regional control

James et al, Radiotherapy with or without chemotherapy for invasive bladder cancer. NEJM 2012 366, 1477-1488

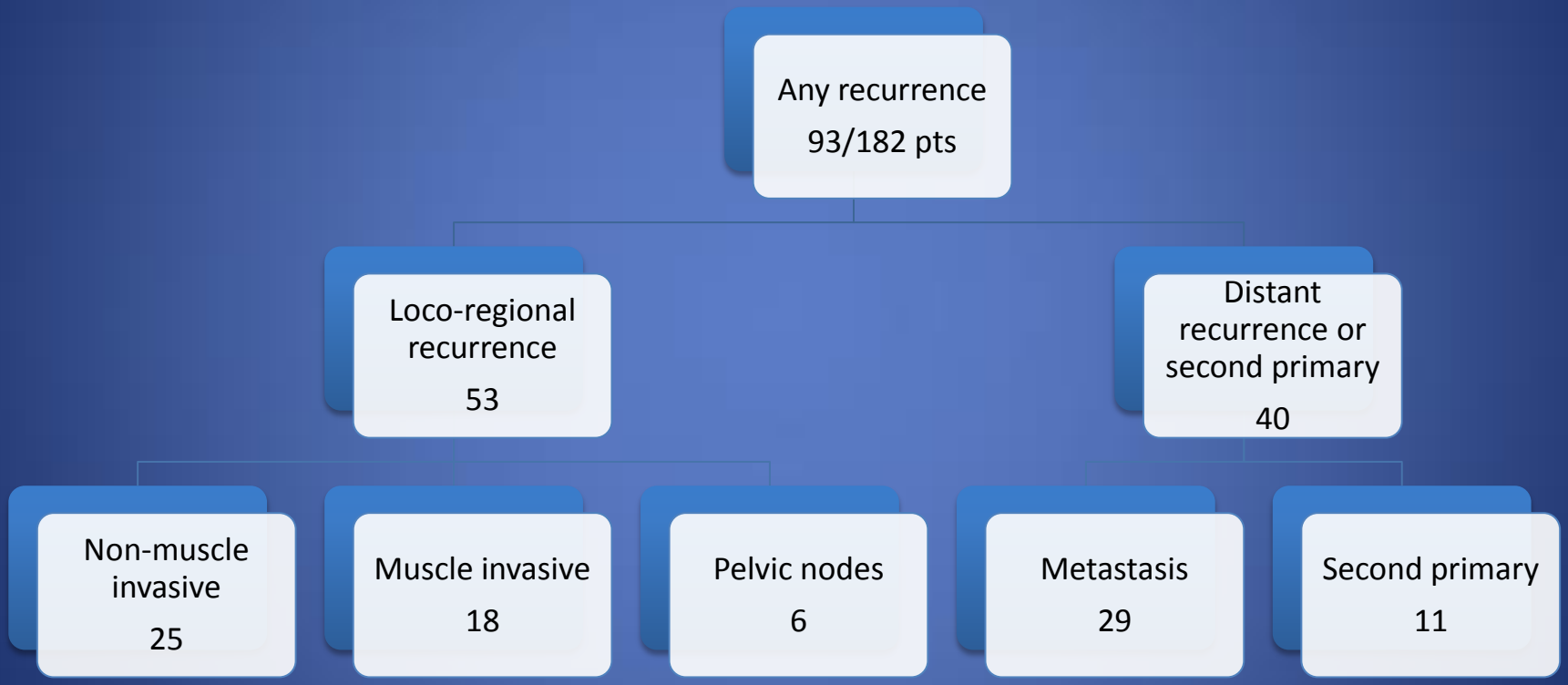
OS in chemotherapy randomisation



LRDFS - consistency across subgroups



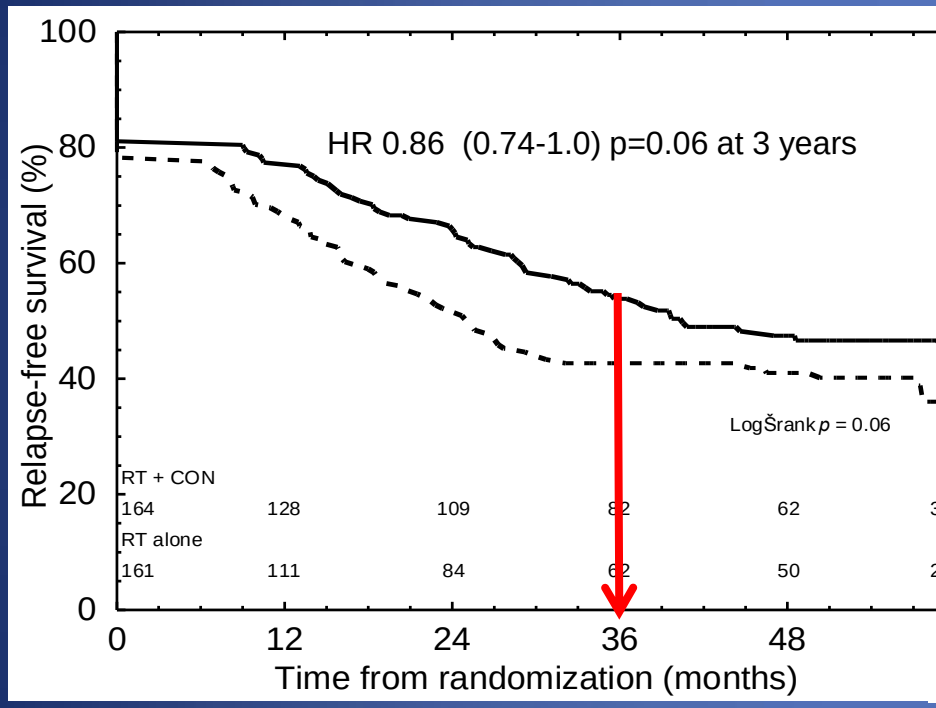
Patterns of recurrence after ChemoRT

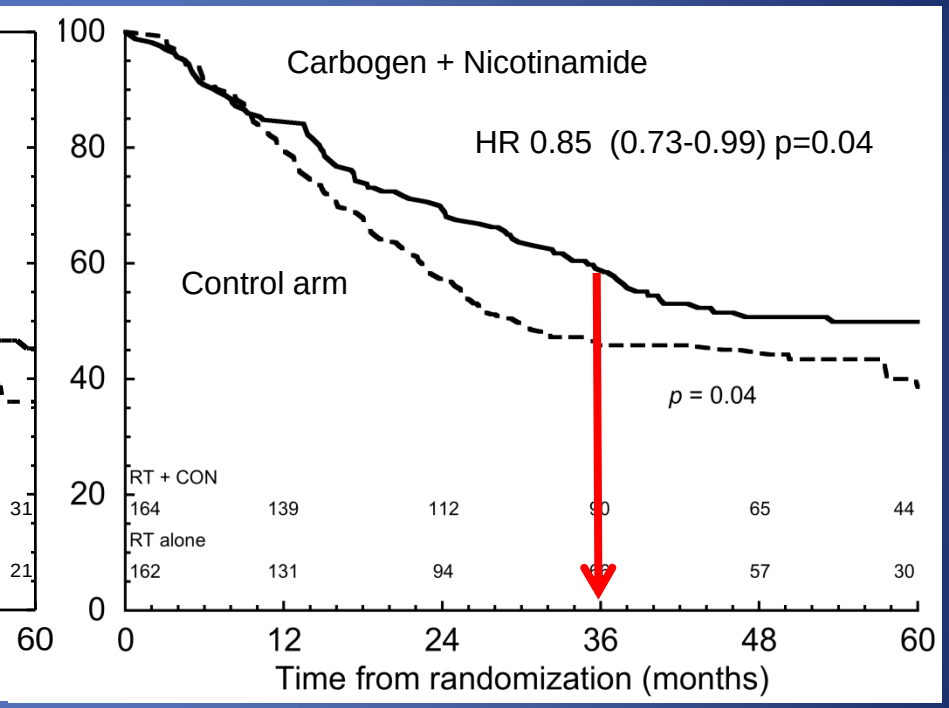


BCON: Aim and endpoints

- To determine whether hypoxia-modifiers Carbogen (95% O2/5% CO2) and Nicotinamide increase efficacy of RT in TCC
- Primary endpoint -cystoscopic control
- Secondary endpoints: overall survival (OS), local relapse-free survival (RFS), urinary and rectal morbidity

BCON Results



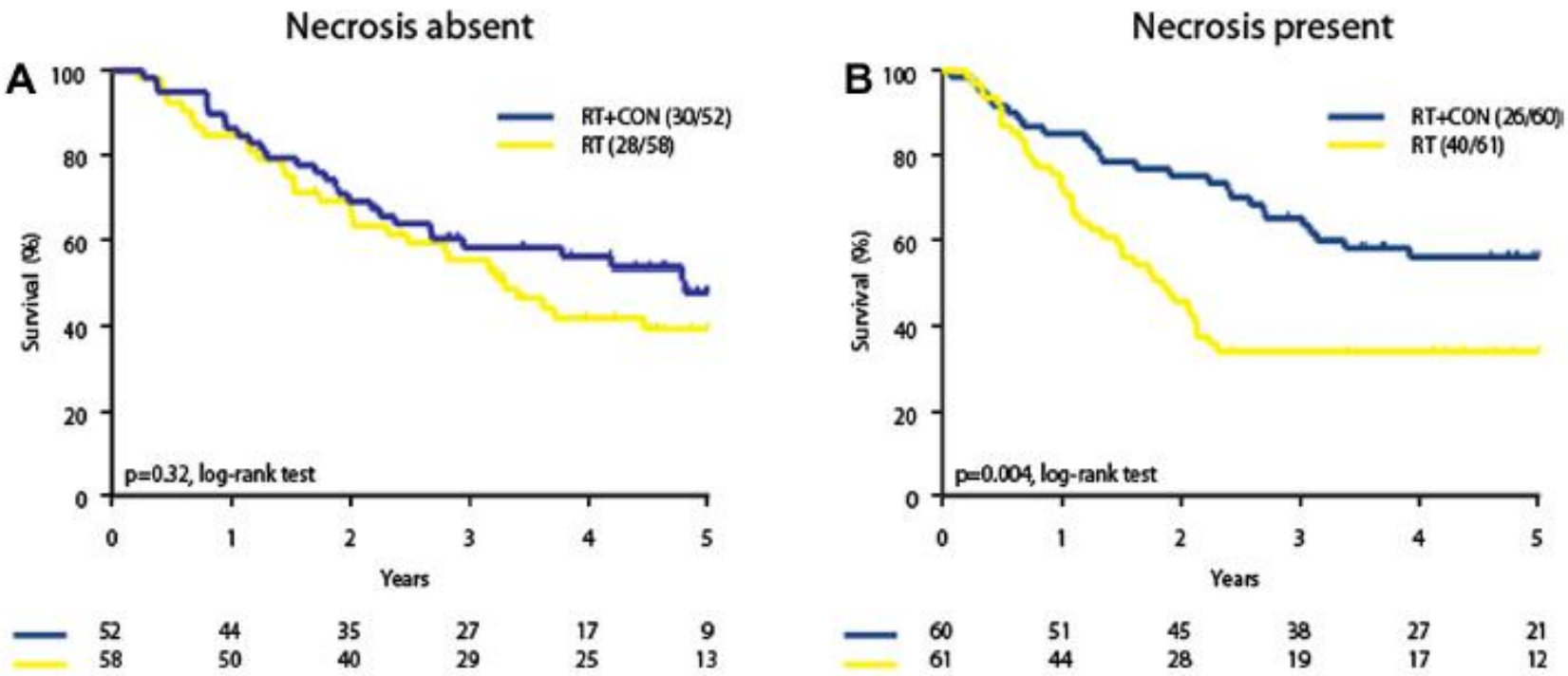


Relapse free survival

Overall survival

Hoskin PJ, Rojas AM, Bentzen SM, et al: Radiotherapy with concurrent carbogen and nicotinamide in bladder carcinoma. J Clin Oncol 28:4912-8, 2010

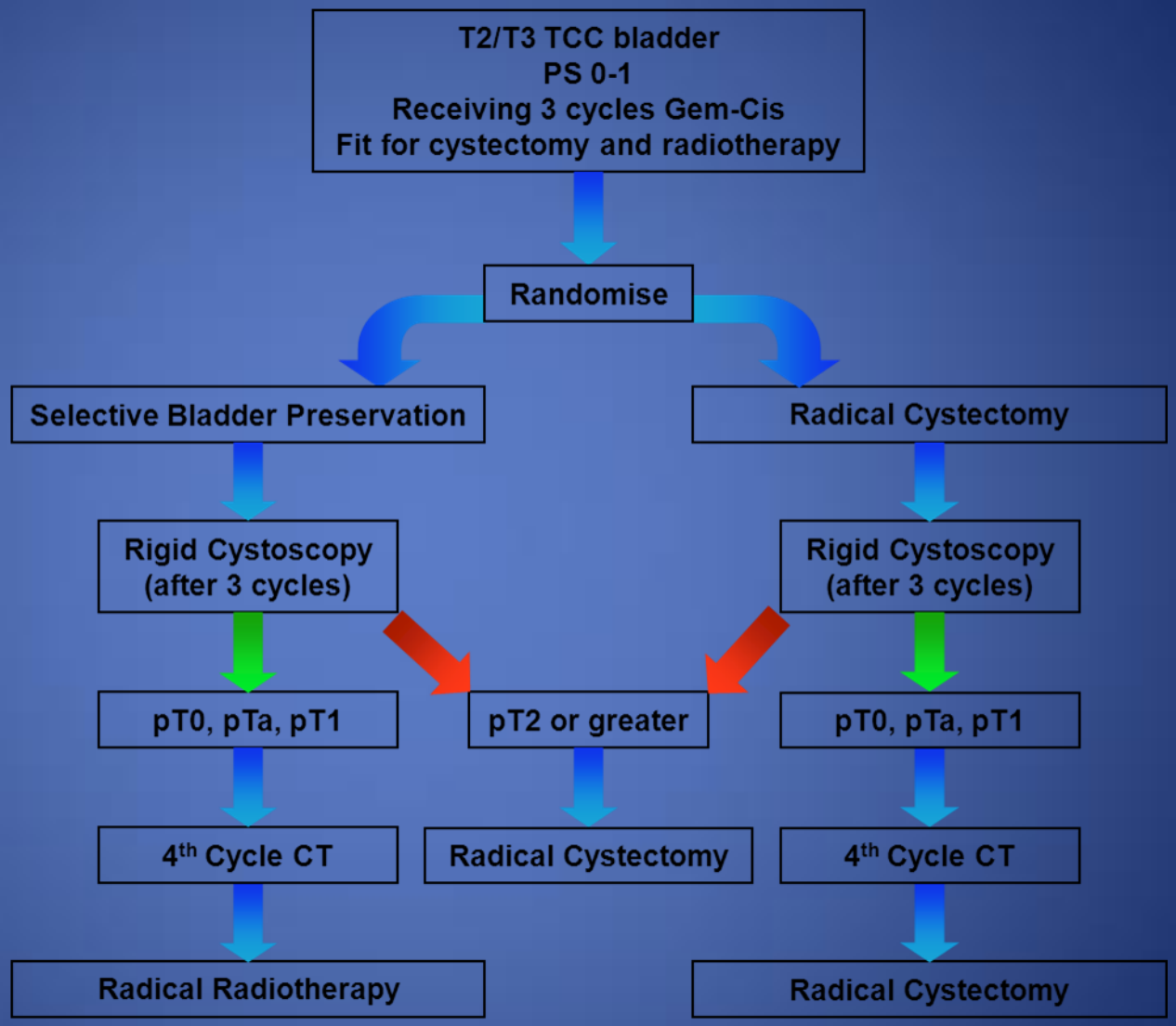
Outcome of BCON according to presence of necrosis Eustace et al R&O 2013



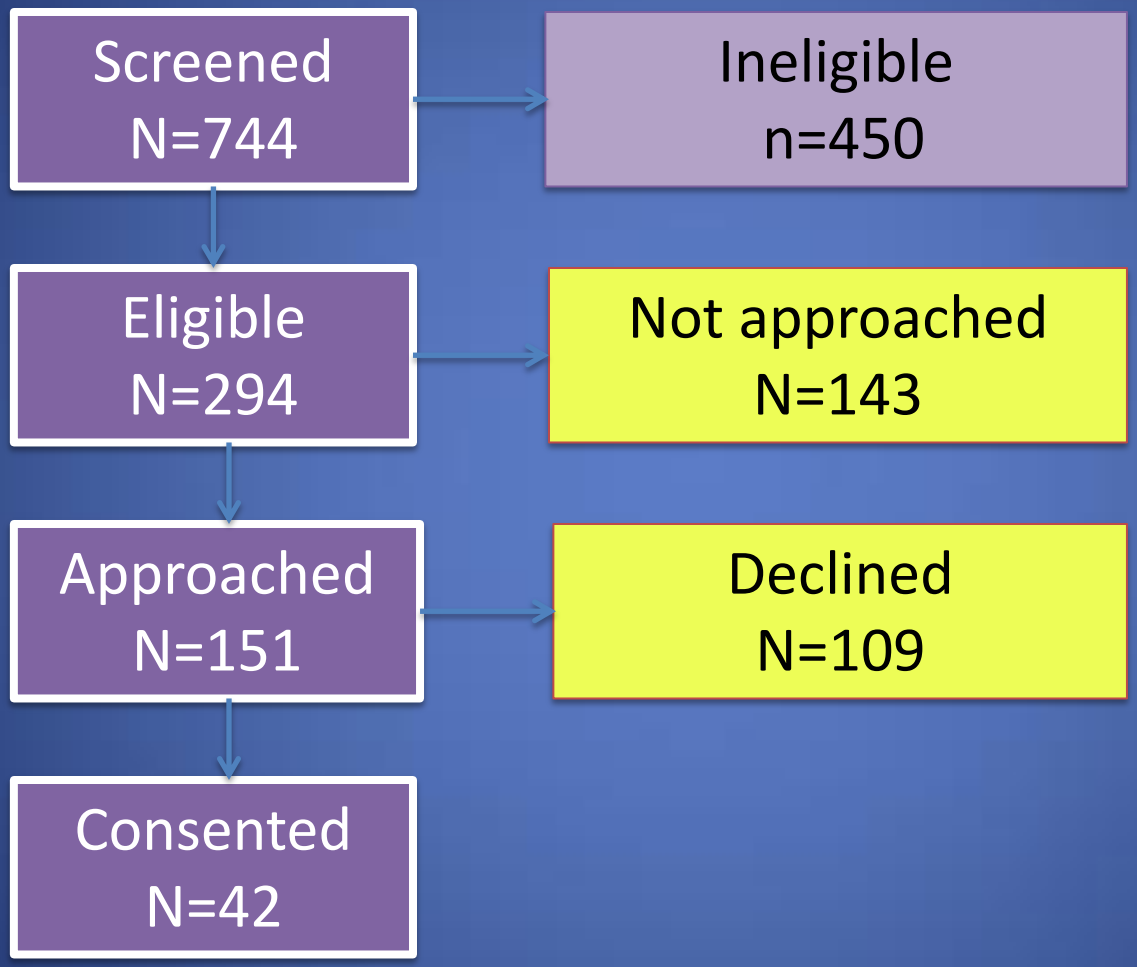
SPARE trial

Feasibility study:
110 patients

Main study:
1015 patients

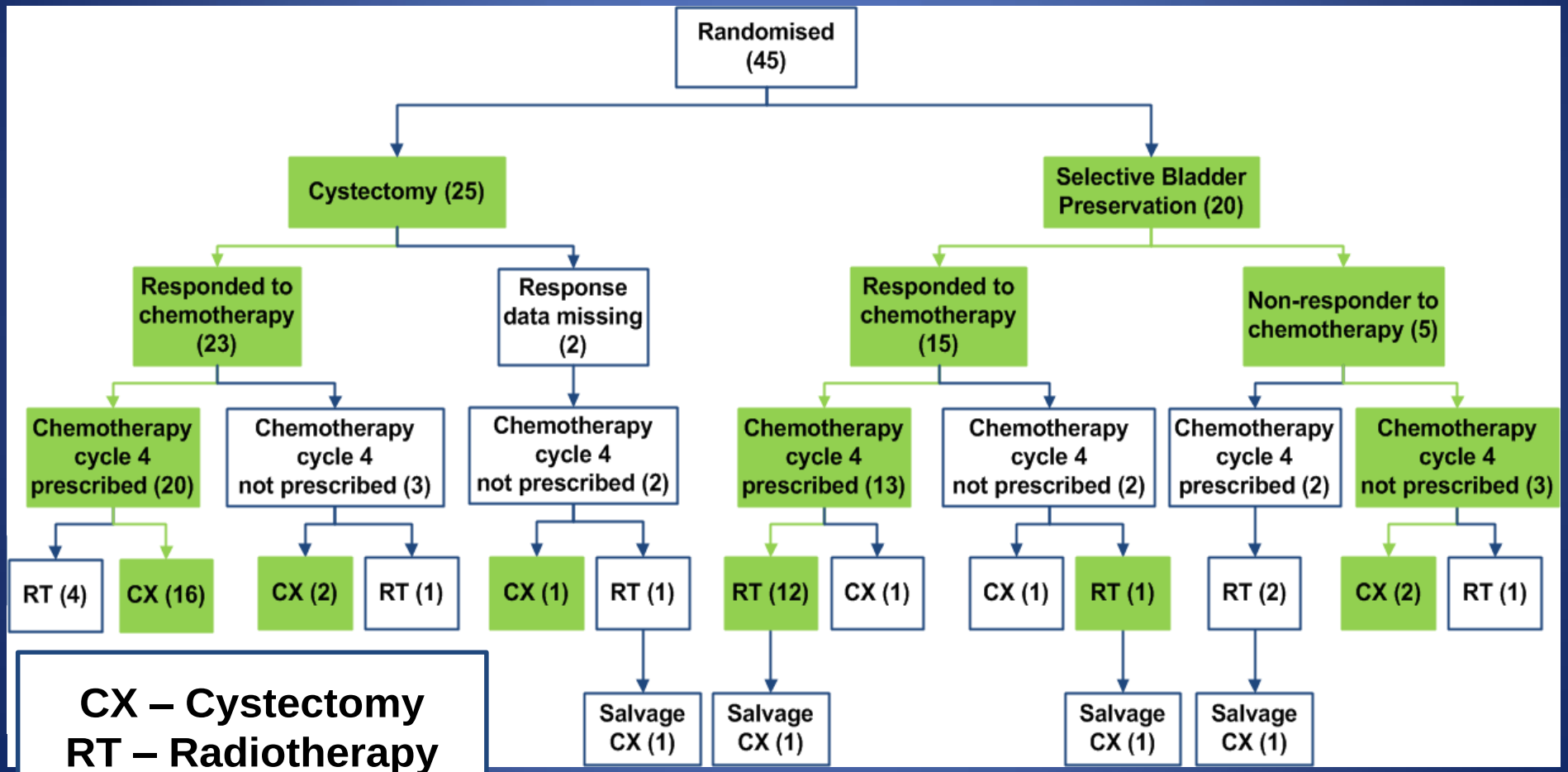


SPARE Trial Screening data (to end 2009)



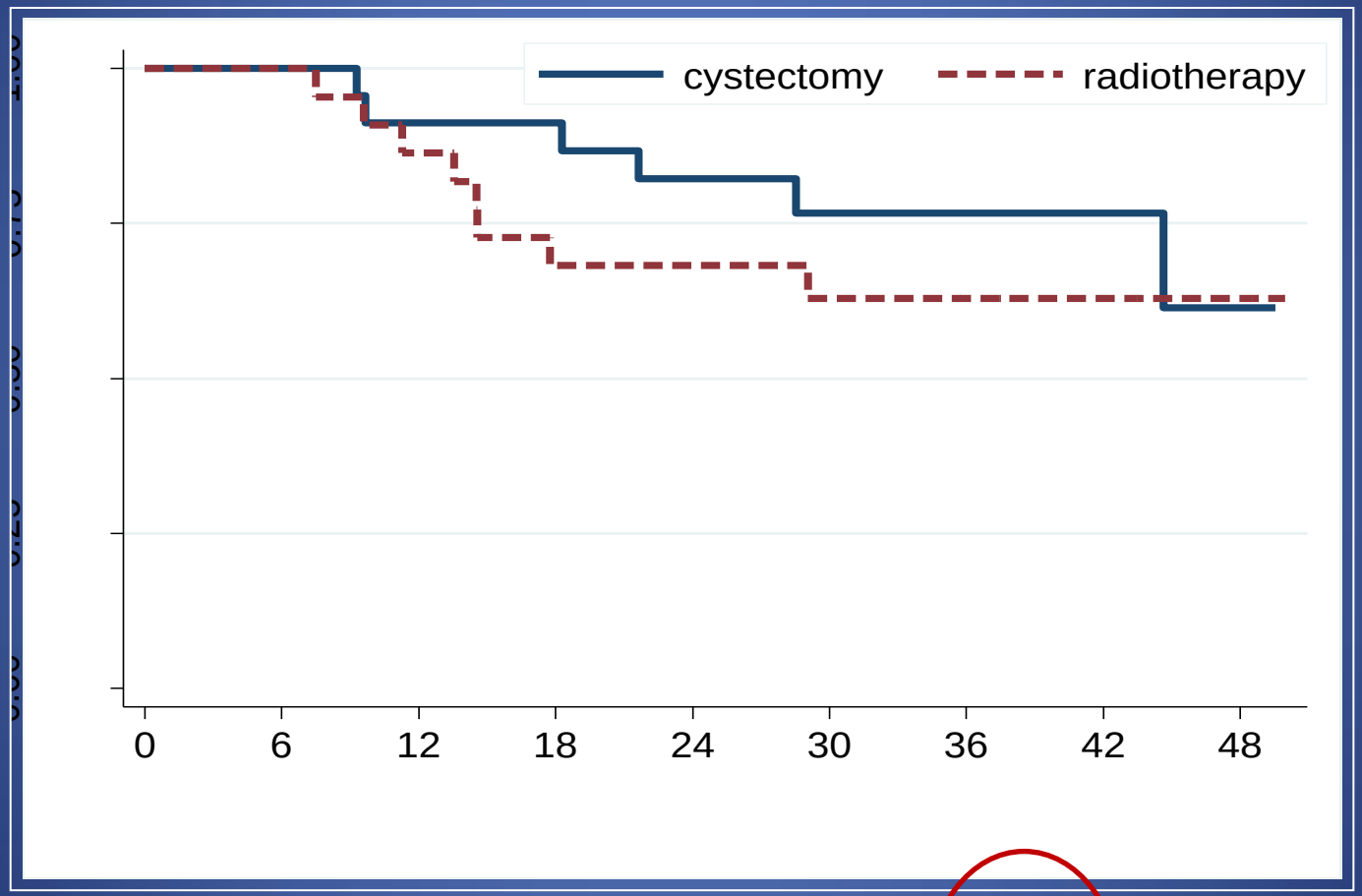
Huddart et al ASTRO 2012

SPARE CONSORT diagram



CX – Cystectomy
RT – Radiotherapy

SPARE: Overall Survival

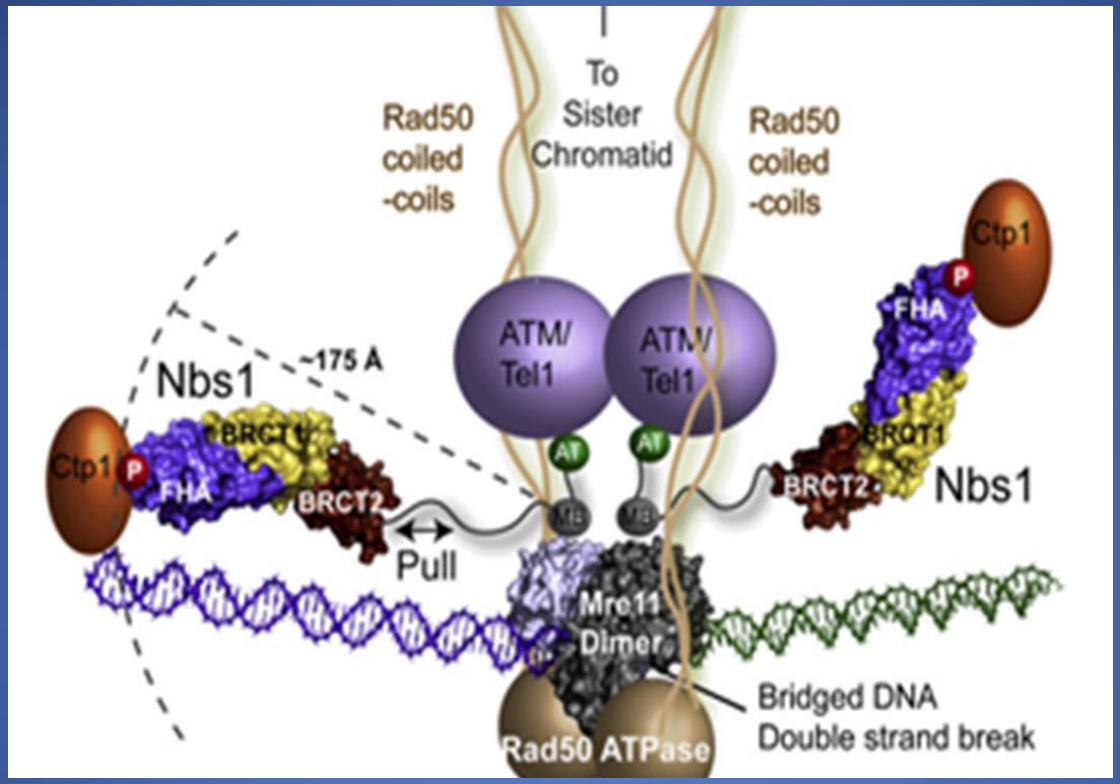


Hazard ratio: 1.49, 95% CI (0.52, 4.3), P=0.46

Lessons from SPARE

- Lower than expected patient number eligible for chemotherapy, radiotherapy and surgery
- Impact of strong physician preferences
- Impact of strong patient preferences (patients find it difficult to be randomised and wish to make their own choice of treatment)
- The importance of excellent consistent and clear communication and patient information

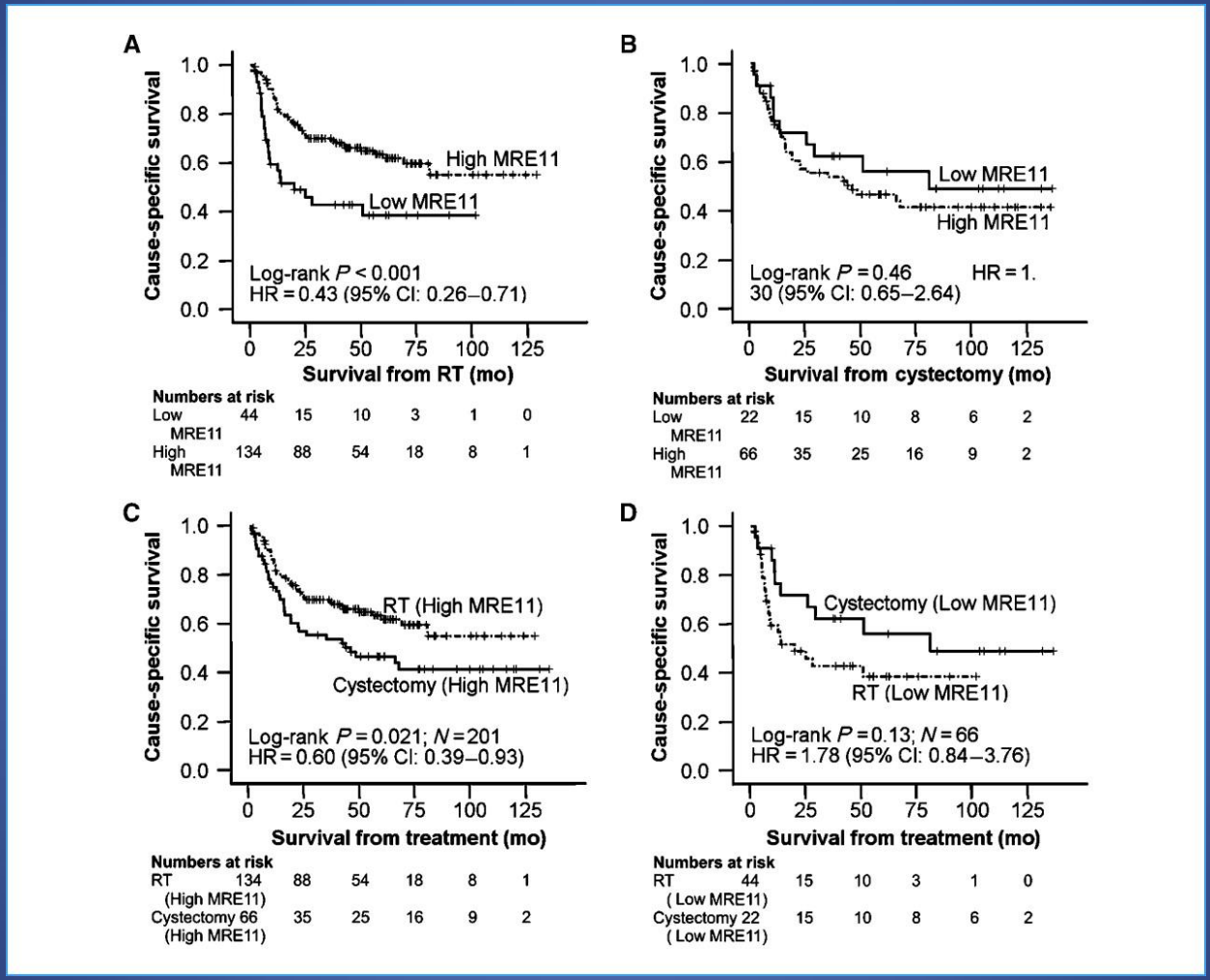
MRE11 hypothesis



Low tumor expression of DNA strand break signaling proteins would be associated with better outcome following radical radiotherapy in bladder cancer due to decreased DNA repair

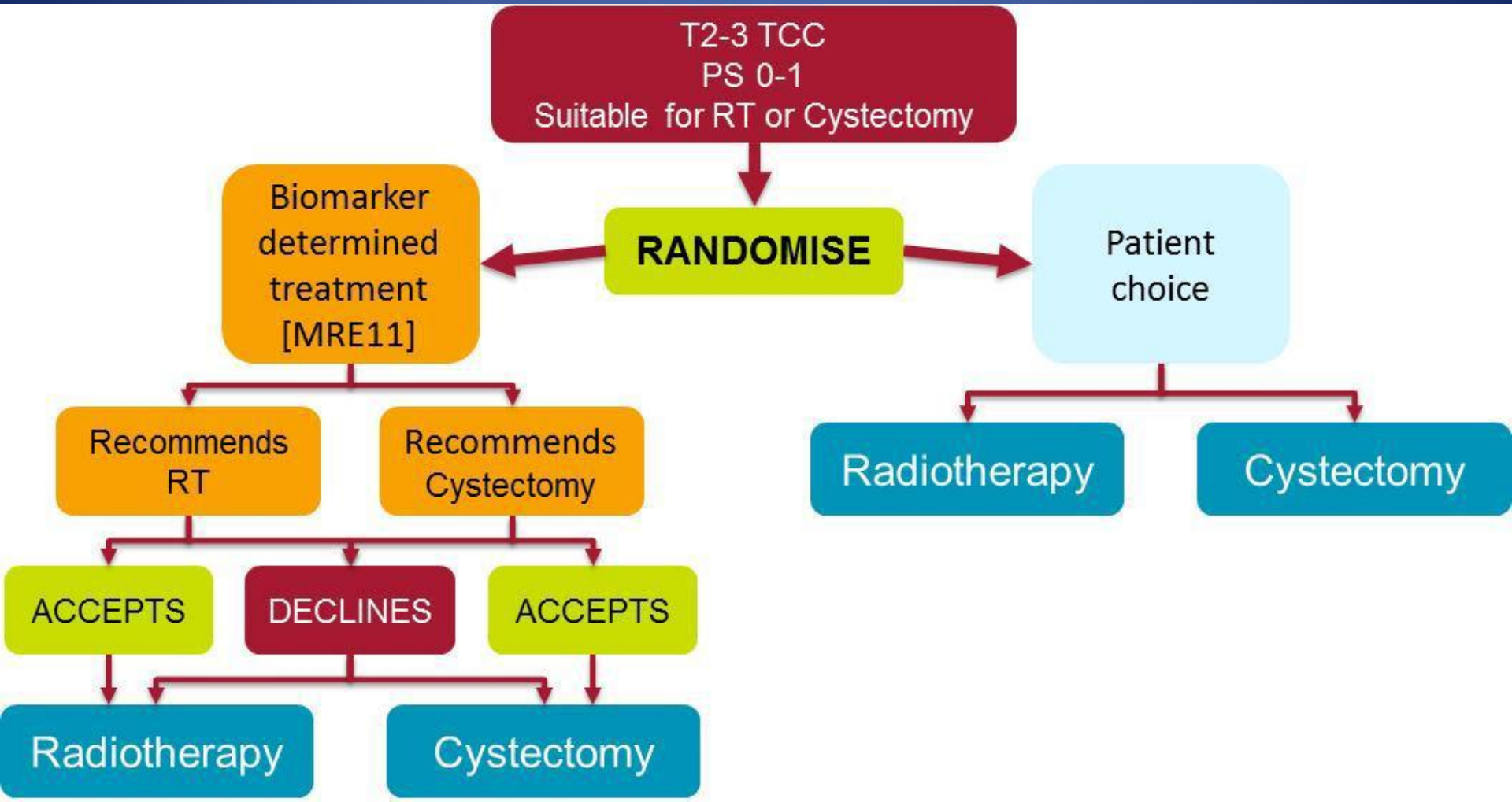
Would not expect it to be related to outcome following surgery, as not mediated via DNA damage mechanisms

MRE11 hypothesis



Choudhury A, Nelson LD, Teo MT, et al. MRE11 expression is predictive of cause-specific survival following radical radiotherapy for muscle-invasive bladder cancer. Cancer Res 2010;70:7017-26

BIOPIC


T2-3 TCC
PS 0-1
Suitable for RT or Cystectomy
RANDOMISE
Biomarker determined treatment [MRE11]
Patient choice
Recommends RT
Recommends Cystectomy
ACCEPTS
DECLINES
ACCEPTS
Radiotherapy
Cystectomy
Radiotherapy
Cystectomy

Conclusions

- No convincing evidence surgery superior to primary bladder preservation with salvage surgery
- Neoadjuvant chemotherapy improves overall survival
- Synchronous chemo-radiation is safe and improves pelvic control and hence is complementary to neoadjuvant treatment
- Markers are emerging which now need prospective evaluation

- Acknowledgements: Professors Peter Hoskin, Nick James and Dr Robert Huddart