Perioperative treatment of muscle-invasive bladder cancer: state of the art and prospects

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Why use peri-operative treatment in bladder cancer?

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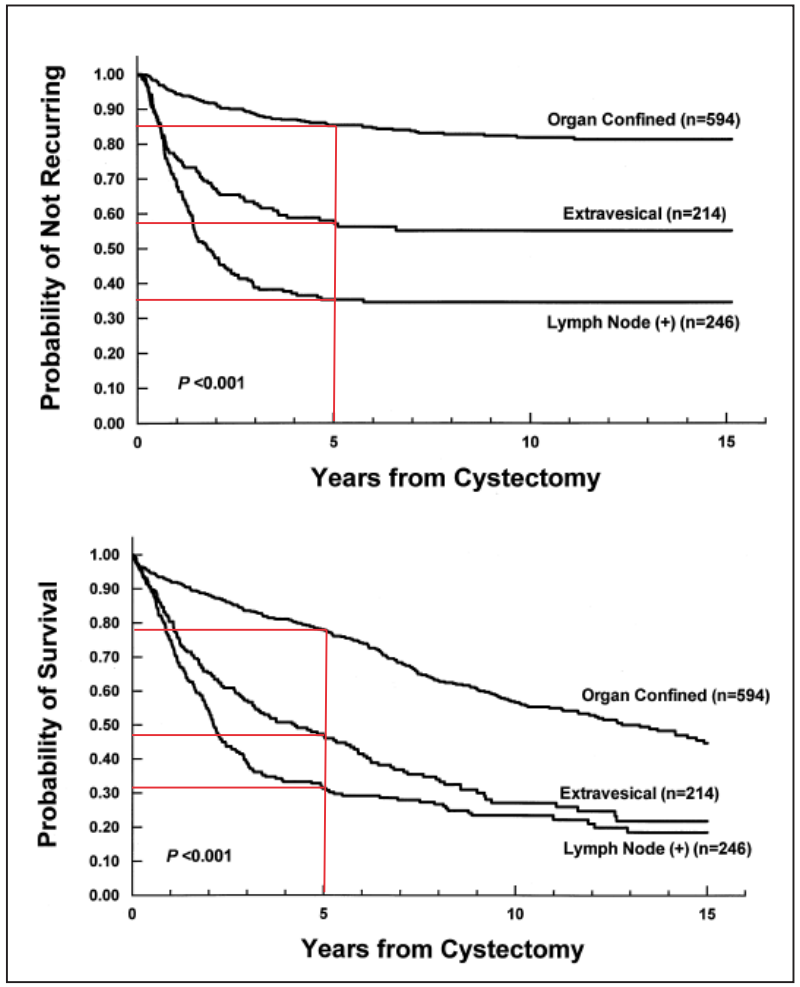
Cystectomy outcomes for MIBC
n=1054

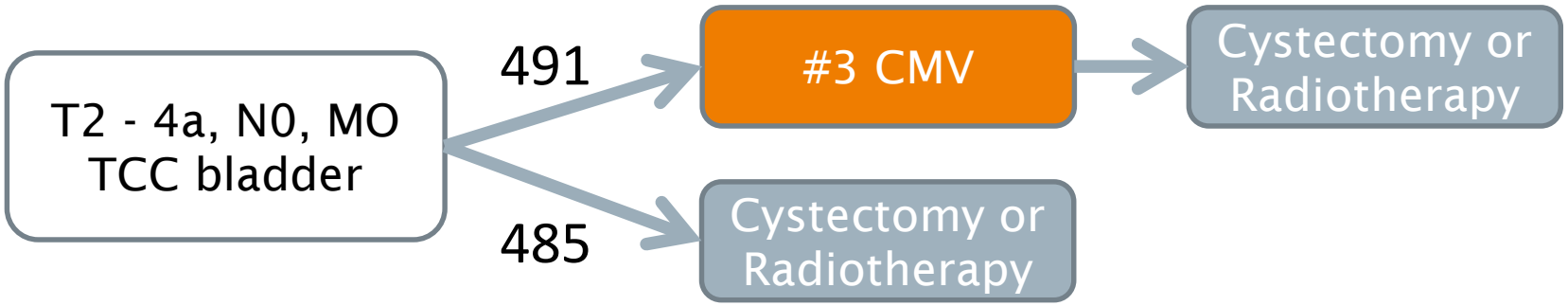


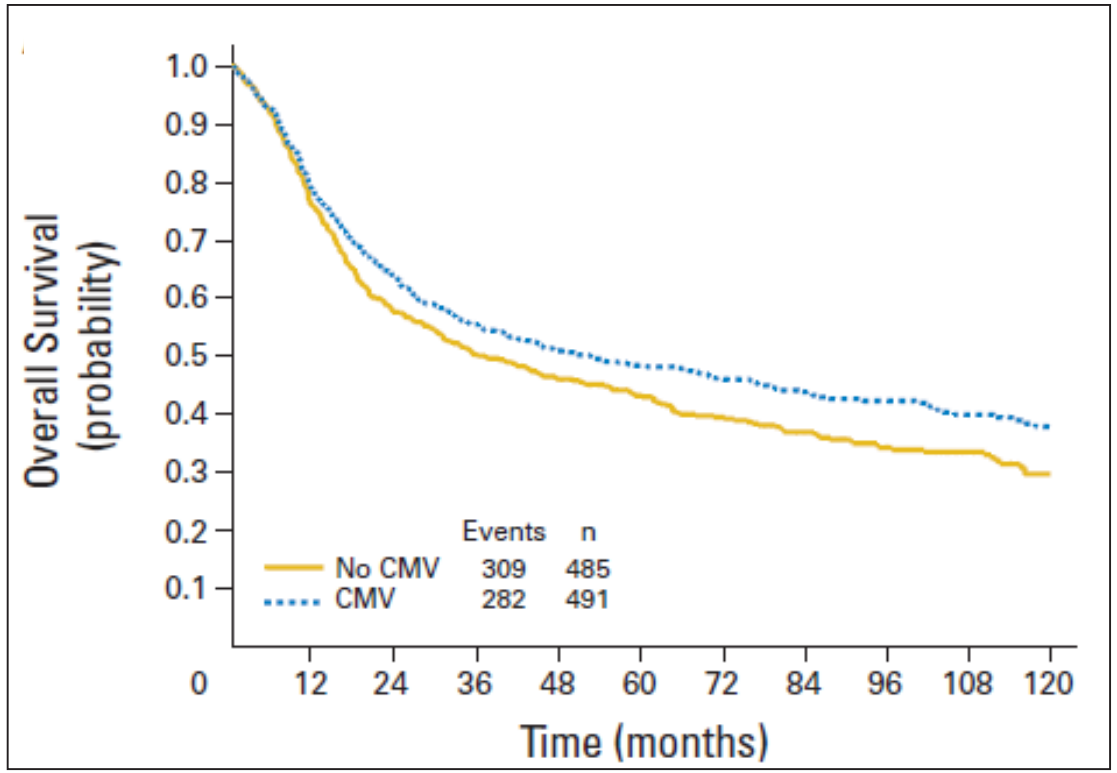
Radical Cystectomy

Radical Cystectomy + Chemotherapy

Stein, J Clin Oncol, 2001

The MRC neoadjuvant trial





10 year overall survival:

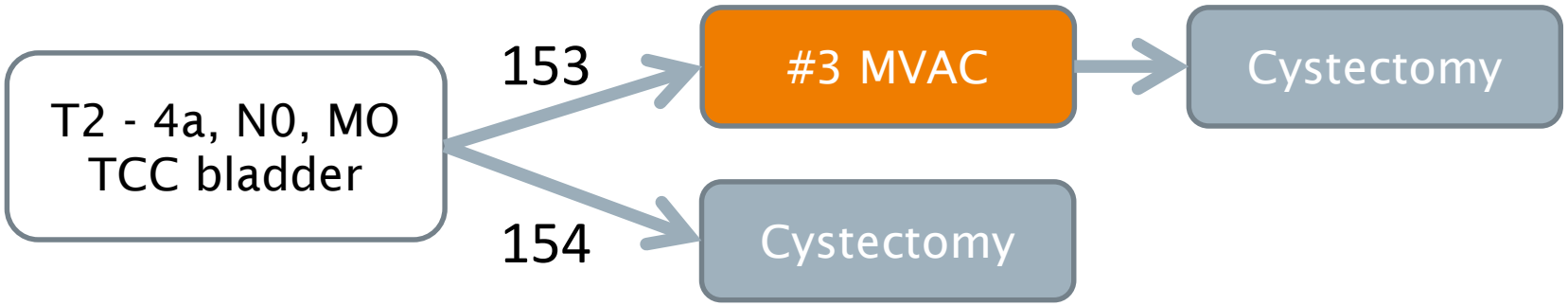
30% versus 36%

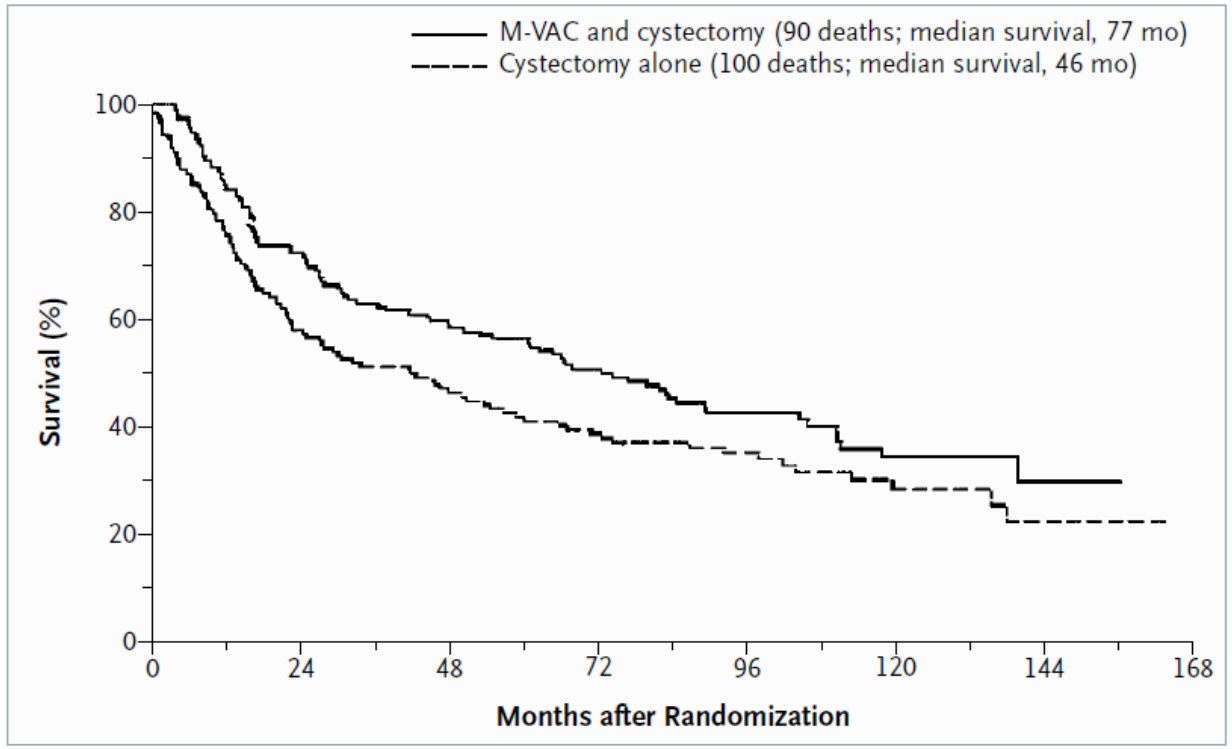
HR 0.84 (95% CI 0.72 – 0.99)

p = 0.037

International Trialists Collaboration, Lancet 1999 and J Clin Oncol 2011

The SWOG 8710 neoadjuvant trial





Median overall survival:

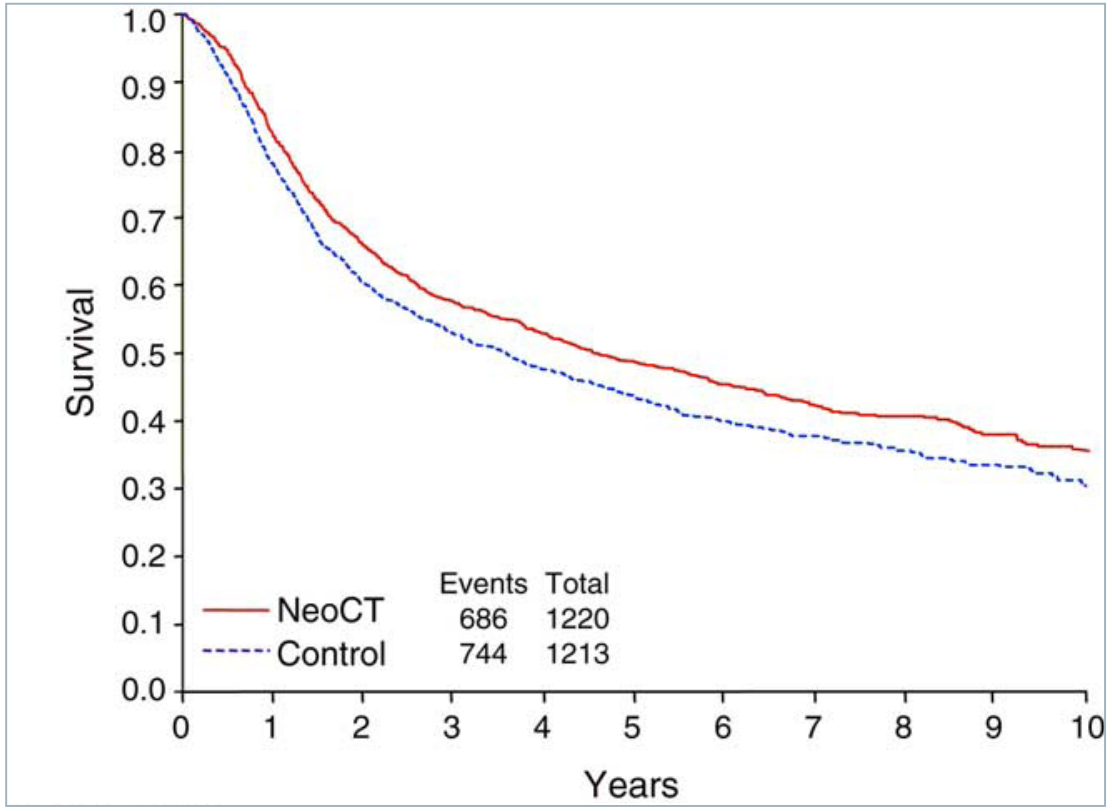
46 (C) versus 77 (C+MVAC) months

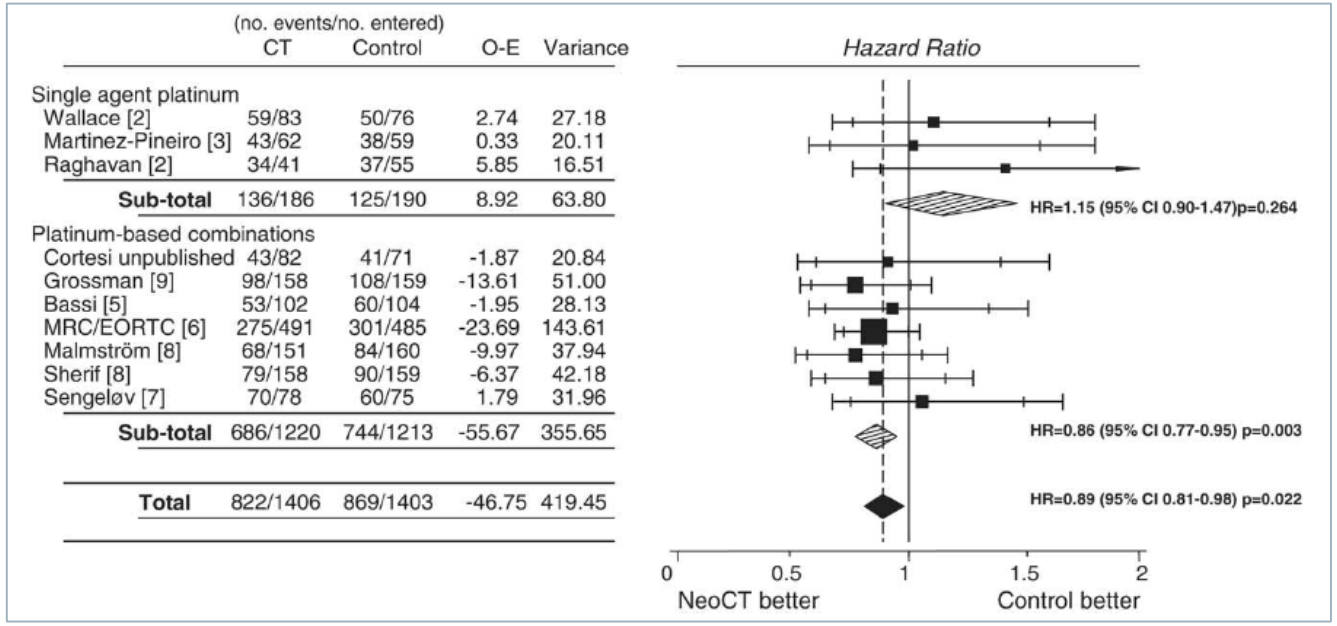
HR 1.33 95% CI 1.00 – 1.76

p = 0.05

Grossman H, N Engl J Med, 2003

ABC Neoadjuvant meta analysis





Advanced Bladder Cancer (ABC) Meta-analysis Collaboration, Eur Urol, 2005

What to use and who is 'fit for cisplatin'?

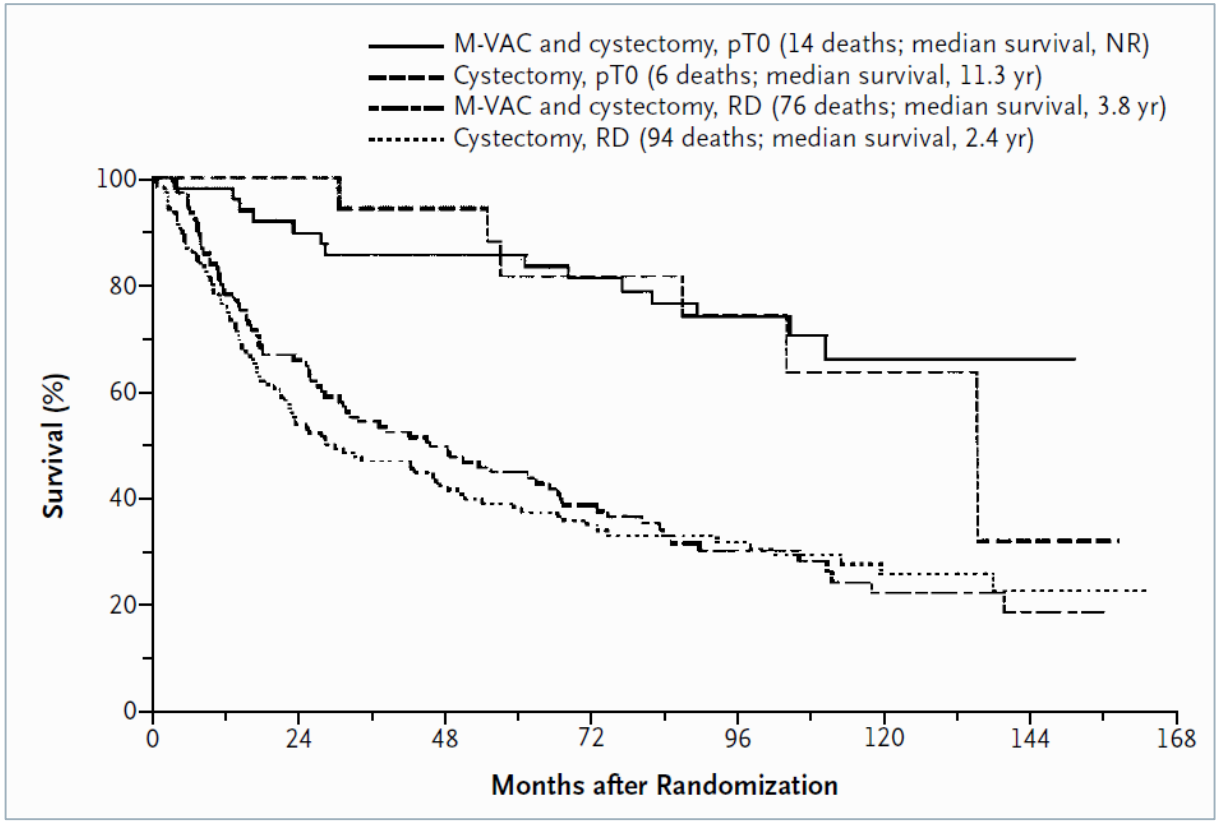
- Most UK centres use 3-4 cycles of cisplatin/gemcitabine
- A few use accelerated MVAC
- Neither of these were tested in a randomised neoadjuvant phase III trial!
- No randomised evidence for benefit for non-cisplatin based regimens (so personally I do not use them…)
- The definition below is now common in UC trials based on consensus opinion. It is not fully consistent with the neoadjuvant MRC or ECOG trials (or my personal practice…)

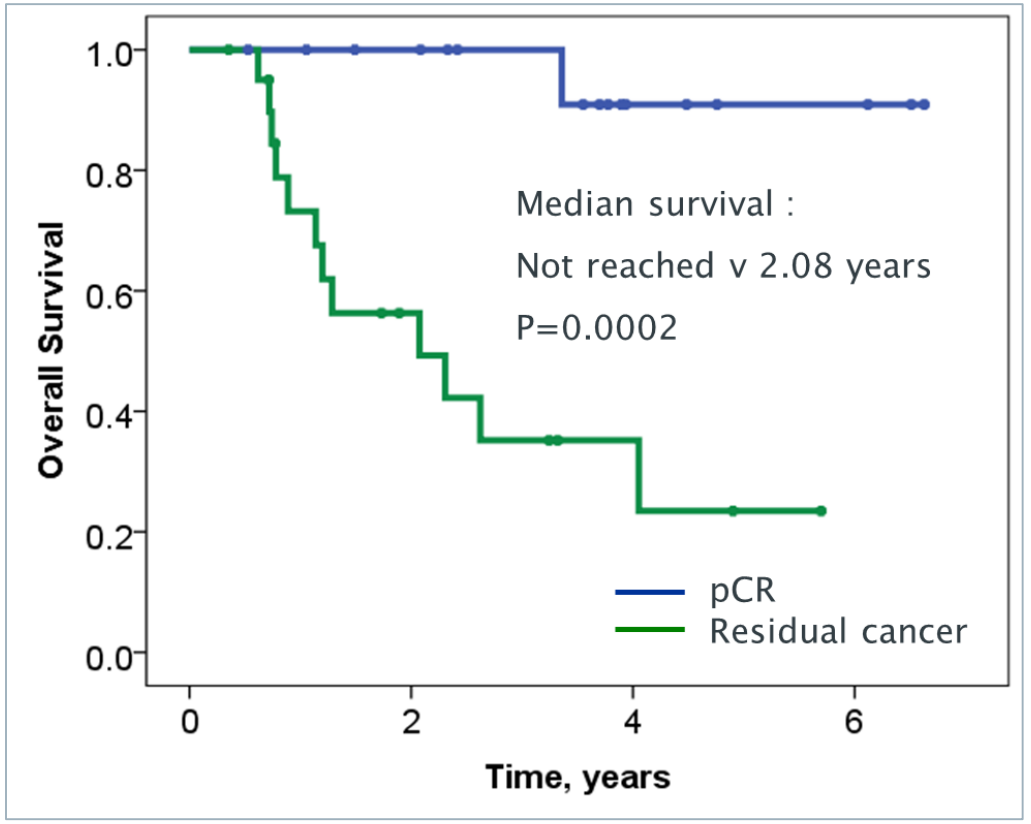
- ECOG performance status ≥ 2
- Creatinine clearance < 60 mL/min
- Grade ≥ 2 hearing loss
- Grade ≥ 2 neuropathy
- NYHA class III cardiac failure

Galsky, J Clin Oncol, 2011

pCR as a prognostic factor at cystectomy

- pCR rate the most important prognostic factor
- 38% with chemo vs 15% without in the MVAC trial





Grossman H, N Engl J Med, 2003

Subgroups and neoadjuvant chemotherapy benefit

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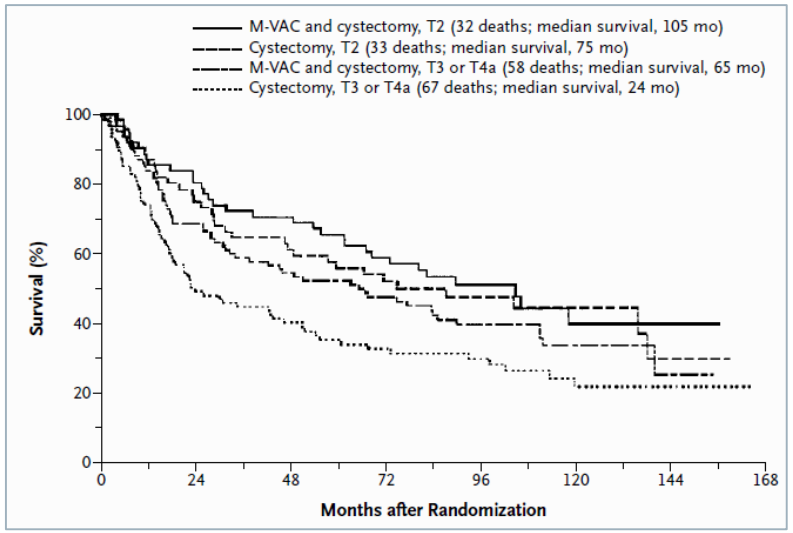
Table 4. Stratified and Unstratified Survival Analysis.*

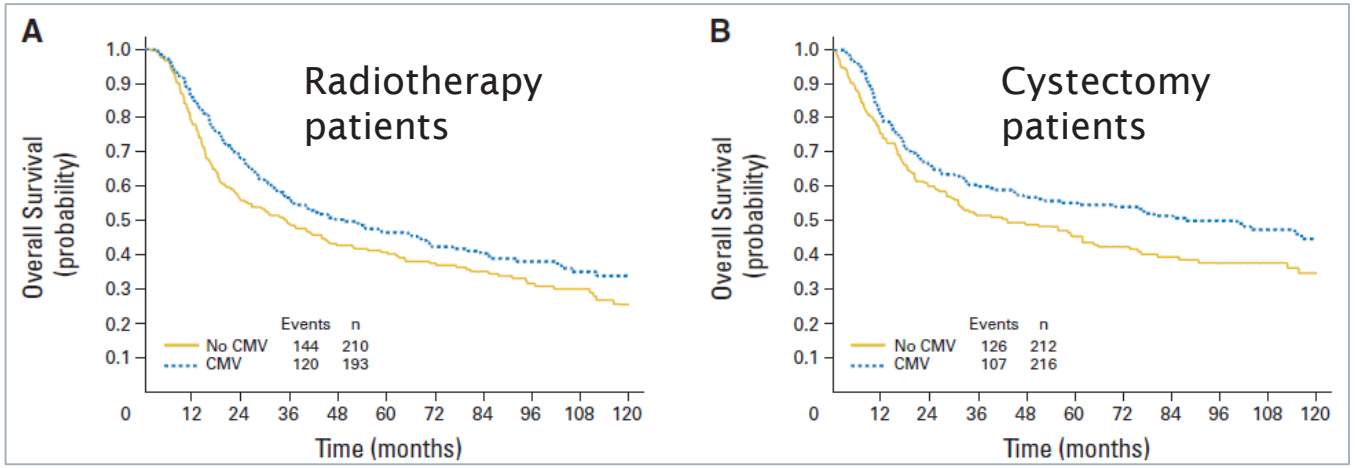
Variable	Median Survival		P Value†
	M-VAC and Cystectomy	Cystectomy Alone	
	months		
Unstratified	77	46	0.05
Primary analysis, stratified according to age and tumor stage			0.06
Stratified according to age			0.05
Age <65 yr	104	67	
Age ≥65 yr	61	30	
Stratified according to tumor stage			0.05
T2	105	75	
T3 or T4a	65	24	

	x^2 value for interaction or trend (degrees of freedom)	p
Age (<55, 55–65, >65 years)	0·77 (1)	0·380
Sex (male, female)	0·75 (1)	0·387
T category (T2, T3, T4a)	0·88 (1)	0·348
Histological grade (G1/G2, G3)	8·58 (1)	0·003*
Local radical treatment (RT, cystectomy, RT and cystectomy)	0·01 (2)	0·908
WHO performance status (0, 1, 2/3)	0·006 (1)	0·939
Nodal status (N0, NX)	0·002 (1)	0·964
Tumour size (<2·5, 2·6–5·0, >5 cm)	3·54 (1)	0·060
Renal function (≤59, 60–69, >69 [GFR])	5·10 (1)	0·024†

RT=radiotherapy; GFR=glomerular filtration rate. *In favour of G3 (ie, benefit of chemotherapy greater in G3 group than in G1/G2 group). †In favour of GFR >69 mL/min (ie, chemotherapy becomes more effective than no chemotherapy as GFR increases).

Table 3: **Results of subgroup analyses**



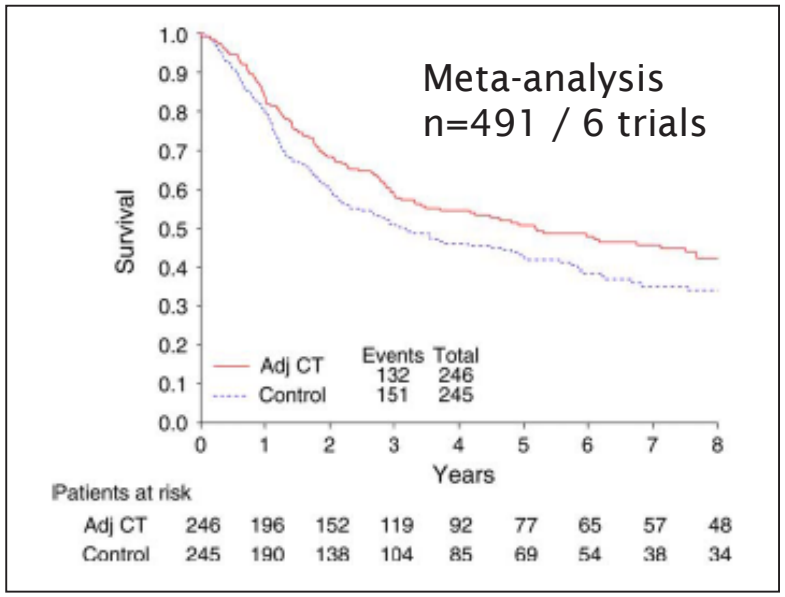


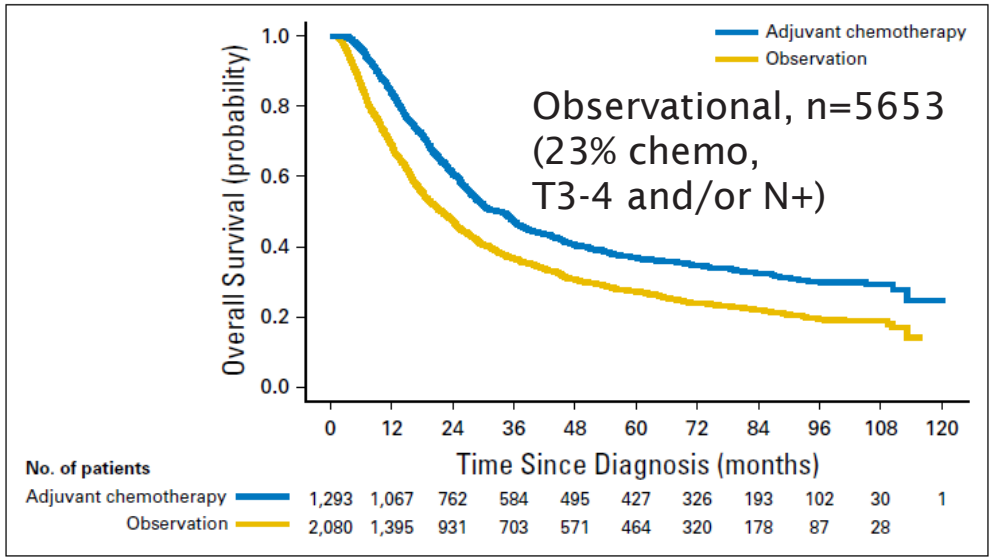
International Trialists Collaboration, Lancet 1999 and J Clin Oncol 2011; Grossman H, N Engl J Med, 2003

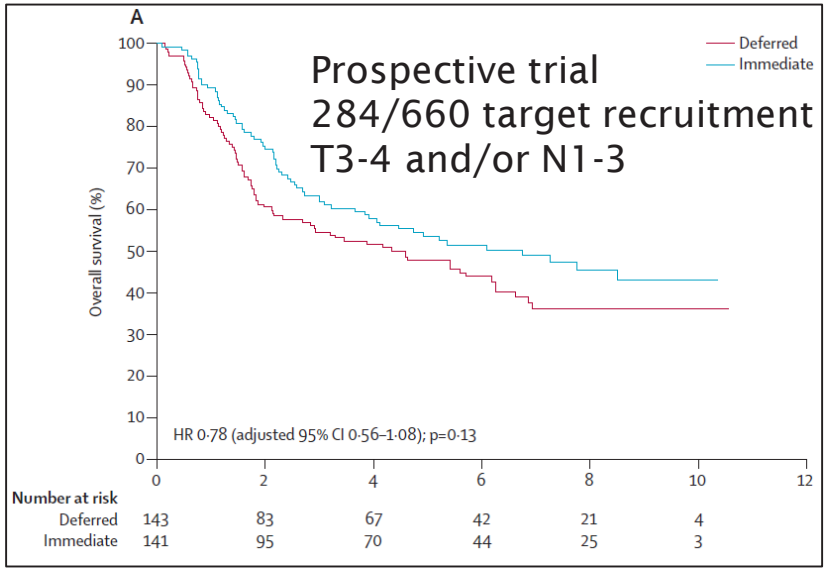
Adjuvant chemotherapy

No single positive ‘adequate’ trial

Similar absolute survival benefit according to available data







Sternberg, Lancet Oncol, 205; Galsky, J Clin Oncol, 2016; ABC Meta-analysis Collaboration, Eur Urol, 2005

Chemo-radiotherapy versus radiotherapy

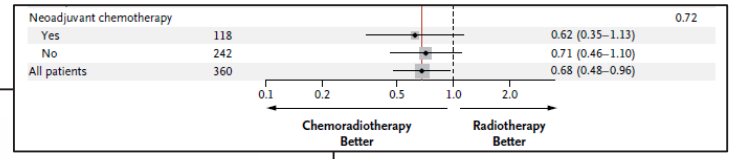
UNIVERSITY OF Southampton

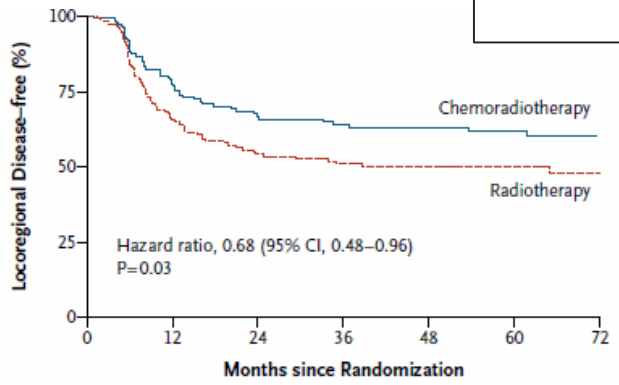
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radiotherapy with or without Chemotherapy in Muscle-Invasive Bladder Cancer

Nicholas D. James, M.B., B.S., Ph.D., Syed A. Hussain, M.B., B.S., M.D., Emma Hall, Ph.D., Peter Jenkins, M.B., B.S., Ph.D., Jean Tremlett, M.Sc., Christine Rawlings, M.Sc., Malcolm Crundwell, M.D., B.Chir., Bruce Sizer, M.B., B.S., Thiagarajan Sreenivasan, M.B., B.S., Carey Hendron, M.Sc., Rebecca Lewis, B.Sc., Rachel Waters, M.Sc., and Robert A. Huddart, M.B., B.S., Ph.D., for the BC2001 Investigators*





2 year locoregional disease free survival: 67% vs. 54%

Hazard ratio 0.68 (95% CI, 0.48 to 0.96; P = 0.03)

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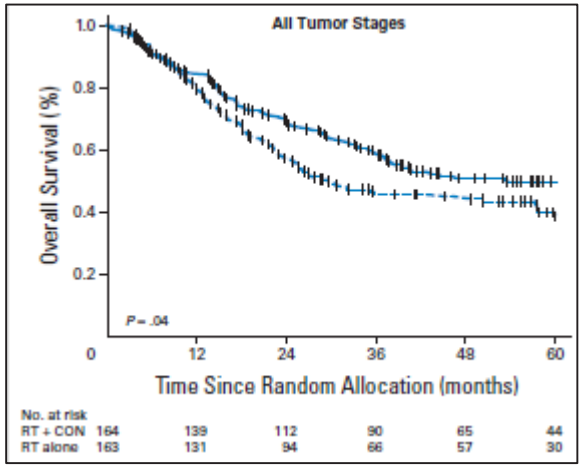
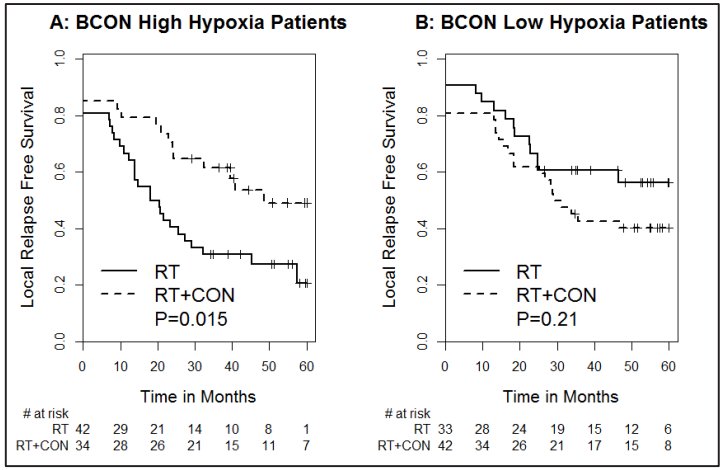
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Radiotherapy With Concurrent Carbogen and Nicotinamide in Bladder Carcinoma

Peter J. Hoskin, Ana M. Rojas, Søren M. Bentzen, and Michele I. Saunders





Yang, Clin Cancer Res, 2017; James, N Engl J Med, 2012; Hoskin, J Clin Oncol, 2010

POUT – adjuvant chemotherapy for upper tract UC

ICR The Institute of Cancer Research

POUT

CANCER RESEARCH UK

Results of POUT - A phase III randomised trial of peri-operative chemotherapy versus surveillance in upper tract urothelial cancer (UTUC)

Alison Jane Birtle*, John David Chester, Robert Jones, Mark Johnson, Michaela Hill, Richard T Bryan, James Catto, Jenny Donovan, Ann French, Chris Harris, Francis Keeley, Roger Kockelbergh, Thomas Powles, Rachel Todd, Lucy Tregellas, Caroline Wilson, Andrew Winterbottom, Rebecca Lewis, Emma Hall, on behalf of the POUT Investigators

*Chief Investigator

PRESENTED AT: **2018 Genitourinary Cancers Symposium**

POUT Trial design

Patients with invasive upper tract urothelial carcinoma (UTUC) within 90 days following nephro-ureterectomy

Surveillance

Platinum based chemotherapy typed by GFR

Follow up 3 monthly to 12 months, 6 monthly to 36 months and annually thereafter:

At each visit: chest imaging, biochemistry & haematology (to 24 months)

6 monthly to 24 months: toxicity assessment (CTCAE v4), cystoscopy (annually thereafter)

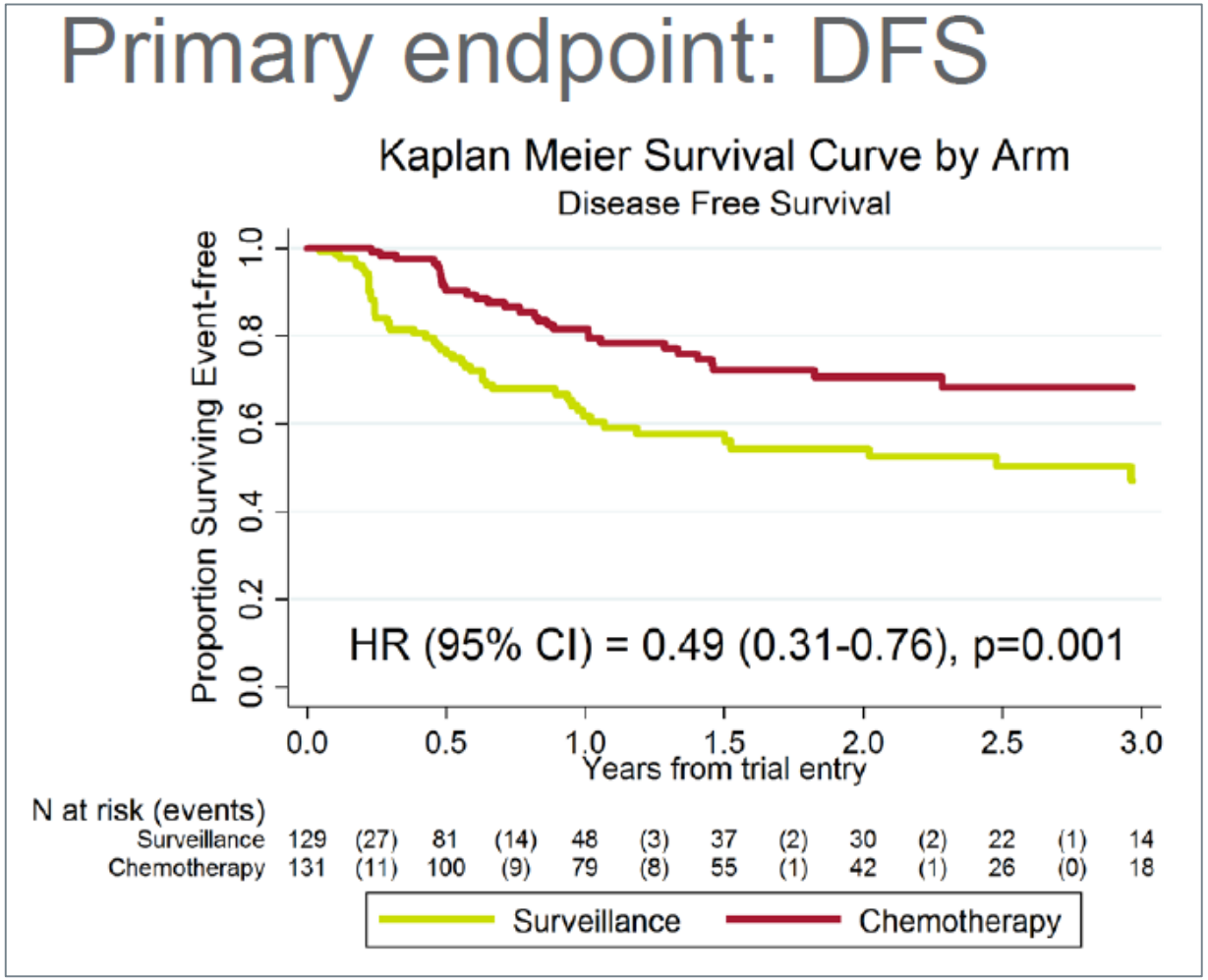
3, 6, 12, 18, 24mths: CT abdo/pelvis (annually thereafter)

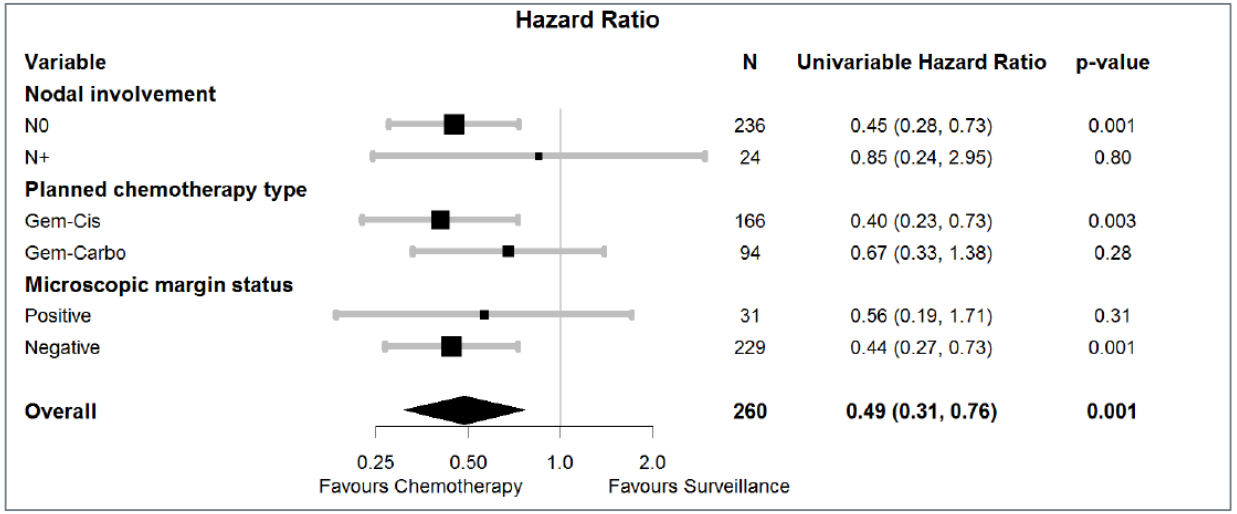
Treatment according to patient and local investigators' decision at relapse

Birtle, GU ASCO 2018, abstract 407

POUT – adjuvant chemotherapy for upper tract UC

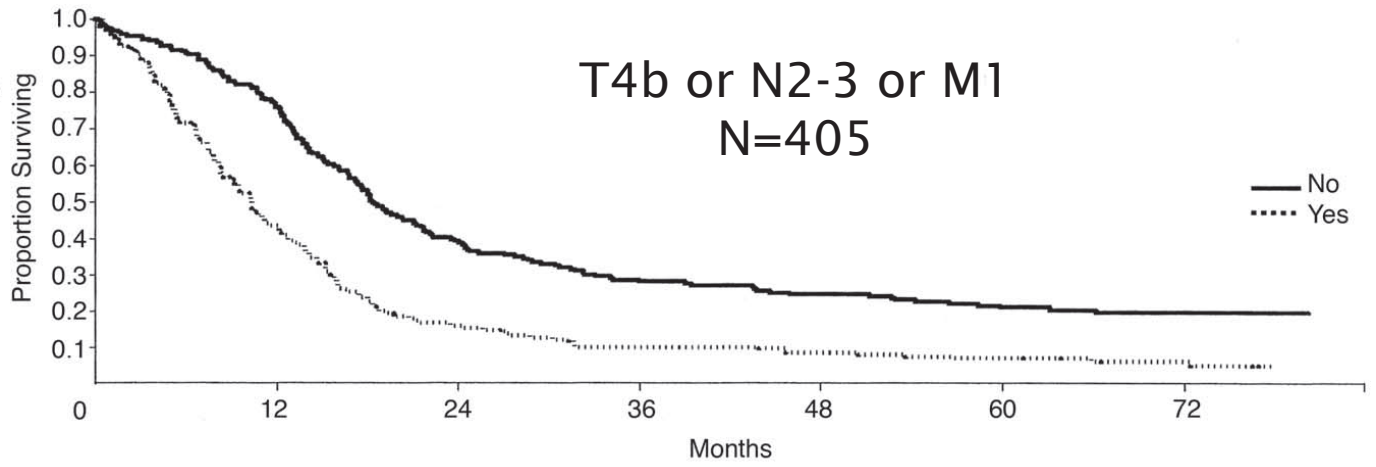
Primary endpoint: DFS



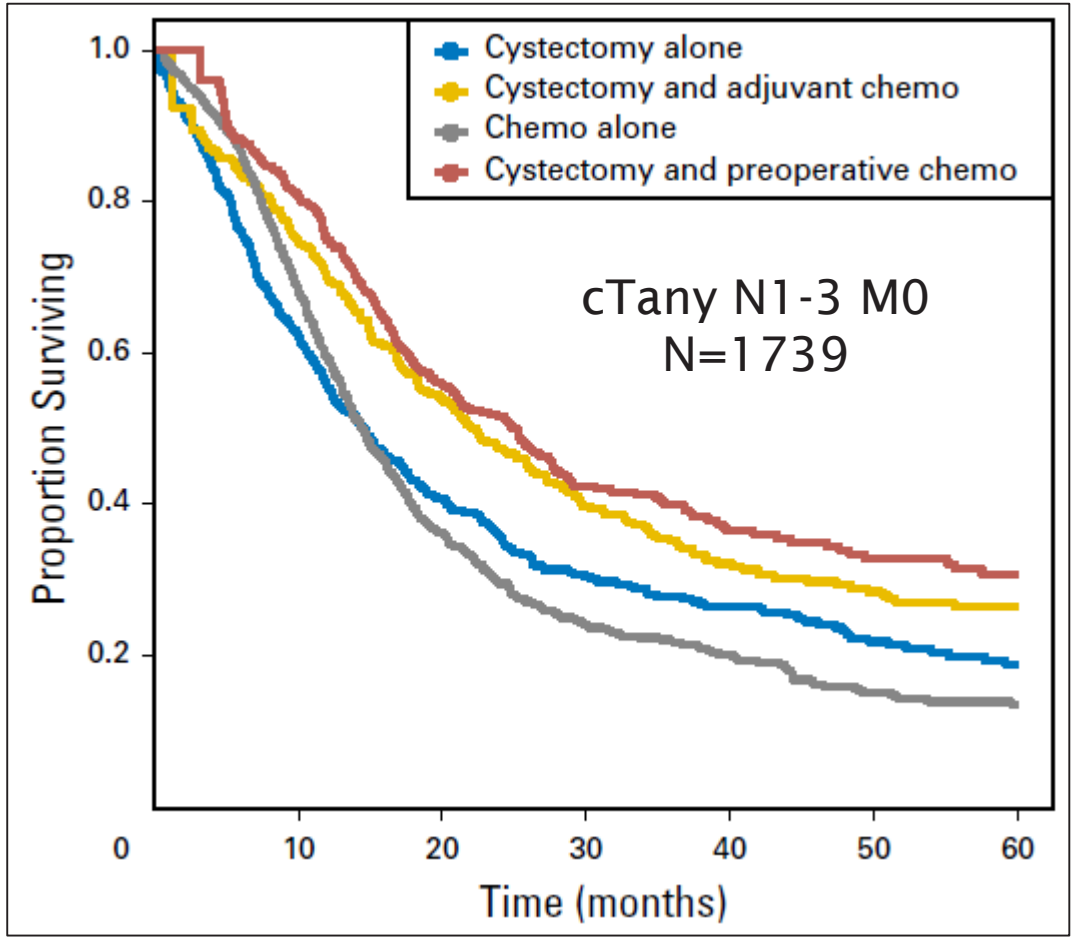


Birtle, GU ASCO 2018, abstract 407

Cure for non-visceral metastatic disease?



	Non-visceral	Visceral (bone, liver, lung)
Median overall survival	18.4	10.3
5 year survival	20.9	6.8



von der Maase H, J Clin Oncol 2005; von der Maase H, J Clin Oncol 2000; Galsky, J Clin Oncol, 2016

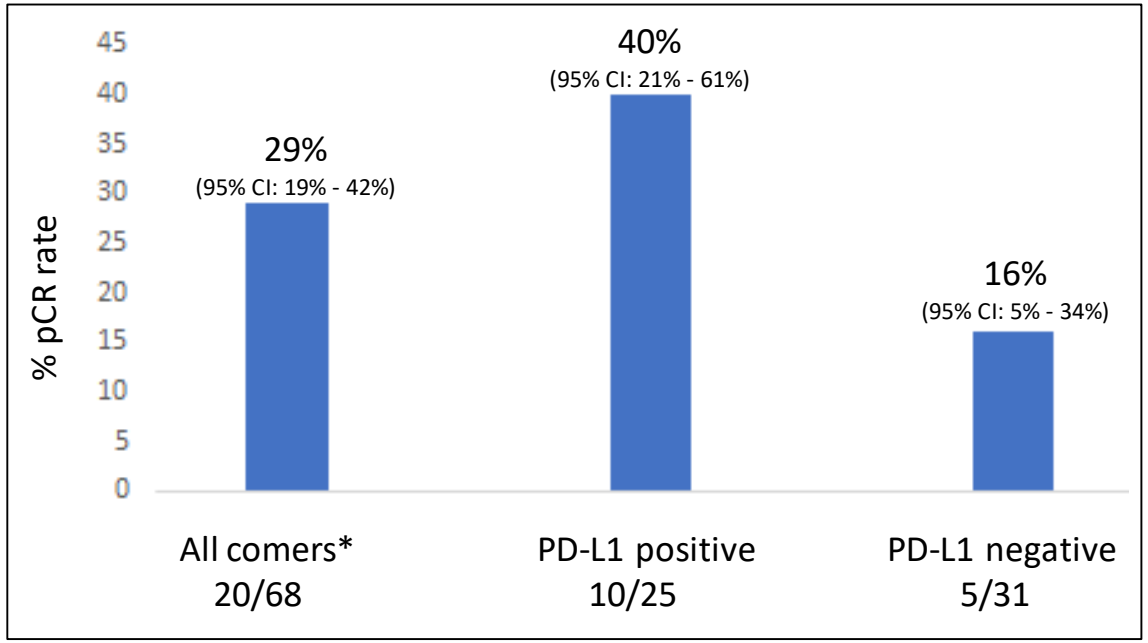
Peri-operative immunotherapy

Neoadjuvant pembrolizumab

Table 3. Pathologic Response to Pembrolizumab

Response	All Treated Patients (N = 50)	PD-L1 CPS ≥ 10% (n = 35)	PD-L1 CPS < 10% (n = 15)
Primary end point			
Pathologic complete response, No. (%)	21 (42)	19 (54.3)	2 (13.3)
95% CI	28.2 to 56.8		
Secondary end point			
Pathologic downstaging to pT<2, No. (%)	27 (54)	23 (65.7)	4 (26.7)
95% CI*	39.3 to 68.2		

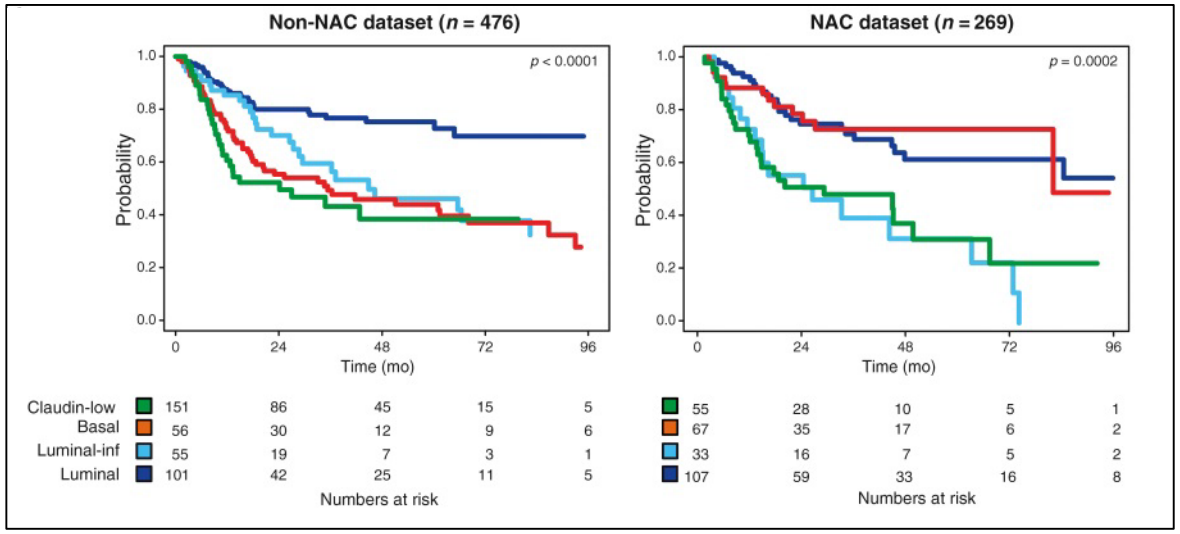
Neoadjuvant atezolizumab

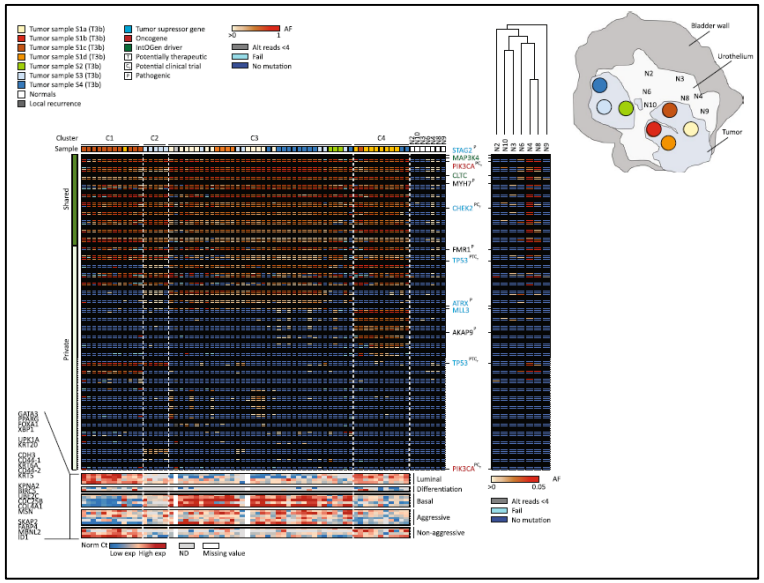


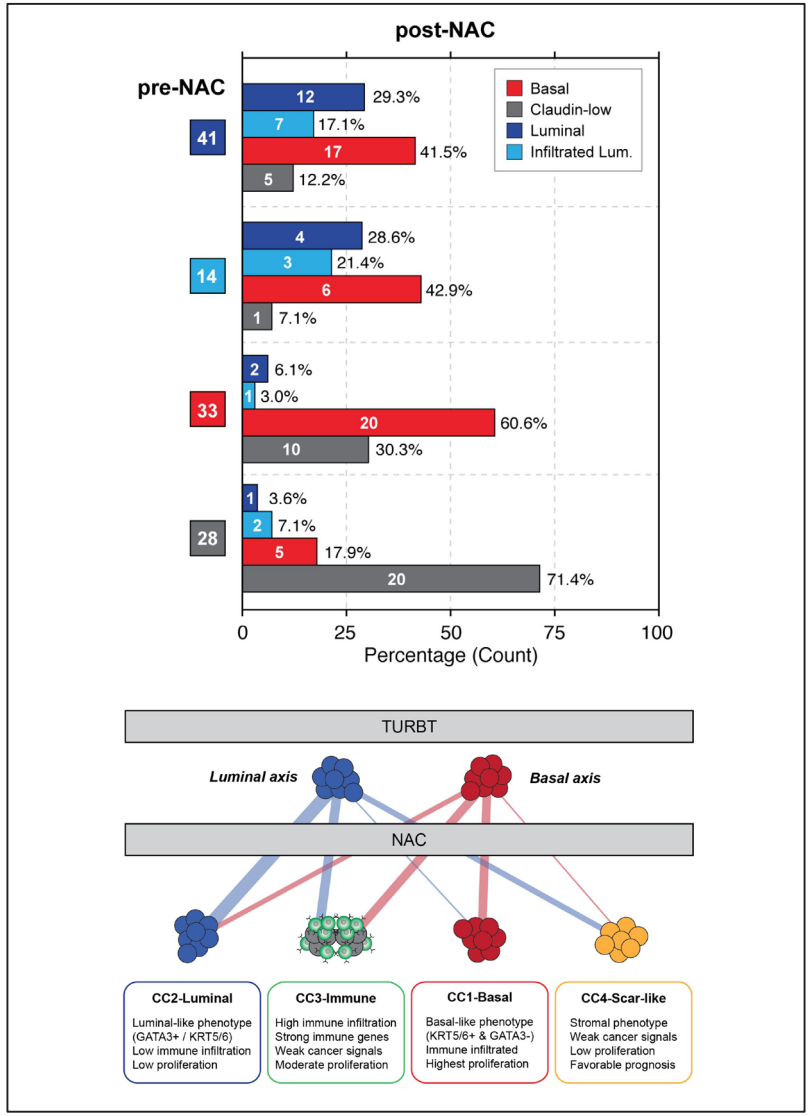
Comparison	Name	n	Setting	Primary endpoint	Completion
Pembrolizumab Observation	AMBASSADOR	739	Adjuvant	OS/DFS	2019
Atezolizumab Observation	IMvigor010	800	Adjuvant	DFS	2022
Nivolumab Placebo	CheckMate274	640	Adjuvant	DFS	2020

Necchi, J Clin Oncol, 2018; Powles et al, ASCO 2018, abstract 4506

Expression subtypes, heterogeneity, class switching







Seiler et al, Eur Urol, 2017; Thomson et al, Sci Rep, 2017; Seiler et al, Clin Cancer Res, 2018

Conclusions

- Cisplatin based neoadjuvant combination chemotherapy provides a modest absolute survival advantage for bladder transitional cell carcinoma
- Adjuvant chemotherapy for bladder cancer has lower level evidence to support its use but appears to provide a similar benefit
- Adjuvant platinum based chemotherapy extends disease free survival in UTUC
- There are no randomised data to support peri-operative non-cisplatin based regimens (except in UTUC)
- Immunotherapy has activity in phase II trials. Level 1 randomised data is awaited
- Radiotherapy outcomes are improved with radio-sensitizers
- Treatment selection holds potential to improve on modest absolute benefits but we lack prospectively validated predictive biomarkers