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RT of the bladder: clinical practice and recent advancements

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#BLADDR22

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Conflicts of interest

- Research funding from CRUK, PCUK, MRC, NIHR, PCUK, Elekta AB
- Honoraria from Bayer PLC, Janssen, AZ, ASTRO, ASCO, Roche, Merck
- Editor in Chief, BMJ Oncology

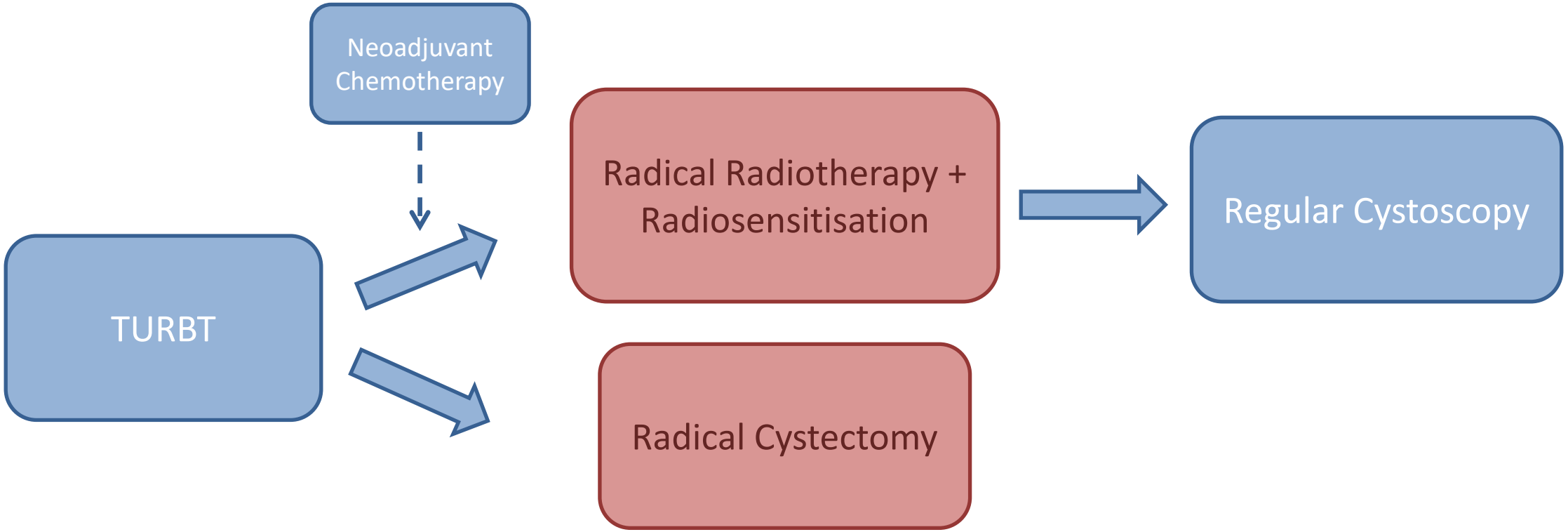
Outline

- Optimal pathway for bladder preservation
- Technological advances
- Combining radiation and immune checkpoint inhibitors

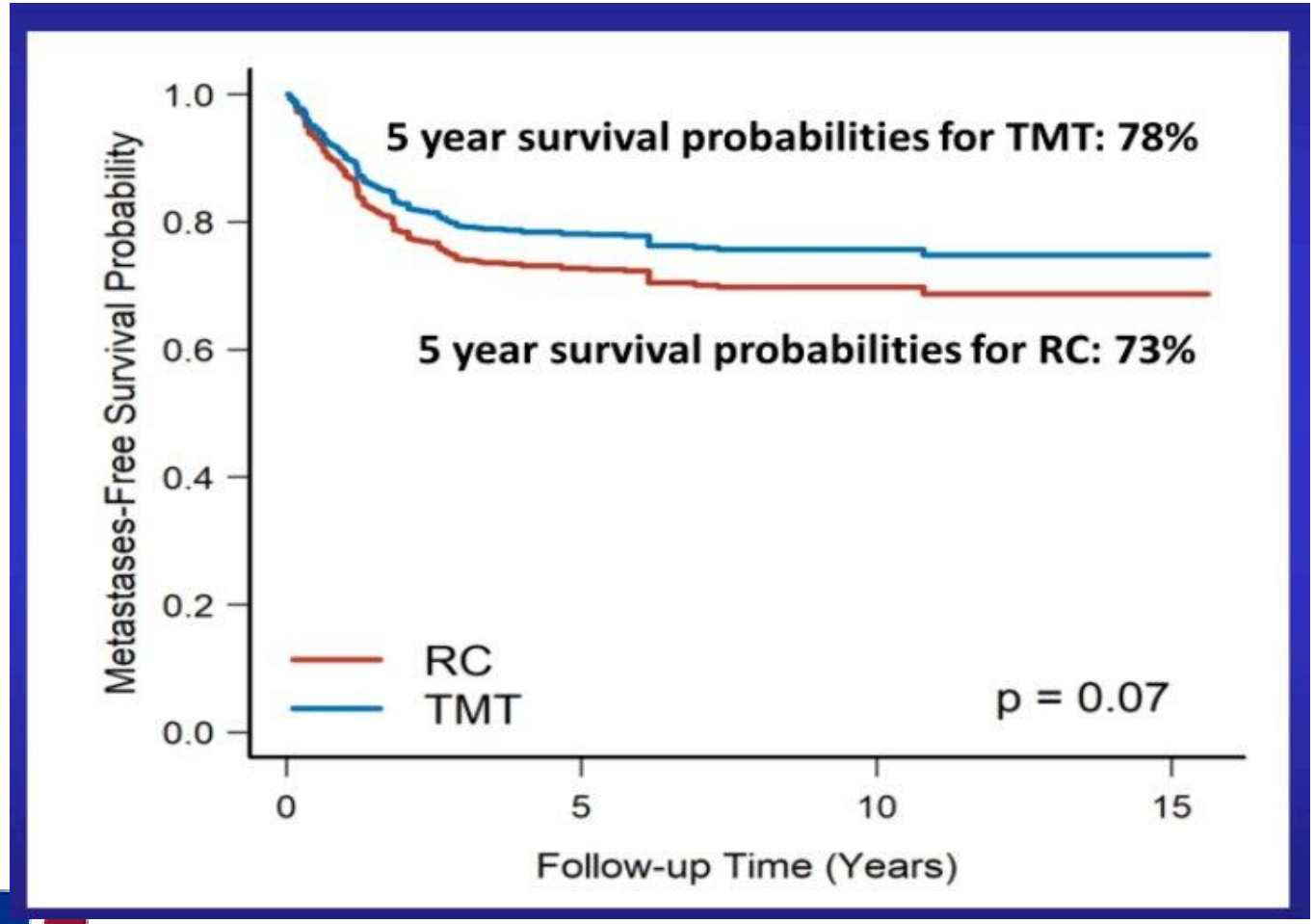
Optimal patients for radical radiotherapy treatment

- Localised-disease muscle-invasive cancer
- Maximal Trans-Urethral Resection of Bladder
- Good bladder function
- WHO PS ≤3

Management of localised muscle-invasive bladder cancer



Contemporary data: Multi-institutional comparison



Trimodality approach favoured:
Distant failure-free survival
(82 vs 78%; p=0.14)

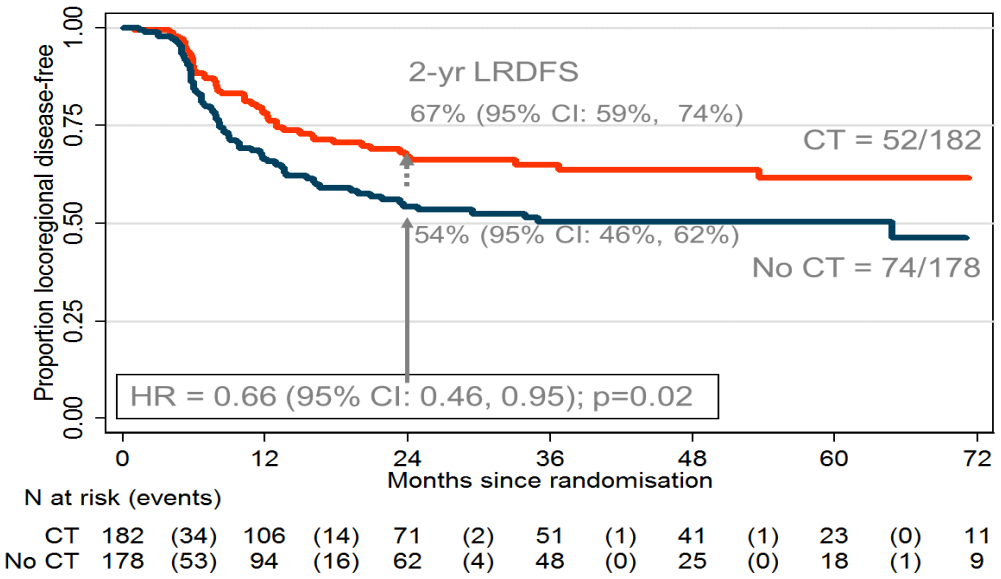
Overall survival
(78 vs 66%; p<0.001)

Cause-specific survival
(85 vs 78%, p=0.02)

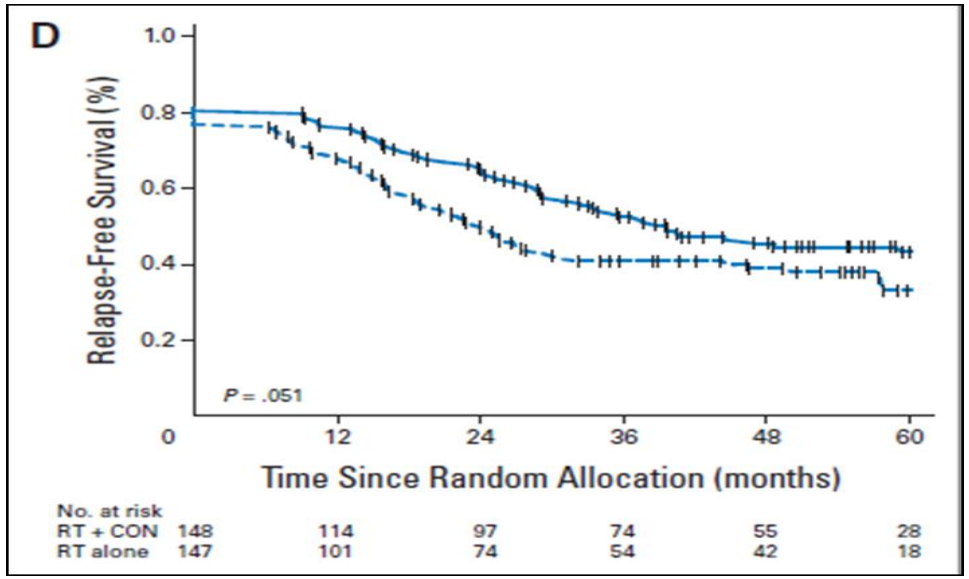
Zlotta et al: JCO 40, no. 6_suppl (February 20, 2022) 433-433

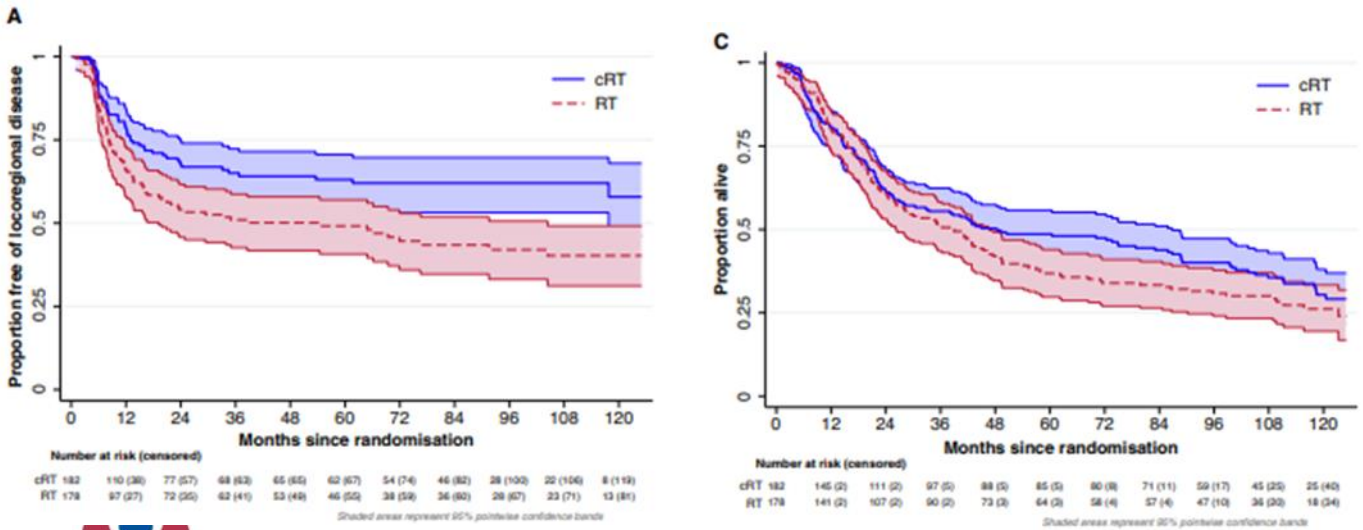
Radiosensitisation is better than radiotherapy alone

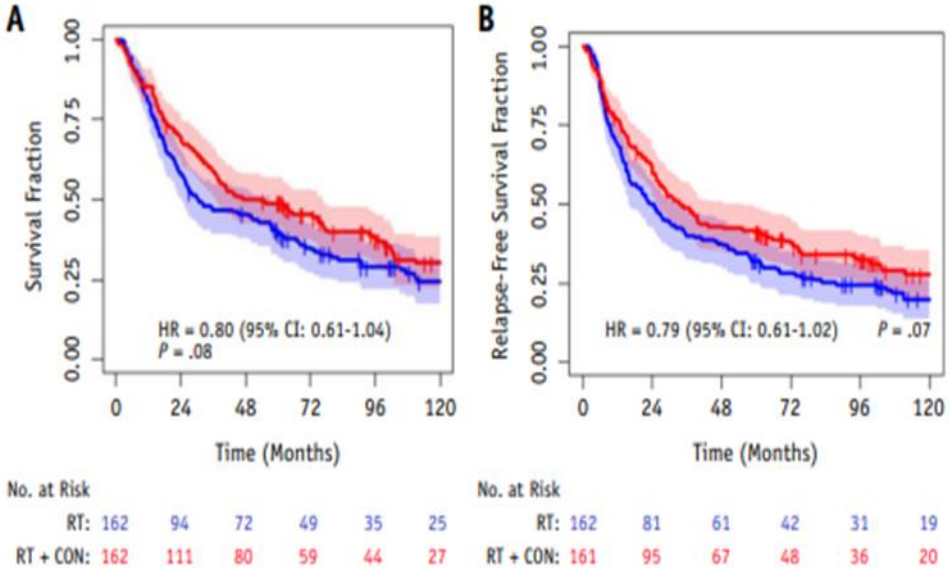
BC2001



BCON







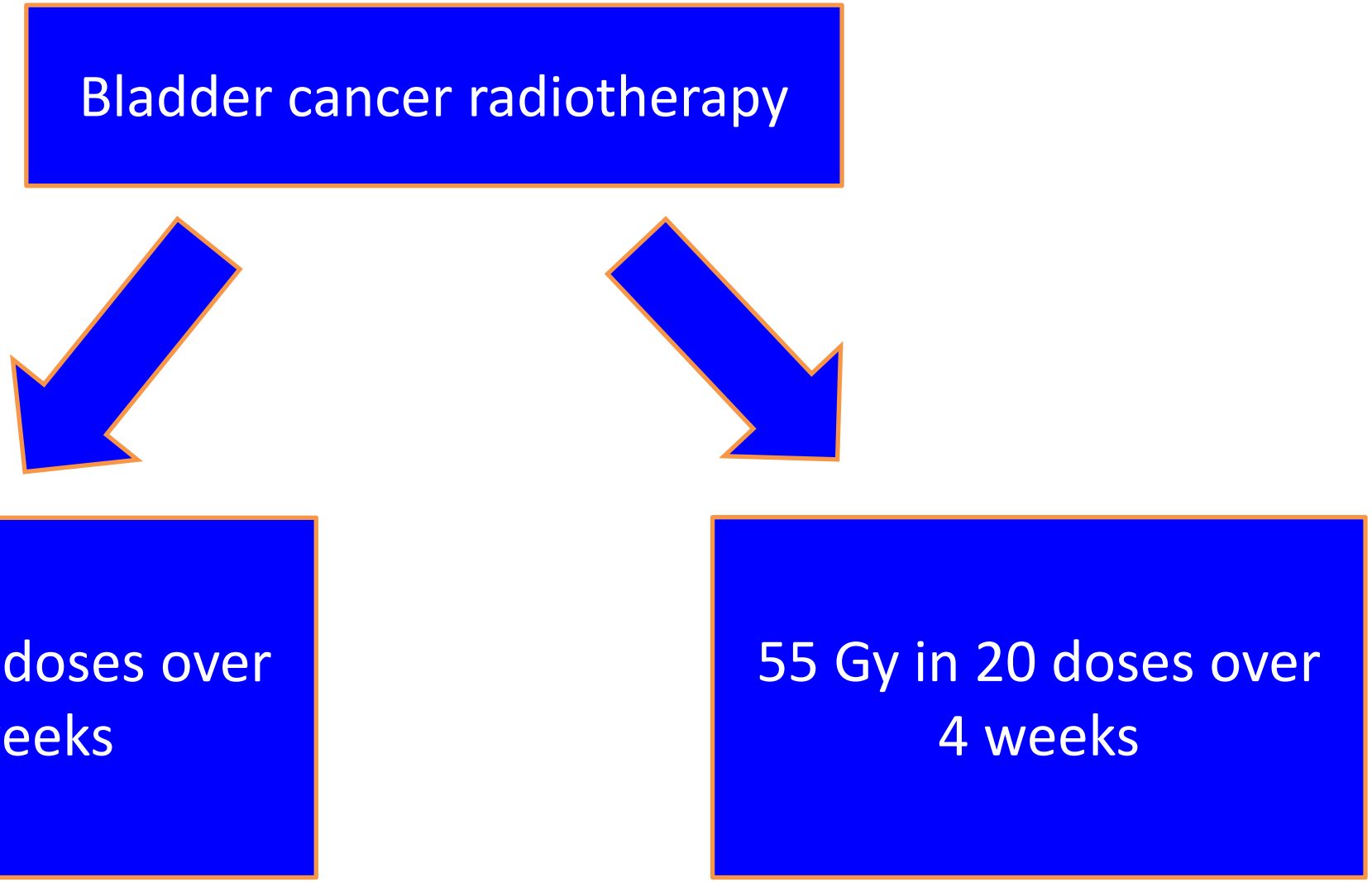
James et al. N Engl J Med. 2012 Apr 19;366(16):1477-88. Hoskin et al. J Clin Oncol. 2010 Nov 20;28(33):4912-8.
Hall et al. Eur Urol. 2022 Sep;82(3):273-279. Song et al. Int J Radiat Oncol Biol Phys. 2021 Aug 1;110(5):1407-1415

Current radiosensitisation: UK practice

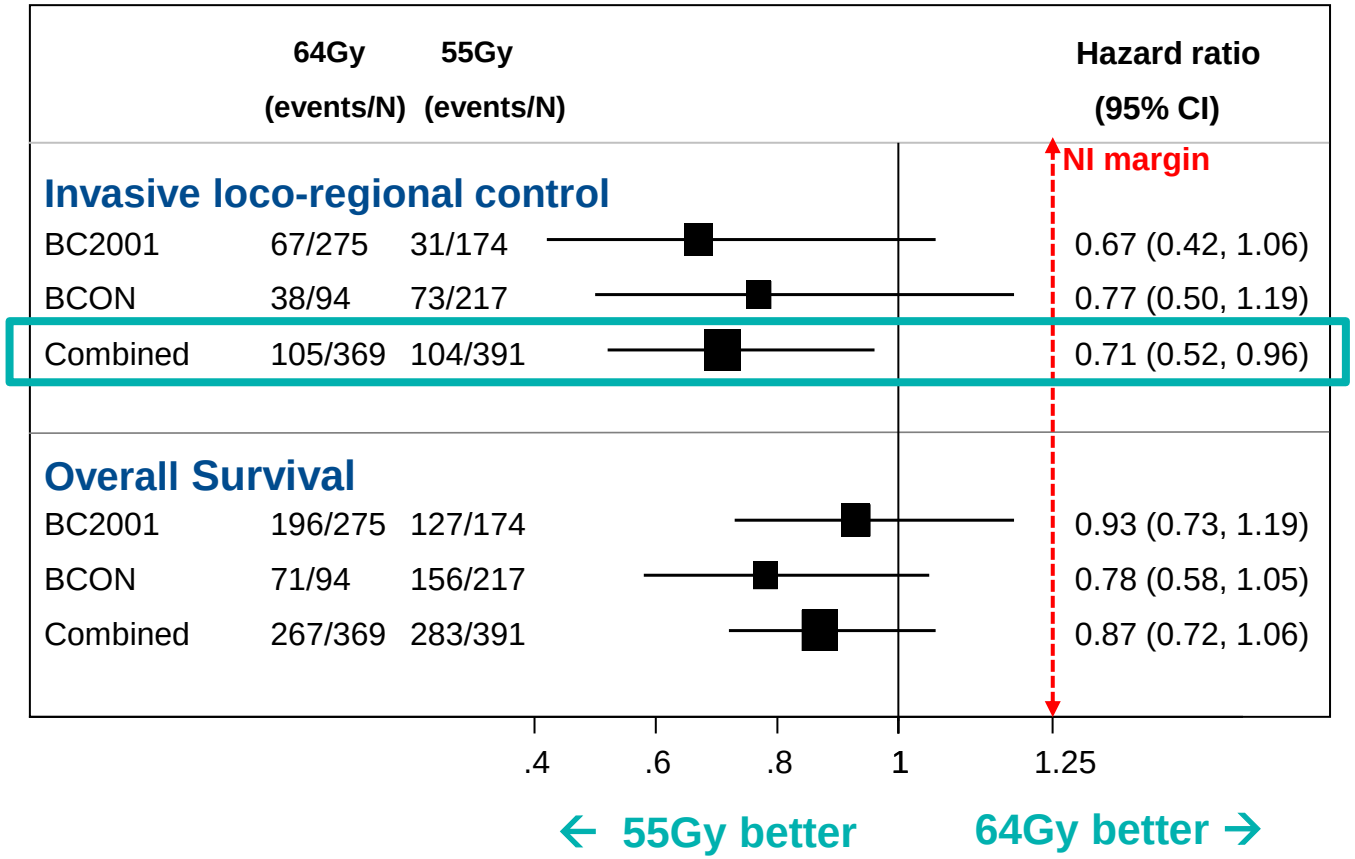
		20 fractions		32 fractions	
N		150		131	
Receiving NAC		77 (51%)		56 (43%)	
	Gemcitabine/cisplatin		65(84%)		49(88%)
	Accelerated MVAC		4 (5%)		0
	Carboplatin/gemcitabine		1(1%)		7 (12%)
	Other		7 (9%)		0
N		137		112	
Receiving CRS		92 (67%)		78 (70%)	
	5FU/Mitomycin		36 (39%)		63(81)%
	Gemcitabine		36 (39%)		6 (8%)
	Cisplatin		3 (3%)		1 (1%)
	Carbogen/nicotinamide		17 (18%)		7(9%)
Both NAC and CRS		58 (39%)		51 (39%)	
No NAC/CRS		36 (24%)		32 (24%)	

Huddart et al. JCO 38 (6). Suppl. 503

Conventional fractionation radiotherapy was the standard of care…



64Gy vs 55Gy comparison – ILRC & OS



95% CI excludes non-inferiority margin (p-value<0.001) AND excludes null difference (superiority p-value 0.026)

55Gy ILRC benefit also seen in patients receiving RT alone: HR 0.72 [CI 0.49-1.05]

Choudhury et al. Lancet Oncol. 2021 Feb;22(2):246-255

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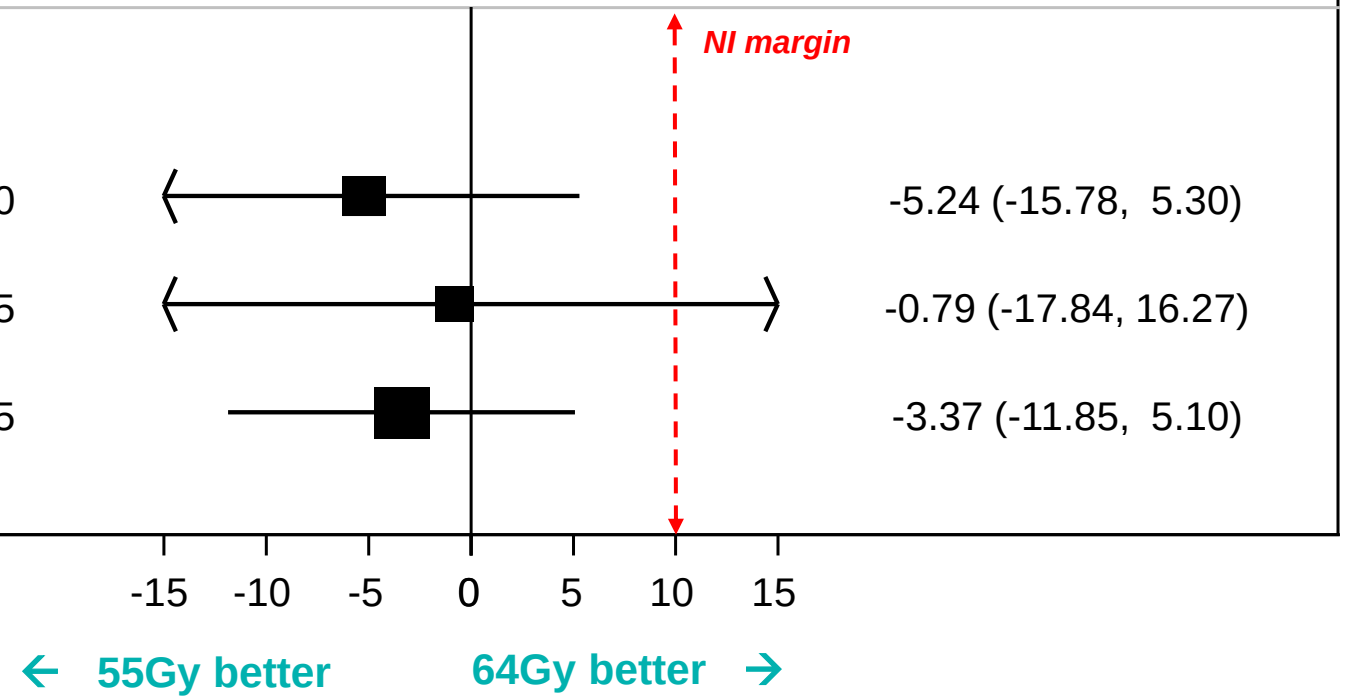
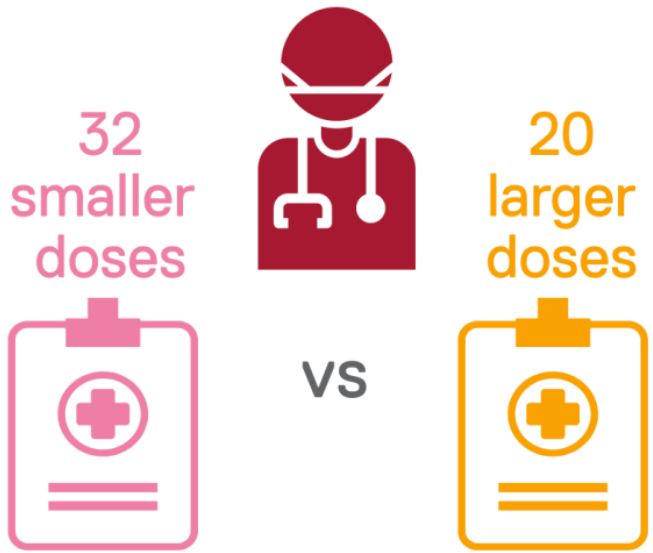
64Gy vs 55Gy comparison – Late toxicity

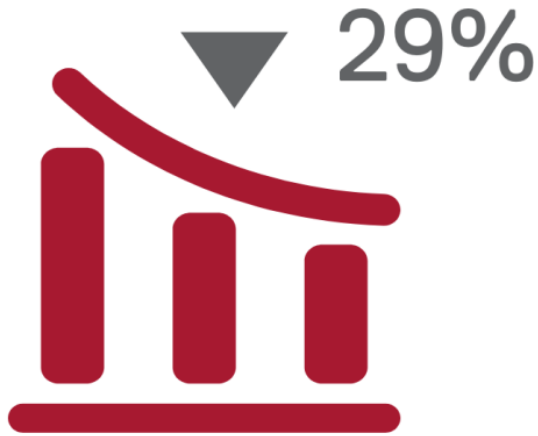
	64Gy (events/N)	55Gy (events/N)	Risk difference (95% CI)
Late bladder and bowel toxicity			
BC2001	62/203	31/120	-5.24 (-15.78, 5.30)
BCON	27/75	66/175	-0.79 (-17.84, 16.27)
Combined	89/278	97/295	-3.37 (-11.85, 5.10)



A shorter radiotherapy course reduces risk of bladder cancer coming back over five years



Two different
radiotherapy schedules compared by researchers

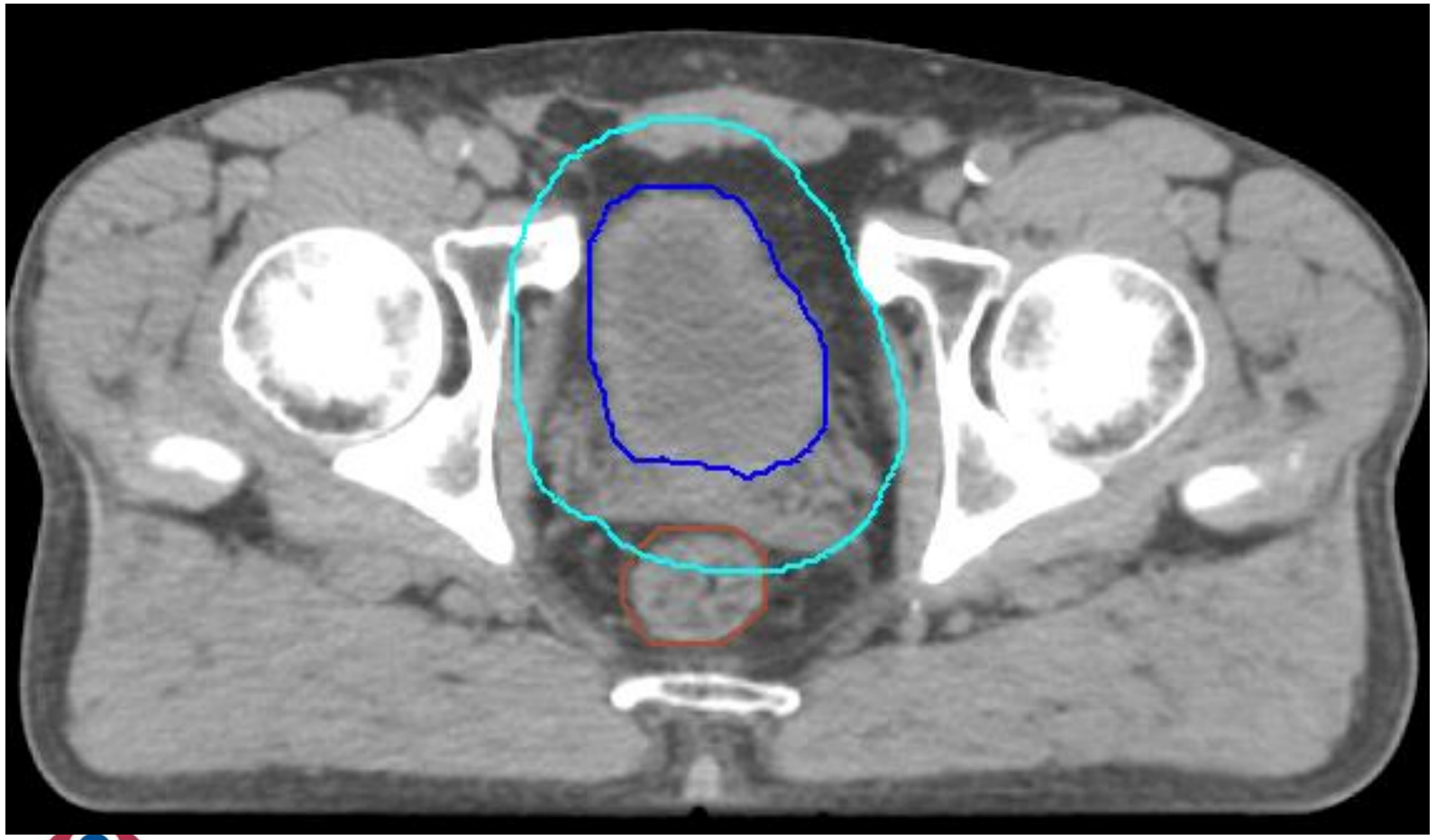


29 per cent
lower risk of cancer coming back on shorter course

12 fewer
hospital visits per patient - reducing Covid-19 related risk

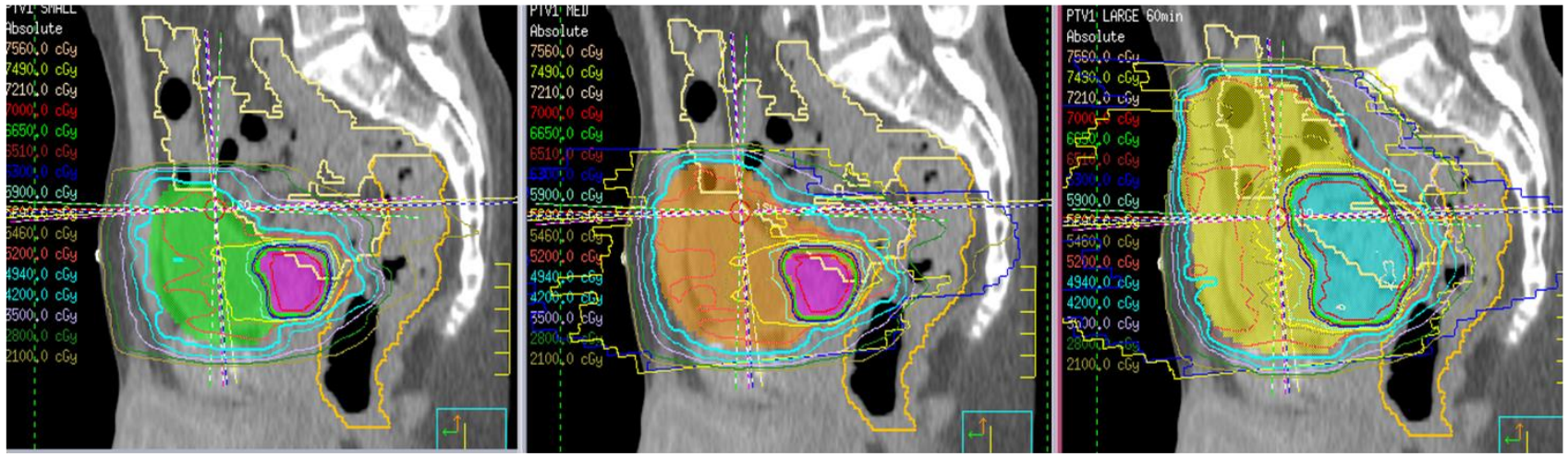
Source: Study published in The Lancet Oncology

3-D conformal radiotherapy reduces toxicity



Further advances in radiotherapy: Adaptive radiotherapy with Plan of the Day 'PoD'

Coronal planning CT scans to illustrate 3 plans for daily selection



Process for Plan selection

MacDonald et al. Clin Oncol (R Coll Radiol). 2013 Sep;25(9):549-56

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The RAIDER Study: results at ASCOGU23?

240 patients with pT2-T4a N0 M0 urothelial bladder carcinoma fulfilling eligibility criteria

120 patients due to receive 32f*

120 patients due to receive 20f*

RANDOMISATION (1:1:2) (within each fractionation cohort)

Group 1:
Standard planning and delivery whole bladder RT (WBRT) (control)

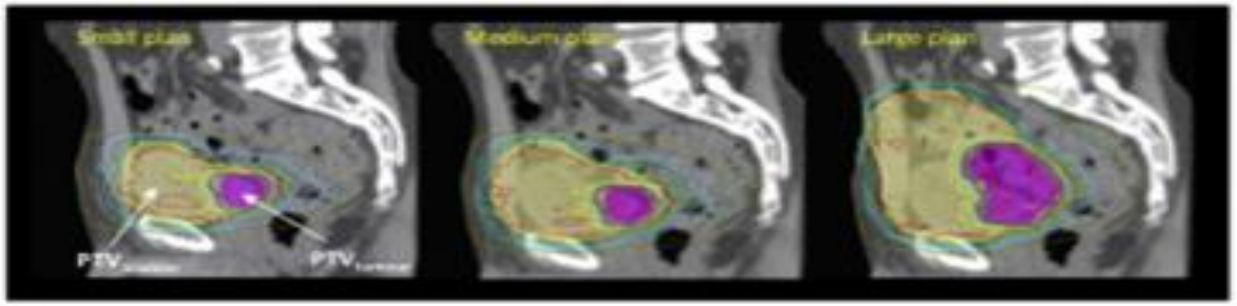
PTV 64Gy in 32f
PTV 55Gy in 20f

Group 2:
Standard dose
Adaptive tumour focused RT (SART)

PTV_{tumour} 64Gy. $PTV_{bladder}$ 52Gy in 32f
PTV_{tumour} 55Gy. $PTV_{bladder}$ 46Gy in 20f

Group 3:
Dose escalated
Adaptive tumour boost RT (DART)

PTV_{tumour} 70Gy. $PTV_{bladder}$ 52Gy in 32f
PTV_{tumour} 60Gy. $PTV_{bladder}$ 46Gy in 20f

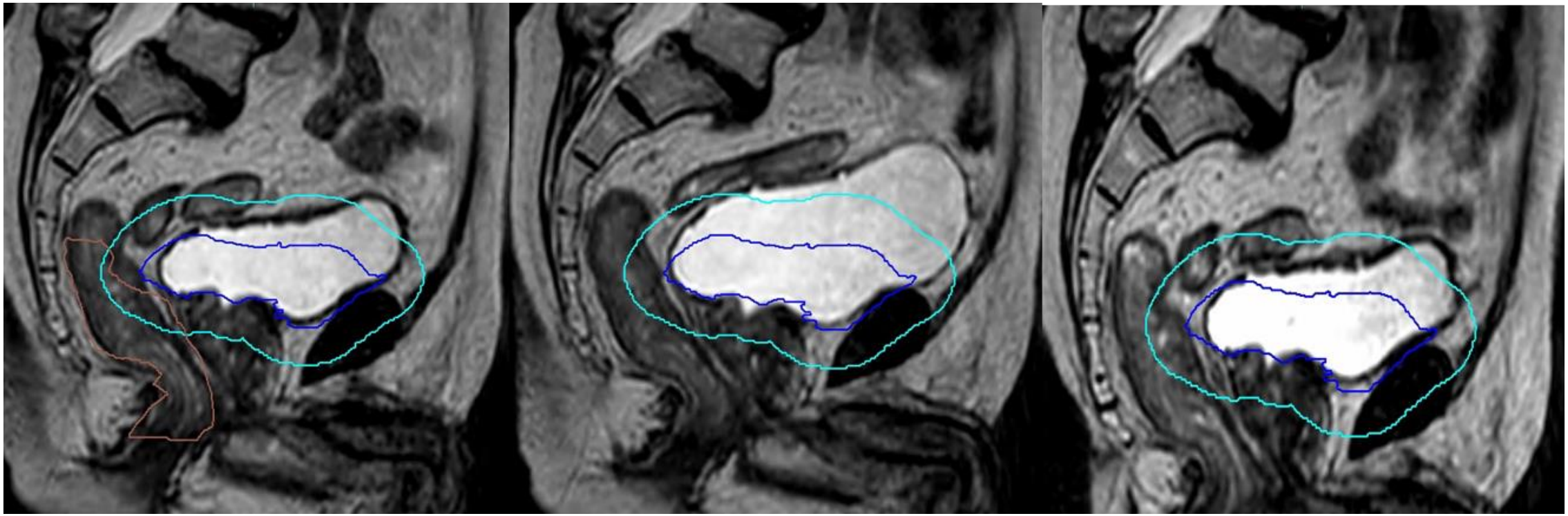


Adaptive radiotherapy strategy using library of 3 plans for treatment delivery in SART and DART arms. Plan selection dependent on anatomy as seen on pre-treatment CBCT acquired at each fraction.

Hafeez et al. BMJ Open. 2020 Dec 31;10(12):e041005.

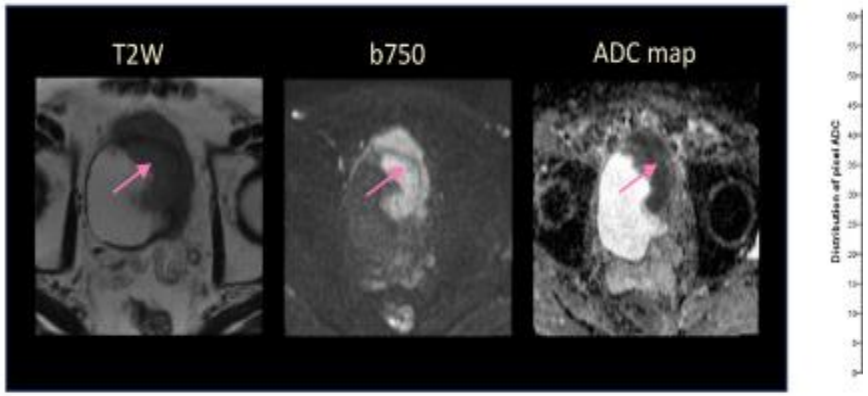
MR-image guided radiotherapy

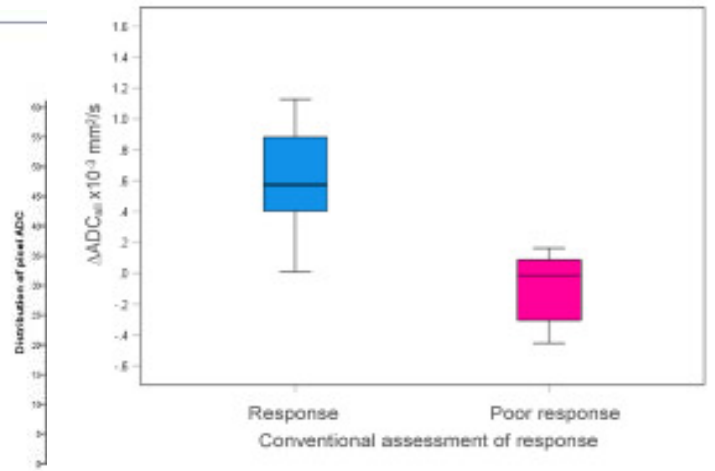
Adapting for daily bladder changes



Functional MRI in radiotherapy

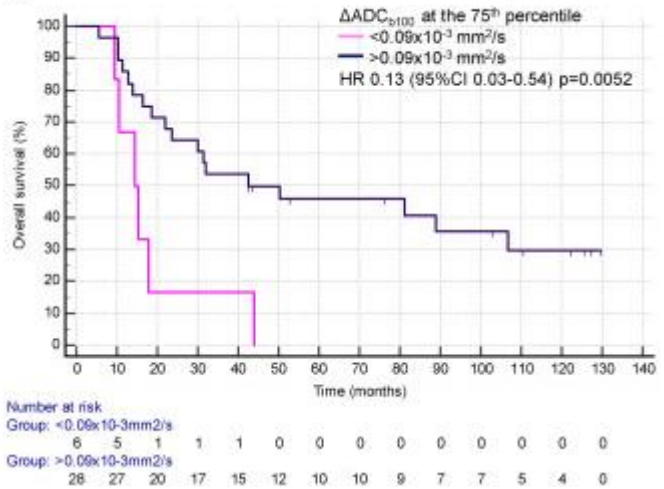
Baseline MRI analysis



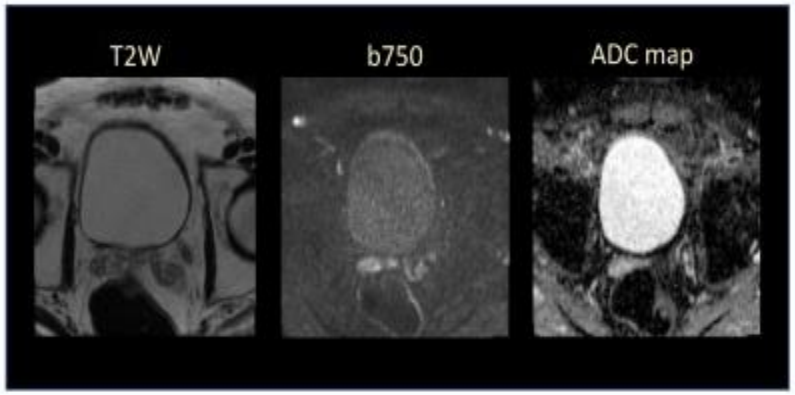


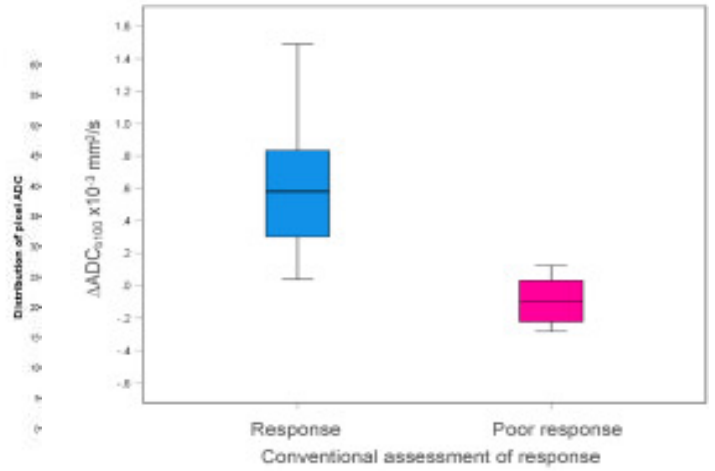
D)

i)



Post radiotherapy MRI analysis





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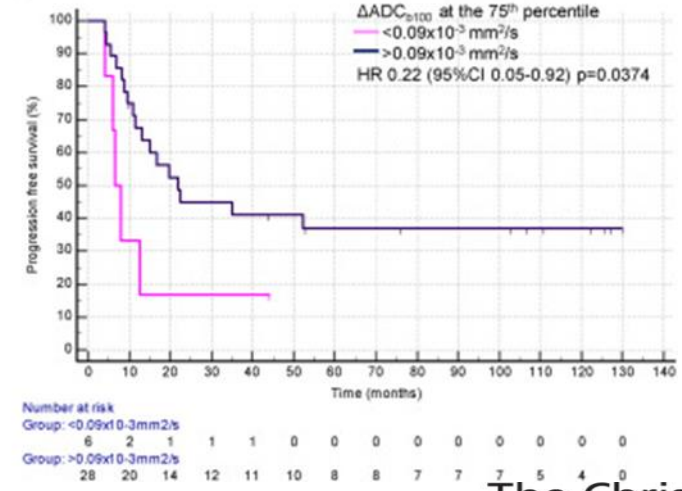

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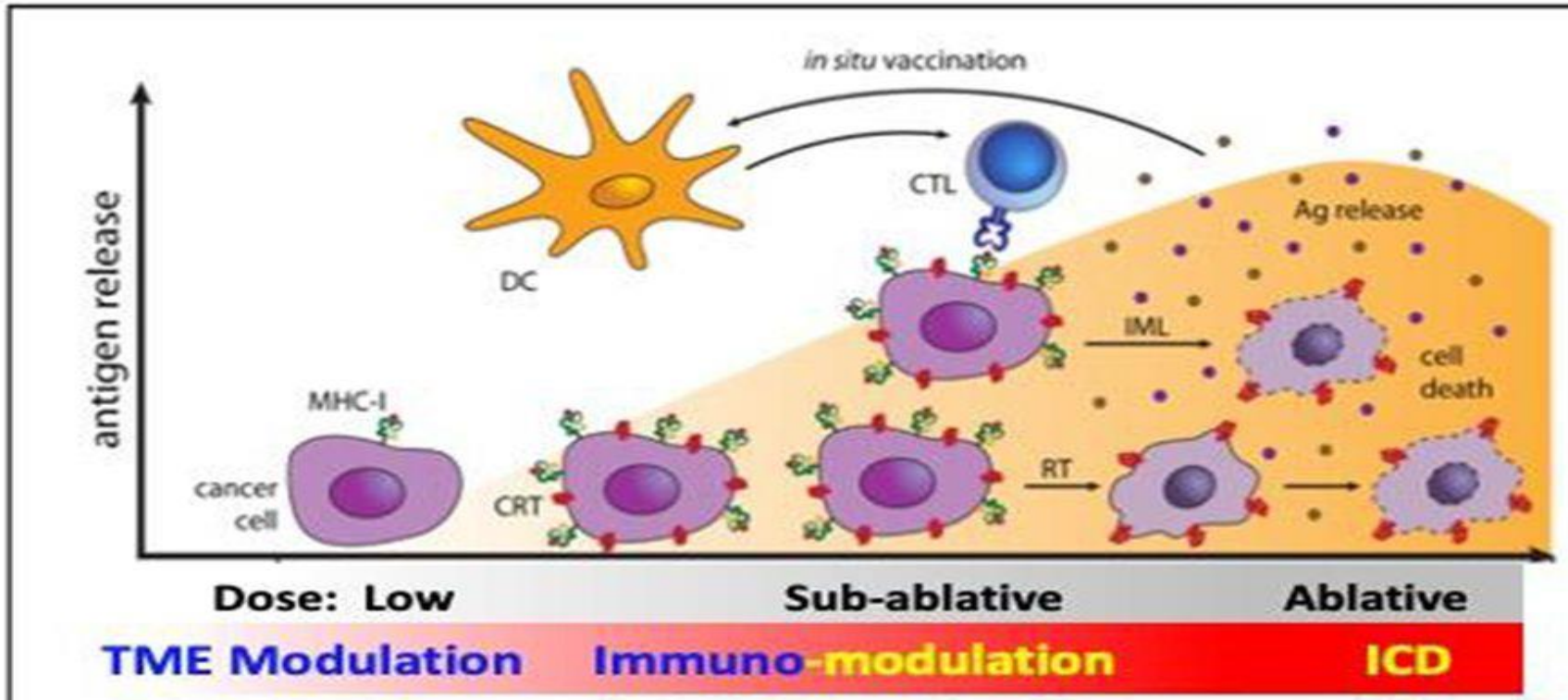
Hafeez et al. Clin Oncol (R Coll Radiol). 2022 Oct;34(10):630-641.

Demaria et al

Radiation Immunogenicity



IM	ICD
Induction of cell surface: - MHC - I - Fas - CD40 - NKG2D - OX40L - 41BBL Inhibition of - PD1 - PDL1	- membrane calreticulin - HMGB1 release - ATP release - Uric acid - S100 - cell surface HSP70

TMEM-RT

↓

Tumor microenvironment modulating RT

~ 0.5 Gy x 4

ImRT
SBRT

↓

Immunomodulatory RT

~ 8 Gy x 3

~ 6 Gy x 5

IART
SRS / SABR

↓

Immunoablative RT

~ 34 Gy x 1

~ 18 Gy x 3

~ 10 Gy x 5

Phase I clinical trials published: more to come….

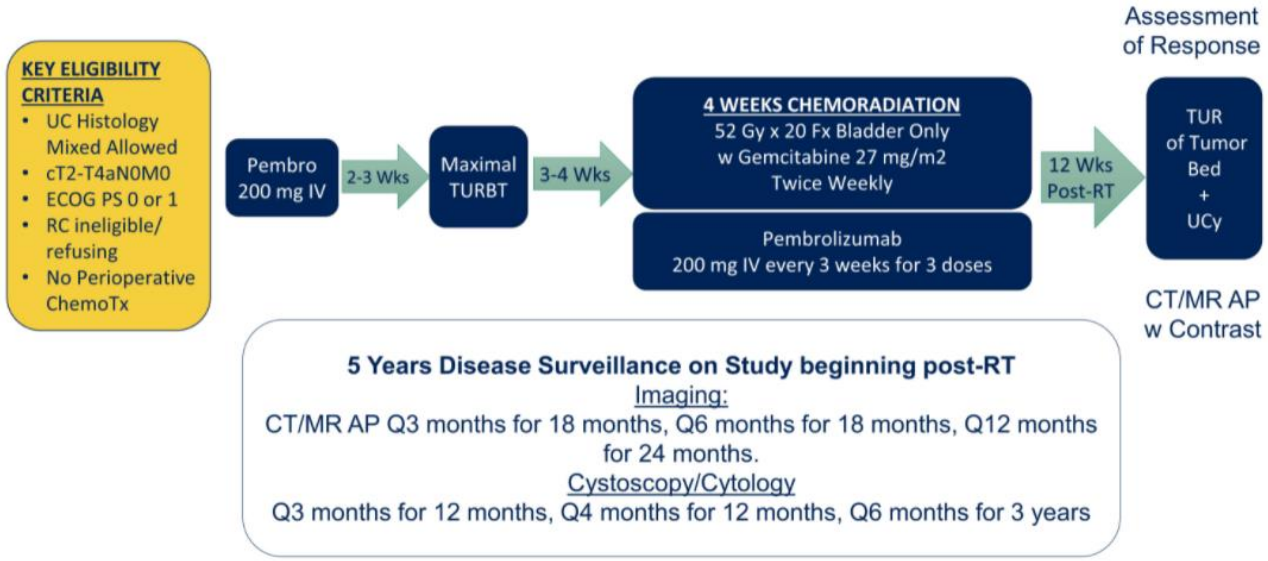
- Significant toxicity with 36 Gy in 6 weekly fractions (2/6 DLT)
- Significant toxicity with 50 Gy in 20 fractions with weekly gem (4/8 colitis)
- Largest phI: 26 patients across three arms: combination of anti-PD-1 & anti-CTLA4 increases toxicity

Table 4 - CTCAE-scored adverse events per regimen

Adverse events	NIVO480		NIVO3 + IPI1				IPI3 + NIVO1		
Grade, *n* (%)	All	3	All	3	4	5	All	3	4
Any event	9 (90)	**1 (10)**	10 (100)	**3 (30)**	**1 (10)**	**1 (10)**	10 (100)	**5 (50)**	**1 (10)**
Gastrointestinal	8 (80)		9 (90)	**2 (20)**	**1 (10)**		6 (100)	**3 (50)**	

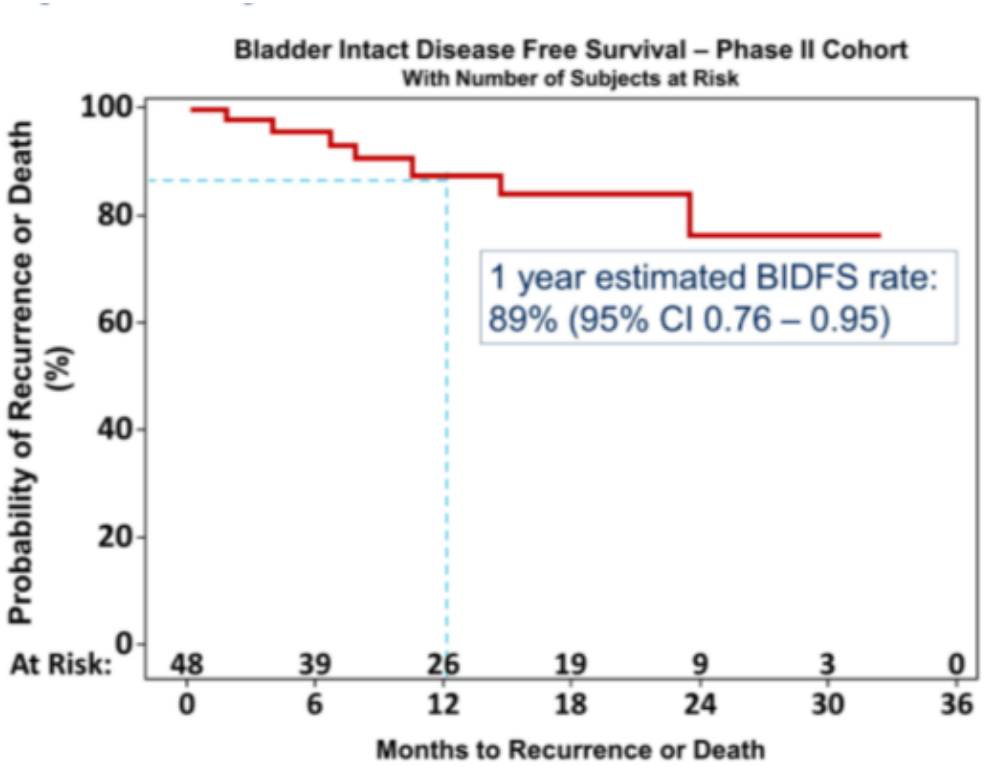
Tree et al. Int J Radiat Oncol Biol Phys. 2018 Aug 1;101(5):1168-1171. Marcq et al. Int J Radiat Oncol Biol Phys. 2021 Jul 1;110(3):738-741
de Ruiter et al. European Urology. *In press*

Concurrent IO: Pembrolizumab/Gemcitabine



	Grade 1 & 2	%
Fatigue	20	41.7%
Nausea	17	35.4%
Diarrhea	16	33.3%
Urinary Urgency	14	29.2%
Rash Maculopapular	11	22.9%
Platelets Decreased	11	22.9%
Anorexia	10	20.8%
Anemia	8	16.7%
White Blood Cell Decreased	8	16.7%
Urinary Tract Pain	6	12.5%
Alanine Aminotransferase	6	12.5%
Aspartate Aminotransferase	6	12.5%
Vomiting	6	12.5%
Chills/Cold/Flu	5	10.4%
Pruritus	5	10.4%
Neutrophil Count Decreased	5	10.4%
Abdominal Pain	4	8.3%

	Grade 3 & 4	%
Diarrhea	2	4.2%
Lymphocyte Count Decreased	2	4.2%
Colitis	2	4.2%
Fatigue	1	2.1%
Anemia	1	2.1%
Urinary Tract Pain	1	2.1%
Abdominal Pain	1	2.1%
Hypokalemia	1	2.1%
Hyponatremia	1	2.1%
Urinary Tract Infection	1	2.1%
Neutropenia	1	2.1%
Febrile Neutropenia	1	2.1%
Protein Losing Enteropathy	1	2.1%
Immune-Related Polyneuropathy	1	2.1%
Colonic Perforation	1	2.1%



Balar et al. (Presented at ASCO 2021)

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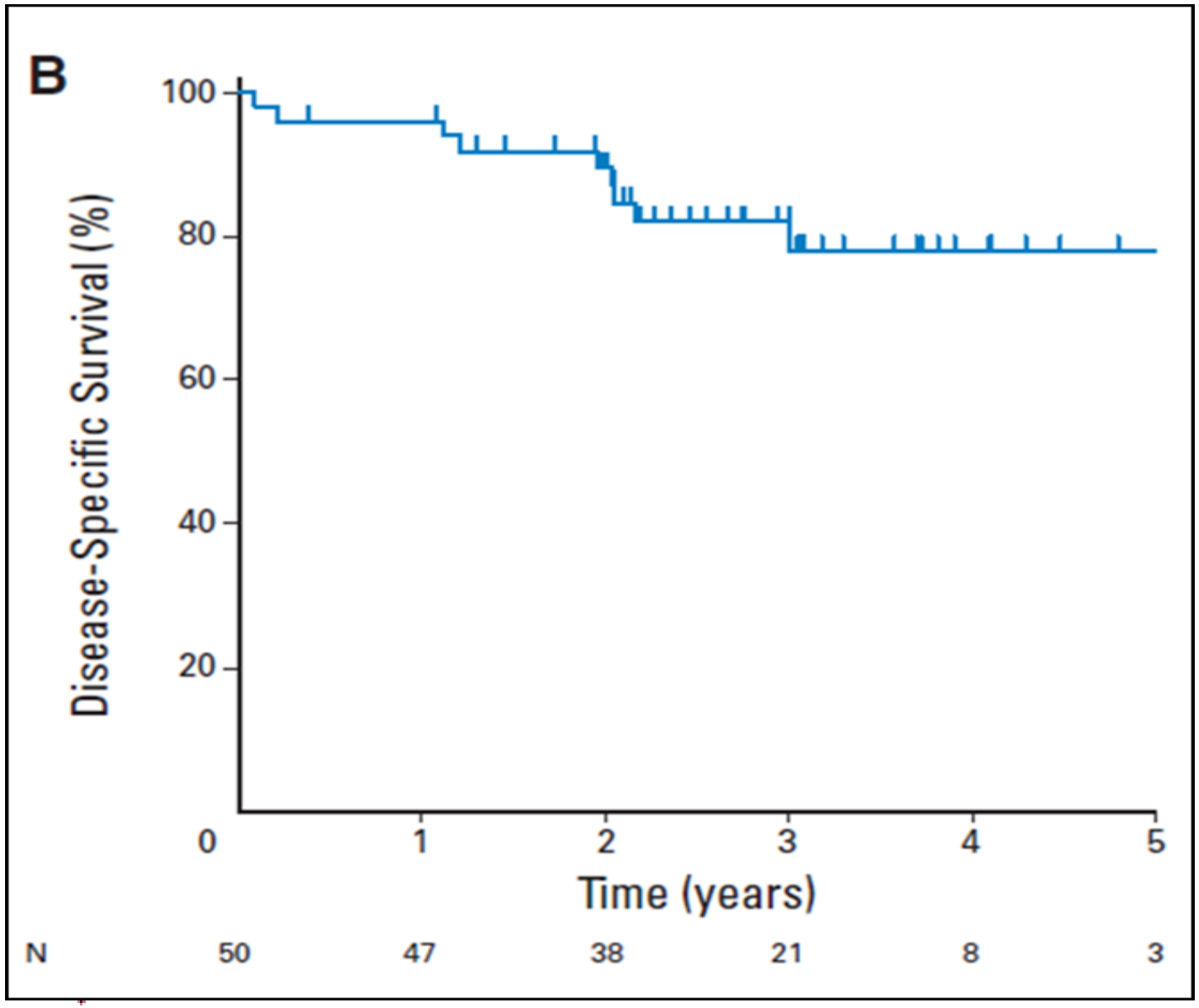

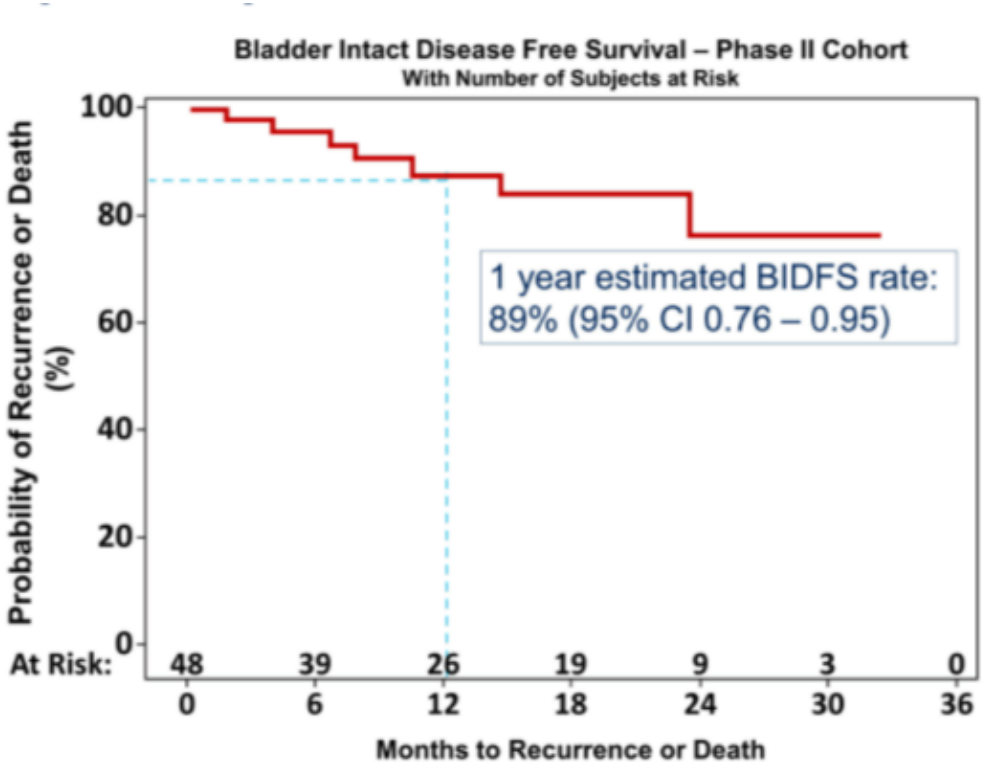

Balar et al. (Presented at ASCO 2021)

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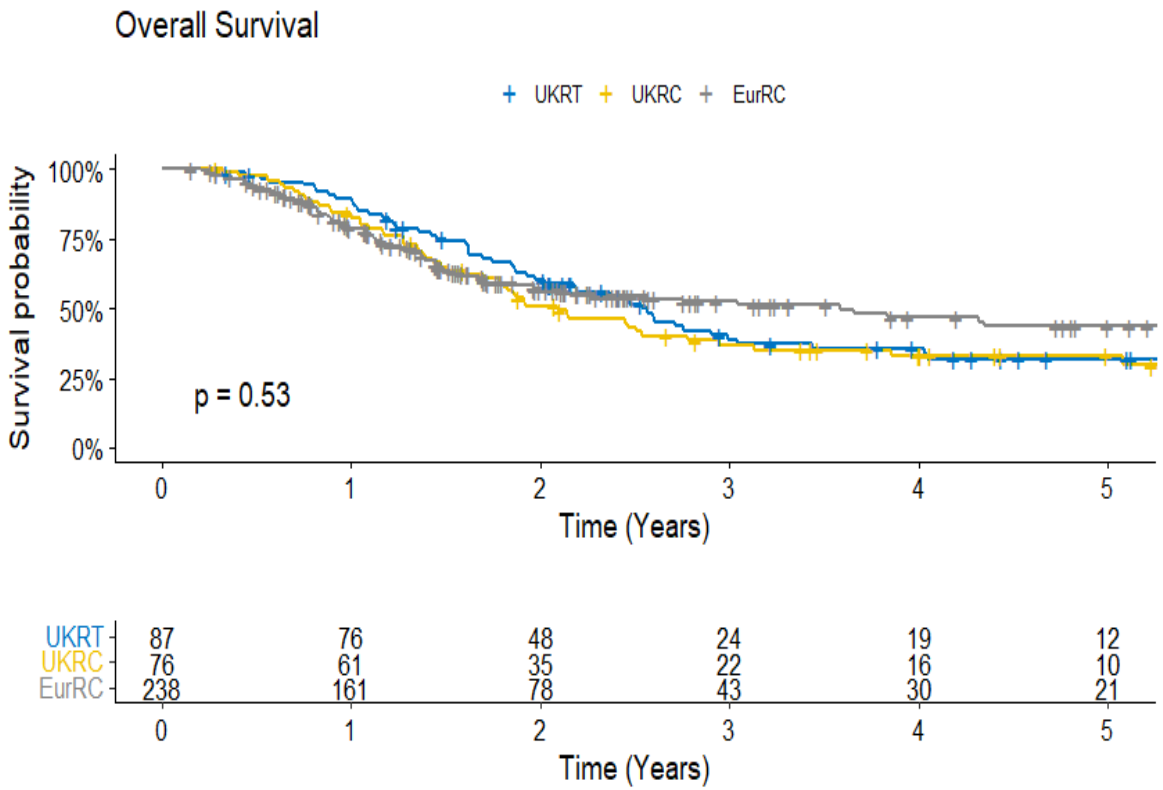
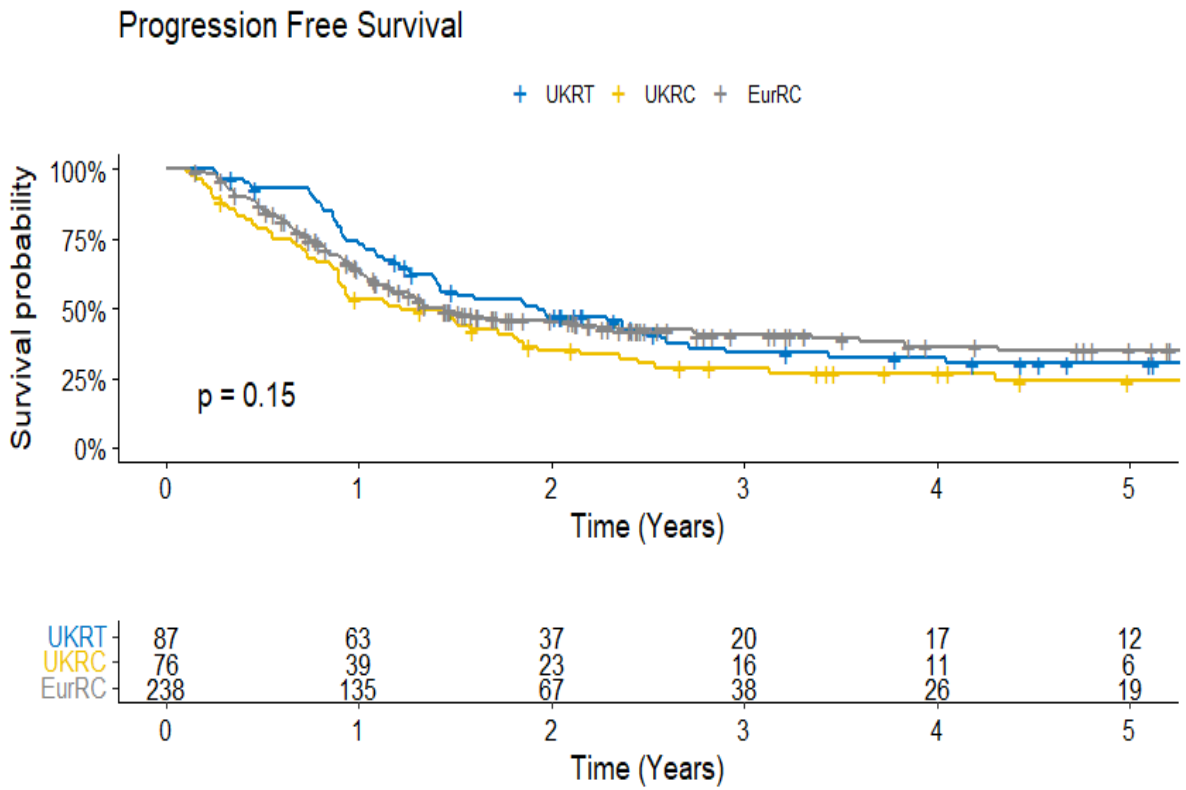
Outcomes of N+ disease with radiotherapy and surgery





Swinton et al. ASTRO 2022

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Conclusions

- Outcomes of radiotherapy with radiosensitisation are comparable to surgery with long term data now avilable
- Advanced technology is improving delivery of radiation
- Further data required on combining radiation and immunotherapy
- N+ disease has a poor prognosis; outcomes with surgery and radiation are equivalent

Questions?