Jornada de Pacientes con Cáncer de vejiga

El papel de la radioterapia en el manejo de Pacientes con cáncer de vejiga

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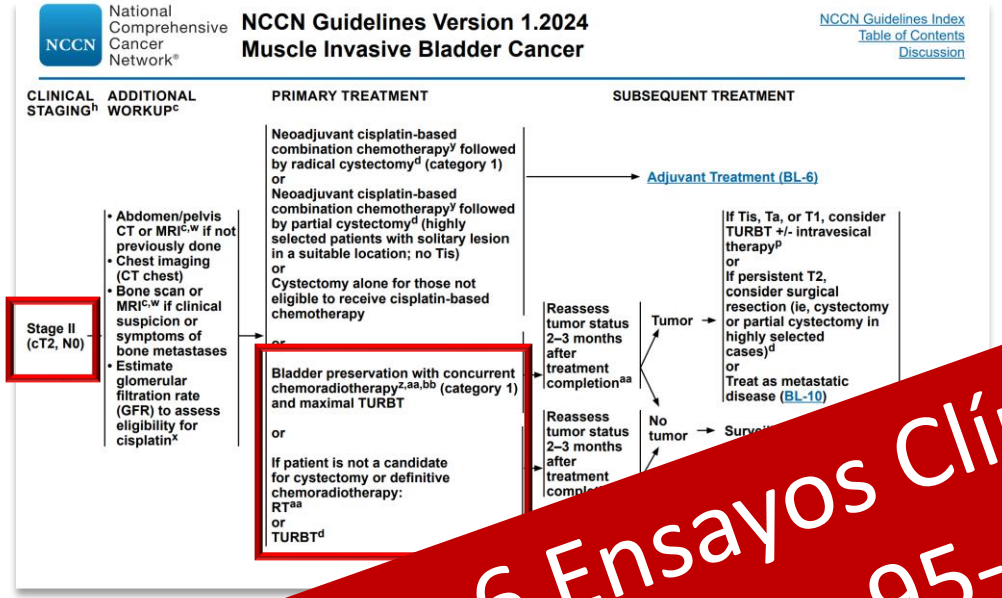
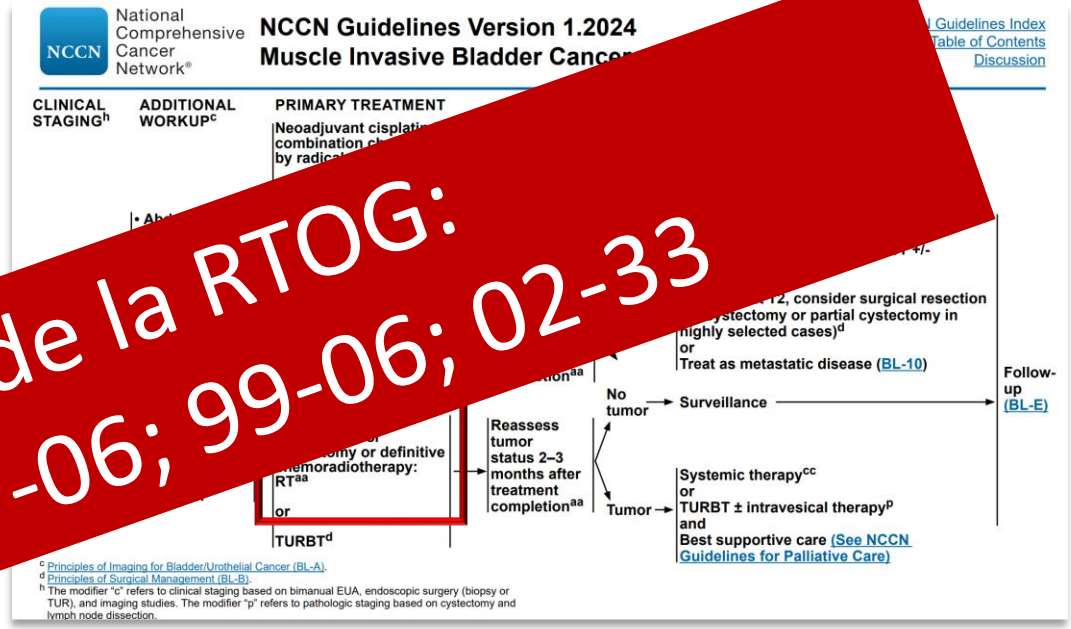
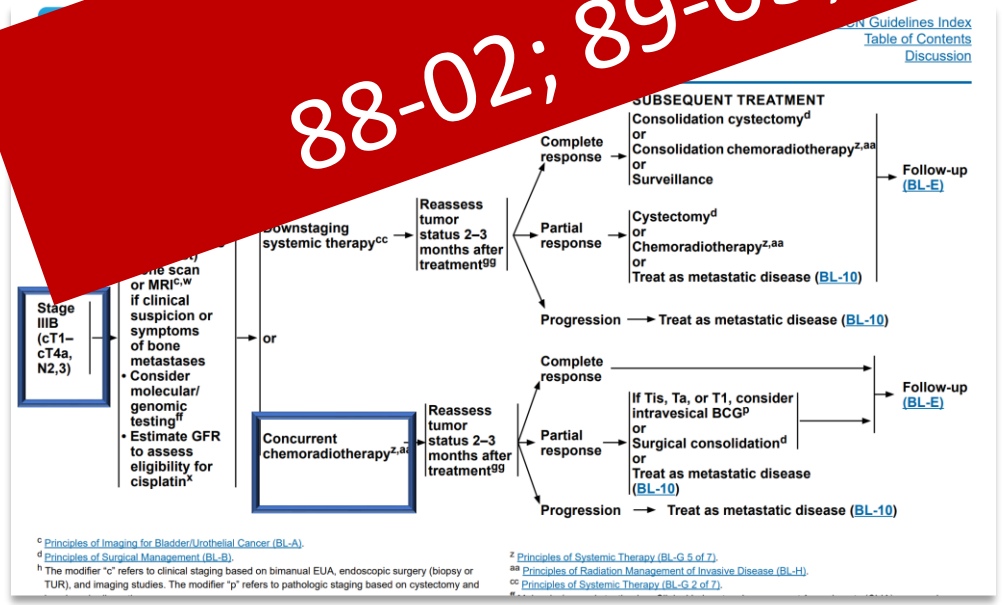
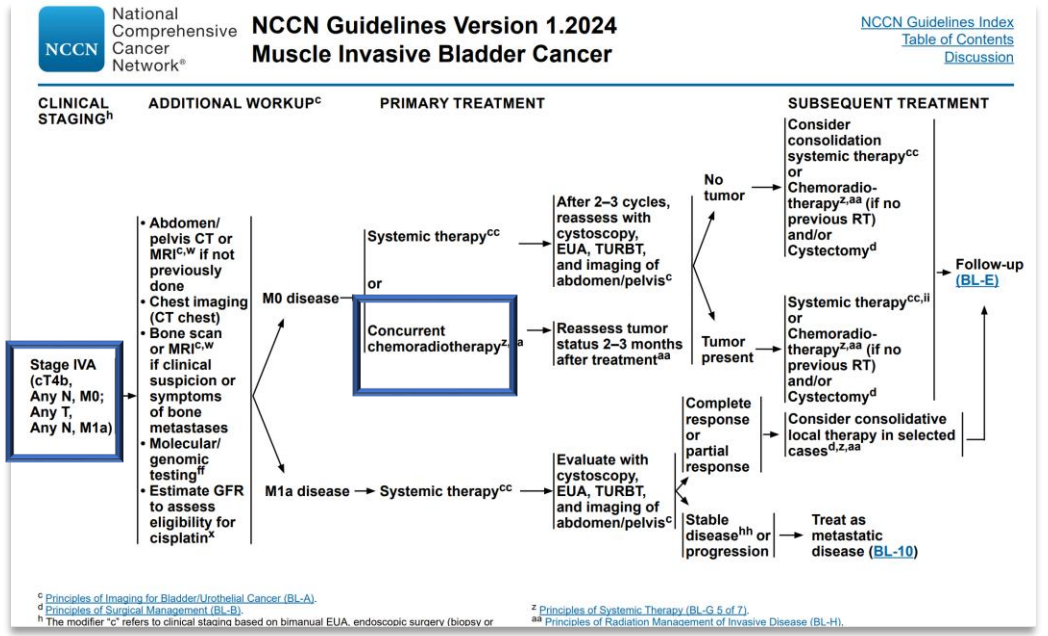
Indications for Bladder Preservation (TMT)







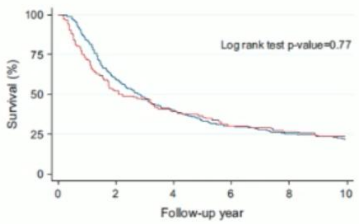


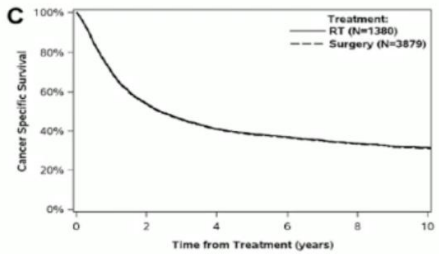
6 Ensayos Clínicos de la RTOG:
88-02; 89-03; 95-06; 97-06; 99-06; 02-33

INTRODUCCION

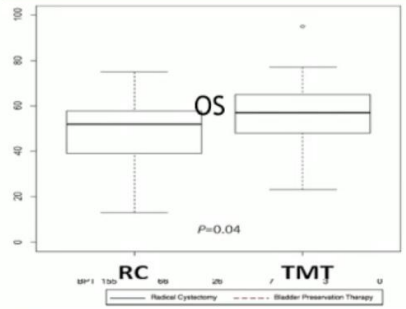
Sources of data comparing RT and surgery for MIBC

Population studies[1-2]





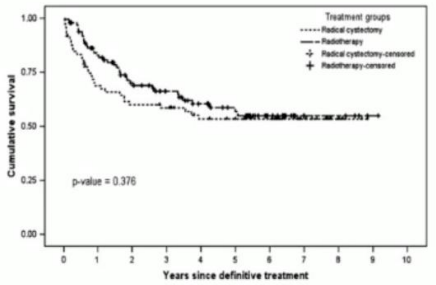
Systematic review



Academic centre comparisons[5]

Series	Stages	N	Overall survival	
Cystectomy			5yr	10yr
USC (Stein et al 2001)	P2-P4a	633	48	32
MSKCC (Dalbagni et al 2001)	P2-P4a	181	36	27
Selective bladder preservation				
Erlangen (Rodel et al 2002)	cT2-4	326	45	29
MGH (Shipley et al 2001)	cT2-4a	190	54	36

Single institution studies[4]



BPT, bladder preservation therapy; MIBC, muscle-invasive bladder cancer; RC, radical cystectomy; RT, radiotherapy

1. Munro et al. Int J Radiat Oncol Biol Phys. 2010; 2. Booth Cm et al. Cancer 2014; 3. Arcangelia et al 2015 Critical reviews in haematology and oncology 95 287-396,4. Kotwal et al. IJROBP 2008 5. Shipley et al Sem radiat Oncol 2005)

There are no randomized studies comparing the two modalities

SPARE TRIAL (NCT00867347)

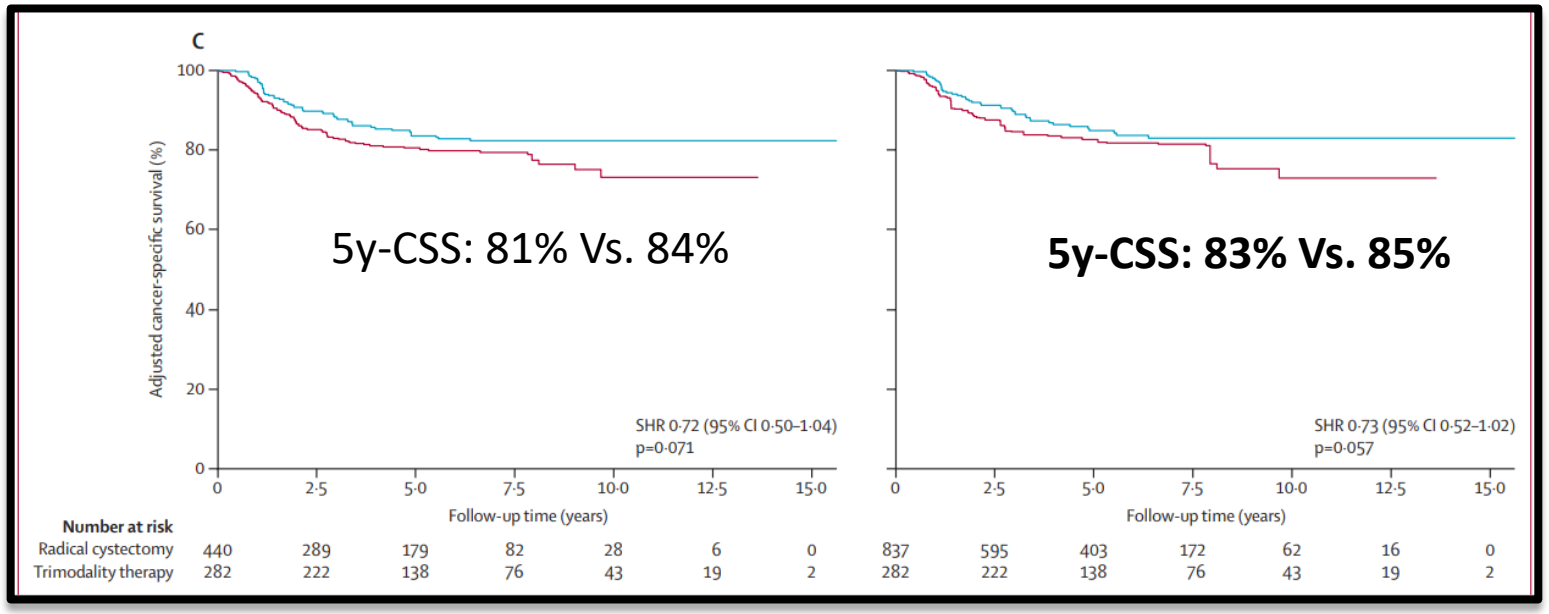
Huddart RA, Birtle A, Maynard L, et al. Clinical and patient-reported outcomes of SPARE – a randomised feasibility study of selective bladder preservation versus radical cystectomy. Published online 2017:639-650. doi:10.1111/bju.13900

- Difficult randomisation due to **strong pre-conceived clinician and patient preference**

Radical cystectomy versus trimodality therapy for muscle Invasive bladder cancer: a multi-institutional propensity score matched and weighted analysis

Zlotta AR. Lancet Oncol. 2023

N=1119



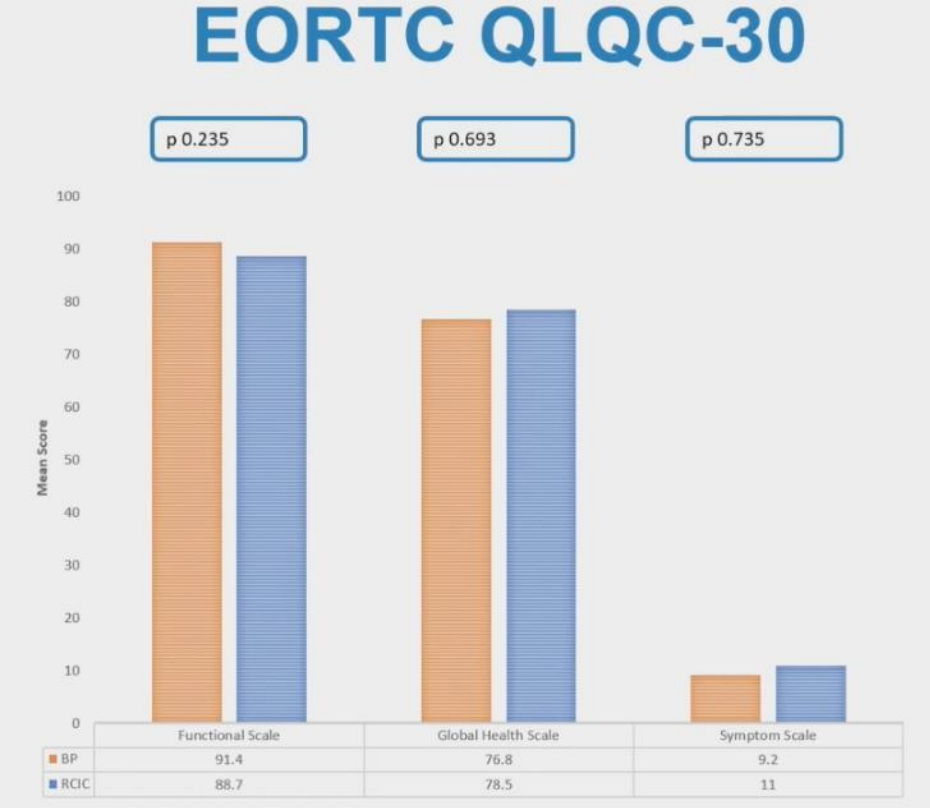
This multi-institutional study provides the best evidence to date showing similar oncological outcomes between radical cystectomy and trimodality therapy for select patients with muscle-invasive bladder cancer.

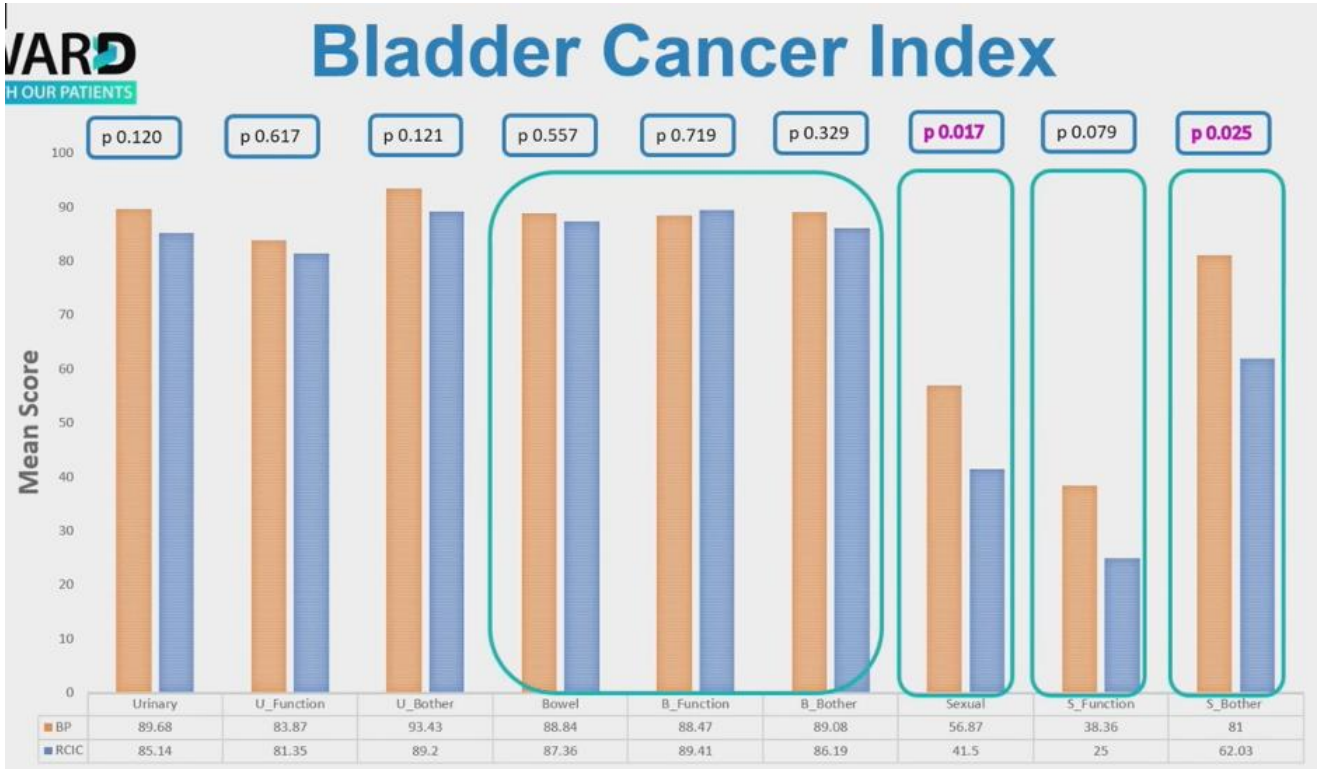
	Before matching			After 3:1 matching		
	Radical cystectomy (n=440)	Trimodality therapy (n=282)*	p value	Radical cystectomy (n=837)†	Trimodality therapy (n=282)*	p value
Age, years	71·2 (63·7–77·2)	71·6 (64·0–78·9)	0·22	71·4 (66·0–77·1)	71·6 (64·0–78·9)	0·76
Sex	..	..	0·31	..	..	0·65
Female	92 (21%)	68 (24%)	..	213 (25%)	68 (24%)	..
Male	348 (79%)	214 (76%)	..	624 (75%)	214 (76%)	..
Carcinoma in situ	..	..	0·096	..	..	0·51
No	324 (74%)	223 (79%)	..	646 (77%)	223 (79%)	..
Yes	116 (26%)	59 (21%)	..	191 (23%)	59 (21%)	..
Clinical T-stage	..	..	0·0024	..	..	0·91
T2	362 (82%)	255 (90%)	..	755 (90%)	255 (90%)	..
T3–4	78 (18%)	27 (10%)	..	82 (10%)	27 (10%)	..
BMI	..	..	0·014	..	..	0·40
<30 kg/m²	340 (77%)	192 (69%)	..	600 (72%)	192 (69%)	..
≥30 kg/m²	100 (23%)	86 (31%)	..	237 (28%)	86 (31%)	..
Missing	0	4	..	0	4	..
Hydronephrosis	..	..	<0·0001	..	..	0·35
No	339 (77%)	255 (90%)	..	740 (88%)	255 (90%)	..
Yes	101 (23%)	27 (10%)	..	97 (12%)	27 (10%)	..
Neoadjuvant or adjuvant chemotherapy	..	..	<0·0001	..	..	0·42
No	259 (60%)	123 (44%)	..	340 (41%)	123 (44%)	..
Yes	176 (40%)	159 (56%)	..	492 (59%)	159 (56%)	..
Missing	5	0		5	0	
Smoking history	..	..	0·57	..	..	0·91
Never smoked	115 (26%)	69 (24%)	..	201 (24%)	69 (24%)	..
Current or former smoker	321 (74%)	213 (76%)	..	632 (76%)	213 (76%)	..
Missing	4	0	..	4	0	..
ECOG status	..	..	0·59	..	..	0·57
0	189 (75%)	218 (77%)	..	392 (76%)	218 (77%)	..
1 or 2	62 (25%)	64 (23%)	..	127 (24%)	64 (23%)	..
Missing	189	0	..	318	0	..

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. *All patients in the trimodality therapy cohort received concurrent radiosensitising chemotherapy. †Of the 282 trimodality therapy patients, with 3:1 matching, nine could only be matched to two radical cystectomy patients, therefore resulting in a total of 837 matched radical cystectomy patients, instead of 846.

Table: **Baseline characteristics before and after matching**

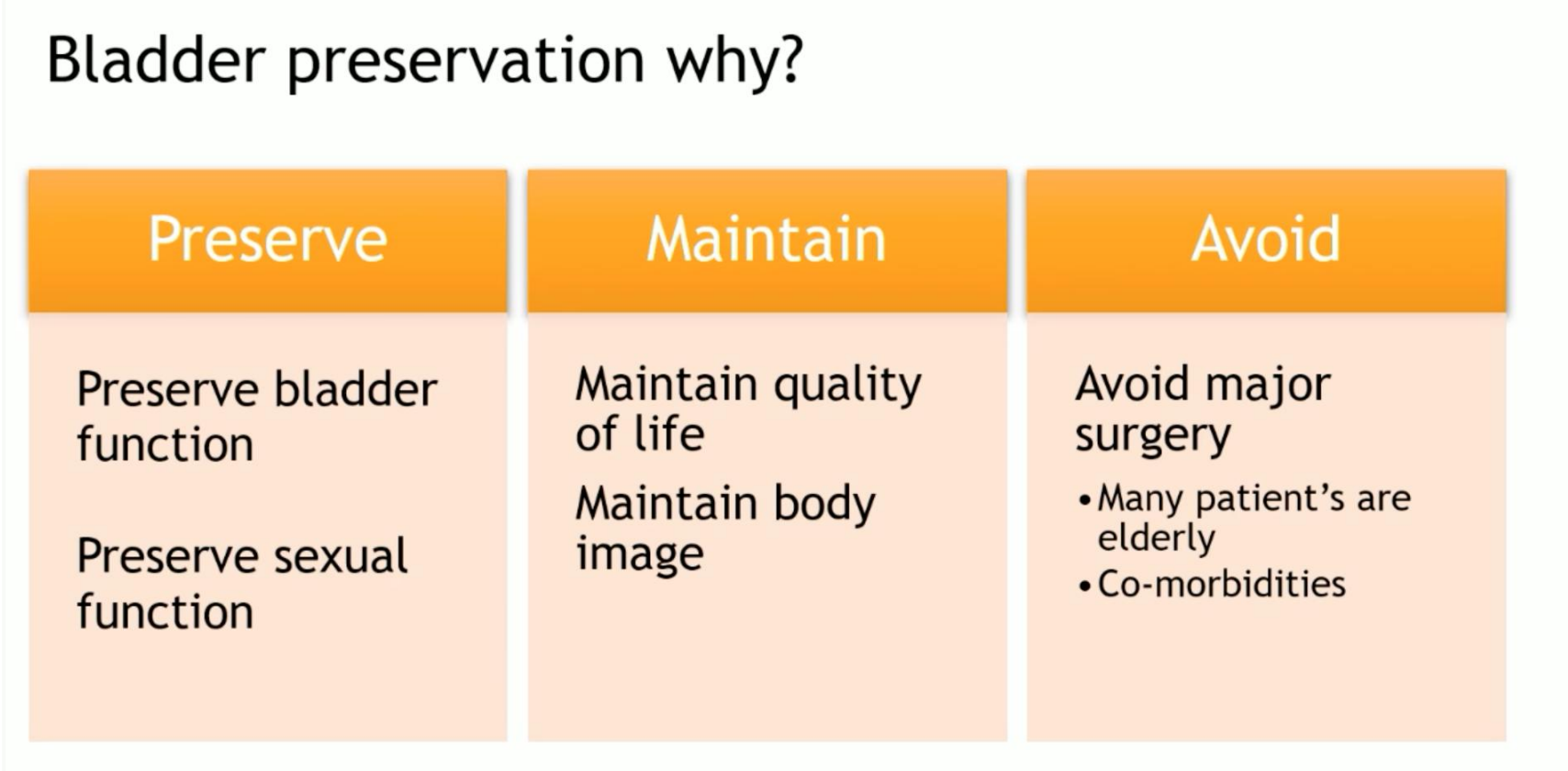
Prospective Comparative Study of Quality of Life in Bladder Cancer Patients Undergoing Cystectomy or Bladder Preservation





- Overall, bladder cancer survivors have good quality-of-life outcomes. There are no differences in urinary and bowel domains with radiotherapy and surgery
- Sexual bother scores are better with radiotherapy compared to radical cystectomy
- Quality-of-life should be central to the decision-making process

Murthy V. ASTRO 2023

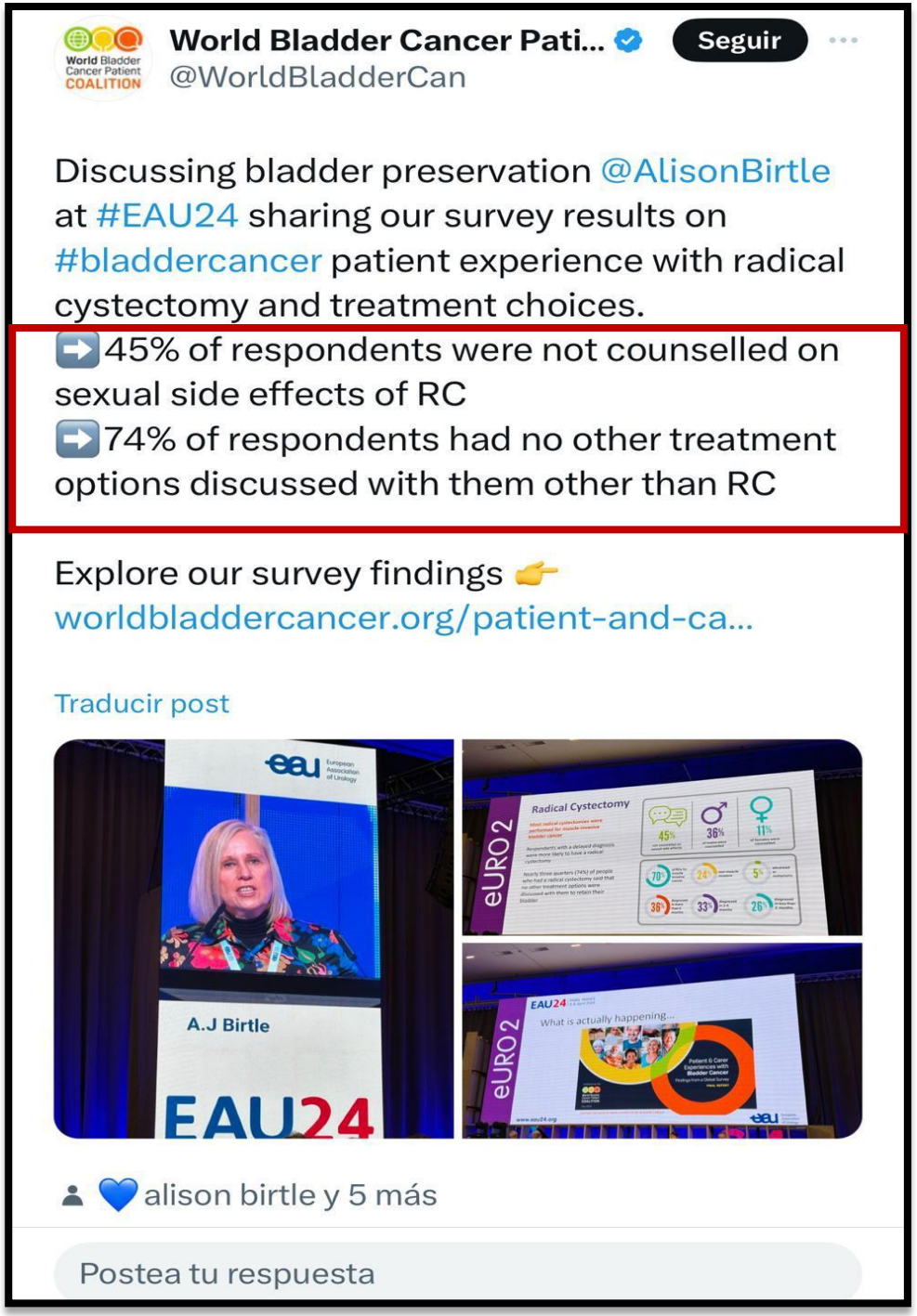


"The best bladder you will ever have is the one you are born with"

Real World Evidence

We are not performing enough trimodal therapy in our clinical practice. It is necessary to improve!!

EAU 2024



Bladder preservation therapy for muscle invasive bladder cancer: the past, present and future

Tomokazu Kimura[1], Hitoshi Ishikawa[2], Takahiro Kojima[1], Shuya Kandori[1], Takashi Kawahara[1], Yuta Sekino[2], Hideyuki Sakurai[2] and Hiroyuki Nishiyama[1,*]

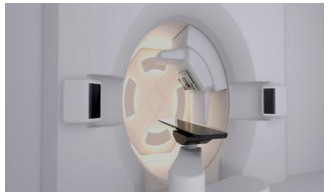
Kimura T. Japanese Journal Clinical Oncology 2020

Table 4. Appropriate indications and contraindications for BPT

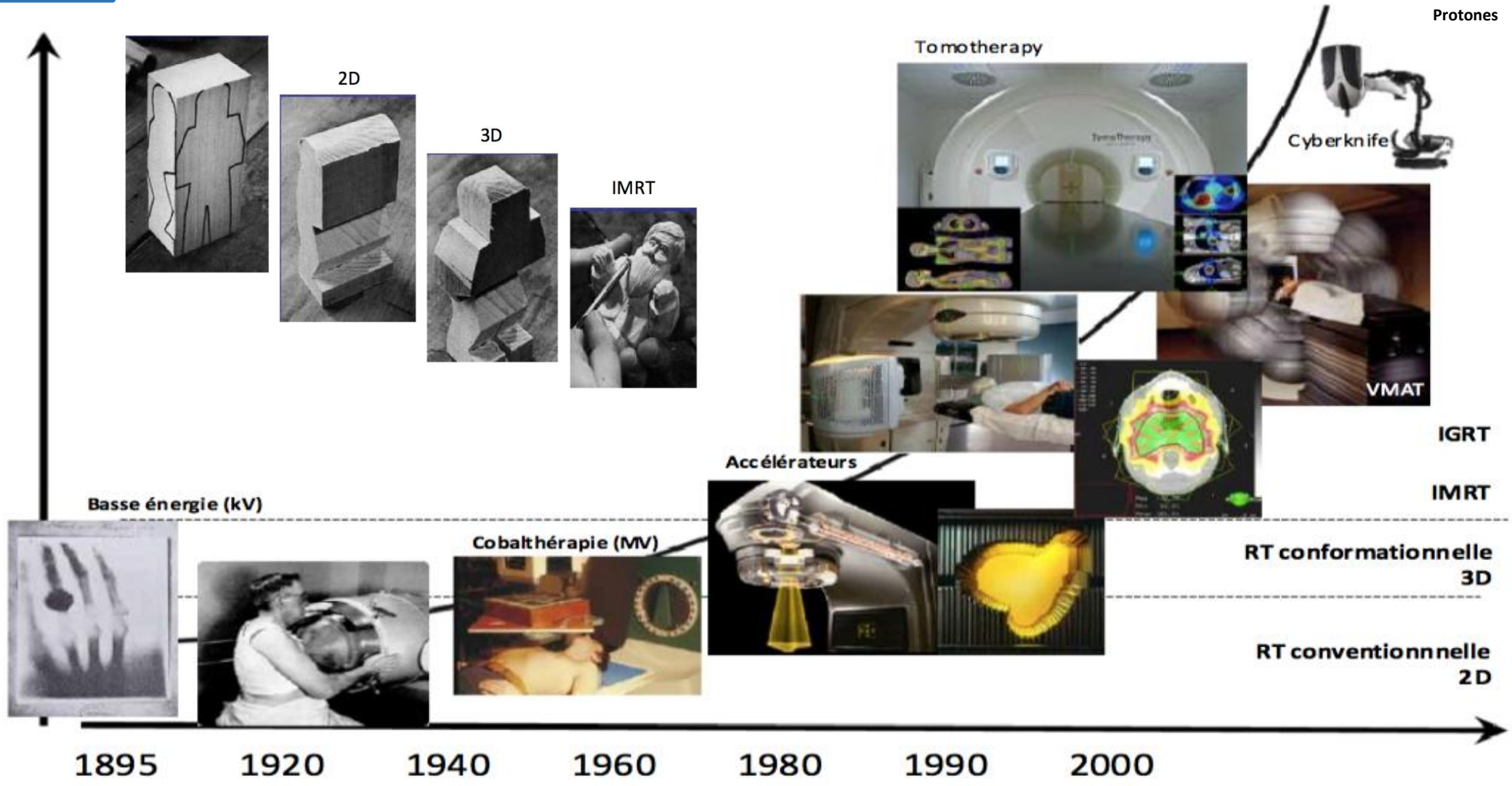
Preferred or ideal	Less than ideal	Contraindications
• T2 • No hydronephrosis • No CIS • Visibly complete TURBT • Unifocal tumor • Good bladder function and capacity	• T3a • Incomplete TURBT • Multifocal tumor • Poor bladder function or capacity • Diffuse CIS	• T3b–T4b • Lymph node-positive disease • Tumor-related hydronephrosis • Prior pelvic radiation therapy • Not a candidate for chemotherapy • Prostatic stromal invasion

TURBT, transurethral resection of the bladder tumor; CIS, carcinoma in situ.

Radiation Oncology Timeline



Protones



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Editorial

Bladder Radiotherapy: Is Cinderella Ready for the Ball?

R.A. Huddart

Institute of Cancer Research, Sutton, Surrey, UK

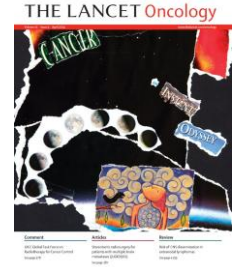
Huddart RA Clinical Oncology 2021

Table 1
Comparison of outcomes of anal and bladder cancer with chemoradiotherapy

	Anal cancer	Bladder cancer
Key study	ACT 1	BC2001
Treatment	5-fluorouracil and mitomycin C Radiotherapy 60 Gy/31 fractions	5-fluorouracil and mitomycin C Radiotherapy 64 Gy/32 fractions
Locoregional failure	~29%	33% (any recurrence) 18% (invasive recurrence)
Overall survival	58%	50%
Salvage/alternative treatment	Abdomino-perineal resection/colostomy	Cysto/prostatectomy Ileostomy
Reference	[16]	[3]

Hypofractionated radiotherapy in locally advanced bladder cancer: an individual patient data meta-analysis of the BC2001 and BCON trials

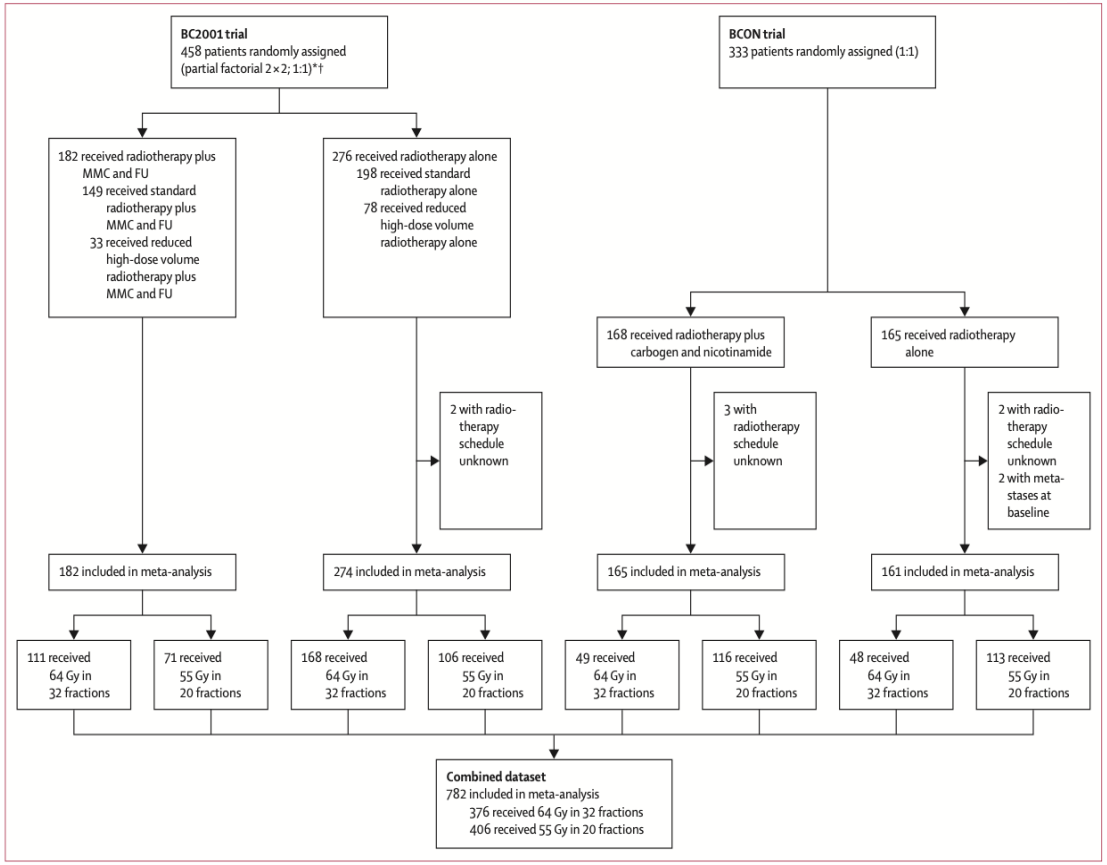
Ananya Choudhury, Nuria Porta*, Emma Hall, Yee Pei Song, Ruth Owen, Ranald MacKay, Catharine M L West, Rebecca Lewis, Syed A Hussain, Nicholas D James†, Robert Huddart†, Peter Hoskin†, on behalf of the BC2001 and BCON investigators*



Choudhury A et al. Lancet Oncol 2021

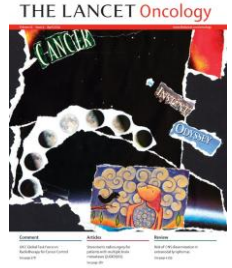
Faster
(Hypofractionation)

	BC2001 trial			BCON trial			Combined dataset		
	64 Gy in 32 fractions (n=279)	55 Gy in 20 fractions (n=177)	Standardised difference, %	64 Gy in 32 fractions (n=97)	55 Gy in 20 fractions (n=229)	Standardised difference, %	64 Gy in 32 fractions (n=376)	55 Gy in 20 fractions (n=406)	Standardised difference, %
Sex									
Female	50 (18%)	37 (21%)	..	17 (18%)	48 (21%)	..	67 (18%)	85 (21%)	..
Male	229 (82%)	140 (79%)	7·5%	80 (82%)	181 (79%)	8·7%	309 (82%)	321 (79%)	7·9%
Age, years	71·4 (8·7)	71·6 (7·9)	1·3%	72·6 (7·6)	73·0 (7·8)	−5·4%	71·7 (8·4)	72·4 (7·8)	7·9%
Radiotherapy plus radiosensitiser	111 (40%)	71 (40%)	0·7%	49 (51%)	116 (51%)	0·3%	160 (43%)	187 (46%)	7·1%
Reduced high-dose volume radiotherapy	75 (27%)	35 (20%)	16·9%	0	0	..	75 (20%)	35 (9%)	32·8%
Tumour stage									
1	1* (<1%)	0	..	13 (13%)	17 (7%)	..	14 (4%)	17 (4%)	..
2	251 (90%)	129 (73%)	..	68 (70%)	147 (64%)	..	319 (85%)	276 (68%)	..
3	20 (7%)	40 (23%)	..	14 (14%)	54 (24%)	..	34 (9%)	94 (23%)	..
4	7 (3%)	8 (5%)	47·6%	2 (2%)	10 (4%)	32·1%	9 (2%)	18 (4%)	42·6%
Unknown	0	0	..	0	1	..	0	1	..
Tumour grade									
1	1 (<1%)	0	..	0	0	..	1 (<1%)	0	..
2	40 (14%)	19 (11%)	..	16 (16%)	30 (13%)	..	56 (15%)	49 (12%)	..
3	236 (85%)	156 (89%)	13·9%	81 (84%)	198 (87%)	9·4%	317 (85%)	354 (88%)	11·1%
Unknown	2	2	..	0	1	..	2	3	..
Extent of resection									
Biopsy or not resected	24 (9%)	23 (13%)	..	25 (26%)	62 (28%)	..	49 (13%)	85 (22%)	..
Complete	175 (63%)	81 (47%)	..	46 (47%)	83 (38%)	..	221 (59%)	164 (42%)	..
Partial	77 (28%)	70 (40%)	34·4%	26 (27%)	73 (33%)	19·6%	103 (28%)	143 (36%)	36·1%
Unknown	3	3	..	0	11	..	3	14	..
Neoadjuvant chemotherapy	65 (23%)	69 (39%)	34·4%	0	0	..	65 (17%)	69 (17%)	0·8%
Haemoglobin, g/dL†	13·1 (1·8)	12·6 (1·8)	27·4%	13·8 (1·7)	13·6 (1·6)	11·3%	13·2 (1·8)	13·1 (1·8)	5·7%



Hypofractionated radiotherapy in locally advanced bladder cancer: an individual patient data meta-analysis of the BC2001 and BCON trials

Ananya Choudhury*, Nuria Porta*, Emma Hall, Yee Pei Song, Ruth Owen, Ranald MacKay, Catharine M L West, Rebecca Lewis, Syed A Hussain, Nicholas D James†, Robert Huddart†, Peter Hoskin†, on behalf of the BC2001 and BCON investigators



Choudhury A et al. Lancet Oncol 2021

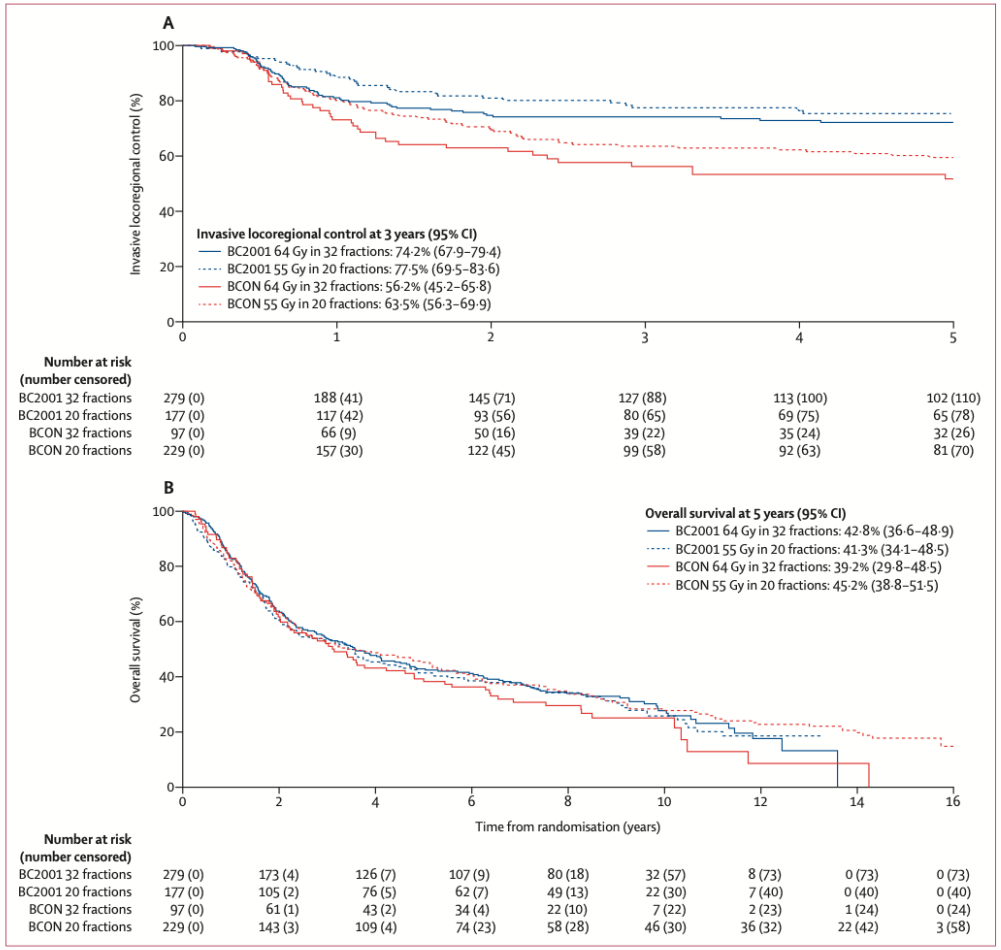
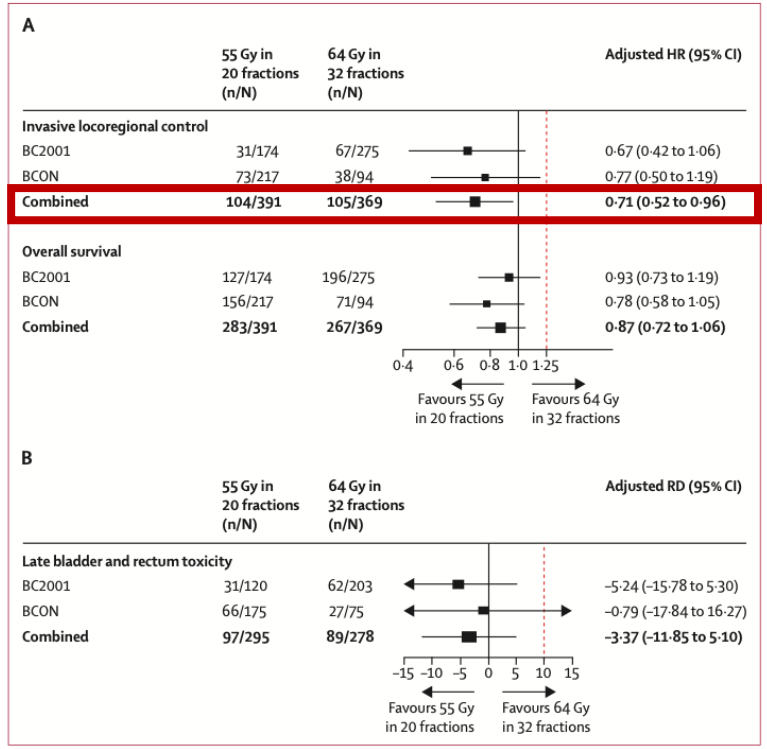


Figure 2: Kaplan-Meier estimates of observed invasive locoregional control (A) and observed overall survival (B) by trial and fractionation group

	64 Gy in 32 fractions (n=278)	55 Gy in 20 fractions (n=295)
2-year late toxicity		
Rectum	7 (3%)	17 (6%)
Bladder	66 (24%)	74 (25%)
Rectum or bladder	69 (25%)*	82 (28%)†
5-year late toxicity		
Rectum	8 (3%)	21 (7%)
Bladder	86 (31%)	88 (30%)
Rectum or bladder	89 (32%)‡	97 (33%)§

LENT-SOMA urinary and rectal dysfunction subscales were recorded up to 5 years after radiotherapy in the BC2001 and BCON trials. LENT-SOMA=Late Effects Normal Tissue Task Force-Subjective, Objective, Management, Analytic. *Four patients with both. †Nine patients with both. ‡Five patients with both. §12 patients with both.

Table 2: **LENT-SOMA grade 3–4 bladder or rectum toxicity after the end of treatment by fractionation groups**

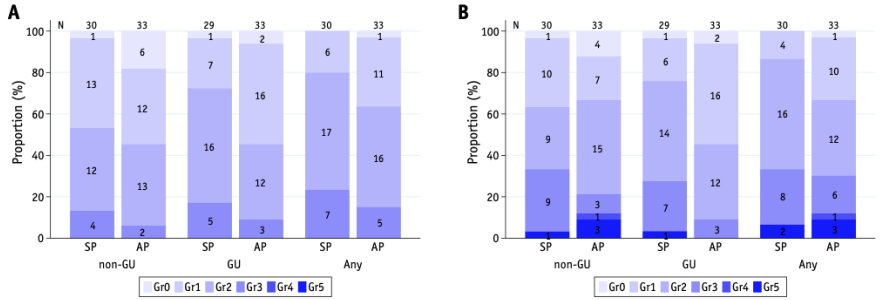


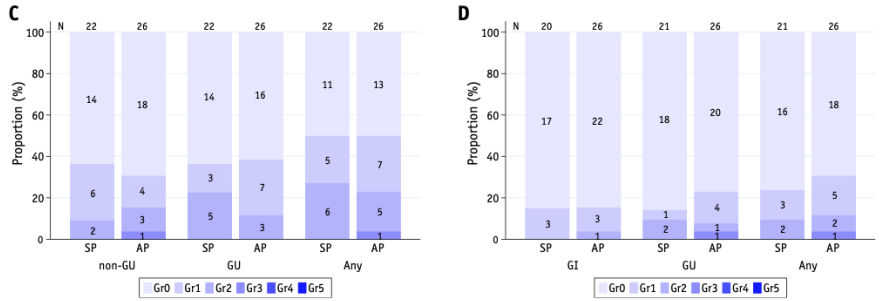
Median follow-up was 10 years

Interpretation A hypofractionated schedule of 55 Gy in 20 fractions is non-inferior to 64 Gy in 32 fractions with regard to both invasive locoregional control and toxicity, and is superior with regard to invasive locoregional control. 55 Gy in 20 fractions should be adopted as a standard of care for bladder preservation in patients with locally advanced bladder cancer.

Clinical Investigation

Clinical Outcomes of a Randomized Trial of Adaptive Plan-of-the-Day Treatment in Patients Receiving Ultra-hypofractionated Weekly Radiation Therapy for Bladder Cancer



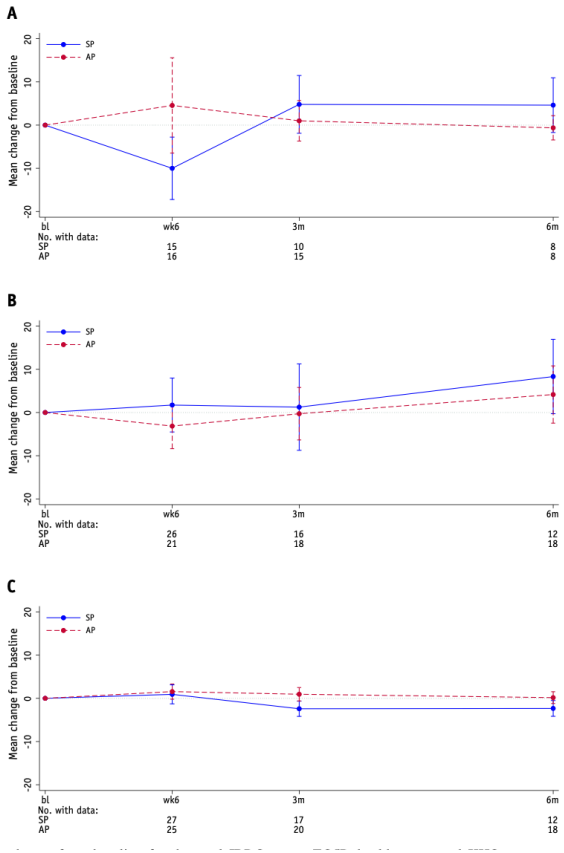


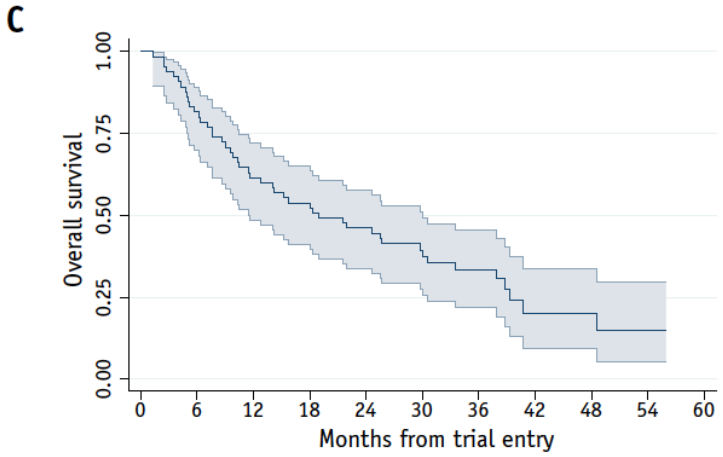
Huddart R et al. Int J Radiat Oncol Biol Phys. 2021

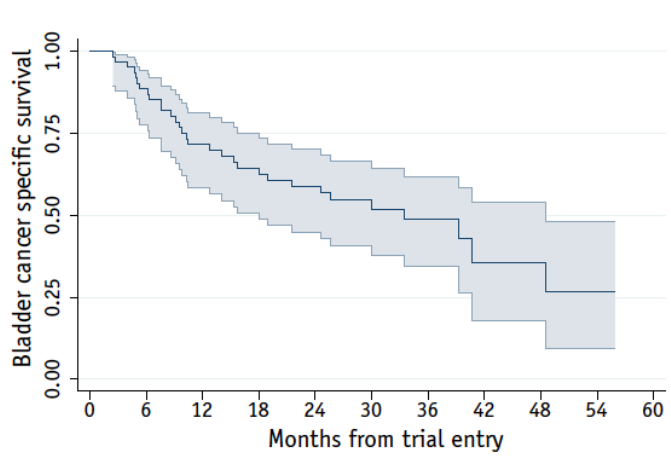
6 fracciones de 6 Gy (semanal)

Edad: 85 años [81-89]

SIN DIFERENCIAS SIGNIFICATIVAS EN SUPERVIVENCIA NI EN TOXICIDAD CRÓNICA

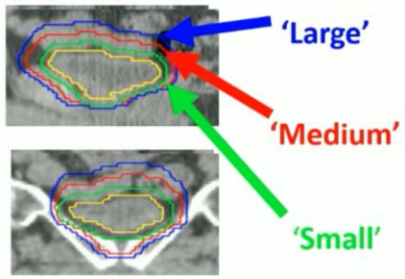


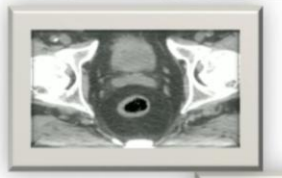




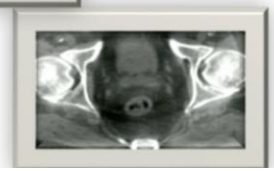
Adaptive Radiotherapy

Plan of the Day





Planning CT



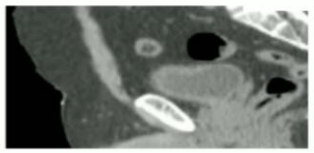
Cone beam CT

Lalondrelle et al. IJROBP 2010

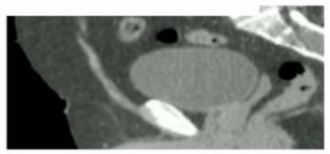
ADAPTIVE RADIOTHERAPY

Bladder
a mobile target

Deformable

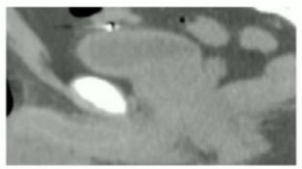


'Empty' bladder

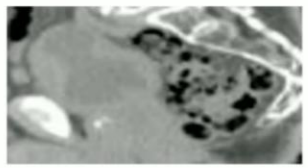


'Empty' bladder

Mobile

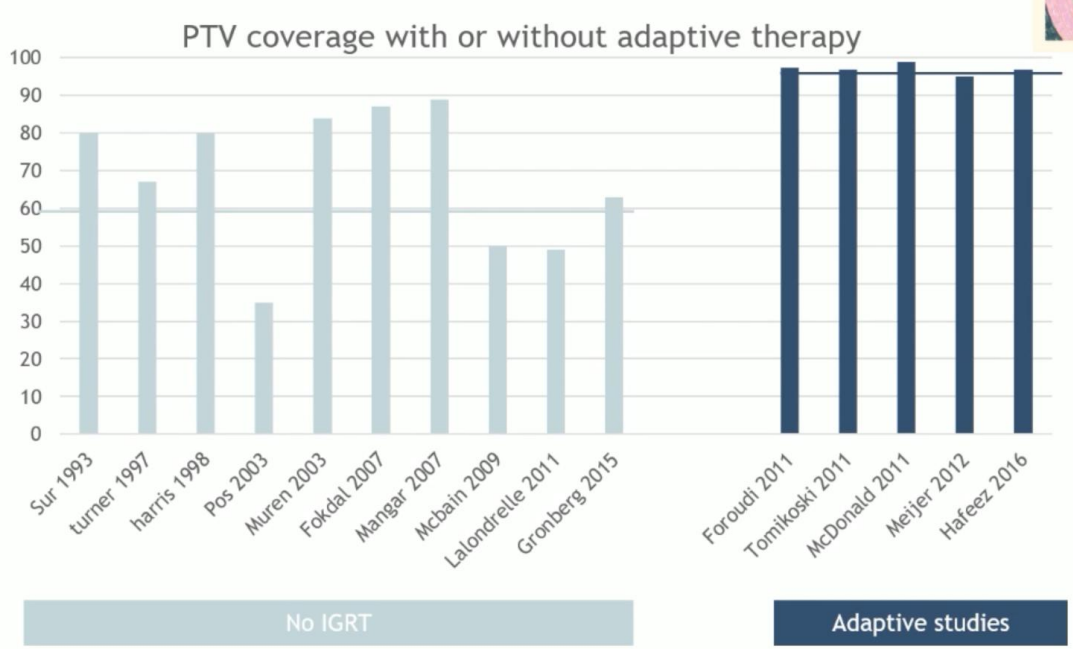


Empty rectum



Full rectum

Summary of studies investigating PTV coverage with or without IGRT in MIBC



ADAPTIVE RADIOTHERAPY

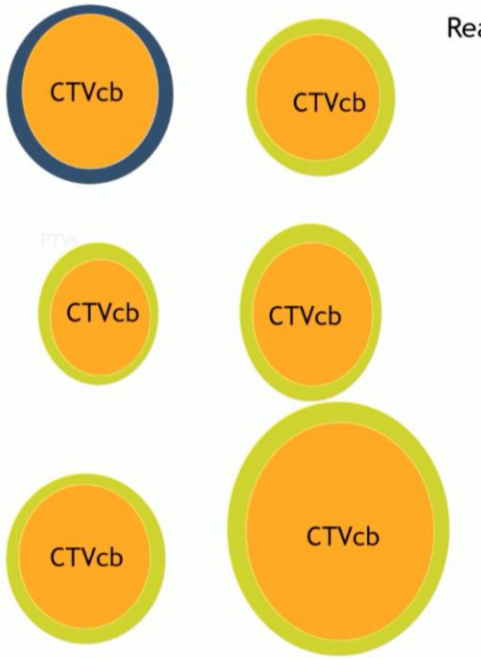
Real time adaptive treatment

The dream – new plan every day

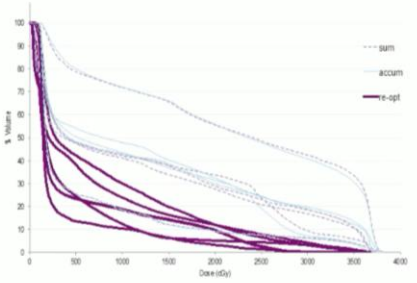
Day one *Day two* *Day three*

Slide courtesy of Dr Alison Tree

Real time Adaptive radiotherapy:



- The mean percentage reduction in volume with PTVre-opt compared to clinical plan selected from the library
- **46% (SD 11.5, range 21.3-68.5).**
- **97%% (29/30) fractions** PTVre-opt was smaller PTV small.



Huddart R et al. ESTRO 2025

Are platforms available to achieve this?

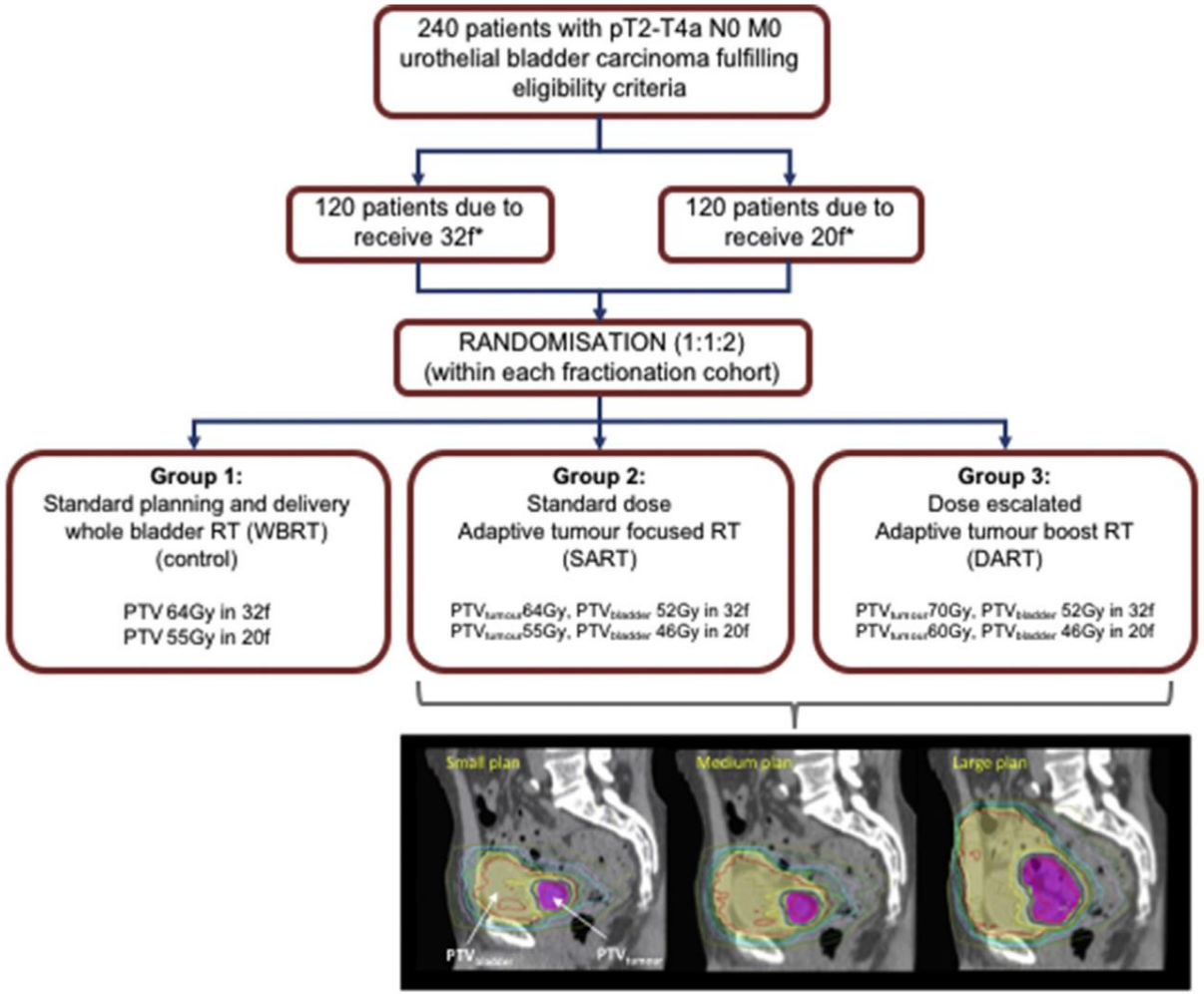
- MR Linacs
  - Elekta Unity
  - Viewray MRidian
- Linac based
  - Ethos (Varian)
  - Radixact (Accuray)
  - Evo (Elekta)

Better Image quality
Functional imaging
Intrafraction monitoring

RAIDER

A **R**andomised phase II trial of **A**daptive **I**mage guided standard or **D**ose **E**scalated tumour boost **R**adiotherapy in the treatment of transitional cell carcinoma of the bladder

Huddart R et al. Eur Urol 2025



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.

Primary endpoint: any ≥grade 3 treatment emergent radiotherapy related late CTCAE toxicity (6-18 months)

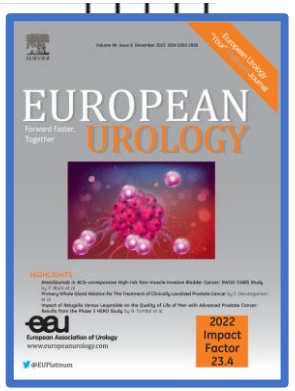
Aim: To exclude ≥20% grade ≥3 (G3+) any radiotherapy related in the DART group

	32f		20f	
	N (%)	90% CI	N (%)	90% CI
Any G3+				
WBRT	2/37 (5.4)	1.0, 16.1	3/30 (10.0)	3.0, 23.9
SART	1/32 (3.1)	0.2, 14.0	1/23 (4.3)	0.2, 19.0
DART	2/57(3.5)	0.6, 10.6	5/58 (8.6)	3.4, 17.3
Radiotherapy related G3+				
WBRT	0/37	0	1/30 (3.3)	0.2, 14.9
SART	0/32	0	1/23 (4.3)	0.2, 19.0
DART	**0/57**	**0**	**1/58 (1.7)**	**0.1, 7.9**

RAIDER

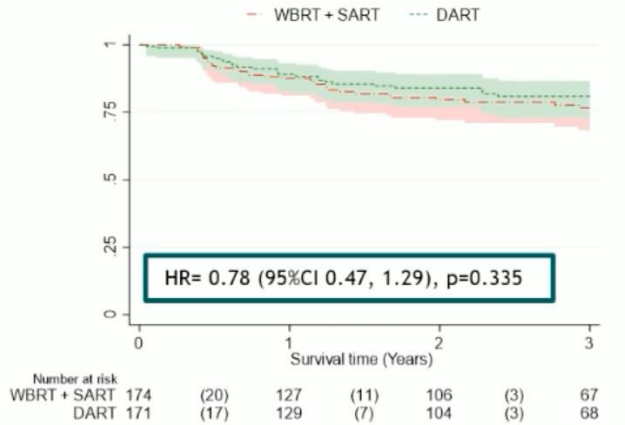
A **R**andomised phase II trial of **A**daptive **I**mage guided standard or **D**ose **E**scalated tumour boost **R**adiotherapy in the treatment of transitional cell carcinoma of the bladder

Huddart R et al. Eur Urol 2025



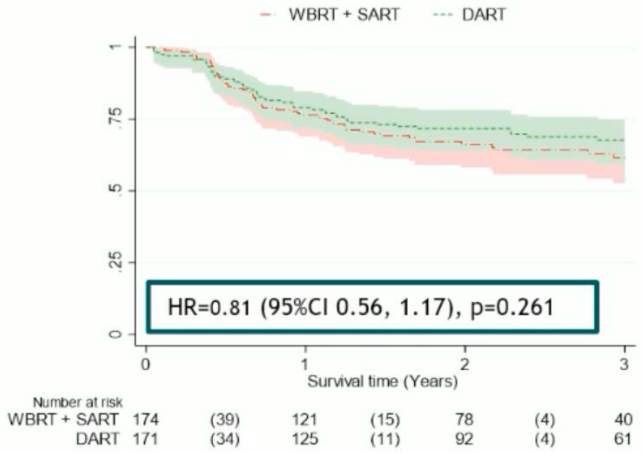
RAIDER disease control outcomes

- Loco-regional *invasive* disease control



2 year event-free rates:
WBRT+SART: 79.7% (95%CI 72.3-85.3)
DART: 84.0% (95%CI 77.1-89.0)

Bladder intact event free survival*

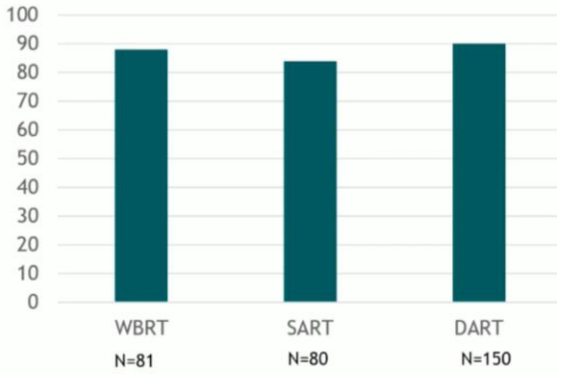


2 year event-free rates:
WBRT+SART: 66.3% (95%CI 58.3-73.1)
DART: 71.7% (95%CI 64.0-78.0)

*Alive without invasive, pelvic, metastatic recurrence and no cystectomy
Salvage cystectomy in 4% of patients to date

Local control at 3 months

- Overall local control at 3 months was 88% (95%CI 84.0-91.7)



- Prof Robert Huddart

Nivolumab plus chemoradiotherapy in patients with muscle-invasive bladder: final results of a phase II, randomized study by the HGUCG (NCT03993249).

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Characteristic	Arm 1 (n=39)	Arm 2 (n=38)	*p*-value
Histology			
• TCC	32 (82.1%)	36 (94.7%)	
• Squamous	3 (7.7%)	2 (5.3%)	.2
• Mixed	3 (7.7%)	0 (0%)	
• missing	1 (2.6%)	0 (0%)	
Multifocal	4 (10.3%)	2 (5.3%)	.67
Hydronephrosis	4 (10.3%)	2 (5.3%)	.67
TURB-T			
• Complete	34 (87.2%)	30 (79%)	.67
• Incomplete	2 (5.1%)	3 (7.9%)	
• Missing	3 (7.7%)	5 (13.1%)	
GFR [median (IQR)]	83 (68-103)	65.5 (49-78)	.014

Study Design (NCT03993249)

Nivolumab Plus Chemoradiotherapy in Patients With nmMIBC Not Undergoing Cystectomy

Patients with nmMIBC, not candidates for radical cystectomy

Key Eligibility:
- Treatment naïve MIBC
- cT2-T4aN0M0
- Urothelial, squamous, glandular histology
- GFR≥ 40ml/min
- PS≤ 1

Previously undergone a vigorous TURBT.

Protocol treatment must begin within 8 weeks following TURB-T

R 1:1

Arm 1: ChemoRT* for 6 or 7 weeks CDDP 20mg d1-d5, d22-d25 or 40mg/m²/week x6

Arm 2: Nivolumab 240mg q14 IV x5, starting 14 days prior to ChemoRT, then 480mg q28 x6 + ChemoRT* for 6 or 7 weeks CDDP 20mg d1-d5, d22-d25 or 40mg/m²/week x 6

Primary endpoint
- LRFR at 2 years

Secondary endpoints
- Toxicity
- BCFFS at 2 years
- OS
- QLQ
- PD-L1 expression

*RT details:
- 3DCRT or IMRT
- Whole bladder 60 Gy, boost 10 Gy (2 Gy/fraction)

After median fup of 33 months, (95% CI 29.4-38.3)

ESTRO 2025

Treatment compliance

COMPLIANCE	Arm1	Arm2	*p*-value
Planned treatment	33 (85%)	23 (61%)	.018
Chemotherapy	35 (90%)	25 (66%)	.024
RT	34 (87%)	32 (84%)	>.99
Nivo	NA	30 (81%)	

Nivolumab plus chemoradiotherapy in patients with muscle-invasive bladder: final results of a phase II, randomized study by the HGUCG (NCT03993249).

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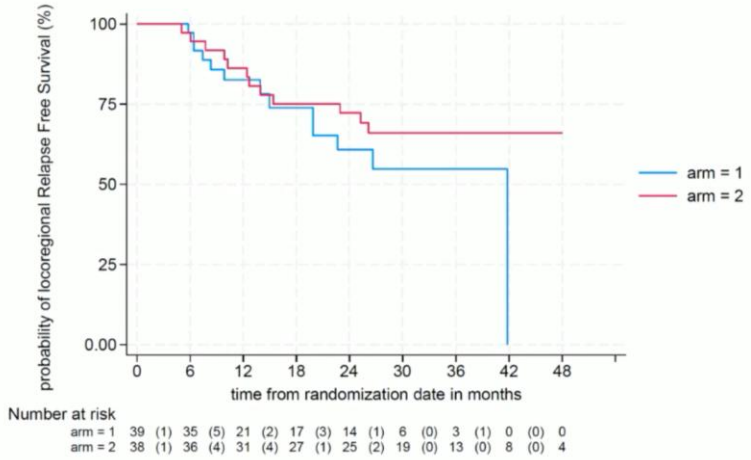
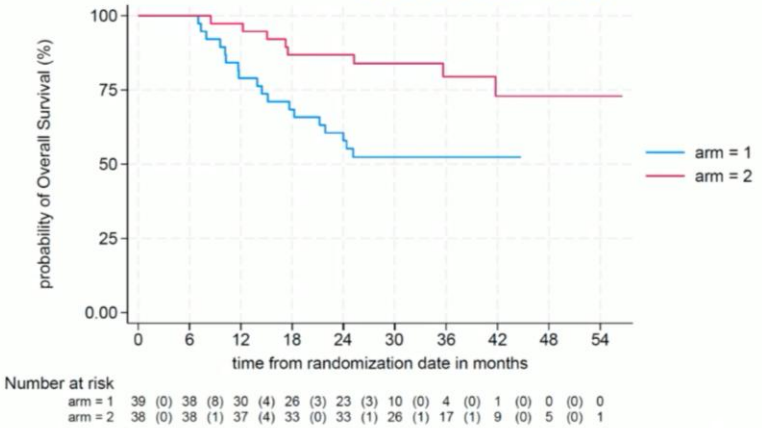
Primary endpoint:LRFR at 2 years



Median (95% CI)	2-y free (95% CI)
RT+CDDP	
41.9	60.8% (39.6-76.6)
RT+CDDP+Nivolumab	
NR	72.3% (54.7%-84.1%)

Efficacy

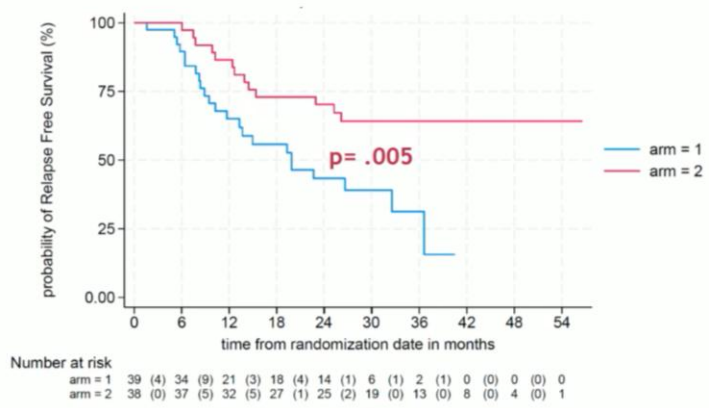
Overall survival



Median (95% CI)	2-y free (95% CI)
RT+CDDP	
NR	60.5% (43.3%-74%)
RT+CDDP+Nivolumab	
NR	86.8% (71.2%-94.3%)

Efficacy

Bladder cancer failure-free survival



Median (95% CI)	2-y free (95% CI)
RT+CDDP	
19.9 (11.7-36.7)	43.4% (26.6%-59%
RT+CDDP+Nivolumab	
NR	70.3% (52.8%-82.3%)

Nivolumab plus chemoradiotherapy in patients with muscle-invasive bladder: final results of a phase II, randomized study by the HGUCG (NCT03993249).

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ESTRO 2025

Toxicity

	Arm 1	Arm 2	p
AEs			
All grade	76 (32.8%)	156 (67.2%)	<.001
Grade ≥3	14 (18.4%)	20 (12.8%)	.26
irAEs			
All grades	0 (0%)	9 (23.7%)	.001
Grade ≥3	0 (0%)	4 (10.5%)	.001

AE Grade≥3	Arm 1	Arm 2
Lab-metabolic	4 (10.3)	6 (15.8)
Urinary	2 (5.1)	6 (15.8)
Anemia	2 (5.1)	5 (13.2)
Creatinine	2 (5.1)	2 (5.3)
Neutropenia	1 (2.9)	5 (13.5)
Thyroid related	0 (0)	4 (10.5)
Cardiovascular	1 (2.6)	2 (5.3)
Nausea	1 (2.6)	1 (2.6)

Conclusions

- The addition of nivolumab to TMT produced a significant increase in BCFFS and OS in patients with nmMIBC not undergoing radical cystectomy.
- The prolongation of BCFFS and OS resulted from a significant decrease in the occurrence of distant metastases in patients receiving nivolumab
- The combination of TMT+Nivolumab was well tolerated without any new safety signals observed
- These results warrant the conduction of a randomized phase III trial to establish nivolumab plus CRT as a new standard for patients with nmMIBC not undergoing radical cystectomy.

CONCLUSIONS

Bladder preservation with trimodality treatment (TMT) is an alternative strategy to radical cystectomy (RC) for the management of localised muscle invasive bladder cancer (MIBC).

Radiotherapy has improved over the last decade with radiosensitisation, image guidance, adaption and shorter treatments.

- **Hypofractionation as a standard.**
- **Adaptive radiotherapy program in bladder cancer.**

Further improvement in results can obteined by continued technical developments, use of biomarkers and additional concomitant therapies.

Though its not for everyone it should be considered and offered to all suitable patients

THANK YOU

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