available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

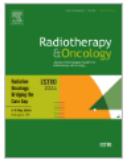
Original Article

Dose-escalated Adaptive Radiotherapy for Bladder Cancer: Results of the Phase 2 RAIDER Randomised Controlled Trial

Robert Huddart [a,b,*], *Shaista Hafeez* [a,b], *Clare Griffin* [a], *Ananya Choudhury* [c], *Farshad Foroudi* [d], *Isabel Syndikus* [e], *Benjamin Hindson* [f], *Amanda Webster* [g,h], *Helen McNair* [a,b], *Alison Birtle* [i,j,k], *Mohini Varughese* [l], *Ann Henry* [m,n], *Duncan B McLaren* [o], *Omi Parikh* [i], *Ashok Nikapota* [p], *Colin Tang* [q], *Emma Patel* [r], *Elizabeth Miles* [r], *Karole Warren-Oseni* [a,b], *Tomas Kron* [s], *Courtney Hill* [t], *Lara Philipps* [a], *Catalina Vassallo-Bonner* [a], *Ka Ching Cheung* [a], *Hannah Gribble* [a], *Rebecca Lewis* [a], *Emma Hall* [a]

ELSEVIER

Radiotherapy and Oncology
Volume 194, Supplement 1, May 2024, Pages S2499-S2502



Clinical - Urology

Digital Poster

2148: Hypofractionated chemoradiotherapy for bladder preservation in muscle-invasive bladder cancer

Anuradha Krishnan, Sheetal Kashid, Namrata Pansande, Priyamvada Maitre, Pallavi Singh, Amit Joshi, Reena Phuralipatram, Gagan Prakash, Mahendra Pal, Amandeep Arora, Vedang Murthy

Dr. Parth Verma
MBBS, MD, Fellow Urogenital Oncology
Consultant Radiation Oncologist
Bharat Cancer Hospital, Surat

CONTEXT

- **Challenges in Bladder Radiotherapy:**
  - Bladder is a mobile and deformable organ.
  - Traditional RT requires large planning margins, leading to potential toxicity and geographical misses.

- **Rationale for Adaptive Radiotherapy (ART):**
  - Image-guided radiotherapy (IGRT) allows for better soft tissue visualization and accuracy.
  - ART aims to minimize treatment volume while maintaining target coverage by adjusting plans based on daily anatomy ("anatomy / plan of the day").
  - Potential to reduce toxicity and allow for dose escalation to the tumor. Single-center studies showed feasibility of dose escalation (e.g., 70 Gy in 32 fractions).

RAIDER Trial – Design and Methodology

- **Trial Design:** International, multicentre, multiarm, two-stage, phase 2 parallel cohort randomised controlled trial
- **Patient Population:**
  - Unifocal, T2-T4aN0M0 urothelial bladder cancer.
  - n=345 (Oct 2015 - Apr 2020) across 46 hospitals (UK, Australia, New Zealand).
- **Randomisation (1:1:2 ratio) Independent Cohorts:**
  - **Standard Whole Bladder Radiotherapy (WBRT) - CONTROL**
    Whole empty bladder 64Gy/32Fr or 55Gy/20Fr
  - **Standard-Dose Adaptive Radiotherapy (SART):**
    Uninvolved bladder 52Gy/32Fr or 46Gy/20Fr + Bladder tumour boost 64Gy/32Fr or 55Gy/20Fr
  - **Dose-Escalated Adaptive Radiotherapy (DART):**
    Uninvolved bladder 52Gy/32Fr or 46Gy/20Fr + Bladder tumour boost 70Gy/32Fr or 60Gy/20Fr
- **Balancing Factors:** Treating hospital, neoadjuvant chemotherapy (yes/no), concomitant radiosensitisation (yes/no).

- **<u>Adaptive Radiotherapy (SART & DART):</u>**
  - Daily cone-beam CT (CBCT) performed before each fraction.
  - Selection of one of three pre-defined plans (small, medium, or large) by an accredited individual, verified by a second.
  - Plan selected to ensure smallest volume enabling coverage of the planning target volume (PTV).
- **Quality Assurance:**
  Comprehensive radiotherapy QA program implemented.
- **Concomitant Therapy:**
  Standard concomitant radiosensitisation encouraged.
- **Follow-up:**
  Regular cystoscopy, imaging, toxicity assessment up to 60 months.

STAGE I : Feasibility Assessment

- **Purpose:**
Determine if DART could be successfully and consistently implemented across multiple treatment centers.

- **Primary Endpoint:**
Proportion of patients receiving DART who met predefined OAR dose constraints for MEDIUM plan

For those not meeting constraints, cases reviewed by the chief investigator or delegate who recommended either proceeding with DART or lowering to SART dose

- **Secondary Endpoint:**
Recruitment rate and the ability of the participating centres to deliver SART and DART treatment as per protocol.

STAGE II : Toxicity Evaluation

- **Purpose:**
To evaluate the safety of the dose-escalated adaptive radiotherapy (DART) in the longer term.

- **Primary Endpoint:**
>20% RT-related late CTCAE ≥Grade 3 toxicities occurring 6-18 months after the end of RT.

Evaluable patients: At least one fraction of allocated treatment + at least one toxicity assessment (6-18 mo post-RT and ≥1 mo before death/recurrence).

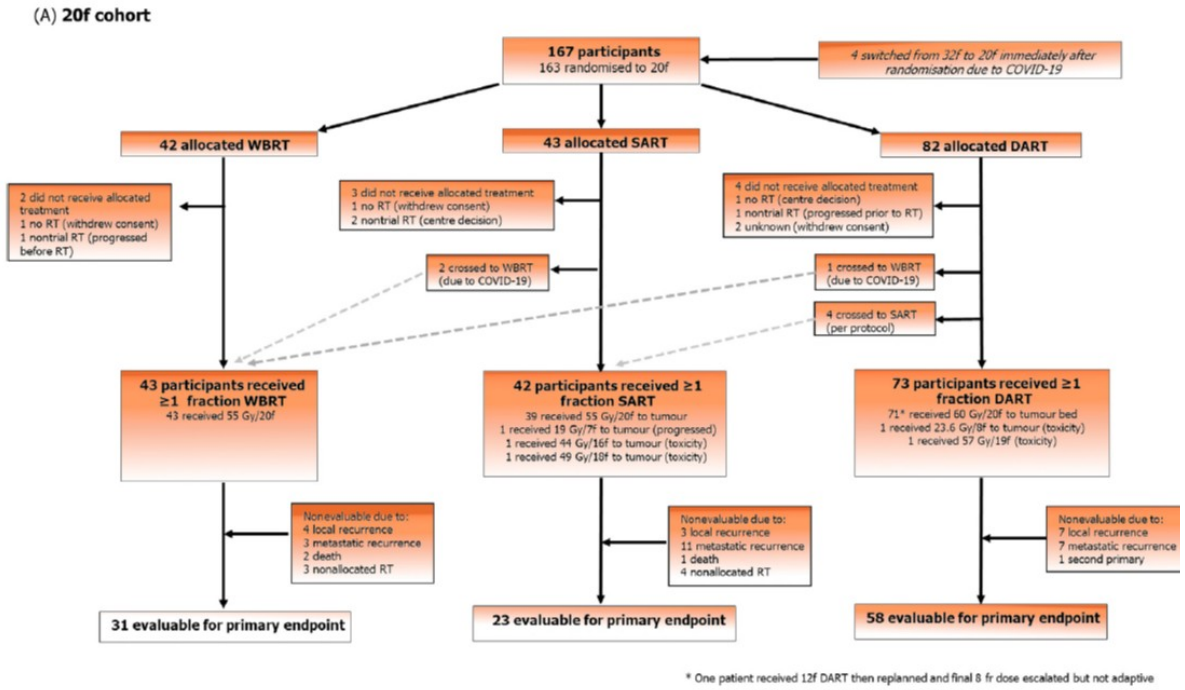
- **Secondary Endpoints:**
  - Acute and late toxicity (CTCAE, RTOG).
  - Patient-Reported Outcomes (EQ5D-5L, KHQ, IBDQ, PRO-CTCAE, ALERT-B).
  - Locoregional (invasive) disease control.
  - Bladder intact event-free survival.
  - Overall survival.

Patient characteristics well balanced between groups

Table 1 – Participant and tumour characteristics at trial entry and treatment details by randomised treatment group

	20f				32f			
	WBRT (*N* = 42)	SART (*N* = 43)	DART (*N* = 82)	Total (*N* = 167)	WBRT (*N* = 45)	SART (*N* = 44)	DART (*N* = 89)	Total (*N* = 178)
Age (yr), median (IQR)	74 (69–80)	74 (65–80)	71 (65–77)	72 (67–79)	72 (67–78)	73 (65–79)	73 (68–79)	73 (67–79)
Gender, *N* (%)								
Male	32 (76)	35 (81)	67 (82)	134 (80)	35 (78)	37 (84)	69 (78)	141 (79)
WHO performance status, *N* (%)								
0	24 (57)	20 (47)	42 (52)	86 (52)	28 (64)	24 (55)	56 (63)	108 (61)
1	15 (36)	21 (49)	29 (36)	65 (39)	11 (25)	19 (43)	30 (34)	60 (34)
2	3 (7)	2 (5)	10 (12)	15 (9)	5 (11)	1 (2)	3 (3)	9 (5)
Unobtainable	0	0	1	1	0	0	0	0
Clinical stage, *N* (%)								
T2	35 (83)	33 (77)	61 (75)	129 (78)	39 (87)	32 (73)	77 (87)	148 (83)
T3a	2 (5)	7 (16)	9 (11)	18 (11)	1 (2)	4 (9)	8 (9)	13 (7)
3b	5 (12)	2 (5)	9 (11)	16 (10)	3 (7)	8 (18)	3 (3)	14 (8)
T4a	0	1 (2)	2 (2)	3 (2)	2 (4)	0	1 (1)	3 (2)
Unobtainable	0	0	1	1	0	0	0	0
Neoadjuvant chemotherapy, *N* (%)								
Yes	21 (50)	24 (56)	43 (52)	88 (53)	20 (44)	18 (41)	42 (47)	80 (45)
Concomitant therapy given								
Yes, *N* (%)	31 (76)	31 (76)	54 (69)	116 (73)	32 (73)	31 (72)	64 (74)	127 (73)
Unobtainable, *N*	1	2	4	7	1	1	3	5

CIS = carcinoma in situ; DART = dose-escalated adaptive radiotherapy; f = fractions; IQR = interquartile range; SART = standard-dose adaptive radiotherapy; WBRT = standard whole bladder radiotherapy; WHO = World Health Organization.
Tumour grade, presence of CIS, presence of residual disease, and type of concomitant therapy given are presented in Supplementary Table 3.



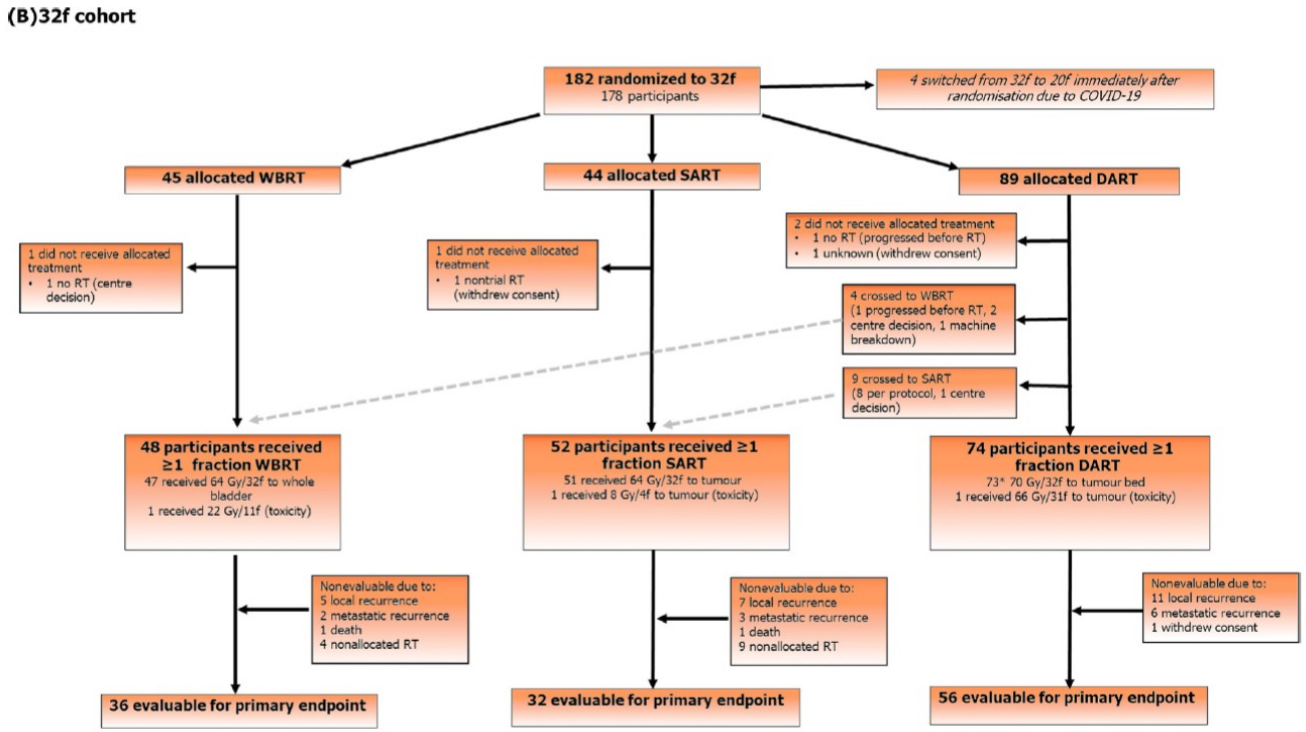


Fig. 1 – RAIDER CONSORT flowchart: (A) 20f cohort and (B) 32f cohort. COVID-19 = coronavirus disease 2019; DART = dose-escalated adaptive radiothe f/fr = fractions; RT = radiotherapy; SART = standard-dose adaptive radiotherapy; WBRT = whole bladder radiotherapy.

RESULTS

STAGE I : Feasibility Assessment

- **DART Feasibility (Meeting Medium Plan Dose Constraints):**
  - ✓ 20f DART: 66/77 (86%) participants met constraints.
  - ✓ 32f DART: 74/82 (90%) participants met constraints.

- **Adaptive Plan Usage (SART & DART):**

  Of 6222 fractions delivered:
  - 37% used small plans.
  - 21% used large plans.

‼ **70% of patients used all three plans at least once.**

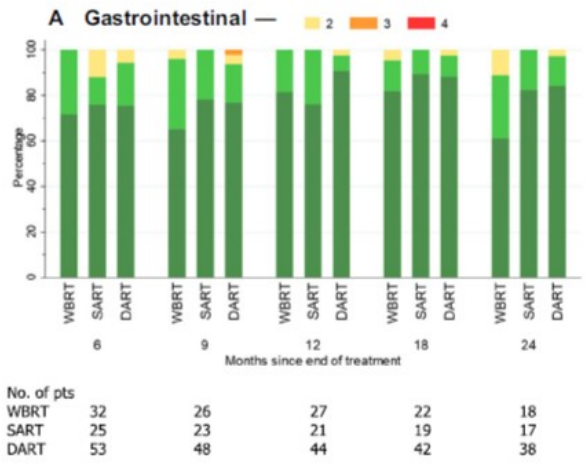
‼ **Only 1.6% used the same plan throughout.**

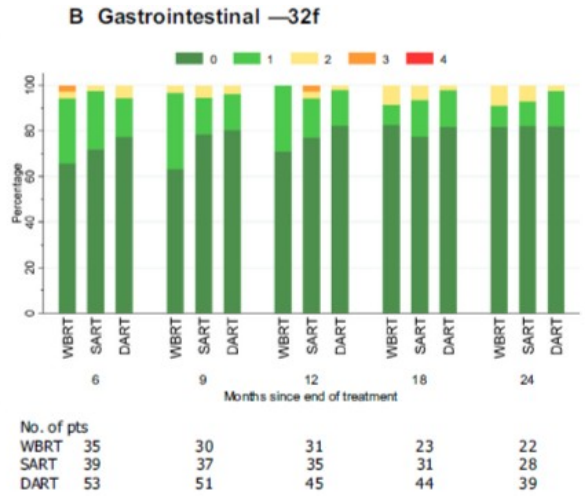
STAGE II : Toxicity Evaluation

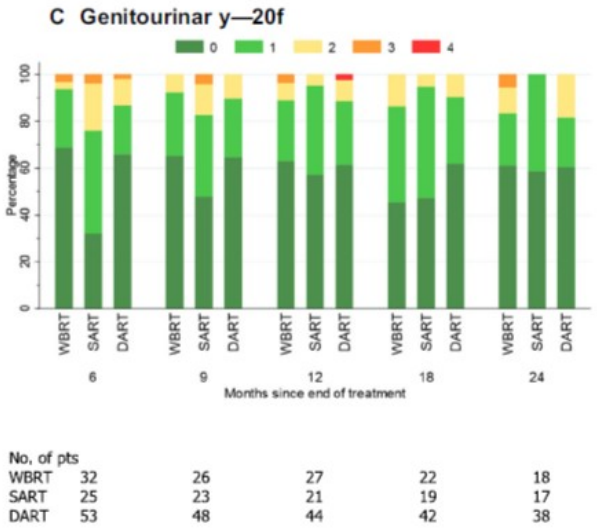
✓ **Primary Endpoint MET!**

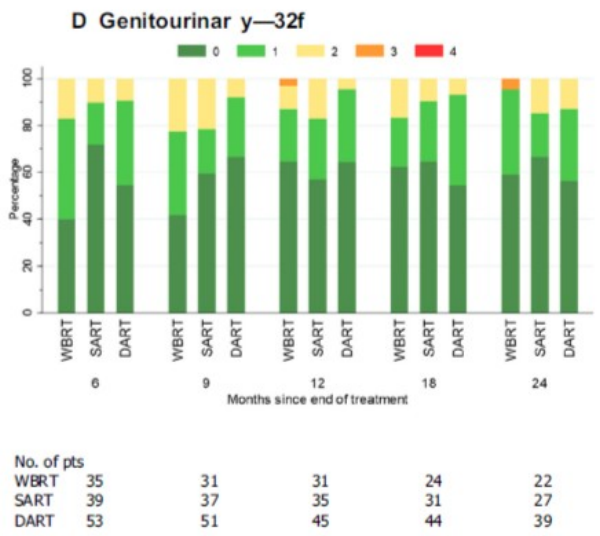
The trial successfully ruled out >20% grade ≥3 radiotherapy-related late toxicity with DART.

- **20f Cohort (Median follow-up 42.1 mo):**
  - DART: 1/58 patients (1.7%, 90% CI 0.1-7.9) had grade ≥3 RT-related toxicity (urosepsis).
  - WBRT: 1/31 (3.2%)
  - SART: 1/23 (4.3%)
- **32f Cohort (Median follow-up 38.2 mo):**
  - DART: 0/56 patients (0%, 90% CI 0-5.2) had grade ≥3 RT-related toxicity.
  - WBRT: 0/36
  - SART: 0/32
- Conclusion: Grade ≥3 late radiotherapy-related toxicity was low with DART.









Overall Late Toxicity

- **Any Late Treatment-Emergent Grade ≥3 DART Toxicity (6-18 mo):**
  - 20f DART: 5/58 (8.6%, 90% CI 3.4 - **17.3**) (Obstruction, Hematuria)
  - 32f DART: 3/56 (5.4%, 90% CI 1.5 - **13.3**) (Fatigue!)
- **Any Late Treatment-Emergent Grade ≥2 DART Toxicity (6-18 mo):**
  - 20f DART: 18/57 (31.0%)
  - 32f DART: 20/56 (35.7%)
- **2-year Cumulative Incidence of RTOG Grade ≥3 Toxicity:**
  - 20f cohort: 2.4%
  - 32f cohort: 1.0%
  - **Lower than historical controls (e.g., BC2001: 13%).**

Patient-Reported Outcomes (PROs)

EQ5D-5L VAS (Overall Health Status):

✓ Maintained at or above baseline, except for a small drop at the end of treatment (20f cohort).

KHQ (Bladder Incontinence Impact & Symptom Severity):

✓ Worst at the end of radiotherapy.

✓ Improved by 12 months, often to better than pre-treatment scores.

Stool Frequency (PRO-CTCAE):

- Worse at the end of treatment for both fractionation cohorts.

✓ No evidence of a detrimental effect of dose escalation on PROs or health-related quality of life.

OUTCOMES

	WBRT + SART	DART	
2-year Locoregional disease control	66% (57 – 73)	74% (66 - 80)	p=0.2, HR 0.8 (95% CI 0.5 – 1.17)
2-Year Invasive locoregional disease control	80% (73 - 86)	83% (76 – 89)	p=0.4
2-Year Bladder Intact Event-Free Survival	67% (59 – 74)	72% (64 – 79)	p=0.3
2-Year OS	77% (70 – 82)	80% (73 – 85)	p=0.4, HR 0.84 (95% CI 0.5 – 1.21)

No significant differences

Salvage Cystectomies

- ✓ Very low rate: 13/345 participants (3.8%).
- ✓ 11 due to disease recurrence.
- ✓ No cystectomies reported due to adverse events.
- ✓ Compares favorably to previous reports (e.g., BC2001: 14%).

Nodal Recurrence: Low, 7% overall; first event in bladder intact EFS for only 2.6%.

KEY POINTS

√ **Successful Dose Escalation**

√ **Low Toxicity**

! **Need for Adaptation:** Most treatments utilized multiple plans

? **Promising Efficacy Signals:**
- Dose escalation showed trends towards improved locoregional control (though not statistically significant).

- OS similar to cystectomy series, low salvage cystectomy rates.

√ **Lower toxicity rates compared to historic bladder cancer trials:**
- Potentially due to adaptive, tumor-focused IMRT plans.

LIMITATIONS

‼ **Phase 2 Design:**
Not powered to compare efficacy.

‼ **Lower Than Expected Overall Toxicity**

‼ **PRO Assessment:**
Compromised by a mid-trial change in instruments, so some patient-reported GI toxicity data are incomplete.

CLINICAL IMPLICATIONS

✓ DART is safe and feasible

✓ Adaptive RT can be delivered across multiple centres with appropriate training and QA

✓ Frequent use of multiple adaptive plans confirms role of adaptive therapy to optimize treatment delivery

How about things closer to home?

ELSEVIER

Radiotherapy and Oncology

Volume 194, Supplement 1, May 2024, Pages S2499-S2502

Clinical - Urology

Digital Poster

2148: Hypofractionated chemoradiotherapy for bladder preservation in muscle-invasive bladder cancer

Anuradha Krishnan, Sheetal Kashid, Namrata Pansande, Priyamvada Maitre, Pallavi Singh, Amit Joshi, Reena Phuralipatram, Gagan Prakash, Mahendra Pal, Amandeep Arora, Vedang Murthy

- **Objective of this Study:**
  - To report the early clinical experience with a shorter radiotherapy schedule (HFRT) for bladder preservation in MIBC patients at a single institution.
  - To compare toxicity and early efficacy outcomes between HFRT and CFRT in their institutional cohort.

Materials & Methods

- **Study Design:** Retrospective analysis of prospectively maintained institutional database.
- **Patient Population:**
  - Consecutive patients with histologically diagnosed muscle-invasive urothelial bladder cancer.
  - Clinicoradiological stage: T1-T4, N0-N+, M0.
  - Treated with curative radiotherapy to the bladder.
- **Assessments:**
  - **Toxicity:**
    - Acute (within 3 months of RT) and late urinary and gastrointestinal (GI) toxicity.
    - Assessed using RTOG and CTCAE criteria.
  - **Efficacy Outcomes (Compared for CFRT and HFRT):**
    - Local Recurrence-Free Survival (LRFS) - (non-invasive or invasive)
    - Invasive Local Recurrence-Free Survival (ILRFS)
    - Disease-Free Survival (DFS) - (invasive bladder recurrence, nodal, or metastatic disease)
    - Bladder Cancer Specific Survival (BCSS)
    - Overall Survival (OS)

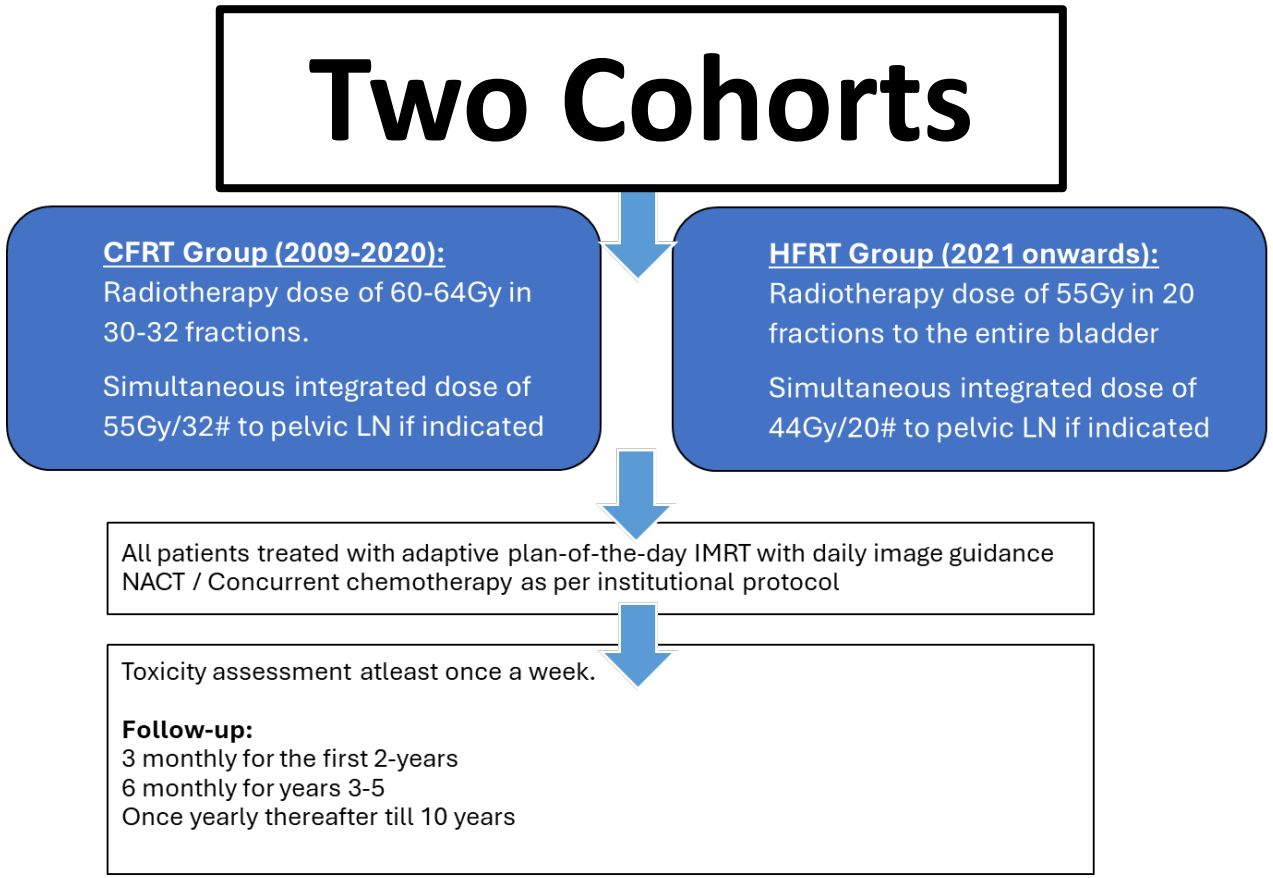


Table 1: Patient characteristics

		Total (n=222)	HFRT (n=50)	CFRT (n=172)
Age (years)	Median, IQR	64 (54-72)	64 (58-70)	64 (53-72)
Sex	Male	194 (87.4)	45 (90)	149 (86.6)
	Female	28 (12.6)	05 (10)	23 (13.4)
T stage	T1	21 (9.5)	07 (14.0)	14 (8.1)
	T2	124 (55.9)	27 (54.0)	97 (56.4)
	T3	61 (27.5)	14 (28.0)	47 (27.3)
	T4	16 (7.2)	02 (4.0)	14 (8.1)
N stage	N0	188 (84.5)	44 (88)	144 (83.7)
	N+	34 (15.5)	6 (12)	28 (16.3)
Target volume	Bladder only	40 (18.0)	12 (24.0)	28 (16.3)
	Bladder + pelvic nodes	182 (82.0)	38 (76.0)	144 (83.7)
Neoadjuvant chemotherapy		69 (31.4)	17 (34)	52 (30.2)
Concurrent chemotherapy	Gemcitabine 75mg/m2	87 (39.2)	23 (46.0)	64 (37.2)
	Cisplatin 30mg/m2	74 (33.3)	14 (28.0)	60 (34.9)
	Others	15 (7.0)	3 (6.0)	12 (7.1)
	None	46 (20.7)	10 (20.0)	36 (20.9)

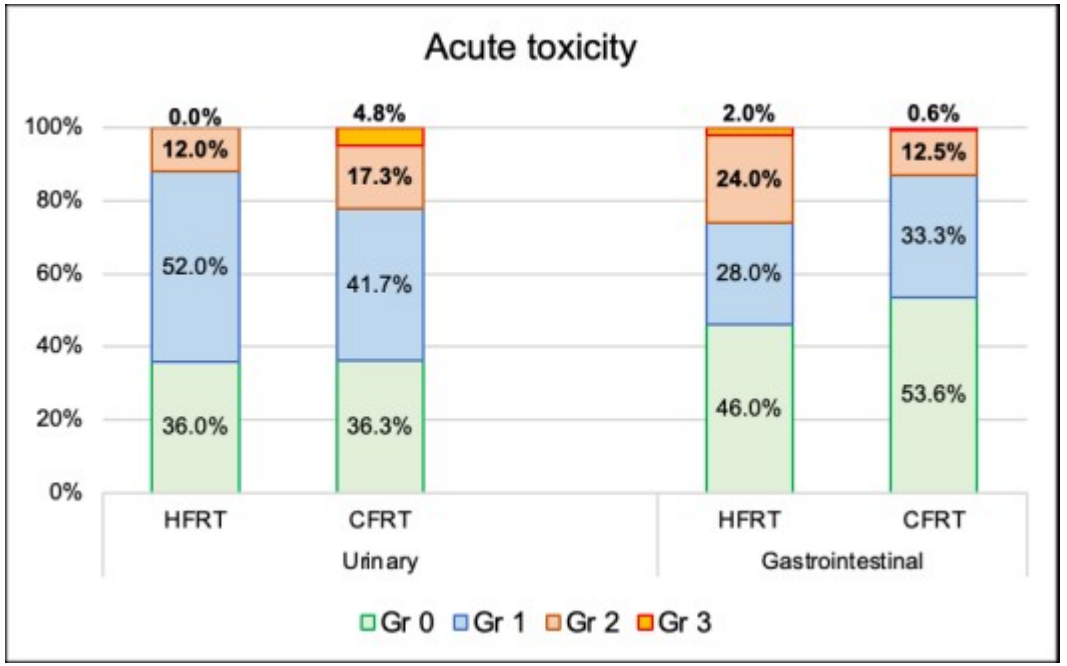
Characteristics comparable between both cohorts.
(Except the sample size!)

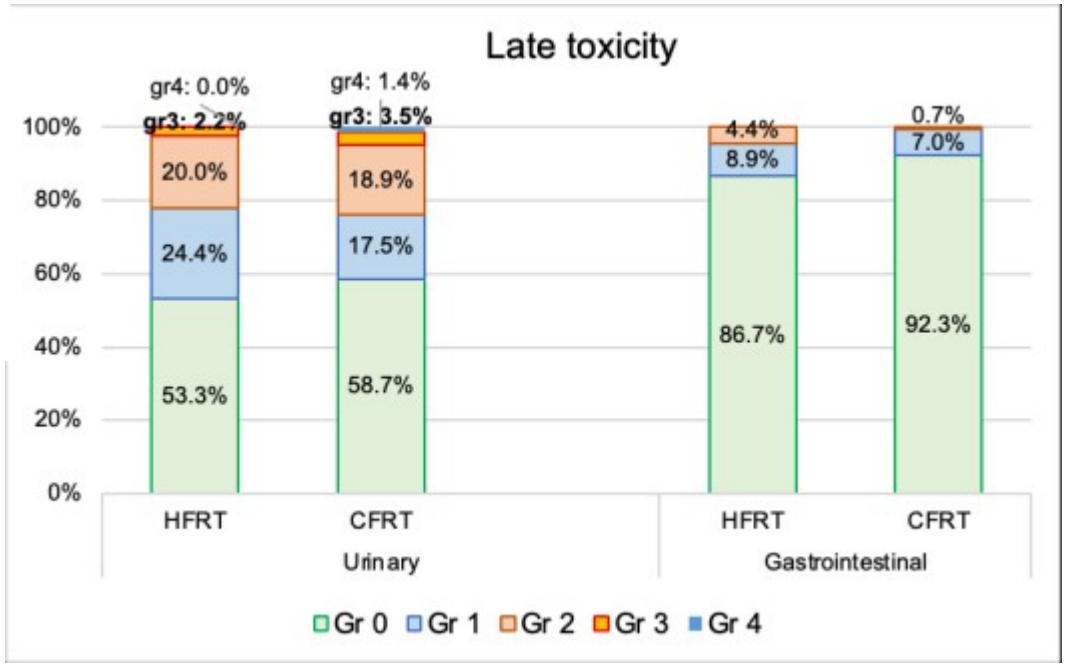
RESULTS

- ✓ **Overall CTRT completion rate – 93.2%**
- ✓ **HFRT 98%**
- ✓ **CFRT 91.9%**

- ✓ **Low overall GI and GU toxicities (Acute and Late)**
- ✓ **Similar between CFRT and HFRT groups**

Higher Grade 2 Late GI toxicities in HFRT group (4.4% vs 0.7%, p=0.08, approaching significance)





OUTCOMES

- **Median followup:**
  Both groups – 32 months
  HFRT – 21 months
  CFRT – 46 months

No Significant Difference!

	HFRT	CFRT	
2-year LRFS	76%	83.4%	p=0.23
2-year invasive LRFS	88.5%	90.2%	p=0.97
2-year Disease free survival	75%	83.3%	p=0.3
2-year BCSS	84.8%	87.2%	p=0.88
2-year OS	79.4%	80.2%	p=0.93

LIMITATIONS

- ‼ **Retrospective analysis**
- ‼ **Single institution experience**
- ‼ **Shorter median FU for HFRT – late toxicity and efficacy data still maturing**

KEY TAKEAWAYS

- ✓ **Real world experience – HFRT has similar acute and late toxicity as CFRT**
- ✓ **Acceptable toxicities DESPITE conc. Gem and pelvic RT**

THANK YOU