*Title Page

Advancing radiotherapy for bladder cancer: Randomised phase II trial of adaptive image guided standard or dose escalated tumour boost radiotherapy (RAIDER)

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1. Current evidence for radical bladder radiotherapy

Cancer cure with organ preservation using radiotherapy has been accepted over surgery in radical treatment of many tumours but there has been slow uptake in muscle invasive bladder cancer (MIBC) (1). The underutilisation of radical bladder radiotherapy has been fueled in part by an absence of randomised controlled trials (2). Historical comparisons often favour surgery (cystectomy) by disregarding the bias that patients receiving cystectomy tend to be younger with less comorbidity and that radiotherapy cohorts are subject to under staging (3-5).

Contemporary evidence attempting to account for these biases demonstrates that radiotherapy when used as part of a multi-modality strategy has equivalent survival outcomes to radical cystectomy (6, 7). Despite this, international guidance still places emphasis on cystectomy as the preferred treatment option with multi-modality organ preservation using radiotherapy as an alternative merely for those unfit or unwilling to undergo surgery (8). This position is less entrenched in the UK as National Institute for Health and Care Excellence (NICE) guidance on bladder cancer published in 2015 recommends offering MIBC patients the choice between both modalities where appropriate and giving them the opportunity to see both a clinical oncologist and a surgeon to support informed decision making (9, 10).

1.1 Radiotherapy with a radiosensitiser

Radical bladder radiotherapy delivered with a radiosensitiser significantly improves outcomes compared to radiotherapy alone (10). Outside the UK, cisplatin is the favoured radiosensitiser (11, 12). In the UK, practice has been largely influenced by phase III randomised evidence from BC2001 which used mitomycin C and 5-fluorouracil with radiotherapy (13). This significantly improved local-regional disease free survival compared to radiotherapy alone (HR 0.68 95%CI, 0.48 to 0.96; p=0.03). Although more acute grade 3 and 4 toxicity was seen in the chemoradiotherapy group there was no significant increase in late toxicity or adverse impact on quality of life (13, 14). In phase I/II studies concurrent gemcitabine has also been shown to be an effective radiosensitiser with bladder radiotherapy (15, 16).

The BCON phase III trial demonstrated improved survival with nicotinamide and carbogen (95% O2 with 5% carbon dioxide) compared to radiation alone (HR 0.86; 95% CI 0.74 to 0.99; p=0.004) (17). It is less widely used than concurrent

chemotherapy (18, 19). One reason for this maybe the practicalities of delivering high flow, high oxygen concentration during radiotherapy. Lack of head to head comparisons means no single radiosensitising regimen is preferred (18).

2 Strategies to improve bladder radiotherapy outcomes

2.1 Image guided adaptive bladder radiotherapy

The bladder is subject to significant inter-fraction filling and shape change. If unaccounted for, it can lead to geographical misses which impede disease control and increase potential treatment related toxicity (20). As no patient interventions are sufficient to minimise this variation, large planning target volume (PTV) margins have been necessary (21-23). Even with cone beam CT (CBCT) soft tissue image guidance, a 1.5cm PTV margin is required to achieve target coverage in >90% fractions (20).

One adaptive radiotherapy solution developed to accommodate the inter-fraction target variation is to generate a library of patient specific treatment plans from varying PTV sizes, which captures the spectrum of likely target volume change (24). CBCT acquired prior to each fraction means the most appropriate PTV and corresponding plan can be selected which covers the target appropriately with minimal normal tissue exposure. This is often referred to as 'plan of the day'. In bladder cancer radiotherapy, selection of the best-fit plan improves bladder coverage while reducing the PTV by approximately 40% compared to single plan based on standard 1.5 cm PTV (25). This in turn significantly reduces integral dose to surrounding normal tissue (20, 25).

2.2 Dose escalation

Despite radiosensitisation most recurrences following radiotherapy occur within the bladder, with a significant proportion (~70%) occurring at the original MIBC tumour site (26). As bladder cancers, especially urothelial carcinomas, exhibit a dose response relationship to radiotherapy, it is hypothesised that higher doses would improve local control and overall survival (27-29).

However, the bladder itself has a normal tissue tolerance which, if exceeded, risks impacting on organ function. 64-65Gy in 2Gy per fraction is the accepted whole bladder tolerance. Adherence to this is necessary to minimise the risk of $\geq$ grade 3 Radiation Therapy Oncology Group (RTOG) late genito-urinary complications to $\leq$6% (30-32).

The possibility of just treating the tumour and sparing normal bladder opens opportunity to reduce toxicity and facilitate dose escalation. Tumour focused partial bladder irradiation has no adverse effect on local control when compared to whole bladder radiotherapy at standard doses (33, 34). Bladder brachytherapy data also provides further evidence that partial bladder irradiation can be achieved safely (29, 35-37). Given that bladder brachytherapy is not widely available in the UK, dose escalation with external beam radiotherapy is attractive.

We have demonstrated in a single centre phase I study (NCT01124682) that plan of the day enables a maximum tolerated dose of 70Gy in 32f to be safely delivered to the bladder tumour (38).

3 RAIDER trial concept

RAIDER (NCT02447549) was designed to test whether an adaptive tumour focused boost can allow an increase in dose to the tumour above the commonly accepted schedules of 64Gy in 32f over 6.5 weeks and 55 Gy in 20 fractions (f) over 4 weeks with a resultant improvement in patient outcomes. (figure 1).

To our knowledge RAIDER is the first international multicentre randomised controlled trial evaluating an image guided adaptive radiotherapy technique The study population are patients with localised unifocal (solitary) MIBC. RAIDER is a two-stage phase II three arm trial with patients randomised (1:1:2) (figure 1) between

i) standard whole bladder radiotherapy (WBRT) delivered using a single plan (control),
ii) standard dose adaptive tumour focused radiotherapy (SART) delivered with a library of plans or,
iii) dose escalated adaptive tumour focused radiotherapy (DART) delivered with a library of plans.

The initial feasibility (stage I) primary endpoint is to determine the proportion of patients in the DART group meeting the pre-defined normal tissue radiotherapy dose constraints (table 1). The secondary endpoints of stage I are the recruitment rate and the ability of the participating centres to deliver SART and DART treatment as per protocol. The primary endpoint of stage II is safety as determined by late $\geq$ grade 3 toxicity occurring 6-18 months following radiotherapy as assessed using Common Terminology Criteria for Adverse Events (CTCAE v.4). The secondary endpoints of stage II are acute toxicity as measured by CTCAE v.4, and patient reported outcomes.

Additional secondary endpoints include health economic related measures, loco-regional MIBC control, progression free survival, and overall survival.

4 Safeguarding radiotherapy quality

To fulfil the RAIDER trial objectives successful transfer of tumour focused 'plan of the day' dose escalation technique from single academic centre to multi centre setting was necessary (38). Poor quality radiotherapy has a critical impact on trial outcomes (39, 40). Consequently, detailed instructions with worked examples were provided in the RAIDER radiotherapy guidelines and rigorous pre-trial and on-trial quality assurances were put in place to ensure that contouring, planning, and plan selection deviations were minimised (41).

Plan selection competency was completed through an online training package, practical workshops, and credentialing assessment (42, 43). The contemporaneous collection and off line review of planning and delivery data enabled central concordance of plan selection to be examined during the trial. This allowed us to be responsive to the educational and training needs of those conducting plan selection (43).

In the UK quality assurance was coordinated by The National Radiotherapy Trials Quality Assurance (RTTQA) Team and in Australia and New Zealand by the Trans-Tasman Radiation Oncology Group (TROG).

5 Early impact

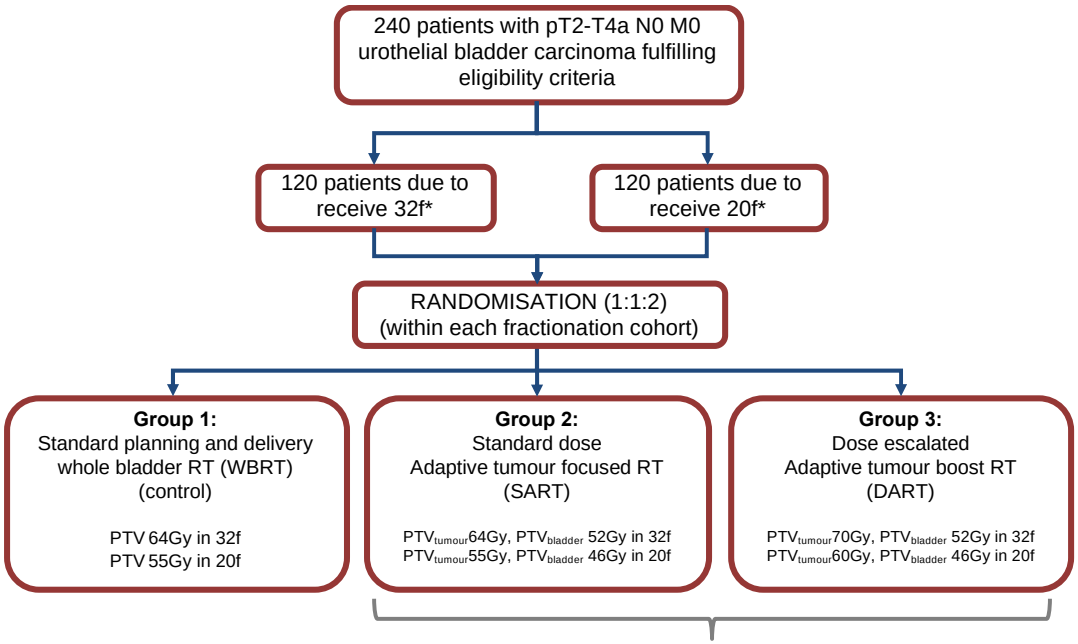
It is well recognised that a driver for change in UK radiotherapy practice has been participation in clinical trials. There are many examples of trial participation leading to wider adoption of new radiotherapy techniques under the direction of a multi-professional trial QA programme (44). The CHHiP trial supported the implementation of IMRT with centres either using the trial as a vehicle to commission IMRT or to roll out inverse or forward planned IMRT for routine prostate treatment (45). Similarly, the standardisation of UK breast radiotherapy practice unarguably began with the START trial. Many centres changed their breast radiotherapy technique in order to comply with the requirements of the trial, which then provided the foundation for more complex

breast radiotherapy implementation in subsequent trials including FAST, IMPORT High and IMPORT Low (46).

In the accompanying paper by Webster et al., we present early evidence of the impact RAIDER trial participation has had particularly on up skilling the treatment radiographer workforce (47). It is estimated that at the time of recruitment completion, over 500 treatment radiographers at 33 UK centres had utilised the RAIDER QA training programme and had met pre-agreed competency standard for plan selection.

We hope that RAIDER will demonstrate feasibility of multi-centre implementation of dose escalated adaptive tumour focused 'plan of the day' radiotherapy. As well as evaluating advances in radiotherapy technology, we believe that RAIDER will contribute to bladder radiotherapy standardisation and provide individual departments support to update their own treatment delivery techniques. RAIDER completed recruitment in Spring 2020, and is expected to report preliminary results in 2021 and mature results in 2022. These results will inform design of a future phase III trial and contribute to the evidence base regarding the optimal organ preserving treatment for patients with MIBC.

Figure 1. Trial overview



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.

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Body-PTV (Normal Tissue)	D_{1cc}	≤105% of prescribed dose	≤110% of prescribed dose	D_{1cc}	≤105% of prescribed dose	≤110% of prescribed dose

*Whole bladder (CTV) constraint was used to aid plan optimisation of the tumour focused (SART and DART) arms in order to ensure normal bladder sparing achieved. Bladder outside PTV_{boost} (i.e. CTV-PTV_{boost}) i.e. normal bladder meeting these contraints was collected for reporting of the RAIDER primary end point.

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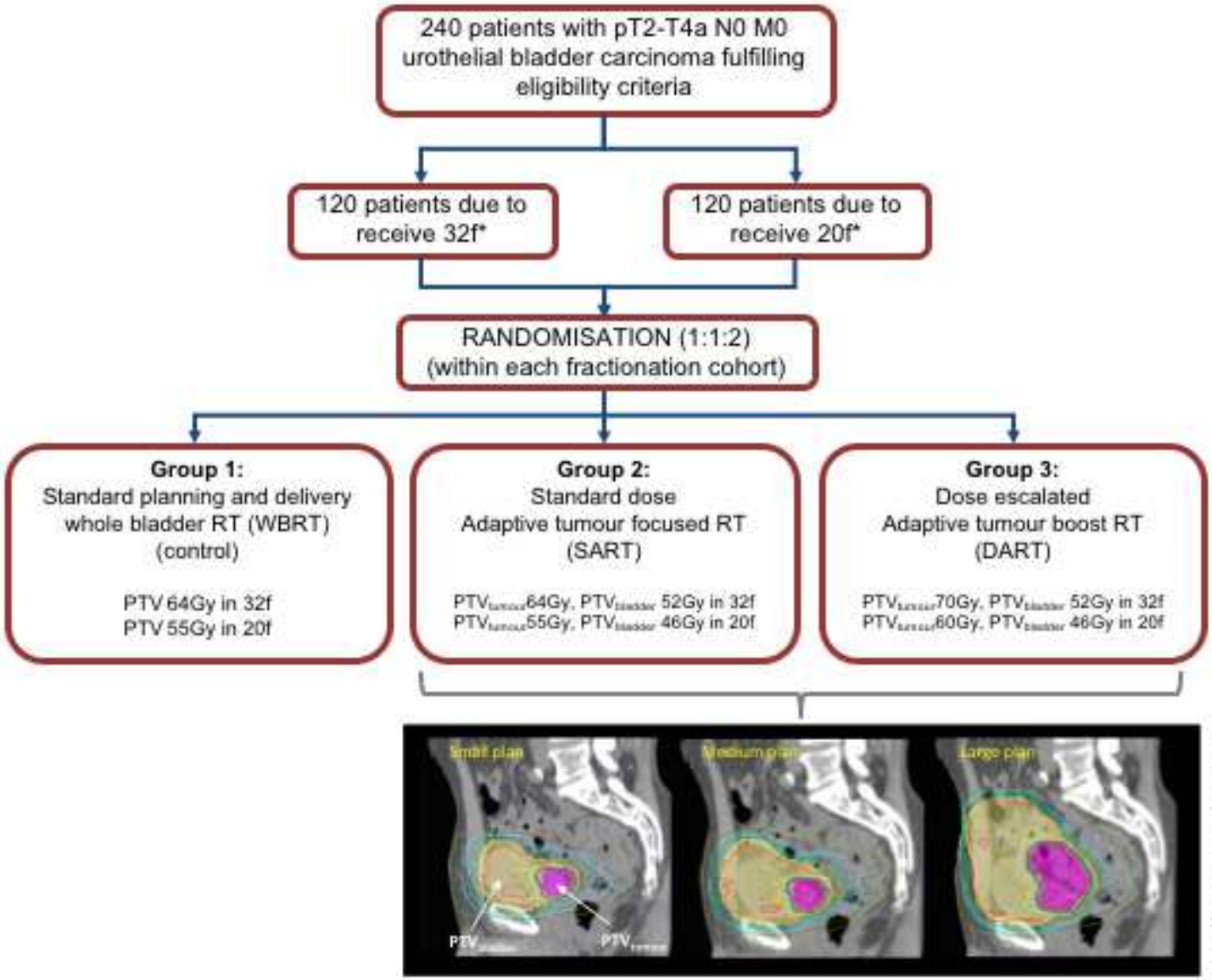

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*Declaration of Interest Statement

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☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

SH reports non-financial support from Elekta (Elekta AB, Stockholm, Sweden), non-financial support from Merck Sharp & Dohme (MSD), personal fees and non-financial support from Roche outside the submitted work; RL and CG have no conflicts to disclose; EH reports grants from Cancer Research UK during the conduct of the study; grants from Accuray Inc., grants from Varian Medical Systems Inc., outside the submitted work; RH reports non-financial support from Janssen, grants and personal fees from MSD, personal fees from Bristol Myers Squibb, grants from Cancer Research UK, other from Nektar Therapeutics, personal fees and non-financial support from Roche, outside the submitted work.

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Failing to close the gap between evidence and clinical practice in radical bladder cancer radiotherapy

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2. Study concepts and design	S.H, R.L, E.H, R.H
3. Literature research	S.H
4. Clinical studies	n/a
5. Experimental studies / data analysis	n/a
6.Statistical analysis	n/a
7.Manuscript preparation	S.H
8. Manuscript editing	S.H, R.L, E.H, R.H

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1. Current evidence for radical bladder radiotherapy

Cancer cure with organ preservation using radiotherapy has been accepted over surgery in radical treatment of many tumours but there has been slow uptake in muscle invasive bladder cancer (MIBC) (1). The underutilisation of radical bladder radiotherapy has been fueled in part by an absence of randomised controlled trials (2). Historical comparisons often favour surgery (cystectomy) by disregarding the bias that patients receiving cystectomy tend to be younger with less comorbidity and that radiotherapy cohorts are subject to under staging (3-5).

Contemporary evidence attempting to account for these biases demonstrates that radiotherapy when used as part of a multi-modality strategy has equivalent survival outcomes to radical cystectomy (6, 7). Despite this, international guidance still places emphasis on cystectomy as the preferred treatment option with multi-modality organ preservation using radiotherapy as an alternative merely for those unfit or unwilling to undergo surgery (8). This position is less entrenched in the UK as National Institute for Health and Care Excellence (NICE) guidance on bladder cancer published in 2015 recommends offering MIBC patients the choice between both modalities where appropriate and giving them the opportunity to see both a clinical oncologist and a surgeon to support informed decision making (9, 10).

1.1 Radiotherapy with a radiosensitiser

Radical bladder radiotherapy delivered with a radiosensitiser significantly improves outcomes compared to radiotherapy alone (10). Outside the UK, cisplatin is the favoured radiosensitiser (11, 12). In the UK, practice has been largely influenced by phase III randomised evidence from BC2001 which used mitomycin C and 5-fluorouracil with radiotherapy (13). This significantly improved local-regional disease free survival compared to radiotherapy alone (HR 0.68 95%CI, 0.48 to 0.96; p=0.03). Although more acute grade 3 and 4 toxicity was seen in the chemoradiotherapy group there was no significant increase in late toxicity or adverse impact on quality of life (13, 14). In phase I/II studies concurrent gemcitabine has also been shown to be an effective radiosensitiser with bladder radiotherapy (15, 16).

The BCON phase III trial demonstrated improved survival with nicotinamide and carbogen (95% O2 with 5% carbon dioxide) compared to radiation alone (HR 0.86; 95% CI 0.74 to 0.99; p=0.004) (17). It is less widely used than concurrent chemotherapy (18, 19). One reason for this maybe the practicalities of delivering high

flow, high oxygen concentration during radiotherapy. Lack of head to head comparisons means no single radiosensitising regimen is preferred (18).

2 Strategies to improve bladder radiotherapy outcomes

2.1 Image guided adaptive bladder radiotherapy

The bladder is subject to significant inter-fraction filling and shape change. If unaccounted for, it can lead to geographical misses which impede disease control and increase potential treatment related toxicity (20). As no patient interventions are sufficient to minimise this variation, large planning target volume (PTV) margins have been necessary (21-23). Even with cone beam CT (CBCT) soft tissue image guidance, a 1.5cm PTV margin is required to achieve target coverage in >90% fractions (20).

One adaptive radiotherapy solution developed to accommodate the inter-fraction target variation is to generate a library of patient specific treatment plans from varying PTV sizes, which captures the spectrum of likely target volume change (24). CBCT acquired prior to each fraction means the most appropriate PTV and corresponding plan can be selected which covers the target appropriately with minimal normal tissue exposure. This is often referred to as 'plan of the day'. In bladder cancer radiotherapy, selection of the best-fit plan improves bladder coverage while reducing the PTV by approximately 40% compared to single plan based on standard 1.5 cm PTV (25). This in turn significantly reduces integral dose to surrounding normal tissue (20, 25).

2.2 Dose escalation

Despite radiosensitisation most recurrences following radiotherapy occur within the bladder, with a significant proportion (~70%) occurring at the original MIBC tumour site (26). As bladder cancers, especially urothelial carcinomas, exhibit a dose response relationship to radiotherapy, it is hypothesised that higher doses would improve local control and overall survival (27-29).

However, the bladder itself has a normal tissue tolerance which, if exceeded, risks impacting on organ function. 64-65Gy in 2Gy per fraction is the accepted whole bladder tolerance. Adherence to this is necessary to minimise the risk of $\geq$ grade 3 Radiation Therapy Oncology Group (RTOG) late genito-urinary complications to $\leq$6% (30-32).

The possibility of just treating the tumour and sparing normal bladder opens

opportunity to reduce toxicity and facilitate dose escalation. Tumour focused partial bladder irradiation has no adverse effect on local control when compared to whole bladder radiotherapy at standard doses (33, 34). Bladder brachytherapy data also provides further evidence that partial bladder irradiation can be achieved safely (29, 35-37). Given that bladder brachytherapy is not widely available in the UK, dose escalation with external beam radiotherapy is attractive.

We have demonstrated in a single centre phase I study (NCT01124682) that plan of the day enables a maximum tolerated dose of 70Gy in 32f to be safely delivered to the bladder tumour (38).

3 RAIDER trial concept

RAIDER (NCT02447549) was designed to test whether an adaptive tumour focused boost can allow an increase in dose to the tumour above the commonly accepted schedules of 64Gy in 32f over 6.5 weeks and 55 Gy in 20 fractions (f) over 4 weeks with a resultant improvement in patient outcomes. (figure 1).

To our knowledge RAIDER is the first international multicentre randomised controlled trial evaluating an image guided adaptive radiotherapy technique The study population are patients with localised unifocal (solitary) MIBC. RAIDER is a two-stage phase II three arm trial with patients randomised (1:1:2) (figure 1) between

i) standard whole bladder radiotherapy (WBRT) delivered using a single plan (control),
ii) standard dose adaptive tumour focused radiotherapy (SART) delivered with a library of plans or,
iii) dose escalated adaptive tumour focused radiotherapy (DART) delivered with a library of plans.

The initial feasibility (stage I) primary endpoint is to determine the proportion of patients in the DART group meeting the pre-defined normal tissue radiotherapy dose constraints (table 1). The secondary endpoints of stage I are the recruitment rate and the ability of the participating centres to deliver SART and DART treatment as per protocol. The primary endpoint of stage II is safety as determined by late $\geq$ grade 3 toxicity occurring 6-18 months following radiotherapy as assessed using Common Terminology Criteria for Adverse Events (CTCAE v.4). The secondary endpoints of stage II are acute toxicity as measured by CTCAE v.4, and patient reported outcomes.

Additional secondary endpoints include health economic related measures, loco-regional MIBC control, progression free survival, and overall survival.

4 Safeguarding radiotherapy quality

To fulfil the RAIDER trial objectives successful transfer of tumour focused 'plan of the day' dose escalation technique from single academic centre to multi centre setting was necessary (38). Poor quality radiotherapy has a critical impact on trial outcomes (39, 40). Consequently, detailed instructions with worked examples were provided in the RAIDER radiotherapy guidelines and rigorous pre-trial and on-trial quality assurances were put in place to ensure that contouring, planning, and plan selection deviations were minimised (41).

Plan selection competency was completed through an online training package, practical workshops, and credentialing assessment (42, 43). The contemporaneous collection and off line review of planning and delivery data enabled central concordance of plan selection to be examined during the trial. This allowed us to be responsive to the educational and training needs of those conducting plan selection (43).

In the UK quality assurance was coordinated by The National Radiotherapy Trials Quality Assurance (RTTQA) Team and in Australia and New Zealand by the Trans-Tasman Radiation Oncology Group (TROG).

5 Early impact

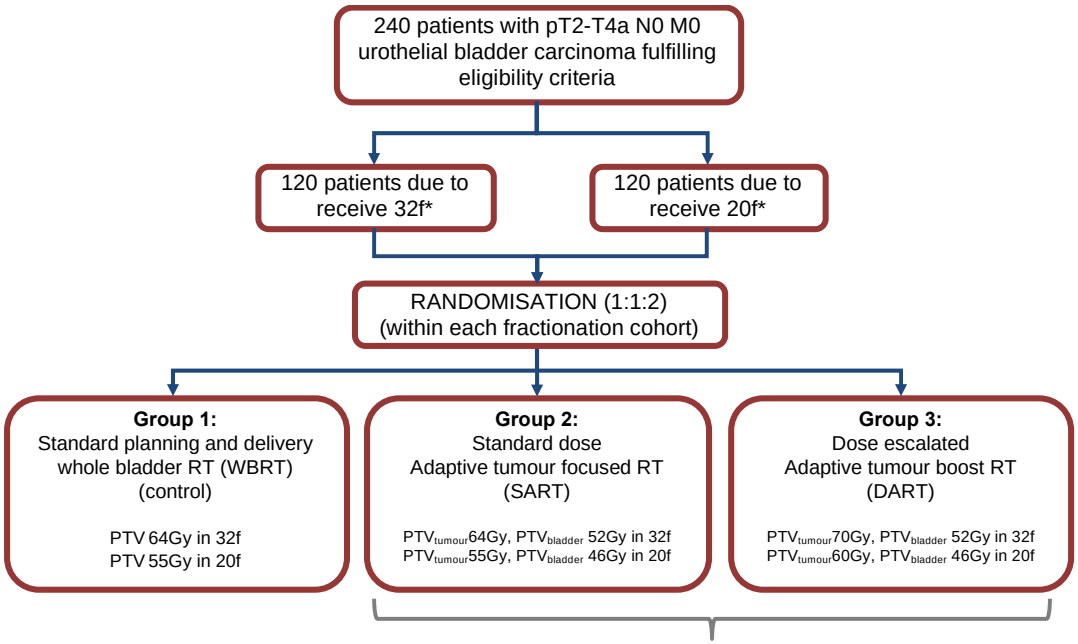
It is well recognised that a driver for change in UK radiotherapy practice has been participation in clinical trials. There are many examples of trial participation leading to wider adoption of new radiotherapy techniques under the direction of a multi-professional trial QA programme (44). The CHHiP trial supported the implementation of IMRT with centres either using the trial as a vehicle to commission IMRT or to roll out inverse or forward planned IMRT for routine prostate treatment (45). Similarly, the standardisation of UK breast radiotherapy practice unarguably began with the START trial. Many centres changed their breast radiotherapy technique in order to comply with the requirements of the trial, which then provided the foundation for more complex

breast radiotherapy implementation in subsequent trials including FAST, IMPORT High and IMPORT Low (46).

In the accompanying paper by Webster et al., we present early evidence of the impact RAIDER trial participation has had particularly on up skilling the treatment radiographer workforce (47). It is estimated that at the time of recruitment completion, over 500 treatment radiographers at 33 UK centres had utilised the RAIDER QA training programme and had met pre-agreed competency standard for plan selection.

We hope that RAIDER will demonstrate feasibility of multi-centre implementation of dose escalated adaptive tumour focused 'plan of the day' radiotherapy. As well as evaluating advances in radiotherapy technology, we believe that RAIDER will contribute to bladder radiotherapy standardisation and provide individual departments support to update their own treatment delivery techniques. RAIDER completed recruitment in Spring 2020, and is expected to report preliminary results in 2021 and mature results in 2022. These results will inform design of a future phase III trial and contribute to the evidence base regarding the optimal organ preserving treatment for patients with MIBC.

Figure 1. Trial overview



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.

*At the time of trial design two radiotherapy schedules were in common use to treat MIBC in the UK, 55 Gy in 20 fractions (f) over 4 weeks and 64Gy in 32f over 6.5 weeks. To manage the inclusion of both fractionation cohorts, the choice of schedule had to be confirmed by each participating site before RAIDER trial commencement and then had to be used for all patients at that site. The study was separately powered for each fractionation cohort (essentially 2 trials in 1) and analysis will thus establish the safety of dose escalation with each fractionation regimen independently.

Table 2. Organ at risk dose constraint guide

Normal tissue	32 fraction cohort			20 fraction cohort		
	Constraint	**Optimal**	**Mandatory**	**Constraint**	**Optimal**	**Mandatory**
Rectum	V30Gy V50Gy V60Gy V65Gy V70Gy		80% 60% 50% 30% 15%	V25Gy V41.7Gy V50Gy V54.2Gy V58.3Gy		80% 60% 50% 30% 15%
Femoral Heads	V50Gy		50%	V41.7Gy		50%
Other Bowel	V45Gy V50Gy V55Gy V60Gy V65Gy V70Gy V74Gy	116cc 104cc 91cc 73cc 23cc 0cc 0cc	139cc 127cc 115cc 98cc 40cc 10cc 0cc	V37.5Gy V41.7Gy V45.8Gy V50Gy V54.2Gy V58.3Gy V61.7Gy	116cc 104cc 91cc 73cc 23cc 0cc 0cc	139cc 127cc 115cc 98cc 40cc 10cc 0cc
***Whole bladder constraint**	V60Gy V65Gy	50% 40% DART 0% SART	80% 50% DART 5% SART	V50Gy V54.2Gy	50% 40% DART 0% SART	80% 50% DART 5% SART
Body-PTV (Normal Tissue)	D_{1cc}	≤105% of prescribed dose	≤110% of prescribed dose	D_{1cc}	≤105% of prescribed dose	≤110% of prescribed dose

*Whole bladder (CTV) constraint was used to aid plan optimisation of the tumour focused (SART and DART) arms in order to ensure normal bladder sparing achieved. Bladder outside PTV_{boost} (i.e. CTV-PTV_{boost}) i.e. normal bladder meeting these contraints was collected for reporting of the RAIDER primary end point.

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