Clinical outcomes of a randomised trial of adaptive plan of the day treatment in patients receiving ultra-hypofractionated weekly radiotherapy for bladder cancer

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Data sharing

Deidentified individual participant data, together with a data dictionary defining each field in the set, will be made available to other researchers on request. The Institute of Cancer Research (ICR) Clinical Trials and Statistics Unit (CTSU) supports wider dissemination of information from the research it conducts and increased cooperation between investigators. Trial data is obtained, managed, stored, shared, and archived according to ICR-CTSU standard operating procedures to ensure the enduring quality, integrity and utility of the data. Formal requests for data sharing are considered in line with ICR-CTSU procedures, with due regard given to funder and sponsor guidelines. Requests are via a standard proforma describing the nature of the proposed research and extent of data requirements. Data recipients are required to enter a formal data sharing agreement, which describes the conditions for release and requirements for data transfer, storage, archiving, publication, and Intellectual Property. Requests are reviewed by the Trial Management Group (TMG) in terms of scientific merit and ethical considerations, including patients' consent. Data sharing is undertaken if proposed projects have a sound scientific or patients' benefit rationale, as agreed by the TMG and approved by the Independent Data Monitoring and Steering Committee, as required. Restrictions relating to patients' confidentiality and consent will be

limited by aggregating and anonymising identifiable patients' data. Additionally, all indirect identifiers that could lead to deductive disclosures will be removed in line with Cancer Research UK data sharing guidelines.

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ABSTRACT

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Purpose

Hypofractionated radiotherapy can be used to treat patients with muscle invasive bladder cancer unable to have radical therapy. Toxicity is a key concern but adaptive "plan-of the day" (POD) image guided radiotherapy delivery (IGRT) could improve outcomes by minimising volume of normal tissue irradiated. The HYBRID trial assessed multi-centre implementation, safety and efficacy of this strategy.

Methods

HYBRID is a phase II randomised trial conducted at 14 UK hospitals. Patients with T2-T4aN0M0 muscle invasive bladder cancer unsuitable for radical therapy received 36Gray in 6 weekly fractions, randomised (1:1) to standard planning (SP) or adaptive planning (AP) using a minimisation algorithm. For AP a pre-treatment cone beam CT was used to select the POD from three plans (small, medium, large). Follow-up included standard cystoscopic, radiological, and clinical assessments. The primary endpoint was non-genitourinary CTCAE ≥grade 3 ($\geq G3$) toxicity within 3-months of radiotherapy. A non-comparative single stage design aimed to exclude $\geq$30% toxicity rate in each planning group in patients who received $\geq$1 fraction of radiotherapy. Local control at 3-months (both groups combined) was a key secondary endpoint.

Results

Between April 15 2014 and August 10 2016, 65 patients were enrolled (SP32; AP33). Median follow up was 38·8 months (IQR 36·8-51·3). Median age was 85 years (IQR 81-89); 68% (44/65) were male, 98% had grade 3 TCC. In 63 evaluable participants, CTCAE

≥G3 non-GU toxicity rates were 6% (2/33, 95% CI: 0·7-20·2%) for AP and 13% (4/30, 95% CI: 3·8-30·7%) for SP. Disease was present in 9/48 participants assessed at 3 months, giving a local control rate of 81·3% (95% CI: 67·4-91·1%).

Conclusions

Plan of the day adaptive radiotherapy was successfully implemented across multiple centres. Weekly ultra-hypofractionated 36 Gray/6 fraction radiotherapy is safe and provides good local control rates in this older patient population.

INTRODUCTION

Half of bladder cancer cases are diagnosed in patients aged over 75, many of whom are not fit for major surgery due to performance status and co-morbidity and/or are unable to attend hospital for four to seven weeks for daily radical radiotherapy [1-4]

This population presents a management dilemma, with unmet and potentially neglected clinical needs. A recent UK Royal College of Radiologist audit showed that just under 50% of patients with potentially curable T2-T4 disease receive either no treatment or palliative radiotherapy only[5], similar to reports elsewhere[6,7]. Despite relatively poor performance status many such patients have a life expectancy of several years, and if left untreated may experience significant disease related symptoms such as haematuria, urinary frequency, dysuria, pelvic pain, urinary incontinence, and urinary obstruction[8].

One option is to use ultra-hypofractionated radiotherapy, shown to be equivalent to daily palliative radiotherapy treatment (35Gray in 10 fractions) in a multicentre randomised phase III trial in MIBC (MRCBA09), conducted in the 1990s [8]. However, the dose of 21Gray in 3 fractions used in MRCBA09 and given over one week is relatively low and three month local cystoscopic control was modest (14/37; 38%). A number of centres have tested an alternative ultra-hypofractionated schedule of 6Gy per fraction weekly to a dose of 30-36Gy over five to six weeks,[9-11] which has a higher biological dose to the tumour than the BA09 schedules[8]. Data on the 6Gy per fraction schedule comes from retrospective reports and a single centre prospective study[9-12].

Bladder radiotherapy has traditionally used large margins between the clinical target volume (CTV) and planning target volume (PTV) to account for intra-fraction variation in position and shape. The extra radiation caused by these large margins could add to

toxicity, a concern in this frail population. Modern image guided adaptive radiotherapy protocols have been described to account for these changes with a view to improving clinical outcomes. One approach is to use a 'plan of the day' where a best fit plan from a pre-prepared library is used to more tightly conform to the target volume. This could be particularly important in the context of ultra-fractionation where each fraction represents over 15% of the total dose and missing target or treating excessively could have a greater proportionate impact than during conventional fractionation were effects may be averaged out. This makes ultra-fractionation an excellent context to test adaptive radiotherapy. Single centre feasibility results of this approach in this population combined with ultra-hypo-fractionated radiotherapy have been reported[12].

To test these approaches on a multicentre basis we designed a non-comparative randomised phase II trial to assess the feasibility, clinical and patient reported outcomes of weekly ultra-hypofractionated radiotherapy with and without adaptive radiotherapy in patients for whom conventional radical treatment for bladder cancer was unsuitable.

METHODS AND MATERIALS

Study design

HYBRID (CRUK/12/055) is a non-comparative randomised phase II trial of ultra-hypofractionated bladder radiotherapy in muscle invasive bladder cancer done at 14 NHS hospitals in the UK. The aims were to assess the feasibility and safety of delivering plan of the day radiotherapy at multiple NHS sites and to assess the overall toxicity, patient reported outcomes and disease control associated with ultra-hypofractionated radiotherapy[13].

Eligible patients were aged at least 18 years, had histologically or cytologically confirmed bladder cancer staged T2-T4a N0 M0, were unable to receive radical cystectomy or daily fractionated radiotherapy for any reason, had an expected survival >6 months and WHO performance status 0-3.

Key exclusion criteria were uncontrolled malignancy in the past two years, prior pelvic radiotherapy or major pelvic surgery, urinary catheter, or any other contra-indication to radiotherapy.

Participants were recruited by their clinical care teams in clinic and provided written informed consent before enrolment. The trial was registered (ISRCTN18815596), approved by the London-Surrey Borders Research Ethics Committee (13/LO/1350), sponsored by The Institute of Cancer Research and conducted in accordance with the principles of good clinical practice. The Clinical Trials and Statistics Unit at The Institute of Cancer Research (ICR-CTSU) coordinated the trial and carried out central statistical data monitoring and all analyses. The trial management group was overseen by independent data monitoring and trial steering committees. The full study protocol is published[13].

Randomisation and masking

Treatment allocation was done centrally by ICR-CTSU within 4-6 weeks before patients were due to start radiotherapy. Participants were assigned 1:1 between standard and adaptive planning using a minimisation algorithm balanced for radiotherapy treatment centre and incorporating a random element. Treatment allocation was not masked.

Procedures

Radiotherapy planning details and quality assurance programme are as described in Hafeez et al 2020[13]. In brief; all participants received 36Gy in 6 fractions to the bladder. Participants in the standard planning group received radiotherapy using one plan throughout treatment. Three treatment plans (small, medium, large) were generated for the adaptive planning (AP) group, with pre-RT cone beam (CB) CT used to select the best fitting 'plan of the day' for each fraction. A quality assurance programme accredited individuals for plan selection. A single expert reviewer (S Hafeez), blinded to outcomes, assessed concordance between online and offline plan selection retrospectively.

Clinical target volume (CTV) encompassed visible tumour, whole bladder and any area of extravesical spread. CTV to PTV expansion margins for SP and AP are given in supplementary table A1. Example of derived PTVs are given in supplementary figure 6A. The margins for the adaptive planning are as derived from modelling work and validated in a subsequent single centre phase 2 study[12,14,15].

Comorbidity was assessed at baseline using the Charlson Comorbidity Index[16]. Clinician assessment of toxicity was conducted weekly on treatment using the National Cancer Institute - Common Terminology Criteria for Adverse Events (CTCAE) v4.0, with full blood count, urea and electrolytes assessed at fractions 2, 4, and 6. CTCAE toxicity was subsequently assessed at four weeks, 3, 6, 12, and 24 months after the final radiotherapy fraction. Radiation Therapy Oncology Group (RTOG) toxicity was assessed by clinicians at 6, 12, and 24 months. Cystoscopic assessment of response was conducted at 3, 6, 12, and 24 months if possible, with urine cytology and CT scan of pelvis if not. Participants were followed up annually from two years for disease related endpoints.

Patient reported outcomes (PRO) were captured using the modified Inflammatory Bowel Disease Questionnaire (IBDQ - bowel function), the King's Health Questionnaire (KHQ - urological function), and the EuroQol five dimensions five levels questionnaire (EQ-5D-5L - overall health status). Questionnaires were completed by participants on paper prior to radiotherapy, at fraction six and three and six months after completing radiotherapy.

Outcomes

The primary endpoint was non-GU CTCAE $\geq$G3 toxicity occurring within the first three months of radiotherapy completion. Secondary endpoints included the proportion of adaptive fractions delivered (i.e. whether the small or large plan was selected, AP group only), appropriate identification of fractions requiring adaptive planning and selection of an appropriate plan, acute toxicity, late toxicity (up to two years), control rate of presenting symptoms, patient reported outcomes assessed using the modified Inflammatory Bowel Disease Questionnaire (IBDQ), EQ5D and Kings Health Questionnaire, local disease control at three months, time to local disease progression, time to invasive local disease progression and overall survival. Time to bladder cancer death was an exploratory endpoint.

Acute adverse events were categorised according to whether they emerged or worsened during treatment and their relationship to treatment. In this report "adverse event" refers to an event that was not present at baseline or was reported at a higher grade than at baseline and "toxicity" refers to the subset of adverse events that were categorised as treatment related.

Categorisation of relatedness of primary endpoint events to study treatment was reviewed by the independent data monitoring committee (IDMC), blinded to planning method.

Statistical analysis

The study was designed to rule out an acute $\geq$G3 non-GU AP toxicity rate of 30% assuming an expected rate of 10%[12]. In each planning group an A'Hern single stage exact design (p0=0·70, p1=0·9, α=0·05, β=0·2), required at least 24/28 evaluable participants to be $\geq$G3 non-GU toxicity free to consider hypofractionated plan of the day radiotherapy safe. A 10% non-evaluable rate was accounted for in the target sample size of 62 patients.

Prospective power calculations were performed for a number of key secondary outcomes. With 62 participants, there was sufficient power to rule out a $\geq$G3 overall acute toxicity rate of hypofractionated radiotherapy of 40% or more (α=0·05, β=0·2) and a 3 month control rate (allowing for 25% non-evaluable patients) of less than 40% (α=0·05, β=0·13). It was estimated that approximately 50% of fractions in the AP group would be adapted[12]. To assess clinical utility of online correction a threshold of 25% of all fractions or one fraction/patient requiring adaption was set. In the AP group, if true agreement between online and offline protocols for plan selection was 85%, plan selection outcomes for 139 fractions would allow us to demonstrate agreement for >75% fractions with 90% power (under a single-stage exact binomial approach).

There were no formal early stopping rules for efficacy or toxicity. However, an initial independent safety review took place when three month data was available for five patients (who had received at least three fractions of radiotherapy) in each planning group.

For the primary endpoint, the evaluable population was all randomised patients who received at least one fraction of radiotherapy. This and other safety endpoints were analysed according to planning method received. Proportions are reported with 95% two-sided exact binomial confidence interval (CI). For the primary and other key endpoints with pre-specified threshold criteria, 90% two-sided confidence intervals are also provided (consistent with 95% one-sided design). Late toxicity is summarised by frequencies and proportions at each time point and over all assessments by planning group and presented graphically. Time to first $\geq$G2 late toxicity analysed using competing risk methodology is also presented. Symptom control (graded the same, worse or better than baseline) was assessed in patients with symptoms reported at baseline and is presented graphically for each planning group.

PRO data were analysed in accordance with the relevant scoring manuals[17-19], with three months as the time point of primary interest. The modified IBDQ consists of 32 questions each graded from 1 (worst possible symptom) to 7 (symptom absent or not changed since before radiotherapy). IBDQ total subscale scores were calculated by summing together all individual scores for patients with answers to all questions in that subscale[17]. The KHQ comprises of three parts with 21 items. For part 1 and 2, items are scored between 0 (best) and 100 (worst) with a four point rating system except for one item in part 1 (general health perceptions) which has a five point rating system[18]. Part 3 is considered as a single item and is scored from 0 (best) to 27 (worst). The EQ5D consist of 5 domains each graded from 1 (worst possible symptom) to 5 (symptom absent) except for 1 domain (pain) which is graded from 1 (worst possible symptom) to 4 (symptom absent)[19]. Change in the mean scores were calculated from baseline to each post treatment time point and compared between randomised

groups at 3 months using the ANCOVA model, adjusting for baseline score. For IBDQ and EQ5D higher scores indicate better health, for KHQ lower scores reflect a better health.

Local control rate at three months is presented for both planning groups combined. To consider the impact of early deaths and missed 3 month assessments, a sensitivity analysis was conducted and assumed (1) bladder cancer related deaths prior to 3 month assessment were evidence of failure of local control and (2) there was disease control at three months if three month assessment was missing but patient was reported as free of disease at a later time-point with no intervening treatment.

Time-to-event endpoints, where the interest is in oncological outcomes of hypofractionation, are analysed in the intention to treat population, summarised by Kaplan-Meier curves and presented for randomised groups combined. For overall survival, alive patients were censored on the date they were last seen. For other endpoints, patients with no event were censored on the date of last assessment of disease status (i.e. date of last cystoscopy, biopsy, urine cytology, or CT scan). Patients who died prior to any follow-up were censored at the date of death.

Analyses were conducted using STATA version 15.0 based on a snapshot of data taken on 10/06/2019.

RESULTS

Patient Characteristics

Sixty-five participants were recruited from 14 UK centres (supplementary table A2) between 15 April 2014 and 10 August 2016. 32 patients were randomised to standard planning (SP) and 33 to adaptive planning (AP) (Figure 1). All participants received radiotherapy given in accordance with their allocated planning method.

Patient characteristics are summarised in table 1. The median age of participants was 85 years (IQR 81-89), 68% (44/65) were male and 98% had grade 3 transitional cell carcinoma histology. A complete trans urethral resection of the bladder tumour (TURBT) had been performed in 31%. The median age-adjusted Charlson comorbidity index score was 7 and ranged from 5 to 11 (IQR 6-8).

Treatment Delivery

58/65 (89%) patients completed six fractions of treatment with the remaining seven patients stopping early (figure 1).

In the AP group 28/33 (85%) patients received at least one fraction using a plan other than the medium plan (95% CI: 68-95%) (supplementary figure A1), either using a small plan only throughout treatment [2/33 (6%)] or using two or more plans during treatment (two plans 22/33 (67%); three plans 4/33 (12%)). Overall, the number of fractions using a plan other than mediums exceeded our target of 25% with 76/193 (39%, 95% CI: 32-47%) fractions delivered using a small plan [46/193 (24%)] or a large plan [30/193 (16%)].

117/193 (60.6%) pre-treatment CBCTs were available for central retrospective review, with a 78% (91/117) concordance rate between on line plan selection and central review. In cases of non-concordance the online plan selection was larger than the reviewer's selection in 20/26 (77%) cases (supplementary table A3). The small plan was selected by the offline reviewer selected in 39/117 (33%) of fractions compared to 28/117 (24%) online selections.

Acute Toxicity

Toxicity rates were lower than the pre-specified threshold in both groups. CTCAE ≥G3 non-GU toxicities were reported in 2/33 (6%, 90% CI: 1·1-17·9%; 95% CI: 0·7-20·2%) participants in the AP group and 4/30 (13%, 90% CI: 4·7-28·0%; 95% CI: 3·8-30·7) in the SP group (Table 2). ≥G3 GI toxicities were reported for one patient per group (included in non-GU toxicities).

≥G3 GU toxicities were more frequent than non-GU, affecting 3/33 (9%, 95% CI: 1·9-24·3%) participants in the AP group and 5/30 (17%, 95% CI: 5·8-35·8%) SP group (Table 2).

The overall incidence of ≥G3 toxicity was lower than the predefined threshold rate of 40% (12/63 (19%, 90% CI: 11·4-29·0%; 95% CI: 10·2-30·9)). The distribution of overall, GU and non-GU toxicities are shown in figure 2. No grade four or five toxicities were reported.

The equivalent data for all acute adverse events regardless of relatedness to treatment are shown in Table 2. Overall 31·7% (20/63) of patients had an acute ≥G3 acute adverse event.

Late Toxicity

Late toxicity is summarised in figure 2 and supplementary figure A2. Overall rates of late toxicity were low. In patients with at least six months' follow up; 2/21 (9·5%) patients in SP group and 3/26 (11·5%) in AP group reported a grade two or greater RTOG toxicity with a single episode of RTOG grade three toxicity reported in an AP patient (cystitis recorded at 24 months follow up) . Time to first ≥G2 toxicity is shown in supplementary figure A3.

Symptom Control

The rate of control at three months of urinary symptoms is shown in supplementary figure A4 for each planning method separately. Haematuria, incontinence, and cystitis were improved in the majority [haematuria 12/16 (75%), incontinence 8/14 (57%), cystitis 11/19 (58%)] of patients with the symptom at baseline. Frequency symptoms, though the same or better in most patients, only improved for the minority [nocturia 8/39 (21%), frequency/urgency 12/36 (33%)].

Patient reported outcomes

There was no statistically significant difference between the two planning groups for IBDQ bowel-related symptoms or for any other IBDQ symptoms, EQ5D health score or KHQ domain scores at 3 months (supplementary table A4, A5 and A6, Figure 3). Of note, the IBDQ demonstrated a worsening in bowel and systemic symptoms at week 6 in the SP group which was not seen in the AP group (supplementary table A4). This improved over the following six months and returned to baseline in both groups. Total IBDQ score, EQ5D health status and KHQ symptom severity score scores over time are shown by patient in supplementary figure A5.

Disease control and survival outcomes

48 participants had disease assessed at three months. Local disease was controlled in, 39/48 participants (81·3%, 90% CI: 69·6-89·9%; 95% CI: 67·4-91·1%). The rates of local control were 17/23 (74%) in SP group and 22/25 (88%) in the AP group. A sensitivity analysis suggested 41/61 (67·2% (90% CI: 56·0-77·1%; 95% CI: 54·0-78·7%)), patients had evidence of local control thus, consistent with the main analysis, ruled out a 3 month control rate of less than 40%.

At a median of 38·8 months follow up, 33 patients have reported 36 recurrences: 21 in the bladder (i.e. local recurrence), 4 in the pelvic nodes and a further 9 at distant

sites (2 nodal and 7 other distant sites). The proportion of patients free of local recurrence at one year was 71·7% (95% CI: 55·9-82·6%) and the proportion free of invasive local recurrence was 85·5% (95% CI: 70·1-93·3%) (Figure 4).

There have been 47 deaths, of which 31 are due to bladder cancer. Median survival was 18·9 months with 61·5% (95% CI: 48·6-72·1%) alive at one year and 46·2% (95% CI: 33·8-57·7%) at two years.

DISCUSSION

We set out to investigate whether the use of adaptive hypo-fractionated radiotherapy to a dose of 36Gy in six fractions, in the context of the first multicentre prospective randomised trial, could be an option for patients with advanced localised bladder cancer who were unable to receive standard radical treatment options. The study met its primary acute toxicity endpoint, ruling out excessive non GU and overall toxicity and demonstrated that local control could be achieved in over 80% of participants at three months with this ultra-hypofractionated weekly regimen. In ultra-fractionated protocols each fraction makes up a substantial proportion of the total treatment so accuracy of delivery is important; as a 'miss' one day is difficult to compensate for. In this context we have, to the best of our knowledge completed the first randomised trial of adaptive 'plan of the day' radiotherapy in bladder cancer. We have shown that a substantial portion of radiotherapy fractions may benefit from the use of a plan different to standard, which could have impacts on toxicity and efficacy that may be particularly important in this elderly, frail population.

Treating this group of patients who by virtue of age, performance status or co-morbidity aren't fit for radical treatment but have potentially curable disease is one of the large challenges facing clinicians treating muscle invasive bladder cancer. This

group of patients represent a substantial and understudied subset of patients. A recent UK study suggested that 47% of patients (representing 2519 patients per year) with T2-T4 N0 bladder cancer are not receiving either radical radiotherapy or surgery[20].

A remarkable feature of this trial was that it included a group of patients with a median age of 85 and significant co-morbidity, as indicated by the Charlson Comorbidity index scores. The ability to complete this randomised study with good quality data, including data on local control and patient reported outcomes, and excellent adherence to allocated treatment, shows that with appropriate flexible design it is possible to involve this patient population in research protocols and they are willing to participate and be enrolled in trials.

Efficacy results from this phase II study are promising. A three month local control rate of over 80%, a one year invasive local recurrence free rate of 86%, median survival of 18·9 months with over 40% of patients surviving two years post treatment suggests that this schedule of 36Gy in six fractions can be effective at controlling disease in patients with bladder cancer. Though survival figures on the face of it are inferior to that reported in trials of chemo-radiotherapy[21], this treatment does still provide a reasonable chance of long term survival and compares favourably with the 55% one year survival in patients receiving palliative treatments and 32% survival with no treatment reported in the RCR audit[5]. In general, these results support the findings of the single centre prospective phase II study that was the pilot for this trial[12]. In the pilot study, which included some patients with metastatic disease, there was local control in 92% of the 33 assessed patients (60% of all patients) with a one year survival of 63% and two year survival of around 35% [12]. Similar results have been reported for

a number of retrospective studies[22] and suggest the 36Gy in 6 fractions regimen may be superior to the hypofractionated schedule of 21Gy in three fractions used in the MRCBA09 trial which reported 38% local control rate in the small number of patients assessed[8].

Though patients did experience a degree of acute toxicity, our trial met pre-set thresholds for acute tolerability and late toxicity seemed uncommon. Thus, this study suggests that the regime of 36Gy in 6f weekly is a regime that can achieve local control in a significant proportion of patients and be tolerated even by an unfit population, making this a real treatment option for this patient population.

This study was also designed to develop preliminary clinical data on the value of an adaptive 'plan of the day' strategy. A significant body of evidence has accumulated that the changes in shape and position of the bladder through a treatment course can lead to geographical miss despite the use of large CTV to PTV margins; which in their own right may contribute to increased toxicity. The advent of pre-treatment soft tissue imaging has been used to develop a number of strategies to improve target coverage and reduce target margins. Foremost of these is the use of 'plan of the day' where one of a pre designed plans of varying sizes is chosen. Previous work with PoD have resulted target coverage higher than historical reports whilst reducing the "average PTV' volume by 28-42%[14,23-26].

Our results here broadly support previous results, with 39% of treatments using either a small or large plan and most patients using either an adapted plan throughout or two or more of the three plans. This exceeds our minimum futility rate of 25% of treatments using an adapted plan and as the medium plan used in this trial is smaller than a standard plan, 84% of treatments were treated with a plan smaller than

normally used. This reflects reports from other studies of PoD radiotherapy. Vestergaard et al reported roughly equal usage of small, medium, and large plans resulting in a roughly 30% reduction in average PTV volume[24], whilst Foroudi et al used small or large plans for around 50% of fractions resulting in a 29% reduction in the high dose radiation volume[23].

It is encouraging that this study was deliverable in an environment where the technique was unfamiliar to most hospitals prior to their participation. As previously reported, all sites undertook a quality assurance program, including a training package on plan selection for which staff members needed to attain a pre-set level of concordance with an expert defined selection to gain approval to select plans for the purposes of trial treatment[27,28]. Central review shows this training was relatively effective, with a 78% concordance, but in most cases the expert reviewer selected a smaller plan, evidencing the need for ongoing peer support and feedback in the implementation of this technique.

This study did have a number of limitations. As a moderate sized non comparative phase II study limited statements can be made about the benefits of adaptive radiotherapy compared to standard radiotherapy or of the 36Gy/6 fraction schedule compared to other treatments. The data are also limited by early deaths and dropouts meaning that not all patients could be assessed for toxicity, local control and patient reported outcomes. Despite these limitations it is encouraging that the number of grade 3-4 non-GU and GU toxicity and adverse events, are numerically lower in the adaptive arm. Additionally, fewer patients stopped radiotherapy early because of adverse events and the higher immediate bowel related QoL is encouraging.

The trends in favour of improved outcomes for adaptive treatments should logically lead to a formal comparative study to confirm the degree of the clinical benefit from adaptive therapy either in this patient group or in studies of patients receiving daily fractionated radiotherapy

CONCLUSIONS

Adaptive ultra-hypofractionated radiotherapy is deliverable with modest toxicity in an elderly unfit population of patients, whilst achieving local control for the majority. It represents a new option for care in this patient population.

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Figures

Figure 1. CONSORT diagram

Figure 1 Legend:

ITT = intention to treat, RT = radiotherapy, BC = bladder cancer, SP = standard planning and AP=adaptive planning.

* Classed as non-evaluable by Trial Steering Committee due to bladder cancer death prior to 3 month assessment or insufficient follow up received

! Stopped treatment early due to toxicity

^ Stopped treatment early due to concomitant illness

Figure 2. Stacked bar chart of the worst grade acute toxicity, acute adverse event, late toxicity and worst RTOG

Figure 2 Legend:

A. Worst grade acute CTCAE toxicity, B. Worst grade acute CTCAE Adverse event, C. Worst grade late CTCAE toxicity and D. Worst grade RTOG. GU = genitourinary, non-GU = non-genitourinary and GI = Gastrointestinal. Adverse event refers to an event that was not present at baseline or was reported at a higher grade than at baseline and toxicity refers to the subset of adverse events that were categorised as treatment related.

Figure 3. Mean change from baseline for the total IBDQ score, EQ5D health status and KHQ symptom severity score

Figure 3 Legend:

A. Change from baseline in IBDQ total score, B. Change from baseline in EQ5D health status score and C. Change from baseline in KHQ Symptom severity measures score. SP = standard planning, AP = adaptive planning, bl = baseline, wk = week, m = month. Error bars represent 95% CIs. Negative numbers represent a decrease in quality of life and positive numbers an increase in quality of life for IBDQ and EQ5D. For KHQ negative numbers represent an increase in quality of life and positive numbers a decrease in quality of life.

Figure 4. Kaplan-Meier plots of time to event

Figure 4 Legend:

A. Time to local recurrence, B. Time to local invasive recurrence, C. Overall survival and D. Time to bladder cancer death. Number of events and number censored are presented cumulative in the extended risk table. Shaded area represents 95% CI.