Research article

A pilot study of patient reported outcomes evaluating treatment related symptoms and quality of life for men receiving high dose rate brachytherapy combined with hypo-fractionated radiotherapy or hypo-fractionated radiotherapy alone for the treatment of localised prostate cancer

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Abstract

Patient Reported Outcome Measures (PROMS) are useful metrics in evidence-based clinical care and translational research. Recording treatment-related symptoms and Quality of Life (QoL) can provide information in counselling patients to aid decision-making. This prospective study tested the feasibility of radiographer-led collection of multiple validated PROMS from Prostate Cancer (PCa) patients comparing High Dose Rate Brachytherapy combined with hypo-fractionated external beam radiotherapy (hEBRT) and hEBRT alone.

From June to August 2017, 20 men with localised PCa (T1-T3aN0M0) consented to participate in the study. Ten patients received combination treatment (37.5 Gray/15 fractions followed by a 15 Gray implant), and ten patients received monotherapy (60 Gray/20 fractions). PROMS were collected at four time-points (1) at baseline, (2) final fraction of hEBRT, (3) 8 weeks after commencing radiotherapy and (4) 12 weeks after commencing radiotherapy. The PROMS used were EPIC-26, IPSS, IIEFF-5 and SF-12. The difference between the two groups were tested using Mann-Whitney U test and Wilcoxon Signed-Rank Test.

All participants completed all PROMS (100% response-rate). The Monotherapy group reported a higher incidence of bowel symptoms compared to the combination group and at Week 12, EPIC-26 bowel summary score demonstrated a statistically significant difference ($p = 0.005$). The prevalence of erectile dysfunction increased within both groups. Maintenance of QoL was reported throughout treatment.

This small study demonstrated feasibility of radiographer-led PROMS collection by 100% completion rate. Streamlining of these tools into integrated technology applications and real time PROMS measurement has the ability to benefit patients and guide clinicians in adapting therapies based on individual need.

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Introduction

Prostate cancer (PCa) is one of the most common malignancies worldwide and in the United Kingdom (UK) accounts for a quarter of all diagnosed cancers in men. In the most recently published statistics from Cancer Research UK (2014) there were 46,690 new cases of PCa and 11,287 deaths in the UK [1]. Incidence is rising, due to increased public awareness in conjunction with more widespread availability of Prostate Specific Antigen (PSA) screening. In Northern Ireland the majority of men are diagnosed at an early stage (23.4% Stage I and 38.4% Stage II) and 18.2% diagnosed at late stage (Stage IV). The five-year survival in 2011–2015 was 88.5% [2].

Definitive treatment options for localised PCa include surgery, external beam radiotherapy (EBRT) and brachytherapy, all having a high success rates for biochemical control.
The success rate for EBRT can be improved further by combining with Androgen Deprivation Therapy (ADT) [3–6] and by escalating the dose delivered per fraction (f). There is abundant evidence showing a clear dose-response relationship with regards to five and ten-year biochemical control and freedom from biochemical failure (FFbF) rates following radical EBRT [7–15]. In the UK, the CHHiP trial (Conventional or hypo-fractionated high dose intensity modulated radiotherapy for prostate cancer) demonstrated 60 Gray (Gy)/20f was non-inferior to 74Gy/37f [16]. This has led to the widespread adoption of the hypo-fractionated external beam radiotherapy (hEBRT) regime 60Gy/20f for localized PCa.

The addition of High Dose Rate brachytherapy (HDR-BT) as a boost to hEBRT is also widely practiced as a method to achieve further dose escalation above the doses that can be safely given by hEBRT alone [17–23]. Multiple studies report improved FFbF rates following radical EBRT [7–15]. In the evidence showing a clear dose-response relationship with regards to five and ten-year biochemical control and freedom from biochemical failure (FFbF) rates following radical EBRT [7–15].

Studies have shown variation in treatment related symptoms, with authors suggesting HDR-BT boost have higher [22], lower [25], and equal [26,27] Gastrointestinal (GI)/Genitourinary (GU) toxicities when compared to hEBRT alone. Acute toxicity data has predominantly been presented using the Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer (EORTC) scoring scheme, where the researcher/clinician rather than the patient have made the assessment.

Patient Reported Outcome Measures (PROMS) are useful metrics in evidence-based clinical care and translational research. Recording treatment-related symptoms and Quality of Life (QoL) scores can provide information in counselling patients to aid decision-making. New technology and new research has led to an increase in the importance of monitoring of participants QoL and treatment-related symptoms. This is driving the demand for PROMs data. This prospective study tested the feasibility of radiographer-led collection of multiple validated PROMS from PCa patients and comparing treatment-related symptoms and QoL between two recently introduced treatment regimens: HDR-BT combined with hEBRT (Combination Group) and hEBRT alone (Monotherapy Group).

Materials and methods

Patients

Following ethical approval, 20 consecutive patients with localised PCa (T1-T3aN0M0) who were to be treated with either HDR-BT combined with hEBRT (n = 10), or hEBRT alone (n = 10) consented to participate in the study.

The Participant Information Sheets (PIS) were provided to potential participants, who were given at least 24 h to decide upon participation. Inclusion criteria and exclusion criteria are listed in Table 1.

Data collection

Data was collected prospectively from all participants. The validated PROMs used are summarised in Table 2. These tools have been widely used in PCa studies.

RTOG/EORTC GI and GU were assessed by a Clinical Oncologist or a suitably qualified Radiographer. This is an observer-reported outcome measure and a subjective measurement of patient symptoms. Symptoms are graded from 0 (asymptomatic) to 5 (death directly related to radiation effects) [37].

External beam radiotherapy

Patients were planned and treated with a ‘comfortably full’ bladder and empty rectum; achieved by self-administering daily micro-enemas and adhering to a bladder filling protocol. The Planning Target Volume (PTV) was defined using Computed Tomography (CT).

| Table 1 | Study inclusion/exclusion criteria. |
|---------|-----------------------------------|
| Inclusion criteria All criteria must apply | Exclusion criteria Ineligible if any of the following apply |
| ≥ 18 years old | Evidence of metastatic disease |
| Histologically confirmed adenocarcinoma of the prostate | Patients who received radiotherapy to prostate and pelvis |
| No evidence of nodal or metastatic disease | Other dose/fractionation technique delivery |
| Elected treatment: HDR-BT Boost (15Gy) combined with hEBRT (37Gy/15f) or hEBRT (60Gy/20f) | Intensity-Modulated Radiotherapy (IMRT) delivery |
| Intensity-Modulated Radiotherapy (IMRT) step and shoot or Volumetric Modulated Arc Therapy (VMAT) delivery | Ability to understand and willingness to sign an informed consent document |

| Table 2 | Summary of study PROMS. |
|---------|------------------------|
| PROM | Summary |
| Expanded Prostate Cancer Index Composite (EPIC-26) | Prostate cancer-specific questionnaire designed to evaluate health related QoL, which is divided into bowel, urinary, sexual and hormonal function and bother domains [28,29] |
| International Prostate Symptom Score (IPSS) | A screening tool and an objective measure of urinary toxicity following prostate brachytherapy treatment [30,31] |
| International Index of Erectile Function (IIEF-5) | Derived from a longer-established 15-item questionnaire [32]. This was developed to diagnose the presence and severity of erectile dysfunction (ED) [33] |
| Medical Outcomes Study 12-Item Short form Health Survey (SF-12) | Generic instrument derived from a longer-established 36-item questionnaire [34]. It was developed for the Medical Outcomes Study, and has been validated in men with PCa [35,36] |

All PROMs were presented to the participant in a booklet. One radiographer was responsible for the distribution and scoring of all PROM questionnaires.

Study participants completed PROMs unaided at 4 time-points; (1) Baseline (prior to commencing radiotherapy); (2) final fraction of hEBRT; (3) 8 weeks from commencement of hEBRT and (4) 12 weeks from commencement of hEBRT. Time-point 2 was on the final fraction of hEBRT, which for the Combination Group was Week 3 and for the Monotherapy Group was Week 4. This time point was selected to improve data collection rates as the questionnaires were completed while the participant attended the hospital. RTOG GI and GU were assessed at baseline, weekly during radiotherapy and Week 12. The Week 8 questionnaires were posted to the participants with a return self-addressed envelope.

Clinical characteristics of participants were collected at baseline including age adjusted Charlson Comorbidity Index (CCI), used to classify comorbidity conditions [38].
**HDR-BT combined with hEBRT**

The EBRT PTV includes a universal 5 mm margin expansion on the prostate and seminal vesicle (SV) volume. The dose/fractionation received was hEBRT 37.5 Gy in 15f followed by a 15 Gy HDR-BT boost.

**hEBRT alone**

The PTV includes the prostate gland and (at least) proximal SV with a universal 10 mm margin except for the 7 mm posterior margin. The median dose to the PTV was the equivalent to 60 Gy in 20f with a minimum of 95% isodose coverage.

**Treatment delivery**

hEBRT was delivered using IMRT/VMAT and verified prior to treatment delivery, first three fractions and weekly thereafter using on-line kilo-voltage Cone beam CT (CBCT). A 5 mm gross error tolerance and a 3 mm systematic error tolerance protocol was adhered to.

**Brachytherapy**

HDR-BT was performed using intra-operative real time 3D ultrasound planning with Oncentra (Elekta AB, Stockholm, Sweden). A standardised template-based catheter configuration was used, and dwell time optimization performed using ultrasound. The Clinical Target Volume (CTV) was defined as the prostate capsule plus any macroscopic extracapsular disease or SV involvement identified on diagnostic images expanded by 3 mm to encompass potential microscopic disease. The CTV was used as the PTV.

**Statistical analysis**

The PROMs were analysed as specified by the developers. Data is presented descriptively. When comparing treatment groups the majority of the data did not demonstrate normal distribution therefore the non-parametric Mann-Whitney U test was performed. The Wilcoxon Signed-Rank Test was performed to compare scores at different time-points within a group. The statistical tests were performed using SPSS statistics for Windows (V24.0, Armonk, NY: IBM Corp).

**Results**

PIS were given to 24 patients, four declined and 20 consented. Ten participants received HDR-BT combined with hEBRT (Combination group) and ten received hEBRT alone (Monotherapy group). All participants were established on ADT for a minimum of six weeks prior to consent and completion of baseline assessments.

Participant clinical characteristics are presented in Table 3. All participants completed treatment without interruption. In the Combination Group, the interval between hEBRT and HDR-BT procedure ranged from 5-15 days. This study achieved excellent participant compliance, with 80 PROM questionnaire booklets returned and analysed (100% response rate).

**Table 3**

| Combination group | Monotherapy group |
|-------------------|-------------------|
| **Mean age year** | 64.5 (range=57–71) |
| T stage % | T2 50 |
| | T3a 50 |
| Mean PSA at diagnosis ng/ml | 7.8 (range=6.5–38) |
| Mean prostate volume cm³ | 35 (range=19–76) |
| CCI | 4 |
| ADT % | Bicarbonate 80 |
| | Goserelin 20 |
| | 0 |
| Baseline Phosphodiesterase-5 (PDe5) inhibitor use % | 0 |

**EPIC-26**

Urinary, bowel, sexual and hormone domains summary scores and standard deviation (SD) are presented in Table 4.

**Urinary summary score**

EPIC-26 Urinary summary scores are presented in Fig. 1. At baseline the urinary function of both groups were equal. For the Combination Group urinary function improved by Week 12 (increase of 3%) with peak symptoms observed at the end of the hEBRT component of the treatment (M = 80.56). For the Monotherapy Group at Week 12 the score had not returned to pre-radiotherapy levels, the peak was observed at the end of hEBRT (M = 69.44). There was no statistical significance difference between the groups at any time-point.

**Bowel summary score**

For both groups the median bowel summary score at baseline was 100. This reduced by 15% and 35% at the end of hEBRT for Combination and Monotherapy groups, respectively. There was a significant difference in the scores at Week 12 for the Combination Group (M = 97.5 SD = 5.4) and Monotherapy Group (M = 75 SD = 14.1); p = 0.005. A statistically significant difference was also seen on the final hEBRT fraction; p = 0.03. There was no significant difference observed at Week 8 (Fig. 2).

**Sexual summary score**

There was a significant difference at baseline for Combination Group (M = 47.00, SD = 22.93) and Monotherapy Group (M = 20.97, SD = 13.99); p = 0.05. At Week 8, the score decreased to 6.25 and 2.09 for Combination and Monotherapy groups, respectively. At Week 12, a small recovery was observed (34 and 15.25) but failed to recover to baseline levels (Fig. 3). Baseline and Week 12 scores within the Combination Group showed a significant difference (p = 0.008), this was not observed in Monotherapy Group.

**Hormone summary score**

There was no significant difference for Combination and Monotherapy groups at any time-point. Although Monotherapy Group symptoms did increase during radiotherapy this had recovered to baseline levels by Week 12 (Fig. 4).

**IPSS**

In the Combination Group, the average IPSS rose from 6 (range=2–16) at baseline to 12 (range=2–19) at the final fraction of hEBRT then decreasing to 7 (range=2–23) at Week 12. For Monotherapy Group, the average IPSS rose from 7 (range=2–22) at baseline to
21 (range-2–35) at the final fraction of hEBRT and decreasing to 12 (range-2–30) at Week 12. At week 12 the proportion of patients with no or minimal urinary symptoms was 60% and 30% for Combination and Monotherapy groups, respectively (Fig. 5). There was a significant difference observed at the final fraction of hEBRT; Combination Group (M = 12.00, SD = 4.58) and Monotherapy Group (M = 20.5, SD = 9.97); p = 0.041.

Table 4
Summary of EPIC-26 results for Combination and Monotherapy groups.

| Time point/Measure | Urinary summary score | Bowel summary score |
|--------------------|-----------------------|---------------------|
|                    | M         | SD     | P    | M*     | SD     | P    |
| Baseline           | Combination Group    | 90.28   | 8.08 | 0.43 | 100     | 7.45 | 0.97 |
|                    | Monotherapy Group    | 90.28   | 18.63|       | 100     | 6.05 |      |
| Final RT           | Combination Group    | 80.56   | 13.72| 0.27 | 85.42   | 18.01| 0.03 |
|                    | Monotherapy Group    | 69.44   | 19.62|       | 64.59   | 25.89|      |
| 8 weeks            | Combination Group    | 83.67   | 9.14 | 0.45 | 91.67   | 19.49| 0.17 |
|                    | Monotherapy Group    | 77.78   | 16.42|       | 75.00   | 16.64|      |
| 12 weeks           | Combination Group    | 93.05   | 14.23| 0.16 | 97.5     | 5.36 | 0.005|
|                    | Monotherapy Group    | 78.73   | 19.23|       | 75.00   | 14.23|      |

| Time point/Measure | Sexual summary score | Hormone summary score |
|--------------------|----------------------|-----------------------|
|                    | M*     | SD     | P    | M*    | SD     | P    |
| Baseline           | Combination Group    | 47.00   | 22.93| 0.05 | 82.50  | 15.71| 0.82 |
|                    | Monotherapy Group    | 20.00   | 13.99|       | 82.50  | 18.29|      |
| Final RT           | Combination Group    | 31.46   | 25.76| 0.12 | 82.50  | 21.35| 0.4  |
|                    | Monotherapy Group    | 10.42   | 9.93 |       | 72.50  | 32.16|      |
| 8 weeks            | Combination Group    | 6.25    | 17.65| 0.11 | 82.50  | 25.48| 0.25 |
|                    | Monotherapy Group    | 2.09    | 9.29 |       | 75.00  | 24.55|      |
| 12 weeks           | Combination Group    | 17.34   | 13.52| 1.0  | 85.00  | 22.61| 0.79 |
|                    | Monotherapy Group    | 15.25   | 11.7 |       | 80.00  | 18.33|      |

* Median.
Having been established on ADT for at least 6 weeks at baseline the prevalence of severe ED for both groups was 20%. This increased to 80% at Week 12 with all patients reporting ED symptoms (Fig. 6). There was no significant difference between Combination and Monotherapy groups. From baseline to Week 12 there was a significant difference in both groups (Combination Group $p = 0.012$; Monotherapy Group $p = 0.03$). At the Week 12 review, 25% of participants were prescribed a PDE-5 inhibitor.

SF-12

A summary component score below 50 indicates below average physical and mental well-being.

**SF-12 physical component summary (PCS)**
The Combination Group reported a 30% decrease in average PCS score from baseline ($M = 51.82$) to Week 12 ($M = 36.25$); the Monotherapy Group reported a smaller decrease of 21% (Fig. 7). There was no significant difference observed for Combination and Monotherapy groups at any time-point.

**SF-12 mental component summary (MCS)**
There was a statistically significant difference at baseline for Combination Group ($M = 53.64$, $SD = 6.21$) and Monotherapy Group ($M = 43.45$, $SD = 10.73$); $p = 0.04$ and at the final fraction of hEBRT; $p = 0.03$ (Combination Group ($M = 53.73$, $SD = 8.28$)) (Monotherapy Group ($M = 42.91$, $SD = 12.71$)). By Week 12, Combination Group had returned to baseline levels. By Week 12, Monotherapy Group reported an improvement in mental well-being from baseline. Overall 60% of participants reported stable or improving mental QoL at Week 12 (Fig. 8).
Incidence of RTOG GI toxicity.

| Time-point/GI RTOG grade | Baseline | Final RT | 12 weeks |
|--------------------------|----------|----------|----------|
|                          | Combination group | Monotherapy group | Combination group | Monotherapy group | Combination group | Monotherapy group |
| 0                        | 10        | 10       | 5        | 2        | 8        | 5        |
| 1                        | 0         | 0        | 4        | 6        | 2        | 3        |
| 2                        | 0         | 0        | 1        | 1        | 0        | 1        |
| 3                        | 0         | 0        | 0        | 1        | 0        | 1        |

Incidence of RTOG GU toxicity.

| Time-point/GU RTOG grade | Baseline | Final RT | 12 weeks |
|--------------------------|----------|----------|----------|
|                          | Combination group | Monotherapy group | Combination group | Monotherapy group | Combination group | Monotherapy group |
| 0                        | 10        | 10       | 9        | 5        | 8        | 7        |
| 1                        | 0         | 0        | 1        | 5        | 2        | 3        |
| 2                        | 0         | 0        | 0        | 0        | 0        | 0        |
| 3                        | 0         | 0        | 0        | 0        | 0        | 0        |

**Discussion**

This prospective study in localised PCa compared treatment-related symptoms and QoL of men receiving HDR-BT combined with hEBRT (Combination Group) and hEBRT alone (Monotherapy Group) using validated questionnaires that have been widely used in Radiotherapy research enabling comparison to other studies.

The EPIC-26 urinary summary score indicated an increase in urinary symptoms with the Combination Group peak observed at the end of hEBRT returning to pre-treatment levels by Week 12 and approaching a return to pre-treatment levels for Monotherapy Group. This trend was also observed in IPSS scores. This would indicate that although participants in both treatment groups experienced increase urinary symptoms they were minimal and short lasting.

A notable effect was observed within EPIC-26 bowel summary scores. There was a statistically significant difference between the groups at Week 12 (p = 0.005) and at the final hEBRT treatment (p = 0.03). This is consistent with other studies that have reported treatment related symptoms of hEBRT. The EPIC-26 sexual summary score (M = 20.97).

Reassuringly the SF-12 demonstrated participants had good mental and physical health throughout and QoL not significantly affected by either treatment. The stability or improvements in mental QoL at Week 12 may be due to a decrease in anxiety associated with the initial apprehension of commencing treatment and/or the information and support provided during their treatment journey.

The RTOG scale is commonly used to describe radiation toxicity in PCa. This assessment is subjective, open to bias where symptoms are graded according to medication or interventions required, and although it is proficient for detecting major toxicities, it can fail to identify items of importance to the patient. The RTOG scale lacks sensitivity and in this study has under-reported symptoms compared to PROMs. The lack of sensitivity of observer reported treatment outcome assessments has been reported previously [45–47]. Under reporting was particularly evident when RTOG GI grades were examined. At the final fraction of hEBRT there were no incidences of RTOG GI Grade 2, while the EPIC-26 bowel summary score showed statistically significant difference. Ideally, observer-reported measures should be used in conjunction with PROMs. The use of PROMs to quantify patients’ symptoms and QoL is of growing importance as technology continues to develop with more complex treatments becoming widely available such as Stereotactic Ablative Radiotherapy. To embed PROMs into clinical practice this requires improvements in clinical interpretability of PRO instruments and effective administration systems.

The administration of PROMs is a burden on time and resources e.g. the National Health Service England PROMs programme costs £825 000 annually [48]. Malhotra et al. demonstrated electronic PROMs (ePROMs) can be successfully implemented into a service and innovative data collection methods improve the ease of administration, data capture rates and lower costs [49]. The implementation of ePROMs is now a realistic goal as the majority of patients now have access to smart-phones, tablet devices and internet access; alongside developments in electronic databases, which enable real-time collection of data. Innovative technology
should be examined, as PROMs are beneficial to health professionals as the information ensures they have an enhanced understanding of the patients’ experience and support shared decision-making [50].

The comparison of treatment-related symptoms and QoL for the two treatment groups within this small study indicate that the combination treatment may have a lower incidence of treatment-related symptoms and may be an appealing choice to patients. However, there is a cohort of patients where HDR-BT is contra-indicated e.g. large prostate volume, transurethral resection of the prostate (TURP) within 6 months, significant urinary obstructive symptoms, pubic arch interference, lithotomy position or anaesthesia not possible. Monotherapy treatment is also a conformal treatment especially when delivered using daily cone-beam CT and VMAT delivery.

There are some potential limitations of this study. This was a non-randomised, single centre study, with a small sample size, which was not powered to demonstrate statistical significance between the two groups. Patient numbers attending the centre for HDR-BT combination therapy at the time of protocol design dictated this sample size. The follow-up period was not adequate to fully determine symptom outcome. Despite these limitations, it does however demonstrate the feasibility of radiographer-led collection of multiple PROMs. There was excellence compliance with 100% of PROMs completed and returned. Further studies evaluating this will be required and may have inherent challenges when sample size increases.

Conclusion

This feasibility study provides new information comparing treatment-related symptoms and QoL at multiple points for combination and monotherapy treatments for localised PCa. Both treatments are well tolerated and have minimal effect on QoL although the results would suggest the higher conformity of the combination treatment has a more favourable treatment-related symptom profile most notably in relation to bowel symptoms. This study confirms the feasibility of radiographer-led collection of multiple PROMs, which is evidenced by the high compliance in this cohort. Streamlining of these tools into integrated technology applications to enable real-time PROMs measurement is key as PROMs have the ability to benefit patients and guide clinicians in adapting therapies based on individual.

Conflict of interest

The authors confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tipsro.2019.01.003.

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