Technical Innovations & Patient Support in Radiation Oncology 9 (2019) 18–25

Contents lists available at ScienceDirect

Technical Innovations & Patient Support in Radiation Oncology

journal homepage: www.elsevier.com/locate/tipsro

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

Karen Crowther [a,*], Aidan Cole [a,b], Pat Shiels [a], Suneil Jain [a,b], Paul Shepherd [c], Darren Mitchell [a]

[a] Radiotherapy Department, Cancer Centre, Belfast City Hospital, Belfast Health and Social Care Trust, Lisburn Road, Belfast, United Kingdom
[b] Centre for Cancer Research and Cell Biology, Queen's University of Belfast, Lisburn Road, Belfast, United Kingdom
[c] Ulster University, Therapeutic Radiography – School of Health Sciences, Belfast, United Kingdom

ARTICLE INFO

Article history:
Received 22 May 2018
Received in revised form 26 November 2018
Accepted 17 January 2019
Available online 22 February 2019

Keywords:
Prostate cancer
Hypo-fractionated
HDR brachytherapy
Patient-reported outcome measures
Quality of life

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.

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.

* Corresponding author at: Radiotherapy Department, Cancer Centre, Belfast City Hospital, 51 Lisburn Road, Belfast BT9 7AB, United Kingdom.
E-mail address: Karen.crowther@belfasttrust.hscni.net (K. Crowther).

https://doi.org/10.1016/j.tipsro.2019.01.003
2405-6324/

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 with HDR-BT boost with either conventional EBRT [24] or hEBRT [25–27].

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].

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
Elected treatment: HDR-BT Boost (15Gy) combined with hEBRT (37Gy/15f) or hEBRT (60Gy/20f)	Conformal radiotherapy technique delivery
Intensity-Modulated Radiotherapy (IMRT) step and shoot or Volumetric Modulated Arc Therapy (VMAT) delivery	Deemed unable to comply with study assessments
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].

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).

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 37.5Gy in 15f followed by a 15Gy 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 60Gy 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).

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

Table 3
Summary of participant's clinical characteristics.

	Combination group	Monotherapy group
Mean age year	64.5 (range-57–71)	68.5 (range-56–80)
T stage %	T2 50 T3a 50	T2 80 T3a 20
Mean PSA at diagnosis ngs/ml	7.8 (range–6.5–38)	7.8 (range–4.6–32.2)
Mean prostate volume cm^3	35 (range 19–76)	33 (range 22–90)
CCI	4	4
ADT %	Bicalutamide 80 Goserelin 20	Bicalutamide 90 Goserelin 10
Baseline Phosphodiesterase-5 (PDe5) inhibitor use %	0	0

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.

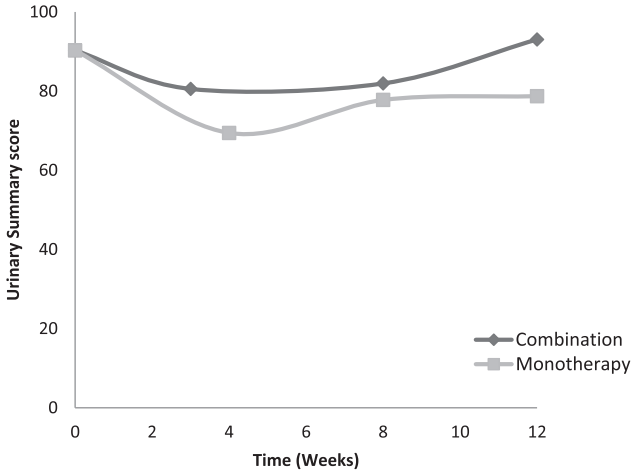

Fig. 1. EPIC-26 Urinary summary scores.

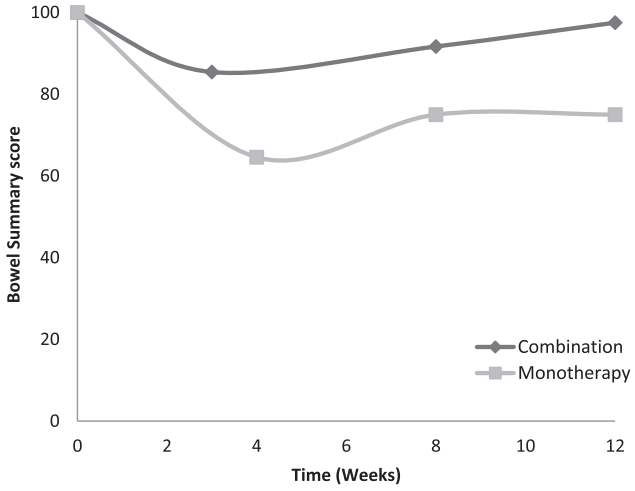

Fig. 2. EPIC-26 Bowel summary scores.

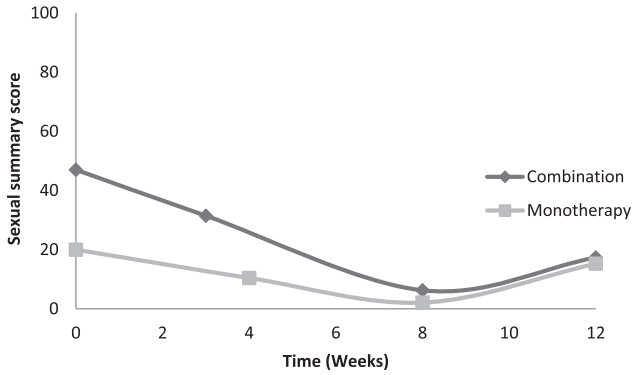

Fig. 3. EPIC-26 Sexual summary scores.

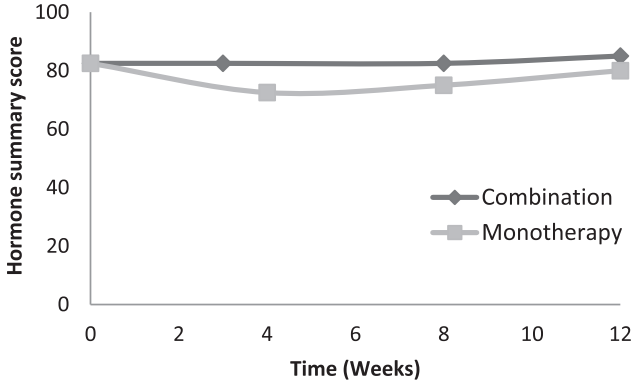

Fig. 4. EPIC-26 Hormone summary scores.

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.

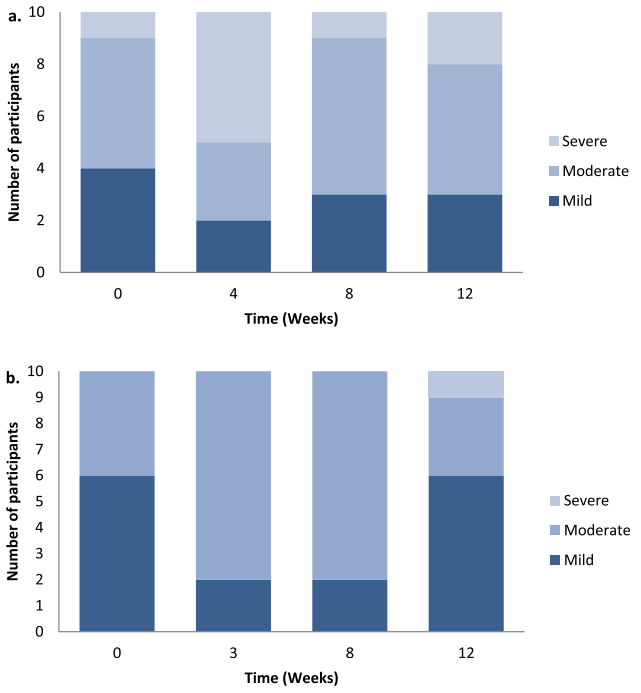

Fig. 5. IPSS-severity grading of symptoms (a) combination group (b) monotherapy group.

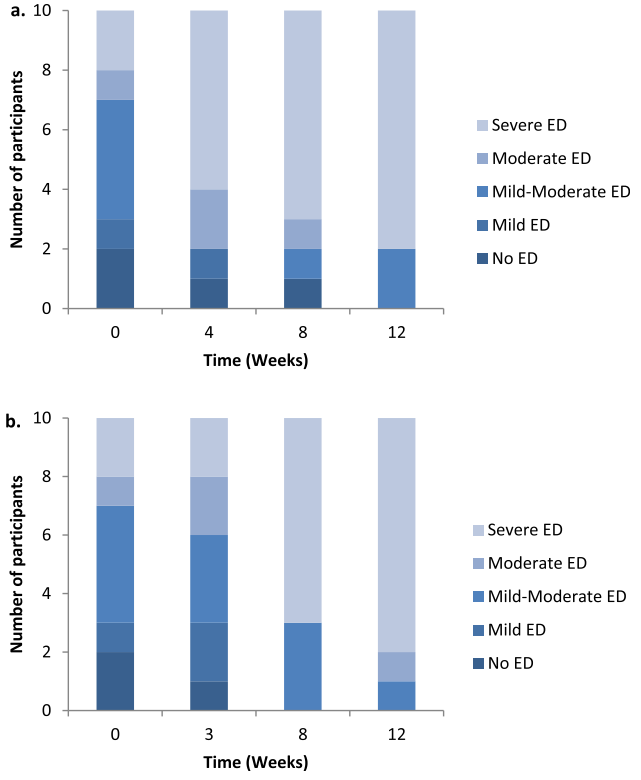

Fig. 6. IIEF-5 severity grading (a) combination group (b) monotherapy group.

IIEF-5

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.

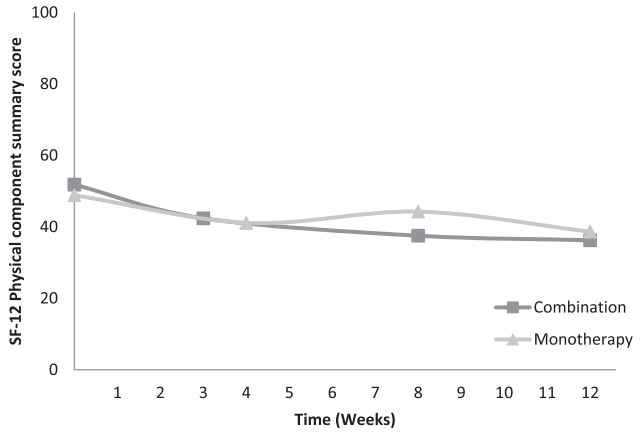

Fig. 7. SF-12 Physical Component Summary scores.

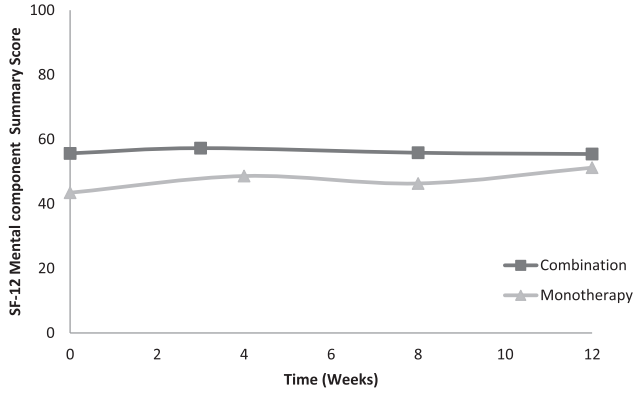

Fig. 8. SF-12 Mental Component Summary scores.

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).

Table 5
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	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

Table 6
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	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

RTOG

All participants were graded RTOG 0–3 for GU and GI symptoms (Tables 5 and 6). Within the Monotherapy Group, there was one incidence of GU RTOG 3 (catheterisation was required due to urinary retention) during hEBRT. The catheter remained in-situ at Week 12.

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 [16,39]. Consideration may be given to the use of smaller PTV margins to achieve a smaller volume of rectum being irradiated. A rectal spacer device is one method used to ensure this. Dosimetry studies have shown this to reduce rectal dose, acute GI toxicity and late rectal bleeding [40–42].

Although there was no significance differences observed between the groups in IIEF-5 scores, there was a statistically significant difference seen within the groups from Baseline to Week 12. Sexual side effects are the well-recognized adverse effects from ADT and include loss of libido and ED [43]. All participants were established on ADT. The increase in ED was greater within the Combination Group (Baseline-Week 12: $p = 0.012$). One hypothesis is this may be due to needle entry via penile bulb but the dominant cause is most probably due to the use of ADT. At Week 12, 25% participants were prescribed PDe5 inhibitors. White et al, 2014, in developing the UK guidance for the management of sexual function resulting from radical radiotherapy and ADT concluded that it is essential patients' are counselled on the importance of early intervention to maintain sexual function [44]. Prostate cancer NICE guidelines also recommend that men should have early and ongoing access to specialist ED services [17]. It should be noted the Monotherapy Group were older and at baseline had a lower 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 contraindicated 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 HDT-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 conformality 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.

References

[1] Cancer Research UK. Prostate Cancer Statistics. Available at: <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer>.

[2] Northern Ireland Cancer Registry. Prostate Cancer. Available from: <http://www.qub.ac.uk/research-centres/nicr/FileStore/OfficialStats/Incidence/>.

[3] Bolla M, Collette L, Blank L, Warde P, Dubois JB, Mirimanoff RO, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC) study: a phase III randomized trial. Lancet 2004;360:103–6. https://doi.org/10.1016/S0140-6736(02)09408-4.

[4] D'Amico AV, Manola J, Loffredo M, Renshaw AA, DellaCroce A. Kantoff PW 6-month androgen suppression plus radiation therapy versus radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial. JAMA 2004;292:821–7. https://doi.org/10.1001/jama.292.7.821.

[5] Laverdiere J, Nabid A, De Bedoya LD, Ebacher A, Fortin A, Wang CS, et al. The efficacy and sequencing of a short course of androgen suppression on freedom from biochemical failure when administered with radiation therapy for T2–T3 prostate cancer. J Urol 2004;171:1137–40. https://doi.org/10.1097/01.ju.0000112979.97941.7f.

[6] Ahmad SS, Duke S, Jena R, Williams MV, Burnet NG. Advances in radiotherapy. BMJ 2012;345:e7765. https://doi.org/10.1136/bmj.e7765 (Published 04 December 2012).

[7] Dearnaley DP, Jovic G, Syndikus I, Khoo V, Cowan RA, Graham JD, et al. Escalated-dose Conformai radiotherapy for localised prostate cancer: long-term overall survival results from the MRC RT01 randomised controlled trial. Eur J Cancer 2011;47(September):11–2. https://doi.org/10.1016/S0959-8049(11)70120-4.

[8] Viani GA, Stefano EJ, Afonso SL. Higher-than-conventional radiation doses in localized prostate cancer treatment: a meta-analysis of randomized, controlled trials. Int J Radiat Oncol Biol Phys 2009;74(5):1405–18. https://doi.org/10.1016/j.ijrobp.2008.10.091.

[9] Beckendorf V, Guerif S, Le Prisé E, Didier Peiffert, Anne-Sophie Baumann, Valérie Bernier, et al. 70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. Int J Radiat Oncol Biol Phys 2011;80(4):1056–63. https://doi.org/10.1016/j.ijrobp.2010.03.04.

[10] Heemsbergen WD, Al-Mamgani A, Slot A, Dielwart MFH, Lebesque JV. Long-term results of the Dutch randomized prostate cancer trial: Impact of dose-escalation on local, biochemical, clinical failure, and survival. Radiother Oncol 2014;110(1):104–9. https://doi.org/10.1016/j.radonc.2013.09.026.

[11] Zelefsky MJ, Yamada Y, Fuks Z, Zhang Z, Hunt M, Cahlon O, et al. Long-term results of conformal radiotherapy for prostate cancer: impact of dose escalation on biochemical tumor control and distant metastases-free survival outcomes. Int J Radiat Oncol Biol Phys 2008;71(4):1028–33. https://doi.org/10.1016/j.ijrobp.2007.11.066.

[12] Kuban D, Tucker SL, Dong L, Starkschall G, Huang EH, Cheung MR, et al. Long-term results of the M.D. Anderson randomized dose-escalation trial for prostate cancer. Int J Radiat Oncol Biol Phys 2008;70(1):67–74. https://doi.org/10.1016/j.ijrobp.2007.06.054.

[13] Kupelian PA, Ciezki J, Reddy CA, Klein EA, Mahadevan A. Effect of increasing radiation doses on local and distant failures in patients with localized prostate cancer. Int J Radiat Oncol Biol Phys 2008;71(1):16–22. https://doi.org/10.1016/j.ijrobp.2007.09.020.

[14] Pollack A, Zagars GK, Smith LG, Lee JJ, von Eschenbach AC, Antolak JA, et al. Preliminary results of a randomized radiotherapy dose-escalation study comparing 70 Gy with 78 Gy for prostate cancer. J Clin Oncol 2000;18:3904–11. https://doi.org/10.1200/JCO.2000.18.23.3904.

[15] Zelefsky MJ, Leibel SA, Gaudin PB, Kutcher GJ, Fleshner NE, Venkatramen ES, et al. Dose escalation with three-dimensional conformal radiation therapy affects the outcome in prostate cancer. Int J Radiat Oncol Biol Phys 1998;41:491–500. https://doi.org/10.1016/S0360-3016(98)00091-1.

[16] Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol August 2016;17(8):1047–60. https://doi.org/10.1016/S1470-2045(16)30102-4.

[17] National Institute of Clinical Excellence guideline 58 – Prostate cancer: diagnosis and treatment. Available at: <www.nice.org.uk/CG058fullguideline>.

[18] Kupelian PA, Reddy CA, Klein EA, Willoughby TR. Short-course intensity-modulated radiotherapy (70 GY at 2.5 GY per fraction) for localized prostate cancer: preliminary results on late toxicity and quality of life. Int J Radiat Oncol Biol Phys 2001;51(4):988–93. https://doi.org/10.1016/j.ijrobp.2007.01.067.

[19] UK national protocol for high dose rate brachytherapy boost in prostate cancer. Peter Hoskin v1.6 Sept 2010.

[20] Hoskin PJ, Colombo A, Henry A, Niehoff P, Paulsen Hellebust T, Siebert FA, et al. GEC/ESTRO recommendations on high dose rate afterloading brachytherapy for localised prostate cancer: an update. Radiother Oncol 2013;107(325–332):5. https://doi.org/10.1016/j.radonc.2013.05.002.

[21] Yamada Y, Rogers L, Demanes DJ, Morton G, Prestidge BR, Pouliot J, et al. American Brachytherapy Society consensus guidelines for high-dose-rate prostate brachytherapy. Brachytherapy 2012;11(1):20–32. https://doi.org/10.1016/j.brachy.2011.09.008.

[22] Hoskin PJ. High dose rate brachytherapy boost treatment in radical radiotherapy for prostate cancer. Radiother Oncol 2000;57(285–288):7.

[23] Hoskin PJ, Rojas AM, Bownes PJ, Lowe GJ, Ostler PJ, Bryant L. Randomised trial of external beam radiotherapy alone or combined with high dose-rate brachytherapy boost for localised prostate cancer. Radiother Oncol 2012;103(217–222):8. https://doi.org/10.1016/j.radonc.2012.01.007.

[24] Khor R, Duchesne G, Tai Kh, Foroudi F, Chander S, Van Dyk S, et al. Direct 2-arm comparison shows benefit of high-dose-rate brachytherapy boost vs external beam radiation therapy alone for prostate cancer. Int J Radiat Oncol Biol Phys 2013;85(3):679–85. https://doi.org/10.1016/j.ijrobp.2012.07.006.

[25] Morton G, Loblaw DA, Sankreacha A, Patrocinio H, Kassouf W, Shenouda G, et al. Single-fraction high dose rate brachytherapy and hypofractionated external beam radiotherapy for men with intermediate risk prostate cancer: an analysis of short and medium term toxicity and quality of life. Int J Radiat Oncol Biol Phys 2009. https://doi.org/10.1016/j.ijrobp.2009.05.054 9.
[26] Zwahlen DR, Andrianopoulos N, Matheson B, Duchesne GM, Millar JL. High-dose-rate brachytherapy in combination with conformal external beam radiotherapy in the treatment of prostate cancer. Brachytherapy 2010;9 (1):27–35. https://doi.org/10.1016/j.brachy.2009.04.007.
[27] Akimoto T, Katoh H, Kitamoto Y, Tamaki T, Harada K, Shirai K, et al. Rectal bleeding after high-dose-rate brachytherapy combined with hypofractionated external-beam radiotherapy for localized prostate cancer: impact of rectal dose in high-dose-rate brachytherapy on occurrence of grade 2 or worse rectal bleeding. Int J Radiat Oncol Biol Phys 2006;65(2):364–70. https://doi.org/10.1016/j.ijrobp.2005.12.017.
[28] Schroeck FR. Expanded prostate cancer index composite (EPIC) 2014:2083–86. 10.1007/978-94-007-0753-5_960.
[29] Wei J, Dunn R, Litwin M, Sandler H, Sanda M. Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. Urology 2000:4295. https://doi.org/10.1016/S0090-4295(00)00858-X.
[30] Stone N. Complications following permanent prostate brachytherapy. Eur Urol 2002;41(4):427–33. https://doi.org/10.1016/S0302-2838(02)00019-2.
[31] Ash D, Bottomley D, Al-Qaisieh B, Carey B, Gould K, Henry A. A prospective analysis of long-term quality of life after permanent I-125 brachytherapy for localised prostate cancer. Radiother Oncol 2007;84(2):135–9. https://doi.org/10.1016/j.radonc.2007.05.020.
[32] Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 1997 Jun;49(6):822–30. https://doi.org/10.1016/S0090-4295(97)00238-0.
[33] Rosen RC, Cappelleri JC, Smith, Lipsky J, Peña BM. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res 1999 Dec;11(6):319–26.
[34] Lebeau T, Perrotte P, Valiquette L, Bénard F, McCormack M, Saad F, et al. Validation of prostate cancer index and SF-12 short forms Available at:. Can J Urol 2005;12(6):2873–9. http://www.ncbi.nlm.nih.gov/pubmed/16401372.
[35] Ware J, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity Available from. Med Care 1996;34(3):220–33. http://www.ncbi.nlm.nih.gov/pubmed/8628042.
[36] Resnick B, Nahm ES. Reliability and validity testing of the revised 12-item Short-Form Health Survey in older adults Available at:. J Nurs Meas 2001;9 (2):151–61. http://www.ncbi.nlm.nih.gov/pubmed/11696939.
[37] Cox JD, Stetz J, Pajak T. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995 Mar 30;31(5):1341–6. https://doi.org/10.1016/0360-3016(95)00060-C.
[38] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987;40(5):373–83.
[39] Aluwini S, Pos F, Schimmel E, van Lin E, Krol S, van der Toorn P, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): acute toxicity results from a randomised non-inferiority phase 3 trial. Lancet Oncol 2015;16(3):274–83. https://doi.org/10.1016/S1470-2045(14)70482-6.
[40] Pinkawa M, Berneking V, König L, Frank D, Bretgeld M, Eble M. Hydrogel injection reduces rectal toxicity after radiotherapy for localized prostate cancer Hydrogelinjektion vermindert die rektale Toxizität nach Radiotherapie bei lokalisiertem Prostatakarzinom. Strahlenther Onkol 2017;193(1):22–8. https://doi.org/10.1007/s00066-016-1040-6.
[41] Yeh J, Lehrich B, Tran C, Mesa A, Baghdassarian R, Yoshida J, et al. Polyethylene glycol hydrogel rectal spacer implantation in patients with prostate cancer undergoing combination high-dose-rate brachytherapy and external beam radiotherapy. Brachytherapy 2016;15(3):283–7. https://doi.org/10.1016/j.brachy.2015.12.007.
[42] Mariados N, Sylvester J, Shah D, Karsh L, Hudes R, Beyer D, et al. Hydrogel spacer prospective multicenter randomized controlled pivotal trial: dosimetric and clinical effects of perirectal spacer application in men undergoing prostate image guided intensity modulated radiation therapy. Int J Radiat Oncol Biol Phys 2015;92(5):971–7. https://doi.org/10.1016/j.ijrobp.2015.04.030.
[43] Mazzola C, Mulhall J. Impact of androgen deprivation therapy on sexual function. Asian J Androl 2012;14(2):198–203. https://doi.org/10.1038/aja.2011.106.
[44] White I, Wilson J, Aslet P, Baxter A, Birtle A, Challacombe B, et al. Development of UK guidance on the management of erectile dysfunction resulting from radical radiotherapy and androgen deprivation therapy for prostate cancer. Int J Clin Pract 2014;69(1):106–23.
[45] Jensen K, Bonde Jensen A, Grau C. The relationship between observer-based toxicity scoring and patient assessed symptom severity after treatment for head and neck cancer. A correlative cross sectional study of the DAHANCA toxicity scoring system and the EORTC quality of life questionnaires. Radiother Oncol 2006;78(3):298–305.
[46] Litwin M, Lubeck D, Henning J, Carroll P. Differences in Urologist and patient assessments of health related quality of life in men with prostate cancer: results of the Capsure database. J Urol 1998;159(6):1988–92.
[47] Christodoulou M, McCloskey P, Stones N, Bayman N, Burt P, Chittalia A, et al. Investigation of a Patient Reported Outcome tool to assess radiotherapy-related toxicity prospectively in patients with lung cancer. Radiother Oncol 2014;112(2):244–9.
[48] Insight & Feedback Team, NHS England. A national patient reported outcome measures (PROMs) programme consultation report; 25 September 2017. Available at: <https://www.england.nhs.uk/wp-content/uploads/2017/10/proms-consultation-report.pdf>.
[49] Malhotra K, Buraimoh O, Thornton J, Cullen Nicholas, Singh Dishan, Goldberg Andrew J. Electronic capture of patient-reported and clinician reported outcome measures in an elective orthopaedic setting: a retrospective cohort analysis. BMJ Open 2016;6:e011975. https://doi.org/10.1136/bmjopen-2016-011975.
[50] Newsham A, Johnston C, Hall G, Leahy M, Smith A, Vikram A, et al. Development of an advanced database for clinical trials integrated with an electronic patient record system. Comput Biol Med 2011;41(8):575–86.