# 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 (37.5Gray/15 fractions followed by a 15 Gray implant), and ten patients received monotherapy (60Gray/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.

**1.0 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 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 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 [2[6](http://www.sciencedirect.com.lcproxy.shu.ac.uk/science/article/pii/S0305737213002259#b0370), 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 assessment has been made by the researcher/clinician rather than the patient.

# This prospective study tested the feasibility of radiographer-led collection of multiple validated PROMS from PCa patients comparing HDR-BT combined with hEBRT (Combination Group) and hEBRT alone (Monotherapy Group).

# ****2.0 Materials and Methods****

**2.1 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 hours to decide upon participation. Inclusion criteria and exclusion criteria are listed in Table 1.

**Table 1 Study inclusion/exclusion criteria**

|  |  |
| --- | --- |
| Inclusion criteriaAll criteria must apply: | Exclusion criteriaIneligible 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 either: 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 |  |

**2.2 Data collection**

Data was collected prospectively from all participants. The PROMs used are summarised in Table 2.

**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] |

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]

PROMs were presented to the participant in a booklet. 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 the final fraction of hEBRT, which was Week 3 for the Combination Group and Week 4 for the Monotherapy Group. These time points were selected to improve data collection rates as the questionnaires were completed in the hospital. RTOG GI and GU were assessed at baseline, weekly during RT and week 12. 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 classifying comorbidity conditions. [38]

**2.3 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).

**2.3.1 HDR-BT combined with hEBRT**

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

**2.3.2 hEBRT alone**

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

**2.3.3 Treatment delivery**

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

**2.4 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.

**2.5 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).

# ****3.0 Results****

PIS were given to 24 patients, 4 declined and 20 consented. 10 received HDR-BT combined with hEBRT (**Combination group**) and 10 received hEBRT alone (**Monotherapy group**). All patients were established on ADT for a minimum of six weeks prior to consent and completing baseline assessments.

Participantclinical characteristics are presented in Table 3.

**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 80T3a 20 |
| Mean PSA at diagnosis ngs/ml  | 7.8 (range- 6.5-38) | 7.8 (range- 4.6-32.2) |
| Mean prostate volume cm3 | 35 (range 19-76) | 33 (range 22-90) |
| CCI | 4 | 4 |
| ADT % | Bicalutamide 80Goserelin 20 | Bicalutamide 90Goserelin 10 |
| Baseline Phosphodiesterase-5 (PDe5) inhibitor use % | 0 | 0 |

All participants completed treatment without interruption. In the Combination Group the interval between hEBRT and HDR-BT procedure ranged from 5-15 days. There was excellent participant compliance with 80 PROM questionnaire booklets completed and analysed (100% response rate).

**3.1 EPIC-26**

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

**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;

**3.1.1 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 also observed at the end of hEBRT (M=69.44). There was no statistical significance difference between the groups at any time-point.

**Fig. 1 EPIC-26 Urinary summary scores**

****

**3.1.2 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).

**Fig. 2 EPIC-26 Bowel summary scores**



**3.1.3 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.

 **Fig. 3 EPIC-26 Sexual summary scores**

******

**3.1.4 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).

**Fig. 4 EPIC-26 Hormone summary scores**



**3.2 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.

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

****

**3.3 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. 6 IIEF-5 severity grading a)combination group b) monotherapy group**

****

**3.4 SF-12**

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

**3.4.1 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.

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

**3.4.2 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).

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

**3.5 RTOG**

All participants were graded RTOG 0-3 for GU and GI symptoms (Table 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.

**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 |

# ****4.0 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, which have been widely used in Radiotherapy research studies enabling comparison to other research 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, this was 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 less rectum is irradiated. 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 significance 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 on-going access to specialist ED services.[45] 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 was 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 and 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. [46-48] 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 bowel summary score showed clinically relevant differences for 60% and 90% of participants in Combination and Monotherapy groups, respectively. Therefore, ideally observer-reported measures should be used in conjunction with PROMs. There is on-going importance to measure PROMs as new technology continues to develop with more complex treatments available such as Stereotactic Ablative Radiotherapy. Embedding PROMs into clinical practice 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. [49] 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. [50] 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 [51].

The results in this small study demonstrate that combination treatment may be an appealing choice to patients. HDR-BT is highly conformal, limiting the dose to the Organs at Risk potentially reducing treatment-related symptoms. However, there is a cohort of patients where HDR-BT is contra-indicated e.g. large prostate volume, [transurethral resection of the prostate](https://www.nhs.uk/conditions/transurethral-resection-of-the-prostate-turp/) (TURP) within 6 months, significant urinary obstructive symptoms, pubic arch interference, lithotomy position or anaesthesia not possible.

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.

# ****5.0 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 in the combination treatment has a more favourable treatment-related symptom profile most notably in bowel symptoms although monotherapy is a highly conformal treatment when delivered using daily cone-beam CT and VMAT delivery.

This prospective study showed excellent compliance with PROMS completion. Both treatment groups tolerated treatment well with minimal impact on QoL. The feasibility of collecting PROMS is evidenced by the high compliance in this cohort. 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.

**6.0 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](https://www.ncbi.nlm.nih.gov/pubmed/?term=Warde%20P%5BAuthor%5D&cauthor=true&cauthor_uid=12126818), [Dubois JB](https://www.ncbi.nlm.nih.gov/pubmed/?term=Dubois%20JB%5BAuthor%5D&cauthor=true&cauthor_uid=12126818), [Mirimanoff RO](https://www.ncbi.nlm.nih.gov/pubmed/?term=Mirimanoff%20RO%5BAuthor%5D&cauthor=true&cauthor_uid=12126818) 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. DOI: [http://dx.doi.org/10.1016/S0140-6736(02)09408-4](http://dx.doi.org/10.1016/S0140-6736%2802%2909408-4)
4. D’Amico AV, Manola J, Loffredo M, [Renshaw AA](https://www.ncbi.nlm.nih.gov/pubmed/?term=Renshaw%20AA%5BAuthor%5D&cauthor=true&cauthor_uid=15315996), [DellaCroce A](https://www.ncbi.nlm.nih.gov/pubmed/?term=DellaCroce%20A%5BAuthor%5D&cauthor=true&cauthor_uid=15315996), [Kantoff PW](https://www.ncbi.nlm.nih.gov/pubmed/?term=Kantoff%20PW%5BAuthor%5D&cauthor=true&cauthor_uid=15315996) 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 DOI:10.1001/jama.292.7.821
5. Laverdiere J, Nabid A, De Bedoya LD [Ebacher A](https://www.ncbi.nlm.nih.gov/m/pubmed/?term=Ebacher%20A%5BAuthor%5D&sort=ac&from=/14767287/ac), [Fortin A](https://www.ncbi.nlm.nih.gov/m/pubmed/?term=Fortin%20A%5BAuthor%5D&sort=ac&from=/14767287/ac), [Wang CS](https://www.ncbi.nlm.nih.gov/m/pubmed/?term=Wang%20CS%5BAuthor%5D&sort=ac&from=/14767287/ac) 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 DOI: <http://dx.doi.org/10.1097/01.ju.0000112979.97941.7f>
6. Ahmad S, Duke S, Jena R, Williams M V and Burnet N G Advances in radiotherapy *BMJ* 2012; 345:e7765 (Published 04 December 2012) Available from: http://www.ncbi.nlm.nih.gov/pubmed/23212681 DOI: 10.1136/bmj.e7765
7. Dearnaley DP, Jovic G, Syndikus I, [Khoo V](https://www.ncbi.nlm.nih.gov/pubmed/?term=Khoo%20V%5BAuthor%5D&cauthor=true&cauthor_uid=24581940), [Cowan RA](https://www.ncbi.nlm.nih.gov/pubmed/?term=Cowan%20RA%5BAuthor%5D&cauthor=true&cauthor_uid=24581940), [Graham JD](https://www.ncbi.nlm.nih.gov/pubmed/?term=Graham%20JD%5BAuthor%5D&cauthor=true&cauthor_uid=24581940) 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):11–12. DOI: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. DOI:10.1016/j.ijrobp.2008.10.091.
9. Beckendorf V, Guerif S, Le Prisé E, [Didier Peiffert](https://www.ncbi.nlm.nih.gov/pubmed/?term=Peiffert%20D%5BAuthor%5D&cauthor=true&cauthor_uid=28622770), [Anne-Sophie Baumann](https://www.ncbi.nlm.nih.gov/pubmed/?term=Baumann%20AS%5BAuthor%5D&cauthor=true&cauthor_uid=28622770), [Valérie Bernier](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bernier%20V%5BAuthor%5D&cauthor=true&cauthor_uid=28622770) 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. DOI:10.1016/j.ijrobp.2010.03.04
10. Heemsbergen WD, Al-Mamgani A, Slot A, Dielwart MFH, Lebesque J V. 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):104–109. DOI: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. DOI:10.1016/j.ijrobp.2007.11.066.
12. Kuban D, Tucker SL, Dong L, [Starkschall G](https://www.ncbi.nlm.nih.gov/pubmed/?term=Starkschall%20G%5BAuthor%5D&cauthor=true&cauthor_uid=17765406), [Huang EH](https://www.ncbi.nlm.nih.gov/pubmed/?term=Huang%20EH%5BAuthor%5D&cauthor=true&cauthor_uid=17765406), [Cheung MR](https://www.ncbi.nlm.nih.gov/pubmed/?term=Cheung%20MR%5BAuthor%5D&cauthor=true&cauthor_uid=17765406) 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. DOI: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. DOI: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;18:3904-3911 DOI:[10.1200/JCO.2000.18.23.3904](https://doi.org/10.1200/JCO.2000.18.23.3904)
15. Zelefsky MJ, Leibel SA, Gaudin PB, Kutcher GJ, Fleshner NE, Venkatramen ES, Reuter VE 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. DOI: [http://dx.doi.org/10.1016/S0360-3016(98)00091-1](http://dx.doi.org/10.1016/S0360-3016%2898%2900091-1)
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. The Lancet Oncology [Volume 17, No. 8](http://www.thelancet.com/journals/lanonc/issue/vol17no8/PIIS1470-2045%2816%29X0008-3), p1047–1060, August 2016 DOI: [http://dx.doi.org/10.1016/S1470-2045(16)30102-4](http://dx.doi.org/10.1016/S1470-2045%2816%2930102-4)
17. National Institute of Clinical Excellence guideline 58 – Prostate cancer: diagnosis and treatment. Available at: [www.nice.org.uk/CG058fullguideline](http://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. International Journal of Radiation Oncology, Biology, Physics2001; 51(4):988-93. DOI: <http://dx.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. Radiotherapy and Oncology 2013; 107: 325-332 5. DOI: 10.1016/j.radonc.2013.05.002
21. Yamada Y, Rogers L, D. Demanes DJ, Morton G, Prestidge BR, Pouliot J et al American Brachytherapy Society consensus guidelines for high-dose-rate prostate brachytherapy Brachytherapy 2012; 11: 20-32 6. doi: 10.1016/j.brachy.2011.09.008
22. Hoskin PJ. High dose rate brachytherapy boost treatment in radical radiotherapy for prostate cancer. Radiotherapy and Oncology, 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. DOI: 10.1016/j.radonc.2012.01.007.
24. R. Khor, G. Duchesne, Kh. Tai, 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, 85 (3) (2013), pp. 679–685 DOI: 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 DOI:10.1016/j.ijrobp.2009.05.054 9.
26. Zwahlen D.R., Andrianopoulos N., Matheson B., Duchesne G.M., Millar J.L.

High-dose-rate brachytherapy in combination with conformal external beam radiotherapy in the treatment of prostate cancer Brachytherapy, 9 (1) (2010), pp. 27–35 DOI: 10.1016/j.brachy.2009.04.007.

1. **x**
2. Horacio Patrocinio
3. Search for articles by this author
4. Affiliations
5. Department of Medical Physics, McGill University Health Centre, Montreal, QC, Canada
6. **x**
7. Wassim Kassouf
8. [Search for articles by this author](http://www.redjournal.org/action/doSearch?searchType=authorLookUp&author=Kassouf,%20Wassim&prod=HA)
9. Affiliations
10. Department of Urology, McGill University Health Centre, Montreal, QC, Canada

**x**

1. George Shenouda
2. Search for articles by this author
3. Affiliations
4. Department of Radiation Oncology, McGill University Health Centre, Montreal, QC, Canada

 [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, 65 (2) (2006), pp. 364–370 DOI: [10.1016/j.ijrobp.2005.12.017](https://doi.org/10.1016/j.ijrobp.2005.12.017)

 [28] Schroeck FR. Expanded Prostate Cancer Index Composite (EPIC). 2014:2083 2086. DOI: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(00). DOI: [http://dx.doi.org/10.1016/S0090-4295(00)00858-X](http://dx.doi.org/10.1016/S0090-4295%2800%2900858-X)

[30] Stone N. Complications Following Permanent Prostate Brachytherapy. *Eur Urol*. 2002;41(4):427–433. DOI: 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. DOI: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. DOI: [http://dx.doi.org/10.1016/S0090-4295(97)00238-0](http://dx.doi.org/10.1016/S0090-4295%2897%2900238-0)

[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](https://www.ncbi.nlm.nih.gov/m/pubmed/?term=B%C3%A9nard%20F%5BAuthor%5D&sort=ac&from=/16401372/ac), [McCormack M](https://www.ncbi.nlm.nih.gov/m/pubmed/?term=McCormack%20M%5BAuthor%5D&sort=ac&from=/16401372/ac), [Saad F](https://www.ncbi.nlm.nih.gov/m/pubmed/?term=Saad%20F%5BAuthor%5D&sort=ac&from=/16401372/ac) et al. Validation of prostate cancer index and SF-12 short forms. Can J Urol. 2005; 12(6):2873–9. Available at: 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. Med Care. 1996; 34(3):220–33. Available from: 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*. J Nurs Meas*. 2001; 9(2):151–61. Available at: 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. DOI: 10.1016/0360-3016(95)00060-C.

[38] Charlson M.E., Pompei P., Ales K.L.,. MacKenzie C.R. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation J Chron Dis, 40 (5) (1987), pp. 373-383

[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. *The Lancet Oncology*, *16*(3), 274-283. DOI: [http://dx.doi.org/10.1016/s1470-2045(14)70482-6](http://dx.doi.org/10.1016/s1470-2045%2814%2970482-6)

[40] Pinkawa, M., Berneking, V., König, L., Frank, D., Bretgeld, M., Eble, M. Hydrogel injection reduces rectal toxicity after radiotherapy for localized prostate cancer. *Strahlentherapie Und Onkologie*, *193*(1), 22-28. DOI: http://dx.doi.org/10.1007/s00066-016-1040-6

[41] Yeh, J., Lehrich, B., Tran, C., Mesa, A., Baghdassarian, R., & Yoshida, J. et al. (2016). Polyethylene glycol hydrogel rectal spacer implantation in patients with prostate cancer undergoing combination high-dose-rate brachytherapy and external beam radiotherapy. *Brachytherapy*, *15*(3), 283-287. DOI: http://dx.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. *International Journal Of Radiation Oncology\*Biology\*Physics*, *92*(5), 971-977. DOI: <http://dx.doi.org/10.1016/j.ijrobp.2015.04.030>

[43] Mazzola, C., Mulhall, J. Impact of androgen deprivation therapy on sexual function. *Asian Journal Of Andrology*, *14*(2), 198-203. DOI: <http://dx.doi.org/10.1038/aja.2011.106>

[44] White, I., Wilson, J., Aslet, P., Baxter, A., Birtle, A., Challacombe, B., Coe, J., Grover, L., Payne, H., Russell, S., Sangar, V., Van As, N. and Kirby, M. (2014). Development of UK guidance on the management of erectile dysfunction resulting from radical radiotherapy and androgen deprivation therapy for prostate cancer. *International Journal of Clinical Practice*, 69(1), pp.106-123.

[45] National Institute for Health and Care Excellence. CG58 Prostate cancer: diagnosis and management.

[46] Jensen, K., Bonde Jensen, A. and Grau, C. (2006). 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. *Radiotherapy and Oncology*, 78(3), pp.298-305.

[47] LITWIN, M., LUBECK, D., HENNING, J. and CARROLL, P. (1998). DIFFERENCES IN UROLOGIST AND PATIENT ASSESSMENTS OF HEALTH RELATED QUALITY OF LIFE IN MEN WITH PROSTATE CANCER: RESULTS OF THE CAPSURE DATABASE. *The Journal of Urology*, 159(6), pp.1988-1992.

[48] Christodoulou, M., McCloskey, P., Stones, N., Bayman, N., Burt, P., Chittalia, A., Harris, M., Lee, L., Pemberton, L., Sheikh, H., Swindell, R. and Faivre-Finn, C. (2014). Investigation of a Patient Reported Outcome tool to assess radiotherapy-related toxicity prospectively in patients with lung cancer. *Radiotherapy and Oncology*, 112(2), pp.244-249.

 [49] 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>

 [50] Malhotra K, Buraimoh O, Thornton J, [Nicholas Cullen](https://www.ncbi.nlm.nih.gov/pubmed/?term=Cullen%20N%5BAuthor%5D&cauthor=true&cauthor_uid=27324718), [Dishan Singh](https://www.ncbi.nlm.nih.gov/pubmed/?term=Singh%20D%5BAuthor%5D&cauthor=true&cauthor_uid=27324718), and [Andrew J Goldberg](https://www.ncbi.nlm.nih.gov/pubmed/?term=Goldberg%20AJ%5BAuthor%5D&cauthor=true&cauthor_uid=27324718). Electronic capture of patient-reported and clinician reported outcome measures in an elective orthopaedic setting: a retrospective cohort analysis. BMJ Open 2016; 6: e011975. DOI: 10.1136/bmjopen-2016-011975

[51] Newsham, A., Johnston, C., Hall, G., Leahy, M., Smith, A., Vikram, A., Donnelly, A., Velikova, G., Selby, P. and Fisher, S. Development of an advanced database for clinical trials integrated with an electronic patient record system. Computers in Biology and Medicine, 41(8), (2011). pp.575-586.

* PROMs have an important role to play in clinical practice;
* The radiographer-led collection of multiple PROMs is feasible;
* Monotherapy Group reported higher levels of bowel toxicity than Combination Group;
* RTOG scale was not of sufficient sensitivity and under-reported symptoms;
* A good QoL was maintained throughout treatment for both treatment groups;