Impact of hypofractionated radiotherapy on patient-reported outcomes in prostate cancer: results up to 5 years in the CHHiP trial (CRUK/06/016)

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Abstract

Background: Moderate hypofractionation is recommended standard of care for localised prostate cancer following the results of trials including CHHiP. Evaluation of long-term patient-reported outcomes (PRO) is important to confirm safety and enhance patient information.

Objective: To determine whether 5-year PRO from the CHHiP Quality of Life (QoL) substudy confirm 2-year findings, and assess patterns over follow-up.

Design/Setting/Participants: Phase III randomised controlled trial recruited 2002-2011. QoL substudy completed accrual 2009; participants followed-up to 5 years after radiotherapy. Analyses use data snapshot taken 26/08/2016. 71 radiotherapy centres (UK, Republic of Ireland, Switzerland, New Zealand); all 57 UK centres participated in QoL substudy. CHHiP recruited 3216 men with localised prostate cancer (cT1b–T3aN0M0).

Interventions: Conventional (74 Gy/37 fractions/7·4 weeks) or hypofractionated radiotherapy (60 Gy/20 fractions/4 weeks or 57 Gy/19 fractions/3·8 weeks) all delivered with intensity-modulated techniques.

Outcomes/Analysis: UCLA-PCI, SF-36 and FACT-P, or EPIC and SF-12 questionnaires at baseline, pre-radiotherapy, 10 weeks, 6, 12, 18, 24, 36, 48, 60 months after radiotherapy. QoL primary endpoint was overall bowel bother.

Results: QoL substudy recruited 2100 patients; 1141 5-year forms were available out of 1957 patients still alive (58%). No statistically significant differences in 5-year prevalence of overall ‘moderate or big’ bowel bother: 19/349 (5.4%), 29/381 (7.6%), and 21/393 (5.3%) for 74Gy, 60Gy and 57Gy; overall urinary or sexual bother at 5 years similar between schedules. Bowel and urinary symptoms remained stable from 2-5 years for all schedules. Some evidence of worsening overall sexual bother from baseline to 5 years less likely in the hypofractionated schedules compared with 74Gy (ORs for increase in bother score versus 74Gy: 0.55 [0.30-0.99], p=0.009 for 60Gy, 0.52 [0.29-0.94], p=0.004 for 57Gy). General QoL scores were similar between schedules at 5 years.

Conclusions: Longer follow-up confirms earlier findings, with similar patient-reported bowel, urinary and sexual problems between schedules overall. Continued low incidence of moderate or high bother confirms that moderate hypofractionation should be standard of care for intermediate risk localised prostate cancer.

Patient Summary

We looked at patient-reported outcomes up to 5 years after treatment in a trial of different radiotherapy schedules for prostate cancer. Findings confirmed that the shorter radiotherapy schedules were as safe as standard radiotherapy in terms of bowel, urinary and sexual problems.

Introduction

Prostate cancer remains the most common cancer in men in the UK [1]. External beam radiotherapy, radical prostatectomy, and brachytherapy are standard options for radical treatment for localised disease, considered to have equivalent tumour control at least up to 10 years [2]. Patients and physicians balance efficacy against side effects in decision-making [3]. Patient-reported outcomes (PRO) detect treatment side-effects more reliably than clinical assessments [4, 5].

The Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy in Prostate Cancer (CHHiP) trial randomised 3216 men with localised prostate cancer undergoing radiotherapy to conventional fractionation (74 Gy in 37 fractions) versus one of two moderately hypofractionated regimens (60Gy in 20 fractions, 57Gy in 19 fractions). At 5.2 years' median follow-up the 60Gy schedule was shown to be non-inferior to conventional fractionation with 5-year biochemical or clinical failure-free rates of 90.6% (95%CI 88.5-92.3) and 88.3% (86.0-90.2) respectively; the 57Gy schedule was not non-inferior (85.9%, 83.4–88.0) [6]. Five-year clinician-reported late genitourinary (GU) and gastrointestinal (GI) toxicity was similar between schedules [6]. These results, with those

from other fractionation trials [7, 8], have led to moderate hypofractionation being recommended as standard of care for external beam radiotherapy [9, 10, 11].

Published results from the CHHiP quality of life (QoL) substudy up to 2-year follow-up showed similar incidence of patient-reported bowel and urinary symptoms between schedules [12]; we report results to 5 years as there is evidence of increasing cumulative incidence of late effects beyond the 2-year time period for both conventional and hypofractionated radiotherapy [13,14].

Materials and Methods

Study design and participants

The CHHiP trial included 3216 men recruited from 71 centres September 2002 to June 2011; full details of design, eligibility and treatment have been published [15]. Participation in the QoL substudy was open to all 57 UK centres and accrued 2100 patients by November 2009. CHHiP is registered ISRCTN97182923.

Procedures

Men were registered before or after starting hormone therapy. Patients with National Comprehensive Cancer Network (NCCN) intermediate or high-risk disease received short-course androgen suppression for 3–6 months before and during radiotherapy (optional for those with low-risk disease). Participants consenting to the QoL substudy were eligible to complete questionnaires at trial entry if they had not commenced hormonal therapy, to minimise impact of hormones. Questionnaires were administered pre-radiotherapy, at 10 weeks and 6, 12, 18, 24, 36, 48 and 60 months after the start of radiotherapy. Full details of QoL instruments have been published [12, 15]. Between 2002 and early 2009 QoL measures consisted of the University of California Los Angeles Prostate Cancer Index (UCLA-PCI) [16], including the Short Form 36 (SF-36) and Functional Assessment of Cancer Therapy-Prostate (FACT-P) [17]. Following a protocol amendment in 2009, the Expanded Prostate Cancer Index Composite (EPIC) [18] and Short Form 12 (SF-12) QoL

instruments were used for newly randomised patients as EPIC was emerging as the international standard QoL instrument for men having radiotherapy [19]. EPIC-50 assessed bowel and urinary domains and EPIC-26 sexual and hormonal domains [20].

For all QoL instruments a higher score represents better quality of life. All questionnaires were scored according to the recommended manuals.

Primary QoL endpoint was overall bowel bother, reported on a 5-point scale (none, very small, small, moderate, big bother) from EPIC or UCLA-PCI. Key secondary endpoints were overall urinary bother and overall sexual bother. Other secondary endpoints related to individual bowel, urinary and sexual items and domain scores from EPIC and UCLA-PCI, and general health-related quality of life (HRQoL) domains from FACT-P, SF-36 and SF-12.

Statistical analysis

Each pair of schedules were compared, with statistical tests at 5 years. CHHiP was not originally powered for QoL analyses; retrospective calculations were reported previously [12].

Cross-sectional analyses compared groups at 5 years using the Mantel-Haenszel chi-squared trend test and the Mann Whitney test. Moderate and severe events were combined due to few severe events. Patients were excluded from cross-sectional analyses if their QoL assessments were outside pre-specified time intervals (Figure 1).

Change from baseline (calculated as post-radiotherapy score minus baseline score) was assessed to account for differences in pre-existing co-morbidity between groups. As more questionnaires were available at the pre-radiotherapy time-point compared with pre-hormone (baseline), pre-radiotherapy data were used as a surrogate baseline for bowel and urinary symptoms unless missing, in which case the baseline data were used. For sexual endpoints and general HRQoL pre-hormone data were used as baseline, as endocrine treatment had a marked influence on these scores at the pre-radiotherapy time-point; patients with no pre-hormone therapy data were excluded from analyses requiring baseline data. Change from baseline was also presented in terms of

proportion of patients experiencing a minimally important difference according to published thresholds [21,22].

For the individual items of overall bowel, urinary and sexual bother, the odds of change in score from baseline to 5 years were modelled using ordinal logistic regression [23] and schedules compared using odds ratios (OR, with 99%CI), where OR<1 favour the hypofractionated schedules, indicating lower odds of an increase in bother score compared with the 74 Gy group. ANCOVA modelling was used to assess change from baseline to 5 years for continuous variables such as domain scores, adjusting for baseline score.

Time to emergent “small or worse” or “moderate or worse” toxicity from 6 months was assessed for individual endpoints using survival analysis methods, excluding patients who had already experienced an event at trial entry or pre-radiotherapy. Endpoints were defined as for the 2-year analyses; censoring patients at date of last QoL assessment or date of death, whichever occurred sooner. Kaplan-Meier cumulative incidence rates of emergent toxicity were estimated (with 99%CI), and schedules compared using the log rank test. Hazard ratios (with 99%CI) were obtained from Cox proportional hazards regression.

There was no imputation of missing questionnaires; domain scores were only calculated if sufficient items were completed according to the relevant scoring manual. Guidance for the EPIC measure specifies that domain scores can be calculated if >80% of the items within a scale are completed [24]; for UCLA-PCI the rule is $\geq$50% of items should be completed within a scale [25].

All hypotheses for the PRO endpoints were 2-sided. There was no formal adjustment of p-values to allow for multiple testing, but the statistical analysis plan pre-specified a conservative cut-off of 0.001 to indicate statistical significance due to the large number of endpoints and hypotheses tested; similarly, 99%CI were used.

Analysis was on an intention to treat basis, using STATA v13.1.

Results

Patients

Baseline characteristics of the 2100 men in the CHHiP QoL sub-study have been reported [12]. Questionnaire return rates from patients remaining eligible (alive and not withdrawn) were over 90% at all time-points up to 2 years, then 88%, 75% and 74% at 3, 4 and 5 years respectively (Figure 1, CONSORT diagram). Baseline characteristics were similar for patients with and without 5-year QoL data except for patients with higher T stage and higher NCCN risk group being less likely to return a 5-year questionnaire (Table A1). By 5 years, 143 patients had died (57 in 74Gy, 36 in 60Gy, 50 in 57Gy).

Bowel, urinary and sexual problems

Prevalence of symptoms

Five-year prevalence of small or worse overall bowel bother was 52/349 (14.9%) for 74Gy, 58/381 (15.2%) for 60Gy and 61/393 (15.5%) for 57Gy; corresponding figures for moderate or worse bowel bother were 19/349 (5.4%), 29/381 (7.6%), and 21/393 (5.3%) respectively (Table 1). Five-year prevalence of overall urinary bother was 58/341 (17.0%), 63/377 (16.7%) and 62/382 (16.2%) with small or worse symptoms, and 23/341 (6.7%), 35/377 (9.3%) and 30/382 (7.8%) with moderate or worse symptoms, for 74Gy, 60Gy and 57Gy respectively. Five-year prevalence of small or worse overall sexual bother was 192/333 (57.7%) for 74Gy, 187/363 (51.5%) for 60Gy and 198/376 (52.7%) for 57Gy; moderate or worse sexual bother was 139/333 (41.7%), 133/363 (36.6%) and 153/376 (40.7%) respectively (Table 2).

Frequencies of overall bowel, urinary and sexual bother were similar between schedules at all time-points (Figure 2). There were no statistically significant differences between the schedules at 5 years for any of the individual bowel, urinary or sexual symptoms or the corresponding domain scores (Tables 1, 2, A2). At 5 years, the most common bowel symptom was loose or liquid stools, with small or worse problems reported by 55/340 (16.2%) in 74Gy, 62/377 (16.4%) in 60Gy and 63/382

(16.5%) in 57Gy (Table 1). The most common urinary problem at 5 years was lack of urinary control, with loss of control reported at least occasionally by 144/343 (42.0%) in 74Gy, 135/378 (35.7%) in 60Gy and 145/388 (37.4%) in 57Gy (Table 2). Over follow-up, the prevalence and severity of sexual problems were higher compared with bowel and urinary symptoms (Figure 2, Tables 1, 2, A2). At 5 years, 244/259 (94.2%) of the 74Gy group, 243/279 (87.1%) for 60Gy and 266/294 (90.5%) for 57Gy reported small or worse problems with being awoken with an erection in the morning or at night, with around half rating this a big problem (Table 2). In contrast, the majority of bowel and urinary symptoms were reported as small or moderate problems.

Change over time

Following a temporary worsening in overall bowel and urinary bother at 10 weeks after radiotherapy, the prevalence of overall bowel, urinary and sexual bother changed little between 6 months and 5 years (Figure 2a, c, e). Overall, from baseline to the 5-year time point, 558/937 patients (59.6%) had no change in overall bowel bother, 523/921 (56.8%) had no change in overall urinary bother, and 161/385 (41.8%) had no change in sexual bother (Figure 2b, d, f). Patterns of change in overall bowel and urinary bother scores from baseline to 5 years were similar between the schedules (Figure 2b and d). There was some evidence of an increase in sexual bother from baseline to 5 years for 74Gy but not the hypofractionated schedules (OR for increase in sexual bother score for 60Gy versus 74Gy: 0.55 (0.30-0.99), p=0.009, and for 57Gy versus 74Gy: 0.52 (0.29-0.94), p=0.004; Figure 2f). Assessing mean change in domain scores from baseline to each time point indicated that bowel, urinary and sexual function were stable from 6 months to 5 years following radiotherapy, with sexual functioning showing the greatest decline at 5 years compared with baseline (Figure 3a, c, e). Bowel and urinary summary domain scores showed only marginally worse symptoms at 5 years compared with baseline, but a greater decline for the sexual summary score was observed for all groups, particularly for 74Gy, at 5 years (Figure 3b, d, f). Changes from baseline to 5 years for bowel and urinary function and summary scores were less than previously-reported minimal important differences (MID) for the majority of patients, but not so for the sexual function

and summary scores, although denominators were smaller for the sexual domain scores (Table A3). There were no statistically significant differences between schedules in bowel, urinary and sexual domain scores at 5 years adjusting for baseline (Figure 3).

Time to event analyses

There were no statistically significant differences between schedules for time to small or worse, and moderate or worse bowel, urinary and sexual problems (Tables A4 and A5, Figure A1). Hazard ratios were very similar to those reported in the 2-year analyses [12]. There was some evidence of higher rates of moderate or worse faecal incontinence in the hypofractionated schedules compared with 74Gy (HRs versus 74Gy: 5.75 (1.15-28.88), p=0.002 for 60Gy, and 4.17 (0.80-21.70), p=0.015 for 57Gy; Table A4). For all treatment groups together, 5-year cumulative incidence of overall bowel bother was 38.0% for small or worse symptoms (99%CI 33.5-42.9) and 19.5% for moderate or worse symptoms (16.4-23.2); corresponding figures for overall urinary bother were 30.9% small or worse symptoms (26.5-35.8) and 17.8% moderate or worse symptoms (14.4-21.8), and for overall sexual bother 69.8% small or worse symptoms (64.1-75.3) and 55.1% for moderate or worse symptoms (49.7-60.7).

General HRQoL domains

At 5 years, HRQoL domains indicating poorest QoL were role limitations (physical) and vitality from the SF-36 (Table A6). HRQoL domain scores were similar between schedules at 5 years (Table A6, and when adjusting for baseline score (Figure 4). Assessing mean change in scores from baseline to each time-point indicated that whilst some HRQoL domains were stable from 2-5 years, others such as role limitations (physical and emotional) declined (Figure 4). Changes from baseline to 5 years for most general HRQoL domains (except for role limitations - physical) were less than previously-reported minimal important differences (MID) for the majority of patients (Table A7).

Discussion

In general, PRO from the CHHiP trial up to 5 years following radiotherapy showed similar prevalence of overall bowel, urinary and sexual problems between fractionation schedules. Five-year rates of bowel and urinary bother were low, but sexual problems remained prevalent, consistent with 2-year findings [12]. Bowel and urinary problems changed little from 6 months to 5 years, with some evidence of worsening in sexual problems (using EPIC), especially in the 74Gy group. Five-year estimates of relative differences between schedules from time to event analyses did not show any statistically significant differences using our pre-defined significance level of p=0.001, consistent with our earlier results [12]. There was a larger decline from baseline in EPIC Bowel summary scores for the moderately hypofractionated schedules compared with conventional fractionation. This was driven by low grade faecal incontinence, which is not assessed in UCLA-PCI, supporting our decision to switch questionnaires, and was not reflected in results for overall bowel bother. There was a markedly lower decline from baseline in EPIC Sexual summary scores (but not UCLA-PCI) for the moderately hypofractionated schedules compared with conventional fractionation. General HRQoL domains showed declines in role limitations (physical) and vitality functioning, but no statistically significant differences between schedules.

Our results are interesting when compared to the PRO results of the Prostate Testing for Cancer and Treatment (ProtecT) trial, in which 1643 men with screen-detected low- or intermediate risk prostate cancer were randomized to active monitoring, radical prostatectomy or radiotherapy to the same dose of 74Gy in 37 fractions with neoadjuvant androgen deprivation [26]. ProtecT reported PRO on 4 domains (urinary, sexual and bowel function using EPIC, and HRQoL) at baseline at the time of diagnosis, at 6 and 12 months after randomization and annually thereafter. The changes in PRO over time in the radiotherapy arm of ProtecT were remarkably consistent with our results from all arms in CHHiP; they reported that bowel, urinary and sexual function deteriorated at 6 months but had recovered towards baseline by 12 months, remaining stable until 6 years' follow-up. Bowel symptoms in the radiotherapy group showed a small long-term difference from baseline (mean reduction in bowel summary score of -3.8 at 5 years) unlike the other groups; urinary and sexual

outcomes became similar to, and often better than, the active monitoring group, which showed a steady decline over time. Mean EPIC urinary summary score fell in the radical prostatectomy arm from 91.9 at baseline to 80.1 at 6 months driven by urinary incontinence although there was partial recovery by 12 months (mean score 88.1) which was maintained for long-term follow-up. Erectile firmness deteriorated in the radiotherapy and active monitoring groups with time, suggesting that some of the changes seen in our study may be the effects of aging. CHHiP analyses suggest that refining radiotherapy dose to penile bulb and rectum will improve sexual function and reduce further rectal side effects [27, 28]. A population-based cohort study comparing treatment options in 1386 men with favourable-risk and 619 with unfavourable-risk prostate cancer showed similar patterns to our findings regarding changes in patient-reported urinary, bowel and sexual outcomes up to 5 years following external-beam radiotherapy [29]. Taken together, these results are highly encouraging that there is no major change in the relative risks of late side effects between conventional and hypofractionated radiotherapy between 2 and 5 years after radiotherapy.

NRG Oncology 0415 randomized men with low risk disease between 73.8Gy in 41 fractions (conventional) versus 70Gy in 28 fractions (hypofractionated) (N=1115) [30] and reported similar scores between schedules for EPIC domains, anxiety, depression, and generic HRQoL at 5.8-years' median follow-up, consistent with our results. They enumerated changes from baseline for mean EPIC bowel, urinary and sexual scores from baseline to 12 months as -3.7, -0.3 and -8.2 (bowel, urinary, sexual, conventional) and -7.5, -1.8 and -8.4 (hypofractionated). Except for the difference in change in sexual function that we presume to be due to the use of hormonal therapy in the CHHiP study, these are consistent with our results for changes from baseline to 12 months for EPIC scores of –5.0, 2.8 and –26.0 (bowel, urinary, sexual 74Gy), -6.3, 1.6 and -9.6 (bowel, urinary, sexual, 60Gy) and -3.9, 1.2 and -19.3 (bowel, urinary, sexual, 57Gy). HYPRO randomised 820 intermediate or high-risk prostate cancer patients to 64.6Gy in 19 fractions or 78Gy in 39 fractions; rates of gastrointestinal or genitourinary symptoms increased in the first 6-12 months then remained stable up to 5 years [31]. In contrast to our findings, sexual activity showed continued improvement at 5

years towards baseline levels following a dip at 6 months; there was some recovery of sexual function in the hypofractionated group. After 3 years, incidence of clinically relevant deterioration of urinary symptoms was 33% for both schedules, with gastrointestinal symptom decline in 38% and 36% for the hypofractionated and conventional schedules respectively; hence, non-inferiority of hypofractionation was not demonstrated for these patient-reported symptoms.

Shaikh et al [32] reported PRO from 303 men randomised to 76Gy in 38 fractions or 70.2Gy in 26 fractions; patients with high-risk disease had elective pelvic nodal irradiation. Overall, no differences between the schedules were seen in any domain, although lower EPIC urinary incontinence scores were reported in the hypofractionated schedule with longer term follow-up. HRQoL outcomes were generally stable over time.

Widmark et al reported the Scandinavian phase III HYPO-RT-PC trial of 1200 men with mainly intermediate risk prostate cancer randomised to 78Gy in 39 daily fractions versus 42.7Gy in 7 fractions (ultra-fractionation) delivered on alternate days without androgen suppression [33]. Frequencies of gastrointestinal, genitourinary or sexual symptoms 5 years after radiotherapy were similar between groups although patients reported higher levels of acute toxicity and urinary symptoms at 12 months following ultra-fractionation. Rates of genitourinary and gastrointestinal symptoms were stable after 6 months, but sexual function deteriorated with time. Fransson has reported their QoL data 6 years after treatment using the Prostate Cancer Symptom Scale (PCSS) and European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ-C30) [34]. Although a higher proportion of men in the ultra-fractionation arm had clinical relevant deterioration in bowel symptoms at the end of radiotherapy, there was no clinically relevant differences in later timepoints for urinary, bowel or sexual functioning between the arms. At the 6-year follow-up the incidence of clinically relevant deterioration between the groups for both overall urinary and bowel bother was 33% for conventional fractionation and 28% for ultra-hypofractionation and for overall sexual bother was 60% and 50%, respectively.

Findings show that the long-term tolerance of the CHHiP technique is excellent and that urinary and bowel PRO are stable from 6 months after treatment. Furthermore, treatment techniques have evolved significantly since the CHHiP trial; only 30% of 900 CHHiP patients with data available were treated with daily online image-guided radiotherapy (IGRT). Fractionation guidelines from the UK Royal College of Radiologists updated in 2019 recommend that intensity-modulated radiotherapy (IMRT) or arc techniques including volumetric arc therapy are used [35]. These would be expected to reduce the incidence of late GU, GI and sexual effects; further benefits may occur with other advances such as IGRT [36] or implanted hydrogel spacers [37].

Strengths of the CHHiP QoL substudy include the large sample size and questionnaire return rates. Although questionnaire returns declined at years 4 and 5, this is not unusual in long-term follow-up studies [38]. Baseline characteristics between patients with and without 5-year data were similar except that patients with missing 5-year questionnaires were more likely to be in a higher NCCN risk group and higher T stage. Patients may have been less willing to complete the QoL questionnaires following relapse. However, since T stage and NCCN risk group were balanced between the randomised groups [12] and data completeness up to 5 years was also similar between groups, missing data are unlikely to have substantially biased the randomised comparisons reported here. QoL instruments used were amended in response to changing understandings of the strengths and weaknesses of different scales and specifically to ensure better capture of symptoms known to be associated with external beam radiotherapy, but poorly captured in UCLA-PCI. This resulted in lower statistical power for symptoms only in EPIC, including faecal incontinence and rectal bleeding and means we cannot rule out small but clinically relevant differences; we therefore strongly encourage future research into the long-term PRO of prostate hypofractionation.

Conclusions

Results to 5-year follow-up show similar patient-reported bowel, urinary and sexual outcomes between schedules and support the use of moderate hypofractionation as the standard of care for men with intermediate risk prostate cancer undergoing external beam radiotherapy.

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Take Home Message

Bowel, urinary and sexual symptoms were similar between schedules up to 5 years. Continued low incidence of moderate/high bowel and urinary bother confirm that moderate hypofractionated radiotherapy should be considered as a standard of care for men with intermediate risk prostate cancer.

References

[1] Cancer Research UK, https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer. Accessed April 2020

[2] Hamdy F, Donovan J, Lane J et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med. 2016. Oct 13;375(15):1415-1424

[3] Xu J, Dailey R, Eggly S, Neale A, Schwartz K. Men's perspectives on selecting their prostate cancer treatment. J Natl Med Assoc. 2011 Jun;103(6):468-78.

[4] Sonn G, Sadetsky N, Presti J, Litwin M. Differing perceptions of quality of life in patients with prostate cancer and their doctors. J Urol 189, 2013. S59-65; discussion S65.

[5] 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, 1988-92.

[6] Dearnaley D, Syndikus I, Mossop H 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. 2016;17(8):1047-60.

[7] Lee W, Dignam J, Amin M et al. Randomized Phase III Noninferiority Study Comparing Two Radiotherapy Fractionation Schedules in Patients With Low-Risk Prostate Cancer. J Clin Oncol. 2016 Jul 10;34(20):2325-32.

[8] Catton C, Lukka H, Gu C et al. Randomized Trial of a Hypofractionated Radiation Regimen for the Treatment of Localized Prostate Cancer. J Clin Oncol. 2017 Jun 10;35(17):1884-1890.

[9] http://www.auanet.org/guidelines/clinically-localized-prostate-cancer-new-(aua/astro/suo-guideline-2017) (date last accessed 22nd April 2020)

[10] http://uroweb.org/guideline/prostate-cancer/ (date last accessed 22nd April 2020)

[11] https://www.england.nhs.uk/publication/clinical-commissioning-policy-hypofractionated-external-beam-radiotherapy-in-the-treatment-of-localised-prostate-cancer-adults/ (date last accessed 22nd April 2020)

[12] Wilkins A, Mossop H, Syndikus I et al. Hypofractionated radiotherapy versus conventionally fractionated radiotherapy for patients with intermediate-risk localised prostate cancer: 2-year

patient-reported outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol. 2015: 16(16):1605-16

[13] Schmid MP, Pötter P, Bombosch V et al. Late gastrointestinal and urogenital side-effects after radiotherapy – Incidence and prevalence. Subgroup-analysis within the prospective Austrian–German phase II multicenter trial for localized prostate cancer. Radiotherapy and Oncology 2012; 104 (1): 114-18

[14] Houben J, McColl G, Kaanders JHAM et al. Patient reported toxicity and quality of life after hypofractionated high-dose intensity-modulated radiotherapy for intermediate- and high risk prostate cancer. Clinical and Translational Radiation Oncology 2021; 29: 40-6.

[15] Dearnaley D, Syndikus I, Sumo G et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: preliminary safety results from the CHHiP randomised controlled trial. Lancet Oncol. 2012;13(1):43-54

[16] Litwin M, Hays R, Fink A, Ganz P, Leake B, Brook R. The UCLA Prostate Cancer Index: development, reliability, and validity of a health-related quality of life measure. Med Care 36, 1002-12 (1998).

[17] Esper P, Mo F, Chodak G, Sinner M, Cella D, Pienta K. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. Urology 1997; 50: 920-8.

[18] 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; 56: 899-905.

[19] Ware J Jr, Kosinski M, Keller S. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996; 34: 220-33.

[20] Szymanski K, Wei J, Dunn R, Sanda M. Development and validation of an abbreviated version of the expanded prostate cancer index composite instrument for measuring health-related quality of life among prostate cancer survivors. Urology 2010; 76: 1245-50.

[21] Jayadevappa R, Malkowicz SB, Wittink M, Wein AJ, Chhatre S. Comparison of distribution- and anchor-based approaches to infer changes in health-related quality of life of prostate cancer survivors. Health Serv Res 2012; 47: 1902–25.

[22] Cella D, Nichol MB, Eton D, Nelson JB, Mulani P. Estimating clinically meaningful changes for the Functional Assessment of Cancer Therapy-Prostate: results from a clinical trial of patients with metastatic hormone-refractory prostate cancer. Value Health. 2009;12(1):124-9. doi: 10.1111/j.1524-4733.2008.00409.x.

[23] Williams, R. Generalized ordered logit/partial proportional odds models for ordinal dependent variables. Stata J 2006; 6: 58-82.

[24] https://medicine.umich.edu/sites/default/files/content/downloads/EPIC-Scoring-2.2002_0.pdf. (date last accessed 12th July 2021)

[25] https://eprovide.mapi-trust.org/instruments/ucla-prostate-cancer-index. (date last accessed 12th July 2021)

[26] Donovan J, Hamdy F, Lane J et al. Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. N Engl J Med. 2016 Oct 13;375(15):1425-1437.

[27] Murray J, Gulliford S, Griffin C et al. Evaluation of erectile potency and radiation dose to the penile bulb using image guided radiotherapy in the CHHiP trial. Clinical & Translational Radiation Oncology 2020; 21: 77-84.

[28] Wilkins A, Naismith O, Brand D et al. Derivation of dose/volume constraints for the anorectum from clinician and patient-reported outcomes in the CHHiP trial of radiotherapy fractionation. Int J Radiat Oncol Biol Phys. 2020 Jan 24. pii: S0360-3016(20)30056-0.

[29] Hoffman K, Penson D, Zhao Z et al. Patient-Reported Outcomes Through 5 Years for Active Surveillance, Surgery, Brachytherapy, or External Beam Radiation With or Without Androgen Deprivation Therapy for Localized Prostate Cancer JAMA. 2020;323(2):149-163.

[30] Bruner D, Pugh S, Lee W et al. Quality of Life in Patients With Low-Risk Prostate Cancer Treated With Hypofractionated vs Conventional Radiotherapy: A Phase 3 Randomized Clinical Trial. JAMA Oncol. 2019 May 1;5(5):664-670.

[31] Wortel R, Oomen-de Hoop E, Heemsbergen W, Pos F, Incrocci L. Moderate Hypofractionation in Intermediate- and High-Risk, Localized Prostate Cancer: Health-Related Quality of Life From the Randomized, Phase 3 HYPRO Trial. Int J Radiat Oncol Biol Phys. 2019 Mar 15;103(4):823-833

[32] Shaikh T, Li T, Handorf E et al. Long-term patient-reported outcomes from a phase 3 randomized prospective trial of conventional versus Hypofractionated radiation therapy for localized prostate Cancer. Int J Radiat Oncol Biol Phys. 2017;97(4):722–31.

[33] Widmark A, Gunnlaugsson A, Beckman L et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. Lancet. 2019 Aug 3;394(10196):385-395

[34] Fransson P, Nilsson P, Gunnlaugsson A, et al Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer (HYPO-RT-PC): patient-reported quality-of-life outcomes of a randomised, controlled, non-inferiority, phase 3 trial. Lancet Oncol. 2021 Feb;22(2):235-245

[35] RCR fractionation guidelines https://www.rcr.ac.uk/publication/radiotherapy-dose-fractionation-third-edition (date last accessed 22nd April 2020)

[36] Murray J, Griffin C, Gulliford S et al. A randomised assessment of image guided radiotherapy within a phase 3 trial of conventional or hypofractionated high dose intensity modulated radiotherapy for prostate cancer. Radiother Oncol. 2020 Jan;142: 62-71.

[37] Hamstra DA, Mariados N, Sylvester J et al. Continued Benefit to Rectal Separation for Prostate Radiation Therapy: Final Results of a Phase III Trial. Int J Radiat Oncol Biol Phys. 2017 Apr 1;97(5):976-985.

[38] Stephens R, Dearnaley D, Cowan R, Sydes M, Naylor S, Fallowfield L on behalf of all the RT01 collaborators. The quality of life of men with locally advanced prostate cancer during neoadjuvant hormone therapy: data from the Medical Research Council RT01 trial (ISRCTN 47772397) BJU International 2006, 99, 301–310.

Figure legends

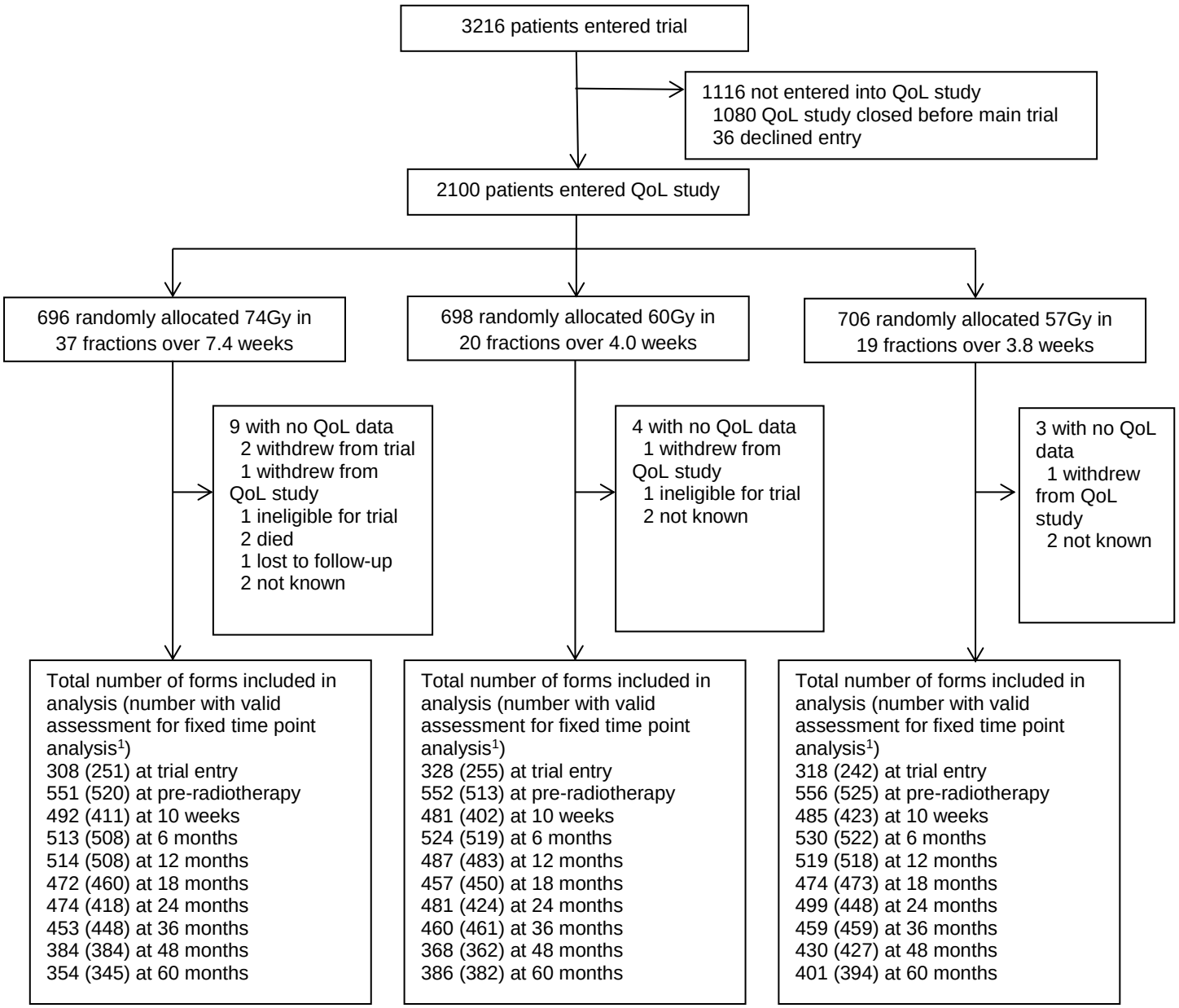
Figure 1: CONSORT diagram

Figure 2: Overall bowel, urinary and sexual bother. Data are prevalence of overall bowel bother (A), change from pre-radiotherapy to 5 years for overall bowel bother (B), prevalence of overall urinary bother (C), change from pre-radiotherapy to 5 years for overall urinary bother (D), prevalence of overall sexual bother (E), and change from pre-radiotherapy to 5 years for overall sexual bother (F). A negative change in bother score from baseline/pre-RT to 5 years indicates an improvement in QoL; positive change in bother score represents worsening QoL. Odds ratios<1 favour the hypofractionated schedules, indicating lower odds of an increase in bother score compared with the 74 Gy group.

Figure 3: Change in bowel, urinary and sexual domain scores from baseline up to 5 years; (a) Bowel function (UCLA-PCI), (b) Bowel summary (EPIC), (c) Urinary function (UCLA-PCI), (d) Urinary summary (EPIC), (e) Sexual function (UCLA-PCI), (f) Sexual summary (EPIC). Data shown are mean and 99%CI. Change in domain score calculated as post-radiotherapy score minus baseline score; a negative change from baseline to 5 years indicates worsening QoL.

Figure 4: Change in general HRQoL domain scores from baseline up to 5 years; (a) FACT-P total score, (b) General health (SF-36), (c) Physical functioning (SF-36), (d) Role limitations, physical (SF-36), (e) Mental health (SF-36), (f) Role limitations, emotional (SF-36). Data shown are mean and 99%CI. Change in domain score calculated as post-radiotherapy score minus baseline score; a negative change from baseline to 5 years indicates worsening QoL.

Figure 1: CONSORT diagram

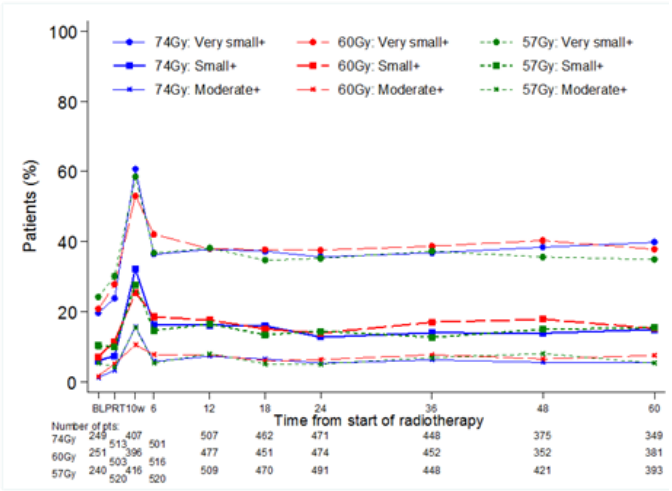


[1] Patients were excluded from the fixed time-point analyses if their QoL assessments were dated outside pre-specified acceptable time intervals: after 1 month of endocrine therapy or after randomisation for baseline; before 3 months or after 1 week of starting radiotherapy for pre-radiotherapy; outside 2 weeks from the expected date of completion for 10 weeks; outside 3 months from expected date of completion for 6-24 months; outside 6 months for 36-60 months.

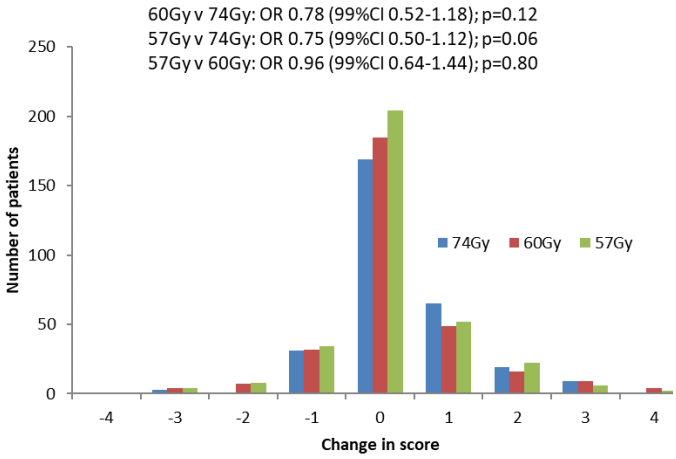
Figure 2: Overall bowel, urinary and sexual bother

Overall bowel bother

A

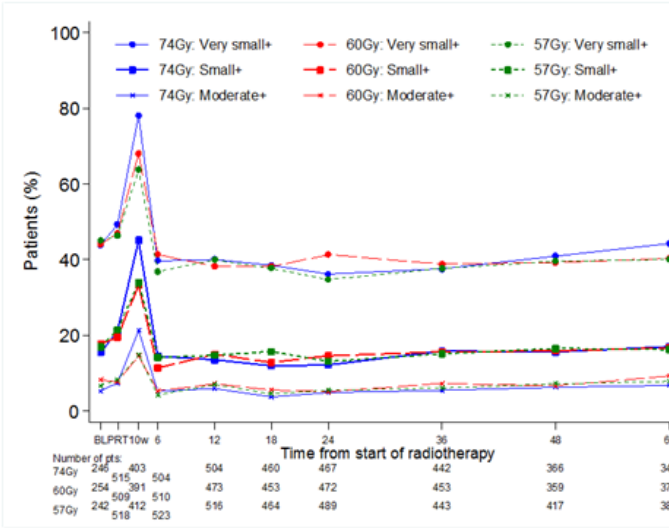


B

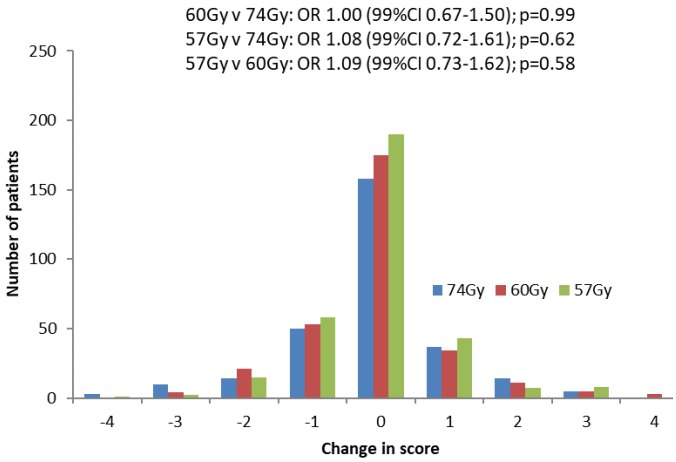


Overall urinary bother

C

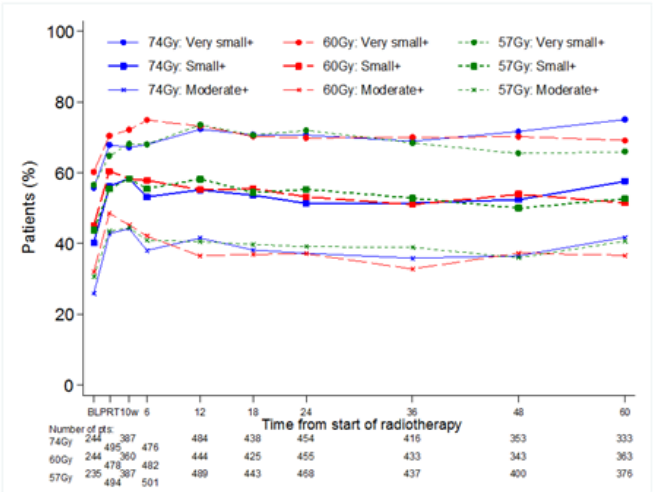


D



Overall sexual bother

E



F

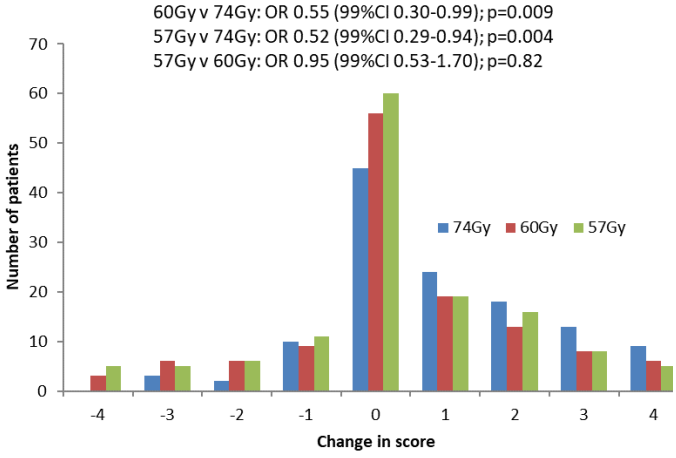
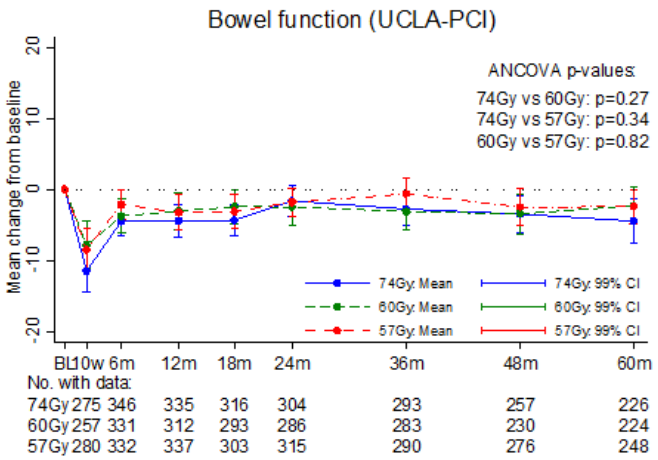
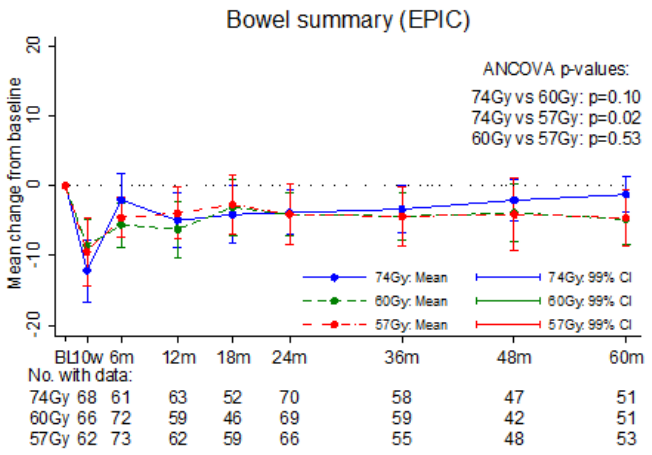


Figure 3: Change in bowel, urinary and sexual domain scores from baseline up to 5 years

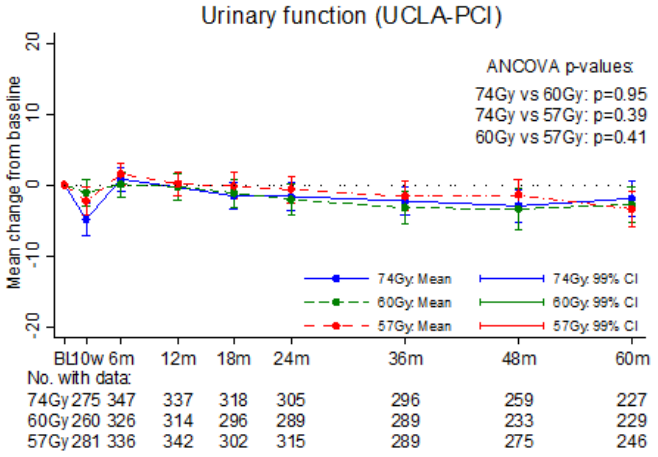
A Bowel function (UCLA-PCI)



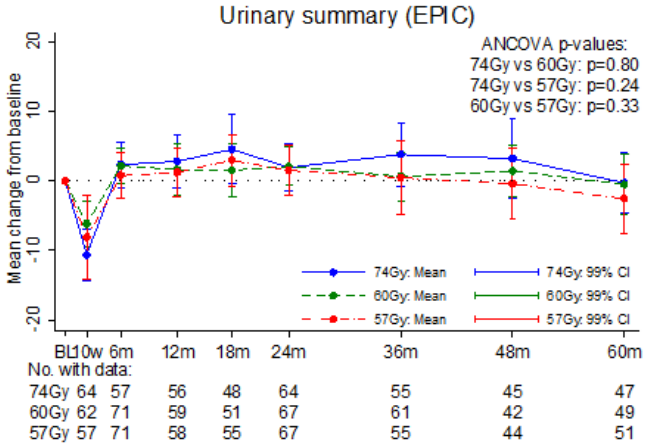
B Bowel summary (EPIC)



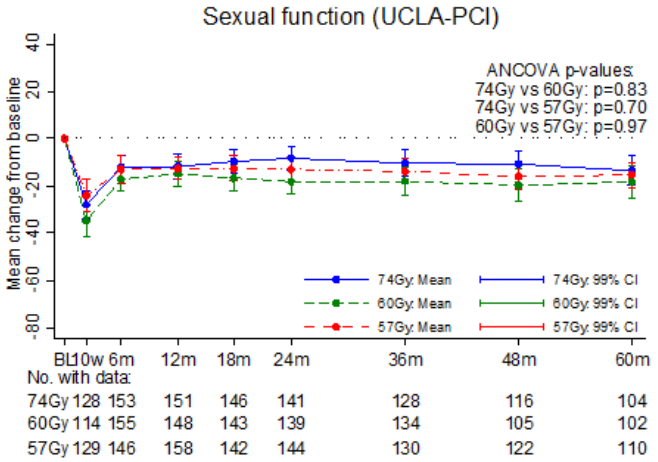
C Urinary function (UCLA-PCI)



D Urinary summary (EPIC)



E Sexual function (UCLA-PCI)



F Sexual summary (EPIC)

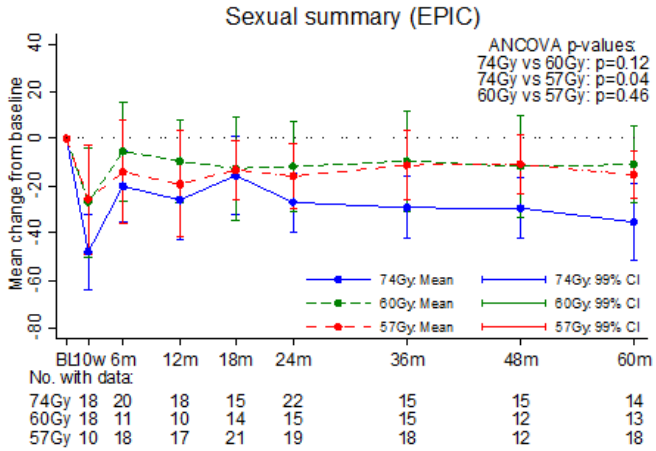
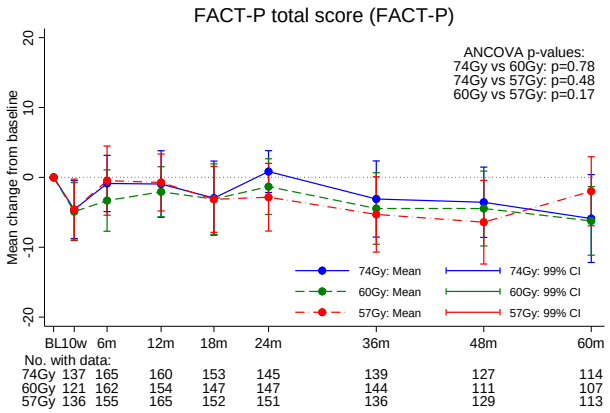
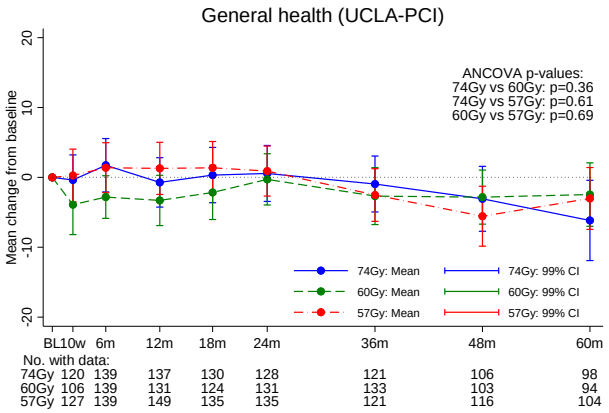


Figure 4: Change in general HRQoL domain scores from baseline up to 5 years

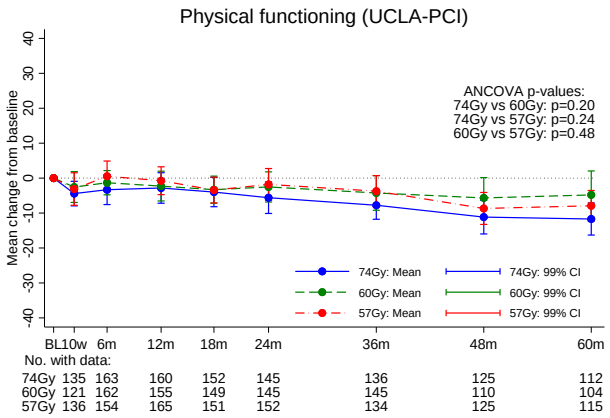
A FACT-P total score



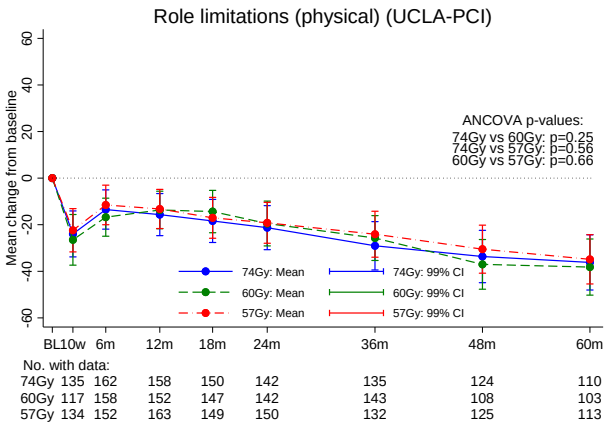
B General health (SF-36)



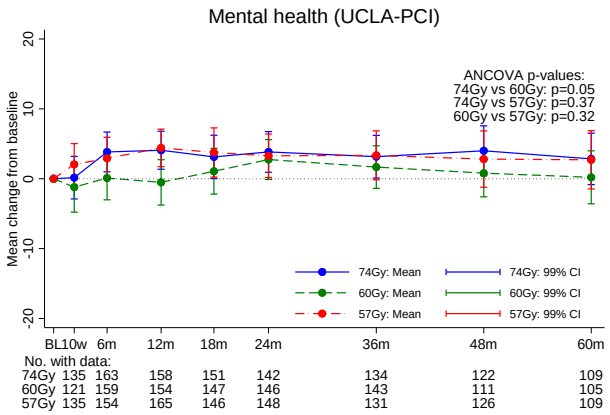
C Physical functioning (SF-36)



D Role limitations, physical (SF-36)



E Mental health (SF-36)



F Role limitations, emotional (SF-36)

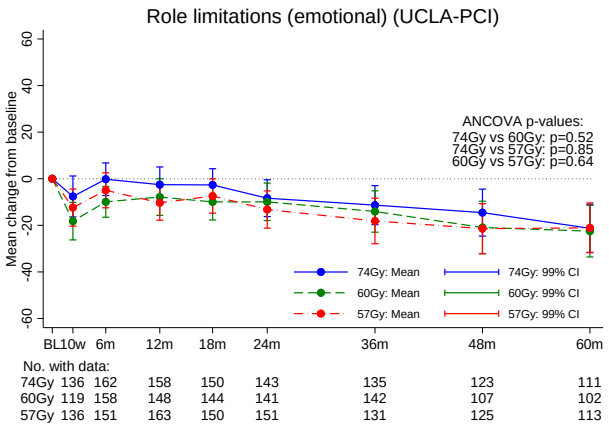


Table 1: Individual bowel symptoms at 5 years for UCLA-PCI and EPIC QoL instruments

Bowel symptoms	**5 years**			**60Gy vs. 74Gy**	**57Gy vs. 74Gy**	**60Gy vs 57Gy**
	74Gy/37f N (%)	**60Gy/20f N (%)**	**57Gy/19f N (%)**	**p-value[1]**	**p-value[1]**	**p-value[1]**
Overall bowel bother (problem); UCLA-PCI & EPIC	N=349	N=381	N=393	0.81	0.69	0.52
None	210 (60.2)	237 (62.2)	256 (65.1)			
V small	87 (24.9)	86 (22.6)	76 (19.3)			
Small	33 (9.5)	29 (7.6)	40 (10.2)			
Moderate	16 (4.6)	21 (5.5)	11 (2.8)			
Big	3 (0.9)	8 (2.1)	10 (2.5)			
Rectal urgency (problem); UCLA-PCI & EPIC	N=341	N=375	N=383	0.56	0.70	0.83
None	246 (72.1)	293 (78.1)	286 (74.7)			
V small	51 (15.0)	28 (7.5)	49 (12.8)			
Small	14 (4.1)	19 (5.1)	15 (3.9)			
Moderate	20 (5.9)	26 (6.9)	21 (5.5)			
Big	10 (2.9)	9 (2.4)	12 (3.1)			
Faecal incontinence (problem); EPIC	N=82	N=96	N=90	0.30	0.86	0.33
	75 (91.5)	83 (86.5)	79 (87.8)			
None	5 (6.1)	9 (9.4)	10 (11.1)			
V small	1 (1.2)	2 (2.1)	1 (1.1)			
Small	1 (1.2)	1 (1.0)	0 (0)			
Moderate	0 (0)	1 (1.0)	0 (0)			
Big						
Rectal bleeding (problem); EPIC	N=82	N=96	N=90	0.22	0.70	0.44
None	73 (89.0)	80 (83.3)	81 (90.0)			
V small	8 (9.8)	13 (13.5)	7 (7.8)			
Small	0 (0)	0 (0)	0 (0)			
Moderate	1 (1.2)	2 (2.1)	0 (0)			
Big	0 (0)	1 (1.0)	2 (2.2)			
Loose or liquid stools (problem); UCLA-PCI & EPIC	N=340	N=377	N=382	0.67	0.30	0.54
None	150 (44.1)	157 (41.6)	145 (38.0)			
V small	135 (39.7)	158 (41.9)	174 (45.5)			
Small	38 (11.2)	42 (11.1)	42 (11.0)			
Moderate	11 (3.2)	14 (3.7)	15 (3.9)			
Big	6 (1.8)	6 (1.6)	6 (1.6)			
Frequency of bowel movements/day; EPIC	N=83	N=96	N=94	0.76	0.50	0.31
<3	72 (86.7)	82 (85.4)	84 (89.4)			
3-4	9 (10.8)	11 (11.5)	9 (9.6)			
5+	2 (2.4)	3 (3.1)	1 (1.1)			
Crampy pain in abdomen/pelvis (problem); UCLA-PCI & EPIC	N=345	N=380	N=393	0.85	0.79	0.64
None	302 (87.5)	331 (87.1)	341 (86.8)			
V small	23 (6.7)	25 (6.6)	28 (7.1)			
Small	9 (2.6)	12 (3.2)	16 (4.1)			
Moderate	5 (1.4)	5 (1.3)	6 (1.5)			
Big	6 (1.7)	7 (1.8)	2 (0.5)			
Bowel distress; UCLA-PCI	N=258	N=281	N=294	0.74	0.93	0.80
None	189 (73.3)	206 (73.3)	215 (73.1)			
Small	53 (20.5)	60 (21.4)	61 (20.7)			
Moderate	12 (4.7)	13 (4.6)	15 (5.1)			
Severe	4 (1.6)	2 (0.7)	3 (1.0)			

[1]p-value from χ^2 trend test

Table 2: Individual urinary and sexual symptoms at 5 years for UCLA-PCI and EPIC QoL instruments

Endpoints	5 years			60Gy vs. 74Gy	57Gy vs. 74Gy	60Gy vs 57Gy
	74Gy/37f N (%)	60Gy/20f N (%)	57Gy/19f N (%)	p-value[1]	p-value[1]	p-value[1]
Urinary symptoms						
Overall urinary bother (problem); UCLA-PCI & EPIC	N=341	N=377	N=382	0.99	0.68	0.68
None	190 (55.7)	225 (59.7)	229 (59.9)			
V small	93 (27.3)	89 (23.6)	91 (23.8)			
Small	35 (10.3)	28 (7.4)	32 (8.4)			
Moderate	20 (5.9)	25 (6.6)	23 (6.0)			
Big	3 (0.9)	10 (2.7)	7 (1.8)			
Urinary control; UCLA-PCI & EPIC	N=343	N=378	N=388	0.27	0.58	0.59
Total control;	199 (58.0)	243 (64.3)	243 (62.6)			
Occasional dribbling;	134 (39.1)	122 (32.3)	127 (32.7)			
Frequent dribbling;	10 (2.9)	9 (2.4)	16 (4.1)			
No control	0 (0)	4 (1.1)	2 (0.5)			
Use of urinary pads/day; UCLA-PCI & EPIC	N=339	N=374	N=380	>0.99	0.74	0.73
None	245 (72.3)	266 (71.1)	279 (73.4)			
1-2	93 (27.4)	106 (28.3)	99 (26.1)			
3+	1 (0.3)	2 (0.5)	2 (0.5)			
Haematuria (problem); EPIC	N=83	N=97	N=96	0.68	0.22	0.23
None	82 (98.8)	95 (97.9)	92 (95.8)			
V small	0 (0)	1 (1.0)	1 (1.0)			
Small	1 (1.2)	0 (0)	1 (1.0)			
Moderate	0 (0)	1 (1.0)	1 (1.0)			
Big	0 (0)	0 (0)	1 (1.0)			
Dysuria (problem); EPIC	N=83	N=97	N=96	0.16	0.05	0.48
None	81 (97.6)	92 (94.8)	88 (91.7)			
V small	2 (2.4)	2 (2.1)	4 (4.2)			
Small	0 (0)	1 (1.0)	0 (0)			
Moderate	0 (0)	1 (1.0)	3 (3.1)			
Big	0 (0)	1 (1.0)	1 (1.0)			
Sexual symptoms						
Overall sexual bother (problem); UCLA-PCI & EPIC	N=333	N=363	N=376	0.05	0.15	0.64
None	83 (24.9)	112 (30.9)	128 (34.0)			
V small	58 (17.4)	64 (17.6)	50 (13.3)			
Small	53 (15.9)	54 (14.9)	45 (12.0)			
Moderate	45 (13.5)	51 (14.0)	55 (14.6)			
Big	94 (28.2)	82 (22.6)	98 (26.1)			
Erection quality (problem); UCLA-PCI & EPIC	N=333	N=363	N=379	0.19	0.18	0.98
None	60 (18.0)	85 (23.4)	82 (21.6)			
Small	77 (23.1)	79 (21.8)	89 (23.5)			
Moderate	80 (24.0)	80 (22.0)	90 (23.7)			
Severe	116 (34.8)	119 (32.8)	118 (31.1)			
Erection frequency (problem); UCLA-PCI & EPIC	N=332	N=363	N=376	0.06	0.08	0.87
None	29 (8.7)	41 (11.3)	40 (10.6)			
V small	30 (9.0)	40 (11.0)	53 (14.1)			
Small	38 (11.4)	55 (15.2)	37 (9.8)			
Moderate	51 (15.4)	44 (12.1)	54 (14.4)			
Big	184 (55.4)	183 (50.4)	192 (51.1)			
Woken with erection morning/night (problem); UCLA-PCI	N=259	N=279	N=294	0.02	0.04	0.66
None	1 (0.4)	11 (3.9)	4 (1.4)			
V small	14 (5.4)	25 (9.0)	24 (8.2)			
Small	33 (12.7)	36 (12.9)	38 (12.9)			
Moderate	73 (28.2)	66 (23.7)	95 (32.3)			
Big	138 (53.3)	141 (50.5)	133 (45.2)			

[1]p-value from χ^2 trend test

Supplementary web appendix

Table A1: Baseline characteristics of patients with and without 5-year questionnaire data

Characteristic	5-year questionnaire data available		p-value[1]
	Yes (%) N=1141	No (%) N=959	
Age in years; median (IQR)	68.4 (63.9, 72.4)	68.7 (63.9, 73.2)	0.370[2]
T-stage			<0.001[3]
T1a/b/c/x	457 (40.0)	313 (32.6)	
T2a/b/c/x	591 (51.8)	543 (56.6)	
T3a/b/x	93 (8.1)	101 (10.5)	
Unknown	0	2 (0.2)	
Gleason score			0.083[3]
≤6	424 (37.2)	324 (33.8)	
7	682 (59.8)	599 (62.5)	
8	35 (3.1)	36 (3.7)	
PSA			0.868[3]
0-4.99	77 (6.7)	69 (7.2)	
5-9.99	444 (38.9)	363 (37.8)	
10-19.99	529 (46.4)	457 (47.6)	
≥20	90 (7.9)	69 (7.2)	
Unknown	1 (0.1)	1 (0.1)	
Median (IQR)	*10.6 (7.3, 15)*	*10.6 (7.4, 14.9)*	0.829[2]
NCCN risk group			0.003[3]
Low	199 (17.4)	134 (14.0)	
Intermediate	825 (72.3)	694 (72.4)	
High	117 (10.2)	131 (13.7)	
Diabetes			0.028[4]
Yes	1026 (89.9)	837 (87.3)	
No	105 (9.2)	117 (12.2)	
Unknown	10 (0.9)	5 (0.5)	
Hypertension			0.792[4]
Yes	683 (59.9)	580 (60.5)	
No	451 (39.5)	374 (39.0)	
Unknown	7 (0.6)	5 (0.5)	
Inflammatory bowel or diverticular disease			0.973[4]
Yes	1093 (95.8)	918 (95.7)	
No	42 (3.7)	35 (3.6)	
Unknown	6 (0.5)	6 (0.6)	
Previous pelvic surgery			0.600[4]
Yes	1042 (91.3)	884 (92.2)	
No	90 (7.9)	70 (7.3)	
Unknown	9 (0.8)	5 (0.5)	
Symptomatic haemorrhoids in past year			0.903[4]
Yes	1034 (90.6)	869 (90.6)	
No	79 (6.9)	65 (6.8)	
Unknown	28 (2.4)	25 (2.6)	
Any previous TURP			0.309[4]
Yes	1013 (88.8)	869 (90.6)	
No	104 (9.1)	76 (7.9)	
Unknown	24 (2.1)	14 (1.5)	

[1] Unknown categories excluded from significance tests; [2] Wilcoxon rank-sum test; [3] Chi-squared test for trend; [4] Chi-squared test

Table A2: Bowel, urinary and sexual domain scores at 5 years for UCLA-PCI and EPIC[1] QoL instruments

Domain score	5 years			60Gy vs. 74Gy	57Gy vs. 74Gy	60Gy vs 57Gy
N Median (IQR)	74Gy/37f	60Gy/20f	57Gy/19f	p-value[2]	p-value[2]	p-value[2]
Bowel						
Bowel function; UCLA-PCI	N=258 93.7 (79.2-100)	N=282 93.7 (79.2-100)	N=294 93.7 (79.2-100)	0.721	0.750	0.964
Bowel bother; UCLA-PCI	N=267 100 (75.0-100)	N=285 100 (75.0-100)	N=300 100 (75.0-100)	0.205	0.264	0.339
Bowel function; EPIC	N=80 92.9 (87.5-98.2)	N=95 96.4 (89.3-100)	N=88 96.4 (85.7-100)	0.364	0.951	0.337
Bowel bother; EPIC	N=81 95.8 (87.5-100)	N=90 95.8 (83.3-100)	N=90 95.4 (83.3-100)	0.972	0.422	0.407
Bowel summary; EPIC	N=80 93.2 (88.5-98.1)	N=89 94.2 (86.5-100)	N=85 92.3 (84.6-98.1)	0.777	0.559	0.433
Urinary						
Urinary function; UCLA-PCI	N=258 100 (78.0-100)	N=283 100 (78.0-100)	N=293 100 (78.0-100)	0.791	0.865	0.973
Urinary bother; UCLA-PCI	N=258 100 (75.0-100)	N=283 100 (75.0-100)	N=293 100 (75.0-100)	0.748	0.487	0.721
Urinary function; EPIC	N=83 100 (88.4-100)	N=97 100 (91.7-100)	N=96 100 (88.4-100)	0.310	0.831	0.392
Urinary bother; EPIC	N=76 85.7 (75.0-92.9)	N=89 89.3 (78.6-96.4)	N=84 89.3 (73.2-92.9)	0.145	0.628	0.328
Urinary incontinence; EPIC	N=76 100 (81.2-100)	N=89 100 (85.5-100)	N=84 100 (79.2-100)	0.238	0.641	0.496
Urinary irritative/ obstructive; EPIC	N=75 89.3 (82.1-92.9)	N=88 92.9 (82.1-96.4)	N=84 89.3 (78.6-94.6)	0.177	0.939	0.189
Urinary summary; EPIC	N=76 91.0 (80.6-95.8)	N=88 92.4 (82.3-97.9)	N=84 91.7 (81.2-95.8)	0.143	0.602	0.351
Sexual						
Sexual function; UCLA-PCI	N=258 16.6 (3.1-43.7)	N=273 22.9 (3.1-53.1)	N=290 19.7 (4.1-46.9)	0.071	0.188	0.558
Sexual bother; UCLA-PCI	N=257 50.0 (0-75.0)	N=272 50.0 (12.5-100)	N=286 50.0 (0-100)	0.019	0.048	0.754
Sexual function; EPIC	N=78 10.0 (0-43.4)	N=94 18.4 (0-48.4)	N=92 26.6 (0-59.2)	0.399	0.162	0.465
Sexual bother; EPIC	N=76 75.0 (37.5-100)	N=92 50.0 (25.0-100)	N=91 50.0 (25.0-100)	0.657	0.719	0.985
Sexual summary; EPIC	N=75 18.0 (12.5-48.7)	N=92 24.3 (16.7-48.7	N=90 30.5 (16.7-62.5)	0.604	0.250	0.368

All scores range from 0-100, with higher scores representing better quality of life; IQR = interquartile range; [1] EPIC-50 used for bowel and urinary domains and EPIC-26 for sexual domains; [2] Mann-Whitney test

Table A3: Decline in bowel, urinary and sexual domain scores from baseline to 5 years according to recommended cut-offs for minimal important difference (MID)

Domain score	MID[1]	Number of patients with decline in domain score ≥MID from baseline to 5 years / total (%)		
		74Gy/37f	60Gy/20f	57Gy/19f
Bowel function; UCLA-PCI	7	70/226 (31.0)	60/224 (26.8)	60/248 (24.2)
Bowel summary; EPIC	15	3/51 (5.9)	8/51 (15.7)	12/53 (22.6)
Urinary function; UCLA-PCI	8	56/227 (24.7)	58/229 (25.3)	67/246 (27.2)
Urinary summary; EPIC	17	5/47 (10.6)	3/49 (6.1)	6/51 (11.8)
Sexual function; UCLA-PCI	8	56/104 (53.8)	69/102 (67.6)	65/110 (59.1)
Sexual summary; EPIC	19	9/14 (64.3)	5/13 (38.5)	8/18 (44.4)

[1] Published in Jayadeppa et al 2012

Table A4: Survival analysis of bowel problems up to 5 years

Bowel endpoints	Schedule	Small or worse events				Moderate or worse events			
		Emergent events up to 5 years / N	Estimate of 5-year cumulative incidence[1], % (99%CI)	HR (99%CI), p-value for comparison with 74Gy	HR (99%CI), p-value for 60Gy vs 57Gy	Emergent events up to 5 years / N	Estimate of 5-year cumulative incidence[1], % (99%CI)	HR (99%CI), p-value for comparison with 74Gy	HR (99%CI), p-value for 60Gy vs 57Gy
Overall bowel bother (UCLA-PCI & EPIC)	**74Gy** **60Gy** **57Gy**	177/601 185/590 162/593	39.2 (31.1-48.7) 39.5 (32.4-47.5) 35.4 (28.1-44.0)	1 1.06 (0.81-1.39), p=0.546 0.87 (0.66-1.15), p=0.200	1.22 (0.93-1.61), p=0.062	99/631 102/630 91/633	20.7 (15.2-28.0) 19.6 (15.1-25.4) 18.3 (13.0-25.3)	1 1.02 (0.71-1.47), p=0.888 0.88 (0.60-1.27), p=0.365	1.17 (0.80-1.69), p=0.281
Rectal urgency (UCLA-PCI & EPIC)	**74Gy** **60Gy** **57Gy**	175/566 192/578 165/563	37.3 (30.3-45.3) 41.3 (34.1-49.4) 34.7 (28.6-41.7)	1 1.08 (0.82-1.41), p=0.490 0.91 (0.69-1.20), p=0.395	1.19 (0.90-1.56), p=0.104	140/590 144/596 125/594	30.9 (24.1-39.1) 31.2 (24.1-39.8) 25.1 (19.9-31.2)	1 1.01 (0.74-1.37), p=0.963 0.85 (0.62-1.17), p=0.202	1.19 (0.87-1.62), p=0.162
Faecal incontinence (EPIC)	**74Gy** **60Gy** **57Gy**	14/206 26/210 25/224	9.7 (4.3-21.0) 14.6 (8.9-23.6) 13.3 (8.1-21.4)	1 1.88 (0.80-4.41), p=0.053 1.70 (0.72-4.03), p=0.107	1.10 (0.53-2.25), p=0.743	3/208 17/210 13/225	1.8 (0.4-8.0) 9.3 (5.0-16.7) 6.7 (3.3-13.2)	1 5.75 (1.15-28.88), p=0.002 4.17 (0.80-21.70), p=0.015	1.38 (0.53-3.56), p=0.381
Rectal bleeding (EPIC)	**74Gy** **60Gy** **57Gy**	9/206 19/211 14/224	5.0 (2.1-11.4) 10.0 (5.6-17.5) 9.0 (3.8-20.4)	1 2.13 (0.75-6.03), p=0.055 1.46 (0.49-4.38), p=0.390	1.47 (0.59-3.63), p=0.274	3/208 9/211 6/226	2.2 (0.4-10.8) 4.8 (2.0-11.1) 4.6 (1.1-17.9)	1 3.00 (0.54-16.74), p=0.082 1.83 (0.29-11.30), p=0.409	1.64 (0.42-6.37), p=0.346
Loose or liquid stools (UCLA-PCI & EPIC)	**74Gy** **60Gy** **57Gy**	173/558 177/569 181/565	39.4 (32.0-47.9) 38.2 (31.0-46.4) 38.1 (31.6-45.4)	1 1.00 (0.76-1.32), p=0.994 1.02 (0.78-1.34), p=0.848	0.98 (0.74-1.28), p=0.831	71/622 87/633 81/632	16.0 (11.1-22.7) 16.7 (11.7-23.6) 16.0 (11.4-22.2)	1 1.22 (0.80-1.84), p=0.229 1.10 (0.72-1.68), p=0.563	1.10 (0.74-1.64), p=0.523
Bowel frequency[2] (EPIC)	**74Gy** **60Gy** **57Gy**	33/199 47/204 52/218	19.2 (12.5-28.8) 29.5 (19.2-43.6) 28.6 (20.4-39.2)	1 1.41 (0.79-2.53), p=0.130 1.46 (0.82-2.59), p=0.086	0.97 (0.58-1.63), p=0.880	5/209 9/213 5/227	3.1 (0.9-10.4) 7.8 (2.4-23.7) 2.6 (0.8-8.2)	1 1.76 (0.42-7.40), p=0.307 0.88 (0.17-4.50), p=0.864	1.99 (0.47-8.39), p=0.208
Crampy pain in abdomen/ pelvis (UCLA-PCI & EPIC)	**74Gy** **60Gy** **57Gy**	91/620 88/602 108/615	19.4 (13.3-27.9) 16.8 (12.8-22.0) 20.9 (16.1-26.9)	1 0.99 (0.67-1.45), p=0.928 1.19 (0.82-1.71), p=0.229	0.83 (0.57-1.20), p=0.199	47/636 55/626 59/640	10.1 (6.5-15.6) 10.0 (7.0-14.1) 12.1 (8.1-17.9)	1 1.19 (0.71-1.98), p=0.384 1.23 (0.74-2.03), p=0.309	0.97 (0.60-1.57), p=0.861
Bowel distress (UCLA-PCI)	**74Gy** **60Gy** **57Gy**	186/416 187/402 163/404	52.5 (43.4-62.3) 53.2 (44.5-62.4) 47.8 (39.4-57.0)	1 1.05 (0.80-1.36), p=0.667 0.84 (0.64-1.11), p=0.107	1.24 (0.94-1.63), p=0.044	80/503 78/492 61/502	19.4 (14.5-25.6) 18.7 (13.9-24.7) 15.3 (10.7-21.7)	1 0.96 (0.63-1.44), p=0.787 0.70 (0.45-1.09), p=0.041	1.36 (0.88-2.12), p=0.069

[1] Estimated at 5 years and 3 months, to allow for late visits; [2] Frequency of bowel movements: “small or worse” defined as 3+ per day, and “moderate or worse” 5+ per day.

Table A5: Survival analysis of urinary and sexual problems up to 5 years

Endpoints	Schedule	Small or worse events				Moderate or worse events			
		Emergent events up to 5 years / N	Estimate of 5-year cumulative incidence[1], % (99%CI)	HR (99%CI), p-value for comparison with 74Gy	HR (99%CI), p-value for 60Gy vs 57Gy	Emergent events up to 5 years / N	Estimate of 5-year cumulative incidence[1], % (99%CI)	HR (99%CI), p-value for comparison with 74Gy	HR (99%CI), p-value for 60Gy vs 57Gy
Urinary endpoints									
Overall urinary bother (UCLA-PCI & EPIC)	**74Gy** **60Gy** **57Gy**	126/512 132/525 108/519	32.8 (25.3-41.7) 32.6 (25.2-41.5) 27.3 (20.6-35.6)	1 0.99 (0.72-1.37), p=0.953 0.80 (0.57-1.12), p=0.085	1.24 (0.89-1.74), p=0.092	78/602 78/599 72/607	16.4 (12.2-21.9) 18.2 (12.8-25.4) 18.2 (12.3-26.6)	1 0.99 (0.65-1.49), p=0.917 0.87 (0.57-1.33), p=0.408	1.13 (0.74-1.73), p=0.441
Loss of urinary control (UCLA-PCI & EPIC)	**74Gy** **60Gy** **57Gy**	184/438 195/462 171/451	52.4 (42.7-62.9) 48.8 (41.8-56.4) 46.3 (38.2-55.2)	1 0.97 (0.75-1.27), p=0.785 0.84 (0.64-1.11), p=0.109	1.15 (0.88-1.51), p=0.177	44/644 66/638 44/644	9.1 (5.7-14.4) 14.4 (9.6-21.2) 10.0 (6.1-16.1)	1 1.50 (0.91-2.47), p=0.035 0.95 (0.55-1.65), p=0.806	1.58 (0.96-2.61), p=0.017
Use of urinary pads[2] (UCLA-PCI & EPIC)	**74Gy** **60Gy** **57Gy**	39/637 44/642 34/651	10.3 (5.6-18.5) 9.2 (5.5-15.1) 9.1 (5.0-16.2)	1 1.08 (0.61-1.90), p=0.704 0.80 (0.43-1.46), p=0.323	1.36 (0.75-2.44), p=0.179	5/650 11/652 8/660	1.3 (0.3-4.9) 2.7 (1.1-6.4) 1.5 (0.6-3.7)	1 2.13 (0.53-8.56), p=0.152 1.50 (0.34-6.52), p=0.465	1.42 (0.43-4.69), p=0.451
Haematuria (EPIC)	**74Gy** **60Gy** **57Gy**	5/206 8/212 7/227	4.6 (1.3-15.7) 3.7 (1.4-9.6) 6.4 (1.8-21.2)	1 1.49 (0.34-6.48), p=0.504 1.17 (0.26-5.32), p=0.789	1.26 (0.33-4.77), p=0.657	3/207 7/212 5/228	2.0 (0.5-8.7) 3.2 (1.1-9.0) 2.4 (0.6-8.9)	1 2.10 (0.35-12.50), p=0.263 1.35 (0.20-8.94), p=0.712	1.55 (0.34-7.03), p=0.449
Dysuria (EPIC)	**74Gy** **60Gy** **57Gy**	13/201 26/210 20/221	7.3 (3.6-14.5) 13.0 (7.9-20.9) 11.1 (6.3-19.3)	1 1.95 (0.81-4.69), p=0.048 1.42 (0.57-3.56), p=0.308	1.37 (0.64-2.96), p=0.283	10/203 17/210 16/223	5.4 (2.4-11.8) 8.5 (4.5-15.7) 9.8 (4.9-19.1)	1 1.64 (0.59-4.58), p=0.225 1.46 (0.52-4.13), p=0.330	1.12 (0.46-2.75), p=0.739
Sexual endpoints									
Overall sexual bother (UCLA-PCI & EPIC)	**74Gy** **60Gy** **57Gy**	188/316 196/312 197/320	73.3 (60.3-84.8) 67.3 (59.1-75.2) 71.0 (61.1-80.3)	1 1.08 (0.83-1.40), p=0.450 1.03 (0.80-1.35), p=0.741	1.05 (0.81-1.36), p=0.653	184/395 179/379 187/387	58.1 (46.9-69.7) 52.0 (44.0-60.5) 56.2 (47.0-65.9)	1 0.98 (0.74-1.28), p=0.830 1.02 (0.78-1.33), p=0.906	0.96 (0.73-1.26), p=0.700
Problem with erection quality (UCLA-PCI & EPIC)	**74Gy** **60Gy** **57Gy**	136/189 162/206 141/194	85.5 (73.2-94.2) 85.4 (75.5-92.8) 79.1 (69.1-87.6)	1 1.14 (0.84-1.54), p=0.249 1.04 (0.76-1.42), p=0.729	1.09 (0.81-1.47), p=0.451	123/236 141/259 144/257	63.1 (51.4-74.8) 63.5 (52.0-74.9) 62.8 (53.5-72.0)	1 0.99 (0.72-1.36), p=0.935 1.05 (0.77-1.45), p=0.672	0.94 (0.69-1.27), p=0.602

Endpoints	Schedule	Small or worse events				Moderate or worse events			
		Emergent events up to 5 years / N	Estimate of 5-year cumulative incidence[1], % (99%CI)	HR (99%CI), p-value for comparison with 74Gy	HR (99%CI), p-value for 60Gy vs 57Gy	Emergent events up to 5 years / N	Estimate of 5-year cumulative incidence[1], % (99%CI)	HR (99%CI), p-value for comparison with 74Gy	HR (99%CI), p-value for 60Gy vs 57Gy
Problem with erection frequency (UCLA-PCI & EPIC)	**74Gy** **60Gy** **57Gy**	140/187 146/195 134/183	85.1 (74.2-93.1) 81.9 (71.8-90.0) 79.8 (69.5-88.3)	1 0.93 (0.68-1.26), p=0.484 1.01 (0.74-1.38), p=0.916	0.92 (0.67-1.25), p=0.470	133/212 150/239 139/229	78.2 (65.6-88.7) 68.5 (58.7-77.9) 68.5 (58.1-78.4)	1 0.95 (0.70-1.29), p=0.660 0.95 (0.70-1.30), p=0.669	1.00 (0.74-1.35), p=0.999
Problem with erection on waking morning/ night (UCLA-PCI)	**74Gy** **60Gy** **57Gy**	83/90 96/100 93/99	N/A 96.7 (87.9-99.6) 95.8 (88.2-99.1)	1 0.93 (0.63-1.37), p=0.600 1.06 (0.72-1.56), p=0.680	0.88 (0.60-1.28), p=0.371	91/112 100/129 110/138	N/A 80.0 (68.0-89.7) 87.6 (75.1-95.6)	1 0.75 (0.51-1.10), p=0.046 0.95 (0.66-1.36), p=0.649	0.80 (0.56-1.15), p=0.113

[1] Estimated at 5 years and 3 months, to allow for late visits; [2] Use of pads: “small or worse” defined as 1+ per day, and “moderate or worse” 3+ per day; N/A = not available (only 1 patient at risk at 5 years and 3 months)

Table A6: General QoL domain scores at 5 years for SF-12, FACT-P and SF-36 QoL instruments

Domain score	5 years			60Gy vs. 74Gy	57Gy vs. 74Gy	60Gy vs 57Gy
N Median (IQR)	74Gy/37f	60Gy/20f	57Gy/19f	p-value[1]	p-value[1]	p-value[1]
SF-12[2]						
Mental health composite	N=79 83.3 (70.8-91.7)	N=94 83.3 (66.7-91.7)	N=95 79.2 (62.5-91.7)	0.916	0.264	0.214
Physical health composite	N=83 79.2 (54.2-91.7)	N=97 79.2 (58.3-91.7)	N=96 75.0 (50.0-91.7)	0.689	0.846	0.503
FACT-P						
Physical wellbeing[3]	N=265 26 (23-27)	N=280 26 (23-27)	N=297 26 (23-27)	0.807	0.925	0.921
Social/family wellbeing[3]	N=263 24 (20-25.7)	N=281 23.3 (19-26)	N=297 24 (20-26)	0.827	0.869	0.912
Emotional wellbeing[4]	N=264 22.8 (20-24)	N=281 22 (20-24)	N=298 22 (19-24)	0.690	0.410	0.666
Functional wellbeing[3]	N=263 24 (21-27)	N=281 25 (20-27)	N=299 24.5 (20-27)	0.353	0.612	0.680
Prostate cancer subscale[5]	N=264 38 (33-42)	N=285 38 (32.7-43)	N=300 39 (32.9-43)	0.566	0.423	0.807
Trial Outcome Index[6]	N=269 87 (73-94.4)	N=287 88 (75-95)	N=304 88 (73.5-95.2)	0.613	0.543	0.941
FACT-G total score[7]	N=265 94 (84-101)	N=281 94 (81-102)	N=299 94 (83-101.2)	0.783	0.925	0.830
FACT-P total score[8]	N=269 132 (112-142)	N=287 130 (113-143)	N=304 131.2 (114-143)	0.882	0.761	0.898
SF-36[2]						
Physical functioning	N=265 80 (60-95)	N=283 85 (65-95)	N=296 82.5 (65-95)	0.173	0.707	0.257
Role limitations (physical)	N=262 25 (0-100)	N=282 25 (0-100)	N=296 25 (0-100)	0.673	0.940	0.613
Role limitations (emotional)	N=263 100 (0-100)	N=282 100 (0-100)	N=298 100 (0-100)	0.946	0.391	0.426
Vitality	N=259 62.5 (50-75)	N=282 62.5 (50-75)	N=295 62.5 (43.7-75)	0.838	0.376	0.274
Mental health	N=258 85 (75-90)	N=282 85 (75-95)	N=295 85 (70-90)	0.464	0.535	0.164
Social functioning	N=270 100 (75-100)	N=289 100 (75-100)	N=306 100 (75-100)	0.908	0.927	0.813
Bodily pain	N=262 90 (57.5-100)	N=282 90 (65-100)	N=295 80 (57.5-100)	0.416	0.902	0.273
General health	N=253 70 (55-80)	N=276 70 (55-85)	N=288 70 (50-80)	0.431	0.605	0.182

[1]Mann-Whitney test; [2]SF-12 and SF-36 scores range from 0-100; FACT-P scores range from 0-28[3] or 0-24[4] or 0-48[5] or 0-104[6] or 0-108[7] or 0-156[8]; higher scores represent better quality of life; IQR = interquartile range

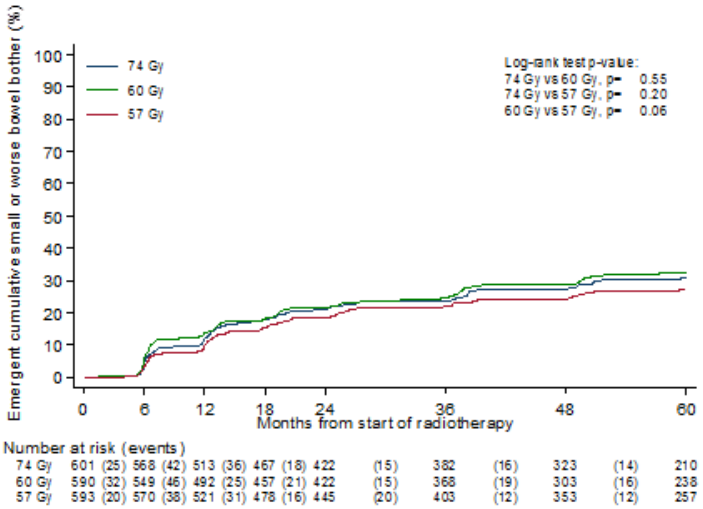
Table A7: Decline in general HRQoL domain scores from baseline to 5 years according to recommended cut-offs for minimal important difference (MID)

Domain score	MID[1]	Number of patients with decline in domain score ≥MID from baseline to 5 years / total (%)		
		74Gy/37f	60Gy/20f	57Gy/19f
FACT-P total score	8[2]	38/114 (33.3)	42/107 (39.2)	40/113 (35.4)
General health (SF-36)	8	42/98 (42.9)	33/94 (35.1)	39/104 (37.5)
Physical functioning (SF-36)	7	56/112 (50/0)	46/104 (44.2)	52/115 (45.2)
Role limitations, physical (SF-36)	14	58/110 (52.7)	58/103 (56.3)	63/113 (55.7)
Mental health (SF-36)	6	22/109 (20.2)	29/105 (27.6)	26/109 (23.8)
Role limitations, emotional (SF-36)	12	34/111 (30.6)	32/102 (31.4)	37/113 (32.7)

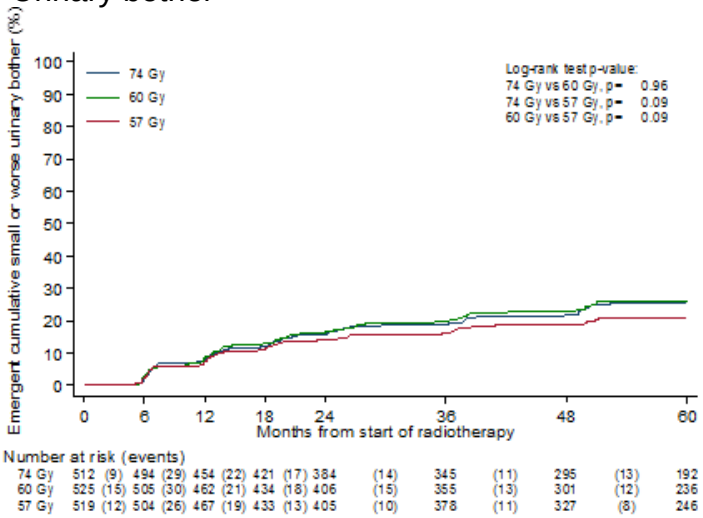
[1] Published in Jayadeppa et al 2012 (SF-36); [2] MID range 6-10 for FACT-P total score published in Cella et al 2009; midpoint (8) has been used above

Figure A1: Kaplan-Meier plots of time to small or worse bowel, urinary and sexual bother

(a) Bowel bother



(b) Urinary bother



(c) Sexual bother