NHS England

Evidence review: Hypofractionated radiotherapy compared with conventional fractionated radiotherapy to treat prostate cancer

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Contents

1. Introduction

Prostate cancer is the most common cancer in men in the UK, with 41,736 new cases in 2011(CRUK, 2015). Since the introduction of prostate-specific antigen (PSA) testing, most men diagnosed have localised disease. Management options include external-beam radiotherapy, brachytherapy, radical prostatectomy, active surveillance (for men with low-risk disease) and watchful waiting (for those unsuitable for radical curative treatment).

All prostate cancer treatments are associated with side-effects. Prostate cancer and its treatment are the leading cause of cancer years lived with disability (Soerjomataram et al, 2012) because prostate cancer is both common, and men with localised disease have a long life expectancy. Management choices are often influenced by potential treatment-related toxicities. Patients with prostate cancer have their care managed by a variety of different specialists working together as part of a tumour specific cancer Multi-Disciplinary Team (MDT). This includes Urologists, Clinical and Medical Oncologists, specialist nurses, Radiologists and Pathologists. Patients with early prostate cancer who are eligible for external beam radiotherapy will usually receive a course of radiotherapy of either 20 daily treatments or 37 daily treatments of external beam radiotherapy (NICE 2014).

External-beam radiotherapy is most appropriate for men with intermediate or high risk disease (NCCN, 2011), and is associated with long-term disease control in most patients (Wolff 2015). About 15,800 men receive radical prostate radiotherapy in the UK every year (NRDS, 2015).

Several phase 3 randomised control trials have shown the benefit of dose escalation (Zarosky et al, 2013. Dearnaley et al. 2014) and high-dose conformal radiotherapy with conventional 2 Gray (Gy) daily fractions (f) to a total dose of 74Gy is the standard of care in the UK (NICE, 2014). However, meta-analysis shows high dose radiotherapy (74Gy-80Gy) is associated with an increased risk (odds ratio of 1·58) of late gastrointestinal toxicity of grade 2 or more compared to lower doses (64Gy-70.2Gy) (Hou et al, 2015).

It is therefore important that any changes to fractionation include the use of advanced radiotherapy techniques which are able to sculpt dose distributions to the prostate target and avoid the organs at risk.

Prostate cancer may have high radiation–fraction sensitivity, which would give a therapeutic advantage to hypofractionated treatment (Brenner et al, 2002, Fowler et al, 2001, Khoo et al, 2008). The relationship between total isoeffective radiation dose and fraction size is described by a linear quadratic model which uses two constants α and β. The ratio α/β is inversely related to the effect of changes in fraction size on normal and malignant tissues. The α/β ratio for most cancers and acute normal tissue reactions is believed to be high and about 10Gy. However for prostate cancer values as low as 1.5Gy has been suggested, which is lower than the 3Gy reported for the late reactions of most normal tissues (including rectum) (Thames et al, 1990). These findings have potentially important therapeutic implications.

The Intervention

Hypofractionated radiotherapy, giving fewer fractions, each with a higher dose, may improve the therapeutic ratio as well as improving resource use and patient convenience. Three large randomised controlled trials have very recently published side effect (Aluwini et al 2016, Lee et al, 2016, Dearnaley et al, 2016) and efficacy outcomes in patients with a range of risk profiles including low risk, intermediate or high risk disease.

2. Summary of results

- Results from four large randomised trials have been reported in the last 12 months, the trials include 6,357 patients. Additionally this review considered results from 3 smaller trials including 544 patients, and one systematic review.
- The largest and most generalizable study to NHS practice is the CHHiP trial which randomised 3,216 patients to receive either conventional fractionated radiotherapy (CFRT) AT 74Gy delivered in 37 fractions over 7.4 weeks, or hypofractionated radiotherapy (HFRT) 60Gy/20 fractions over 4 weeks or 57Gy/19 fractions over 3.8 weeks.
- The CHHiP study confirms that the 60Gy/20 fractions schedule is safe and effective when compared to the CFRT with 90.6% of patients biochemical/clinical failure free at 5 years compared to 88.3% in the CFRT group. 60Gy was shown to be non-inferior, hazard radio 0.84 compared to the CFRT group at 5 years.
- There was no difference in long term genitourinary and gastrointestinal side effects

at 5-years, although data showed acute short-lasting acute side effects peaked sooner in the HFRT group at 4-5 weeks.

- Evidence from the CHHiP trial shows that treatment of the prostate with seminal vesicles is safe and effective at 60Gy/20. The PROFIT trial has used the same HFRT schedule as CHHiP and results published in abstract form,though exclude from this review further demonstrate non-inferiority compared to CFRT.
- In relation to patient sub-groups, there was generalizable evidence from a number of studies that exclusion criteria when considering the patient cohort eligible should include prostate when treating the pelvic nodes at the same time and patients with pre-existing GI and/or GU problems.
- For other patient inclusion/exclusion factors evidence from across the other randomised controlled trials(HYPRO, and RTOG 0415, Pollack et al 2013) highlight the need to carefully consider patient selection, case mix, and risk stratification for HFRT schedules though both of these studies used differing schedules to CHHiP and PROFIT.

3. Methodology

This Evidence Review has been undertaken in accordance with the standards set out in NHS England's 'Guidance on conducting evidence reviews for specialised commissioning products'.

The Policy Working Group developed and agreed the PICO (see section 9) and agreed the search terms for the review in October 2016. Abstracts and full text articles were screened by the public health and clinical lead of the PWG for studies that met the inclusion criteria for the review.

Database searches were conducted between 31st October 2016 and 3rd November 2016.

Searches included the following databases: NICE Evidence Search, TRIP database, MEDLINE, EMBASE, CINAHL.

4. Results

Included studies

64 citations were identified from database searches, following the removal of duplicate citations. 46 were considered potentially relevant to the review and the full text obtained.
13 of these studies; 10 trial based papers, 1 systematic review, and 2 available only as a conference abstracts, met all the inclusion criteria. The abstracts were excluded as per NHS England's guidance on the production of clinical evidence reviews resulting in 11 full papers eligible for review.

Most trials that met the inclusion criteria were conducted in multiple centres; The most notable trials, the CHHiP trial and HYPRO trial, which between them accounted for 6 of the 11 full papers included in the review. The characteristics of the trials included in this evidence review are included below in table 1. 9 of the trials were phase 3 Randomised Controlled Trials (RCTs), with one of the trials a phase 2 trial. The single systematic review (Tree et al, 2014) is excluded from Table due to the differences in methodology of the study and non-trial design.

Table 1. Summary of included trials and study design

Trials included	References	Setting	Number	Age*	Hypofractionation Schedule(s)	Hypofractionation duration	Conventional schedule	Follow up
CHHiP	Dearnaley 2016, Dearnaley 2012, Wilkins 2015	UK, 71 centres	3216	69, 69	60Gy in 20F , 57Gy in 19F	4 weeks, 3.8 weeks	74Gy in 37F	5-year
HYPRO	Inrocci 2016, Aluwini 2016, Aluwini 2015, Wortel 2016	Netherlands, 7 centres	804	70	64.6Gy in 19F	6.5 weeks	78Gy in 39F	5-year
RTOG 0415	Lee 2016	USA, multiple centres	1115	67	70Gy in 28F	5.6 weeks	73.8Gy in 41F	5-year
Pollack et al	Pollack 2013	USA, Single centre	303	66.7	70.2GY in 26F	Not reported	76Gy in 36F	5-year
Arcangeli et al	Arcangelli 2012	Italy, Single centre	168	75	62Gy in 20F	5 weeks	80Gy in 40F	5.8-years
Wu et al	Wu 2012	Canada, 4 centres	73	69	55Gy in 16F	Not reported	N/A	4-years
*Median where reported								

Fractionation schedules and study hypotheses

Table 1 demonstrates the variation in the published trials in relation to the hypofractionated schedules used, and the conventional fractionated radiotherapy comparators, and duration the hypofractionated schedule has been delivered over.

The CHHiP trial and PROFIT trial (abstract only) are the most directly comparable in relation to the use of the 60Gy/20F schedule delivered over a 4 week period. The RTOG 0415 trial and Pollack's study also use the same hypofractionation schedule; though also have differing conventional RT comparators.

The HYPRO trial's main differences are the higher dose used and longer duration of hypofractionation delivery over 6.5 weeks.

The hypotheses and accompanying technical designs of the trials are also highly relevant. The HYPRO study has been designed with the hypotheses that hypofractionation would increase efficacy compared with conventional fractionation. The HYPRO study has been designed as a superiority study, with the primary hypothesis that hypofractionation would increase 5-year relapse free survival by 10%. Increasing survival to 80% from a baseline of 70% compared to conventional fractionation.

Conversely, the CHHiP, RTOG 0415, and PROFIT trials have been designed with a non-inferiority hypothesis with the null hypothesis that hypofractionated schedules were not worse than conventional RT when comparing relapse free survival at 5-year follow up. Although these studies vary in their inclusion criteria, use of androgen deprivation therapy, and the hypofractionated schedule (RTOG 0415) and conventional comparators (PROFIT, RTOG 0415) the similarities in non-inferiority design mean that there is some merit in overarching comparisons between these studies primary outcome measures.

The systematic review included (Tree et al. 2014) a wide range of studies and corresponding fractionation schedules. The study reports ranges of results where applicable but has not included a meta-analyses, due to the wide heterogeneity across the included studies.

Clinical inclusion criteria

The included studies varied in relation to their clinical inclusion criteria (Table 2). In the CHHiP trial, most men enrolled had low risk or intermediate risk disease. The authors report 12% who had high risk disease at baseline. In HYPRO the authors included intermediate and high risk patients. The PROFIT trial has recruited intermediate risk patients, and the

RTOG 0515 low risk patients.

Table 2. Clinical inclusion criteria and risk stratification*

Trials included	References	PSA	Gleason	Low risk	Int - risk	High risk	WHO status	ADT
CHHiP	Dearnaley 2016, Dearnaley 2012, Wilkins 2015	<40ng/ml	<8	T1b-T3aN0M0			0-1	Intermediate and high risk patients
HYPRO	Inrocci 2016, Aluwini 2016, Aluwini 2015, Wortel 2016	<60ng/L	>8		T1b-T4NX-N0MX-M0		0-2	66% of cohort
RTOG 0415	Lee 2016	<10	2-6	T1b-T2c			0-2	Excluded
Pollack et al	Pollack 2013	<10-20+	5-10			>Ct3	NR	24mth in high risk, 4mth in int risk
Arcangeli et al	Arcangelli 2012	NR	NR			T2c	NR	All patients
Wu et al	Wu 2012	<10-20	6-7	T1-T2a	T1-T2c		NR	Prior ADT excluded

Table 1 footnotes:

ADT: Androgen deprivation therapy is a hormone therapy used to reduce the levels of male hormones (androgens)in the body to stop them affecting prostate cancer cells.

Gleason: The Gleason score is used to assess the cancer cells within the prostate. The score is a measure of how aggressive the tumour is. The higher the score, the more likely it is that the cancer will grow more quickly.

PSA: Prostate Specific Antigen is a risk assessment measure for prostate cancer and used post diagnosis alongside the Gleason score and grading to assess the behaviour of the cancer.

WHO status: Is a standardised scoring system of 0-5 which attempts to quantify the patient's activities of daily life and wellbeing. A score of 0 refers to a patient asymptomatic, fully active and able to carry on all pre-disease activities without restriction, 1= symptomatic but restricted in physically strenuous activity, 2 = symptomatic <50% in bed during day, 3 = symptomatic >50% in bed, 4= Bedbound / completely disabled, 5 = Death (http://ecog-acrin.org/resources/ecog-performance-status)

All of the included studies varied in relation to androgen deprivation therapy (ADT), as summarised in table 2. Furthermore some studies reported results and multivariate analysis across risk groups and/or ADT use. Where significant these results are presented in the data extraction tables for this review.

Primary outcome measures

Primary outcome measures differed between studies, but most used a combination of the

following primary and/or secondary outcome measures which is helpful for the overall comparability of oresults, notwithstanding the differing schedules, case mix, follow up and statistical methods:

- Proportion of patients experiencing biochemical or disease free survival at 5 year follow up
- Genitourinary toxicity, classified using RTOG* Grade 2 or worse toxicity at specified follow up points
- Gastrointestinal toxicity, classified using RTOG* Grade 2 or worse at specified follow up points
- Patient reported outcomes

*Studies used the standardised Radiation Therapy Oncology Group (RTOG) toxicity grading. This scores bowel and bladder symptoms from 0 (no symptoms) to 5 (causing death).

Table 3. Primary outcomes measures of included studies.

Study	Trial	Primary outcome*
Dearnaley 2016	CHHiP	Biochemical failure free survival
Dearnaley 2012	CHHiP	>G2 toxicity
Wilkins 2015	CHHiP	QOL Bowel bother
Inrocci 2016	HYPRO	Relapse free survival
Aluwini 2016	HYPRO	>G2 GU and GI toxicity
Aluwini 2015	HYPRO	Cumulative GU and GI toxicity
Wortel 2016	HYPRO	Erectile function
Lee 2016	RTOG 0415	Disease free survival
Pollack 2013		Biochemical and/or disease failure
Arcangelli 2012		Freedom from biochemical failure
Wu 2012		G3 toxicity GI and GU
*G2/3 = Grade 2/3		
GU = Genitourinary		
GI = Gastrointestinal		

5. Discussion

Consistency of findings

Survival outcomes

Tables 8 and 9 summarise the primary outcome measures of the included studies. Two further recent editorials in The Lancet and Journal of Clinical Oncology have also considered the consistency between studies, and these editorials have referenced the results of PROFIT trail abstract (Catton et al, 2016) which has been excluded from this formal review but referenced in the discussion section below..

The CHHiP trial (Dearnaley et al, 2016, Wilkins et al, 2015, Dearnaley et al, 2011) is the largest published trial to date with 3216 men recruited from 71 centres. The final efficacy study (Dearnaley et al, 2016) reported that after a median follow-up of 62 months the proportion of patients who were biochemical/clinical failure free at 5 years was: for 74 Gy 88.3% (95% confidence interval 86.0-90.2); 60 Gy 90.6% (88.5-92.3); 57 Gy 85.9% (83.4-88.0). 60 Gy was shown to be non-inferior to 74 Gy (hazard ratio 0.84) but non-inferiority could not be claimed for 57 Gy (hazard ratio 1.20). There was no heterogeneity of effect for different risk groups. Overall survival was similar between CFRT and HFRT groups; of 252 deaths reported, only 16% were prostate cancer related .

The PROFIT (Catton et al, 2016) trial is the most directly comparable to the CHHiP trial, however, only abstract data and additional reported results from a recent editorial (Dearnaley et al, 2016) are available and is therefore not available for full inclusion in this review. Based on available data in total, 1206 men with intermediate-risk prostate cancer were recruited from 27 sites and received CFRT of 78 Gy/39 fractions over 8 weeks or HFRT 60 Gy/20 fractions over 4 weeks. The primary end point was biochemical-clinical failure: the critical hazard ratio for non-inferiority was 1.32. The median follow-up was 6.0 years. The 5 year biochemical-clinical failure event rate was 21% in both groups (hazard ratio 0.96).

RTOG 0415 (Lee et al, 2016), another non-inferority trial, reported results for a total of 1092 men comparing daily schedules of 73.8 Gy/41 fractions (1.8 Gy/fraction) with 70 Gy/28 fractions (2.5 Gy/fraction). The median follow-up was 5.8 years. The estimated 5 year disease-free survival was 85% for CFRT and 86% for HFRT (hazard ratio 0.85). The

cumulative incidence of biochemical recurrence at 5 years was 8% and 6% in the CFRT and HFRT groups, respectively (hazard ratio 0.77). Both end points met the protocol-specified non-inferiority criterion (hazard ratio<1.52, P< 0.001). Overall 5 year estimated survival was similar at 93%. Deaths were most commonly due to cardiovascular disease and secondary cancers.

The HYPRO trial (Inrocci et al 2016, Aluwini et al, 2016, Aluwini et al, 2015) has explored the hypothesis that dose-escalated hypofractionated treatment can be given to improve disease control rates but without increasing side-effects. In total, 804 patients with intermediate-risk and high-risk prostate cancer were randomly assigned to receive either CFRT 78 Gy/39 fractions in 8 weeks or HFRT with 64 Gy/19 fractions (3.4 Gy/fraction) in 6.5 weeks (three fractions per week). Sixty-six per cent of men had concomitant ADT. The principal aim was to detect a 10% improvement (hazard ratio¼ 0.63) in 5 year relapse free survival with hypofractionation. A key secondary aim was to show the non-inferiority of hypofractionation for cumulative incidence of grade >2 acute and late genitourinary/ gastrointestinal toxicity (critical hazard ratios set at 1.1/1.13, respectively).These results are reported in the section below. The proportion of patients free of biochemical/clinical failure at 5 years was 81%/ 77% (hazard ratio 0.86; P¼0.36) for HFRT/CFRT groups, respectively (Inrocci et al, 2016).

Of the remaining trials which reported survival metrics, two were single centre RCTs. Pollack (et al, 2013) reported results for 303 patients randomised to 70.2Gy in 26 fractions for HFRT compared to 76Gy in 38 fractionation for CFRT. The 5-year biochemical disease failure rates were 21.4% (14.8-28.7) for CFRT and 23.2% (16.4-31.0) for HFRT (p=0.745). No statistically significant difference was reported between the two groups. Arcangelli (et al, 2012) reported results from Italy based on inclusion of 168 patients randomised to receive either 80Gy at 2Gy per fraction in 8 weeks of CFRT or 62Gy at 3.1Gy per fraction in 5 weeks. Patients received combination of 9 months androgen deprivation therapy. Biochemical failure rates found a risk reduction by hypofractionation of 10.3% between the two groups with a HR reported of 0.34 (0.21-0.56).

Genitourinary and Gastrointestinal toxicity outcomes

In the CHHiP trial, Acute Radiation Therapy Oncology Group (RTOG) bowel and bladder symptoms peaked sooner with HFRT schedules (4 - 5 weeks) than CFRT (7 - 8 weeks)

and there was a higher proportion of grade 2 peak gastrointestinal toxicity in both hypofractionated groups (CFRT 25%: HFRT 38%; P < 0.0001) but by 18 weeks both bowel and bladder toxicity was similar for CFRT/HFRT. There were no differences in long-term side-effects between CFRT and HFRT groups in either the proportion or cumulative incidence of patients reporting a RTOG grade 2 gastrointestinal/genitourinary toxicity at 5 years (cumulative incidence: 74 Gy: 13.7%/9.1%; 60 Gy: 11.9%/11.7%; 57 Gy: 11.3%/6.6%). Nevertheless there was a slightly higher rate of grade 2 gastrointestinal/genitourinary side-effects in the 60 Gy group compared with 57 Gy at 2 and 5 years. Patient reported outcomes suggest an overall low incidence of gastrointestinal and genitourinary symptoms in all treatment groups.

The PROFIT trial, from the limited abstract results available at the time of this review reported acute genitourinary/gastrointestinal toxicity as similar in both arms of trial, based on the abstract review. However, late gastrointestinal toxicity favoured the 60 Gy arm (grade 2 CFRT 9%: HFRT14%; P=0.006 (Catton et al, 2016).

In the RTOG 0415 trial (Lee et al, 2016), the reported results for toxicity show acute gastrointestinal/genitourinary side-effects were similar in the randomised groups. Late grade 2 gastrointestinal/ genitourinary adverse events were increased with hypofractionation (HFRT 22%/30%: CFRT 14%/23%). The authors concluded that this HFRT schedule was non-inferior to CFRT, although with an increased risk of late toxicity.The authors and subsequent editorials suggest that this increase in side-effects is “perhaps expected” as the 2.0 Gy equivalent doses are about 70 Gy/76 Gy for the CFRT/HFRT groups, respectively.

In the HYPRO trial (Inrocci et al, 2016) the authors reported cumulative grade 3 late genitourinary toxicity was higher with hypofractionation (HFRT 19%, CFRT 13%; P¼0.02), but the incidence of grade 2 bowel toxicity at 3 years was similar (CFRT 18%, HFRT 22%). The authors concluded that the study could not confirm that HFRT was non-inferior for either acute or late genitourinary/gastrointestinal toxicity compared with CFRT.

It is notable that compared to the CHHiP study, the short-term increase in acute gastrointestinal but not genitourinary toxicity with hypofractionation is similar, however, the excess late side-effects probably relate to the higher biologically effective dose and difference in treatment techniques used in the HYPRO trial, most particularly the reduction in total dose to the seminal vesicle target volume in CHHiP.This has also been

noted in the recent accompanying editorials (Dearnaley 2016b).

Addressing the limitations of trials

The radiobiological interpretation of the results of the four predominant multi-centre hypofractionated prostate trials (CHHiP, RTOG 0415, HYPRO, and PROFIT) present the following considerations:

Radiobiological interpretation:

The CHHiP trial suggests that 60 Gy/20 fractions is equivalent to about 76Gy/38 fractions - very like the 78Gy/39 fractions in PROFIT. The recent clinical oncology editorial summarises the identical outcomes in the two arms of the PROFIT study as ideal for calculating the a/b ratio for prostate cancer. Using the outcomes at 5 years the a/b ratio is estimated as 1.3 Gy, which is lower than the estimate from the CHHiP trial of 1.8 Gy which used ADT in most patients (Dearnaley et al 2016b).

The HYPRO study had a hypofractionated schedule designed to be equivalent to 90.4 Gy in 2 Gy/fraction (assuming a/b of 1.5 Gy) compared with 78 Gy/39 fractions for CFRT, yet the increase in outcome at 5 years was only 3.4%. The schedule was protracted by delivering three fractions per week and it may be that the effect of overall treatment time contributed, with the course taking 6.5 weeks as per the presentation in table 1. Similarly the hypofractionated arm of the RTOG 0415 trial should also have resulted in less biochemical failures than the standard arm (assuming a low a/b ratio), yet there is only a 2% increase in prostate-specific antigen control at 5 years (Dearnaley et al, 2016b).

Clinical predictors for adverse events and/or relapse

The HYPRO trial results show that a strong independent predictor of relapse was high risk (>25%) of seminal vesicle involvement. Conversely the authors also report lower failure rates for the HFRT group in patients with a Gleason score <6.

For genitourinary and gastrointestinal toxicity a number of the studies included reported statistically significant results following treatment for those patients reporting toxicity at baseline. In particular Pollack (et al 2013) concluded that the hypofracitonation regimen used is most appropriate for men without “substantial baseline urinary dysfunction”. The

RTOG 0415 trial also noted that patients with large prostates may be at higher risk of adverse events (Lee et al, 2016).

The HYPRO authors have also published a single abstract (Wortel et al, 2016) relating to sexual function outcomes. Whilst excluded from this review, the abstract notes that sexual function outcomes including erectile deterioration and orgasmic function were similar between both arms of the study and that no statistically significant differences between the HFRT and CFRT groups were observed.

Table 2 also highlights the variation in androgen replacement therapy in the studies inclusion and exclusion. In the HYPRO study, the authors note the variation in delivery across clinical settings. The CHHiP study and PROFIT study use the same HFRT schedule, however PROFIT excludes ADT. The CHHiP trial authors note that short course ADT was used in 97% of the cohort (Dearnaley, 2016) and therefore limits generalisability to this group of patients.

A major caveat with all the studies included is that none were designed to address some of these specific clinical sub-grouping questions. It is likely further refinement of study designs and sub-group analyses are needed to address these questions more robustly.

Generalisability of findings

The CHHiP trial is likely to be most generalizable to the NHS in England given the participation of NHS centres in the study, and the CFRT dose aligning with NICE guidelines applicable to current routine clinical practice.

The emerging results from the PROFIT trial,though not available as a full paper for inclusion, utilising the same HFRT schedule and time duration (4 weeks) also provides confidence that this schedule is not worse than the CFRT schedules in these studies. Crucially the hazard ratio's reported in both studies do not suggest any additional excess harmful effects, both in terms of relapse free survival and adverse events.

The HYPRO trial HFRT schedule, as concluded by the authors, was not deemed to be non-inferior and therefore is not recommended for adoption in routine clinical practice. The considerations above in terms of radiobiological dose, and toxicity. The time duration of the delivery of treatment has also been hypothesised as a contributing factor and is 2.5

weeks longer than the CHHiP and PROFIT schedules used.

6. Conclusion

Hypofractionated radiotherapy has been shown to be both safe and effective when delivered at 60Gy / 20fraction schedule over a four week period when compared to conventional radiotherapy.

Clear criteria regarding clinical factors including risk stratification and patient selection will be required to minimise the risk of genitourinary and gastrointestinal toxicity

7. Evidence Summary Tables

Hypofractionated radiotherapy compared with conventional fractionated radiotherapy to treat prostate cancer									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Dearnaley et al. 2016	*Randomised control trial*	*Rrandomised, phase 3, non-inferiority trial that recruited men with localised prostate cancer* *(pT1b–T3aN0M0). Patients were randomly assigned (1:1:1) to conventional (74 Gy delivered in 37 fractions over* *7·4 weeks) or one of two hypofractionated schedules (60 Gy in 20 fractions over*	*(pT1b–T3aN0M0). Patients were randomly assigned (1:1:1) to conventional (74 Gy delivered in 37 fractions over* *7·4 weeks) or one of two hypofractionated schedules (60 Gy in 20 fractions over 4 weeks or 57 Gy in 19 fractions over*	*Primary*	*time to biochemical or clinical failure* *Long-term side-effects including grade 2 or worse bowel and bladder adverse events*	*The proportion of patients who were biochemical or clinical failure free at 5 years was:* ***74 Gy**: 88·3% (95% CI 86·0–90·2),* ***60 Gy**: 90·6% (88·5–92·3)* ***57 Gy**: 85·9% (83·4–88·0)* ***60 Gy was non-inferior to 74 Gy** (HR 0·84 [90% CI 0·68–1·03], pNI=0·0018)* ***non-inferiority could not be claimed for 57 Gy compared with 74 Gy** (HR 1·20 [0·99–1·46], pNI=0·48)*	10	*DIRECT STUDY*	The CHHiP trial is, as stated by the authors, the largest randomised treatment study undertaken in localised prostate cancer. Baseline groups well balanced and includes mainly intermediate risk patients. Robust multi-centre study design related to UK NHS settings so high quality in terms of generalisability. Some potential for selection bias as only intermediate and high risk selected and there is variation in grading Non-inferiority design is appropriate design to answer the commissioning question. Conclusions suggest using the 60Gy 20F schedule could make treatment more convenient for patients delivered in 4 weeks. This is significant compared to the HYPRO study where the HFRT schedule was both higher and also delivered over a longer period of 6.5 weeks.

		4 weeks or 57 Gy in 19 fractions over	*3·8 weeks) all delivered with intensity-modulated techniques. Most patients were given radiotherapy with 3–6 months* *of neoadjuvant and concurrent androgen suppression*	*Clinical effectiveness/Safety*	*Long-term side-effects including grade 2 or worse bowel and bladder adverse events*	*There were no significant differences in either* *the proportion or cumulative incidence of side-effects 5 years after treatment using three clinician-reported as well as* *patient-reported outcome measures. The estimated cumulative 5 year incidence of Radiation Therapy Oncology* *Group (RTOG) grade 2 or worse bowel and bladder adverse events was 13·7% (111 events) and 9·1% (66 events) in the* *74 Gy group, 11·9% (105 events) and 11·7% (88 events) in the 60 Gy group, 11·3% (95 events) and 6·6% (57 events)* *in the 57 Gy group, respectively. No treatment-related deaths were*			

						reported.			

Hypofractionated radiotherapy compared with conventional fractionated radiotherapy to treat prostate cancer									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Inrocci et al. 2016. Lancet	*Open-label, randomised, phase 3 trial at seven Dutch radiotherapy centres*	*Patients with intermediate-risk to high-risk T1b–T4NX–N0MX–M0 localised prostate cancer, a prostate-specific antigen concentration of 60 μg/L or less, and a WHO performance status of 0–2.*	*hypofractionated radiotherapy of 64·6 Gy (19 fractions of 3·4 Gy, three fractions per week)* *or conventionally fractionated radiotherapy of 78·0 Gy (39 fractions of 2·0 Gy, five fractions per week). Based on*	*Primary*	*The primary endpoint was relapse-free survival*	*5-year relapse-free survival was 80·5% (95% CI 75·7–84·4) for patients assigned hypofractionation and:* *77·1% (71·9–81·5) for those allocated conventional fractionation* *(adjusted hazard radio 0·86, 95% CI 0·63–1·16; log-rank p=0·36).*	6	*DIRECT STUDY*	One of four papers included in the ER relating to the HYPRO trial. This study was designed based on power calculation to detect a clinically significant improvement in relapse free survival for patients undergoing hypofractionation compared to conventional fractionation. The final reported hazard ration reported (0.86 CI 0.63-1.16) demonstrates that the hypofractioanted regime used in this trial is not significantly better than conventional RT. The hypofractionated dose was given over a 6 week period in this trial, as opposed to 4 weeks in the CHHiP trial. Caveats to this trial include the androgen replacement therapy protocols which varied by site of delivery – the majority of patients in this trail received this. The significant variable for relapse free survival in hypofractionate group was gleason score <6.
				Clinical effectiveness/Safety	*5-year relapse free survival post hoc multivariate analysis on gleason score, androgen deprivation therapy dose and risk*	*In post-hoc multivariate analyses, a Gleason score of* *7 or lower and*			

			an estimated α/β ratio for prostate cancer of 1·5 Gy, the equivalent total dose in fractions of 2·0 Gy was 90·4 Gy for hypofractionation compared with 78·0 Gy for conventional fractionation.		*group.*	*androgen deprivation therapy for longer than 12 months versus none were associated with a decreased risk of relapse (table 2). Patients in seminal vesicle dose group 3 (>25% risk of vesicle involvement) had an increased risk of relapse compared with those in group 1 (risk <10%; table 2). Age, PSA concentration, T stage, prostate volume, and treatment were not associated with relapse free survival.*			Study generalizable to Dutch healthcare setting. Baseline groups well balanced..

Hypofractionated radiotherapy compared with conventional fractionated radiotherapy to treat prostate cancer									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**

Lee et al. 2016. Journal of Clin Onc.	*Phase 3 Randomized non-inferiority study*	*Men >18 years with prostate adenocarcinoma. T1b to T2c, Gleason score 2-6, PSA <10.* *Additional criteria: no nodal or distant metastatic disease, Zubrod performance status <2, no prior bilateral orchiectomy, chemo, RT, cryosurgery, or definitive surgery for prostate cancer.*	*Conventional RT(C-RT) 73.8Gy in 41 fractions.over 8.2 weeks.* *Hypofractionated RT (H-RT)70Gy in 28 fractions over 5.6 weeks*	*Primary*	*5 year disease free survival*	*C-RT 85.3% (95%CI: 81.9-88.1)* *H-RT86.3% (95%CI: 83.1-89.0)* *Hazard ratio 0.85 (95%CI: 0.64-1.14)* *Non-inferiority required DFS outcomes HR <1.52* *P=0.001*	9	DIRECT	Large RCT in U.S setting with >1,000 participants. Baseline groups well balanced. Study limitations could include large non-inferiority margin with HR of 1.52 set at threshold at 0.05 significance limit. Authors note dose in control group lower comparably to other studies and trials in this area so may have overestimated benefits of H-RT in this context. Adverse events based on clinical information as opposed to patient reported outcomes as in other studies which have also found that adding patient reported outcomes increases toxicity events. Finally patient group exclusively low risk patients whereby outcome measures of survival may favour improved outcomes at 5 year follow up. Seminal vesicles and pelvis lymph nodes not irradiated.
				Secondary	*Biochemical recurrence* *Overall survival* *Genitourinary and GU toxicity*	*C-RT 8.1%, H-RT 6.3%, p=<0.01* *C-RT 93.2%, H-RT 92.5%, p=.08* *Late grade 2 and 3 GI and GU adverse events were increased at 3 years for H-RT. Full cumulative data in paper table 1* *HR 1.31-1.59*			

Hypofractionated radiotherapy compared with conventional fractionated radiotherapy to treat prostate cancer									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Tree et al. 2014. Clinl Onc	*Systematic review*	*52 papers full text review:* *n=37 for hypofractionation studies with inclusion criteria of at least 30 patients treated with hypofractionated schedule.* *n=15 relating to prostate sterotactic radiotherapy' inclusion criteria if papers described clinical cohorts of prostate cancer patients*	*Hypofractionated radiotherapy, sterotactic body radiotherapy*	*Primary*	*Range of 5 year Biochemical control rates, stratified by reported risk group (%)*	*Moderate hypofractionation schedules dose fraction 2.5-4.0Gy* *Low risk: 73.8-100%* *Intermediate risk: 55.7-96.4%* *High risk: 31.4-88%* *Profound hypofractionation schedules does fraction 6.7-10Gy* *Low risk: 90-100%* *Intermediate risk: 85%* *High risk: 81-90%*	4	2	This systematic review presents results from a range of studies split by hypofractionation dose 'moderate' and 'profound'. Some data is also provided for SABR for prostate cancer which is out of scope of this evidence review and search criteria. The search terms used in the systematic review are applicable and the range of studies relevant to the research questions. Tables 1-3 are summarised in terms of high level outcomes, it is therefore not possible to interrogate any further demographic or baseline characteristics from the studies included. There is also variation in terms of dose fractions between the studies and in numbers of participants with the largest having 936 participants and the smallest 42. The authors present funnel plots for the stratification of risk groups against survival outcomes to demonstrate the variation in outcomes by hypofractionation schedules. It is not clear what case mix adjustments have been made in the models to account for differences between study populations. No meta analyses of BCFS or toxicity is included relating to the included studies.

		treated with >5Gy/fraction as monotherapy			*Late grade 2 genitourinary toxicity* *Late grade 2 gastrointestinal toxicity*	*Moderate hypofractionation: 0-28%* *Profound: 1-20%* *Moderate hypofracitonation: 0-25%* *Profound: 0-11.4%*			The authors conclude that further larger RCTs are required and note the importance of the CHHiP trial noting that the results of this study "will probably give the clearest answer as to the clinical benefits of moderate hypofractionation".

Hypofractionated radiotherapy compared with conventional fractionated radiotherapy to treat prostate cancer									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**

Aluwini et al. 2016. Lancet	*Open-label, randomised, phase 7 trial at seven Dutch radiotherapy centres*	*N=820 410 both groups* *Patients (44-85years old) with intermediate-risk to high-risk T1b–T4NX–N0MX–M0 localised prostate cancer, a prostate-specific antigen concentration of 60 μg/L or less, and a WHO performance status of 0–2.*	*hypofractionated radiotherapy of 64·6 Gy (19 fractions of 3·4 Gy, three fractions per week)* *or conventionally fractionated radiotherapy of 78·0 Gy (39 fractions of 2·0 Gy, five fractions per week). Based on an* *estimated α/β ratio for prostate cancer of 1·5 Gy, the equivalent total dose in fractions of 2·0 Gy was 90·4 Gy for* *hypofractio*	*Secondary ??** **Primary end point was relapse free survival this paper reports on secondary endpoints:*	*Grade 2 or worse genitourinary toxicity at 3 years* *Cumulative incidence Hazard Ration at 3 years* *Cumulative Grade 3 or worse genitourinary toxicity at 3 years* *Sub-group significant variables:* *Age >70 years* *Adjuvant hormonal therapy*	*Standard fractionation: 39% (95% CI 34.2-44.1)* *Hypofractionation: 41.3% (95% CI: 36.6-46.6)* *1.16 (90%CI:0.98-1.38)* *Standard fractionation: 12.9% (95% CI 9.7-16.7)* *Hypofractionation: 19% (95% CI: 15.2-23.2)* *P=0.021* *HR 1.56 (1.26-1.93 P<0.0001)* *1.36 (1.07-1.74 P=0.012)*	6	*DIRECT STUDY*	One of four papers included in the ER relating to the HYPRO trial. Baseline groups well balanced but noting that mean age in trial older than in other trials reviewed with median age of patients included at 71 years. Study potentially underpowered to conclude non-inferiority compared to standard fractionation. The authors note that the 8% threshold set of non-inferiority based on sample size of 800 patients may have been too stringent. It is also worth noting that in this trial the hypofractionation group received the treatment over a longer time period than in other studies, where the difference between the standard schedules was only 1.5 weeks in total. The hypofractionated dose was given over a 6 week period in this trial, as opposed to 4 weeks in the CHHiP trial. Mixed methods for collection of toxicity data in this trial. Clinical notes supplemented by patient questionnaires and authors reported a significant increase in reported toxicity when the qualitative data was added and analysed. Adding the questionnaire data resulted in increases in reported late toxicity of 51% and 26% respectively for GU and Gastrointestinal toxicity. Authors note that just analysing clinical note data did not change conclusions relating to non-inferiority and this factor may be more of an issue for other trials where clinical notes solely used – thus potential for under-reporting. Caveats to this trial include the androgen replacement therapy protocols which varied by site of delivery – the majority of patients in this trail received this. Furthermore the inclusion of the
				Secondary	*Grade 2 or worse gastrointestinal toxicity*	*Standard: 17.7% (95%CI: 14.1-21.9)*			

			nation compared with 78・0 Gy for conventional fractionation. *Toxicity results are presented at 5 year (60 mth) follow up*		*Cumulative incidence at 3 years* *Cumulative Grade 3 or worse gastrointestinal toxicity at 3 years* *Sub-group significant variables:* *Seminal vesicles treated to prescribed dose vs <10% risk of seminal vesicle involvement*	*Hypofractionation: 21.9% (95%CI: 18.1-26.4%)* *1.19 (90%CI: 0.93-1.52)* *Standard: 2.6% (95%CI: 1.2-4.7)* *Hypofractionation: 3.3% (95%CI: 1.7-5.6%)* *P=0.55* *HR 1.65 (1.02-2.67 p=0.042)*			seminal vesicle in the target volume may have contributed to an enhanced incidence of acute toxicity, alongside the older patient cohort and existing symptoms reported at baseline.

Hypofractionated radiotherapy compared with conventional fractionated radiotherapy to treat prostate cancer									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						Standard fractionation:			

Aluwini et al. 2015. Lancet	*Open-label, randomised, phase 3 trial at seven Dutch radiotherapy centres*	*Patients (44-85years old) with intermediate-risk to high-risk T1b–T4NX–N0MX–M0 localised prostate cancer, a prostate-specific antigen concentration of 60 μg/L or less, and a WHO performance status of 0–2.*	*hypofractionated radiotherapy of 64·6 Gy (19 fractions of 3·4 Gy, three fractions per week)* *or conventionally fractionated radiotherapy of 78·0 Gy (39 fractions of 2·0 Gy, five fractions per week). Based on an* *estimated α/β ratio for prostate cancer of 1·5 Gy, the equivalent total dose in fractions of 2·0 Gy was 90·4 Gy for* *hypofractionation compared*	*Secondary ???** **Primary end point was relapse free survival this paper reports on secondary endpoints:*	*Grade 2 or worse genitourinary toxicity* *Cumulative incidence by 120 days* *Sub-group significant variables: Increased frequency at night >7 times Grade 3*	*n=73(22%)* *Hypofractionation: n=75(23%)* *Standard: 57.8% (95%CI 52.9-62.7)* *Hypofractionation: 60.5% (95%CI 55.8-65.3)* *Differences in Cis p=0.43* *Standard: n=27 (7%)* *Hypofractionation: n=46 (12%)* *P=0.019*	6	*DIRECT STUDY*	One of four papers included in the ER relating to the HYPRO trial. Baseline groups well balanced but noting that mean age in trial older than in other trials reviewed. This study was designed based on power calculation to detect a clinically significant improvement in relapse free survival for patients undergoing hypofractionation compared to conventional fractionation, therefore it was not powered or designed to specifically look at toxicity as primary outcomes. The authors note that it is possible that the study was underpowered to conclude non-inferiority compared to standard fractionation. The authors note that the 8% threshold set of non-inferiority based on sample size of 800 patients may have been too stringent. It is also worth noting that in this trial the hypofractionation group received the treatment over a longer time period than in other studies, where the difference between the standard schedules was only 1.5 weeks in total. The hypofractionated dose was given over a 6 week period in this trial, as opposed to 4 weeks in the CHHiP trial. Compared to other trials this study only collected at timepoints of 4 weeks, 6 weeks and 3 months. Caveats to this trial include the androgen replacement therapy protocols which varied by site of delivery – the majority of patients in this trail received this. Furthermore the inclusion of the seminal vesicle in the target volume may have contributed to an enhanced incidence of acute toxicity.
				Secondary	*Grade 2 or worse gastrointestinal toxicity* *Cumulative incidence by 120 days* *Sub-group significant*	*Standard: n=43 (13%)* *Hypofractionation: n=42 (13%)* *Standard: 31.25% (95% CI: 26.6-35.8)* *Hypofractionation: 42% (95% CI:37.2-46.9)* *P=0.0015*			

			with 78・0 Gy for conventional fractionation. *Toxicity results are presented 3 months following radiotherapy.*		*variables: Increased frequency >6 times*	*Standard: n=31 (8%)* *Hypofractionation: 58 (15%)* *P=0.0035*			

Hypofractionated radiotherapy compared with conventional fractionated radiotherapy to treat prostate cancer									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Wilkins et al.	*Randomised*	*2100 men consented to*	*(pT1b–T3aN0M0).*	*Primary*	*Overall bowel bother at24mths*	*p-values @24mth*	9	*DIRECT STUDY*	This paper (2015) from the CHiiP trial reports on A subset analysis of 2100 men who consented to be

2012	*control trial – QOL sub-study*	*QOL study* *conventional (74 Gy delivered in 37 fractions over* *7·4 weeks) n=696* *or one of two hypofractionated schedules (60 Gy in 20 fractions over 4 weeks n=698* *or 57 Gy in 19 fractions over* *3·8 weeks) n=706*	*Patients were randomly assigned (1:1:1) to conventional (74 Gy delivered in 37 fractions over* *7·4 weeks) or one of two hypofractionated schedules (60 Gy in 20 fractions over 4 weeks or 57 Gy in 19 fractions over* *3·8 weeks) all delivered with intensity-modulated techniques.* *All patients were given radiotherapy with 3–6 months* *of*			*74vs60=p=0.64* *75vs57=p=0.59* *No overall bother at 24mths in:* ***74 Gy**: 66% n=269* ***60 Gy**: 65% n=266* ***57 Gy**: 65% n=282* *Very Small bother* ***74 Gy**: 22% n=92* ***60 Gy**: 22% n=91* ***57 Gy**: 21% n=93* *Small bother* ***74 Gy**: 22% n=92* ***60 Gy**: 22% n=91* ***57 Gy**: 21% n=93* *Moderate* ***74 Gy**: 5% n=19* ***60 Gy**: 6% n=23* ***57 Gy**: 5% n=21* *Severe*			part of the QOL study. Follow up is 2 years. A number of different qualitative instruments have been used in this study, with a change in questionnaire stated once the study has commenced: - UCLA Prostate Cancer Index - Short form SF-36 - Functional Assessment of Cancer Therapy Prostate (FACT-P) - Expanded Prostate Cancer Index (EPIC) - Sf-12 QOL Completed at baseline, pre-RT, 10wk post RT, 6,12,18,24mth All validated instruments but UCLA PCI switched during study due to refinements required. Baseline groups well balanced. Table 2 and appendix 4 of paper provides range of outcomes modelling as secondary analysis on bowel, bladder and sexual function QOL between the fractionation. Alongside headline results reported, the temporary increase in bowel bother at 10weeks was also highlighted – this peak is also referenced in the discussion aligning with toxicity results reported in a separate study (2012) of the trial. Overall this study demonstrated no clinically meaningful differences in QOL outcomes between the schedules. There is very limited data on QOL outcomes in other trials and therefore this is likely to

			neoadjuvant and concurrent androgen suppression			***74 Gy***: *<1% n=4* ***60 Gy***: *<1% n=3* ***57 Gy***: *<1% n=3*			be generalizable.
				Secondary	*Overall urinary bother*	*No significant differences reported – full data in online appendix of paper. P values reported:* *74vs60Gy P=0.69* *74VS57Gy P=0.47* *60VS57Gy P=0.74*			
				Secondary	*Overall sexual bother*	*No significant differences reported – full data in online appendix of paper. P values reported:* *74vs60Gy P=0.39* *74VS57Gy P=0.33* *60VS57Gy P=0.92*			

Hypofractionated radiotherapy compared with conventional fractionated radiotherapy to treat prostate cancer									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Dearnaley et	*Randomised*	*457 men recruited to*	*(pT1b–T3aN0M0).*	*Primary*	*Proportion of patients with Grade 2 or worse*	*Bowel toxicity*	9	*DIRECT*	This early paper (2012) from the CHHiP trial reports

al. 2012	*control trial – preliminary results from phases 1 and 2*	*stages 1 and 2 with localised prostate cancer (T1B-T3A N0 M0)* *(Patients were randomly assigned (1:1:1) to conventional (74 Gy delivered in 37 fractions over* *7·4 weeks) n=153* *or one of two hypofractionated schedules (60 Gy in 20 fractions over 4 weeks n=153* *or 57 Gy in 19 fractions over* *3·8 weeks) n=151* *all delivered with intensity-*	*Patients were randomly assigned (1:1:1) to conventional (74 Gy delivered in 37 fractions over* *7·4 weeks) or one of two hypofractionated schedules (60 Gy in 20 fractions over 4 weeks or 57 Gy in 19 fractions over* *3·8 weeks) all delivered with intensity-modulated techniques.* *All patients were given radiotherapy with 3–6 months* *of*		*toxicity at 2 years on the RTOG scale*	***74 Gy**: 4.3% (1.6-9.2) n=6/138 had bowel toxicity of grade 2 or worse at 2 years* ***60 Gy**: 3.6% (1.2-8.3) n=5/137 bowel toxicity >Grade 2* ***57 Gy**: 1.4% (0.2-5.0) n=2/143 bowel toxicity>Grade2* *Bladder toxicity* ***74 Gy**: 2.2% (0.5-6.2) n=3/138 had bladder toxicity of grade 2 or worse at 2 years* ***60 Gy**: 2.2% (0.5-6.3) n=3/137 bladder toxicity >Grade 2* ***57 Gy**: 0% (0.0-2.6) n=0/143 bladder toxicity>Grade2*		*STUDY*	on toxicity outcomes after 2 years of follow up. Robust study design related to UK NHS settings so high quality in terms of generalisability. Baseline groups well balanced. Acute bowel and bladder effects peaked sooner in experimental groups than standard fractionation group at 4-5 weeks compared to 7-8 weeks. Table 2 of paper provides range of outcomes modelling as secondary analysis on bowel, bladder and sexual function between the fractionation. Overall this study demonstrated no clinically meaningful differences in acute toxicity between the schedules. Some differences observed to other trials, cited reasons selection factors, adherence to normal dose constraints or inverse planning methods.
				Secondary	*Proportion of patients with Grade 2 or worse toxicity at 18 weeks*	*Bowel toxicity* *74 Gy: 2.3% n=3/1129 had bowel toxicity of grade 2 or worse at 2 years* *60 Gy: 2.3% n=3/132 bowel*			

		modulated techniques. Most patients were given radiotherapy with 3–6 months *of neoadjuvant and concurrent androgen suppression*	*neoadjuvant and concurrent androgen suppression*			*toxicity >Grade 2* *57 Gy: 0.8% n=1/129 bowel toxicity>Grade2* *Bladder toxicity* *74 Gy: 7% n=7/129 had bladder toxicity of grade 2 or worse at 2 years* *60 Gy: 7.6% n=10/132 bladder toxicity >Grade 2* *57 Gy: 7% n=9/129 bladder toxicity>Grade2*			
				Secondary	*LENT/SOM sexual dysfunction scores*	*Table 2 of paper - shows that scores were not significantly different in randomized groups at any point*			

Hypofractionated radiotherapy compared with conventional fractionated radiotherapy to treat prostate cancer									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Arcangeli et	*RCT*	*168 patients with high risk*	*Conventional*	*Primary*	*Freedom from biomechanical failure*	*35/168(21%)*	5	*DIRECT*	This single centre RCT is smaller in participant numbers than other trials reviewed and was

al.2012		*prostate cancer.*	*fractionation (CF): 80GY/2GY per fraction in 8 weeks* *Hypofractionation (HF): 62GY/3.1GY in 5 weeks.*		*(FFBF)*	*Risk reduction =10%* *HR 0.34 95%ci 0.21-0.56* *Reduction significant by PSA level of 20ng/ml or less HR 0.15 95% CI: 0.03-0.71*		*STUDY*	published in 2012, when the HF evidence base was emerging. Baseline groups are described as well balanced but note that this trial focusses explicitly on the 'high risk' spectrum of patients, as opposed to more recent trails encompassing broader sub-groups. Limited generalisability as single centre only and aside from age no demographic data on ethnicity or deprivation group to make wider comparisons. Study powered to detect isoeffectiveness between the trial arms and dose regimen of 80/2GY vs 62/3.1GY slightly differs from other trials. HF delivered in 5 weeks as opposed to 8 weeks. 70mth follow up confirms that BF rates effect is reduced compared to earlier studies . Authors speculate on subgroup of iPSA >20 group significant results that impact is dues to HF impact on smaller tumour burden in these patients.
				Secondary	*Local failure*	*11/168 (31%* *)* *No significant differences detected between HF/CF either in all patients or specific prognostic sub-groups.*			
				Secondary	*Distant failure*	*16/35(46%)* *HR: 0.57 95%CI:0.33-0.98* *Significant in patients with Gleason score of 4+3or higher.*			
				Secondary	*Overall survival*	*No sig difference in either arm of trial* *HF VS CF 92% VS 82%*			

					Cancer specific survival	*No sig difference in either arm of trial* *HF VS CF 98% VS 92%*			

Hypofractionated radiotherapy compared with conventional fractionated radiotherapy to treat prostate cancer*)*									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Pollack et al. 2013. J Clin Oncology	*RCT*	*men with favorable- to high-risk prostate cancer.* *307 patients between 2002 and 2006 (Fig 1), and 303 were* *assessable, with 152 randomly assigned to receive CIMRT and 151 to receive* *HIMRT. The*	*randomly allocated to receive 76 Gy in 38 fractions at 2.0 Gy per fraction (conventional* *fractionation intensity-modulated radiation therapy [CIMRT]) versus 70.2 Gy in 26 fractions at 2.7*	*Primary/Secondary*	*Cumulative incidence of biochemical and/or clinical disease failure (BCDF)*	*There were 303 assessable patients with a median follow-up of 68.4 months. No significant* *differences were seen between the treatment arms in terms of the distribution of patients by* *clinicopathologic or treatment-related (ADT use and length) factors. The 5-year rates of BCDF were* *21.4% (95% CI, 14.8% to 28.7%) for*	5	*DIRECT STUDY*	This single centre RCT is smaller in participant numbers than other trials reviewed, however, presents some of the most comprehensive data relating to GI and GU toxicity. Baseline groups are described as well balanced but noted that HIMRT group includes larger proportion of 65-74 yr old patients (49.7 compared to 40.8). Limited generalisability as single centre only and aside from age no demographic data on ethnicity or deprivation group to make wider comparisons. As per other studies, trial is powered to detect improvement of 15% fewer BCDFs in HIMRT group at 0.05 significance level -sample size achieved necessary numbers for power calculation. Dose regimen of 76/36@2GY vs 70.2/26@2.7GY slightly differs from other trials. HIMRT delivered in 2.5 fewer weeks paper states but not clear on total

		use of long-term ADT was planned for 24 months in those *classified as high risk per the protocol (prostate-specific antigen [PSA] _ 20* *ng/mL; Gleason score [GS] of 8 to 10, _ cT3, or GS7 _ four biopsy cores* *positive).*	*Gy per fraction (hypofractionated IMRT [HIMRT])*			*CIMRT and 23.3% (95% CI, 16.4% to 31.0%) for HIMRT* *(P _ .745).*			week duration from paper.
				Clinical effectiveness/Safety	*Toxicity GI*	*In the prevalence plots (Figs 3A and 3B), a predominance of* *grade 1 acute GI reactions (Fig 3A, 3-month post-RT values) was* *observed, without difference between the arms (P _ .57). By 6* *months, GI reactions had declined, and no difference was found* *between baseline and 5-year GI effects based on 96 CIMRT (P_.29)* *and 85 HIMRT (P _ .49) patients. The overall (crude) incidences of* *grade 0, 1, 2, and 3 worst late GI reactions were 18.5%, 58.9%,*			

						20.5%, *and 2.0% for CIMRT versus 28.2%, 53.7%, 16.1%, and 2.0% for* *HIMRT (P _ .39 comparing grade _ 2 rates of 22.5% v 18.1%;* *Fig 3C).*			
				Primary/Secondary *Clinical effectiveness/Safety*	*Toxicity GU*	*In terms of GU function, the prevalence plots (Fig 3B) revealed* *that many patients had compromised function at baseline mainly* *because of urinary frequency-urgency syndrome. A substantial increase* *in acute GU grade_2 adverse effects was observed, which did* *not differ by treatment arm (P _ .58). Although a reduction in the* *prevalence of adverse effects was evident by 6 months,*			

						the 5-year rates *of grade _ 2 GU effects were higher than baseline in both arms* *(CIMRT, 14.6% v 5.2%; P _ .029 and HIMRT, 15.3% v 10.6%;* *P_.371).* *The 5-year cumulative risks of grade_2GUadverse effects were 37.9%(95%CI, 29.7% to 46.1%)* *for CIMRT and 39.1% (95% CI, 30.6% to 47.4%) for HIMRT (Fig3D)* *Baseline factors were examined for association with onset of late* *GU toxicity. The International Prostate Symptom Score (IPSS),21 a* *35-point questionnaire assessing urinary function, is routinely*			

						used in *clinical practice and has been related to late GU toxicity using pre-treatment* *cut points of 10 to 15.22,23 Setting the cut point at 12, to correspond* *with the upper quartile for our study patients, revealed a strong* *association with grade _ 2 late reactions for the whole group (P _* *.003).*			

Hypofractionated radiotherapy compared with conventional fractionated radiotherapy to treat prostate cancer*)*									
Study refere	**Study Design**	**Population characteristi**	**Interventio n**	**Outcome measure**	**Outcome measures**	**Results**	**Quality of Evidence**	**Applicability**	**Critical Appraisal Summary**

nce		cs		type			Score		
Wu et al. 2011. Radiotherapy and Oncology	*Multi Centre Phase II study*	*Low risk (T1-T2a, Gleason score 6, and PSA >10) and intermediate risk (T1-T2c, Gleason 7, and/or PSA 10-20)*	*Hypofractionated radiotherapy, 55Gy in 16 fractions (4 fractions/week, 3.4Gy per fraction)*	*Primary*	*Cumulative incidence of any late grade 3 or 4 toxicity, either urinary or bowel (combined)*	*7% (95%CI 3-16)* *Grade 2+ 33% (95%CI: 24-46)*	4	DIRECT	Phase 2 study limited to 73 patients recruited between 2004 and 2006.25% low risk and 75% intermediate risk patients. Study conducted across 4 treatment centres covering population of circa 5million in U.S. No comparator group in this study. Percentages only reported and a mix of clinical and patient reported outcomes. Strengths of study include the 4 year follow up period and use of patient reported outcome measures. Limitations include lack of central QA of radiation therapy in the study, introduction of image guidance as new treatment delivery in centres during the study, and clinician based primary outcome measure which could incorporate observer and / o r measurement bias into the results, particularly as conducted across four treatment centres.
				Secondary	*Biochemical (PSA nadir +2) or biopsy proven relapse at 4 years*	*9% (95%CI: 4-18)*			
				Secondary	*Patient reported outcomes* *Urinary function at 3 years*	*Moderate to severely problematic 6%* *Greatest average reduction in multi-function scores seen at 2 years (mean-7SD 16)* *Moderately problematic 6%*			
					Bowell function at 3 years	*Greatest average reduction in multi-function scores seen at 2 years (mean-7SD 20)*			

8. Grade of evidence table

Use of Intervention X Vs. Comparator Y to treat Indication Z *(Create separate table for studies with different comparators)*					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Biochemical failure free survival at 5 years	*Dearnaley 2016*	*10*	direct	*A*	*Biochemical Failure Free Survival means that after undergoing a prostate cancer treatment the patients' prostate-specific antigen (PSA) level does not rise more than 2 ng/mL from nadir PSA (lowest concentration recorded at any time after commencement of androgen deprivation therapy or radiotherapy). Generally, patients who undergo prostate cancer radiotherapy should have low PSA levels after treatment under 2.0 ng/mL. Biochemical (PSA) relapse is a reasonable indicator of who will go on to develop clinically relevant recurrent prostate cancer.* *The CHHiP trial (Dearnaley et al, 2016) reported that after a median follow-up of*
	Inrocci 2016	*6*	*direct*		
	Lee 2016	*9*	*direct*		
	Arcangelli 2012	*5*	*direct*		
	Pollack 2013	*5*	*direct*		

					62 months the proportion of patients who were biochemical/clinical failure free at 5 years was: • *74 Gy 88.3% (95% confidence interval 86.0-90.2);* • *60 Gy 90.6% (95% confidence interval 88.5-92.3);* • *57 Gy 85.9% (95% confidence interval 83.4-88.0).* *A study only provides an estimate of the true value of the parameter of interest (e.g. proportion or Hazard Ratio). However, the true population value would be contained within the 95% confidence interval on 95% of occasions a study is conducted and the confidence interval then calculated.* *Description of the magnitude of change of the health metric (where possible)* *The study assessed if hypofractionated radiotherapy schedules were non-inferior when compared with conventional radiotherapy schedules. A non-inferior treatment is not clinically worse.* *The critical hazard ratio (HR) is the method used to compare Biochemical Free Survival rates between groups and assess if there is non-inferiority.* *A treatment is assessed as non-inferior if the HR was below 1.208 and the 90% confidence interval did not contain this value.*

					60 Gy was shown to be non-inferior to 74 Gy (HR 0.84, 90% confidence interval 0.68-1.03, p=0.0018). Non-inferiority could not be claimed for 57 Gy (HR 1.20, 90% confidence interval 0.99-1.46, p=0.48). There was no heterogeneity of effect for different prostate cancer risk groups (i.e. the effect size was the same). *Patients will receive their radiotherapy course in fewer treatments and over a shorter time period.* *The CHHiP trial (Dearnaley et al, 2016) is the largest and most generalizable study to NHS practice comparing hypofractionated radiotherapy (HFRT) with conventional fractionated radiotherapy (CFRT) for the treatment of prostate cancer.* *It is a well-conducted, high quality, randomised controlled trial testing the hypothesis that HFRT is non-inferior for outcomes compared with CFRT.*
GI and GU toxicity	*Dearnaley 2012*	*9*	*direct*	*A*	*Radiotherapy, when being used to treat prostate cancer, may cause unwanted bowel (gastrointestinal) and bladder (genitourinary) symptoms.* *Safety outcomes in the CHHiP study were measured using the Radiation Therapy Oncology Group toxicity grading. This scores bowel and bladder symptoms from 0 (no symptoms) to 5 (causing death).* *Short term results reported bowel and*
	Aluwini 2015	*6*	*direct*		
	Aluwini 2016	*6*	*direct*		
	Wu 2012	*4*	*direct*		

					bladder symptoms peaked sooner with HFRT schedules (4 - 5 weeks) than CFRT (7 - 8 weeks). There was a higher proportion of grade 2 peak gastrointestinal toxicity in both HFRT groups (CFRT 25%: HFRT 38%; P < 0.0001). By 18 weeks both bowel and bladder toxicity was similar for CFRT/HFRT. *There were no differences in long-term side-effects between CFRT and HFRT groups in either the proportion or cumulative incidence of patients reporting grade 2 gastrointestinal/genitourinary toxicity at 5 years (cumulative incidence: 74 Gy: 13.7%/9.1%; 60 Gy: 11.9%/11.7%; 57 Gy: 11.3%/6.6%). There was a slightly higher rate of grade 2 gastrointestinal/genitourinary side-effects in the 60 Gy group compared with 57 Gy at 2 and 5 years.* *Patient reported outcomes suggest an overall low incidence of gastrointestinal and genitourinary symptoms in all treatment groups.* *The CHHiP study confirmed that HFRT (60Gy/20 fractions schedule) is safe and effective when compared to CFRT. It is a study of high quality and generalizable to NHS practice.*
QOL/ Patient Reported Outcomes	*Dearnaley 2016*	*10*	*direct*	*A*	*Radiotherapy, when being used to treat prostate cancer, may cause unwanted bowel (gastrointestinal) and bladder (genitourinary) symptoms.* *Safety outcomes in the CHHiP study were measured using the Radiation Therapy Oncology Group toxicity grading. This scores bowel and bladder symptoms from 0 (no symptoms) to 5 (causing death).* *Short term results reported bowel and*
	Wilkins 2012	*9*	*direct*		
	Aluwini 2015	*6*	*direct*		
	Aluwini 2016	*6*	*direct*		
	Wu 2012	*4*	*direct*		

					bladder symptoms peaked sooner with HFRT schedules (4 - 5 weeks) than CFRT (7 - 8 weeks). There was a higher proportion of grade 2 peak gastrointestinal toxicity in both HFRT groups (CFRT 25%: HFRT 38%; P < 0.0001). By 18 weeks both bowel and bladder toxicity was similar for CFRT/HFRT. *There were no differences in long-term side-effects between CFRT and HFRT groups in either the proportion or cumulative incidence of patients reporting grade 2 gastrointestinal/genitourinary toxicity at 5 years (cumulative incidence: 74 Gy: 13.7%/9.1%; 60 Gy: 11.9%/11.7%; 57 Gy: 11.3%/6.6%). There was a slightly higher rate of grade 2 gastrointestinal/genitourinary side-effects in the 60 Gy group compared with 57 Gy at 2 and 5 years.* *Patient reported outcomes suggest an overall low incidence of gastrointestinal and genitourinary symptoms in all treatment groups.* *The CHHiP study confirmed that HFRT (60Gy/20 fractions schedule) is safe and effective when compared to CFRT. It is a study of high quality and generalizable to NHS practice.*

9. Primary Outcome table

Study	Trial	Primary outcome	Hypofractionation results for primary outcome (90% CI unless stated)	Statistical significance	Study conclusion
Dearnaley 2016	CHHiP	Biochemical failure free survival	60Gy = 90.6% (88.5-92.3)	0.84 (0.68-1.03)	60Gy schedule non-inferior to conventional RT
			57Gy = 85.9% (83.4-88.0)	1.20 (0.99-1.46)	57Gy not non-inferior to conventional RT
Dearnaley 2012	CHHiP	>G2 toxicity	GI - 60Gy = 3.6% (1.2-8.3)	NR	GU and GI toxicity equally well tolerated at 5 year follow up
			GU - 60Gy = 2.2% (0.5-6.2)	NR	
			GI -57Gy = 1.4 (0.2-5.0)	NR	GU and GI toxicity equally well tolerated at 5 year follow up
			GI -57Gy = 2.2% (0.5-6.3)	NR	
Wilkins 2015	CHHiP	QOL Bowel bother	60Gy = 65%	P=0.64	No statisitically significances in patients reported outcomes from baseline to 2-year follow up
			57GY = 65%	P=0.59	No statisitically significances in patients reported outcomes from baseline to 2-year follow up
Inrocci 2016	HYPRO	Relapse free survival	64Gy = 80.5 (75.5-84.4)	HR 0.86 (0.63-1.16)	HR 0.86 (0.63-1.16) Not non-inferior. HRs insufficient to reject the null hypothesis.
Aluwini 2016	HYPRO	>G2 GU and GI toxicity	GU = 23%	HR 1.16 (0.98-1.38)	Not non-inferior. HRs insufficient to reject the null hypothesis.
			GI = 13%	HR 1.19 (0.93-1.52)	Hazard ratios not sufficient to reject null hypothesis. G4Gy schedule not non inferior to conventional RT
Aluwini 2015	HYPRO	Cumulative GU and GI	GU = 23%	P = 0.89	Cumulative incidence higher in HF arm, no
			GI = 13%	P = 0.9	Cumulative incidence higher in HF arm, no non-inferior
Lee 2016	RTOG 0415	Disease free survival	86.3 (95% CI: 83.1-89.0)	HR 0.85 (0.64-1.14)	60Gy schedule non-inferior to conventional RT
Pollack 2013		Biochemical and/or disease failure	23.3% (95% CI: 16.4-31.0)	P=0.745	No statistically significant differnces between HF and conventional RT groups
Arcangelli 2012		Freedom from biochemical failure	21%	0.34 (0.21-0.56)	Significant benefit of HF schedule in PSA >20ng group
Wu 2012		G3 toxicity GI and GU	G3 = 7% (95% CI: 3-16)	NR	No comparator group in this study. Concludes HF schedule clinically feasible.
			G2 = 33% (95% CI: 24-46)	NR	

10. Literature Search Terms

PICOS and Research Question Template

Hypofractionated RT Review

Reference: NHS England/ XX/P/X

1. Search strategy

Question(s)	
Identify all aspects of the topic that need to be explored in order to develop a policy • Is it a specialised service? • Is it in tariff? • Is it, or can it be, adequately covered by the appropriate detail in the service specification? • Is it very low volume or does it have a low number of requests, such as less than 10 per year? If it is low volume then it may not merit a clinical commissioning policy or may be deferred to the next round of policy reviews. • Does it appear too difficult to establish an evidence base or find suitable evidence to support a new clinical commissioning policy? If there is such limited evidence that it will not be possible to answer the review question then it will not be possible to generate a clinical commissioning policy. • Is it a clinical area included within the scope? If not, then a clinical commissioning policy may not be suitable for this	
Search strategy *Indicate all terms used in the search*	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	- *Patients diagnosed with prostate cancer, eligible for radiotherapy treatment* *{Low, intermediate, and high risk patients all included in most recent trials}*
I – Intervention Which intervention, treatment or approach should be used?	- *Hypofractionated High-dose Intensity Modulated Radiotherapy* - 60Gy/20f over 4 weeks as per CHHiP trial
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	- Conventional fractionated radiotherapy - Standard NICE guidance for patients with early prostate cancer who are eligible for external beam radiotherapy is to receive 37 daily treatments of 2Gy/day (total dose 74Gy) of external beam radiotherapy as recommended by NICE in 2008
O – Outcomes What is really important for the	**Efficacy** - Overall survival - Prostate cancer specific relapse free survival at 5

patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	years **Clinical Measures** - gastrointestinal and - genitourinary toxic effects **Quality of life** - Quality of life / patient reported outcomes
Assumptions / limits applied to search *As above.*	

11. Search Strategy

Appendix: Search strategies

Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches	Results
1	exp *Prostatic Neoplasms/	93269
2	(prostat* adj2 (cancer* or neoplasm* or tumor* or tumour*)).ti.	65481
3	1 and 2	55995
4	*Dose Hypofractionation/	48
5	((radiation or radiotherapy) adj5 hypofractiona*).ti.	906
6	((dose or dosage or dosimetry or schedule*) adj5 hypofractiona*).ti.	140
7	4 or 5 or 6	976
8	((conventional* or standard or radical) adj5 (radiotherapy or radiation) adj5 fractiona*).ti.	142
9	((dose or dosage or dosimetry or schedule*) adj5 fractiona*).ti.	964
10	*dose fractionation/	1855
11	8 or 9 or 10	2762
12	3 and 7 and 11	45
13	limit 12 to (english language and yr="2006 -Current")	38

Embase 1996 to 2016 Week 44

#	Searches	Results
1	exp *prostate cancer/	97314
2	(prostat* adj2 (cancer* or neoplasm* or tumor* or tumour*)).ti.	81719
3	1 and 2	72422
4	*hypofractionated radiotherapy/	208
5	((radiation or radiotherapy) adj5 hypofractiona*).ti.	1536

6	((dose or dosage or dosimetry or schedule*) adj5 hypofractiona*).ti.	230
7	4 or 5 or 6	1679
8	((conventional* or standard or radical) adj5 (radiotherapy or radiation) adj5 fractiona*).ti.	176
9	((dose or dosage or dosimetry or schedule*) adj5 fractiona*).ti.	626
10	8 or 9	790
11	3 and 7 and 10	17
12	limit 11 to (english language and yr="2006 -Current")	17

CINAHL Friday, November 04, 2016 6:44:11 AM

#	Query	Limiters/Expanders	Last Run Via	Results
S11	S3 AND S6 AND S9	Limiters - Published Date: 20060101-20161231; English Language Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	5
S10	S3 AND S6 AND S9	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	5
S9	S7 OR S8	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	28
S8	TI ((dose or dosage or dosimetry or schedule*) N5 fractiona*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	21

S7	TI (((conventional* or standard or radical) N5 (radiotherapy or radiation)) N5 fractiona*))	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	7
S6	S4 OR S5	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	94
S5	TI ((dose or dosage or dosimetry or schedule*) N5 hypofractiona*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	13
S4	TI ((radiation or radiotherapy) N5 hypofractiona*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	88
S3	S1 OR S2	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	9,588
S2	TI (prostat* N2 (cancer* or neoplasm* or tumor* or tumour*))	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	6,967
S1	(MM "Prostatic	Search modes -	Interface -	

	Neoplasms+")	Boolean/Phrase	EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL with Full Text	

NICE Evidence – Guidelines

(intitle:prostate OR intitle:prostatic)
AND
(hypofractiona* OR fractiona*)
AND
(radiotherapy OR "radiation therapy")
Limit: Guidance
Limit: 01/01/2006 – 01/11/2016
13 results

TRIP Pro

(title:prostate or title:prostatic)(hypofractionationated or hypofractionation or hypofractional or fractional or fractionated or fractionation)(radiotherapy or "radiation therapy")
Limited to: Guidelines
7 results
Date limit: 2006-current
3 results

12. Evidence selection

- Total number of publications reviewed: 64
- Total number of publications considered relevant: 46
- Total number of publications selected for inclusion in this briefing: 12

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