URN 2106: Stereotactic ablative radiotherapy (SABR) for the treatment of localised prostate cancer (adults)

Narrative summary of papers presented for review

Three papers were presented for review by NHS England. Paper 1 is a non-inferiority randomised controlled trial (RCT; phase III; PACE-B) conducted in 38 centres in the UK, Ireland and Canada. Patients (n=874) with low or intermediate risk, histologically confirmed prostate cancer were randomly assigned (1:1) to stereotactic body radiotherapy (SABR) or conventionally or moderately hypofractionated radiotherapy (control radiotherapy, CRT). Paper 2 reports the interim (24 month) safety outcomes for 97% (n=844) of the patients included in the RCT reported in Paper 1 (PACE-B). Paper 3 is a second non-inferiority RCT (phase III; HYPO-RT-PC) conducted in 12 centres in Sweden and Denmark. Patients (n=1200) with intermediate to high risk, histologically confirmed prostate cancer were randomly assigned (1:1) to ultra-hypofractionation or conventional fractionation radiotherapy (CRT).

Paper 1: van As et al pre-print. A Phase III randomized controlled trial of Stereotactic Body Radiotherapy in localized prostate cancer.

This paper reports on a multicentre, international, phase III, non-inferiority RCT (n=874; PACE-B) comparing SABR (n=433) to CRT (n=441) in adult men (≥18 years) diagnosed with low or intermediate risk,[1] histologically confirmed prostate cancer that were unsuitable or unwilling to have radical prostatectomy. Patients with a primary Gleason grade 4 or higher disease, any National Comprehensive Cancer Network (NCCN) high risk factors, previous pelvic radiotherapy, previous treatment for prostate cancer or bilateral hip prostheses were excluded. Patients were enrolled from August 2012 to January 2018 from 38 centres in the UK, Ireland and Canada. Median patient age was 69.8 years (range 45.8 to 84.5) in the SABR group and 69.7 years (range 48.1 to 86.7) in the CRT group. All patients were of male sex. The highest numbers of patients identified as White or Black ethnicity in both groups (SABR: White 84.8%, Black 8.1%, Southern Asian 4.6%, East Asian 0.9%, Mixed 0.5%, Other 1.2%; CRT: White 89.1%, Black 5.9%, Southern Asian 2.3%, East Asian 0.7%, Mixed 0.5%, Other 1.6%). The majority of patients were of intermediate prostate risk score, 92.6% in the SABR group and 90.7% in the CRT group; of these, approximately one quarter were of NCCN favourable[2] intermediate risk (SABR: 21.5%, CRT: 26.5%). Median prostate specific antigen (PSA) was 7.9 ng/mL (range

[1] Patients with low risk prostate cancer had T1 or T2 disease (defined on MRI), Gleason 3+3 and PSA≤10ng/mL. Patients with intermediate risk prostate cancer had T1 or T2 disease (defined on MRI), and at least one of the following factors Gleason 3+4 or PSA 10.1 to 20.0 ng/mL.
[2] The authors state that at the time of trial design, the current NCCN classifications for favourable and unfavourable intermediate-risk disease did not exist.

0.5 to 20.0 ng/mL) in the SABR group and 8.1 ng/mL (range 0.8 to 20.0 ng/mL) in the CRT group.

SABR dose was 36.25Gy in five fractions to 95% of the PTV (planning target volume) and a secondary target dose of 40Gy to 95% of the CTV (clinical target volume) over one to two weeks either daily or on alternate days. The CRT dose was initially 78Gy in 39 fractions but following a protocol amendment (24 March 2016) 62Gy in 20 fractions was also permitted; centres could choose their own schedules but must maintain it for all patients. Androgen deprivation therapy was not permitted. Results were reported at baseline, 12 weeks, and months six, nine and 12 and then annually until year five; the primary outcome was biochemical or clinical failure at up to five years follow-up. Median follow-up was 74.0 months (interquartile range (IQR) 64.8 to 86.3). Concomitant treatments at baseline included alpha blockers (16.6% in SABR group, 15.4% in CRT group), aspirin (SABR: 16.9%, CRT: 18.1%) and statins (SABR: 31.6%, CRT: 36.1%); genitourinary treatments at baseline included anticholinergics for bladder symptoms (SABR: 2.8%, CRT: 3.2%) 5-alpha reductase inhibitors for prostatic hypertrophy (SABR: 2.5%, CRT: 2.0%) and phosphodiesterase-5 inhibitors for erectile dysfunction (SABR: 1.4%, CRT: 3.0%).

Paper 2: Tree et al 2022. Intensity-modulated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): 2-year toxicity results from an open-label, randomised, phase 3, non-inferiority trial.

This paper reports on the 24 month safety outcomes (n=844) of the RCT reported in Paper 1 (PACE-B). A total of 414 patients in the SABR group and 430 patients in the CRT group had two year follow-up data and were included in this paper, 97% of the RCT population.

Paper 3: Widmark et al 2019. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial.

This paper reports on the five-year outcomes of a multicentre, international, phase III, non-inferiority RCT (n=1200; HYPO-RT-PC) comparing ultra-hypofractionation (n=598) or conventional external beam fractionation radiotherapy (CRT; n=602) in adult men (aged 18 to 75 years) diagnosed with intermediate to high risk,[3] histologically confirmed prostate cancer. Patients on androgen deprivation therapy were excluded. Patients were enrolled from July 2005 to November 2015 from 12 centres in Sweden and Denmark. Median patient age was 68 years (IQR 64 to 72) in the SABR group and 69 years (range 65 to 72) in the CRT group. Ethnicity was not reported. The majority of patients were of intermediate prostate risk score, 89% in the SABR group and 89% in the CRT group. Median PSA was 8.7 ng/mL (IQR 6.0 to 12.2 ng/mL) in the SABR group and 8.6 ng/mL (IQR 5.7 to 12.0 ng/mL) in the CRT group.

[3] Intermediate-to-high risk prostate cancer was categorised as stage T3a, a Gleason score of at least 7or PSA of at least 10ng/mL. The maximum PSA allowed was 20ng/mL.

Twenty patients were removed from the study prior to prescribed radiotherapy and were not included in per-protocol analyses.[4] Patients in the ultra-hypofractionation group (n=589) received 42.7Gy in seven fractions for three days per week over 2.5 weeks (inclusive of two weekends). Patients in the CRT group (n=591) received 78.0Gy in 39 fractions for five days per week for eight weeks. Total radiotherapy treatment time was a median of 16 days (IQR 15 to 17 days) in the ultra-hypofractionation group and a median of 57 days (IQR 55 to 59 days) in the CRT group. Results were reported at baseline, at the end of radiotherapy, months three, six, nine, 12 and then every six months; this paper focussed on long-term outcomes, primarily 5-10 year outcomes. Median follow-up was 5.0 years (IQR 3.1 to 7.0 years). Concomitant treatments were not reported.

Effectiveness

Biochemical or clinical failure (BCF) event-free rate / failure free survival

Van As et al (pre-print; PACE-B RCT) reported that at a median follow-up of 74.0 months (IQR 64.8 to 86.3) of patients with prostate cancer of low or intermediate risk, 26 biochemical failure events had occurred in the SABR group (n=433) compared to 36 events in the CRT group (n=441). A total of 10 participants in the SABR group commenced androgen deprivation therapy (ADT) compared to 19 in the CRT group (hazard ratio (HR) 0.55, 95% CI 0.26 to 1.20, p-value not reported).

Van As et al (pre-print; PACE-B RCT) also reported that the five-year BCF[5] event free-rates were 95.8% (95% CI 93.3% to 97.4%) for SABR and 94.6% (95% CI 91.9% to 96.4%) for CRT (absolute group difference 1.43%, 90% CI -0.60% to 2.78%[6], p-value not reported). SABR was shown to be non-inferior to CRT for patients with prostate cancer with low or intermediate risk (HR 0.73, 90% CI 0.48 to 1.12, p=0.004). A test for superiority was not significant (p=0.22). Competing risks analysis indicated no evidence of a statistically significant difference in BCF event-free rates between treatment groups (p=0.18).

Widmark et al (2019; HYPO-RT-PC) reported that after median 5.0 years follow-up (IQR 3.1 to 7.0 years) of patients with intermediate to high risk prostate cancer,100 BCF events[7] occurred in the ultra-hypofractionation group (n=589) and 102 events in the CRT group (n=591; p-value not reported). Failure-free survival at five years was 84% (95% CI 80% to 87%) in the ultra-hypofractionation group and 84% (95% CI 80% to 87%) in the CRT group; there was no evidence of a statistically significant difference between the groups (HR 1.002, 95% CI 0.760 to 1.320, p=0.99). Ultra-

[4] Twenty people were removed as they died (unrelated to prostate cancer; n=2), withdrew consent (n=10) or were found to be ineligible (n=8) immediately before or after radiotherapy. No further information was given. All sample sizes given in the paper are relevant to the per-protocol analyses and do not include these patients.
[5] Biochemical failure was based on PSA rises (Phoenix criteria, with three consecutive rises required for failure before 24 months to rule out post-radiotherapy “bounce”), commencement of androgen deprivation therapy (ADT) or date of orchidectomy. Clinical failure was based on local recurrence, nodal recurrence, distant metastases and/or death from prostate cancer.
[6] For the primary outcome, the hazard ratio and absolute difference are presented with 90% confidence intervals.
[7] A biochemical failure was defined as PSA progression according to RTOG and the American Society for Radiation Oncology’s Phoenix definition as nadir plus 2.0 ng/mL. A local clinical failure was defined as a tumour-induced change in urinary symptoms of such magnitude that a change of treatment was necessary; distant clinical failure was defined as detection of metastases by x-ray, bone scan, CT or ultrasound.

hypofractionation radiotherapy was found to be non-inferior to CRT (adjusted HR 1.002, 95% CI 0.758 to 1.325, p-value not reported).

One included paper reported no statistically significant difference in biochemical or clinical failure at a median 74.0 months follow-up between patients with low or intermediate risk prostate cancer treated with SABR (n=443) compared to patients treated with CRT (n=441) (BCF event-free rates: 95.8% vs 94.6%); non-inferiority was demonstrated. A second included paper reported no statistically significant difference in biochemical or clinical failure at median five year follow-up between patients with intermediate to high risk prostate cancer treated with ultra-hypofractionation radiotherapy (n=589) compared to patients treated with CRT (n=591) (BCF events: 100 vs 102); ultra-hypofractionation radiotherapy was demonstrated to be non-inferior to CRT.

Overall survival

Van As et al (pre-print; PACE-B RCT) reported that for men with prostate cancer with low or intermediate risk, 46/433 (10.6%) patients in the SABR group and 33/441 (7.5%) patients in the CRT group had died at a median 74.0 months follow-up (IQR 64.8 to 86.3 months); there was no evidence of a statistically significant difference in overall survival between treatment groups (HR 1.41, 95% CI 0.90 to 2.20, p-value not reported). Four deaths were due to prostate cancer and 28 to other cancers; this was not described by treatment group.

Widmark et al (2019; HYPO-RT-PC) reported five year overall survival rates for patients with intermediate to high risk prostate cancer, demonstrating no evidence of a statistically significant difference in overall survival between treatment groups (ultra-hypofractionation: n=589, CRT: n=591; HR 1.11, 95% CI 0.73 to 1.69, p-value not reported). Overall survival at five years in the ultra-hypofractionation group was 94% (95% CI 92% to 96%) and 96% (95% CI 95% to 98%) in the CRT group. During the follow-up period a total of 19 patients died due to prostate cancer (n=8 in the ultra-hypofractionation group and n=11 in the CRT group) and 70 patients died due to other causes (n=35 in both groups).

One included paper reported no statistically significant difference in overall survival at median 74.0 months follow-up between patients with low or intermediate risk prostate cancer treated with SABR (n=443) compared to patients treated with CRT (n=441). A second included paper reported no statistically significant difference in five year overall survival rate between patients with intermediate to high risk prostate cancer treated with ultra-hypofractionation radiotherapy (n=589) compared to patients treated with CRT (n=591).

Cumulative incidence of prostate cancer death

Widmark et al (2019; HYPO-RT-PC) reported that there was no statistically significant difference in the cumulative incidence of prostate cancer death at five years in patients with intermediate to high risk prostate cancer. This was 2% (95% CI 1% to 4%) in the ultra-hypofractionation group (n=589) and <1% (95% CI 0% to 1%) in the CRT group (n=591) (p=0.46).

One included paper reported no statistically significant difference in the cumulative incidence of prostate cancer death at five years in patients with intermediate to high risk prostate cancer treated with ultra-hypofractionation therapy (n=589) compared to patients treated with CRT (n=591).

Erectile dysfunction

Van As et al (pre-print; PACE-B RCT) reported erectile dysfunction for men with prostate cancer with low or intermediate risk using the Common Terminology Criteria for Adverse Events (CTCAE v4.03, grade ≥ 2). There was no evidence of a statistically significant difference between the groups in erectile dysfunction symptoms at five years follow-up (SABR: 78/296 (26.4%); CRT: 86/296 (29.1%); p=0.46).

Widmark et al (2019; HYPO-RT-PC) reported no evidence of a statistically significant difference in erectile dysfunction symptoms[8] between patients with intermediate to high risk prostate cancer that received ultra-hypofractionation radiotherapy (baseline n=507, 10 years n=21) compared to CRT (baseline n=506, 10 years n=20) at any timepoint between baseline and 10 years follow-up (approximate range of erectile dysfunction scores[9]: ultra-hypofractionation: 30% to 90%; CRT: 35% to 85%).

One included paper reported no statistically significant difference in erectile dysfunction symptoms at five years follow-up between patients with low or intermediate risk prostate cancer treated with SABR (n=296) compared to patients treated with CRT (n=296). A second included paper reported no statistically significant difference in erectile dysfunction symptoms at any timepoint between baseline and 10 years follow-up between patients with intermediate to high risk prostate cancer treated with ultra-hypofractionation radiotherapy (baseline n=507, 10 years n=21) compared to patients treated with CRT (baseline n=506, 10 years n=20).

Safety

Serious adverse events

Van As et al (pre-print; PACE-B RCT) reported serious adverse events for men with prostate cancer with low or intermediate risk using the Common Terminology Criteria for Adverse Events (CTCAE v4.03). Six participants (1.3%) in the SABR group (n=443) and six participants (1.4%) in the CRT group (n=441) reported treatment related serious adverse events at five years follow-up.

One included paper reported the same number of treatment related serious adverse events (six) in patients with low or intermediate risk prostate cancer treated with SABR (n=443) or CRT (n=441) at five years follow-up.

[8] Measured using the Prostate Cancer Symptom Scale questionnaire, specifically the question “Can you get an erection without aids?”.
[9] Scores were only presented graphically and were a combination of “unable to achieve erection” and “unable to achieve an erection sufficient for intercourse”.

Genitourinary (GU) toxicity

Tree et al (2022; PACE-B RCT) reported the proportion of patients with prostate cancer with low or intermediate risk with GU toxicity (grade ≥ 2) at two years follow-up using both the Common Terminology Criteria for Adverse Events (CTCAE v4.03) and the Radiation Therapy Oncology Group (RTOG) assessment tool. RTOG GU toxicity was reported in 3% of the SABR group (13/384; 95% CI 1.9% to 5.9%)) and 2% of the CRT group (8/381; 95% CI 1.0% to 4.3%)) (absolute difference: 1.3%, 95% CI -1.3% to 4.0%, p=0.39, non-significant difference). There was evidence of a statistically significant higher CTCAE GU toxicity at 24 months in the SABR group (47/414, 12%) compared to the CRT group (25/430, 7%) (absolute difference 5.7%, 95% CI 1.6% to 9.8%, p=0.010).

Tree et al (2022; PACE-B RCT) also reported evidence of a statistically significant difference in cumulative incidence of GU toxicity at two years using both CTCAE criteria and the RTOG tool. Cumulative incidence rates using the RTOG tool were 18.3% for patients that received SABR (n=414, 75 events; 95% CI 14.9% to 22.4%) and 10.6% for patients that received CRT (n=430, 45 events; 95% CI 8.0% to 14.0%; HR 1.80, 95% CI 1.25 to 2.61, p=0.0015). Cumulative incidence rates using the CTCAE criteria were 32.3% for patients that received SABR (132 events; 95% CI 28.0% to 37.0%) and 19.8% of patients that received CRT (84 events; 95% CI 16.3% to 23.9%; HR 1.73, 95% CI 1.32 to 2.28, p=0.0001).

Tree et al (2022; PACE-B RCT) also reported the most frequently reported GU toxicity to be increased urinary frequency; this peaked at 15 months in the SABR group (30/315, 10% and nine months in the CRT group (18/404, 5%). The same paper also reported a higher proportion of patients who had a *"minimally clinically important difference in urinary incontinence in the SABR group than in the CRT group (p=0.011) and in the urinary irritative-obstruction in the SABR group than in the CRT (p=0.012)."*

Van As et al (pre-print; PACE-B RCT) reported the proportion of patients with prostate cancer with low or intermediate risk with GU toxicity (grade ≥ 2) at five years follow-up using both the CTCAE and RTOG assessment tool. CTCAE GU toxicity was reported in 8.7% of the SABR group (31/355) and 6.7% of the CRT group (24/357; p=0.32, non-significant difference); RTOG GU toxicity was reported in 7.3% (SABR, 26/355) and 4.5% (CRT, 16/357) of the treatment groups (p=0.11, non-significant difference). There was evidence of a statistically significant difference in cumulative incidence for GU toxicity at any time to five years reported using the RTOG tool, with 26.9% of patients that received SABR (95% CI 22.8% to 31.5%) and 18.3% of patients that received CRT reporting toxicity (95% CI 14.8% to 22.5%; HR 1.59 (1.18 to 2.12), p<0.001).

Van As et al (pre-print; PACE-B RCT) also reported no statistically significant difference between treatment groups at five years follow-up in urinary incontinence (median EPIC[10] urinary incontinence score, SABR: n=355, 96.9, IQR 73.0 to 100; CRT: n=357, 100, IQR 79.3 to 100; p=0.45) or urinary obstruction (median EPIC

[10] Expanded Prostate Cancer Index Composite shore form (EPIC-26), a patient reported questionnaire.

urinary obstruction score, SABR: 93.8, IQR 81.3 to 100; CRT: 93.8, IQR 81.3 to 100; no p-value reported). Van As et al (pre-print; PACE-B RCT) reported no statistically significant difference between treatment groups at five years in sexual subdomain scores (p=0.87; no further results presented).

Widmark et al (2019; HYPO-RT-PC) reported that patients with intermediate to high risk prostate cancer in the ultra-hypofractionation group reported statistically significantly higher levels of acute urinary symptoms[11] at the end of radiotherapy (treatment end: ultra-hypofractionation, n=439; CRT, n=464; p=0.0066; three months follow-up: ultra-hypofractionation, n=330; CRT, n=336; p=0.018) and at one-year follow-up (ultra-hypofractionation, n=425; CRT, n=427; p=0.0036) when compared to patients receiving CRT (ultra-hypofractionation mean score at one-year: 2.06, 95% CI 1.82 to 2.30; CRT mean score at one-year: 1.58, 95% CI 1.37 to 1.78; p=0.0036). At all other follow-up timepoints (baseline to 10 years follow-up) there was no statistically significant difference between the groups in urinary symptom reporting.

One included paper reported a statistically significantly higher genitourinary (GU) toxicity at two years follow-up in patients treated with SABR (n=384) compared to patients treated with CRT (n=381) for prostate cancer with low or intermediate risk. Two included papers (reporting on the same RCT: PACE-B) reported a statistically significant higher cumulative GU toxicity in patients treated with SABR compared to patients treated with CRT for low or intermediate risk prostate cancer (at two (SABR, n=414; CRT, n=430) to five (SABR, n=355; CRT, n=357) years follow-up). A third included paper reported a statistically significant higher GU toxicity at three months (ultra-hypofractionation, n=330; CRT, n=336) and one year (ultra-hypofractionation, n=425; CRT, n=427) follow-up in patients with intermediate to high risk prostate cancer treated with ultra-hypofractionation radiotherapy compared to patients treated with CRT. No significant differences between the treatment groups were seen at other time points.

Gastrointestinal (GI) toxicity

Tree et al (2022; PACE-B RCT) reported the proportion of patients with prostate cancer with low or intermediate risk with GI toxicity (grade ≥ 2) at two years follow-up using both the CTCAE and the RTOG assessment tool; there was no statistically significant difference between the groups at 24 months follow-up when using either tool. RTOG GI toxicity was reported in 2% (SABR: 6/384; 95% CI 0.1% to 3.5%) and 3% (CRT: 11/382; 95% CI 1.5% to 5.3%) of the treatment groups (absolute difference: -1.3%, 95% CI -3.9% to 1.1%, p=0.32). Using the CTCAE criteria, GI toxicity was 3% and 4% at 24 months in the SABR group and the CRT group, respectively (SABR: 13/414; CRT: 16/430; absolute difference -0.8%, 95% CI -3.8% to 2.2%, p=0.70).

Tree et al (2022; PACE-B RCT) also reported no evidence of a statistically significant difference in cumulative GI toxicity rates at two years using both CTCAE criteria and

[11] Urinary toxicity was patient-reported using the Prostate Cancer Symptom Scale (PCSS) questionnaire and the question “Do you have problems with your urinary tract?”.

the RTOG tool. Cumulative incidence rates using the RTOG tool were 7.8% for patients that received SABR (n=384, 32 events; 95% CI 5.6% to 10.9%) and 8.1% in patients that received CRT (n=382, 34 events; 95% CI 5.8% to 11.1%; HR 0.98, 95% CI 0.60 to 1.58, p=0.92). Cumulative incidence rates using the CTCAE criteria were 12.5% for patients that received SABR (n=384, 51 events; 95% CI 9.6% to 16.1%) and 12.3% for patients that received CRT (n=382, 52 events; 95% CI 9.5% to 15.8%; HR 1.02, 95% CI 0.70 to 1.51, p=0.91).

Van As et al (pre-print; PACE-B RCT) reported the proportion of patients with prostate cancer with low or intermediate risk with GI toxicity (grade ≥ 2) at five years follow-up using both the CTCAE and the RTOG assessment tool. CTCAE GI toxicity was reported in 2.5% of the SABR group (9/355) and 1.7% of the CRT group (6/357; p=0.43, non-significant difference); RTOG GI toxicity was reported in 0.8% (SABR, 3/354) and 0.3% (1/355) of the population (p=0.37, non-significant difference). There was no evidence of a statistically significant difference in the cumulative incidence for GI toxicity at any time to five years when reported using the RTOG tool, with 10.7% of patients that received SABR (95% CI 8.1% to 14.2%) and 10.2% of patients that received CRT reporting toxicity (95% CI 7.7% to 13.5%; HR 1.03, 95% CI 0.68 to 1.56, p=0.94). There was no statistically significant difference between treatment groups in bowel symptoms (median EPIC bowel subdomain scores, SABR: 100, IQR 87.5 to 100; CRT: 95.8, IQR 87.5 to 100; p=0.10) at five years follow-up.

Widmark et al (2019; HYPO-RT-PC) reported that patients with intermediate to high risk prostate cancer treated with ultra-hypofractionation radiotherapy (n=569) reported statistically significantly higher levels of acute bowel symptoms[12] at the end of radiotherapy (treatment end: ultra-hypofractionation, n=440; CRT, n=463; p<0.0001) and at the eight-year follow-up (ultra-hypofractionation, n=73; CRT, n=61; p=0.035) when compared to patients treated with CRT (n=578). At all other follow-up timepoints (baseline to 10 years follow-up) there was no statistically significant difference between the groups in bowel symptom reporting.

Two included papers (reporting on the same RCT: PACE-B) reported no statistically significant difference between SABR and CRT for incidence and cumulative incidence of gastrointestinal (GI) toxicity for patients with low or intermediate risk prostate cancer at two (SABR, n=384; CRT n=382) and five years (SABR, n=354; CRT, n=355) follow-up. A third included paper reported a statistically significant higher GI toxicity (immediately following radiotherapy (ultra-hypofractionation, n=440; CRT, n=463) and at eight-year follow-up (ultra-hypofractionation, n=73; CRT, n=61) in patients with intermediate to high risk prostate cancer treated with ultra-hypofractionation radiotherapy compared to patients treated with CRT.

References

[12] Bowel toxicity was patient-reported using the Prostate Cancer Symptom Scale (PCSS) questionnaire and the question “Do you have problems with your stool?”

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