The POINTER-PC study- determining optimal radiotherapy for pelvic nodal recurrence in prostate cancer

Prostate cancer (PCa) is the commonest cancer in the UK, with more than 55,000 new diagnoses across England in 2023[1, 2]. Most patients present with non-metastatic localised or locally advanced PCa and can be treated with curative intent by radical prostatectomy (RP) with or without post-operative radiotherapy or definitive radiotherapy and/or brachytherapy[3].

Pelvic nodal oligorecurrent prostate cancer

Nearly a third of patients initially treated for non-metastatic PCa with curative intent may experience biochemical recurrence (BCR), characterised by a rise in prostate specific antigen (PSA)[4]. Increased use of positron emission tomography-computed tomography (PET-CT), especially prostate specific membrane antigen (PSMA) PET-CT, during early BCR frequently identifies low volume pelvic lymph node disease, known as nodal oligorecurrent PCa[5, 6]. There is no clear standard of care for management of nodal oligorecurrent PCa. Several treatment options are available, including Stereotactic Body Radiotherapy (SBRT) to involved node(s) alone, Extended Nodal Irradiation (ENI) to encompass pelvic nodal regions at risk of microscopic spread in addition to delivering a simultaneous integrated boost (SIB) to macroscopically involved node(s) and androgen deprivation therapy (ADT) with or without androgen receptor pathway inhibitors (ARPIs) or docetaxel chemotherapy[3, 7].

Radiotherapy approaches to treatment of nodal oligorecurrent prostate cancer

Of the two radiotherapy treatments for nodal oligorecurrent PCa, SBRT has been increasingly used as it is convenient, given in 3-5 fractions, with excellent local control and minimal toxicity[8]. Three randomised phase 2 studies have evaluated SBRT for oligorecurrent PCa, including pelvic nodal recurrence[9-11]. These studies suggest that SBRT is well tolerated and can delay further disease progression. Despite these promising data, there is an absence of phase 3 level evidence regarding impact of SBRT on metastasis-free survival (MFS) or overall survival in PCa. In addition, sites of microscopic disease within pelvic nodal regions may not be identified using PET-CT and observational data have demonstrated that further disease progression following SBRT often occurs within the pelvis[12, 13]. New nodal recurrences could be treated by repeated SBRT, but the ability to deliver further radiation may be significantly compromised by the prior treatment and/or be less effective[14]. This has led to increasing interest in the potential of ENI to prevent further progression by treatment of nodal regions which could harbour microscopic disease. Promising survival outcomes are reported from phase 2 clinical trials and observational studies for ENI compared with SBRT[15-23]. Although there is concern that the larger radiotherapy volumes used with ENI compared with SBRT could result in more toxicity, especially following prior primary prostate/ post-

operative radiotherapy, the risk of significant late bowel and urinary toxicities appears to be low. A summary of clinical trial and observational data for ENI vs SBRT is shown in the **Table**.

STORMing progress

PEACE V Salvage Treatment of OligoRecurrent nodal prostate cancer Metastases (STORM) is the first study to provide randomised phase 2 evidence of the benefits of ENI versus metastasis directed therapy (MDT), defined as pelvic nodal treatment using either SBRT or salvage pelvic lymph node dissection (only 6% of participants in STORM received surgery for MDT)[19]. In STORM, 196 participants were randomised to either ENI or MDT, with 6 months ADT given in both arms. The primary endpoint was MFS, with an alpha level of 20% . STORM demonstrated improved 4-year MFS with ENI compared with MDT (76% vs 63%, HR 0.62 (95% CI 0.44-0.86), p=0.063). In addition, biochemical relapse-free survival (57% vs 41%, p=0.014), locoregional relapse-free survival (85% vs 62%, p=0.0047) and ADT-free survival (77% vs 60%, p=0.049) were also improved with ENI vs MDT.

No statistically significant difference in clinician-assessed ≥grade 2 cumulative bowel (9% vs 7%, p=0.93) and urinary (31% vs 28%, p=0.73) toxicity was observed between the ENI and MDT arms. Interestingly, radiation was also delivered to the prostatic fossa in 42% and 25% of participants in the ENI and MDT arms, respectively. In post-hoc analyses, across both arms ≥grade 2 bowel (OR 4.6 (95% CI 1.5-15.8), p=0.0085) and urinary (OR 1.85 (95% CI 0.95-3.60), p=0.068) toxicities appeared to be higher when the prostatic fossa was irradiated compared to when it was either not irradiated or had previously been irradiated. On the other hand, participants who received prostatic fossa irradiation either during STORM or prior to trial entry appeared less likely to develop subsequent local recurrence than those without prostatic fossa irradiation (HR 3.01 (95% CI 1.62-5.6), p=0.023).

STORM has shown that ENI appears to result in better MFS, biochemical control and reduced risk of further pelvic recurrence compared with SBRT with comparable bowel and urinary toxicities. It has established ENI as a potential standard treatment for nodal oligorecurrent PCa, pending phase 3 confirmation. Whether ENI impacts overall survival compared with SBRT remains to be determined- insufficient events had occurred to date in STORM to report this endpoint.

POINTing the way forward

The Yorkshire Cancer Research funded Pelvis Or Involved Node Treatment: Eradicating Recurrence in Prostate Cancer (POINTER-PC) randomised controlled trial (RCT) is the first phase 3 study designed to definitively determine optimal radiotherapy for nodal oligorecurrent PCa[20]. POINTER-PC will recruit 480 participants over 4 years from up to 40 UK radiotherapy centres. Participants will be randomised 2:1:1 to SBRT in 5 fractions, ENI in 20 fractions (ENI-20) or ENI in 5 fractions (ENI-5). The study opened to recruitment in January 2025.

Similar to STORM, POINTER-PC will evaluate whether ENI is superior to SBRT for the primary endpoint of 3-year MFS[19, 20]. A co-primary endpoint will evaluate whether ENI-5 is non-inferior to ENI-20 for 3-year participant-reported late bowel toxicity. There are several differences between the two studies. As a phase 3 RCT, POINTER-PC has been developed to deliver practice-changing evidence of radiotherapy for nodal oligorecurrent PCa, which is reflected in its larger sample size (480 vs 196 participants) and more stringent type I error control (5% vs 20% significance level) for the ENI vs SBRT alone comparison, whilst targeting a similar clinically-relevant treatment effect (HR=0.65)[20]. POINTER-PC will not use salvage pelvic lymph node dissection, which reflects UK practice and takes account of recent data which suggest that surgery may be less effective than radiotherapy in this setting and is associated with morbidity[24]. In addition, participants previously treated with radical prostatectomy without subsequent prostatic fossa irradiation are not currently eligible for POINTER-PC. This decision was initially taken because of concerns regarding potential for increased toxicity with concurrent irradiation of prostatic fossa, especially with the ultra hypofractionated ENI-5 arm. However, this eligibility criterion is being reviewed and may be expanded to incorporate these patients.

There are subtle differences in the MFS definitions used in the two studies. In POINTER-PC, MFS was initially defined as progression of the treated lesion, new nodal (including pelvic nodal), bone or visceral metastatic disease or death due to PCa[20]. In comparison, in STORM the MFS definition is new metastatic recurrence or death due to PCa[19]. POINTER-PC will report patterns of failure, time to metastatic progression or death due to prostate cancer, and, also as with STORM, includes biochemical progression-free survival as a key secondary endpoint[19, 20]. Considering the STORM data, however, the MFS definition in POINTER-PC may be adjusted so that it better aligns with STORM. The STORM results will also permit refinement of the sample size required to address this primary endpoint in POINTER-PC.

STORM delivered ENI as 45 Gy in 25 fractions over 5 weeks + 65 Gy SIB, while POINTER-PC will evaluate two shorter schedules: 44 Gy in 20 fractions over 4 weeks + 54 Gy SIB in the ENI-20 arm and 25 Gy in 5 fractions on alternate days over 10 days + 30-40 Gy SIB in the ENI-5 arm. POINTER-PC therefore presents a unique and valuable opportunity to evaluate both 20 and 5-fraction ENI schedules in the recurrence setting, based primarily on patient-focused toxicity endpoints. This aligns with the growing evidence base for convenient moderate and ultra hypofractionated schedules for primary and post-operative PCa treatment[25-30].

Despite some differences between the interventions and endpoints across the two studies, there clearly is tremendous potential to combine data in the future to gain further insights into the optimal radiotherapy volume to treat nodal oligorecurrent PCa.

Defining the optimal treatment for nodal oligorecurrent prostate cancer

The evidence base for treatment of recurrent PCa is rapidly evolving. The recently published EMBARK phase 3 RCT demonstrated efficacy of early integration of ARPIs for patients with high-risk BCR, defined as PSA doubling time ≤9 months and a PSA of ≥1 ng/ml and ≥nadir + 2 ng/ml, following

previous RP and radiotherapy, respectively[31]. Five-year MFS was 87.3%, 80.0% and 71.4% for patients treated with enzalutamide and ADT, enzalutamide monotherapy and ADT alone, respectively.

This raises questions about the most appropriate treatment combinations to use for nodal oligorecurrent PCa and also highlights the potential for PET-CT to guide decision making. EMBARK used conventional imaging for participant selection, which has limited performance to detect recurrent disease at the low PSA levels which characterise early BCR[6]. With PSMA PET-CT, a substantial proportion of patients with BCR will have pelvic nodal oligorecurrence without more distant metastatic disease. In a recent analysis of participants from prospective trials who would have met EMBARK eligibility criteria, 40% had PSMA PET-CT detected pelvic nodes despite negative conventional imaging[32]. Considering that in EMBARK, grade 3+ toxicities were observed in 17.6% and 16.1% of participants in the enzalutamide-ADT and enzalutamide monotherapy arms, respectively, POINTER-PC will determine whether patients with nodal oligorecurrence can achieve long-term disease control with ENI and SBRT, avoiding or deferring the need to commence ARPIs or other systemic therapy which may be associated with significant toxicity[31].

This does not ignore the potential to improve outcomes for patients at high risk of distant metastatic progression by combining radiotherapy with intensification of systemic therapy[33]. POINTER-PC will permit additional systemic therapies (ARPIs or docetaxel) following radiotherapy, and stratification for this has been incorporated into the design to account for the potential impact on MFS. In addition, through its Cancer Research UK funded Prospective Sample Collection Award, POINTER-PC represents a unique opportunity to develop future personalised approaches to treatment. Analysis of diagnostic/prostatectomy histology, pre and post-radiotherapy blood samples and PET-CT images may help to identify prognostic biomarkers which could enable stratification of patients by risk of further disease progression, highlighting where the focus should be treatment intensification to optimise disease related outcomes or de-intensification to minimise additional toxicity.

In summary, we hope that the radiotherapy community will fully embrace POINTER-PC to provide practice-changing evidence based on both clinical and patient-reported outcomes. This unique opportunity builds on the strong foundation provided by STORM to determine the optimal radiotherapy to improve outcomes for our patients with pelvic nodal oligorecurrent PCa.

Table: Summary of selected ongoing and previous clinical trials and observational studies of ENI and SBRT for pelvic nodal oligorecurrent prostate cancer

Study	Year	Type	Population	Imaging	Number	Intervention(s)	Outcomes	Toxicity

POINTER-PC[20]	2025	Randomised phase 3	1-3 pelvic nodes after previous RP and post-operative RT or definitive RT and/or brachytherapy	PSMA or choline PET-CT	Total 480: SBRT 240 ENI-5 120 ENI-20 120	SBRT + 12 months ADT vs ENI-5 + 12 months ADT vs ENI-20 + 12 months ADT ARPI or docetaxel permitted post RT	3-year MFS (ENI vs SBRT) and 3-year PROM assessed late bowel toxicity (ENI-5 vs ENI-20)	PROM and clinician assessed toxicity
STORM[19]	2025	Randomised phase 2	1-5 pelvic nodes after previous RP with or without post-operative RT or definitive RT	PSMA PET-CT 82% Choline PET-CT 18%	196	ENI +/- prostatic fossa + 6 months ADT vs MDT* +/- prostatic fossa + 6 months ADT	4-year MFS 76% vs 63%, p=0.063 4-year bRFS 57% vs 41%, p=0.014 4-year lrRFS 85% vs 62%, p=0.0047	≥Grade 2 cumulative bowel toxicity 9% vs 7%, p=0.93 Post-hoc analysis: increased ≥grade 2 bowel toxicity with inclusion of prostate

							4-year ADT-free survival 77% vs 60%, p=0.049	bed, OR 4.6 (95% CI 1.5-15.8), p=0.0085 ≥Grade 2 cumulative urinary toxicity 31% vs 28%, p=0.73 Post-hoc analysis: increased ≥grade 2 urinary toxicity with inclusion of prostatic fossa, OR 1.85 (95% CI 0.95-3.60), p=0.068
OLIGOPELVIS[21, 22]	2021	Single arm phase 2	1-5 pelvic nodes after previous RP with or without post-	Choline PET-CT	67	ENI +/- prostatic fossa + 6 months ADT	2-year PFS 81%	5-year ≥grade 2 late bowel toxicity 4%

			operative RT or definitive RT				5-year PFS 39%	5-year ≥grade 2 late urinary toxicity 4%
PLATIN-4/PLATIN-5[23]	2024	Single arm phase 2	Pelvic nodes after previous RP with or without post-operative RT	PSMA PET-CT 44.9% or conventional 55.1%	78	PLATIN-4: ENI + prostatic fossa PLATIN-5: ENI 24 months ADT (45% received ≥24 months, 55% received <18 months ADT)	PLATIN-4: Median PFS 66 months Median OS not reached PLATIN-5: Median PFS 39 months Median OS 117 months	4% late grade 3+ GU/GI toxicity Decline in 5-year quality of life (fatigue, role, physical)
Fodor et al[16, 17]	2017	Single arm phase 2	Pelvic nodes after previous RP with or without post-operative RT or definitive RT	Choline PET-CT	60	ENI +/- prostatic fossa + median 30 months ADT	5-year bRFS 36% 10-year bRFS 24%	10-year incidence of ≥grade 2 late bowel toxicity 0% 10-year incidence of

								≥grade 2 late rectal toxicity 5% 10-year incidence of ≥grade 2 late urinary toxicity 20%
De Bleser et al[15]	2019	Retrospective cohort	1-5 pelvic nodes after previous RP with or without post-operative RT or definitive RT	PSMA, choline or FDG PET-CT or conventional	506: ENI 197 SBRT 309	ENI +/- prostatic fossa + median 6 months ADT vs SBRT + median 6 months ADT	3-year MFS 77% vs 68%, p=0.01	Late toxicity 15.7% vs 5.2%, p<0.001
Lépinoy et al[18]	2019	Retrospective cohort	Pelvic or retroperitoneal[†] nodes after previous RP with or without post-operative RT or definitive RT	Choline PET-CT	62	ENI vs IFRT[‡] +/- ADT (48.1% in ENI group, median 6 months vs 5.7% in IFRT group, median 2.6 months)	3-year TTF 88.3% vs 55.3%, p=0.0094	≥Grade 2 late bowel toxicity 11.1% ≥Grade 2 late urinary toxicity 20% 1 x Grade 4 toxicity (rectovesical

								fistula) in the ENI group

*MDT was SBRT in 94% and surgery in 6% of participants allocated to MDT arm

†Retroperitoneal radiotherapy delivered to 29.6% of patients

‡ In SBRT group, SBRT was used in 82.9% of patients and IMRT/3 dimensional conformal radiotherapy was used in 17.1% of patients

ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; bRFS, biochemical relapse-free survival ENI, extended nodal irradiation; CI, confidence interval; ENI-5, extended nodal irradiation in 5 fractions; ENI-20, extended nodal irradiation in 20 fractions; FDG, fluorodeoxyglucose; IFRT, involved field radiotherapy; MDT, metastasis directed therapy; lrRFS, locoregional relapse-free survival; MFS, metastasis-free survival; OR, odds ratio; PET-CT, positron emission tomography-computed tomography; PFS, progression-free survival; PROM, participant reported outcome measure; PSMA, prostate specific membrane antigen; RP, radical prostatectomy; RT, radiotherapy; SBRT, Stereotactic Body Radiotherapy; TTF, time to treatment failure

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