Technoleg Iechyd Cymru
Health Technology Wales

Topic Exploration Report [1]

Salvage high dose rate brachytherapy (HDR-BT) for localised relapse of prostate cancer after prior curative intent radiotherapy.

What is a Topic Exploration Report?

Topic Exploration Reports are not health technology assessments. These reports provide a high-level briefing on new topics submitted to Health Technology Wales and are not based on exhaustive or systematic literature searches. Instead, they rely on a focussed scan of key resources.

What evidence is used in a Topic Exploration Report?

Priority is given to summarising the most relevant or useful evidence, rather than covering all possible evidence. Information reported is typically based on abstracts and study authors' own conclusions, rather than detailed scrutiny of full texts.

What are the aims of a Topic Exploration Report?

Topic Exploration Reports offer an overview of the available evidence on a topic and aim to highlight any uncertainties or gaps in the evidence. These reports outline the quantity and type of evidence found, but no critical appraisal or formal evidence synthesis is conducted.

How should a Topic Exploration Report be used?

Topic Exploration Reports can be used to indicate what evidence may be available for a topic, and do not provide definitive guidance on how a technology should be used. The evidence presented within the reports should be interpreted with caution.

[1] Cyfieithu dogfennau HTW wedi'u cyhoeddi o'r Saesneg i'r Gymraeg
Translation of published technical HTW documents from English into Welsh

Topic exploration report number	TER596
Topic	Salvage high dose rate brachytherapy (HDR-BT) for localised relapse of prostate cancer after prior curative intent radiotherapy.
Summary of findings	HTW researchers identified one NICE guideline on the diagnosis and management of prostate cancer, one systematic review, two systematic review with meta-analyses, six observational studies (including one study reporting on health-related quality of life outcomes (QoL) and one retrospective study), and three ongoing trials. However, there is overlap in the included primary studies referenced in the systematic reviews. Across the evidence base, the primary treatment, T-stage, number of fractions used, and the comparators, varied. HTW researchers did not identify studies reporting on the cost-effectiveness of salvage HDR-BT. Based on the evidence identified in this TER, salvage HDR-BT tends to be associated with increased levels of toxicity compared with people undergoing primary treatment alone, however, based on the conclusions of two meta-analyses, salvage HDR-BT tends to be associated with a statistically significant lower level of gastrointestinal toxicity when compared with prostatectomy. Key uncertainties to note are that there is a lack of prospective randomised controlled trials in this area and if this topic were to process to a fuller appraisal, the exact comparator or choice of comparators, and the previous treatments used could be explored to potentially narrow down the scope of the review.

Introduction and aims

Context

Prostate cancer is the most common cancer in men in the UK and is on the rise. In Wales, 2261 men were diagnosed with the disease in 2020, with incidence peaking in people aged 65-74 years (Public Health Wales 2023). However, survival rates are increasing with 97% of men who are diagnosed with prostate cancer in Wales surviving for five years or longer in 2016-20 (Public Health Wales 2023). Information from the topic proposer suggests approximately 800 men undergo curative intent external beam radiotherapy in Wales per year. Between 10-25% of these men will relapse in the years after treatment and an estimated 3-10% of these men will have local failure alone (in the prostate without nodal or distant metastases).

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People with local failure may be suitable for a second curative salvage treatment such as prostatectomy or salvage HDR-BT. Currently in Wales, salvage radical prostatectomy is the only available curative option for local failure after radiotherapy. People unsuitable for surgery may have hormone treatment (prostap) and would then undergo chemotherapy. Salvage prostatectomy is only available for selected patients and can be associated with severe bowel and urinary side effects. Salvage HDR-BT involves temporarily inserting thin tubes into the prostate gland for radiation to destroy cancer cells (Prostate Cancer UK 2023). As the radiation is directed at the prostate, the nearby cells receive a smaller dose of radiation, and it is less likely to cause damage to nearby tissue (Prostate Cancer UK 2023).

Salvage HDR-BT is available in tertiary specialist cancer centres only, such as Velindre Cancer Centre in Cardiff. Information from the topic proposer suggests that there would not be additional equipment needed to deliver an expansion of the brachytherapy service, however there would be some requirement for brachytherapy staff to be appropriately trained and some additional theatre capacity would need to be funded.

Health Technology Wales researchers searched for evidence on salvage HDR-BT for localised relapse of prostate cancer after prior primary treatment.

Evidence overview

Guidelines

HTW researchers identified one guideline on the diagnosis and management of prostate cancer relating to untreated newly presenting patients (NICE 2019). The guideline states that people should consider brachytherapy in combination with external beam radiotherapy for people with Cambridge Prognostic Group (CPG) 2, 3, 4 and 5 localised or locally advanced prostate cancer. However, brachytherapy alone is not recommended in people with CPG 4 and 5 localised or locally advanced prostate cancer.

Secondary research

HTW researchers identified one systematic review (Chatzikonstantinou et al. 2017), two systematic reviews with meta-analyses (Valle et al. 2021, Creta et al. 2024), six additional observational studies that were not referenced in the reviews and three ongoing trials. However, at least five of the studies referenced in Chatzikonstantinou et al. (2017) are also referenced in Valle et al. (2021). The systematic reviews note further prospective and randomised studies would be beneficial in this patient population.

Creta et al. (2024) reported on local salvage strategies in people with local prostate cancer recurrence following primary external-beam radiation therapy (EBRT). Overall, 28 studies (6 prospective and 22 retrospective) including 1544 patients were included. Two-year recurrence-free survival (RFS) was 84.0% (95% CI: 67.0–93.0%) for brachytherapy, which was higher than the

other salvage strategies. Severe gastrointestinal toxicity were estimated to be 2%, 3%, 3%, 4%, and 11% following cryotherapy, BT, high-intensity focused ultrasound (HIFU), EBRT, and salvage radical prostatectomy, respectively.

Valle et al. (2021) explored local salvage therapies after radiotherapy. The analysis compared the efficacy and toxicity of salvage radical prostatectomy, HIFU, cryotherapy, SBRT, LDR-BT, and HDR-BT. A total of 150 studies were included for analysis, although only 16 papers evaluated HDR-BT which included four prospective studies. It is unclear from the paper whether any randomised controlled trials were included. Valle et al. (2021) gave an estimated 5-year relapse free survival of 53% (adjusted value) (46%–59%) for prostatectomy and 58% (52–64%) for HDR-BT (p=0.2). Severe GU toxicity was significantly lower with salvage HDR-BT than with radical prostatectomy (adjusted values: 9.6% versus 21% p=0.002). Severe GI toxicity was reported as significantly lower with salvage HDR-BT when compared with prostatectomy (adjusted rates 1.8% vs 0.0%, p=0.003).

Chatzikonstantinou et al. (2017) published a systematic review on HDR-BT as salvage treatment for locally recurrent prostate cancer after definitive radiotherapy. The review included 11 papers and the follow up times ranged from four to 191 months. Dosages ranged from 19.0 gray (Gy) in two fractions to 42.9 Gy in 6 fractions. The 5-year biochemical control ranged from 18–77%. Late grade 3 genitourinary (GU) and gastrointestinal (GI) toxicity was 0–32% and 0–5.1%, respectively.

Primary research

Six primary studies that were not referenced in the systematic reviews were published between 2020 and 2023 (Chitmanee et al. 2020, Mayrata et al. 2021, Rasing et al. 2023, Slevin et al. 2020, van Son et al. 2020, Mäkelä et al. 2023). All studies assess the effectiveness of salvage HDR-BT in people who have previously received primary treatment, however salvage HDR-BT was not compared to other salvage treatment options.

Before and after design studies

Four studies (Chitmanee et al. 2020, Mayrata et al. 2021, Rasing et al. 2023, Slevin et al. 2020) with a before and after design report clinical outcomes.

Chitmanee et al. (2020) evaluated focal HDR-BT (one dose of 19 Gy) in people who had locally recurrent prostate cancer who previously received non-surgical primary treatment between 2013-2019 with a median follow-up of 21 months (N=50). Biochemical progression-free survival at 2 and 3 years was 63% and 46%, respectively. Other outcomes included grade 3 GI toxicity (N=3), severe lower urinary tract symptoms (N=2), erectile dysfunction (N=1), and urethral stricture requiring surgery (N=4).

Mayrata et al. (2021) evaluated the toxicity, PSA kinetics, and cancer control of salvage HDR-BT (total dose of 24 Gy, two doses of 12 Gy) in 12 patients between 2017-2019 with locally recurrent prostate cancer, after receiving primary HDR-BT (19 Gy) in 2014, with a median follow-up time of 26 months. Outcome measures included grade 2 GU toxicity (N=4), acute GI toxicity (N=0), late grade 2 GU toxicity (N=2), grade 3 toxicity (N=0), and biochemical failure after salvage treatment (N=2).

Rasing et al. (2023) reported the recurrence characteristics after focal salvage HDR-BT (one dose of 19 Gy) between 2013-2021 in 175 patients who previously received HDR-BT (19 Gy), with a median follow-up time of 36 months. Outcome measures included the year biochemical recurrence-free survival, local recurrences (LR) free survival, in-field LR-free survival, out-of-field LR-free survival, any-recurrence-free survival and androgen deprivation therapy (ADT) free survival, which were 43% (95%CI 34%–52%), 51% (41%–61%), 70% (61%–80%), 92% (88%–97%), 42% (32%–52%) and 86% (80%–92%), respectively.

Evidence overview

Slevin et al. (2020) report on the efficacy and toxicity outcomes of salvage HDR-BT (one dose of 19 Gy) for locally recurrent prostate cancer in 43 patients who had prior LDR-BT or stereotactic body radiation therapy (SBRT) between 2015-2018 with a median follow-up time of 26 months. Estimates for biochemical progression free survival at 1-, 2- and 3-years post salvage treatment were 95.2%, 70.6% and 41.8% respectively. Incidences of grade 2 GU and GI toxicities were 39 and 6 patients respectively, and grade 3 late GU toxicity was observed in one patient.

Retrospective studies

One retrospective study was identified reporting on biochemical disease-free survival, GU and GI toxicity (Mäkelä et al. 2023). The study analysed 100 prostate cancer patients who had locally relapsed after previous radiotherapy and were treated with salvage HDR-BT (total dose of 24 Gy, 8 Gy in three fractions). The 3-year biochemical disease-free survival and overall survival were 74% (confidence interval [CI] 95%: 60–87%) and 93% (CI 95%: 84–100%), respectively. Acute Grade 1–2 GU toxicity was reported in 70 people and acute grade 1 GI toxicity was observed in eight patients.

Patient reported quality of life outcomes

One study report on health-related QoL outcomes only, after patients received salvage HDR-BT (van Son et al. 2020). van Son et al. (2020) report health-related quality of life outcomes (HR-QoL) from the patient's perspective in 100 people who received salvage HDR-BT. HR-QoL was assessed by the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-PR25 questionnaire. Domains were urinary and bowel symptoms, and sexual activity/functioning, with a median follow-up of 20 months. Urinary symptoms and sexual functioning scores declined over time and a better baseline score of sexual function was observed in the baseline figures ($p<0.01$).

Cost-effectiveness studies

HTW researchers did not identify studies reporting on the cost-effectiveness of salvage HDR-BT. Information from the topic proposer suggest that there could be cost savings made through avoidance of multiple expensive non-curative systemic anti-cancer therapy (SACT) treatment options.

Ongoing studies

HTW researchers identified three ongoing trials referenced overleaf. Estimated completion dates include 1 March 2035, 31 March 2025 and 31 May 2026.

Areas of uncertainty

Noted in the systematic reviews, there is a lack of prospective randomised controlled trials in this area.

If this topic were to proceed to a fuller appraisal, the exact comparator or choice of comparators and the previous treatments used could be explored, to potentially narrow down the scope of the review.

The dosages and patient characteristics would need to be explored to ensure fair comparisons and treatment options for this specific patient population who have undergone prior radiotherapy.

Literature search results

Health technology assessments and guidance

NICE. (2019). Prostate cancer: diagnosis and management. NG131. National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/ng131 [Accessed 6 March 2025].

Evidence reviews and economic evaluations

Creta M, Shariat SF, Marra G, et al. (2024). Local salvage therapies in patients with radio-recurrent prostate cancer following external beam radiotherapy: a systematic review and meta-analysis. Prostate Cancer and Prostatic Diseases. doi: 10.1038/s41391-024-00883-3. Available at https://doi.org/10.1038/s41391-024-00883-3

Chatzikonstantinou G, Zamboglou N, Rödel C, et al. (2017). High-dose-rate brachytherapy as salvage modality for locally recurrent prostate cancer after definitive radiotherapy : A systematic review. Strahlenther Onkol. 193(9): 683-91. doi: 10.1007/s00066-017-1157-2. Available at: https://pubmed.ncbi.nlm.nih.gov/28623436/

Valle LF, Lehrer EJ, Markovic D, et al. (2021). A Systematic Review and Meta-analysis of Local Salvage Therapies After Radiotherapy for Prostate Cancer (MASTER). Eur Urol. 80(3): 280-92. doi: 10.1016/j.eururo.2020.11.010. Available at: https://pubmed.ncbi.nlm.nih.gov/33309278/

Individual studies

Chitmanee P, Tsang Y, Tharmalingam H, et al. (2020). Single-Dose Focal Salvage High Dose Rate Brachytherapy for Locally Recurrent Prostate Cancer. Clin Oncol (R Coll Radiol). 32(4): 259-65. doi: 10.1016/j.clon.2019.10.008. Available at: https://pubmed.ncbi.nlm.nih.gov/31708350/

Mäkelä L, Bergroth R, Taipale L, et al. (2023). Salvage HDR brachytherapy for prostate cancer: a high-volume center experience on 100 consecutive patients. Scand J Urol. 57(1-6): 36-40. doi: 10.1080/21681805.2023.2168048. Available: https://pubmed.ncbi.nlm.nih.gov/36724186/

Mayrata E, Espinosa JM, Büchser D, et al. (2021). Salvage brachytherapy for locally recurrent prostate cancer after single-fraction 19 Gy high-dose-rate brachytherapy: toxicity, prostate-specific antigen kinetics, and cancer control. J Contemp Brachytherapy. 13(1): 12-7. doi: 10.5114/jcb.2021.103581. Available at: https://pubmed.ncbi.nlm.nih.gov/34025731/

Rasing MJA, Peters M, van Son M, et al. (2023). Recurrence characteristics after focal salvage HDR brachytherapy in prostate cancer. Radiother Oncol. 180: 109495. doi: 10.1016/j.radonc.2023.109495. Available at: https://pubmed.ncbi.nlm.nih.gov/36708924/

Slevin F, Hodgson S, Rodda SL, et al. (2020). Efficacy and toxicity outcomes for patients treated with focal salvage high dose rate brachytherapy for locally recurrent prostate cancer. Clin Transl Radiat Oncol. 23: 20-6. doi: 10.1016/j.ctro.2020.03.010. Available at: https://pubmed.ncbi.nlm.nih.gov/32368626/

van Son M, Monninkhof E, Peters M, et al. (2020). Health-related quality of life after ultrafocal salvage high-dose-rate brachytherapy for radiorecurrent prostate cancer: reporting the patient's perspective. Clin Transl Radiat Oncol. 25: 81-7. doi: 10.1016/j.ctro.2020.10.002. Available at: https://pubmed.ncbi.nlm.nih.gov/33134565/

Background references

Prostate Cancer UK. (2023). High dose-rate (HDR) brachytherapy. Prostate Cancer UK. Available at: https://prostatecanceruk.org/prostate-information-and-support/treatments/high-dose-rate-brachytherapy [Accessed 5 March 2025].

Public Health Wales. (2023). Cancer incidence in Wales [2002-2020]. Available at: https://phw.nhs.wales/services-and-teams/welsh-cancer-intelligence-and-surveillance-unit-wcisu/cancer-reporting-tool-official-statistics/cancer-incidence/ [Accessed 5 March 2025].

Ongoing research

1. *F-SHARP: a Phase I/II trial of focal salvage high-dose rate brachytherapy for radio recurrent prostate cancer*

Solanki AA, Yoo RK, Adams W, et al. (2024). F-SHARP: a Phase I/II trial of focal salvage high-dose-rate brachytherapy for Radiorecurrent prostate cancer. BJU Int. 133(2): 188-96. doi: 10.1111/bju.16150. Outcomes will include GU and GI toxicity rate, biochemical failure, patterns of clinical progression, disease specific and overall survival, and health-related quality of life. The status of the ongoing trial is unknown, and an updated was last posted in June 2020. As of March 2025, published results were not posted. The estimated completion date is 31 March 2025. Available at: https://clinicaltrials.gov/study/NCT03312972

2. *Salvage HDR for Locally Recurrent Prostate Cancer.*

Currently marked as recruiting. Estimated primary completion date of 1 March 2025. Estimated study completion date of 1 March 2035. Primary outcome is the time to castration-resistant prostate cancer. Secondary outcomes include erectile disfunction, urinary and bowel symptoms. Available at: https://scanmedicine.com/clinicaltrials/NCT04231006

3. *A Study of Focal Salvage High-Dose-Rate Brachytherapy for Prostate Gland Only Recurrence.*

Currently marked as recruiting. Estimated completion date of 31 May 2026. Primary outcomes include Number of patients with prostate-specific antigen (PSA) levels rising of 2ng/ml or above, Incidence of treatment related adverse events. Secondary outcome is progression free survival. Available at: https://www.clinicaltrials.gov/study/NCT04645810

Date of search	6 March 2025
Concepts used	Salvage HDR brachytherapy OR salvage high dose rate brachytherapy OR high dose rate brachytherapy AND localised relapse of prostate cancer OR prostate cancer.

Proposed research question and evidence selection criteria (if selected)

Proposed Research question	**What is the clinical and cost effectiveness of salvage HDR brachytherapy for localised relapse of prostate cancer after prior curative radiotherapy?**

	Inclusion criteria	Exclusion criteria
Population	People with local recurrence after prostate cancer treatment (suitable for second curative treatment)	People with metastatic recurrence
Intervention	Salvage HDR brachytherapy (such as SABR, EHFRT, HDR-BT)	First line treatment
Comparison/ Comparators	Salvage radical prostatectomy	
Outcome measures	Overall survival Relapse free survival Biochemical progression-free survival PROMS Treatment related toxicity Health related QoL Resource use Economic outcomes	

Proposed speciality	**Cancer**