Clinical and research challenges in prostate cancer recurrence

Date: October 2024

Main contributor: Abel Tesfai[1]

Contributors to early drafts and review design:
Natalia Norori[1], Alexandra Naranjo[1], Tayla Maloney[2], Joseph Woollcott[2], Patricia Smith[3], Matthew Hobbs[4], Hayley Luxton[4] and Simon Grieveson[4]

Special thanks to members of the Clinical Advisory Group[5] and to Dr Neil MacLachlan who shared his case study for use in the review

1 Data & Evidence, Prostate Cancer UK
2 Policy & Health Influencing, Prostate Cancer UK
3 Specialist Nurses, Prostate Cancer UK
4 Research Team, Prostate Cancer UK
5 Clinical Advisory Group members at Prostate Cancer UK

PROSTATE CANCER UK

Summary of key challenges/questions reported in this review:

1. Traditional definitions of prostate cancer recurrence do not reflect modern UK clinical practice
2. There are no set of universally adopted and implemented PSA thresholds to denote recurrence by reporting laboratories, across the UK. This is important for post treatment follow-up care.
3. Clinical recurrence can be detected by novel imaging modalities, in the presence of very low levels of PSA, but long-term outcomes are unclear
4. It is also unclear what number and proportion of UK patients suffer from local/regional/metastatic recurrence following radical treatment (across different imaging modalities)
5. Challenges remain in the treatment selection and management of patients after recurrence

Disclaimer: This review does not endorse specific imaging techniques or treatment. For readers interested in clinical guidance, Prostate Cancer UK's Specialist Nurses provide men with the support they need. Our published guides are also available through our website.

Contents

Introduction 3

Prostate cancer recurrence definition and clinical challenges 4

The role of imaging technology in the detection and management of prostate cancer recurrence 5

Real-world data challenge: how big of a problem is prostate cancer recurrence in the UK? 6

Strengths 7

Limitations 7

Conclusion 8

Acknowledgements 8

References 9

1.0 Introduction

Prostate cancer is the most common male cancer in the UK, with an average of 52,000 men diagnosed with prostate cancer every year and an average of 12,000 deaths attributed to prostate cancer every year (1). Approximately 10,000 men are also diagnosed with stage 4 prostate cancer which indicates cancer spread to nearby tissues, lymph nodes and in some cases distant organs (2).

The number of new cases of prostate cancer is estimated to increase to 214,452 in Western Europe by 2040; this will place additional burden on primary and secondary care services (3). An increase in the incidence of prostate cancer may also lead to a surge in the detection of localised disease and primary curative treatments such as radical prostatectomy and radiotherapy. Radical treatments have previously been shown to be effective, with the Prostate Testing for Cancer and Treatment (ProtecT) trial reporting a 97% survival rate after a median follow-up of 15 years (4–6). These treatments also bring down levels of prostate-specific antigen (PSA) in blood. More specifically, PSA levels become undetectable within several weeks after radical prostatectomy unless residual cancer is present (7). While patients treated with radiotherapy or brachytherapy reach their nadir (lowest PSA value) between 18 months to three years after treatment when treated without Androgen Deprivation Therapy (ADT). In either case, the lowest recorded PSA can be used as a new baseline for future observations.

In the UK, patients are monitored regularly after treatment using established PSA thresholds. For example, patients treated with radiotherapy have blood tests every six months for the first five years and then every year after that if levels remain stable within the acceptable range (8–11). Nonetheless, some patients (with or without symptoms) go on to suffer from biochemical recurrence, which is signified by a rise in PSA (12,13).

Crucially, biochemical recurrence only raises the suspicion of prostate cancer, which in turn triggers the need for further investigations. Clinical recurrence, on the other hand, refers to the return of cancer, as determined by imaging or biopsy. Clinical recurrence may occur concurrently with or following biochemical recurrence. In this scenario, imaging helps determine if the cancer is localised, regional or metastatic, as part of the restaging process (**Figure 1**). Imaging can also inform treatment choices, including local salvage therapies (14–16).

However, despite a plethora of studies on recurrence and the availability of UK clinical guidelines on recurrence, routinely collected national data (real-world data) on recurrence has historically not been available. This has limited, among other things, our ability to optimise treatments for UK patients with different characteristics and pre-treatment risk features (17–22). This lack of real-world data and evidence has led to recent efforts to develop investigative tools/models, using routinely collected and linked datasets, on cancer diagnoses, treatments, and outcomes (23).

Therefore, this review aims to detail some key challenges in recurrence, focusing on the advent of novel imaging techniques and the potential utility of real-world datasets.

2.0 Prostate cancer recurrence definition and clinical challenges

Biochemical recurrence can be defined as a repeated rise in PSA (0.2ng/mL) in a post-radical prostatectomy setting (24,25). Similarly, definitions of recurrence by the Radiation Therapy Oncology Group and American Society for Therapeutic Radiology and Oncology group Phoenix Conference have helped inform clinical practice. More specifically, according

to this consensus, biochemical recurrence, also called radiorecurrent prostate cancer (after the use of external beam therapy), can be defined as a rise in PSA by 2 ng/mL or more above the nadir (26,27). This definition also factors in benign rises in PSA, which can occur through a phenomenon known as 'PSA bounce'. PSA bounce may be observed 21 months after radiotherapy (including brachytherapy and external beam therapy) but does not indicate cancer or cancer progression (26,28).

In UK clinical practice, biochemical recurrence, following radical prostatectomy, can be defined as i) two consecutive rises in PSA, with a PSA $\geq$0.1 ng/mL or ii) three consecutive PSA rises (29). Whereas, in patients treated by radiotherapy (with or without hormone therapy), recurrence can be defined by the presence of PSA $\geq$ nadir plus 2ng/mL (26).

However, many uncertainties and challenges remain (30–36). For example, various definitions of prostate cancer recurrence have been used across treatment trials, making trial comparisons more difficult. Moreover, traditional definitions of biochemical recurrence do not i) apply to all treatment modalities, including focal therapies such as cryosurgery, ii) correlate with disease progression or severity and iii) reflect advancements in imaging. These definitions were also developed at a population level (26). As a result, the clinical value of these definitions to Black men, whose baseline levels of PSA may differ from the general UK population, and to transgender women (receiving oestrogen), are not clear (37–39).

Various clinical challenges have also been highlighted in follow-up care. Some of these were detailed in a patient testimony by Dr Neil MacLachlan, at Prostate Cancer UK's Specialist Conference (March 2024), which led to a failure to detect biochemical recurrence following radical prostatectomy treatment. For example, under current practice, it is possible for PSA test referrals initiated by a GP, with a detailed knowledge of patient treatment history, to be misinterpreted by another GP. This issue may also occur if the GPs operating in primary practice change in the years following a patient's initial treatment. This is an important consideration as many years can pass between treatment and recurrence, which would require GPs to look at years of notes. Moreover, this issue may be compounded by the fact that laboratory reports are not provided under specific post-treatment thresholds, with laboratories relying instead on the GP to provide accurate clinical interpretation. This occurs because there is currently no set of universally adopted and implemented PSA thresholds, by reporting laboratories, to indicate recurrence.

For Dr Neil MacLachlan, such issues resulted in the detection of prostate cancer, 9 years after his initial diagnosis, and only after an investigation was conducted following conversations with another patient and his clinician. Also, in Dr Neil MacLachlan's case, prostate cancer recurrence was detected after a prostate-specific membrane antigen (PSMA) positron-emission tomography (PET)/Computed Tomography (CT) scan but not after a Magnetic Resonance Imaging (MRI) scan. These issues led Dr Neil MacLachlan to feel 'let down' and call for improvements in reporting and care. Dr Neil MacLachlan suggested possible solutions such as i) the use of a 'survivorship care plan' which can be given to the patient on discharge from secondary care, and then shared with the GP, along with handover notes from the surgeon and ii) the inclusion of treatment history in PSA test referral forms.

3.0 The role of imaging technology in the detection and management of prostate cancer recurrence

Conventional imaging modalities include CT and Technetium-99m bone scans that check for cancer spread to the bone, nodes and other areas. MRI of the prostate can also determine the presence of localised recurrence (40–42). However, more sensitive modalities have subsequently emerged, making it possible to detect local recurrence in up to 50% of men with a PSA rise (43).

More recent imaging modalities include PET/CT scans, which are composed of images from CT scans and signals from radioactive tracers in areas of the body with cancer cells. Different types of radiotracers can be used for PET/CT, including 18F-Fluciclovine, radiolabelled choline and prostate-specific membrane antigen (PSMA) tracers. PSMA tracers, for example, work by targeting PSMA, a protein that is elevated in prostate cancer cells and can be used as part of PET/CT to image soft tissue and perform whole-body imaging. Tracers can be used in different scenarios within the recurrence setting, such as post-radical prostatectomy and prostate bed radiotherapy, with trade-offs linked to the selection of specific radiotracers (44).

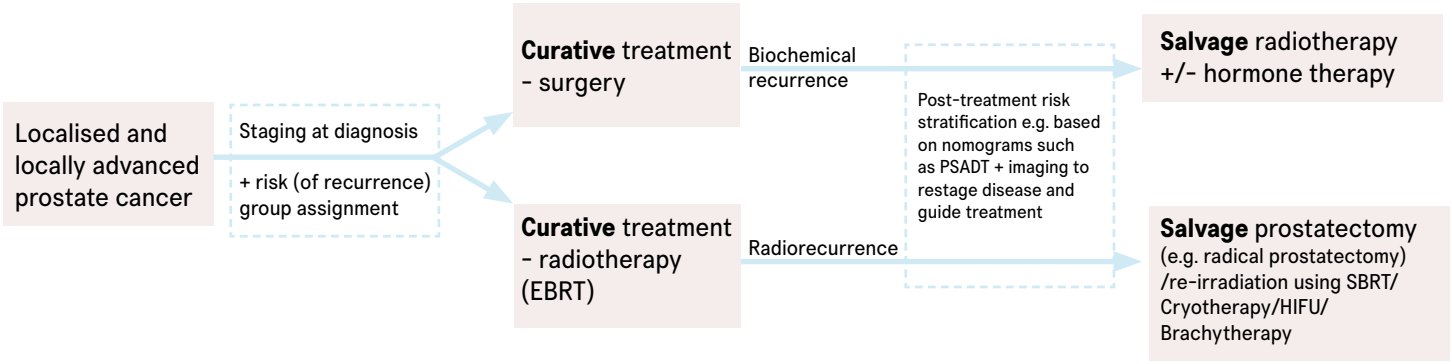
Various studies have helped assess the performance of tracers across different levels of PSA. For example, PSMA-based tracers such as Gallium-68 (68Ga), have been shown to produce relatively high contrast images, compared to radiolabelled choline, with superior performance reported at relatively low levels of PSA including at <1ng/mL. One sequential imaging study also reported that 43.8% of patients with negative F-choline-PET/CT had sites of recurrent disease detected using 68Ga-PSMA-PET/CT (45). Similarly, 68Ga-PSMA-PET/CT has been reported to be superior at detecting prostate cancer at PSA levels of 1.0-1.9ng/mL when compared to 18F-fluciclovine PET/CT (46). Such findings have helped inform guidance, produced by the Royal College of Radiologists, based on i) treatment history, ii) PSA levels, and iii) availability of different tracers, which may be impacted by factors such as radiotracer half-life as well as sites/scale of manufacture (44,47–49).

Imaging can also inform treatment choices in the biochemical recurrence setting to stop disease progression of localised disease (**Figure 1**), alongside other measures/factors such as treatment history, PSA doubling time (PSADT), disease characteristics (stage and grade), quality of life including sexual function and patient treatment tolerability and preferences (43,50–53). In particular, imaging can help determine the suitability of (as well as guide) salvage treatment options (54). For example, a single-centre, open-label, phase 2/3 EMPIRE-1 trial examined the use of 18F-fluciclovine-PET over conventional imaging in guiding salvage radiotherapy, based on the selection of target volume, guided by 18F-fluciclovine-PET uptake. As a result, improved event-free survival was reported after a median follow-up of 3.52 years. Similarly, 68Ga-PSMA-PET/CT imaging can be used to guide salvage radiotherapy to the prostate bed, due to improved sensitivity and specificity over conventional imaging, in the detection of metastatic and lymph node cancer at recurrence (16,55,56). However, it is important to note that the UK follows international consensus, which recommends, among other things, not to rely solely on imaging to inform treatment decisions (52).

Furthermore, the long-term survival outcomes for patients whose cancer was detected by PSMA-PET/CT, and who were then subsequently treated, have yet to be elucidated (57). There is also limited prospective evidence on the long-term clinical value of salvage treatments, i.e. in treating localised recurrence in the context of 10-year life expectancy (58–60). Of relevance, salvage treatments are also associated with an increase in the severity of side effects when compared to primary curative treatment (61). This is explored in detail elsewhere (29,54,61–64). Also, although beyond the scope of this review, several other treatment options have been studied, which may complement or be used instead of salvage treatment. This poses significant challenges in treatment selection and management of patients. For example, questions remain on the optimal use of ADT (such as the duration of use and patient preference) and hormone-based strategies more generally (54,65–67). Furthermore, the management of prostate cancer recurrence disease continues to evolve, with studies such as

the Efficacy Study of Enzalutamide Plus Leuprolide in Patients With Nonmetastatic Prostate Cancer (EMBARK) trial study, proposing the use of treatment intensification regimen in patients with high-risk biochemically recurrent disease i.e. in those with PSADT ≤9 and PSA ≥2 ng/mL above nadir after radiation (68,69).

Figure 1. ▼ Curative and salvage treatment options for men with localised and locally advanced prostate cancer. Curative treatments include radical prostatectomy and external beam radiation therapy (EBRT). EBRT includes dose-escalated intensity modulated radiation therapy with image-guided RT. Risk stratification includes PSA doubling time (PSADT). In the localised radio-recurrent scenario, there are several treatment options available, including stereotactic body radiotherapy (SBRT), brachytherapy, high-intensity focused ultrasound (HIFU) and cryotherapy. Crucially, for patients, not all treatment options are available outside certain centres and trial studies.



4.0 Real-world data challenge: How big of a problem is prostate cancer recurrence in the UK?

International studies have previously cited that biochemical recurrence can occur in i) around 30% of patients treated with radical prostatectomy (35,70) and in up to 50% of patients treated with radical localised treatment (within 10 years) (69). However, these often-cited values do not reflect the complexity of real-world practice. In particular, they do not distinguish between patients who have been i) stratified according to their risk of disease progression pre-and/or post-treatment and ii) who have undergone different levels (intensity) of treatment. For example, in a meta-analysis study known as Leviathan, a model was developed which demonstrated that the mean time from local failure (following radiotherapy) to distant metastases was 23.6 (7.1-54.8) months for high-risk patients and 37.4 (6.5-61.4) months for intermediate-risk patients, after a median follow-up of 11 years (71). Similarly, another study found that distant failure rates were as low as 4% in a high-risk patient cohort who went on to be treated with a radiation dose of 78 Gy, over a median follow-up period of 9 years, while patients treated with 70 Gy were associated with distant failure rates of 19% and were more likely to die from prostate cancer (72,73).

NHS England National Cancer Registration and Analysis Service (NCRAS) contains routinely collected data on primary tumours diagnosed within the NHS. NCRAS can also be used to link multiple datasets, including recurrence data from the Cancer Outcomes and Services Dataset (COSD) and imaging data and has the potential to provide more accurate population-wide data on the prevalence of recurrence in England. Leveraging such data may improve care by reducing heterogeneity in practice across the country and aid in individual patient management. In particular, real-world data may help to reduce rates of recurrence and disease progression (74), particularly for those at high-risk of biochemical

recurrence (21,22,75–77) and patient populations associated with worse outcomes. For instance, a UK study reported that the likelihood of receiving radical treatment is influenced by ethnicity and age (78,79). Such disparities may in turn, translate to differences in rates of recurrence (80,81).

Historically, codes for recurrence have not been embedded into routinely collected national datasets. However, more recent COSD releases include recurrence codes which can be used to inform real-world studies. Despite this, there are several challenges related to the use of this data in the short term, including the fact that this data has not yet reached maturity due to i) the number of patients with coded data and ii) the length of time it takes for recurrence to emerge post-treatment. Consequently, this reduces the ability of researchers to conduct meaningful and robust analyses of relevant datasets.

However, one UK-based epidemiological study funded by the National Institute for Health and Care Research (NIHR) and led by Dr Kate Walker and Professor Jan van der Meulen from the London School of Hygiene & Tropical Medicine aims to examine patient data (England) sourced from cancer registries and national cancer audits, to ultimately establish a reliable method for identifying (initially) bowel cancer recurrence (23).

More specifically, the project aims to construct linked datasets which capture patient journeys, using diagnostic processes, imaging, treatment pathways, and mortality data. It also seeks to compare 4 indicators to detect recurrence including a set of clinical rule-based indicators, unsupervised machine learning (a sub-domain of machine learning), prognostic modelling and supervised machine learning. Data from a subset of patients will then be validated and compared to a proxy measure of prostate cancer recurrence, namely cancer death within 3 plus years of receiving localised treatment. The optimal indicator, identified from statistical modelling and machine learning, will then be applied to breast and prostate cancer recurrence. In so doing, the investigators hope to facilitate future studies by e.g. investigating long-term outcomes of patients with recurrence and producing prediction models which facilitate treatment selection. This study is due to be completed by 2025.

5.0 Strengths

To the best of our knowledge, this review is the first to detail both the research and clinical challenges related to the application of modern imaging modalities and acquisition of real-world datasets in the recurrence setting. Key challenges related to the definition of prostate cancer recurrence are also distilled, along with clinical challenges in care and reporting, highlighted via patient testimony. Finally, this review spotlights research which aims to tackle the lack of real-world data and evidence in recurrence, within the UK.

6.0 Limitations

This review has several limitations. For example, this review was not supported by a wide and formalised consultation process and was also not evidenced by survey data/Freedom of Information Act request. Therefore, the conclusions made in this review are not supported by data which is representative of modern UK clinical practice. Furthermore, as this is a narrative review and not a systematic review, it is subject to selection bias and may not include an exhaustive list of recent and relevant developments.

7.0 Conclusion

Failure to cure localised prostate cancer disease by either surgery or radiotherapy may lead to prostate cancer recurrence. Imaging helps to detect recurrence and aids in restaging disease and informing treatment selection. The emergence of newer imaging modalities and associated radiotracers, such as 68Ga-PSMA-PET/CT, provides the advantage of increased sensitivity for the detection of recurrent disease at low levels of PSA. However, the widespread availability of novel imaging technologies such as PSMA-PET/CT and radiotracers, across the UK, has yet to be reported and may exacerbate existing inequalities. Questions also remain on how to manage patients with contradictory results from the use of different imaging modalities and the long-term outcomes of decisions informed by imaging.

Furthermore, the historic absence of patient codes for prostate cancer recurrence creates significant barriers to the accurate identification, collection and analysis of patient datasets. This limits our ability to conduct population-wide studies and i) estimate the risk of and ii) evaluate the effect of prostate cancer recurrence. The proposed creation of clinical indicators and validated proxy measures for prostate cancer recurrence may, in the future, help to harness the power of real-world data by, among other things, facilitating our ability to conduct long-term clinical trial follow-up studies and to assess treatment efficacy and quality of care in the UK.

8.0 Acknowledgments

The reviewer would like to acknowledge members of the Clinical Advisory Group as well as Prostate Cancer UK staff in helping guide the development of this review. The reviewer would particularly like to acknowledge members of the Research Team who advised in the design stage of the review and who also fund research on prostate cancer recurrence through Prostate Cancer UK's 'Transformation Impact Awards'.

9.0 References

1. Data and Evidence | Prostate Cancer UK [Internet]. 2024 [cited 2024 Oct 8]. Available from: https://prostatecanceruk.org/for-health-professionals/data-and-evidence

2. Prostate Cancer UK. Prostate Cancer UK. 2023 [cited 2024 Apr 9]. There's a huge North-South divide in prostate cancer diagnoses. We need your help to change it. Available from: https://prostatecanceruk.org/about-us/news-and-views/2023/01/huge-north-south-divide-in-prostate-cancer-diagnoses

3. James ND, Tannock I, N'Dow J, Feng F, Gillessen S, Ali SA, et al. The Lancet Commission on prostate cancer: planning for the surge in cases. The Lancet. 2024 Apr;403(10437):1683–722.

4. Johansson JE. Natural History of Early, Localized Prostate Cancer. JAMA. 2004 Jun 9;291(22):2713.

5. Helgstrand JT, Røder MA, Klemann N, Toft BG, Brasso K, Vainer B, et al. Diagnostic characteristics of lethal prostate cancer. Eur J Cancer. 2017 Oct;84:18–26.

6. Hamdy FC, Donovan JL, Lane JA, Metcalfe C, Davis M, Turner EL, et al. Fifteen-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. N Engl J Med. 2023 Apr 27;388(17):1547–58.

7. Turkbey B, Oto A, Allen BC, Akin O, Alexander LF, Ari M, et al. ACR Appropriateness Criteria® Post-Treatment Follow-up of Prostate Cancer: 2022 Update. J Am Coll Radiol. 2023 May;20(5):S164–86.

8. Follow-up after treatment for prostate cancer | Macmillan Cancer Support [Internet]. [cited 2024 May 8]. Available from: https://www.macmillan.org.uk/cancer-information-and-support/prostate-cancer/follow-up-after-treatment-for-prostate-cancer

9. NHS Guy's and St Thomas'. NHS Guy's and St Thomas'. 2022. Overview. Prostate cancer surgery follow-up. Available from: https://www.guysandstthomas.nhs.uk/health-information/prostate-cancer-surgery-follow-up

10. Prostate Cancer UK. Prostate Cancer UK. 2024 [cited 2024 Apr 9]. Follow-up after treatment. Available from: https://prostatecanceruk.org/prostate-information-and-support/treatments/follow-up-after-treatment

11. EAU. EAU. 2024. EAU Guidelines. Prostate Cancer. 7. Follow Up. Available from: https://uroweb.org/guidelines/prostate-cancer/chapter/followup#note_898

12. Prostate Cancer UK. Prostate Cancer UK. 2023 [cited 2024 Apr 9]. Just diagnosed. Localised prostate cancer. Available from: https://prostatecanceruk.org/prostate-information-and-support/just-diagnosed/localised-prostate-cancer

13. Prostate Cancer UK. Prostate Cancer UK. 2023 [cited 2024 Apr 9]. Treatments. If your prostate cancer comes back. Available from: https://prostatecanceruk.org/prostate-information-and-support/treatments/if-your-prostate-cancer-comes-back

14. Kitajima K, Murphy RC, Nathan MA, Froemming AT, Hagen CE, Takahashi N, et al. Detection of Recurrent Prostate Cancer After Radical Prostatectomy: Comparison of 11 C-Choline PET/CT with Pelvic Multiparametric MR Imaging with Endorectal Coil. J Nucl Med. 2014 Feb;55(2):223–32.

15. Sobol I, Zaid HB, Haloi R, Mynderse LA, Froemming AT, Lowe VJ, et al. Contemporary Mapping of Post-Prostatectomy Prostate Cancer Relapse with 11 C-Choline Positron Emission Tomography and Multiparametric Magnetic Resonance Imaging. J Urol. 2017 Jan;197(1):129–34.

16. Light A, Ahmed HU, Shah TT. The unclear role of PET–CT in localized radiorecurrent prostate cancer. Nat Rev Urol. 2022 Oct;19(10):573–4.

17. Mahal BA, Berman RA, Taplin ME, Huang FW. Prostate Cancer–Specific Mortality Across Gleason Scores in Black vs Nonblack Men. JAMA. 2018 Dec 18;320(23):2479.

18. McHugh J, Saunders EJ, Dadaev T, McGrowder E, Bancroft E, Kote-Jarai Z, et al. Prostate cancer risk in men of differing genetic ancestry and approaches to disease screening and management in these groups. Br J Cancer. 2022 Jun 1;126(10):1366–73.

19. Lillard JW, Moses KA, Mahal BA, George DJ. Racial disparities in Black men with prostate cancer: A literature review. Cancer. 2022 Nov;128(21):3787–95.

20. Tsodikov A, Gulati R, De Carvalho TM, Heijnsdijk EAM, Hunter-Merrill RA, Mariotto AB, et al. Is prostate cancer different in black men? Answers from 3 natural history models. Cancer. 2017 Jun 15;123(12):2312–9.

21. Tilki D, Preisser F, Graefen M, Huland H, Pompe RS. External Validation of the European Association of Urology Biochemical Recurrence Risk Groups to Predict Metastasis and Mortality After Radical Prostatectomy in a European Cohort. Eur Urol. 2019 Jun;75(6):896–900.

22. Jackson WC, Suresh K, Tumati V, Allen SG, Dess RT, Salami SS, et al. Intermediate Endpoints After Postprostatectomy Radiotherapy: 5-Year Distant Metastasis to Predict Overall Survival. Eur Urol. 2018 Oct;74(4):413–9.

23. Identifying Cancer Recurrence within Patient Care Pathways across Linked National Clinical Datasets - NIHR Funding and Awards [Internet]. [cited 2024 Apr 25]. Available from: https://fundingawards.nihr.ac.uk/award/NIHR132459

24. Shore ND, Moul JW, Pienta KJ, Czernin J, King MT, Freedland SJ. Biochemical recurrence in patients with prostate cancer after primary definitive therapy: treatment based on risk stratification. Prostate Cancer Prostatic Dis. 2024 Jun;27(2):192–201.

25. Lowrance WT, Breau RH, Chou R, Chapin BF, Crispino T, Dreicer R, et al. Advanced Prostate Cancer: AUA/ASTRO/SUO Guideline PART I. J Urol. 2021 Jan;205(1):14–21.

26. Roach M, Hanks GE, Thames HD, Schellhammer PF, Shipley WU, Sokol GH, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: Recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys. 2006 Jul 15;65(4):965–74.

27. Rud E, Baco E, Lien D, Klotz D, Eggesbø HB. Detection of Radiorecurrent Prostate Cancer Using Diffusion-Weighted Imaging and Targeted Biopsies. Am J Roentgenol. 2014 Mar;202(3):W241–6.

28. Kishan AU. PSA bounce, prognosis, and clues to the radiation response. Prostate Cancer Prostatic Dis. 2021 Dec;24(4):937–8.

29. Parker C, Clarke N, Cook A, Kynaston H, Petersen P, Catton C, et al. Timing of radiotherapy after radical prostatectomy (RADICALS-RT): a randomised, controlled phase 3 trial. Lancet Lond Engl. 2020;396(10260):1413- 1421.

30. Schaeffer EM, Srinivas S, Adra N, An Y, Barocas D, Bitting R, et al. Prostate Cancer, Version 4.2023, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2023 Oct;21(10):1067–96.

31. Cornford P, Van Den Bergh RCN, Briers E, Van Den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. Part II—2020 Update: Treatment of Relapsing and Metastatic Prostate Cancer. Eur Urol. 2021 Feb;79(2):263–82.

32. Morgan TM, Boorjian SA, Buyyounouski MK, Chapin BF, Chen DYT, Cheng HH, et al. Salvage Therapy for Prostate Cancer: AUA/ASTRO/SUO Guideline Part I: Introduction and Treatment Decision-Making at the Time of Suspected Biochemical Recurrence after Radical Prostatectomy. J Urol. 2024 Apr;211(4):509–17.

33. Morgan TM, Boorjian SA, Buyyounouski MK, Chapin BF, Chen DYT, Cheng HH, et al. Salvage Therapy for Prostate Cancer: AUA/ASTRO/SUO Guideline Part II: Treatment Delivery for Non-metastatic Biochemical Recurrence After Primary Radical Prostatectomy. J Urol. 2024 Apr;211(4):518–25.

34. Morgan TM, Boorjian SA, Buyyounouski MK, Chapin BF, Chen DYT, Cheng HH, et al. Salvage Therapy for Prostate Cancer: AUA/ASTRO/SUO Guideline Part III: Salvage Therapy After Radiotherapy or Focal Therapy, Pelvic Nodal Recurrence and Oligometastasis, and Future Directions. J Urol. 2024 Apr;211(4):526–32.

35. Freedland SJ, Humphreys EB, Mangold LA, Eisenberger M, Dorey FJ, Walsh PC, et al. Death in Patients With Recurrent Prostate Cancer After Radical Prostatectomy: Prostate-Specific Antigen Doubling Time Subgroups and Their Associated Contributions to All-Cause Mortality. J Clin Oncol. 2007 May 1;25(13):1765–71.

36. Cookson MS, Aus G, Burnett AL, Canby-Hagino ED, D'Amico AV, Dmochowski RR, et al. Variation in the Definition of Biochemical Recurrence in Patients Treated for Localized Prostate Cancer: The American Urological Association Prostate Guidelines for Localized Prostate Cancer Update Panel Report and Recommendations for a Standard in the Reporting of Surgical Outcomes. J Urol. 2007 Feb;177(2):540–5.

37. Barlow M, Down L, Mounce LTA, Merriel SWD, Watson J, Martins T, et al. Ethnic differences in prostate-specific antigen levels in men without prostate cancer: a systematic review. Prostate Cancer Prostatic Dis. 2023 Jun;26(2):249–56.

38. Crowley F, Mihalopoulos M, Gaglani S, Tewari AK, Tsao CK, Djordjevic M, et al. Prostate cancer in transgender women: considerations for screening, diagnosis and management. Br J Cancer. 2023 Jan 19;128(2):177–89.

39. Down L, Barlow M, Bailey SER, Mounce LTA, Merriel SWD, Watson J, et al. Association between patient ethnicity and prostate cancer diagnosis following a prostate-specific antigen test: a cohort study of 730,000 men in primary care in the UK. BMC Med. 2024 Mar 1;22(1):82.

40. Awiwi MO, Gjoni M, Vikram R, Altinmakas E, Dogan H, Bathala TK, et al. MRI and PSMA PET/CT of Biochemical Recurrence of Prostate Cancer. RadioGraphics. 2023 Dec 1;43(12):e230112.

41. Jetty S, Loftus JR, Patel A, Gupta A, Puri S, Dogra V. Prostate Cancer—PET Imaging Update. Cancers. 2023 Jan 28;15(3):796.

42. Royal College of Radiologists. Recommendations for cross-sectional imaging in cancer management. Prostate Tumours [Internet]. Royal College of Radiologists; 2022 Apr. Available from: https://www.rcr.ac.uk/media/myddegya/rcr-publications_recommendations-for-cross-sectional-imaging-in-cancer-management-second-edition-15-prostate-tumours_april-2022.pdf

43. Parker C, Castro E, Fizazi K, Heidenreich A, Ost P, Procopio G, et al. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020 Sep;31(9):1119–34.

44. Evidence-based indications for the use of PET-CT in the United Kingdom 2022 | The Royal College of Radiologists [Internet]. [cited 2024 Apr 29]. Available from: https://www.rcr.ac.uk/our-services/all-our-publications/clinical-radiology-publications/evidence-based-indications-for-the-use-of-pet-ct-in-the-united-kingdom-2022/

45. Bluemel C, Krebs M, Polat B, Linke F, Eiber M, Samnick S, et al. 68Ga-PSMA-PET/CT in Patients With Biochemical Prostate Cancer Recurrence and Negative 18F-Choline-PET/CT. Clin Nucl Med. 2016 Jul;41(7):515–21.

46. Tan N, Oyoyo U, Bavadian N, Ferguson N, Mukkamala A, Calais J, et al. PSMA-targeted Radiotracers versus 18F Fluciclovine for the Detection of Prostate Cancer Biochemical Recurrence after Definitive Therapy: A Systematic Review and Meta-Analysis. Radiology. 2020 Jul;296(1):44–55.

47. GIRFT. GIRFT Urology: Towards Better Diagnosis & Management of Suspected Prostate Cancer [Internet]. The British Association of Urological Surgeons; 2024 Apr. Available from: https://gettingitrightfirsttime.co.uk/wp-content/uploads/2024/04/GIRFT-Urology-Towards-Better-Diagnosis-Management-of-Suspected-Prostate-Cancer-FINAL-V1-April-2024-1.pdf

48. Giesel FL, Knorr K, Spohn F, Will L, Maurer T, Flechsig P, et al. Detection Efficacy of 18 F-PSMA-1007 PET/CT in 251 Patients with Biochemical Recurrence of Prostate Cancer After Radical Prostatectomy. J Nucl Med. 2019 Mar;60(3):362–8.

49. Fendler WP, Calais J, Eiber M, Flavell RR, Mishoe A, Feng FY, et al. Assessment of 68 Ga-PSMA-11 PET Accuracy in Localizing Recurrent Prostate Cancer: A Prospective Single-Arm Clinical Trial. JAMA Oncol. 2019 Jun 1;5(6):856.

50. Van Den Broeck T, Van Den Bergh RCN, Briers E, Cornford P, Cumberbatch M, Tilki D, et al. Biochemical Recurrence in Prostate Cancer: The European Association of Urology Prostate Cancer Guidelines Panel Recommendations. Eur Urol Focus. 2020 Mar;6(2):231–4.

51. Simon NI, Parker C, Hope TA, Paller CJ. Best Approaches and Updates for Prostate Cancer Biochemical Recurrence. Am Soc Clin Oncol Educ Book. 2022 Jul;(42):352–9.

52. Dirix P, Dal Pra A, Khoo V, Carrie C, Cozzarini C, Fonteyne V, et al. ESTRO ACROP consensus recommendation on the target volume definition for radiation therapy of

macroscopic prostate cancer recurrences after radical prostatectomy. Clin Transl Radiat Oncol. 2023 Nov;43:100684.

53. Blood P. What Is the Life Expectancy of Men Older Than 75 Years Who Are Treated with Radiation for Prostate Cancer? Int J Radiat Oncol. 2005 Oct;63:S113–4.

54. Matsukawa A, Yanagisawa T, Fazekas T, Miszczyk M, Tsuboi I, Kardoust Parizi M, et al. Salvage therapies for biochemical recurrence after definitive local treatment: a systematic review, meta-analysis, and network meta-analysis. Prostate Cancer Prostatic Dis [Internet]. 2024 Sep 13 [cited 2024 Sep 19]; Available from: https://www.nature.com/articles/s41391-024-00890-4

55. Hope TA, Eiber M, Armstrong WR, Juarez R, Murthy V, Lawhn-Heath C, et al. Diagnostic Accuracy of 68 Ga-PSMA-11 PET for Pelvic Nodal Metastasis Detection Prior to Radical Prostatectomy and Pelvic Lymph Node Dissection: A Multicenter Prospective Phase 3 Imaging Trial. JAMA Oncol. 2021 Nov 1;7(11):1635.

56. Houshmand S, Lawhn-Heath C, Behr S. PSMA PET imaging in the diagnosis and management of prostate cancer. Abdom Radiol. 2023 Jul 26;48(12):3610–23.

57. Mattana F, Muraglia L, Rajwa P, Zattoni F, Marra G, Chiu PKF, et al. Metastatic Sites' Location and Impact on Patient Management After the Introduction of Prostate-specific Membrane Antigen Positron Emission Tomography in Newly Diagnosed and Biochemically Recurrent Prostate Cancer: A Critical Review. Eur Urol Oncol. 2023 Apr;6(2):128–36.

58. Parker CC, Petersen PM, Cook AD, Clarke NW, Catton C, Cross WR, et al. Timing of radiotherapy (RT) after radical prostatectomy (RP): long-term outcomes in the RADICALS-RT trial (NCT00541047). Ann Oncol. 2024 Jul;35(7):656–66.

59. Ekanger C, Helle SI, Reisæter L, Hysing LB, Kvåle R, Honoré A, et al. Salvage Reirradiation for Locally Recurrent Prostate Cancer: Results From a Prospective Study With 7.2 Years of Follow-Up. J Clin Oncol. 2024 Jun 1;42(16):1934–42.

60. Trock BJ, Han M, Freedland SJ, Humphreys EB, DeWeese TL, Partin AW, et al. Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy. JAMA J Am Med Assoc. 2008;299(23):2760–9.

61. Shah TT, Kanthabalan A, Otieno M, Pavlou M, Omar R, Adeleke S, et al. Magnetic Resonance Imaging and Targeted Biopsies Compared to Transperineal Mapping Biopsies Before Focal Ablation in Localised and Metastatic Recurrent Prostate Cancer After Radiotherapy. Eur Urol. 2022 Jun;81(6):598–605.

62. Chen CP, Weinberg V, Shinohara K, Roach M, Nash M, Gottschalk A, et al. Salvage HDR Brachytherapy for Recurrent Prostate Cancer After Previous Definitive Radiation Therapy: 5-Year Outcomes. Int J Radiat Oncol. 2013 Jun;86(2):324–9.

63. Prostate Cancer UK. High intensity focused ultrasound (HIFU) | Prostate Cancer UK [Internet]. [cited 2024 Apr 11]. Available from: https://prostatecanceruk.org/prostate-information-and-support/treatments/hifu

64. Valle LF, Lehrer EJ, Markovic D, Elashoff D, Levin-Epstein R, Karnes RJ, et al. A Systematic Review and Meta-analysis of Local Salvage Therapies After Radiotherapy for Prostate Cancer (MASTER). Eur Urol. 2021 Sep;80(3):280–92.

65. Parker CC, Kynaston H, Cook AD, Clarke NW, Catton CN, Cross WR, et al. Duration of androgen deprivation therapy with postoperative radiotherapy for prostate cancer: a comparison of long-course versus short-course androgen deprivation therapy in the RADICALS-HD randomised trial. The Lancet. 2024 Jun;403(10442):2416–25.

66. Dess R, Sun Y, Jackson W, Jairath N, Kishan A, Wallington D, et al. Association of Presalvage Radiotherapy PSA Levels After Prostatectomy With Outcomes of Long-term Antiandrogen Therapy in Men With Prostate Cancer. JAMA Oncol. 2020;6(5):735-743.

67. Overview | Prostate cancer: diagnosis and management | Guidance | NICE [Internet]. [cited 2023 Apr 21]. Available from: https://www.nice.org.uk/guidance/ng131

68. D'Amico AV, Whittington R, Malkowicz SB, Weinstein M, Tomaszewski JE, Schultz D, et al. PREDICTING PROSTATE SPECIFIC ANTIGEN OUTCOME PREOPERATIVELY IN THE PROSTATE SPECIFIC ANTIGEN ERA. J Urol. 2001 Dec;166(6):2185–8.

69. Freedland SJ, De Almeida Luz M, De Giorgi U, Gleave M, Gotto GT, Pieczonka CM, et al. Improved Outcomes with Enzalutamide in Biochemically Recurrent Prostate Cancer. N Engl J Med. 2023 Oct 19;389(16):1453–65.

70. Biochemical recurrence in patients with prostate cancer after primary definitive therapy: treatment based on risk stratification | Prostate Cancer and Prostatic Diseases [Internet]. [cited 2024 Apr 25]. Available from: https://www.nature.com/articles/s41391-023-00712-z

71. Ma TM, Chu FI, Sandler H, Feng FY, Efstathiou JA, Jones CU, et al. Local Failure Events in Prostate Cancer Treated with Radiotherapy: A Pooled Analysis of 18 Randomized Trials from the Meta-analysis of Randomized Trials in Cancer of the Prostate Consortium (LEVIATHAN). Eur Urol. 2022 Nov;82(5):487–98.

72. Kuban DA, Levy LB, Cheung MR, Lee AK, Choi S, Frank S, et al. Long-Term Failure Patterns and Survival in a Randomized Dose-Escalation Trial for Prostate Cancer. Who Dies of Disease? Int J Radiat Oncol. 2011 Apr;79(5):1310–7.

73. Chang AJ, Autio KA, Roach III M, Scher HI. "High-Risk" Prostate Cancer: Classification and Therapy. Nat Rev Clin Oncol. 2014 Jun;11(6):308–23.

74. Moghul M, Somani B, Lane T, Vasdev N, Chaplin B, Peedell C, et al. Detection rates of recurrent prostate cancer: 68Gallium (Ga)-labelled prostate-specific membrane antigen versus choline PET/CT scans. A systematic review. Ther Adv Urol. 2019 Jan;11:175628721881579.

75. Royce T, Chen M, Wu J, Loffredo M, Renshaw A, Kantoff P, et al. Surrogate End Points for All-Cause Mortality in Men With Localized Unfavorable-Risk Prostate Cancer Treated With Radiation Therapy vs Radiation Therapy Plus Androgen Deprivation Therapy: a Secondary Analysis of a Randomized Clinical Trial. JAMA Oncol. 2017;3(5):652-658.

76. Freiberger C, Berneking V, Vögeli TA, Kirschner-Hermanns R, Eble MJ, Pinkawa M. Long-term prognostic significance of rising PSA levels following radiotherapy for localized prostate cancer – focus on overall survival. Radiat Oncol. 2017 Dec;12(1):98.

77. Choueiri TK, Chen M, D'Amico AV, Sun L, Nguyen PL, Hayes JH, et al. Impact of postoperative prostate-specific antigen disease recurrence and the use of salvage therapy on the risk of death. Cancer. 2010 Apr 15;116(8):1887–92.

78. Parry MG, Boyle JM, Nossiter J, Morris M, Sujenthiran A, Berry B, et al. Determinants of variation in radical local treatment for men with high-risk localised or locally advanced prostate cancer in England. Prostate Cancer Prostatic Dis. 2023 Jun;26(2):257–63.

79. Powell IJ, Banerjee M, Sakr W, Grignon D, Wood DP, Novallo M, et al. Should African-American men be tested for prostate carcinoma at an earlier age than white men? Cancer. 1999 Jan 15;85(2):472–7.

80. Hamilton RJ, Aronson WJ, Presti JC, Terris MK, Kane CJ, Amling CL, et al. Race, biochemical disease recurrence, and prostate-specific antigen doubling time after radical prostatectomy: Results from the SEARCH database. Cancer. 2007 Nov 15;110(10):2202–9.

81. Freedland SJ, Vidal AC, Howard LE, Terris MK, Cooperberg MR, Amling CL, et al. Race and risk of metastases and survival after radical prostatectomy: Results from the SEARCH database. Cancer. 2017 Nov;123(21):4199–206