Recent advancements in personalized management of prostate cancer biochemical recurrence after radical prostatectomy

Fabian Falkenbach[a,b], *Jonas Ekrutt*[a] *and Tobias Maurer*[a,c]

Purpose of review
Biochemical recurrence (BCR) after radical prostatectomy exhibits heterogeneous prognostic implications. Recent advancements in imaging and biomarkers have high potential for personalizing care.

Recent findings
Prostate-specific membrane antigen imaging (PSMA)-PET/CT has revolutionized the BCR management in prostate cancer by detecting microscopic lesions earlier than conventional staging, leading to improved cancer control outcomes and changes in treatment plans in approximately two-thirds of cases. Salvage radiotherapy, often combined with androgen deprivation therapy, remains the standard treatment for high-risk BCR postprostatectomy, with PSMA-PET/CT guiding treatment adjustments, such as the radiation field, and improving progression-free survival. Advancements in biomarkers, genomic classifiers, and artificial intelligence-based models have enhanced risk stratification and personalized treatment planning, resulting in both treatment intensification and de-escalation.

Summary
While conventional risk grouping relying on Gleason score and PSA level and kinetics remain the foundation for BCR management, PSMA-PET/CT, novel biomarkers, and artificial intelligence may enable more personalized treatment strategies.

Keywords
biochemical recurrence, prostate cancer, prostate-specific membrane antigen imaging, recurrent prostate cancer

INTRODUCTION

Biochemical recurrence (BCR) after definitive treatment of prostate cancer (PCa) is a common phenomenon that occurs in up to half of all patients [1]. Given this high prevalence, the substantial heterogeneity in cancer control outcomes following BCR is unsurprising [2]. Pivotal work by Pound and later Freedland *et al.*, relying on Walsh's radical prostatectomy (RP) series at John Hopkins, showed >20 years ago that BCR is often indolent despite being the universal predecessor to metastatic progression [3,4]. Back then, Freedland *et al.* identified Gleason score $\geq$ 8 and short PSA doubling time as major risk factors for rapid disease progression [4]. Both criteria were incorporated into the EAU BCR risk categories and are still invariably used in guidelines today [1,5,6], although prostate-specific membrane antigen imaging (PSMA) positron emission tomography (PET)/computed tomography (CT), biomarkers, and artificial intelligence (AI) approaches have recently redefined how and if a "PSA value alone" should be treated.

REVIEW

Prostate-specific membrane antigen imaging-PET/CT

Serum PSA levels broadly correlate with the volume of prostate (cancer) tissue [7,8]. After surgical removal of the prostate, PSA measurements can detect BCR before it is visible on conventional imaging. Early detection of cancer recurrence may enable the curation of localized therapy, thereby delaying or ideally eliminating the need for long-term

[a]Martini-Klinik Prostate Cancer Center, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [b]Cancer Prognostics and Health Outcomes Unit, Division of Urology, University of Montreal Health Center, Montreal, Quebec, Canada and [c]Department of Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Correspondence to Fabian Falkenbach, MD, Martini-Klinik Prostate Cancer Center, University Medical Center Hamburg-Eppendorf, Hamburg 20246, Germany. Tel: +49 173 900 71 61;
e-mail: f.falkenbach@uke.de

Curr Opin Urol 2025, 35:000–000
DOI:10.1097/MOU.0000000000001305

KEY POINTS

- Prostate-specific membrane antigen imaging (PSMA)-PET/CT imaging and derived treatment aid in the development of personalized therapeutic strategies. Specifically, radiation field planning and the necessity for concomitant androgen deprivation therapy may be significantly improved.
- Genomic and artificial intelligence-based biomarkers complement the classic characteristics of prostate cancer in tailoring treatment. Therefore, de-escalation of toxic treatments may be safely achieved in low-risk patients.

systemic therapy. PSMA-PET/CT can visualize microscopic prostate cancer lesions before correlating morphological changes are visible on conventional imaging [9–16]. Therefore, BCR with negative PSMA-PET/CT behaves differently from BCR with negative conventional staging [16,17]. This challenges current treatment algorithms, which are based predominantly on level-1-evidence generated in the pre-PSMA era. But emerging evidence suggest improved cancer control by PSMA-guided treatment algorithms for BCR [13,17,18]. For instance, Meijer *et al*. reported improved cancer control outcomes for salvage radiotherapy (SRT) patients with PSMA-PET/CT, compared to those using conventional imaging [17]. PSMA-PET/CT can alter the BCR treatment plans in up to two-thirds of cases [13,19–24]. PSMA-derived personalized treatment results in both treatment intensification and de-escalation [11,25–27]. For (high-risk) BCR post-RP, the standard treatment is SRT to the prostatic fossa plus/minus the pelvis because local recurrences are frequent and the sensitivity of local biopsies after radical prostatectomy as well as conventional imaging is low [28]. The addition of short-term androgen deprivation (ADT) to SRT may be considered in patients with adverse prognostic features, although the heterogeneity of trial designs and patient populations precludes a clear recommendation [29–31]. Recently, the EMBARK trial improved metastasis-free survival in high-risk BCR patients receiving enzalutamide with/without ADT [32]. However, many patients with EMBARK-like disease would be positive on PSMA-PET/CT [33▪] and are potential candidates for local salvage therapies [34]. The primary aim of PSMA-PET/CT in that setting is to rule out prostate cancer lesions outside the standard radiation field but not to confirm local recurrences [13,21,22]. PSMA-PET/CT is highly predictive of progression-free survival following SRT for BCR postprostatectomy [25]. EAU high-risk BCR is associated with more frequent positive PSMA-PET/CT findings and the EAU BCR risk classification remains prognostic relevant in PSMA-PET/CT staged patients as well [12,35,36]. In patients with distant metastases, the substantial toxicity of SRT on urinary continence, stricture formation or other genitourinary / gastrointestinal toxicities may outweigh the potential oncological benefits of local treatment intensification [37–40]. Conversely, patients with BCR without distant metastases on PSMA-PET/CT especially benefit from SRT independent of local findings [25,41▪▪,42▪▪,43]. For instance, Scharl *et al*. found no difference in progression-free survival after SRT in patients with miN0 and miM0 with and without local PSMA-PET-avid findings [41▪▪]. If pelvic recurrences are visible on PSMA-PET/CT, enhanced targeting by tailored radiation templates or PSMA-radioguided surgery may improve cancer control outcomes [13,19–22,34,44,45]. This may be particularly pertinent to concomitant nodal radiotherapy. The prospective randomized SPPORT trial, including BCR patients postprostatectomy without PSMA-PET/CT, showed significantly improved progression free survival for the addition of nodal radiotherapy to prostate bed radiotherapy and short-term androgen deprivation therapy (5-year progression-free survival: 87.4 vs. 81.3%) [31]. In a PSMA-PET/CT mapping study by Boreta *et al*., pelvic lymph node metastases were present in 47/125 patients eligible for SRT [13]. Therefore, the addition of nodal radiotherapy may be even more beneficial if the template and indication is tailored to personalized PSMA-PET/CT findings. Indeed, previous evidence suggests a cancer control benefit by metastasis-directed therapy for nodal recurrences [26,27,44,46]. If no recurrences in the pelvis are visible on PSMA-PET/CT, patients especially benefit from local SRT [41▪▪,42▪▪,43,47▪▪]. Specifically, Harsini *et al*. recently reported a three-year progression-free survival of 94% for SRT patients with negative PSMA-PET/CT compared to 71% for their non-SRT counterparts [47▪▪]. Similarly, Adebahr *et al*. reported a favorable three-year metastasis free survival of 88% in SRT patients with negative PSMA-PET/CT [42▪▪]. However, the sensitivity of PSMA-PET/CT for micro-metastases is limited, which are common in prostate cancer [48,49]. In conclusion, SRT should be initiated timely after BCR, independent of local findings on PSMA-PET/CT; however, the radiotherapy template should be adjusted accordingly to PSMA-PET/CT findings if available. Conversely, in most studies, initial prostate cancer characteristics, such as Gleason score or seminal vesicle infiltration, were significant predictors of cancer control outcomes. Therefore, it may be hypothesized that in a well selected subset of PSMA-negative patients with

favorable cancer characteristics, SRT may be safely delayed or even omitted [50]. Two PSMA-PET/CT guided nomograms recently showed promising results in translating these observations into improved SRT decision planning [51,52].

Biomarker, genomic alterations, and artificial intelligence

The strongest and most established biomarker for SRT is the absolute PSA level. (Very) early vs. late SRT is classified by a PSA threshold of 0.2–0.5 ng/ml, and early SRT was invariably associated with improved cancer control outcomes [29,53,54,55▪▪,56]. For instance, Tilki *et al.* reported increased mortality if SRT was administered at a PSA level above 0.25 ng/ml [55▪▪]. Notably, pre-SRT PSA levels were also highly predictive of survival in patients with negative PSMA-PET/CT results [42▪▪]. In PSMA-PET/CT staged patients with BCR postprostatectomy, PSMA-PET/CT findings and PSA significantly correlated with SRT response, whereas classical clinical parameters such as Gleason score did not [43]. Moreover, patients with higher pre-SRT PSA levels may benefit more from the addition of ADT to SRT [56]. A systematic review of the available literature suggested a risk stratification approach for SRT ± ADT relying on PSA levels, surgical margin status, and Gleason score [57]. Similarly, Preisser *et al.* validated the EAU BCR risk classification using PSA doubling time and the Gleason score as decision tools for SRT [58]. In addition to these classic clinical parameters, several novel biomarkers based on genomic alterations or tissue characteristics have been tested in the BCR setting. Pooled data from the prospective STOMP and ORIOLE trials suggested higher efficacy of metastasis-directed therapy in patients with high-risk somatic mutation albeit small sample size of such individuals [27]. Moreover, rapid disease progression in prostate cancer patients with genetic alterations may be seen as a rationale for earlier treatment intensification in the context of BCR, although specific data addressing the BCR setting are still limited. Gallagher *et al.* reported that BRCA2 carriers exhibited a trend towards faster progression from BCR to castrate resistance compared to non-carriers [59]. Similarly, specific single nucleotide polymorphisms have been linked to a shorter time from BCR to death [60]. Basic science considerations suggested more rapid metastatic progression after BCR in TP53-enriched prostate cancer patients [61,62]. Several commercially available biomarkers, which were primarily established in a localized setting, are slowly extending their indications into the BCR realm as well. As a biomarker with the most convincing evidence, Decipher Prostate, a commercial 22-Gene Genomic Classifier, has shown promising results in risk at BCR [63–66]. Specifically, the Decipher genomic classifier score was an independent predictor of disease progression and overall survival in patients who underwent SRT [66]. Moreover, patients with a high Decipher score benefitted more from the addition of long-term ADT, whereas patients with a low Decipher score did not [64]. As a consequence, the Decipher score has been implemented in the current NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) [5]. Similarly, Prolaris, a cell cycle progression marker, was strongly associated with the SRT response and metastatic progression in a small sample of BCR patients [67]. Specific studies addressing the use of Oncotype Dx Prostate in the BCR setting are lacking [68]. In the search for better risk stratification, more complex models have been proposed using AI. Because the Gleason score at initial radical prostatectomy was invariably a significant predictor of risk after BCR, using AI techniques to provide more granular risk scoring of radical prostatectomy specimens appears especially appealing. Several AI-based models have achieved pathologist-like grading of radical prostatectomy specimens [69–72]. ArteraAI is a multimodal AI digital pathology-based biomarker that has been validated for prostate cancer prognosis and as a decision aid for ADT in addition to initial radiotherapy [73–75]. At the 2024 AUA annual meeting, Morgan *et al.* reported the initial results of its use in the BCR setting. Specifically, ArteraAI was an independent biomarker for metastatic progression [76,77]. Similarly, AI techniques have also been used within large institutional databases for the development of improved prognostic models in the BCR setting [78▪,79,80]. Sabbagh *et al.* developed and externally validated an AI model for the prediction of metastatic progression after SRT for BCR. Relying on the same clinical variables, this model outperformed the classical Tendulkar model slightly (AUC 0.72 vs. 0.60) [78▪]. However, it must be mentioned that AI techniques, such as gradient boosting or random forest classification, consume substantially more "degrees of freedom" and estimate substantially more parameters than traditional prediction models. Therefore, the (modest) improved predictability must be weighed against the lessened interpretability and vulnerability to statistical flukes and overfitting.

CONCLUSION

While there is a broad consensus that BCR treatment decisions should be based on risk factors, precise treatment algorithms are lacking: who should receive SRT and to what extent? Who should receive

concomitant ADT and for how long? The integration of PSMA-PET/CT, novel biomarkers, and AI exhibits great potential for tailoring more personalized therapeutic strategies. However, long-term data with clear survival benefit are still lacking.

Acknowledgements

We thank Pierre I. Karakiewicz, Freed Saad, Lars Budäus, Derya Tilki, Markus Graefen, Felix Preisser, Philipp Mandel, and Thomas Steuber for their critical review and valuable feedback.

Financial support and sponsorship

No external funding was received for the study.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Tilki D, van den Bergh RCN, Briers E, *et al.*, EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer. Part II-2024 update: treatment of relapsing and metastatic prostate cancer. Eur Urol 2024; 86:164–182.
2. Van den Broeck T, van den Bergh RCN, Arfi N, *et al.* Prognostic value of biochemical recurrence following treatment with curative intent for prostate cancer: a systematic review. Eur Urol 2019; 75:967–987.
3. Pound CR, Partin AW, Eisenberger MA, *et al.* Natural history of progression after PSA elevation following radical prostatectomy. JAMA 1999; 281:1591–1597.
4. Freedland SJ, Humphreys EB, Mangold LA, *et al.* Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. JAMA 2005; 294:433–439.
5. National Comprehensive Cancer Network, Inc. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for prostate cancer V.1.2025. 2025 [cited 2024 Dec 4]. Available at: https://www.nccn.org/.
6. Morgan TM, Boorjian SA, Buyyounouski MK, *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; 211:526–532.
7. Andolfi C, Vickers AJ, Cooperberg MR, *et al.* Blood prostate-specific antigen by volume of benign, gleason pattern 3 and 4 prostate tissue. Urology 2022; 170:154–160.
8. Falkenbach F, Schmalhofer ML, Tian Z, *et al.* Size and SUVmax define the contribution of nodal metastases to PSA in oligorecurrent prostate cancer. Prostate 2025; 85:105–111.
9. Hofman MS, Lawrentschuk N, Francis RJ, *et al.* Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. Lancet 2020; 395:1208–1216.
10. Afshar-Oromieh A, da Cunha ML, Wagner J, *et al.* Performance of [(68)Ga]Ga-PSMA-11 PET/CT in patients with recurrent prostate cancer after prostatectomy-a multicentre evaluation of 2533 patients. Eur J Nucl Med Mol Imaging 2021; 48:2925–2934.
11. Armstrong WR, Kishan AU, Booker KM, *et al.* Impact of prostate-specific membrane antigen positron emission tomography/computed tomography on prostate cancer salvage radiotherapy management: results from a prospective multicenter randomized phase 3 trial (PSMA-SRT NCT03582774). Eur Urol 2025; 87:97–99.
12. Ferdinandus J, Fendler WP, Farolfi A, *et al.* PSMA PET validates higher rates of metastatic disease for European Association of Urology Biochemical recurrence risk groups: an international multicenter study. J Nucl Med 2022; 63:76–80.
13. Boreta L, Gadzinski AJ, Wu SY, *et al.* Location of recurrence by gallium-68 PSMA-11 PET scan in prostate cancer patients eligible for salvage radiotherapy. Urology 2019; 129:165–171.
14. Giesel FL, Knorr K, Spohn F, *et al.* Detection efficacy of 18F-PSMA-1007 PET/CT in 251 patients with biochemical recurrence of prostate cancer after radical prostatectomy. J Nucl Med 2019; 60:362–368.
15. Fendler WP, Calais J, Eiber M, *et al.* Assessment of 68Ga-PSMA-11 PET accuracy in localizing recurrent prostate cancer: a prospective single-arm clinical trial. JAMA Oncol 2019; 5:856–863.
16. De Visschere PJL, Standaert C, Fütterer JJ, *et al.* A systematic review on the role of imaging in early recurrent prostate cancer. Eur Urol Oncol 2019; 2:47–76.
17. Meijer D, Eppinga WSC, Mohede RM, *et al.* Prostate-specific membrane antigen positron emission tomography/computed tomography is associated with improved oncological outcome in men treated with salvage radiation therapy for biochemically recurrent prostate cancer. Eur Urol Oncol 2022; 5:146–152.
18. Deijen CL, Vrijenhoek GL, Schaake EE, *et al.* PSMA-11-PET/CT versus choline-PET/CT to guide stereotactic ablative radiotherapy for androgen deprivation therapy deferral in patients with oligometastatic prostate cancer. Clin Transl Radiat Oncol 2021; 30:1–6.
19. Morris MJ, Rowe SP, Gorin MA, *et al.* Diagnostic performance of 18F-DCFPyL-PET/CT in men with biochemically recurrent prostate cancer: results from the CONDOR Phase III, Multicenter Study. Clin Cancer Res 2021; 27:3674–3682.
20. Fendler WP, Ferdinandus J, Czernin J, *et al.* Impact of 68Ga-PSMA-11 PET on the management of recurrent prostate cancer in a prospective single-arm clinical trial. J Nucl Med 2020; 61:1793–1799.
21. Habl G, Sauter K, Schiller K, *et al.* 68 Ga-PSMA-PET for radiation treatment planning in prostate cancer recurrences after surgery: individualized medicine or new standard in salvage treatment. Prostate 2017; 77:920–927.
22. Henkenberens C, Derlin T, Bengel FM, *et al.* Patterns of relapse as determined by 68Ga-PSMA ligand PET/CT after radical prostatectomy: Importance for tailoring and individualizing treatment. Strahlenther Onkol Organ Dtsch Rontgengesellschaft Al 2018; 194:303–310.
23. Calais J, Fendler WP, Eiber M, *et al.* Impact of 68Ga-PSMA-11 PET/CT on the management of prostate cancer patients with biochemical recurrence. J Nucl Med 2018; 59:434–441.
24. Sonni I, Eiber M, Fendler WP, *et al.* Impact of 68Ga-PSMA-11 PET/CT on staging and management of prostate cancer patients in various clinical settings: a prospective single-center study. J Nucl Med 2020; 61:1153–1160.
25. Emmett L, Tang R, Nandurkar R, *et al.* 3-Year freedom from progression after 68Ga-PSMA PET/CT-triaged management in men with biochemical recurrence after radical prostatectomy: results of a prospective multicenter trial. J Nucl Med 2020; 61:866–872.
26. Phillips R, Shi WY, Deek M, *et al.* Outcomes of observation vs. stereotactic ablative radiation for oligometastatic prostate cancer: the ORIOLE Phase 2 Randomized Clinical Trial. JAMA Oncol 2020; 6:650–659.
27. Deek MP, Eecken KV der, Sutera P, *et al.* Long-term outcomes and genetic predictors of response to metastasis-directed therapy versus observation in oligometastatic prostate cancer: analysis of STOMP and ORIOLE trials. J Clin Oncol 2022; 40:3377–3382.
28. Rouvière O, Vitry T, Lyonnet D. Imaging of prostate cancer local recurrences: why and how? Eur Radiol 2010; 20:1254–1266.
29. Shipley WU, Seiferheld W, Lukka HR, *et al.* Radiation with or without antiandrogen therapy in recurrent prostate cancer. N Engl J Med 2017; 376:417–428.
30. Carrie C, Magné N, Burban-Provost P, *et al.* Short-term androgen deprivation therapy combined with radiotherapy as salvage treatment after radical prostatectomy for prostate cancer (GETUG-AFU 16): a 112-month follow-up of a phase 3, randomised trial. Lancet Oncol 2019; 20:1740–1749.
31. Pollack A, Karrison TG, Balogh AG, *et al.* The addition of androgen deprivation therapy and pelvic lymph node treatment to prostate bed salvage radiotherapy (NRG Oncology/RTOG 0534 SPPORT): an international, multicentre, randomised phase 3 trial. Lancet 2022; 399:1886–1901.
32. Freedland SJ, de Almeida Luz M, De Giorgi U, *et al.* Improved outcomes with enzalutamide in biochemically recurrent prostate cancer. N Engl J Med 2023; 389:1453–1465.
33. ■ Holzgreve A, Armstrong WR, Clark KJ, *et al.* PSMA-PET/CT findings in patients with high-risk biochemically recurrent prostate cancer with no metastatic disease by conventional imaging. JAMA Netw Open 2025; 8: e2452971.

The EMBARK trial has changed the landscape of BCR treatment. This trial evaluated how many EMBARK-like patients would exhibit lesions on PSMA-PET/CT.

34. Falkenbach F, Lischewski F, Knipper S, *et al.* Prostate-specific membrane antigen–radioguided surgery in an EMBARK-like cohort of patients with oligorecurrent hormone-sensitive prostate cancer: delay in systemic treatment. Eur Urol Focus 2025. [Online ahead of print]
35. Dong L, Su Y, Zhu Y, *et al.* The European Association of Urology Biochemical Recurrence Risk Groups predict findings on PSMA PET in patients with biochemically recurrent prostate cancer after radical prostatectomy. J Nucl Med 2022; 63:248–252.
36. Scharl S, Zamboglou C, Strouthos I, *et al.* European association of urology risk stratification predicts outcome in patients receiving PSMA-PET-planned salvage radiotherapy for biochemical recurrence following radical prostatectomy. Radiother Oncol J Eur Soc Ther Radiol Oncol 2024; 194:110215.

37. Patel SA, Patil D, Smith J, *et al.* Postprostatectomy radiotherapy timing and long-term health-related quality of life. JAMA Netw Open 2024; 7:e2440747.

38. Nyarangi-Dix JN, Steimer J, Bruckner T, *et al.* Postprostatectomy radiotherapy adversely affects urinary continence irrespective of radiotherapy regime. World J Urol 2017; 35:1841–1847.

39. Kneebone A, Fraser-Browne C, Duchesne GM, *et al.* Adjuvant radiotherapy versus early salvage radiotherapy following radical prostatectomy (TROG 08.03/ANZUP RAVES): a randomised, controlled, phase 3, noninferiority trial. Lancet Oncol 2020; 21:1331–1340.

40. Parker CC, Clarke NW, Cook AD, *et al.* Timing of radiotherapy after radical prostatectomy (RADICALS-RT): a randomised, controlled phase 3 trial. Lancet 2020; 396:1413–1421.

41. ■■ Scharl S, Zamboglou C, Strouthos I, *et al.* Salvage radiotherapy is effective in patients with PSMA-PET-negative biochemical recurrence- results of a retrospective study. Radiother Oncol J Eur Soc Ther Radiol Oncol 2023; 184:109678.

This retrospective, multicenter analysis provided convincing evidence that SRT should also be directly initiated in BCR patients with negative PSMA-PET/CT.

42. ■■ Adebahr S, Althaus A, Scharl S, *et al.* The prognostic significance of a negative PSMA-PET scan prior to salvage radiotherapy following radical prostatectomy. Eur J Nucl Med Mol Imaging 2024; 51:558–567.

Along with the two other studies above, this retrospective, multicenter study supported also the usage of early SRT for BCR patients with negative PSMA-PET/CT.

43. Emmett L, van Leeuwen PJ, Nandurkar R, *et al.* Treatment outcomes from 68Ga-PSMA PET/CT-informed salvage radiation treatment in men with rising PSA after radical prostatectomy: prognostic value of a negative PSMA PET. J Nucl Med 2017; 58:1972–1976.

44. Knipper S, Lischewski F, Koehler D, *et al.* Biochemical response of <0.1 ng/ml predicts therapy-free survival of prostate cancer patients following prostate-specific membrane antigen–targeted salvage surgery. Eur Urol Oncol 2025; 8:270–277.

45. Knipper S, Falkenbach F, Maurer T. Radioguided surgery for lymph node metastases in prostate cancer. Curr Opin Urol 2024; 34:266–272.

46. Harsini S, Wilson D, Saprunoff H, *et al.* Outcome of patients with biochemical recurrence of prostate cancer after PSMA PET/CT-directed radiotherapy or surgery without systemic therapy. Cancer Imaging 2023; 23:27.

47. ■■ Harsini S, Martineau P, Plaha S, *et al.* Prognostic significance of a negative PSMA PET/CT in biochemical recurrence of prostate cancer. Cancer Imaging 2024; 24:117.

This posthoc analysis of a prospective clinical trial also supported the concept of SRT in PSMA-PET/CT-negative BCR patients.

48. Jilg CA, Drendel V, Rischke HC, *et al.* Detection rate of (18)F-choline PET/CT and (68)Ga-PSMA-HBED-CC PET/CT for prostate cancer lymph node metastases with direct link from PET to histopathology: dependence on the size of tumor deposits in lymph nodes. J Nucl Med 2019; 60:971–977.

49. Falkenbach F, Kachanov M, Leyh-Bannurah SR, *et al.* Size of lymph-node metastases in prostate cancer patients undergoing radical prostatectomy: implication for imaging and oncologic follow-up of 2705 lymph-node positive patients. World J Urol 2024; 42:38.

50. Celli M, De Giorgi U, Caroli P, *et al.* Clinical value of negative 68Ga-PSMA PET/CT in the management of biochemical recurrent prostate cancer patients. Eur J Nucl Med Mol Imaging 2021; 48:87–94.

51. Zamboglou C, Peeken JC, Janbain A, *et al.* Development and validation of a multiinstitutional nomogram of outcomes for PSMA-PET-based salvage radiotherapy for recurrent prostate cancer. JAMA Netw Open 2023; 6:e2314748.

52. Karpinski MJ, Hüsing J, Claassen K, *et al.* Combining PSMA-PET and PROMISE to re-define disease stage and risk in patients with prostate cancer: a multicentre retrospective study. Lancet Oncol 2024; 25:1188–1201.

53. Fossati N, Karnes RJ, Colicchia M, *et al.* Impact of early salvage radiation therapy in patients with persistently elevated or rising prostate-specific antigen after radical prostatectomy. Eur Urol 2018; 73:436–444.

54. Abugharib A, Jackson WC, Tumati V, *et al.* Very early salvage radiotherapy improves distant metastasis-free survival. J Urol 2017; 197(Pt 1):662–668.

55. ■■ Tilki D, Chen MH, Wu J, *et al.* Prostate-specific antigen level at the time of salvage therapy after radical prostatectomy for prostate cancer and the risk of death. J Clin Oncol 2023; 41:2428–2435.

This trial showed that SRT should be administered for BCR patients at low PSA levels, if at least one risk factor was present at radical prostatectomy (pT3/4 or Gleason score $\geq$8).

56. Dess RT, Sun Y, Jackson WC, *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; 6:735–743.

57. Spratt DE, Dess RT, Zumsteg ZS, *et al.* A systematic review and framework for the use of hormone therapy with salvage radiation therapy for recurrent prostate cancer. Eur Urol 2018; 73:156–165.

58. Preisser F, Abrams-Pompe RS, Stelwagen PJ, *et al.* European Association of Urology Biochemical Recurrence Risk classification as a decision tool for salvage radiotherapy—a multicenter study. Eur Urol 2024; 85:164–170.

59. Gallagher DJ, Gaudet MM, Pal P, *et al.* Germline BRCA mutations denote a clinicopathologic subset of prostate cancer. Clin Cancer Res 2010; 16:2115–2121.

60. Song X, Ru M, Steinsnyder Z, *et al.* SNPs at SMG7 associated with time from biochemical recurrence to prostate cancer death. Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol 2022; 31:1466–1472.

61. Hong MKH, Macintyre G, Wedge DC, *et al.* Tracking the origins and drivers of subclonal metastatic expansion in prostate cancer. Nat Commun 2015; 6:6605.

62. Nientiedt C, Budczies J, Endris V, *et al.* Mutations in TP53 or DNA damage repair genes define poor prognostic subgroups in primary prostate cancer. Urol Oncol 2022; 40:8.e11–8.e18.

63. Spratt DE, Yousefi K, Deheshi S, *et al.* Individual patient-level meta-analysis of the performance of the decipher genomic classifier in high-risk men after prostatectomy to predict development of metastatic disease. J Clin Oncol 2017; 35:1991–1998.

64. Feng FY, Huang HC, Spratt DE, *et al.* Validation of a 22-gene genomic classifier in patients with recurrent prostate cancer: an ancillary study of the NRG/RTOG 9601 Randomized Clinical Trial. JAMA Oncol 2021; 7:544–552.

65. Jairath NK, Dal Pra A, Vince R, *et al.* A systematic review of the evidence for the decipher genomic classifier in prostate cancer. Eur Urol 2021; 79:374–383.

66. Dal Pra A, Ghadjar P, Hayoz S, *et al.* Validation of the Decipher genomic classifier in patients receiving salvage radiotherapy without hormone therapy after radical prostatectomy – an ancillary study of the SAKK 09/10 randomized clinical trial. Ann Oncol 2022; 33:950–958.

67. Koch MO, Cho JS, Kaimakliotis HZ, *et al.* Use of the cell cycle progression (CCP) score for predicting systemic disease and response to radiation of biochemical recurrence. Cancer Biomark Sect Dis Markers 2016; 17:83–88.

68. Vera G, Rojas PA, Black JB, San Francisco IF. Usefulness of tissue biomarkers versus prostate-specific membrane antigen-positron emission tomography for prostate cancer biochemical recurrence after radical prostatectomy. Cancers 2024; 16:2879.

69. Huang W, Randhawa R, Jain P, *et al.* Development and validation of an artificial intelligence-powered platform for prostate cancer grading and quantification. JAMA Netw Open 2021; 4:e2132554.

70. Ström P, Kartasalo K, Olsson H, *et al.* Artificial intelligence for diagnosis and grading of prostate cancer in biopsies: a population-based, diagnostic study. Lancet Oncol 2020; 21:222–232.

71. Pantanowitz L, Quiroga-Garza GM, Bien L, *et al.* An artificial intelligence algorithm for prostate cancer diagnosis in whole slide images of core needle biopsies: a blinded clinical validation and deployment study. Lancet Digit Health 2020; 2:e407–e416.

72. Kartasalo K, Bulten W, Delahunt B, *et al.* artificial intelligence for diagnosis and gleason grading of prostate cancer in biopsies-current status and next steps. Eur Urol Focus 2021; 7:687–691.

73. Esteva A, Feng J, van der Wal D, *et al.* Prostate cancer therapy personalization via multimodal deep learning on randomized phase III clinical trials. NPJ Digit Med 2022; 5:71.

74. Spratt DE, Tang S, Sun Y, *et al.* Artificial intelligence predictive model for hormone therapy use in prostate cancer. NEJM Evid 2023; 2:EVIDoa2300023.

75. Armstrong AJ, Liu VY, Selvaraju RR, *et al.* Development and validation of an AI-derived digital pathology-based biomarker to predict benefit of long-term androgen deprivation therapy with radiotherapy in men with localized high-risk prostate cancer across multiple phase III NRG/RTOG trials. J Clin Oncol 2023; 41(Suppl):5001–15001.

76. Morgan TM, Ren Y, Tang S, *et al.* PD42-11 development and validation of a multimodal artificial intelligence (MMAI)-derived digital pathology-based biomarker predicting metastasis for radical prostatectomy patients with biochemical recurrence in nrg/rtog trials. J Urol 2024.

77. AUA 2024: development and validation of a MMAI-derived digital pathology-based biomarker predicting metastasis for radical prostatectomy patients with biochemical recurrence in NRG/RTOG trials. [cited 2025 Apr 11]. Available at: https://www.urotoday.com/conference-highlights/aua-2024/aua-2024-prostate-cancer/151828-aua-2024-development-and-validation-of-a-mmai-derived-digital-pathology-based-biomarker-predicting-metastasis-for-radical-prostatectomy-patients-with-biochemical-recurrence-in-nrg-rtog-trials.html.

78. ■ Sabbagh A, Tilki D, Feng J, *et al.* Multiinstitutional development and external validation of a machine learning model for the prediction of distant metastasis in patients treated by salvage radiotherapy for biochemical failure after radical prostatectomy. Eur Urol Focus 2024; 10:66–74.

Sabbagh *et al.* demonstrated the feasibility of machine learning for predicting metastatic progression in BCR patients relying on three large institutional databases.

79. Beinecke JM, Anders P, Schurrat T, *et al.* Evaluation of machine learning strategies for imaging confirmed prostate cancer recurrence prediction on electronic health records. Comput Biol Med 2022; 143:105263.

80. Janbain A, Farolfi A, Guenegou-Arnoux A, *et al.* A machine learning approach for predicting biochemical outcome after PSMA-PET-guided salvage radiotherapy in recurrent prostate cancer after radical prostatectomy: retrospective study. JMIR Cancer 2024; 10:e60323.