PIONEER
ACADEMIC PUBLISHING LIMITED

Current Research in Medical Sciences
ISSN 2958-0390
www.pioneerpublisher.com/crms
Volume 4 Number 2 March 2025

Prostate Cancer Radiotherapy: Current Status, Clinical Challenges, and Future Strategies

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doi:10.56397/CRMS.2025.03.08

Abstract

The radiation therapy for prostate cancer plays a central role in the overall management of the disease, covering a wide range of applications, including radical treatment for localized tumors, postoperative adjuvant/rescue radiotherapy, and palliative treatment for advanced metastatic lesions. With the advancement of radiotherapy technologies and optimization of combined treatment strategies, the precision and safety of prostate cancer radiotherapy have significantly improved. However, key clinical challenges remain: how to determine the suitability of radical surgery or radiotherapy, balance the increase in radiation dose with toxicity control, the choice between adjuvant or salvage radiotherapy for postoperative recurrence, and the synergistic mechanisms and applicable populations for radiotherapy combined with novel endocrine drugs or immunotherapy. This article systematically reviews the current status and recent advances in prostate cancer radiotherapy, explores the management of radical radiotherapy, postoperative adjuvant radiotherapy (ART), and salvage radiotherapy (SRT), the management of radiotherapy toxicity, and individualized treatment strategies in the context of new technologies. It further investigates cutting-edge technologies such as AI-guided radiotherapy planning and Flash ultra-high-speed radiotherapy, with the aim of providing evidence-based support for clinical decision-making and research translation.

Keywords: prostate cancer, radiation therapy, toxicity management, individualized therapy, artificial intelligence, Flash ultrafast radiotherapy

1. Introduction

Prostate cancer is the second most common malignancy among men worldwide (Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al., 2021), with a continuously increasing number of new cases (James ND, Tannock I, N'Dow J, Feng F, Gillessen S, Ali SA, et al., 2024). Current treatment options for prostate cancer mainly include surgery, radiotherapy, endocrine therapy, and chemotherapy, with radiotherapy playing a particularly crucial role throughout the entire treatment process. Although the technology for prostate cancer radiotherapy is relatively mature, there are still controversies in the selection of

optimal timing of radiotherapy and the combination with endocrine therapy (Latorzeff I, Le Guevelou J & Sargos P., 2023). With advances in treatment technologies, prostate cancer radiotherapy requires greater precision and personalization to achieve a balance between minimizing clinical side effects and maximizing disease control benefits (Martin NE & D'Amico AV., 2014).

2. Radical Radiotherapy

Radical prostatectomy (RP) and radical radiotherapy (RT) are the main treatment options for intermediate- and high-risk localized prostate cancer (Hamdy FC, Donovan JL, Lane JA, Metcalfe C, Davis M, Turner EL, et al., 2023). Surgery aims to achieve cure by removing the prostate and surrounding tissues, while radiotherapy kills cancer cells through high-dose radiation. In recent years, significant advancements have been made in radiotherapy techniques, including the application of intensity-modulated radiotherapy (IMRT), stereotactic body radiotherapy (SBRT), and proton therapy, which have greatly improved the precision and efficacy of radiotherapy (Daly T., 2020). Studies have shown that no differences in overall survival or progression-free survival were observed between radical prostatectomy and radical radiotherapy, indicating that radical radiotherapy is as effective as surgery (Hamdy FC, Donovan JL, Lane JA, Metcalfe C, Davis M, Turner EL, et al., 2023). Additionally, radical radiotherapy has lower urinary toxicity, but carries a slightly higher risk of gastrointestinal issues. However, severe gastrointestinal problems and incontinence are very rare. This conclusion has been confirmed in other studies comparing radical radiotherapy with radical prostatectomy for localized prostate cancer (van As N, Yasar B, Griffin C, Patel J, Tree AC, Ostler P, et al., 2024; Chen RC, Basak R, Meyer A-M, Kuo T-M, Carpenter WR, Agans RP, et al., 2017). Clinicians should consider the short- and long-term effects of treatment on the urinary tract, gastrointestinal system, and sexual function, as well as the risks of disease progression and the patient's financial situation when choosing the most appropriate treatment.

Radical radiotherapy can also be combined with endocrine therapy (ADT) to achieve better disease control, prolonging progression-free survival and overall survival. For patients with intermediate- and high-risk localized prostate cancer, the combination of radiotherapy and ADT has been shown to significantly improve treatment outcomes, enhancing progression-free survival and overall survival rates (D'Amico AV, Manola J, Loffredo M, Renshaw AA, DellaCroce A & Kantoff PW, 2004; D'Amico AV, Chen M-H, Renshaw AA, Loffredo M & Kantoff PW., 2008; Jones CU, Hunt D, McGowan DG, Amin MB, Chetner MP, Bruner DW, et al., 2011). ADT slows prostate cancer growth by inhibiting the secretion of androgens, thereby enhancing the effectiveness of radiotherapy. However, the duration of ADT remains controversial. Some studies suggest that 4 to 6 months of ADT may be sufficient for intermediate-risk patients, while for high-risk patients, the duration of ADT may need to be longer, potentially up to 2 to 3 years (Zapatero A, Guerrero A, Maldonado X, Alvarez A, Gonzalez San Segundo C, Cabeza Rodríguez MA, et al., 2015).

3. Adjuvant Radiotherapy

Adjuvant radiotherapy (ART) is an important adjunctive treatment following radical prostatectomy for prostate cancer, aimed at reducing the risk of local recurrence and distant metastasis in high-risk patients (Daly T, Hickey BE, Lehman M, Francis DP & See AM., 2011). In recent years, several randomized controlled trials have deeply investigated the efficacy, optimal timing, and combined treatment strategies of ART, providing important evidence-based medical support for clinical practice. In studies such as SWOG 8794, patients with high-risk characteristics were included, such as pathological staging of T3N0M0 or higher, and Gleason score $\geqslant$ 7. These characteristics indicate a higher risk of recurrence following radical prostatectomy. The SWOG 8794 trial included 473 high-risk prostate cancer patients, and the results showed that patients who received ART had significantly better biochemical recurrence-free survival (bRFS), prostate cancer-specific survival (PCSS), and overall survival (OS) rates compared to the observation group. Similarly, the EORTC 22911, ARO 96-02, and FinnProstate trials consistently showed that ART has significant advantages in improving these key survival metrics (Thompson IM, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, et al., 2009; Bolla M, Poppel H van, Tombal B, Vekemans K, Pozzo LD, Reijke TM de, et al., 2012; Wiegel T, Bottke D, Steiner U, Siegmann A, Golz R, Störkel S, et al., 2009; Hackman G, Taari K, Tammela TL, Matikainen M, Kouri M, Joensuu T, et al., 2019).

For patients with positive lymph nodes, adjuvant radiotherapy can also offer survival benefits (Abdollah F, Karnes RJ, Suardi N, Cozzarini C, Gandaglia G, Fossati N, et al., 2014; Abdollah F, Dalela D, Sood A, Keeley J, Alanee S, Briganti A, et al., 2018; Jegadeesh N, Liu Y, Zhang C, Zhong J, Cassidy RJ, Gillespie T, et al., 2017; Touijer KA, Karnes RJ, Passoni N, Sjoberg DD, Assel M, Fossati N, et al., 2018), with even more significant survival benefits in high-risk positive lymph nodes patients (Gleason score 8-10 or three or more affected lymph nodes). Moreover, when adjuvant radiotherapy is combined with adjuvant androgen deprivation therapy, a more apparent trend of reduced mortality is observed (Froehner M, Coressel Y, Koch R, Borkowetz A, Thomas C, Wirth MP, et al., 2022). These findings suggest that postoperative adjuvant radiotherapy is an effective treatment option for high-risk prostate cancer patients.

In addition, the combination therapy strategies for ART are continually being explored. The combination of adjuvant radiotherapy with hormone therapy has been shown to significantly improve patients' disease-free survival and progression-free survival (Omrcen T, Hrepic D, Boraska Jelavic T & Vrdoljak E., 2015). Some studies indicate that long-term androgen deprivation therapy (ADT, 24 months) significantly improves progression-free survival compared to short-term ADT (6 months), although it does not improve overall survival (OS). The incidence of grade 3 or higher toxicities was 14% in the short-term ADT group and 19% in the long-term ADT group (p=0.025), but no treatment-related deaths occurred (Cc P, H K, Ad C, Nw C, Cn C, Wr C, et al., 2024). Therefore, when deciding on the duration of ADT, the benefits and adverse effects of long-term ADT need to be carefully weighed. For patients with a longer life expectancy who can tolerate the side effects of ADT, long-term ADT is recommended.

4. Salvage Radiotherapy

Salvage radiotherapy (SRT) is the standard treatment for biochemical recurrence after radical prostatectomy (Terlizzi M, Limkin EJ, Moukasse Y & Blanchard P., 2022). Studies have shown that salvage radiotherapy is one of the treatments that may cure recurrent prostate cancer, especially when treatment is started at a low prostate-specific antigen (PSA) level, which leads to better outcomes (Morgan TM, Boorjian SA, Buyyounouski MK, Chapin BF, Chen DYT, Cheng HH, et al., 2024). The NCCN guidelines recommend a radiation dose of 64-72 Gy to the prostate bed for patients with biochemical recurrence after radical prostatectomy and no distant metastasis. If there is clinically confirmed local recurrence by biopsy or imaging, the radiation dose should be increased further. For patients at risk of pelvic lymph node metastasis, a preventive dose of 45-50 Gy is recommended; for imaging-confirmed recurrent pelvic lymph nodes, the recommended dose is 60-70 Gy (Schaeffer EM, Srinivas S, Adra N, Ahmed B, An Y, Bitting R, et al., 2024). However, some trials have indicated that increasing the radiation dose to the prostate bed in patients with biochemical recurrence alone does not improve biochemical progression-free survival, but results in a higher incidence of gastrointestinal toxicity (Ghadjar P, Hayoz S, Bernhard J, Zwahlen DR, Hölscher T, Gut P, et al., 2021). The safety and efficacy of hypofractionated radiation therapy in SRT remains a question that needs to be analyzed and explored in further experiments.

The addition of endocrine therapy can provide patients with additional survival benefits. Several studies have shown that SRT combined with ADT can improve disease-free survival, progression-free survival, and overall survival (Carrie C, Magné N, Burban-Provost P, Sargos P, Latorzeff I, Lagrange J-L, et al., 2019; Dess RT, Sun Y, Jackson WC, Jairath NK, Kishan AU, Wallington DG, et al., 2020). Therefore, the combination of SRT and ADT is recommended to improve patient prognosis.

Currently, research indicates that SRT has the same disease control effect as ART but may reduce urinary and gastrointestinal toxicity (Kneebone A, Fraser-Browne C, Duchesne GM, Fisher R, Frydenberg M, Herschtal A, et al., 2020; Sargos P, Chabaud S, Latorzeff I, Magné N, Benyoucef A, Supiot S, et al., 2020; Parker CC, Petersen PM, Cook AD, Clarke NW, Catton C, Cross WR, et al., 2024). This finding has led current guidelines to recommend SRT over ART. However, the studies included in the above research have a relatively small proportion of patients with a Gleason score of $\geqslant 8$. The efficacy of SRT in this population still requires further evaluation.

5. Palliative Radiotherapy

Palliative radiotherapy for prostate cancer is a treatment method aimed at advanced or

metastatic prostate cancer, intended to alleviate symptoms, improve quality of life, and extend survival rather than cure the disease. This treatment is suitable for patients whose cancer has spread to the bones or other parts of the body or who experience pain or other discomforts. The bones are a common site for distant metastasis in prostate cancer, and after bone metastasis occurs, patients may experience pathological fractures, spinal cord compression, pain, and other bone-related events that affect their quality of life. Currently, the standard treatment for alleviating pain from metastatic lesions and preventing adverse events such as fractures caused by bone metastasis is external beam radiotherapy (Fischer-Valuck BW, Baumann BC, Apicelli A, Rao YJ, Roach M, Daly M, et al., 2018).

Prostate cancer patients with low metastatic burden (defined as ⩽4 bone metastases, with or without distant lymph node involvement) who undergo palliative radiotherapy may benefit from a 3-year overall survival rate (Müller A-C, Aebersold DM, Albrecht C, Böhmer D, Flentje M, Ganswindt U, et al., 2022). Commonly used fractionation schemes are designated as short-course treatment ([SC-RT]: 1 session of 8 Gy and 5 sessions of 20 Gy) and long-course treatment ([LC-RT]: 10 sessions of 30 Gy and 15 sessions of 37.5 Gy). Several prospective randomized trials and meta-analyses have compared the differences in pain control effects between different fractionated treatment regimens, finding similar pain control outcomes. LC-RT is associated with improved overall survival (OS), but no OS differences were observed between 37.5 Gy and a single 8 Gy session or 5 sessions of 20 Gy. Short-course treatment can reduce treatment costs and has economic advantages. LC-RT remains the most common fractionated treatment scheme for palliative bone metastasis in PCa patients, though the use of palliative SC-RT is increasing. Therefore, many medical associations, including the American Society for Radiation Oncology (ASTRO), have released practice guidelines advocating for single-session or shorter courses of radiotherapy (Fischer-Valuck BW, Baumann BC, Apicelli A, Rao YJ, Roach M, Daly M, et al., 2018).

6. Toxicity Management of Radiotherapy

Although radiotherapy can provide significant survival benefits for prostate cancer patients, its toxic side effects should not be ignored, as they can have a substantial negative impact on the patient's quality of life. Common adverse reactions to prostate cancer radiotherapy include radiation cystitis, urethral stricture, and proctitis, while less common side effects include urethral fistula, gastrointestinal fistula, and bone toxicity (Matta R, Chapple CR, Fisch M, Heidenreich A, Herschorn S, Kodama RT, et al., 2019). Currently, the toxic side effects of radiotherapy can be reduced by optimizing radiotherapy plans, using image-guided radiotherapy (IGRT) to refine the treatment process, and adopting hypofractionated radiotherapy regimens (De Bari B, Arcangeli S, Ciardo D, Mazzola R, Alongi F, Russi EG, et al., 2016).

For mild urinary or intestinal toxicity, symptomatic treatments such as pain relief and anti-inflammatory medications are typically used to alleviate symptoms. In terms of urinary system toxicity, urinary obstruction and urethral stricture are common severe adverse reactions. Acute obstruction is usually managed with catheterization and medication, while advanced obstruction may require endoscopic or surgical treatment to improve symptoms. For urethral stricture, initial treatments include dilation and/or visual endoscopic urethrotomy. After these treatments, patients may experience recurrent strictures, which may require open urethroplasty or urethral reconstruction using flaps or grafted tissue (Matta R, Chapple CR, Fisch M, Heidenreich A, Herschorn S, Kodama RT, et al., 2019).

In terms of the gastrointestinal system, rectal bleeding is a common adverse reaction. For mild toxicity, oral medications such as metronidazole combined with ciprofloxacin can be used, or local treatments such as 4% formaldehyde enemas may be applied. For refractory rectal bleeding, hyperbaric oxygen therapy may be required, as it promotes healing by stimulating capillary angiogenesis in the bladder. For grade 3 or higher proctitis, if bleeding is difficult to control, endoscopic treatment may be necessary. In some cases, surgery may be required, such as defunctioning loop colostomy, Hartmann's procedure, resection and anastomosis, or pull-through procedures. Surgery is typically considered a last resort, as these patients often have a higher risk of complications and mortality (Matta R, Chapple CR, Fisch M, Heidenreich A, Herschorn S, Kodama RT, et al., 2019).

7. Individualized Radiotherapy Strategies for Prostate Cancer

With the support of molecular biomarkers, image guidance, and artificial intelligence (AI) technologies, developing appropriate personalized radiotherapy strategies can significantly improve the precision and efficacy of radiotherapy. The Decipher score is a biomarker-based scoring tool that assesses the risk of recurrence and the likelihood of metastasis in prostate cancer patients. This tool helps identify which prostate cancer patients are more aggressive, thereby guiding treatment decisions and optimizing follow-up management (Jairath NK, Dal Pra A, Vince R, Dess RT, Jackson WC, Tosoian JJ, et al., 2021). PSMA PET/CT is a molecular imaging technology with high sensitivity and specificity, capable of accurately detecting recurrent lesions even at lower PSA levels. By accurately localizing the scope of lesions, it reduces radiation exposure to normal tissues, improving treatment efficacy. It has demonstrated significant value in salvage radiotherapy after biochemical recurrence and targeted therapy for oligometastatic lesions, greatly enhancing lesion detection capability and optimizing treatment decisions (Mena E, Lindenberg L & Choyke P., 2022). Currently, the application of artificial intelligence (AI) in prostate cancer radiotherapy management shows enormous potential. Machine learning algorithms can analyze large amounts of clinical and imaging data to optimize radiotherapy plans, ensuring maximum therapeutic effect and minimizing side effects in dose distribution (Pang Y, Wang H & Li H., 2022). Additionally, AI can be used to predict radiotherapy-related toxicities, for example, by analyzing patients' genomic data and clinical characteristics to identify high-risk patients in advance, thereby enabling preventive measures (Rydzewski NR, Helzer KT, Bootsma M, Shi Y, Bakhtiar H, Sjöström M, et al., 2023). These AI-driven models provide strong technical support for personalized radiotherapy.

8. Future Direction

Although immunotherapy has achieved significant and durable effects in certain cancer types, similar success has not been realized in prostate cancer patients. This may be related to the low mutational burden and tumor immunogenicity of prostate cancer (Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SAJR, Behjati S, Biankin AV, et al., 2013). Radiotherapy not only directly kills tumor cells but also activates the immune system by inducing immunogenic cell death (ICD). The combination of radiotherapy and immunotherapy has shown great potential in clinical studies, but significant survival benefit has not yet been achieved in clinical trials, partly due to insufficient treatment timing or dosage strategies (Green M, Feng, Felix Y, Mehra, Rohit, & Spratt DE., 2017). Therefore, further optimization of patient selection criteria and treatment plans is needed, as well as the evaluation of novel targets and combination strategies with radiotherapy, to advance the application of immunotherapy and radiotherapy in prostate cancer.

Flash radiotherapy is an ultrahigh dose rate radiation therapy technique that can deliver a high dose of radiation in an extremely short time (usually on the millisecond scale), while minimizing damage to normal tissues and effectively killing tumor cells. Additionally, Flash radiotherapy can shorten treatment times, with the treatment time for each beam reduced from 1 minute to less than 1 second, thereby reducing instability caused by organ motion (Kaulfers T, Lattery G, Cheng C, Zhao X, Selvaraj B, Wu H, et al., 2024). Its application in prostate cancer treatment holds great potential, but further biological and clinical research is needed to validate its safety and long-term effects.

9. Discussion

Radiotherapy for prostate cancer plays a central role in the overall disease management but still faces several challenges in clinical practice. Radical radiotherapy is an important treatment option for intermediate- to high-risk localized prostate cancer, with efficacy comparable to radical surgery and lower urinary tract toxicity. However, the gastrointestinal toxicity of radical radiotherapy should not be overlooked, and careful consideration is required in clinical practice. Furthermore, the combination of radiotherapy and androgen deprivation therapy (ADT) significantly enhances treatment outcomes, but the optimal duration of ADT remains controversial. Future research should focus on further optimizing radiotherapy techniques to reduce toxic reactions and establish clear strategies for the best application of ADT. The management strategies for postoperative adjuvant radiotherapy (ART) and salvage radiotherapy (SRT) are also continuously being refined. ART has shown

significant advantages in reducing the risk of local recurrence and distant metastasis in high-risk patients, but its combination strategies, such as with endocrine therapy, still need further exploration. As the standard treatment for biochemical recurrence after radical prostatectomy, SRT is more effective at lower PSA levels, but more research is needed to determine whether adjuvant radiotherapy or salvage radiotherapy is more suitable for high-risk patients with a Gleason score of $\geqslant$8.

The management of radiotherapy toxicity is crucial for improving patients' quality of life. Although advances in radiotherapy techniques have reduced the incidence of toxic reactions, urological and gastrointestinal toxicities remain significant concerns. Optimizing radiotherapy plans, using image-guided radiotherapy (IGRT) techniques, and employing hypofractionated radiotherapy regimens can help reduce side effects to some extent. For existing toxic reactions, appropriate treatment measures should be taken based on their severity to enhance the patient's quality of life. Future directions will continue to focus on achieving better therapeutic outcomes while reducing radiotherapy-related adverse effects, which greatly requires personalized radiotherapy management and the development of new technologies. Currently, the development of cutting-edge technologies such as artificial intelligence and Flash ultrahigh-dose rate radiotherapy holds great potential for application, but their long-term effects and safety still need further verification.

References

Abdollah F, Dalela D, Sood A, Keeley J, Alanee S, Briganti A, et al. (2018). Impact of Adjuvant Radiotherapy in Node-positive Prostate Cancer Patients: The Importance of Patient Selection. *European Urology*, *74*(3), 253–256.

Abdollah F, Karnes RJ, Suardi N, Cozzarini C, Gandaglia G, Fossati N, et al. (2014). Impact of Adjuvant Radiotherapy on Survival of Patients with Node-Positive Prostate Cancer. *JCO*, *32*(35), 3939–3947.

Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SAJR, Behjati S, Biankin AV, et al. (2013). Signatures of mutational processes in human cancer. *Nature*, *500*(7463), 415–421.

Bolla M, Poppel H van, Tombal B, Vekemans K, Pozzo LD, Reijke TM de, et al. (2012). Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). *The Lancet*, *380*(9858), 2018–2027.

Carrie C, Magné N, Burban-Provost P, Sargos P, Latorzeff I, Lagrange J-L, et al. (2019). 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. *The Lancet Oncology*, *20*(12), 1740–1749.

Cc P, H K, Ad C, Nw C, Cn C, Wr C, et al. (2024). 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. *Lancet (London, England)*, *403*(10442). doi:10.1016/S0140-6736(24)00549-X.

Chen RC, Basak R, Meyer A-M, Kuo T-M, Carpenter WR, Agans RP, et al. (2017). Association Between Choice of Radical Prostatectomy, External Beam Radiotherapy, Brachytherapy, or Active Surveillance and Patient-Reported Quality of Life Among Men with Localized Prostate Cancer. *JAMA*, *317*(11), 1141–1150.

D'Amico AV, Chen M-H, Renshaw AA, Loffredo M, Kantoff PW. (2008). Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. *JAMA*, *299*(3), 289–295.

D'Amico AV, Manola J, Loffredo M, Renshaw AA, DellaCroce A, Kantoff PW. (2004). 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial. *JAMA*, *292*(7), 821–827.

Daly T, Hickey BE, Lehman M, Francis DP, See AM. (2011). Adjuvant radiotherapy following radical prostatectomy for prostate cancer. *Cochrane Database Syst Rev.*, (12), CD007234.

Daly T. (2020). Evolution of definitive external beam radiation therapy in the treatment of prostate cancer. *World J Urol.*, *38*(3), 565–591.

De Bari B, Arcangeli S, Ciardo D, Mazzola R, Alongi F, Russi EG, et al. (2016). Extreme

hypofractionation for early prostate cancer: Biology meets technology. *Cancer Treatment Reviews*, 50, 48–60.

Dess RT, Sun Y, Jackson WC, Jairath NK, Kishan AU, Wallington DG, et al. (2020). Association of Presalvage Radiotherapy PSA Levels After Prostatectomy with Outcomes of Long-term Antiandrogen Therapy in Men with Prostate Cancer. *JAMA Oncol.*, *6*(5), 735–743.

Fischer-Valuck BW, Baumann BC, Apicelli A, Rao YJ, Roach M, Daly M, et al. (2018). Palliative radiation therapy (RT) for prostate cancer patients with bone metastases at diagnosis: A hospital-based analysis of patterns of care, RT fractionation scheme, and overall survival. *Cancer Med.*, *7*(9), 4240–4250.

Froehner M, Coressel Y, Koch R, Borkowetz A, Thomas C, Wirth MP, et al. (2022). Acceptance and efficacy of recommended adjuvant radiotherapy in patients with positive lymph nodes at radical prostatectomy: a preference-based study. *World J Urol.*, *40*(6), 1463–1468.

Ghadjar P, Hayoz S, Bernhard J, Zwahlen DR, Hölscher T, Gut P, et al. (2021). Dose-intensified Versus Conventional-dose Salvage Radiotherapy for Biochemically Recurrent Prostate Cancer After Prostatectomy: The SAKK 09/10 Randomized Phase 3 Trial. *European Urology*, *80*(3), 306–315.

Green M, Feng, Felix Y, Mehra, Rohit, and Spratt DE. (2017). Convergence of Immunotherapy, Radiotherapy and Prostate Cancer: Challenges and Opportunities. *Immunotherapy*, *9*(9), 695–699.

Hackman G, Taari K, Tammela TL, Matikainen M, Kouri M, Joensuu T, et al. (2019). Randomised Trial of Adjuvant Radiotherapy Following Radical Prostatectomy Versus Radical Prostatectomy Alone in Prostate Cancer Patients with Positive Margins or Extracapsular Extension. *European Urology*, *76*(5), 586–595.

Hamdy FC, Donovan JL, Lane JA, Metcalfe C, Davis M, Turner EL, et al. (2023). Fifteen-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. *New England Journal of Medicine*, *388*(17), 1547–1558.

Jairath NK, Dal Pra A, Vince R, Dess RT, Jackson WC, Tosoian JJ, et al. (2021). A Systematic Review of the Evidence for the Decipher Genomic Classifier in Prostate Cancer. *European Urology*, *79*(3), 374–383.

James ND, Tannock I, N'Dow J, Feng F, Gillessen S, Ali SA, et al. (2024). The Lancet Commission on prostate cancer: planning for the surge in cases. *Lancet*, *403*(10437), 1683–1722.

Jegadeesh N, Liu Y, Zhang C, Zhong J, Cassidy RJ, Gillespie T, et al. (2017). The role of adjuvant radiotherapy in pathologically lymph node-positive prostate cancer. *Cancer*, *123*(3), 512–520.

Jones CU, Hunt D, McGowan DG, Amin MB, Chetner MP, Bruner DW, et al. (2011). Radiotherapy and short-term androgen deprivation for localized prostate cancer. *N Engl J Med.*, *365*(2), 107–118.

Kaulfers T, Lattery G, Cheng C, Zhao X, Selvaraj B, Wu H, et al. (2024). Pencil Beam Scanning Proton Bragg Peak Conformal FLASH in Prostate Cancer Stereotactic Body Radiotherapy. *Cancers (Basel)*, *16*(4), 798.

Kneebone A, Fraser-Browne C, Duchesne GM, Fisher R, Frydenberg M, Herschtal A, et al. (2020). Adjuvant radiotherapy versus early salvage radiotherapy following radical prostatectomy (TROG 08.03/ANZUP RAVES): a randomised, controlled, phase 3, non-inferiority trial. *Lancet Oncol.*, *21*(10), 1331–1340.

Latorzeff I, Le Guevelou J, Sargos P. (2023). Radiation therapy post radical prostatectomy: who, when and why? *Curr Opin Support Palliat Care*, *17*(1), 47–54.

Martin NE, D'Amico AV. (2014). Progress and controversies: Radiation therapy for prostate cancer. *CA: A Cancer Journal for Clinicians*, *64*(6), 389–407.

Matta R, Chapple CR, Fisch M, Heidenreich A, Herschorn S, Kodama RT, et al. (2019). Pelvic Complications After Prostate Cancer Radiation Therapy and Their Management: An International Collaborative Narrative Review. *European Urology*, *75*(3), 464–476.

Mena E, Lindenberg L, Choyke P. (2022). The Impact of PSMA PET/CT Imaging in Prostate Cancer Radiation Treatment. *Semin*

Nucl Med., *52*(2), 255–262.

Morgan TM, Boorjian SA, Buyyounouski MK, Chapin BF, Chen DYT, Cheng HH, et al. (2024). 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. *Journal of Urology*, *211*(4), 509–517.

Müller A-C, Aebersold DM, Albrecht C, Böhmer D, Flentje M, Ganswindt U, et al. (2022). Radiotherapy for hormone-sensitive prostate cancer with synchronous low burden of distant metastases. *Strahlenther Onkol.*, *198*(8), 683–689.

Omrcen T, Hrepic D, Boraska Jelavic T, Vrdoljak E. (2015). Combination of adjuvant radiotherapy and androgen deprivation therapy after radical prostatectomy in high risk prostate cancer patients — results from retrospective analysis. *J BUON*, *20*(4), 1061–1067.

Pang Y, Wang H, Li H. (2022). Medical Imaging Biomarker Discovery and Integration Towards AI-Based Personalized Radiotherapy. *Front Oncol.*, *11*, 764665.

Parker CC, Petersen PM, Cook AD, Clarke NW, Catton C, Cross WR, et al. (2024). Timing of radiotherapy (RT) after radical prostatectomy (RP): long-term outcomes in the RADICALS-RT trial (NCT00541047). *Ann Oncol.*, S0923-7534(24)00105–4.

Rydzewski NR, Helzer KT, Bootsma M, Shi Y, Bakhtiar H, Sjöström M, et al. (2023). Machine Learning & Molecular Radiation Tumor Biomarkers. *Seminars in Radiation Oncology*, *33*(3), 243–251.

Sargos P, Chabaud S, Latorzeff I, Magné N, Benyoucef A, Supiot S, et al. (2020). Adjuvant radiotherapy versus early salvage radiotherapy plus short-term androgen deprivation therapy in men with localised prostate cancer after radical prostatectomy (GETUG-AFU 17): a randomised, phase 3 trial. *Lancet Oncol.*, *21*(10), 1341–1352.

Schaeffer EM, Srinivas S, Adra N, Ahmed B, An Y, Bitting R, et al. (2024). NCCN Guidelines Index Table of Contents Discussion. *Prostate Cancer*.

Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin.*, *71*(3), 209–249.

Terlizzi M, Limkin EJ, Moukasse Y, Blanchard P. (2022). Adjuvant or Salvage Radiation Therapy for Prostate Cancer after Prostatectomy: Current Status, Controversies and Perspectives. *Cancers (Basel)*, *14*(7), 1688.

Thompson IM, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, et al. (2009). Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term follow up of a randomized clinical trial. *J Urol.*, *181*(3), 956–962.

Touijer KA, Karnes RJ, Passoni N, Sjoberg DD, Assel M, Fossati N, et al. (2018). Survival Outcomes of Men with Lymph Node-positive Prostate Cancer After Radical Prostatectomy: A Comparative Analysis of Different Postoperative Management Strategies. *European Urology*, 73(6), 890–896.

van As N, Yasar B, Griffin C, Patel J, Tree AC, Ostler P, et al. (2024). Radical Prostatectomy Versus Stereotactic Radiotherapy for Clinically Localised Prostate Cancer: Results of the PACE-A Randomised Trial. *European Urology*, 86(6), 566–576.

Wiegel T, Bottke D, Steiner U, Siegmann A, Golz R, Störkel S, et al. (2009). Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. *J Clin Oncol.*, *27*(18), 2924–2930.

Zapatero A, Guerrero A, Maldonado X, Alvarez A, Gonzalez San Segundo C, Cabeza Rodríguez MA, et al. (2015). High-dose radiotherapy with short-term or long-term androgen deprivation in localised prostate cancer (DART01/05 GICOR): a randomised, controlled, phase 3 trial. *Lancet Oncol.*, *16*(3), 320–327.