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Review Article

Integrating Biochemical Profiles with Artificial Intelligence to Predict Hormone Therapy Efficacy in Prostate Cancer Patients

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Abstract: Prostate cancer remains one of the most prevalent malignancies among men globally, with androgen deprivation therapy (ADT) being a cornerstone of treatment for advanced and high-risk localized disease. However, the clinical efficacy of hormone therapy varies significantly among patients, often resulting in overtreatment or suboptimal outcomes. Emerging research suggests that integrating biochemical profiles with artificial intelligence (AI) offers a promising strategy to refine therapeutic decision-making and predict individual responses to ADT. This review examines current advances in AI-driven predictive models that incorporate biochemical, genomic, and clinical data to forecast hormone therapy outcomes in prostate cancer patients. We highlight key studies that utilize histopathology-based AI, androgen receptor (AR) splice variant detection, metabolic gene signatures, and multi-omics approaches to stratify patients based on ADT benefit and duration requirements. Models such as the Multimodal Artificial Intelligence (MMAI) biomarker and other machine learning frameworks trained on large randomized clinical trial cohorts demonstrate the capacity to differentiate between patients who are likely to benefit from ADT and those for whom it offers minimal advantage. Despite these advancements, limitations persist. Most current AI models rely heavily on imaging and standard clinical variables, with limited incorporation of dynamic biochemical markers such as testosterone levels, androgen metabolism genes, or proteomic data. Additionally, challenges related to model interpretability, data heterogeneity, and external validation hinder widespread clinical adoption. This review underscores the potential of integrating biochemical profiles with AI to optimize hormone therapy in prostate cancer. A multidisciplinary approach involving bioinformatics, molecular biology, and clinical oncology is essential to advance predictive accuracy and personalized treatment. Future directions should prioritize the inclusion of multi-omics data, improved model transparency, and prospective validation in diverse patient populations. This paradigm shift could lead to more effective, targeted hormone therapy, minimizing toxicity and enhancing long-term outcomes for prostate cancer patients.

Keywords: prostate cancer, androgen deprivation therapy, artificial intelligence, biochemical markers, predictive modeling

1. INTRODUCTION

Prostate cancer is among the most prevalent malignancies affecting men globally, with hormone therapy—particularly androgen deprivation therapy (ADT)—remaining a cornerstone of treatment for advanced or high-risk disease [1]. While ADT can significantly delay disease progression by suppressing androgen signaling, its benefits vary widely across patients. Some individuals experience rapid biochemical recurrence or progress to castration-resistant prostate cancer (CRPC), while others may

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not require such intensive intervention. Moreover, hormone therapy is associated with considerable adverse effects, including metabolic syndrome, cardiovascular risk, and diminished quality of life [2]. This variability underscores the urgent need for predictive tools that can help tailor hormone therapy to individual patients more effectively. Biochemical markers such as prostate-specific antigen (PSA), testosterone levels, androgen receptor (AR) variants, and metabolic profiles have been investigated for their potential to predict treatment response [3]. Emerging evidence also suggests that metabolomic signatures—such as alterations in tryptophan metabolism, lipid oxidation pathways, and steroidogenesis—can distinguish between hormone-sensitive and hormone-resistant prostate cancers [4]. Artificial intelligence (AI), particularly machine learning (ML), offers new avenues for integrating diverse biochemical, molecular, and clinical data to build predictive models for treatment response. These models can detect complex patterns that may be missed by traditional statistical analyses, enabling a more nuanced understanding of how biochemical profiles influence hormone therapy outcomes [5]. For instance, a recent AI-based model using clinical and pathological data from randomized clinical trials successfully stratified prostate cancer patients based on their likely benefit from short-term ADT combined with radiotherapy. Despite promising advances, challenges remain in translating AI-driven models into clinical practice. Many studies are retrospective, lack external validation, or are based on small sample sizes, limiting generalizability [6]. Additionally, the integration of heterogeneous biochemical datasets—ranging from serum markers to multi-omics data—requires careful model training and validation to avoid overfitting and ensure clinical relevance. In this review, we explore the current landscape of integrating biochemical profiles with AI to predict hormone therapy efficacy in prostate cancer patients. We discuss key biochemical markers, recent developments in AI-driven predictive modeling, and the challenges and opportunities in advancing this field toward personalized treatment strategies.

2. AI-DERIVED BIOMARKERS FOR PREDICTING ADT BENEFIT

Recent studies have developed AI models that combine digital pathology images and clinical data to predict which prostate cancer patients will benefit from androgen deprivation therapy (ADT). For instance, a large model was trained using pretreatment biopsy slides and clinical features from over 5,700 patients across multiple phase III randomized trials to predict distant metastasis under radiotherapy with or without ADT. In the validation cohort from the NRG/RTOG 9408 trial, the model effectively distinguished a subgroup (34%) for whom ADT significantly reduced distant metastasis, showing a sub distribution hazard ratio (s HR) of approximately 0.34, while the "model-negative" group showed no significant benefit (s HR ≈ 0.92) [7]. This model not only provides clinical utility but also exemplifies how AI-based pathology interpretation can influence treatment decisions. The implications are that many patients might be spared the adverse effects of ADT if the AI model deems the treatment non-beneficial for them. While the model incorporates both imaging and clinical parameters, its performance shows that histologic AI features carry predictive power for therapy outcomes. However, the model's integration with deeper biochemical variables remains limited [8]. Another study extended this concept to predict not just whether ADT would be effective but also the optimal duration of ADT. The Multimodal Artificial Intelligence (MMAI) model used pretreatment biopsy histopathology along with standard clinical variables (e.g., age, PSA, Gleason score, T-stage) from multiple phase III clinical trials to predict differential benefit from long-term vs. short-term ADT when combined with radiotherapy. In the RTOG 9202 validation cohort (n ≈ 1,192; median follow-up ~17 years), long-term ADT significantly reduced distant metastasis in the MMAI-positive group (s HR = 0.64), while no benefit was observed in the MMAI-negative group (s HR ≈ 1.06) [9]. These results reinforce the idea that predictive AI biomarkers can move beyond binary treatment decisions to personalize treatment duration, which is particularly relevant in ADT due to its long-term side effects like cardiovascular risks and metabolic syndrome (Spratt et al., 2023). Still, these AI-derived models primarily focus on imaging

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and clinical characteristics and do not yet incorporate molecular or biochemical markers such as androgen levels or metabolic indicators [10].

3. INTEGRATION OF METABOLIC / GENE SIGNATURES WITH ADT RESPONSE PREDICTION

Beyond histopathological AI, recent studies have explored the use of metabolic or gene expression signatures to predict ADT response and disease progression. One study identified a four-gene metabolism-related signature, selected via stepwise regression, that predicted biochemical progression-free survival (b PFS) at 1-, 3-, and 5-year intervals with high area under the curve (AUC) values when combined with PSA, Gleason score, and T-stage. Enrichment analyses showed significant associations with the androgen response pathway, indicating the model's relevance to hormone therapy efficacy [11]. This type of signature helps bridge the gap between biochemical understanding and AI-based prediction, offering a more mechanistic insight into treatment response. Importantly, the model was validated with external datasets, and its predictive capacity remained consistent, highlighting its generalizability [12]. However, the use of surrogate endpoints such as b PFS rather than direct ADT response limits the conclusions we can draw about its ability to guide treatment decisions. In another study, researchers developed an eight-gene steroid hormone pathway signature (including CA2, HSD17B, SULT1E1, among others) that was linked to worse progression-free intervals in both univariate and multivariate models [13]. This signature was validated using external datasets such as PCS and PAM50, and was strongly correlated with aggressiveness in prostate cancer, supporting the concept that androgen metabolism plays a crucial role in therapy outcomes [14]. Though not explicitly designed to predict ADT response in a treatment-randomized setting, the prognostic power of such signatures implies that they could inform therapy decisions if tested prospectively [15]. These models offer a pathway to integrate molecular mechanisms more directly into clinical decision-making, but current evidence largely stems from retrospective, observational datasets, limiting their immediate clinical utility.

4. STRENGTHS, LIMITATIONS, AND CURRENT GAPS

A key strength of current AI-based biomarkers is their foundation on high-quality randomized clinical trial data, such as the NRG/RTOG cohorts. This gives credibility to models like the ADT-benefit classifier and MMAI, which are trained and validated on robust, well-annotated datasets with long follow-up periods [16]. These conditions enable confident estimation of therapy impact on metastasis and survival outcomes. However, a significant limitation lies in the exclusion of detailed biochemical data such as circulating androgen levels, hormone receptor status, and proteomic or metabolomic profiles. Most models rely on pathology images and basic clinical data, which may omit important biochemical predictors of resistance or responsiveness to ADT [17]. This results in a predictive gap, where models may be accurate but not mechanistically transparent or biochemically informative. Additionally, endpoints vary across studies: some use distant metastasis, while others focus on biochemical recurrence or overall survival. These inconsistencies make it difficult to directly compare model efficacy or generalize findings across trials. Moreover, ethnic and geographic homogeneity in trial populations may limit the external validity of current models, especially in diverse healthcare settings [18]. Interpretability is another concern. While AI models can be highly predictive, they often function as "black boxes," providing clinicians with limited insight into *why* a given prediction was made. Without transparency, integration into routine clinical practice remains a challenge [19]. This reinforces the need for models that not only predict accurately but also align with known biochemical and pathophysiological mechanisms.

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5. EMERGING OPPORTUNITIES AND FUTURE DIRECTIONS

Going forward, there is a clear opportunity to integrate multi-omics data—such as metabolomics, proteomics, and hormone profiles—into AI models for ADT decision-making. Including measurements of testosterone, dihydrotestosterone (DHT), androgen receptor (AR) splice variants, and steroidogenic enzyme activity could enhance prediction of ADT efficacy [20]. Prospective trials incorporating such data alongside standard imaging and pathology would enable a truly integrative approach. Moreover, new interpretability techniques like SHAP (Shapley Additive explanations) and LIME (Local Interpretable Model-agnostic Explanations) can help clarify the contribution of individual features to a model's prediction. This would facilitate clinician trust and support shared decision-making in real-time care scenarios [21]. Transparent models that show both "how" and "why" treatment benefit is predicted will be essential for adoption. Finally, implementation considerations such as cost, accessibility, and infrastructure must be addressed. While whole-slide imaging and advanced AI tools may be available in tertiary centers, many regional or low-resource settings may benefit more from simplified models using accessible biochemical markers. Thus, hybrid models combining minimal omics with core clinical and imaging features may strike the best balance between accuracy and practicality [22].

6. CONCLUSION

The integration of biochemical profiles with artificial intelligence (AI) represents a transformative frontier in optimizing hormone therapy for prostate cancer. While current AI-based predictive models primarily rely on pathology, imaging, and clinical variables, growing evidence suggests that incorporating biochemical markers—including metabolic, proteomic, and hormonal signatures—can substantially enhance both the precision and interpretability of these systems. Such integration could provide a more mechanistic understanding of treatment response, allowing clinicians to move beyond population-level predictions to individualized therapeutic strategies grounded in tumor biology and systemic physiology. Recent randomized clinical trials and high-quality cohort studies underscore the promise of multimodal AI frameworks in refining androgen deprivation therapy (ADT) initiation, intensity, and duration, with early findings suggesting improved risk stratification and more judicious use of therapy. Despite these advances, several barriers must be addressed before widespread clinical application. The standardization of biochemical endpoints across institutions remains a critical challenge, as variability in assay platforms, measurement techniques, and biomarker thresholds can undermine reproducibility and generalizability. Moreover, ensuring diversity in training datasets is essential to prevent algorithmic bias and guarantee equitable utility across global patient populations with heterogeneous genetic and environmental backgrounds. Another challenge lies in the technical and computational demands of integrating deep biochemical datasets into model design, which require robust data curation, advanced feature engineering, and sophisticated validation pipelines. Looking ahead, future efforts should prioritize large-scale prospective validation studies that embed AI-biochemical models into real-world clinical workflows, ensuring that predictions translate into meaningful improvements in patient outcomes. Parallel advances in explainable AI will be vital to enhance interpretability, enabling clinicians and patients to understand how specific biochemical features influence predictions and treatment recommendations. Finally, strategies to ensure broad accessibility—through open-source platforms, shared datasets, and regulatory frameworks that support equitable deployment—will be essential to maximize global benefit. Ultimately, the convergence of AI and biochemical profiling has the potential not only to personalize ADT but also to redefine the paradigm of precision oncology in prostate cancer, aligning treatment with the unique biological and clinical profile of each patient.

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