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Platinum Opinion Editorial

More Than Words: Defining Adjuvant, Consolidative, and Salvage Treatment after Radical Prostatectomy

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The most common oncologic outcome after radical prostatectomy (RP) for localized prostate cancer is an absence of disease, defined as undetectable prostate-specific antigen (PSA; <0.1 ng/ml). However, given the broad adoption of active surveillance as the primary treatment for low-risk disease, the proportion of RP procedures for intermediate-risk, high-risk, and even locally advanced or oligometastatic prostate cancer continues to rise [1]. Together with recent increases in cases presenting with more advanced prostate cancer, the proportion of patients at high risk of residual or recurrent disease after surgery is rising [1].

While the traditional goal of surgery is eradication of all evidence of prostate cancer, the literature indicates that this is not achieved in the 5–20% of patients with detectable PSA after RP [2,3]. Moreover, 15–35% of those who do achieve undetectable PSA (<0.1 ng/ml) will experience biochemical recurrence (BCR) after RP [2,3]. With the greater use of ultrasensitive PSA assays, multiparametric magnetic resonance imaging, prostate-specific membrane antigen (PSMA) positron emission tomography (PET), and genomic classifier testing, the definition of clinical states after RP is rapidly evolving. This ambiguity, coupled with an increasing emphasis on avoiding both overtreatment and undertreatment, has resulted in substantial variation in practice patterns [2–4]. Decisions regarding whether and when to order additional testing or administer additional treatment after RP are complex. To avoid confusion and advance science, we advocate for a re-evaluation of the current nomenclature.

Secondary treatment after RP has traditionally been categorized as “adjuvant” or “salvage”. Adjuvant treatment refers to treatment in the absence of detectable disease, either local or distant, while salvage refers to treatment for patients who initially have no evidence of disease and subsequently experience recurrence [5]. What are clinicians to do with patients who do not fit into these categories, such as those with PSA persistence after RP? Multiple randomized clinical trials testing the role of "adjuvant" therapy have included patients with persistently detectable PSA, and more recent trials and guidelines classify treatment in this setting as "salvage" therapy. Yet, the limited evidence available suggests that these men may be at particularly high risk of adverse cancer outcomes in comparison to men with high-risk features at RP but achieve an undetectable PSA and men with an initially undetectable PSA after RP and a subsequent rise (BCR) [5–7].

With multiple definitions of BCR in the literature, along with data supporting salvage treatment at PSA as low as ≤0.25 ng/ml in patients with International Society of Urological Pathology (ISUP) grade group 4-5 or pT3-4 disease [8], patients may be treated at very low, but detectable PSA levels below conventional definitions of BCR. The aforementioned differences in inclusion criteria in prior trials testing the role of adjuvant radiation therapy further complicate the efforts of clinicians trying to make decisions for patients today. While current guidelines provide precise definitions of clinical states in advanced prostate cancer [5], similar clarity is lacking for patients with residual versus recurrent cancer after RP. We therefore propose the addition of “consolidative” therapy as a term to accurately capture the intent of treating residual disease still present after RP, which is distinct from both adjuvant and salvage treat-

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Table 1 – Proposed definitions for disease states and recommended treatments after radical prostatectomy

Clinical state	Definition of clinical state	Treatment recommendation
Undetectable PSA after RP: Absence of disease with low clinical suspicion	Undetectable PSA Favorable pathology	Surveillance
Undetectable PSA after RP: Absence of disease with high clinical suspicion	Undetectable PSA Concerning pathology o pN+ o ISUP grade group 4-5 AND pT3b-4 ± positive margin	Surveillance or adjuvant therapy
PSA persistence after RP: Persistence of disease with low clinical suspicion	Detectable PSA immediately after RP Favorable pathology Absence of radiographic evidence of disease	Surveillance or consolidative therapy
PSA persistence after RP: Persistence of disease with high clinical suspicion	Detectable PSA immediately after prostatectomy Concerning pathology o pN+ o pT3-4 ± positive margin o ISUP grade group 3-5Radiographic evidence of disease on molecular imaging	Consolidative therapy
PSA recurrence after RP: Biochemical recurrence	Period of undetectable PSA followed by detectable PSA	Salvage therapy (early) or surveillance
Metastatic disease	Evidence on conventional imaging or pathology	Management of metastatic prostate cancer

ISUP = International Society of Urological pathology; RP = radical prostatectomy; PSA = prostate-specific antigen.

ment (Table 1). We advocate for this distinction as PSA persistence is associated with worse oncologic outcomes and the intent and type of treatment is different [9]. Spratt et al [9] found that 95% of patients with PSA persistence received radiation therapy (RT) before metastasis, and on multivariable analysis PSA persistence was associated with a fourfold increase in the risk of developing metastases. At 15 yr after RP, survival rates for patients with an initially persistent versus undetectable PSA after RP were 53.0% versus 93.2% ($p < 0.001$) for metastasis-free survival, 64.7% versus 81.2% ($p < 0.001$) for overall survival, and 75.5% versus 96.2% ($p < 0.001$) for cancer-specific survival [3]. These authors recommended up-front treatment after RP in high-risk patients as part of a planned multimodal approach [2,3].

This proposed three-tiered classification of patients with undetectable PSA, PSA persistence, and PSA recurrence, and treatment types as adjuvant, consolidative, and salvage, better describes the clinical states and treatment decisions being made. On the basis of data from the RADICALS-RT, GETUG-AFU17, and RAVES trials and meta-analysis [6], patients with undetectable PSA should be monitored closely for PSA recurrence and offered early salvage RT, which is preferred to late salvage RT. Adjuvant RT for patients with undetectable PSA after RP remains an approach to consider only for those patients at the highest risk for recurrence, that is, pN1 or ISUP grade group 4-5 and pT3-4 tumors [7,8]. Conversely, patients with PSA persistence should receive information to guide decision-making about consolidative treatment rather than adjuvant treatment, and we would argue that treatment when the PSA never became undetectable is not "salvage" treatment as the patient was never disease-free. PSA persistence may in fact help in explaining the clinical benefit in three randomized trials that examined adjuvant RT (SWOG 8794, EORTC 22911, and FinnProstate). The up to 35% of patients with PSA ≥0.1 ng/ml included in these trials would be better classified as having received consolidative treatment. Early consolidative treatment would have benefited patients with PSA persistence, and withholding or delaying this treatment for these high-risk patients would not be standard practice today. Adoption of this nomenclature will allow future trials to more accurately align with clinical outcomes, compare the efficacy of various consolidative treatments, and compare the efficacy of various approaches to management of this high-risk population. Furthermore, we believe that the use of "consolidative therapy" as a term will become increasingly important in the face of rapidly increasing use of PSMA PET for men with detectable PSA after RP. In this setting, PSMA PET was able to identify the site of disease in 38% of patients with PSA <0.5 ng/ml and therefore inform subsequent therapy [10]. While lesions identified on PSMA PET and not confirmed by conventional imaging or biopsy do not currently meet criteria for metastases in current trials and guidelines, outside of a clinical trial, treatment would frequently be considered. A clearer understanding of the differential performance of this technology in patients with PSA persistence versus BCR is critical to the development of appropriate use criteria for systemic and targeted treatments.

In conclusion, patients with PSA persistence following RP represent a growing group with particularly high risk of adverse oncologic outcomes. Addition of the term "consolidative therapy" to the lexicon of clinicians managing prostate cancer will allow for more direct clinical alignment and the development of robust, better-informed, evidence-based treatment recommendations.

Conflicts of interest: The authors have nothing to disclose.

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