Comparing outcomes between neoadjuvant hormonal therapy followed by prostatectomy versus upfront prostatectomy in high-risk prostate cancer: The road ahead

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SUMMARY

Neoadjuvant treatment before definite surgical resection is the standard of care for many malignancies, but prostate cancer is not one of them. Ravi *et al.* performed a comparative analysis of oncological outcomes in high-risk prostate cancer (HRPC) patients who either received 6 months of neoadjuvant androgen deprivation therapy (ADT) with a novel hormonal agent before radical prostatectomy (RP), designated as the neo-RP cohort or those who underwent an upfront RP, designated as the RP cohort.[1] HRPC was defined as Gleason grade ≥8, prostate-specific antigen (PSA) >20 ng/ml, and/or ≥cT3 disease. Patients included in the neo-RP group were treated with either enzalutamide or abiraterone in a trial setting between 2010 and 2016.[2-4] The RP cohort included patients undergoing upfront RP between 2010 and 2016 with similar baseline disease characteristics as the neo-RP cohort. The decision to initiate adjuvant or salvage therapy was at the discretion of the treating physician in both cohorts. The primary outcomes were the development of biochemical recurrence (BCR) and metastasis-free survival (MFS). A total of 112 and 247 patients in the neo-RP and RP cohorts were analyzed after propensity score matching and inverse probability of treatment weighting (IPTW). Before IPTW, the neo-RP cohort had higher rates of Gleason 9–10 cancer (46% vs. 24%), cT3 disease (22% vs. 5%), and PSA ≥20 ng/ml (14% vs. 7%); after IPTW, the two cohorts were balanced. In the neo-RP and RP cohorts, the mean age was 61 years in both, mean PSA (ng/ml) at diagnosis was 15 and 12, 50% and 46% had Gleason scores of 9–10, and 77% and 78% had T1 or T2 tumors, respectively. Pathological outcomes were favorable in the neo-RP group as compared to the RP group with 11 (10%) and 13 men (12%) achieving a pathological complete response and minimal residual disease (i.e. ≤5 mm residual tumor), respectively, and a lower incidence of positive margins (13% vs. 56%) and pT3-T4 disease (55% vs. 72%, both $P < 0.01$). The pathological nodal burden was similar between groups. At a median follow-up after RP of 3.7 years and 4 years for the neo-RP and RP groups, time to BCR was significantly longer in the neo-RP group (weighted hazard ratio =0.25 [95% confidence interval 0.18–0.37], $P < 0.01$), with 3-year freedom from BCR of 59% and 15%, respectively, along with longer MFS (weighted HR = 0.26 [0.15–0.46], $P < 0.01$), with 3-year MFS of 96% and 68%, respectively. Eight (7%) and 63 (24%) men received adjuvant radiotherapy (± ADT) and 38 (34%) and 118 (46%) men received salvage radiotherapy (± ADT) with a median time to therapy of 7.6 and 4.1 months, in the neo-RP and RP groups, respectively, with both rates lower in the neo-RP group.

COMMENTS

This study addresses an important issue regarding the role of neoadjuvant therapies in patients with HRPC, planned for RP to improve pathological as well as oncological outcomes. The authors enrolled patients who were initially treated on either of the three trials for neoadjuvant therapy between 2010 and 2016[2-4] to form a cohort to compare with patients undergoing upfront RP. During this time, there was scant evidence to suggest that neoadjuvant therapy improved outcomes after RP. No standard guidelines recommended the use of neoadjuvant hormonal therapy before RP.

It is unclear what influenced the authors to start neoadjuvant therapy in such patients. Using patients from these studies may have unmeasured confounders and affect the results. Further, the regimen used in the neo-RP cohort was not standardized. This generalization leads to the assessment of the concept as a whole and not a single agent. It is also unclear whether all the patients comprising the neo-RP cohort were indeed high risk. Details regarding surgical management, i.e. RP, surgical team, and routes of access, and whether it was standardized across all studies and different centers should have been included as this affects the pathological and oncological outcomes, thus affecting adjuvant and salvage therapy, leading to unmeasured bias. Receipt of ADT or radiation therapy regardless of PSA was

an endpoint for BCR and thus indications for adjuvant and salvage therapy in both cohorts should have been mentioned in the results. The median time to follow-up in the neo-RP cohort was 3.7 years, which is relatively small. A similar study as quoted by the authors had a median follow-up of 6 years and even that was not considered long enough to merit a change in the prevalent evidence.[5] In the neo-RP cohort, two out of three studies did not have a defined post-RP follow-up and their results might have underreported BCR and MFS.

Overall, this is a well-conducted observational study but had a heterogeneous cohort of patients. The ongoing PROTEUS trial (NCT03767244) evaluating neoadjuvant (and adjuvant) ADT +/- apalutamide in HRPC may lead to new treatment practices, but would not answer the question of benefit of neoadjuvant therapies before RP compared to RP alone. In the current era of multiple novel hormonal agents and chemotherapy, it would be prudent to conduct well-defined phase III randomized controlled trials comparing standardized neoadjuvant hormonal therapy or chemotherapy, with or without ADT in patients undergoing RP versus upfront RP, to establish the role of neoadjuvant therapy.

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Received: 28.11.2022, **Revised:** 19.12.2022,

Accepted: 09.03.2023, **Published:** 31.03.2023

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

Access this article online	
Quick Response Code:	Website: www.indianjurol.com
	DOI: 10.4103/iju.iju_409_22

How to cite this article: Bhargava P. Comparing outcomes between neoadjuvant hormonal therapy followed by prostatectomy versus upfront prostatectomy in high-risk prostate cancer: The road ahead. Indian J Urol 2023;39:173-4.