Prognostic impact of residual cancer burden (RCB) on long-term outcomes after neoadjuvant (neo) androgen receptor pathway inhibitor (ARPI) and radical prostatectomy (RP) for high-risk localized prostate cancer (HRLPC): a pooled analysis of phase 2 trials

Praful Ravi, Lucia Kwak, Andres Acosta, Saahil Rastogi, Wanling Xie, David Einstein, Peter Chang, Andrew Wagner, Rana McKay, Adam Kibel, Mary-Ellen Taplin

Background
6 months (mths) of neo-ARPI prior to RP for HRLPC has shown promising results in a series of phase 2 trials, with 15-20% of patients experiencing pathologic complete response (pCR) or minimal residual disease (≤5mm residual tumor, MRD). However, longer-term outcomes and the prognostic impact of residual cancer burden (RCB) at RP has not been evaluated.

Methods
Data from patients (pts) treated on 5 neoadjuvant trials evaluating 6mths of neo-ARPI (abiraterone [abi], enzalutamide [enza], abi+enza, abi+apalutamide) and androgen deprivation therapy (ADT) at our institution between 2006 to 2018 were pooled. All pts had central pathology review performed to evaluate pCR/MRD and RCB on the RP specimen. RCB was quantified as the calculated tumor volume adjusted for tumor cellularity. Metastasis-free survival (MFS) was defined as the time from RP to development of metastasis outside of the pelvis on CT, bone scan or MRI, or death from any cause, or censored at the date of last follow-up. Utilizing the Contal & O'Quigley method, the optimal cut-off value for RCB, distinguishing high- and low-risk groups for MFS, was determined based on the log-rank statistic. A dichotomous RCB cut-off was chosen between 5% and the 95% percentiles of the RCB distribution for patients with residual disease (RCB>0). Multivariate Cox proportional hazards model was used to quantify the association of RCB with MFS after adjusting for age, biopsy Gleason score, and clinical T stage.

Results
218 pts were evaluable. 154 pts (71%) had Gleason 8-10 at biopsy, 42 (20%) had cT3-4 disease and 40 (18%) had a baseline PSA ≥20ng/mL. Overall, 170 (78%) were classified as NCCN high/very-high risk and 48 (22%) as unfavorable intermediate-risk. At RP, 117 pts (54%) had ypT3 and 23 (11%) had pN1 disease, while 24 pts (11%) had pCR and 24 (11%) had MRD; The median RCB was 0.05cm^3 (IQR 0.00-0.32). During a median follow-up of 5yrs, 45 pts developed metastases and 11 died; 5-yr MFS rate was 83% (95% CI 77-88). On multivariate analysis, a higher RCB was associated with poorer MFS (HR 1.26 [1.04-1.52]), along with cT3-4 disease (HR 2.86 [1.54-5.30]). RCB index categories were defined as RCB-0 (no residual disease [i.e. pCR]; n=24), RCB-1 (<0.003cm^3; n=35), RCB-2 (0.003-0.627cm^3; n=121) and RCB-3 (≥0.672cm^3, n=29). 5-yr MFS rates were 100%, 90% (72-97), 82% (73-88) and 63% (40-79) for pts with RCB-0, RCB-1, RCB-2 and RCB-3, respectively.

Conclusions
5-yr MFS rate with 6mths of neo-ARPI prior to RP for HRPLC was 83%. The depth of pathologic response was prognostic for MFS, with a 100% 5-yr MFS in patients achieving pCR. RCB could be used to guide intensified adjuvant strategies in pts with residual disease at RP after neo-ARPI. Expert pathology review of pts treated in this manner is crucial.

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