EDITORIAL

Clinical Research

Radiotherapy in patients with node-positive prostate cancer after radical prostatectomy

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In most solid cancers, the presence of clinical or pathological lymph node involvement is an indication for radiotherapy, if not chemoradiotherapy. Infact, bi- and tri-modality therapy is the standard of care for most cancers. However, despite prostate cancer being common, >75% of the randomized trials in non-metastatic prostate cancer have utilized radical radiotherapy as the backbone of treatment. Few phase III trials have been conducted using radical prostatectomy (RP), and those that have primarily focused on the use of adjuvant (ART) or early salvage radiotherapy (SRT). Thus, there remain large voids of high-level evidence to support the optimal treatment of men with locally advanced prostate cancer with RP.

Recently, the results of the ARTISTIC meta-analysis demonstrated early SRT to have similar biochemical recurrence rates to ART. However, only ~40% of patients in this cohort recurred by 5-year post-RP and almost no patients had multiple high-risk features or pN1 disease. It is estimated that >90% of men will recur post-RP who have pN1 disease, and thus it remains unclear if ART may be superior in this population. To investigate this, Schaufler et al. [1]. present a hypothetical pragmatic trial based on RADICALS-RT trial design of immediate ART versus observation in patients with pN1 disease who were treated between years 2006 and 2015 identified through the National Cancer Database (NCDB). This retrospective analysis showed that reduction in all-cause mortality by immediate RT compared to observation did not reach statistical significance in all patients, but was significant in patients with Gleason 8–10 disease (HR 0.59, $p = 0.01$), ≥2 positive lymph nodes (HR 0.49, $p = 0.04$), or negative surgical margins (HR 0.5, $p = 0.02$). As the authors indicate, there are numerous limitations with the study methodology and they were not able to capture the use and duration of ADT or timing of salvage therapy in the observation arm. Given the known low utilization of early SRT in the real-world, it is probable that this analysis did not test ART versus early SRT.

The optimal management of pN1 disease is controversial. The small <100 patient ECOG 3886 trial demonstrated superiority of life-long ADT vs deferred ADT [2]. Additionally, Granfors et al. reported the results of a small randomized trial showing that overall survival was improved with RT plus ADT vs RT alone in pN1 disease [3]. In a cohort analysis from STAMPEDE in men with clinical node involvement (cN1), RT was associated with improved failure-free survival (HR 0.48, 95% CI 0.29–0.79) [4]. Accordingly, a rational approach would be to utilize RT in the pN1 setting. Currently, NRG Oncology has an open trial (NRG GU008) in men with pN1 disease and PSA > 0.01 ng/mL, where the control arm is RT plus 2 years of ADT. A trial comparing ADT vs RT plus ADT was proposed, but there lacked equipoise to use ADT alone given its non-curative potential. Thus, the current functional standard of care is RT plus long-term ADT despite the gaps in evidence. The NRG GU008 trial will determine if the addition of apalutamide improves outcomes further.

Given the increased utilization of PSMA PET/CT imaging, the detection of cN1 disease will increase. NCCN guidelines remain clear that only highly selected patients with known cN1 prior to surgery should undergo RP, and thus the incidence of pN1 will decrease with time as these patients will be managed with definitive radiotherapy plus ADT and abiraterone. While ART should not be pursued for most patients post-RP with pN0 disease, it remains unclear if there would be any difference in outcomes between ART and early SRT in the setting of pN1 disease. A systematic review of SRT notes a 2.6% decline in biochemical control with every 0.1 increase in PSA after prostatectomy [5], and given >90% of men with pN1 disease will recur, at the very minimum a lower threshold of 0.05 ng/mL may be more appropriate to trigger early SRT. If the PSA becomes detectable prior to complete urinary healing post-RP, ADT can be initiated to delay the start of SRT until 6 months post-RP.

In summary, Schaufler et al. ask an important question in a population space without level 1 evidence. However, given the high probability of recurrence in patients with pN1 disease and a potential window for cure, we believe very early SRT with ADT should be strongly considered.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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