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Elective Nodal Radiotherapy for Prostate Cancer: For None, Some, or all?

Nicholas G Zaorsky, MD, MS,*,† and Daniel E Spratt, MD‡

*Department of Radiation Oncology, Penn State Cancer Institute, Hershey, PA; †Department of Public Health Sciences, Penn State College of Medicine, Hershey, PA; and ‡Department of Radiation Oncology, University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, OH

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For prostate cancer, use of elective pelvic lymph node radiotherapy (PNRT) is controversial, and investigators have been aiming to find a role for the treatment for over 50 years. The fundamental premise for recommending PNRT is that a subset of patients with radiographic node negative disease will harbor pathologically node positive disease, and PNRT would translate into improved oncologic outcomes with minimal additional toxicity.

Until recently, we have had no high level evidence to suggest that there is any improvement in oncologic outcomes from PNRT.[1,2] The prior GETUG-01[2] trial demonstrated no benefit of PNRT using relatively small field sizes, and RTOG 9413[1] demonstrated that the winning arm was prostate-only RT with adjuvant ADT. Data have shown that the superior border of even L5/S1 on RTOG 9413 may have been inadequate as it did not capture the common iliac lymph nodes, which are common sites of drainage for prostate cancer.[3] Beyond no demonstrable efficacy, PNRT historically was very toxic with a ≥3-fold increase in grade ≥2 bowel toxicity over prostate-only RT.[4] However, even in more contemporary randomized trials, PNRT is not side effect free. In RTOG 0534,[5] a small but statistically significant increase in acute grade ≥2 gastrointestinal toxicity was found from the addition of PNRT to short-term ADT (6.9% versus 3.9%, $p < 0.001$). Acute grade ≥2 and grade ≥3 hematological toxicity was also worse with the addition of PNRT (5.1% versus 1.8%, and 2.6% versus 0.2%, respectively, $p = 0.002$). Late toxicity was also an increased with late grade ≥2 hematological toxicity (4.1% versus 1.6%, $p = 0.044$).

Although it is undeniable that a subset of patients may harbor pelvic nodal metastases, we must not forgot that both PNRT arms in RTOG 9413 had inferior outcomes to prostate-only RT with adjuvant ADT arm.[1] While some may state it is impossible for PNRT to cause worse outcomes, we must remember that "we don't know what we don't know". However, what we do know is the immune system, specifically infiltrating CD8+ T-cells, play a critical role in radiation induced cell death and radiosensitivity.[6] Furthermore, larger field sizes have been shown to induce a greater suppressive effect on peripheral T-cells compared to smaller RT volumes.[7] PNRT causes a greater reduction in lymphocytes, which could potentially result in worse local tumor control outcomes of the primary. Additionally, the doses used with PNRT (often ≤42-50 Gy EQD2) may be inadequate to eradicate microscopic disease - even adjuvant radiotherapy doses to treat microscopic disease are ≥60 Gy. We also now know from PSMA PET imaging data that historical RTOG contouring atlases missed significant portions of where recurrent nodal disease resides. Even with PSMA PET, pathologic nodal assessment has a sensitivity of only ~45%, and thus we miss more than we see even with advanced molecular imaging.[8,9] Furthermore, patients with nodal metastases may have circulating disease and already have distant micrometastatic disease, rendering PNRT potentially futile. Thus, delivering PNRT to all patients with unfavorable intermediate- or high-risk disease is of unclear benefit with a proven potential for harm.

We now have two trials that have demonstrated biochemical control benefits of PNRT. However, these were *not* in unselected patient populations. The first has only been presented, RTOG 0534,[5] and was in a mostly early salvage RT

Corresponding author: Nicholas Zaorsky, MD, MS; E-mail: nicholaszaorsky@gmail.com

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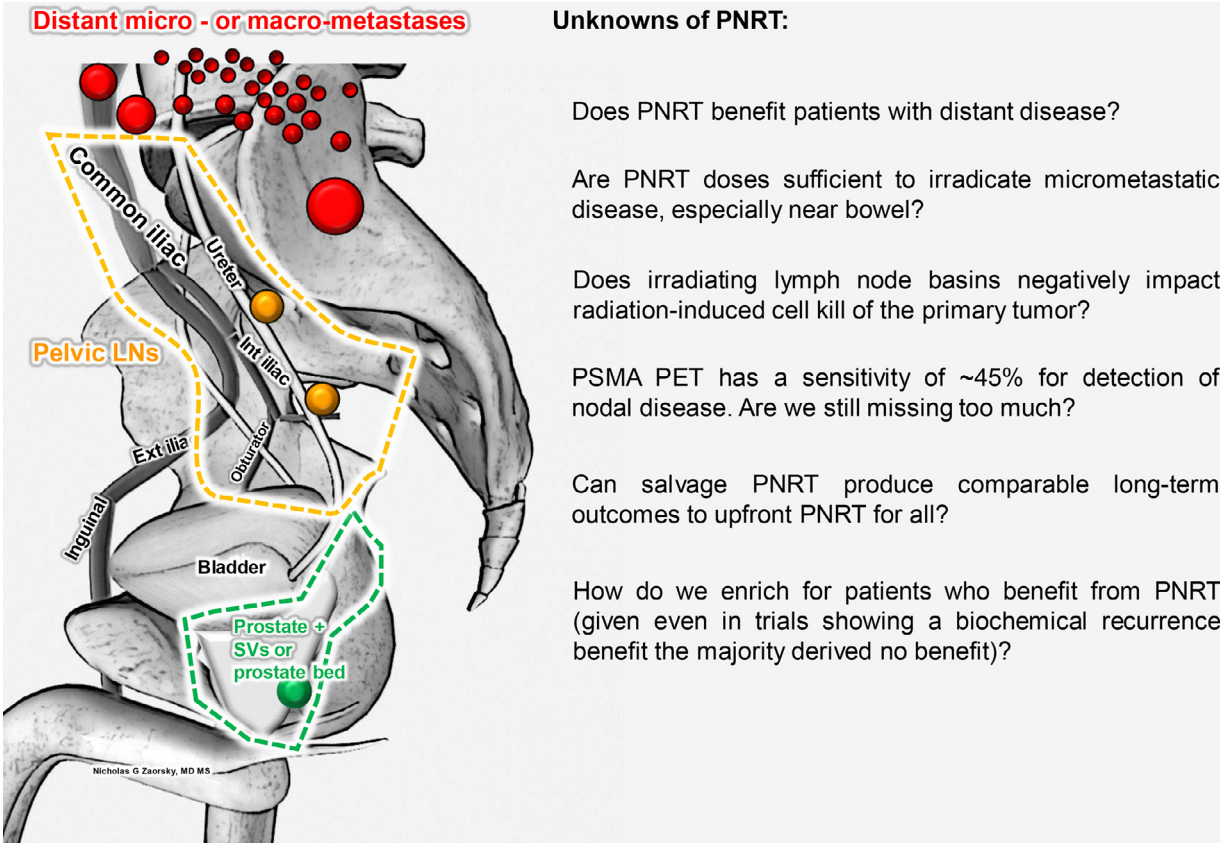

Fig. 1. The fundamental premise for recommending PNRT is that a subset of patients with radiographic node negative disease will harbor pathologically node positive disease, and PNRT would translate into improved oncologic outcomes with minimal additional toxicity. In the left panel, one would only be irradiating the pelvic nodes, and there would not be occult metastases. As of 2021, several unanswered questions about PNRT remain (right panel).

population post-prostatectomy. Patterns of failure post-RP, especially with PSAs ≤1 ng/mL, are different than in localized prostate cancer; they are predominantly in the prostate bed and/or the pelvic LNs. Consistent with this and looking at arms 2 and 3 of the trial (prostate bed plus ADT +/- PNRT), patients with PSA levels >0.34 ng/mL (the median PSA on the trial) were the only subset of patients who derived a biochemical control benefit (primary endpoint), with no significant differences in metastasis or survival. Notably, biochemical control has repeatedly been shown to not be a surrogate endpoint for survival.[10] Patients with lower PSAs did not demonstrate even a biochemical recurrence benefit, and may reflect that with higher PSAs there is an increased probability of harboring nodal rather than local only disease.

The second trial was the recent POP-RT trial, which also has a selected patient population.[11] Over 80% of patients on POP-RT underwent PSMA PET scans, restricted patients to NCCN high-risk disease, and screened out patients with nodal and distant metastasis. Thus, patients remaining on the trial had a more favorable prognosis and lower risk of harboring distant disease than a totally unselected high-risk population. They demonstrated a significant improvement in biochemical control from PNRT. Toxicity has yet to be reported. Additionally, the post-hoc metastasis-free survival benefit was driven by molecular imaging detected PSA recurrences, which despite a very large effect size, had no impact on overall survival. Given that metastasis-free survival has repeatedly been shown to be a surrogate endpoint, this begs the question if molecular imaging defined metastasis-free survival is effectively event-free survival, which is not a surrogate endpoint.[10] It also begs the question if 'salvage of these nodal recurrences in the prostate-only arm is effective and negates any impact on overall survival.

What we still don't know is:

1. Can we extrapolate the data from RTOG 0534[5] and POP-RT[11] to all unselected localized prostate cancer patients?
   a. We believe we should wait for the results of RTOG 0924, where the control arm is prostate-only RT. Thus, it remains experimental to deliver PNRT in an unselected population.
   b. RTOG 0534 is an entirely different disease state and should not be extrapolated to localized prostate cancer.
   c. As PSMA PET becomes widespread, the results from POP-RT seem appropriate to justify selective PNRT in PET negative high-risk patients.

2. Is PNRT to all upfront superior to providing salvage nodal RT in the subset that recurs?
   a. The majority of patients never recur after prostate-only RT in localized prostate cancer, and a subset recur even after PNRT. It is probable that the classic debate of adjuvant vs salvage may result in minimal net benefit of upfront PNRT for all.

In summary, although we have new data to support the use of PNRT for biochemical control in select subsets of patients (PSMA PET negative high-risk localized and post-RP BCR PSA >0.34 ng/mL), we still await the results of the definitive trial in the use of PNRT in localized prostate cancer, RTOG 0924. We must remember that we have evidence that PNRT has zero level 1 evidence of any impact on survival,[1,2,5,11] and significantly increases toxicity, even with improved techniques.[5] There remains concern that PNRT doses are inadequate for micrometastatic disease, the clear negative impact of PNRT on hematologic toxicity and depletion of lymphocytes, and it remains challenging to identify the subset of patients who will have occult disease outside of the pelvis.[8,9] Adoption of the experimental arm of RTOG 0924, use of PNRT, we accept is "a" standard of care, but it fundamentally begs the question why RTOG 0924 was conducted if we are to ignore our prior phase III trial results.[1,2] Thus, we caution the ubiquitous use of PNRT until RTOG 0924 is reported. If the results of RTOG 0924 are negative, and the use of PNRT was appropriately experimental as deemed by the trial protocol, millions of men will have received this treatment without clear benefit and potential harm.

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