



# Pelvic nodal radiotherapy in Gleason grade group 5 prostate cancer

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We read the Editorial Comment by Taussky and Delouya with great interest (1). They pose the question: why do radiation oncologists continue to debate whole pelvis radiation therapy (WPRT) given that two negative randomized trials have been published? We would counter that this discussion can and should continue for a number of reasons, the foremost being that the jury is still out.

One must first acknowledge that the purported benefit of WPRT can only be realized if there is microscopic disease in the pelvic lymph nodes. If patients have too low of a risk of nodal disease (as would be expected of the patients on Groupe d'études des tumeurs urogenitales (GETUG)-1, and most patients with Gleason grade group 1–2 disease), then WPRT would offer no benefit above prostate-only radiotherapy. If patients have too high of a risk of extrapelvic disease, then WPRT would also offer no benefit over prostate-only radiotherapy. Thus, as Chen alluded to in his initial Editorial about our manuscript, one must find a clinical situation in which the risk of having microscopic disease is “just right” to warrant a benefit to WPRT—the “Goldilocks problem” (2). Taussky and Delouya argue that our previous article does not “put WPRT in the ‘just right’ category.” We assume that by their statement, the authors mean that we have not identified this group either. On the contrary, our intent was not to say which porridge is the right temperature, only to say whether it was too hot or too cold for patients with Gleason grade group 5 prostate cancer. This is a question that has certainly *not* been answered by any previous randomized trial. In fact, RTOG 9413—a four arm trial—enrolled a grand total of

139 patients with Gleason grade group 5 disease, while the GETUG-01 trial enrolled 99 patients with Gleason grade group 4–5 disease (of which the majority likely had Gleason grade group 4 disease). This leaves a *maximum* of 238 patients across six trial arms from two trials, none of which included stratification for Gleason grade group 5 disease and none of which reported outcomes in this subgroup. Is the role of WPRT really settled in this subgroup?

It is also important to acknowledge the design and limitations of these trials. RTOG 9413, with its complex, factorial design was initiated to examine both the sequencing of androgen deprivation therapy (ADT) and the role of WPRT. The updated 10-year results do show evidence of a benefit in progression free-survival and biochemical failure when comparing WPRT to prostate-only radiotherapy among men receiving neoadjuvant and concurrent hormonal therapy. The major criticism is that outcomes in men receiving prostate-only radiotherapy with adjuvant ADT were similarly good. This *a priori* unexpected interaction of the sequencing of ADT with radiation field size complicated the results, though one could argue that if men are to receive neoadjuvant/concurrent ADT, the trial supports WPRT. The GETUG-1 study, which did not show a difference in progression-free survival, admittedly had a more straightforward design (3). The differences in patient populations, treatment fields, and use of ADT have been discussed extensively (4–6) and cannot be repeated here due to space constraints. But a critical consideration for both trials is the low dose of radiation given to the primary tumor. With emerging evidence that local control

can translate to improved clinical outcomes (7-9), we must consider whether local control needs to be optimized before a benefit to WPRT can be seen.

We, like the authors of the Editorial Comment, eagerly await the results of RTOG 0924 (which will likely meaningfully report in approximately 10 years, not in 2021 as the authors state) as well as the PIVOTAL trial [NCT01685190]. But we acknowledge that well-designed randomized trials are incredibly resource intensive, requiring not only significant expenditure of time and money, but also the sacrifices of patients who are willing to be randomized on a trial. A decade's worth of patients will need our help making decisions about their treatment before then. And even when these trials report, as was the case with RTOG 9413 and GETUG-01, who is to say that patients with Gleason grade group 5 disease will be well-represented in the patient populations?

Moreover, as the authors of the Editorial Comment themselves point out, data from advanced imaging studies do in fact confirm that a fair number of appropriately selected patients indeed have microscopic disease in the pelvis. Should such patients not be considered for WPRT because RTOG 9413 and GETUG-01 were negative? While that argument could be made, it would appear the authors themselves advocate in using PSMA PET/CT to guide treatment. But what should be done if a PSMA PET were not available, or if we were to acknowledge that the sensitivity is not 100%? Would this not imply a role for WPRT in selected patients?

In medicine, one must be careful not to throw out the baby with the bathwater. The vast heterogeneity amongst patient and disease characteristics within oncology frustratingly makes us unable to make confident clinical decisions based on sweeping generalizations. Our goal is continuing to granulate the indications for treatments. In the meantime, we must discuss and debate complex questions, involve patients in the decision-making process, and conduct research that will further the field to the best of our ability.

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