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Reply to “Letter to the Editor regarding “Timing of radiotherapy (RT) after radical prostatectomy (RP): Long-term outcomes in the RADICALS-RT trial [NCT00541047]”, by C. C. Parker et al.”

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PII: S0923-7534(24)00140-6

DOI: <https://doi.org/10.1016/j.annonc.2024.05.001>

Reference: ANNONC 1473

To appear in: *Annals of Oncology*

Received Date: 2 May 2024

Accepted Date: 6 May 2024



Please cite this article as: Parker C, Catton C, Clarke N, Meidahl P, Parmar M, Parulekar W, Sydes M, Reply to “Letter to the Editor regarding “Timing of radiotherapy (RT) after radical prostatectomy (RP): Long-term outcomes in the RADICALS-RT trial [NCT00541047]”, by C. C. Parker et al.”, *Annals of Oncology* (2024), doi: <https://doi.org/10.1016/j.annonc.2024.05.001>.

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Reply to “Letter to the Editor regarding “Timing of radiotherapy (RT) after radical prostatectomy (RP): Long-term outcomes in the RADICALS-RT trial [NCT00541047]”, by C. C. Parker et al.”

We are grateful to Mazzone et al. for their kind words about the RADICALS-RT trial¹. We agree that the results of any trial are most relevant to patients with characteristics well represented in the trial population. Inevitably, however, there is need to extrapolate to patients outside of those represented in the trial, but such extrapolation needs to be done carefully and cautiously. Only a minority of patients who joined RADICALS-RT had multiple adverse risk factors. The trial was not powered for subgroup analysis by risk factors.

The ARTISTIC meta-analysis of randomised controlled trials of adjuvant versus salvage radiotherapy has reported subgroup analyses with respect to biochemical PFS [1]. These analyses did not identify any subgroup that benefitted from adjuvant radiotherapy. We understand that the meta-analysis will be updated to address longer-term outcomes such as freedom from distant metastases and overall survival – although given the results on biochemical PFS, it seems unlikely that the results on these longer-term outcome measures will be any different. These longer-term analyses will provide the best evidence available as to whether any subgroup can be identified to benefit from adjuvant radiotherapy.

How should we counsel patients with multiple adverse risk factors at radical prostatectomy? As Mazzone et al. cite, Tilki et al. have reported a propensity-weighted, retrospective comparison that generates the hypothesis that adjuvant radiotherapy may be beneficial for patients with multiple adverse risk factors [2]. However, we do not think that such non-randomised analyses provide a sufficiently robust basis for clinical decision making.

In theory, the patient who would benefit from adjuvant radiotherapy is one who harbours persistent local disease after surgery, without micrometastatic disease, and for whom early salvage radiotherapy would be unsuccessful. Whether such patients exist is uncertain. If they do, it may be that they do not have multiple adverse risk factors at surgery. Patients with multiple adverse risk factors are likely to have micrometastatic, as well as local, disease.

We agree that “selected high-risk patients may benefit from adjuvant radiotherapy”. However, the other side of the same coin is that we do not have any good evidence that such patients do benefit from adjuvant radiotherapy. We just don’t know. However, we do know that adjuvant radiotherapy comes at a price in terms of bladder and bowel morbidity. Our view is that adjuvant radiotherapy

cannot be routinely recommended to any subgroup until we can be confident that it does more good than harm.

1. Letter to the Editor regarding “Timing of radiotherapy (RT) after radical prostatectomy (RP): Long-term outcomes in the RADICALS-RT trial [NCT00541047], by C. C. Parker et al.”
Mazzone et al. *Annals of Oncology* (in this issue ref please update at compilation).
2. Vale CL, Fisher D, Kneebone A, Parker C, Pearse M, Richaud P, et al. Adjuvant or early salvage radiotherapy for the treatment of localised and locally advanced **prostate** cancer: a prospectively planned systematic review and meta-analysis of aggregate data. *Lancet*. 2020 Oct 31;396(10260):1422-1431
3. Tilki D, Chen MH, Wu J, Huland H, Graefen M, D'Amico AV . **Adjuvant** Versus Early Salvage Radiation Therapy After Radical Prostatectomy for pN1 **Prostate** Cancer and the Risk of Death..*J Clin Oncol*. 2022 Jul 10;40(20):2186-2192.

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COI: None to declare

Funding: None to declare