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APPENDIX

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.urology.2017.06.054.

EDITORIAL COMMENT

With this article the authors highlight an ever important clinical question: Do we achieve any meaningful benefit for the patient with our treatments? They report the updated long-term follow-up of a matched-pair analysis on adjuvant radiotherapy (RT) for pT2pN0 prostate cancer (PCa) with a single positive surgical margin after radical prostatectomy (RP).[1] Adjuvant RT was associated with less local and biochemical recurrences, but this did not seem to (significantly) translate into less distant metastases or improved overall survival.

Long-term follow-up of the patient cohort is of extreme importance in this study, certainly because of the general indolent disease course of these mainly low-grade pT2 patients. Most studies on adjuvant RT include more patients higher at risk of recurrence and thus need shorter follow-up to show significant results (inherently due to the higher number of events).[2] The noteworthy median follow up of 20 years could, however, also be a drawback for the generalizability of the results with changes in diagnosis, techniques, (additional) treatments and follow-up over the years. The continuously changing management and treatments in PCa make it hard to assess the real impact of 1 parameter on hard outcome parameters as overall survival when this is not assessed with a randomized clinical trial design. The limitations noted by the authors are therefore certainly of relevance when interpreting their results. The low number of events (low grade pT2 disease), the number of patients (76vs76, included in the historical cohort) and the number of patients at risk at 20 years follow-up imply that showing a (metastasis free-)survival benefit in this study is unlikely.

The main goal of adjuvant RT seems however achieved: reduction in the risk of local recurrences from 12%to3%. Of the patients that did not receive adjuvant RT 14% received salvage RT. Supplementary Table 1 reveals even an impact of adjuvant RT also on distant metastasis when considering salvage RT as a competing risk (hazard ratio 0.12 [95% CI 0.02-0.95], $P = .04$). The potency of adjuvant RT in R1 disease is herein confirmed. We need to await the results of the RADICALS, GETUG17 and RAVES trial, who hopefully could give more insight into the benefit of adjuvant versus early salvage treatments.[3,4]

The question remains: what is significant prostate cancer and (how) do we need to treat it? Data of the PIVOT-trial showed no significant reduction of RP on PCa mortality or overall survival compared to observation at 20year follow-up.[5] The main goal of cancer treatment is to cure or to considerably prolong the life of the patient, this with the best possible quality-of-life. The ever balancing of efficiency/morbidity, effectiveness and cost-efficiency. In the future, we will need to better identify those patients at risk of relapse but also keep in mind to look out if we can change anything on patient outcome by subjecting them to these additional therapies.[6,7] For now, adjuvant RT for all pT2 R1 PCa tumors certainly seems debatable, as well as the prevalence of R1 in organ-confined disease.

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AUTHOR REPLY

We thank Poelaert et al for their editorial and for emphasizing the importance of ensuring a meaningful benefit with the treatments we provide. Our overarching objective should be to optimize our patients' quantity or quality of life.

As such, we respectfully submit that in men with otherwise no biochemical evidence of disease after radical prostatectomy (RP), the main goal of adjuvant radiation (ART) should be to improve survival, not merely to reduce risk of radiographic local prostate cancer (PCa) recurrence. Prostatic bed recurrences in the modern era are almost always asymptomatic and can be salvaged. Moreover, local recurrence is virtually always preceded by biochemical recurrence in the absence of adjuvant hormone therapy,[1] permitting timely detection. Symptomatic local progression after RP is exceedingly rare.

Conversely, radiation after RP is associated with the potential for morbidity, including urinary incontinence, bladder neck strictures, hospital admissions, secondary procedures, and secondary malignancies.[2] Much like the need to reduce overtreatment of newly diagnosed PCa, the routine administration of ART to all men with any adverse pathologic feature may also constitute overtreatment and needs to be re-evaluated.

Positive surgical margins, extraprostatic extension, and seminal vesicle invasion are adverse pathologic features after RP that have classically led to the consideration of ART and were pooled together in the randomized trials.[3-5] Our data draw into question the use of ART based on a single positive surgical margin as the only adverse risk factor. In addition to mirroring several findings in the randomized trials, our findings are also consistent with the paper by Abdollah et al[6] that was quoted by Poelaert et al. They report no benefit with ART in a cohort of men who had either a positive surgical margin or ≥pT3 disease, unless they also had 2 or more of the following risk factors: Gleason ≥8, ≥pT3, or positive lymph nodes.

With 20 years of follow-up in our cohort with pT2R1N0 PCa, the vast majority of deaths were related to non-PCa causes. Of note, we did *not* find an associated metastasis-free survival benefit in our main analysis or in our sensitivity analysis that considered salvage radiation as a competing event (see Table 2 and Supplementary Table S1).

Although the low number of "events" can be criticized, on the other hand, very few men died of PCa in this population (4 men who received ART and 3 men who did not receive ART), and the 20-year risk of distant metastasis for men in the no-ART group was only 6.7%. Even if we hypothetically demonstrated a 30% relative risk reduction in distant metastasis, which was only seen in 1 ART trial,[5] this would correspond to a 2.0% absolute risk reduction in risk of distant metastasis and a number needed to treat of approximately 50 to prevent metastasis in 1 patient. The number needed to treat would be even higher to prevent a cancer-specific death. We must then ask ourselves, even if our study is underpowered, would this degree of overtreatment be acceptable in light of the alternative approach of prostate-specific antigen monitoring and early salvage radiation?

We agree that the clinical trials comparing adjuvant with early salvage radiation will inform this debate. Until then, we urge clinicians to use a risk-adapted approach, and we caution against over-reliance on intermediate outcomes in the setting of a disease with a long natural history and the opportunity for death from competing causes.

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