Letter to the Editor on: A. Siegmann et al. Dose Escalation for Patients with Decreasing PSA during Radiotherapy for Elevated PSA after Radical Prostatectomy Improves Biochemical Progression-Free Survival. Results of a Retrospective Study

in: Strahlenther Onkol 2011;187:467–72 (No. 8) (DOI 10.1007/s00066-011-2229-3)

P. Ghadjar[1], D. Zwahlen[2], D.M. Aebersold[1]: Selection Bias is Not a Good Reason for Dose Intensification in Patients with PSA Recurrence after Radical Prostatectomy

The retrospective analysis by Siegmann et al. seems to be based on a selection bias in favor of the 70.2 Gy group and, thus, the conclusion "…patients with decreasing PSA during SRT after RP should have a better outcome after receiving 70.2 instead of the standard 66.6 Gy…" appears misleading.
As far as reported, PSA measurements during SRT were performed from 2002 onwards, and patients with decreasing PSA during SRT received a total dose of 70.2 Gy (n = 67). The remaining patients (n = 234) consisted of patients with either stable or increasing PSA during SRT (as treated from 2002 onwards), or probably with unknown PSA status during SRT (as treated before 2002). The latter patients were treated with a total dose of 66.6 Gy.

Patients with decreasing PSA during SRT have most likely a higher chance of improved PSA outcome (e.g., undetectable PSA after SRT, long-term PSA control) as opposed to patients with unknown, stable, or even increasing PSA values during SRT due to several reasons, including decreased risk of disease outside the prostate bed and higher radiation responsiveness. Therefore, this selection bias favors the 70.2 Gy group – at least in part –irrespective of the applied total dose.

We recommend to include the information "PSA decrease during SRT yes vs. no" as a variable to the multivariable analysis to control for this bias and also to acknowledge the significantly shorter follow-up of the 70.2 Gy cohort (21 vs. 31.6 months) as a limitation.

We agree with the authors that a prospective trial is needed and would like to refer to the Swiss Group for Clinical Cancer Research (SAKK) Phase III trial 09/10 which is currently recruiting patients in Switzerland, Germany, and Hungary, comparing 64 Gy (equivalent to 66.6 Gy with 1.8 Gy single doses using an α/β ratio of 3 Gy) vs. 70 Gy in patients without macroscopic biochemical recurrence after prostatectomy [www.clinicaltrials.gov; identifier number NCT01272050]. The trial will include 250 patients and will hopefully clarify the question of dose intensification in the salvage radiotherapy setting after prostatectomy.

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Response by A. Siegmann[1], D. Bottke[2], J. Faehndrich[1], et al.: Appropriate Selection is a Good Reason for Dose Escalation in Salvage Radiotherapy, SRT

In their letter, Dr. Gadhjar et al. criticize selection bias in our SRT study [4], but do not offer in what respect the selection was flawed. They point out correctly that in our retrospective analysis, the PSA response during SRT was unknown for "early" patients and state that the selection favored the high-dose cohort. Indeed – and this is stated in our paper – the favorable factors of responders were the rationale for the selection. But, as is conceded in the letter, only a part of the advantage is attributable to these factors. A preliminary analysis of a larger cohort with PSA monitored during SRT (but still a short follow-up) confirmed the positive effect for the high-dose group.

We welcome the prospective trial of SAKK, analyzing dose escalation in SRT. However, the suggested equivalence of 64 Gy in 2 Gy fractions to 66.6 Gy in 1.8 Gy fractions should be regarded with care. The α/β ratio of prostate cancer is still under discussion. Values below 2 have been suggested by Fowler and others [1, 2] and would result in a higher BED from the 2 Gy scheme. An α/β ratio as high as 30 [3] would have the opposite effect. It is also an issue to include and stratify patients with relevant risk parameters appropriately.

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