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LETTER TO THE EDITOR

Comment to Impact of postmastectomy radiotherapy on the outcomes of breast cancer patients with T1-2 N1 disease; an individual patient data analysis of three clinical trials

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Abdel-Rahman [1] analyzed the overall survival-rate and disease-free survival of T1-2 N1 breast cancer patients after mastectomy, who were adjuvantly treated with various modern chemotherapeutic drugs (anthracyclines, taxanes) in 3 prospective phase III chemotherapy trials. His analysis suggested no potential benefits of an additional adjuvant postmastectomy radiotherapy (PMRT). The included trials were the BIG 02/98 [6], the BCIRG 001 [7] and the BCIRG-005 [5] trials. The author concludes that in T1-2 N1 breast cancer patients who have received modern chemotherapy drugs PMRT does not provide any benefit for overall and disease-free survival. Prospective studies are necessary.

Comment

PMRT has shown a survival benefit in many randomized trials and meta-analyses, in addition to a reduction in loco-regional recurrence rate (LRR) in locally advanced breast cancer. The Early Breast Cancer Trialist' Collaborative Group (EBCTCG) demonstrated that PMRT resulted in a reduction in LRR after 10 years from 21 to 4.3% in patients with 1–3 positive lymph nodes and from 49.4 to 41.5% after mastectomy for breast cancer [4].

Many of the included studies analysed patients who were treated in the 1970s and 1980s with old-fashioned chemotherapy regimens. A retrospective analysis of the MD Anderson Cancer Center recently provided a comparison of PMRT at different time periods (1978–1997 versus 2000–2007). While the results for the PMRT group were similar at both time intervals, the group without PMRT had a significant reduction in 5-year LRR ($p < 0.001$) within the modern chemotherapy regimes [8].

The intention of the currently discussed study by Abdel-Rahman is an analysis of the benefit of PMRT in the era of new taxane-based chemotherapy. This, however, was not an endpoint of the three studies included in his meta-analysis so that it corresponds to a retrospective, non-randomized analysis. In principle, this increases the risk of imbalances between potential prognostic factors of patients with or without PMRT, and thus for selection bias.

In fact, a higher lymph node involvement ratio, a higher proportion of G3 tumors and Her2/neu positive tumors, PMRT patients had less favorable tumor characteristics, indicating a negative selection bias to the disadvantage of the PMRT group. Theoretically, therefore, to reliably estimate the effect of PMRT on survival times, one should be corrected for any variable that affects the probability of obtaining PMRT. This was attempted by the author using a propensity score analysis, in which each patient from the PMRT group is assigned a patient from the non-PMRT group with the same or as close as possible propensity score. This has the disadvantage of reducing the sample size. However, some obvious influencing factors remained unadjusted for, such as the lymph node ratio, as well as any unknown

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factors whose influence on the probability of PMRT could theoretically be minimized only by randomization.

Randomized studies on radiotherapy from the same study era, such as the MA.20 study [10] and the EORTC 22922 study [9] clearly demonstrate a significant effect of locoregional radiotherapy on local and distant control, as well as disease-free survival [3]. In addition to radiotherapy of the infra- and supraclavicular lymph regions, these studies also included irradiation of the parasternal lymphoid region as target volume. In the study commented here, only 69.8% of patients in the PMRT group received irradiation the supraclavicular lymph regions, and only 19.8% of the parasternal lymph drainage pathways. However, the latter was probably instrumental in the success of the EORTC 22922 and MA.20 study. It is also possible and quite probable that radiotherapy in this work simply compensated for the significantly worse prognostic factors.

It should be noted that about 30% of the patients in the study commented here lacked information on the resection status and for about 20% of the patients on the Her-2/neu status was missing.

Several other important data were not available, for example data on endocrine therapy. In 52.3% of patients treated with PMRT and 25.2% of non-PMRT-patients, there was no information on which breast (left or right) the cancer was located in. Furthermore, due to missing data, the smoking status of the patients could not be included in the Cox-analysis; this was only available for one of the studies and had recently been correlated with a poorer relapse-free survival [2].

Conclusion

In summary, no conclusive conclusion can be derived from this study. The S3 guideline for breast cancer, as well as international guidelines, continue to recommend PMRT in patients with 1–3 lymph node metastases in the presence of other risk factors. Further evidence in this situation will hopefully be provided by the results of the randomized SUPREMO trial, which investigated the effect of PMRT in patients with pT1-2 pN1, pT2 pN0 (if G3 and/or L1 is present) or pT3 pN0.

Conflict of interest C. Matuschek, D. Krug, R.J. Klement and R. Baumann declare that they have no competing interests.

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