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Reply to 'The St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2017: the point of view of an International Panel of Experts in Radiation Oncology' by Kirova et al.

The St Gallen Writing Committee on behalf of the St Gallen Panel thanks the authors for their letter [1]. The St Gallen Consensus process is built upon the collective recommendations from a multidisciplinary, international panel of breast cancer experts, including radiation/clinical oncologists. The goal is to recommend standard approaches to breast cancer management based on the integration of data from clinical trials and other types of evidence including subset analyses, and outcomes from biologically determined subtypes of breast cancer with experiences drawn from contemporary practice including innovations in surgery, radiotherapy, and systemic treatment. We note that the recent AJCC staging revisions also now integrate traditional stage distribution with biologically determined breast cancer subtypes for most appropriately gauging clinical risk. The St Gallen Panel provides consensus [2] on many controversial areas but does not adhere to a process prerequisite for broad guidelines.

Based on such considerations, and fully cognizant of the data referred to by the letter writers, the multidisciplinary Panel confirmed that postmastectomy radiotherapy and that regional nodal irradiation might be safely avoided in selected node-positive patients with N1 axillary involvement and a tumour with a favourable biological and clinical profile. This represents an opportunity to tailor treatment more effectively for women with breast cancer.

The Panel also reviewed and discussed the increase of reconstructive surgery and the impact of these quickly developing techniques (including skin sparing types of mastectomy) and technologies on delivering postoperative radiation therapy and cancer outcomes. We would like to emphasize that the goal is not to compromise adjuvant therapies simply to achieve less surgery or better reconstruction. However, the general opinion at the consensus meeting was that the current evidence and clinical expertise does allow to 'de-escalate' treatment in many women. Therefore, making individualized choices well in line with evidence-based medicine should be an option for early stage breast cancer patients.

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Analyzing the impact of depth of response on survival in patients with metastatic non-small-cell lung cancer

We read with great interest the article by McCoach et al. [1] investigating the association of depth of response (DepOR) with survival in patients with metastatic non-small-cell lung cancer. The authors found that good response (such as maximal tumor shrinkage of 76%–100%) was associated with longer progression-free survival (PFS) and overall survival (OS) compared with non-responders, estimated by a very low hazard ratio (HR) of 0.03. We believe that these results are prone to survival bias. Already in 1983 and re-emphasized in 2008, Anderson et al. [2] discussed the statistical challenges of analyzing survival by tumor response. Anderson et al. [2] pointed out that a bias occurs when patients are categorized into good and bad responder groups at baseline and then survival in these groups is compared. This approach is biased because in order to obtain a good response individuals have to survive long enough to belong to the good responder group. On the other hand, there is no condition on survival for the non-responders. This bias is called time-dependent bias or immortal time bias, as described by van Walraven et al. [3] and Gill et al. [4].

The analysis of McCoach et al. [1] is prone to immortal time bias, because DepOR develops over time, but patients were categorized based on DepOR into responder groups using the maximal tumor shrinkage. Hence, DepOR is considered as being already known at baseline. However, a good tumor response of 75%–100% shrinkage usually takes a couple of months to develop.

There are methodological papers addressing the presence of time-dependent bias and its impact, such as van Walraven et al. [3] and Beyersmann et al. [5]. Beyersmann et al. [5] delivered an easy mathematical proof showing that in the presence of time-dependent bias the HRs are always smaller than they actually are. Consider the results of McCoach et al. in more detail: the Kaplan–Meier curves for PFS show no events during the first 5–6 months for the good responder group. This is not surprising as most of the patients have not had a tumor shrinkage of more than 75% within the first 6 months whereas all events occurred during the first 6 months in the non-responder group. This reflects the time dependency of response and results in an extremely low HR. However, with the results of Beyersmann et al. [5] we can show that the HR is closer to 1.

There are appropriate approaches for the investigation of treatment response and survival. Treatment response can be considered as a time-dependent covariate or a landmark approach can be carried out [2].

Ignoring time dependency leads to seriously biased results and therefore to wrong conclusions. This is a crucial topic and the time dependency of treatment response needs to be taken into account when investigating the association with survival. We hope that our letter leads to a better awareness of the immortal time bias and hence improves investigations.

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