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Commentary on "Prognosis according to the timing of recurrence in breast cancer" (Ann Surg Treat Res 2023;104:1-9)

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Dear Editor,

We read with great interest the paper by Lee et al. [1] on prognosis according to the timing of recurrence. Whether the overall survival (OS) of a patient is different if they relapse early (within 5 years from diagnosis) *vs.* late (after 5 years) is an important clinical research question that is worth addressing as it can help to inform future treatment guidance in the clinic. Lee et al. [1] investigated the impact of these recurrence time points with standard statistical tools such as the Kaplan-Meier curves, Cox proportional hazards models, and time to OS starting from diagnosis until death. However, a precise statistical analysis of the impact of an "early" *vs.* a "late" recurrence on the future prognosis of an individual patient requires careful consideration.

In essence, whenever patients are grouped according to post-baseline (post-diagnosis in this case) follow-up information, the so-called immortal time bias [2-4] is a potential issue that needs to be taken into account. Immortal time bias refers to the bias that can arise when there are time intervals during the observation period in which the event of interest cannot occur (=immortal time period). This usually happens when the follow-up periods are not correctly handled during analysis. In the context of Lee et al.'s article [1], the immortal time bias refers to the time interval between diagnosis and recurrence. As a matter of—only seemingly trivial—principle, for a patient to recur, they need to survive until the time point of recurrence. In other words, the "theoretical" risk of a "late" recurrence necessarily means that the patient needs to survive for at least 5 years! Otherwise, no late recurrence can occur. Hence, if one investigates the time period from diagnosis until death in patients with late recurrences, all patients in this group will inevitably have survived at least 5 years (that's their "immortal" time!). The bias can be seen very clearly in Fig. 1–3 in the article of Lee et al. [1]; the Kaplan-Meier curves for the late recurrence group stay in a horizontal straight line at 100% until at least 60 months, and only thereafter start to drop. As a misleading but logical consequence, all late recurrence patients seem to have higher survival rates than patients with early recurrences. It is also not surprising that all P-values indicate a highly significant effect, which, however, does not reflect reality.

Furthermore, one must be aware that not just the late recurrence group is impacted by this immortal time bias. For example, if a tumor recurs already after 2 years (and the individual patient is categorized according to the early recurrence cohort), the patient still will have survived at least 2 years (i.e., their immortal time in this case). Therefore, the risk of death after recurrence will be underestimated if the first 2 years are not attributed correctly to the no-recurrence group.

We understand that such a mistake can occur quite easily as we (and all clinical trialists) must always be very careful to not fall into this trap, as well. This also underlines the importance of a thorough statistical peer-review of manuscripts potentially subject to this bias, as the immortal time bias issue has been known for quite some time now (see for example [5]).

Nevertheless, we believe that addressing this issue is crucial to avoid any misinterpretation of the data as this might have consequences for treatment decisions and patient lives. We, therefore, invite Lee and colleagues to reanalyze this precious

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data set with better-suited methods such as time-dependent Cox models, landmark analyses [6], or any other more sophisticated statistical methodology. If considered helpful, we are certainly willing to offer our statistical expertise in a collaborative effort to actually and reliably better understand the changes in prognosis in relation to time of recurrence.

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Conflict of Interest

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