Ki67 in breast cancer: a useful prognostic marker?

We read with great interest the article by Denkert et al. [1] about the prognostic role of Ki67 in breast cancer patients treated with neoadjuvant therapy. We think, however, that the different composition of population in clinical practice in comparison with population in the trial could be kept in mind.

Among the 1475 cases of breast cancer diagnosed in 2004–2005 in residents in the area of Firenze and Prato, collected by Tuscan Cancer Registry, and with Ki67 score available, we found a low Ki67 expression (≤15%) in more than half of the cases (58% of total); moreover, in this population-based database, the luminal A cases constituted 70% of the series [2] while, in the trial by Denkert [1], they were 53% of the total. Probably, in the population by trial, the low-risk breast cancer patients are underrepresented, and this feature can influence the results about the prognostic effect of Ki67 in this group.

We carried out an ROC curve to assess the best cutoff of Ki67 for predicting overall survival among the luminal A and B cases: a value of 15%, as proposed by Denkert et al. [1], correctly classified only 55% of cases, with a sensitivity of 64% and specificity of 54%. The other Ki67 cutoff (35%) proposed by Denkert et al. [1] correctly classified 83% of luminal cases: the specificity was 90.4% but the sensitivity, that is the ability to identify the patients with high risk to die, was low (20.1%).

We think that the prognostic role of Ki67 in a normal population remains unclear, even in luminal breast cancers. Therefore, further studies need to correctly evaluate the use of this marker in the clinical practice.

A. Caldarella*, E. Crocetti & E. Paci
Clinical and Descriptive Epidemiology Unit, Institute for Study and Cancer Prevention (ISPO), Florence, Italy
(*E-mail: a.caldarella@ispo.toscana.it)

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references

Reply to Ki67 in breast cancer: a useful prognostic marker!

We appreciate the letter by Caldarella et al. They have evaluated Ki67 in a cohort from the Tuscan Cancer Registry [1] and compared the results with the data published in our recent manuscript [2]. The main difference between both studies is the different selection of patients. GeparTrio was a chemotherapy trial with inclusion criteria that excluded most of the luminal low-risk tumors. Consequently, the percentage of tumors with a Ki67 of less than 15% was approximately one-third in GeparTrio, while it was two-third in the registry cohort.

There are some open technical questions to the registry data: were the Ki67 values determined by exact counting rather than estimation? How was standardization achieved? These technical issues are more difficult to control in a registry-based setting. Furthermore, slightly different values might be obtained in core biopsies and in large tumor sections due to intratumoral heterogeneity. It would be extremely interesting to perform the complete cut point analysis using the cutoff finder approach and the molecular subtype radar diagrams, as described in our paper, also in the registry population. Cutoff finder [3] is freely available on a webpage (http://molpath.charite.de/cutoff/). A direct comparison with the same approach would stimulate the discussion in this area.

Furthermore, it would be interesting to stratify the registry data according to the different treatment that was given to the patients. We have shown in Figure 4 of our paper that Ki67 is a negative prognostic factor for tumors with poor response to chemotherapy, while it is a positive prognostic factor for tumors with a pathological complete response, which demonstrates that the therapy approach will also change the results that we get out of the Ki67 analysis.

However, despite these open questions, the investigation by Caldarella et al. illustrates a very important issue: there is no ‘normal population’ in breast cancer, and it always depends on the viewpoint of the researcher. From an epidemiology point of view, a normal population is a registry-based population. However, for many of these patients, the determination of Ki67 might not be needed, because they are low risk anyway and would not require additional treatment. From the view of a clinical oncologist, a normal population is a population from a clinical trial with defined entry criteria and identical treatment. Even if we would define a cut point using a large registry cohort,
this cut point might not be relevant for a chemotherapy cohort with different baseline characteristics and different therapy approaches. Similarly, a cut point defined in one chemotherapy trial might be different in a second chemotherapy trial with different treatment and response rate. From our point of view, this shows that a data-derived cut point optimization is not possible. However, this does not imply that Ki67—and other proliferation markers—are not useful; it just shows that the cut points are context dependent. Ki67 could be measured as a continuous marker with a robust and standardized methodological approach, such as image analysis. In addition, the scientific community could define cut points for different practical purposes.

C. Denkert1* & G. von Minckwitz2

1 Institute of Pathology, Charité-Universitätsmedizin Berlin, Berlin, Germany
2 German Breast Group, Neu-Isenburg, Germany
(*E-mail: carsten.denkert@charite.de)

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Meta-analysis procedure for the effect of statin on the recurrence of prostate cancer

Overviewing the recent publication, Park et al. [1] conducted a meta-analysis to clarify the effect of statin on the recurrence of prostate cancer with special reference to two major treatments. In this letter, I have a concern on their basic procedure of selecting information stratified by the use of statin.

First, the authors selected appropriate references according to the standard flow diagram, but there was a difficulty of extracting information for conducting pooled estimates in studies of radiotherapy. Namely, the number with positive outcome in statin treatment group and control group can be identified three of seven studies. Almost the same meta-analysis was presented by Mass et al. [2], and Park et al. added one reference from proceeding.

Second, although hazard ratios (HRs) with 95% confidence intervals were listed in their Figure 2, Zaorsky et al. selected three of seven patients with statistical significance. Park et al. also noted in their discussion that ‘four studies, three did not address biochemical recurrence’ [4]. The one study that did address this outcome (Lavery et al. [5]) reported a nonsignificant effect of statins on biochemical recurrence among men treated with radical prostatectomy, which is consistent with the findings of the other radical prostatectomy studies.

T. Kawada

Department of Hygiene and Public Health, Nippon Medical School, Bunkyo-Ku, Tokyo, Japan
(*E-mail: kawada@nms.ac.jp)

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Reply to ‘Meta-analysis procedure for the effect of statin on the recurrence of prostate cancer’ by T. Kawada

We greatly appreciate Dr Kawada’s interest in our meta-analysis. The respondent makes several points worthy of additional discussion.

The first comment explores the challenges of extracting information to determine pooled estimates of the outcome variable. As we noted in our discussion, we excluded 4 of 17 potentially eligible studies that failed to report a unified effect estimate for biochemical recurrence as a function of peritreatment statin use [1]. Of these four studies, three did not address biochemical recurrence [2–4]. The one study that did address this outcome (Lavery et al. [5]) reported a nonsignificant effect of statins on biochemical recurrence among men treated with radical prostatectomy, which is consistent with the findings of the other radical prostatectomy studies.