

In Response to “Intratumor Distribution of Ki-67 Antigen Beyond Labeling Index for Clinical Decision Making: A New Way of Counting”



To the Editor:

We appreciate the opportunity to respond to the letter by Bulloni et al.¹ We also thank Bulloni et al. for the comments made in their letter and further discussion on the use of Ki67 in clinical practice in malignant pleural mesothelioma (MPM) and other tumors.

In his letter to the editor, Dr. Bulloni acknowledges and agrees with the predictive potential of Ki67 immunohistochemistry in clinical practice. In our article, we have revealed the prognostic value of Ki67 as a marker in patients with MPM treated with extended pleurectomy/decortication (ePD). Our results are in line with the score-based, multiparameter grading system reported by Pelosi et al.,² wherein they have reported that necrosis, Ki67, and mitotic count are valuable markers for prognosis independent of the histologic subtype in MPM.

To find that Ki67 can be used in clinical practice, we have revealed that “there was a congruency rate of 87% between eP/D samples and purported biopsy samples represented by pseudo-tissue microarrays constructed by 10 randomly piked-up 2-mm-sized regions for each tumor.”

Dr. Bulloni accurately points out that although in 87% of the cases the pseudotissue microarrays are representative for the tumor expression of Ki67, there is

a heterogeneous distribution of Ki67 between different pseudomicroarray regions. Dr. Bulloni rightfully notes that the biological implications of this distribution are not addressed and subsequently refers to a study done by himself and colleagues in lung neuroendocrine neoplasms (NENs). In this study, he reports, with machine learning algorithms, that the distribution of Ki67 within 30 lung NENs is predictive of outcome (alive versus death).³

As our initial finding was that Ki67 expression within the resected tumor was prognostic for outcome, our aim was to investigate if a biopsy before surgery would be representative of overall Ki67 expression within the tumor (>10% versus <10%), which holds true in 87% of biopsies taken.⁴ Indeed, we did not elaborate any further on the biological mechanism and potential predictive value of the degree of intratumoral heterogeneity of Ki67.

Although this is a valuable suggestion, we consider the number of patients probably too low and the material too limited to elucidate on the biological aspect and draw firm conclusions on the clinical implications of Ki67 distribution within the tumor without undue speculation. Nevertheless, the tailored algorithm used by Pelosi et al.³ could maybe clarify the importance of Ki67 distribution in patients with MPM treated by eP/D as his study was done in 30 patients. From the data provided in the abstract by Pelosi et al., it is not yet clear exactly which spatial parameters or types of distribution are related to clinical outcome in lung NEN. Knowing exactly what kind of distribution represents worse clinical outcome could help us to identify the biological mechanism that is responsible. Therefore, we are looking forward to more data on the study done by Pelosi et al.

Perhaps the most important question concerning distribution of Ki67 is whether two tumors with an identical average Ki67 expression, but different distribution (homogeneous/heterogeneous), will have different clinical outcomes. For now, we speculate that a tumor with a heterogeneous expression with very high levels of Ki67 in some parts of the tumor has a worse clinical outcome compared with a more homogenous expression. As MPM is a polyclonal tumor,⁵ specific clonal cells in the tumor with high Ki67 expression are likely to reflect a more aggressively growing neoplasm. In a heterogeneous tumor, we would expect the clonal cells with high proliferation rates to have a growth advantage and thus increase the overall Ki67 expression within the tumor.

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Again, we thank the authors for their interesting comments on our study and are looking forward to more data on Ki67 distribution in lung NEN and maybe MPM. We hope that large-scale studies will provide further results on the prognostic/predictive value of Ki67 in MPM and help us understand the biological effects of the distribution of Ki67 within the tumor.

CRediT Authorship Contribution Statement

Robert A. Belderbos: Conceptualization, Investigation, Writing—original draft.

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References

1. Bulloni M, Pattini L, Pelosi G. Intratumor distribution of Ki-67 antigen beyond labeling index for clinical decision-making: a new way of counting. *JTO Clin Res Rep*. 2021;2:100207.
2. Pelosi G, Papotti M, Righi L, et al. Pathologic grading of malignant pleural mesothelioma: an evidence-based proposal. *J Thorac Oncol*. 2018;13:1750-1761.
3. Pelosi G, Bulloni M, Papotti M, et al. Intratumor heterogeneity of Ki-67 is a powerful and histology-independent resource to dissect clinical outcome of lung neuroendocrine neoplasms by means of artificial intelligence tools (Abstract #1949). *Mod Pathol*. 2020;33:1811-1812.
4. Belderbos RA, Maat AP, Baart SJ, et al. Ki67 (MIB-1) as a prognostic marker for clinical decision making before extended pleurectomy decortication in malignant pleural mesothelioma. *JTO Clin Res Rep*. 2021;2:100155.
5. Comertpay S, Pastorino S, Tanji M, et al. Evaluation of clonal origin of malignant mesothelioma. *J Transl Med*. 2014;12:301.