 DOI: 10.3217/978-3-85125-954-4-20

Scientific Spotlight: Computer-assisted mitotic count using a deep learning-based algorithm improves interobserver reproducibility and accuracy

Christof A. Bertram
University of Veterinary Medicine Vienna
Veterinärplatz 1
1210 Vienna, Austria
Christof.Bertram@vetmeduni.ac.at

Marc Aubreville
Technische Hochschule Ingolstadt
Esplanade 10
85049 Ingolstadt, Germany
Marc.Aubreville@thi.de

Robert Klopfleisch
Freie Universität Berlin
Robert-von-Ostertag-Str. 15
14163 Berlin, Germany
Robert.Klopfleisch@fu-berlin.de

Enumeration of tumor cells undergoing cell division (mitotic figures) is a very practicable method to quantify tumor proliferation as it can be determined in histological sections with routine staining methods. The mitotic count (number of mitotic figures per 2.37 mm² tumor area) has been shown to correlate strongly with patient outcome in several humans and animals tumors types. Tumors with a higher amount of proliferating cells are associated with a more aggressive tumor behavior and thus are more likely to result in death of the patient. Therefore, this prognostic test is routinely conducted by pathologists for many tumor types. The diagnostic task of the mitotic count is to find the tumor region with the highest density of mitotic figures (hotspot) and to count all mitotic figures within this area. Both subtasks of the mitotic count are, however, problematic for human experts as:

- Mitotic figures can only be spotted at high magnification and a tumor section may comprise of thousands of fields of view exceed the human mental capacity and time availability to screen the entire tumor.
- Mitotic figures can easily be overlooked due to the high complexity of histological images.
- Mitotic figures can be difficult to distinguish from other cell structures (such as necrotic cells) with similar morphological appearance.

Subsequently, marked observer variability is well known for the mitotic count. In order to improve the accuracy and reproducibility of the mitotic count, computer-assistance using deep learning-based algorithms with verification by pathologists have been proposed. Whereas most previous studies have focused on developing mitotic figure algorithms, there are only few studies that evaluate the implementation of those algorithms into a diagnostic workflow.

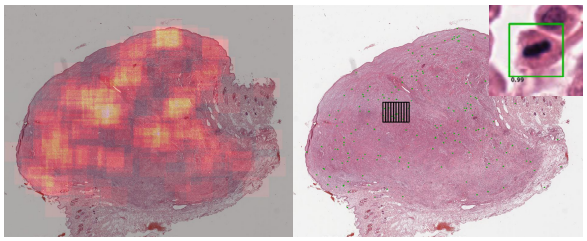

Figure 1. Algorithmic heatmap of mitotic density in the tumor (left image) is based on the algorithmic predictions (right image; green boxes). Based on current recommendations, the area with the highest density (black box in the right image) should be selected for the mitotic count.

In our study [1], we compared the performance between the routine method (without computer-assistance, stage 1), with computer-assisted mitotic counts using algorithmically preselected hotspot tumor areas (stage 2, Fig. 1) and visualisation of mitotic figures candidates within this hotspot tumor area (stage 3, inset Fig. 1). The deep learning-based algorithms was developed with a dataset of 32 mast cell tumor cases comprising 48,880 mitotic figure annotations. The three mitotic count approaches were conducted by 23 pathologists in 50 cases of canine mast cell tumors. A ground truth for the mitotic figures in the hotspot location of stage 2 and 3 was created by a pathologist assisted by immunohistochemistry for phosphohistone H3, which is a specific staining for mitotic figures.

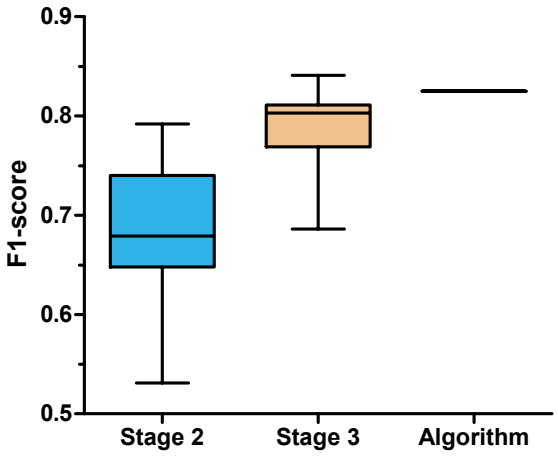

Figure 2. Comparison of the mitotic figure detection performance (F1-score) by 23 pathologists in the same tumor area without (stage 2) and with (stage 3) visualization of mitotic figure candidates detected by a deep learning-based algorithm. The performance of the algorithm without review by a pathologists exceeds most study participants. Data taken from [1]

The experiment found that pathologists had higher mitotic counts in stage 2 with the preselected tumor area than in stage 1 with area selection by each pathologists. Our work demonstrates that algorithms are superior in analysing the mitotic density in large tumor sections. The ability to identify and classify individual mitotic figures was compared between stage 2 (no further computer assistance) and stage 3 (visualization of mitotic figure candidates). The F1-score was higher in stage 3 for all 23 pathologists with an average increase of 10.7 percentage points (Fig. 2). Most notably the number of false negative mitotic figures was reduced by 37.4% proving the tremendous benefits of highlighting mitotic figure candidates in the images.

In conclusion, this study [1] demonstrates the benefits of computer-assisted mitotic counts for a routine diagnostic workflow. The reproducibility and accuracy of identifying hotspot tumor locations and detecting individual mitotic figures was markedly improved. Further benefits could be an improved diagnostic efficiency, which was not systematically evaluated in our study. Further studies are needed to improve robustness of mitotic figure algorithms to different sources of domain shift, particularly image from different scanners and tumor sections with suboptimal tissue quality, in order to allow a widespread application of the software solutions.

References

[1] Christof A Bertram, Marc Aubreville, Taryn A Donovan, Alexander Bartel, Frauke Wilm, Christian Marzahl, Charles-Antoine Assenmacher, Kathrin Becker, Mark Bennett, Sarah Corner, et al. Computer-assisted mitotic count using a deep learning–based algorithm improves interobserver reproducibility and accuracy. *Veterinary Pathology*, 59(2):211–226, 2022.