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Automated nuclear morphometry as a prognostic marker in canine cutaneous mast cell tumors

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Abstract

The prognosis of canine cutaneous mast cell tumors (ccMCT) is evaluated by various histologic parameters including the variability in size and shape of tumor nuclei (nuclear pleomorphism). Traditionally, nuclear pleomorphism is estimated by pathologists. However, a more precise measurement could be achieved by automated morphometry, which was investigated in this study. Eighty-six annotated images from ccMCT were used to develop a nuclear segmentation model, which yields an IoU of 0.79 on the test set. The prognostic value was determined on 96 ccMCT cases with known patient outcomes by two-fold cross-validation. Several features of nuclear size and shape were extracted from the segmentation mask and the ideal combination and thresholds of these features were determined by an XGBoost model independently for the two dataset splits. Tumor-related death was predicted on the left-out data set part with an AUC of 0.82 and 0.86, respectively. This study shows a high prognostic value of algorithmic nuclear morphometry in ccMCT. Future studies should compare the algorithm with estimates by pathologists.

1. Introduction

Canine cutaneous mast cell tumors (ccMCTs) are one of the most frequent skin tumors in dogs. These tumors are potentially malignant and histologic examination of the tumor cells is important to prognosticate patient outcome. Among other cellular criteria, the variability of nuclear size and shape (nuclear pleomorphism) has a well-known prognostic relevance for ccMCT and many other tumor types. Traditionally, nuclear pleomorphism is estimated by pathologists into vaguely defined categories. An alternative to the subjective assessment is the precise measurement of nuclei in digital images (nuclear morphometry). The manual measurement of nuclear size by pathologists has already been investigated in previous studies [2]; however, routine use is not to be expected since it is quite time-consuming (10 minutes per measurement were reported in this study). In comparison, fully-automated morphometry using deep learning-based algorithms would be a very practical solution, assuming that the nuclei can be accurately segmented. Deep learning methods for nuclear segmentation have been extensively researched previously [3].

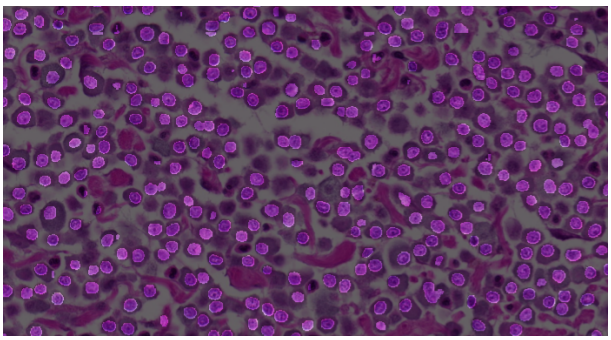

Figure 1. Algorithmic segmentation mask of tumor nuclei as an overlay on the histologic section of a ccMCT.

2. Material and Methods

2.1. Development of a segmentation model

Hematoxylin & Eosin-stained sections of 65 ccMCTs were digitized by a whole slide imaging scanner at $0.25 \frac{\mu m}{px}$. For development of the ground truth dataset, 86 representative regions of 0.1185 mm² were selected and the boundaries of 41,145 tumor nuclei were annotated using the software Slide Runner 2.0.0 [1]. The dataset was split for training (N = 62 cases), validation (N = 11 cases) and testing (N = 13 cases) of a UNet++ model [3]. Small objects and connected nuclei were removed.

2.2. Evaluation of prognostic relevance

For evaluation of the prognostic value, 96 additional cases of ccMCT with known tumor-specific survival of the patient were collected. The cases were split into two parts for two-fold cross-validation. Of each case, up to 5 regions (0.1185 mm²) were extracted and used for analysis.

An algorithm was developed that post-processes the derived nuclear segmentation mask (see above) by computing the eccentricity and solidity (nuclear shape) as well as area and diameter (nuclear size) for each nucleus. For each of these features, the standard deviation, variance, mean and median value were calculated. The ideal combination of theses features was determined with an XGBoost model for each of the two cross-validation folds.

3. Results

Evaluated on the segmentation validation data set, the model yielded an intersection over union (IoU) of 0.788 and a Dice score of 0.772 (see Fig. 1).

Tumor-related death was predictable on the validation sets with AUC values of 0.82 and 0.86, with the accuracy being 79.2% and 93.8%, respectively (Fig. 2 and Table 1).

Dataset split	AUC	Accuracy	Sensitivity	Specificity
1	0.82	79.2%	66.7%	81.0%
2	0.86	93.8%	71.4%	97.6%

Table 1. Prognostic value (tumor-related death) of the nuclear morphometry algorithm.

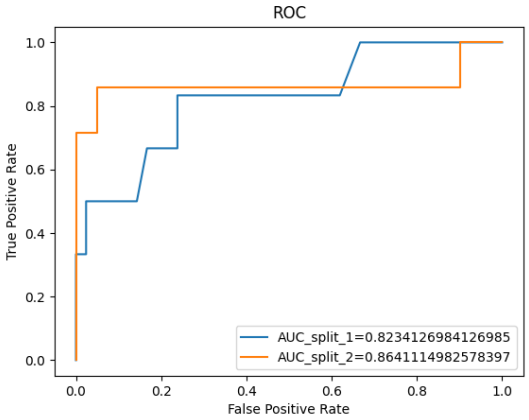

Figure 2. Receiver Operating Characteristic curves for tumor-related death of dogs with ccMCT based on algorithmic nuclear morphometry.

4. Discussion

Our results show that automated nuclear morphometry based on a deep learning model can provide an accurate prognosis in ccMCT. Due to its high time-efficiency and reproducibility, this methods seem promising for routine diagnostic use. Future studies should compare the prognostic value of automated nuclear morphometry with the pathologist's estimates and with other prognostic tests, such as the mitotic count, in large study populations. The influence of different image properties (such as between different whole slide image scanners), tumor types and image artifacts on algorithmic performance need to be evaluated.

References

[1] Marc Aubreville, Christof Bertram, Robert Klopfleisch, and Andreas Maier. SlideRunner. In *Bildverarbeitung für die Medizin 2018*, pages 309–314. Springer, 2018.

[2] Mafalda Casanova, Sandra Branco, Inês Berenguer Veiga, André Barros, and Pedro Faísca. Stereology in grading and prognosis of canine cutaneous mast cell tumors. *Veterinary Pathology*, 58(3):483–490, 2021.

[3] Zongwei Zhou, Md Mahfuzur Rahman Siddiquee, Nima Tajbakhsh, and Jianming Liang. Unet++: A nested u-net architecture for medical image segmentation. volume 11045 LNCS, 2018.