Is predicting metastatic pheochromocytoma and paraganglioma still effective without using methoxytyramine?

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Is predicting metastatic phaeochromocytoma and paraganglioma still effective without methoxytyramine?

We were intrigued by a recent Article from Christina Pamporaki and colleagues published in *The Lancet Digital Health* about using machine learning to predict the development of metastases in phaeochromocytoma and paraganglioma (PPGL).[1] PPGLs have a metastatic rate of up to 20%. Although all PPGLs have the potential to metastasise, no clinical or histopathological methods are currently available to predict metastatic disease.[1]

Pamporaki and colleagues introduced a model to predict metastasis using nine parameters. The top three most important features in the model were a previous history of PPGL, tumour location, and tumour volume. Including a *SDHB* mutation status did not significantly enhance the model's accuracy. Plasma methoxytyramine and metanephrine concentrations ranked as the fourth and fifth parameters, respectively, with similar scores.

Due to inherently low concentrations of methoxytyramine, standard assays are unsuitable for measurements. Liquid chromatography with tandem mass spectrometry[2] can be used to detect methoxytyramine with superior analytical sensitivity and selectivity, but it is not widely available in clinical laboratories. Therefore, measurements of methoxytyramine are not universally included in the screening of PPGL.[3] We questioned whether we could build an effective PPGL metastasis prediction model without methoxytyramine and create machine learning models from the published dataset.[1]

We used the PyCaret 3.0[4] methoxytyramine library in Python to create and compare models. After removing missing data rows, models were created using ten-fold cross-validation on 747 patients, with 522 in the training set and 225 in the test set. Assessing the model's robustness involved rigorous training on a subset of data followed by testing on an unseen hold-out dataset. The Categorical Boosting Classifier had the highest scores for the area under the receiver operating characteristic curve (AUC) of 0·946, with an accuracy of 0·900 on the training dataset. Other models and corresponding explanations are available in the appendix. The model without methoxytyramine's prediction on the test dataset had an accuracy of 0·893, AUC of 0·919, 72% sensitivity, and 95% specificity.

Pamporaki's best model achieved an accuracy of 0·907, AUC of 0·942, 83% sensitivity, and 92% specificity.[1] The performance of the model without methoxytyramine decreased slightly, but its AUC remained greater than 0·9 with an even higher specificity than the model with methoxytyramine proposed by Pamporaki and colleagues (95% *vs* 92%). Our model could therefore be universally applied for PPGL metastasis prediction.

Machine learning models are being increasingly used in health care and to support medical decisions. Therefore, we created a Web-App tool accessible for clinicians to obtain a probability risk rate to predict metastasis in patients with PPGL using eight parameters.

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1 Pamporaki C, Berends AMA, Filippatos A, et al. Prediction of metastatic pheochromocytoma and paraganglioma: a machine learning modelling study using data from a cross-sectional cohort. *Lancet Digit Health* 2023; **5:** e551–59.

2 Liu L, Xie W, Song Z, et al. Addition of 3-methoxytyramine or chromogranin A to plasma free metanephrines as the initial test for pheochromocytoma and paraganglioma: which is the best diagnostic strategy. *Clin Endocrinol (Oxf)* 2022; **96:** 132–38.

3 Rao D, Peitzsch M, Prejbisz A, et al. Plasma methoxytyramine: clinical utility with metanephrines for diagnosis of pheochromocytoma and paraganglioma. *Eur J Endocrinol* 2017; **177:** 103–13.

4 Ali M. PyCaret 3.0: an open source, low-code machine learning library in Python. https://pycaret.gitbook.io/docs/ (accessed Dec 7, 2023).

See **Online** for appendix

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