Using U-Nets for Tumour Bud detection in Colorectal Cancer pathology slides.

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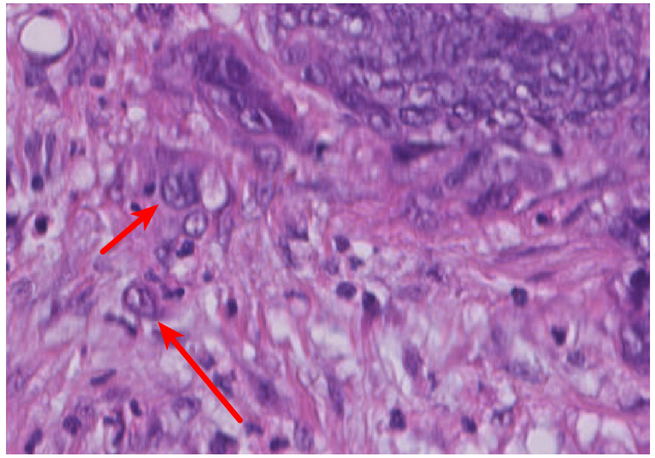
What is a Tumour Bud?

- A cluster of 4 or fewer tumour cells [1].
- A bud must be within 500 um of the leading edge of the invasive front of a solid tumour [1].
- Peritumoral / Intratumoural budding.



[1] Lugli A, Kirsch R, Ajioka Y, et al. Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016. Mod Pathol. 2017. doi:10.1038/modpathol.2017.46.

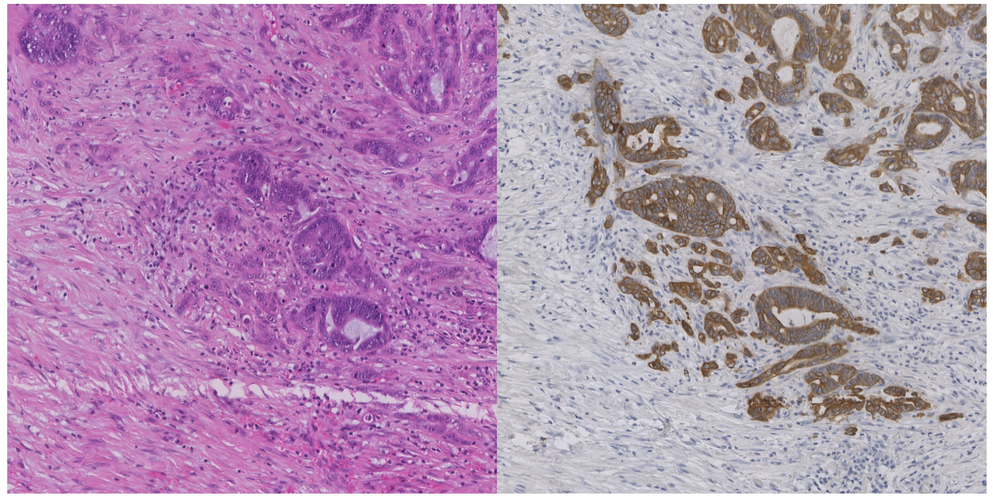
Why are Tumour Buds significant?

- Budding has been linked to patient outcome.
- TBs are an independent predictor of survival in stage II CRC patients [1].
- Correlation between intra-tumoural budding and lymph node metastasis [1].

[1] Lugli A, Kirsch R, Ajioka Y, et al. Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016. Mod Pathol. 2017. doi:10.1038/modpathol.2017.46.

Current methods for TB scoring and reporting

- 2016 ITBCC - Bud Scoring definition.
- Most often assessed in HE / AE1AE3 (Cytokeratin) stains.
- Manually counted by pathologists.
- Not yet included in UK standard diagnostic reporting [2].



H&E vs AE1AE3

[2] Loughrey M. B, Quirke, P, Shepherd N.A. Standards and datasets for reporting cancers: Dataset for histopathological reporting of colorectal cancer . https://www.rcpath.org/uploads/assets/c8b61ba0-ae3f-43f1-85ffd3ab9f17cfe6/G049-Dataset-for-histopathological-reporting-of-colorectal-cancer.pdf [accessed 22/05/2020].

Current methods for TB scoring and reporting

There is considerable interest in the phenomenon of tumour budding at the advancing margin of colorectal cancers, with accumulating evidence that it is of clinical value in predicting the risk of lymph node metastatic disease in stage pT1 colorectal cancers (section 10.5) and in identifying high risk stage II colorectal cancer potentially benefitting from adjuvant chemotherapy.[57–61] Following a recent international consensus meeting, a set of recommendations for assessing tumour budding in colorectal cancer has been issued.[62]
Should these result in improved reproducibility of assessment, sensitivity and specificity for the prediction of aggressive disease, the guideline will be amended, but assessment of tumour budding is not currently considered a core data item.

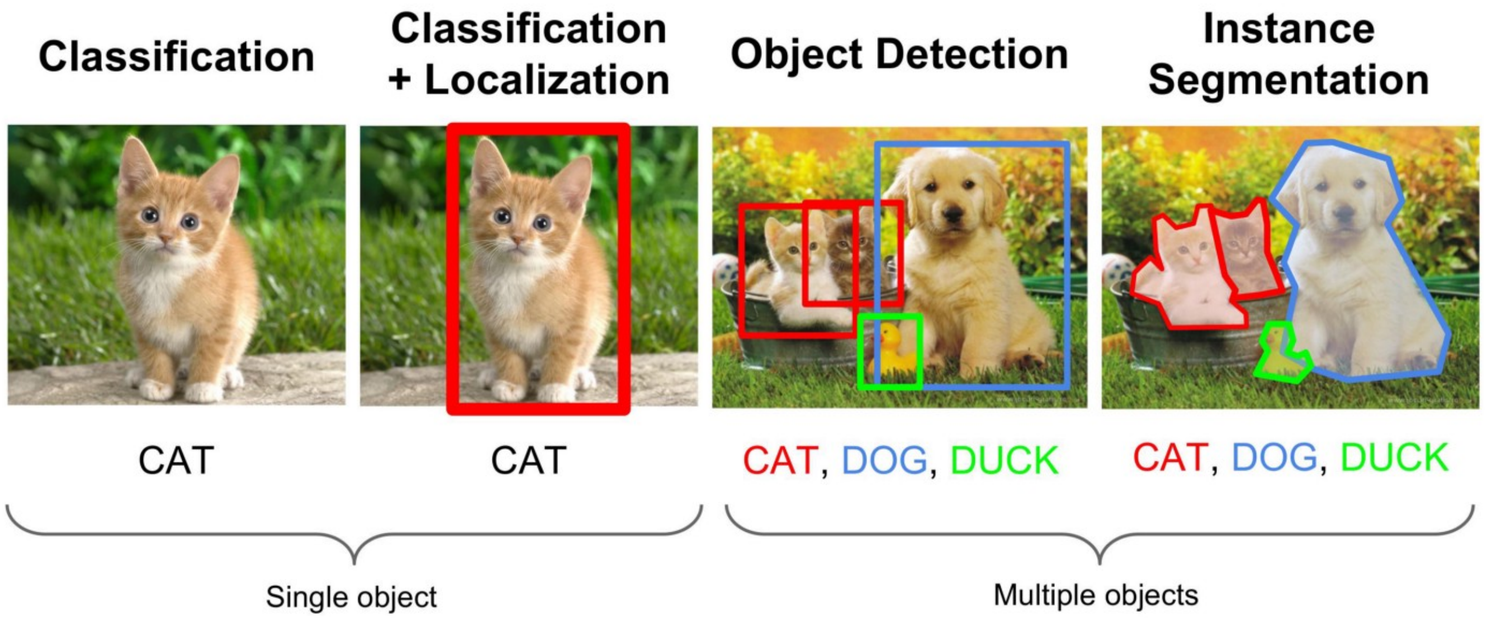
Current guidelines : Royal College of Pathologists. [2]

[2] Loughrey M. B, Quirke, P, Shepherd N.A. Standards and datasets for reporting cancers: Dataset for histopathological reporting of colorectal cancer . https://www.rcpath.org/uploads/assets/c8b61ba0-ae3f-43f1-85ffd3ab9f17cfe6/G049-Dataset-for-histopathological-reporting-of-colorectal-cancer.pdf (accessed 22/05/2020).

Why is automation necessary?

- To standardise the process of bud scoring and tackle the problem of inter-observer variability.
- To reduce resources required to have it be included in routine diagnostic reporting and therefore benefit patients.
- As a research tool to analyse existing datasets.

Methods for Object Detection



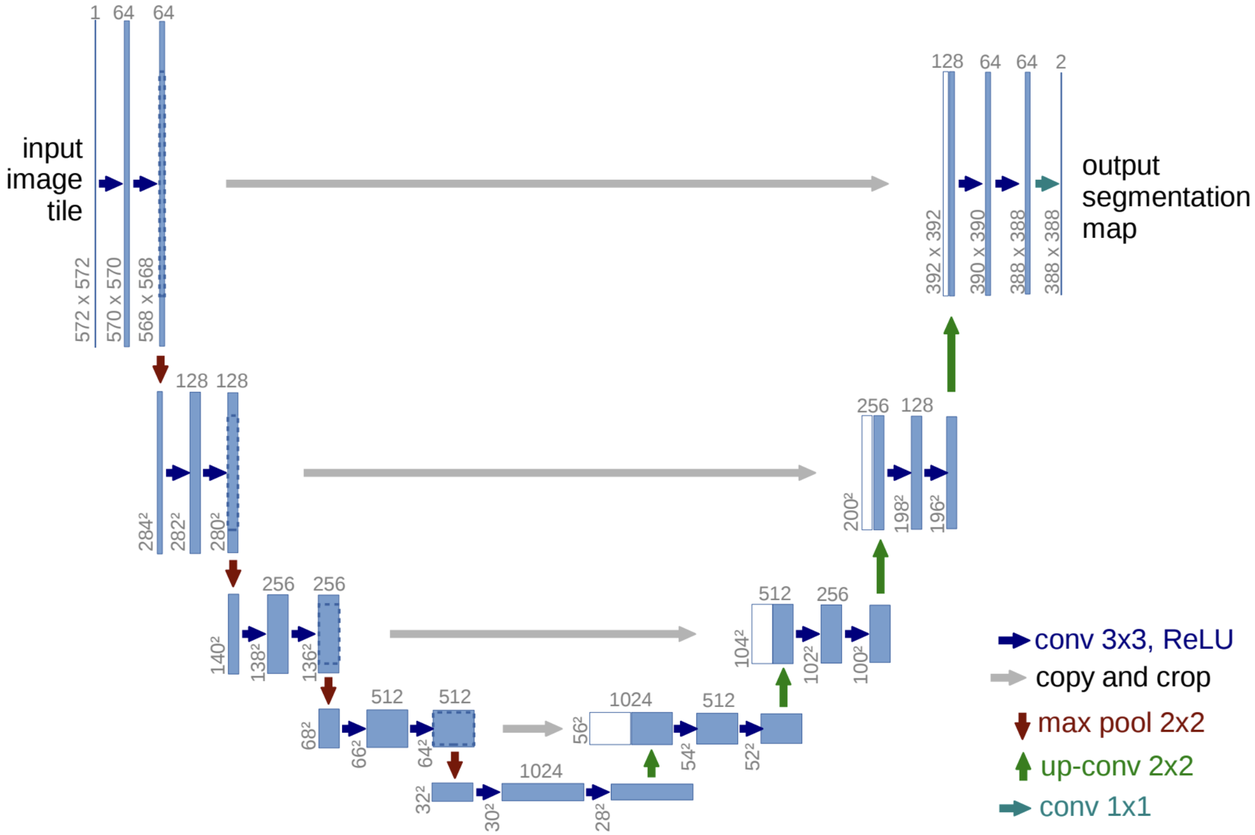
Object Detection methods [3]

[3] Ouaknine, A., 2020. Review Of Deep Learning Algorithms For Object Detection. [online] Medium. Available at: https://medium.com/zylapp/review-of-deep-learning-algorithms-for-object-detection-c1f3d437b852 [Accessed 22 May 2020].

The U-Net Model

- Encoder (often a CNN)
- Compressed vector representation of input image
- Decoder
- Skip Connections

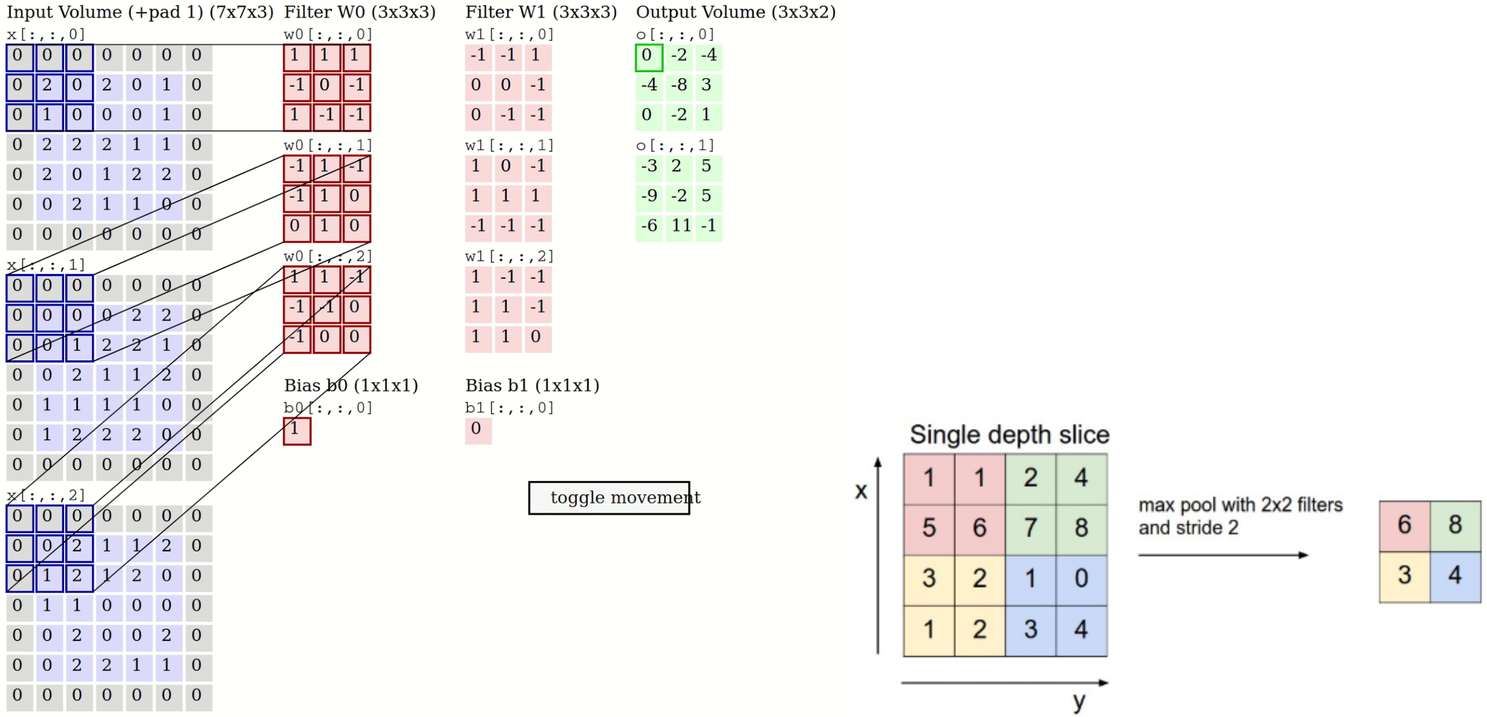
The U-Net Model



The original U-Net model [4]

[4] Ronneberger, O., Fischer, P. and Brox, T. (2015). U-Net: Convolutional Networks for Biomedical Image Segmentation. arXiv. [online] Available at: https://arxiv.org/abs/1505.04597.

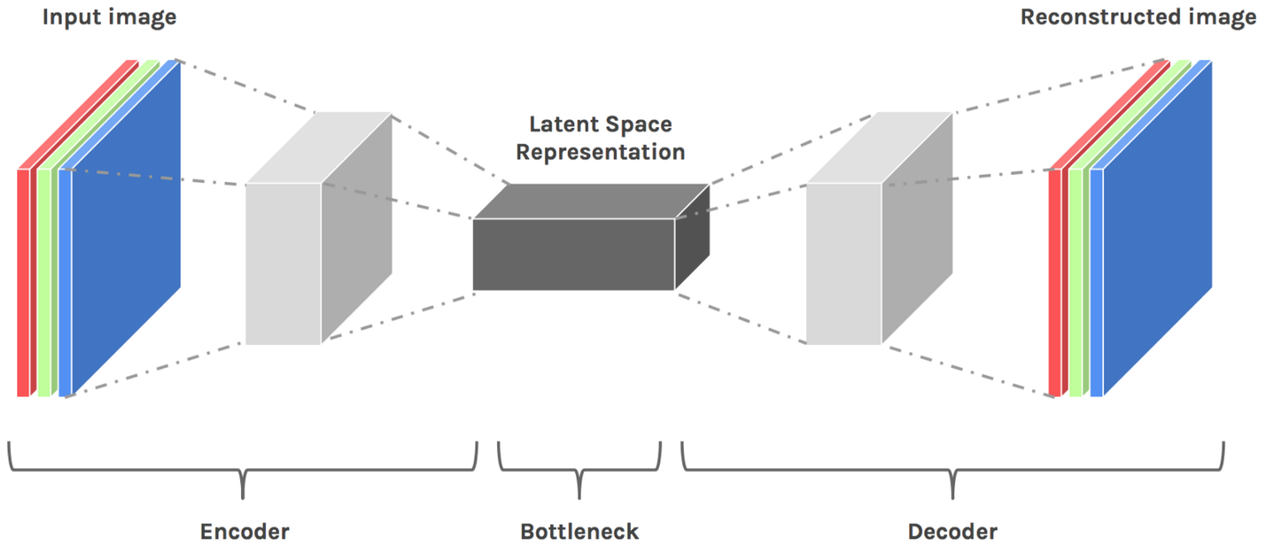
CNN Building Blocks



Stanford CS231n Convolutional Neural Networks [5]

[5] Stanford University (2012). CS231n Convolutional Neural Networks for Visual Recognition. [online] Available at: https://cs231n.github.io/convolutional-networks/ [Accessed 22 May 2020].

The U-Net model



Latent space visualization [6]

[6] Despois, J. (2017). Latent space visualization — Deep Learning bits 2. [online] Hackernoon.com. Available at: https://hackernoon.com/latent-space-visualization-deep-learning-bits-2-bd09a46920df [Accessed 22 May 2020].

Approach

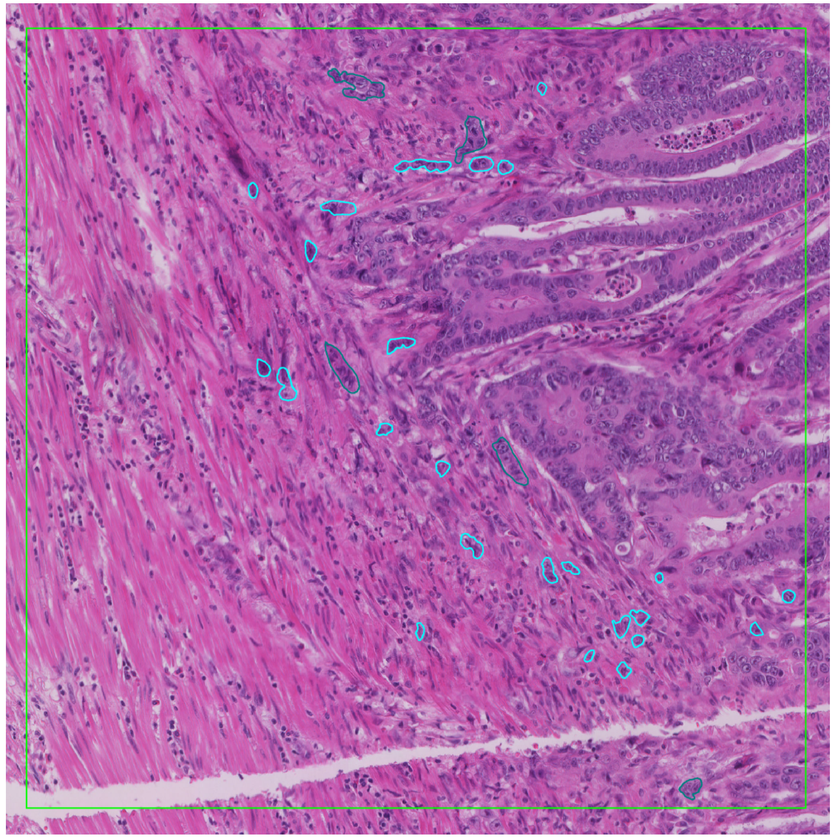
- Cytokeratin (AE1AE3) first as proof of concept. Then H&E.
- Manually annotate CRC slides using QuPath [7].
- Generate Ground Truth masks for image patches containing buds.
- Train a U-Net segmentation model based on Inception V3 / Mobile Net V2.

[7] Bankhead, P. et al. (2017). QuPath: Open source software for digital pathology image analysis. Scientific Reports. https://doi.org/10.1038/s41598-017-17204-5

Dataset

- 2000 H&E slides provided by the Glasgow Tissue Research Facility.
- 43 IHC / HE pairs
- 75k pixels^2 ~ 5.6 Gigapixels
- 1.1 TB

Ground Truth



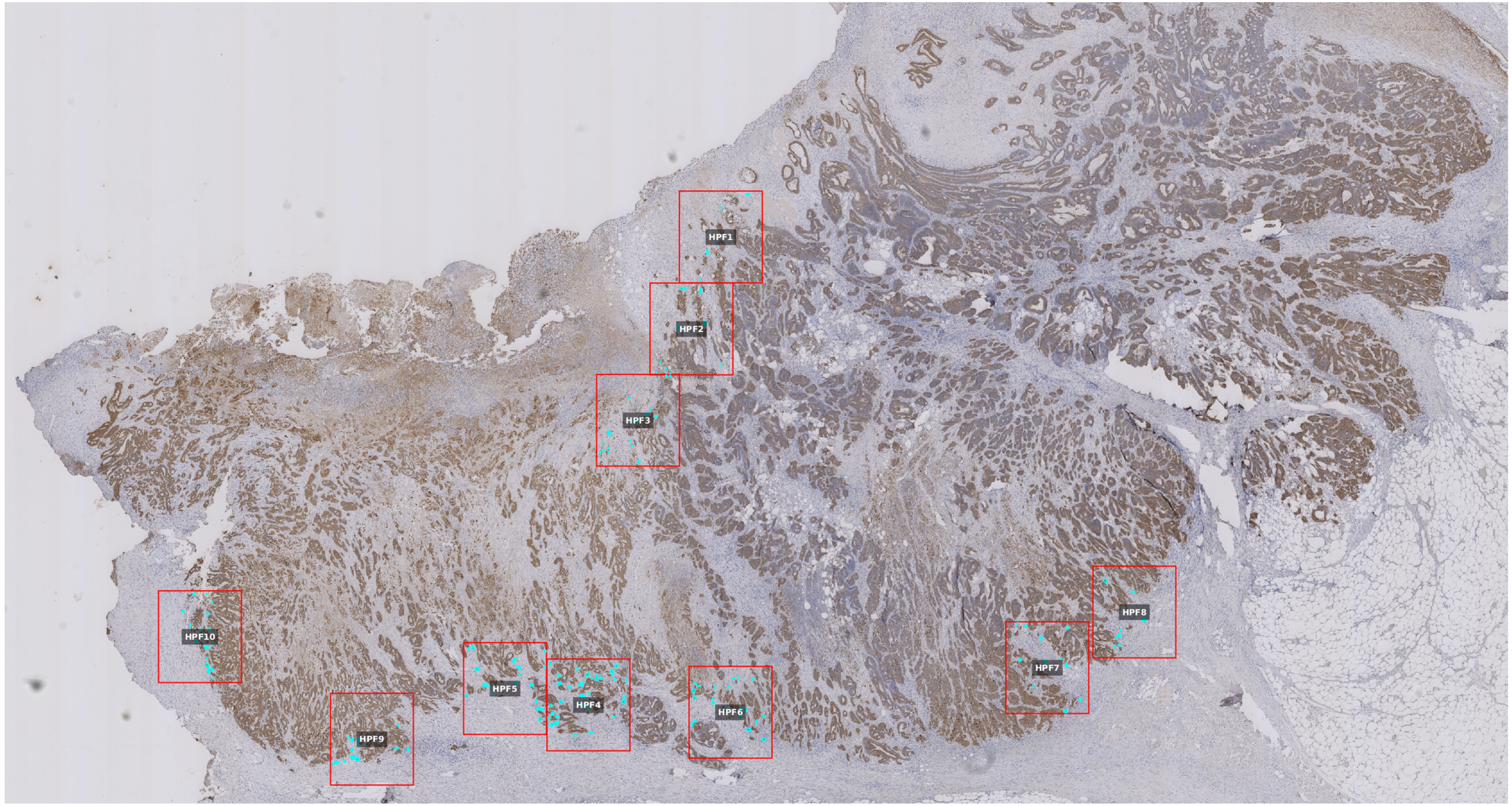
Manual Annotation in QuPath

Generated Masks

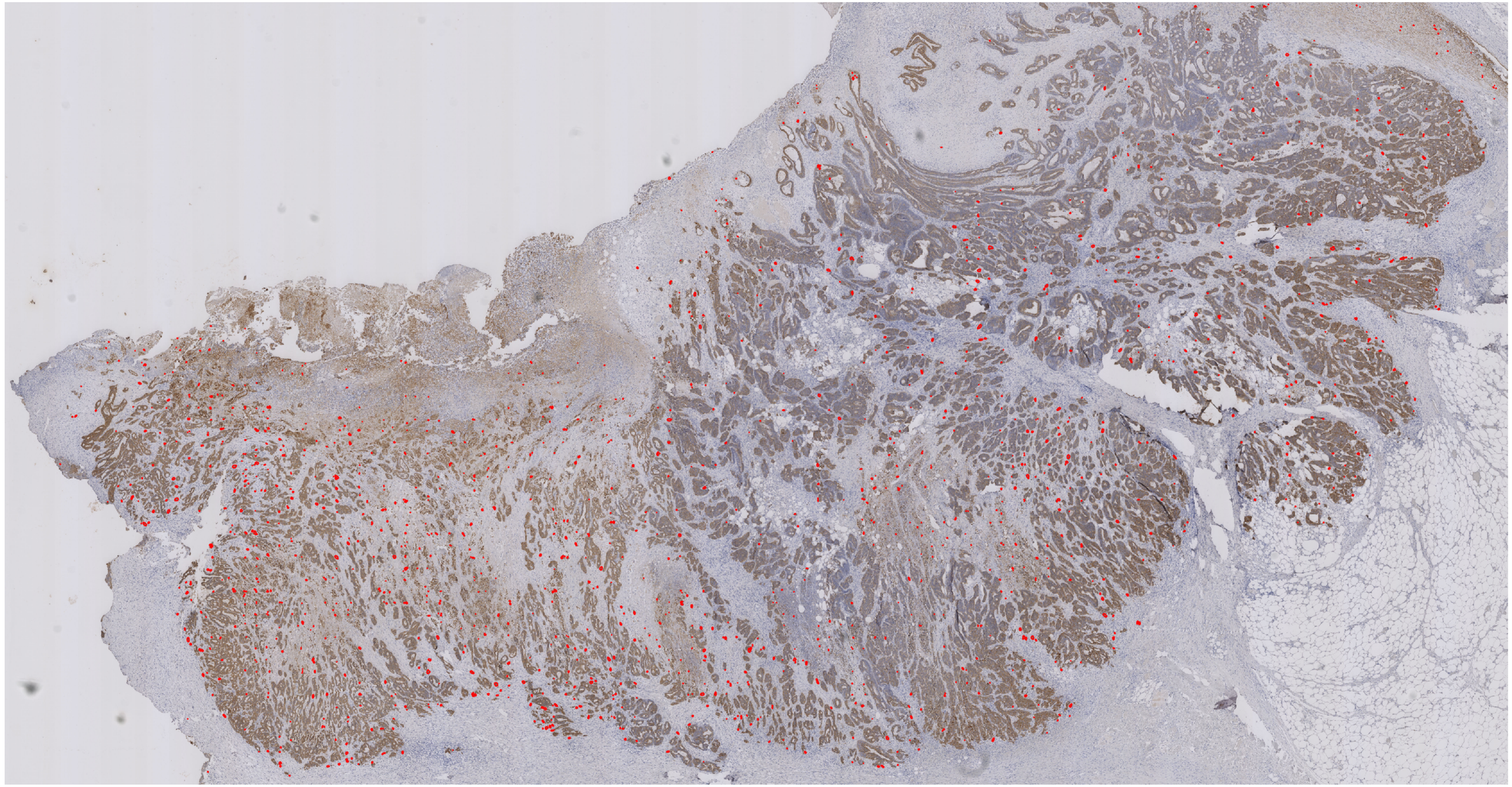
Training

- Data augmentation : rotation, translation, flipping and mirroring is carried out.
- U-Net model is built with Tensorflow v2 + Keras.
- Transfer learning used with Inception V3 and Mobile Net V2 pre-trained weights.
- Trained using early stopping, until training and validation loss start to diverge.
- 60 - 120 epochs.
- AE1AE3 model current best pixel accuracy 98.7%

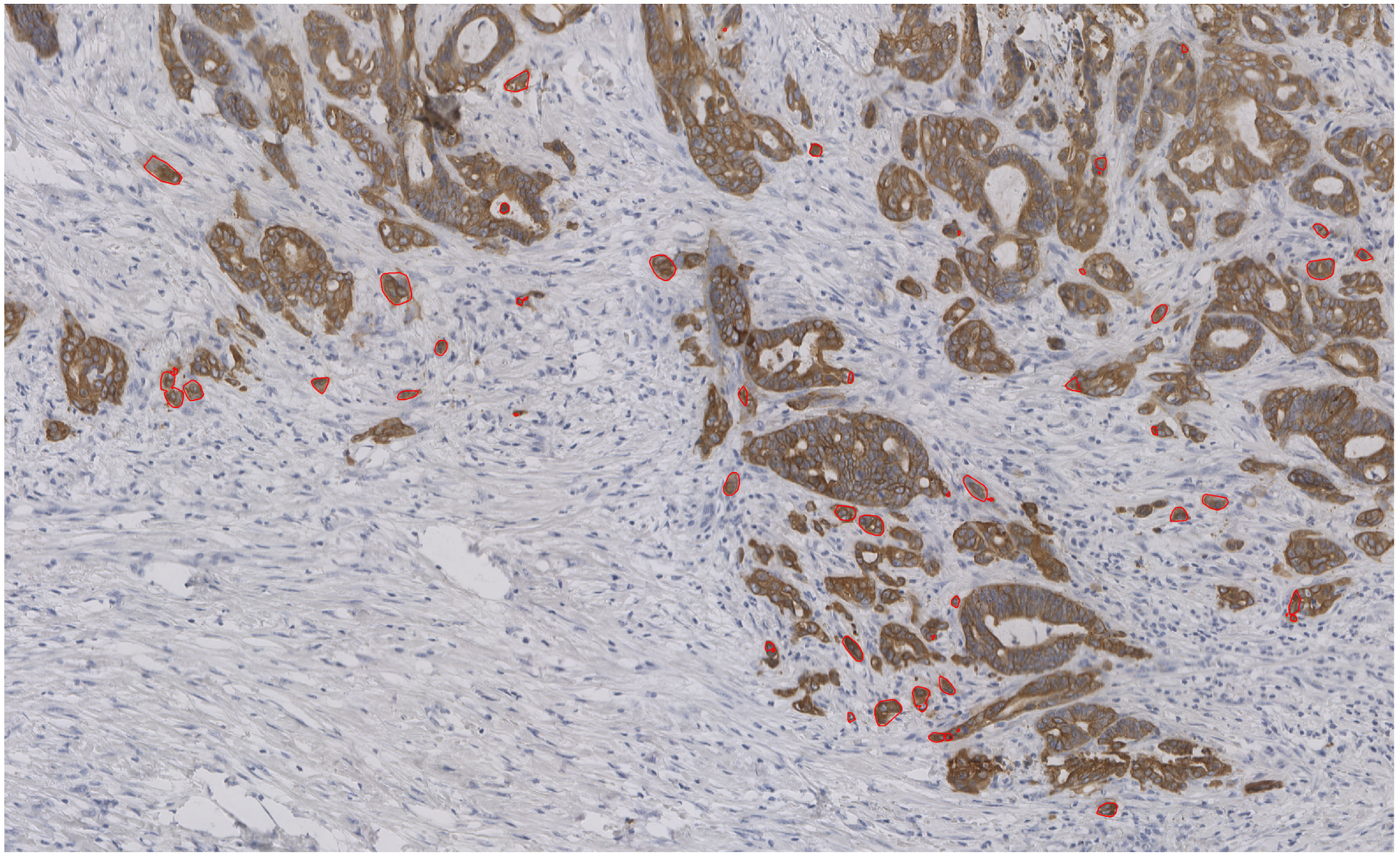
Example manual annotation



Example automated annotation



Example automated annotation



Future goals

- Extend model to H&E.
- Generate ITBCC buding grade scores from processed images.
- Investigate how absolute count and hotspot count correlates with patient outcome.

Thank You to

- Professor Robert Insall
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Thank you

Questions or Feedback?