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QUANTITATIVE PATHOLOGY

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Automated tumour budding quantification in T1 colorectal carcinoma HE slides: association to lymph node metastasis

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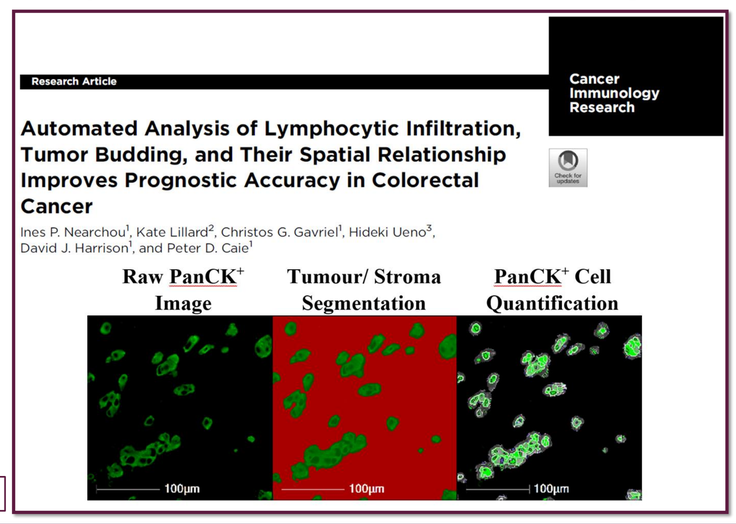
BACKGROUND

Tumour budding (BD) is a significant predictor of lymph node metastasis (LNM) in T1 colorectal cancer (CRC) and is increasingly considered in treatment decision making. However, despite the previous great efforts in developing a reproducible BD scoring method, inter-observer agreement remains sub-optimal. Previously, by using HALO® and HALO AI™ image analysis platform we have shown that BD can be quantified in an objective, reproducible and standardised way using immunofluorescence images of stage II CRC. The aim of this study was to automatically quantify BD in HE slides of T1 CRC and assess its association with LNM. A deep learning algorithm was applied on a Japanese cohort of 197 T1 CRC cases to automatically detect tumour buds using HALO and HALO AI image analysis platform. Various automated BD quantification methods were employed including recording the number and density of buds across the entire invasive front (IF) and at a hotspot area. Here, we demonstrate that the use of deep learning algorithms could prove to be promising for the objective, standardised and reproducible BD quantification in HE slides as well as for assisting pathologists in making treatment recommendations.



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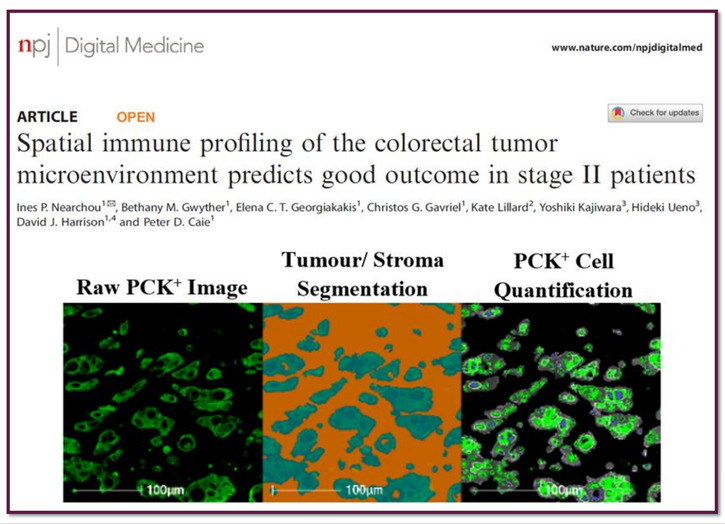

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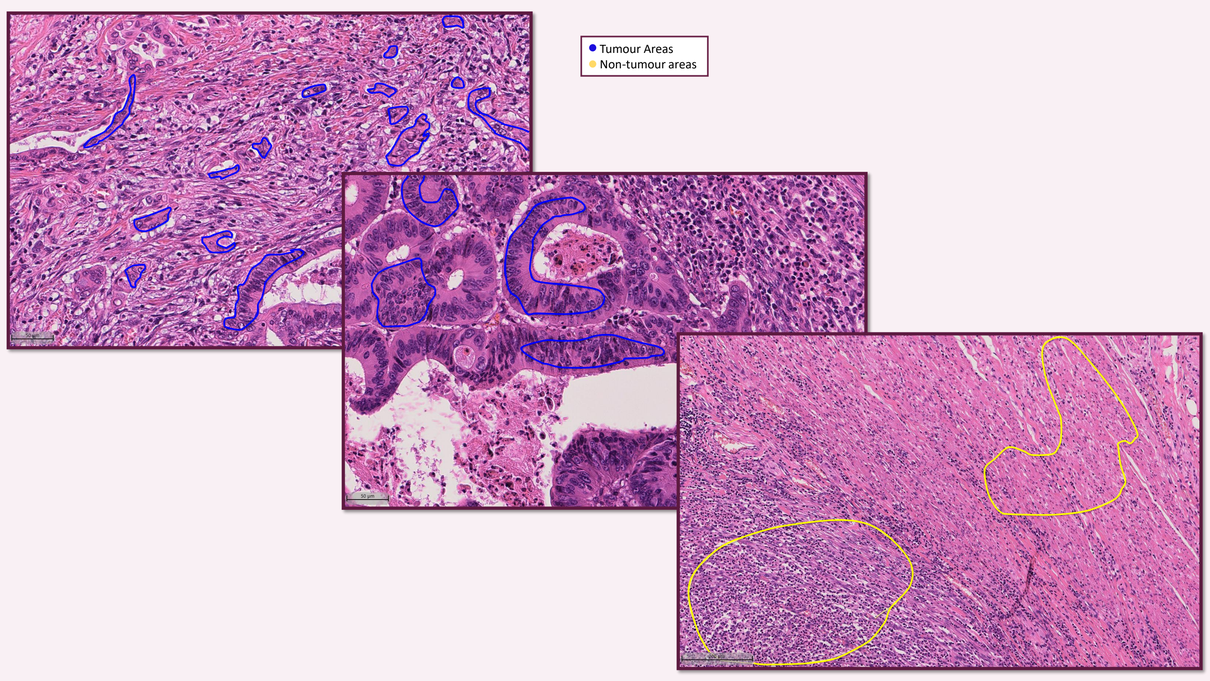
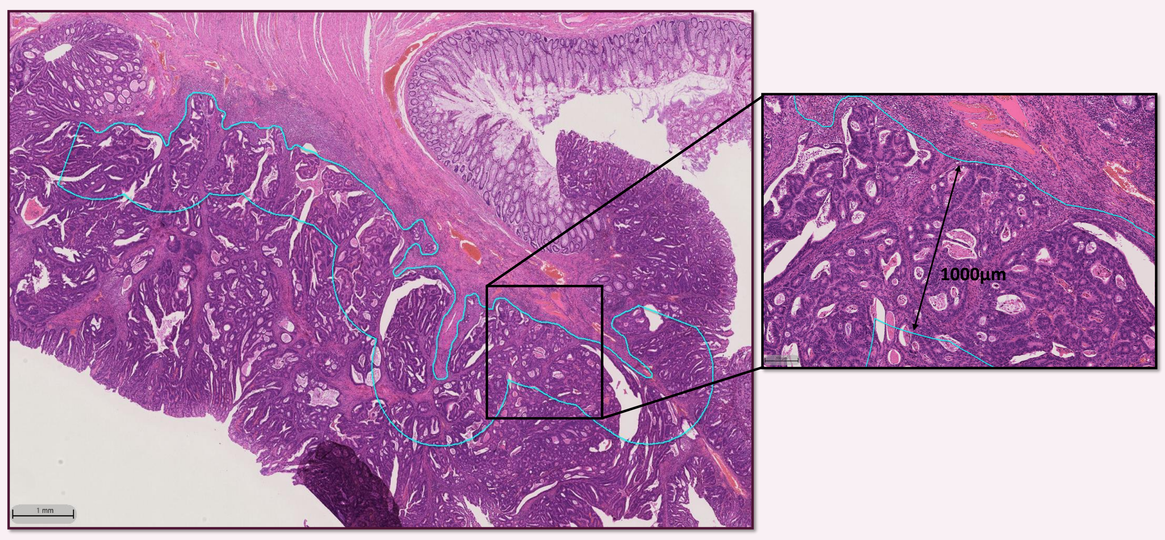
HALO® and HALO AI™ IMAGE ANALYSIS WORKFLOW

1 CLASSIFIER TRAINING



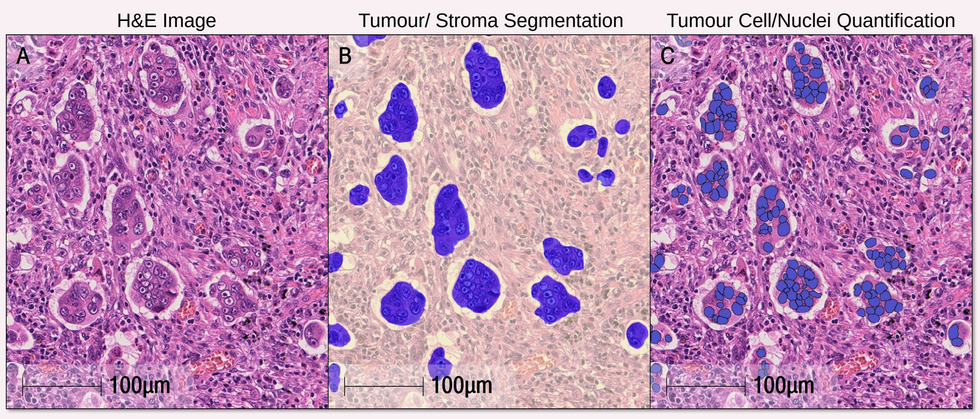
Tumour and non-tumour annotations were used to train a binary DenseNet v2 classifier (HALO-AI) to segment tumour from any other tissue type present within the slide.

2 TUMOUR BUDDING ASSESSMENT REGION



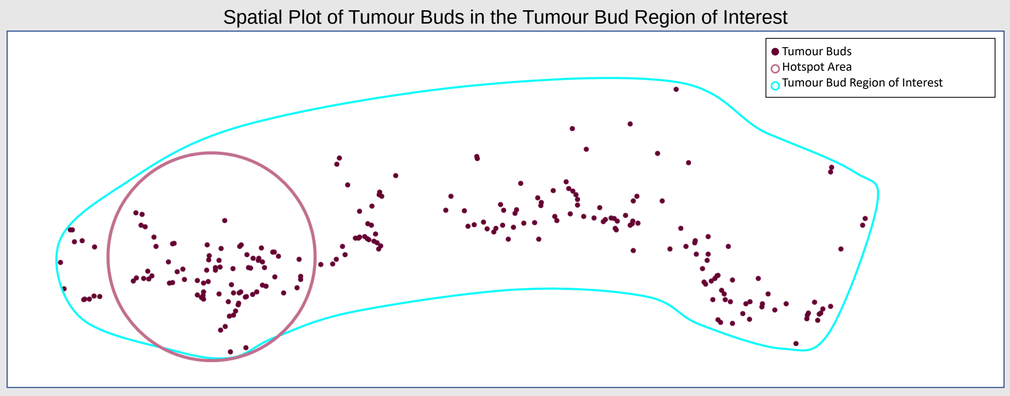
The invasive tumour front (tumour-host interface) was manually annotated within the HALO software. An invasive tumour front border of 1000µm inward from the invasive tumour front was automatically generated and was used as the tumour bud region of interest.

3 AUTOMATED TUMOUR BUDDING DETECTION



By applying the trained DenseNet v2 classifier on the images, all tumour and non-tumour areas were automatically segmented. (A) Raw H&E image, (B) Automatic tumour/stroma segmentation, tumour in blue and non-tumour areas in yellow, (C) Nuclear detection and quantification within the automatically segmented tumour regions.

4 HOTSPOT ANALYSIS



Using the X,Y location of each tumour bud detected as a centroid, the tumour bud region of interest was divided into multiple circular fields of view with an area of 0.785mm^2. The number of tumour buds present within each field of view was collected and the maximum number of tumour buds within the densest field of view (hotspot) per case was recorded.

RESULTS

Univariate logistic regression was performed to assess the predictive value of each parameter of interest for LN metastasis. **All automated BD parameters were found to be significantly associated with LNM** using univariate logistic regression. Multivariate logistic regression was then performed to compare the predictive power for LN metastasis of these parameters to other gold-standard features assessed currently in the clinic such as tumour grade, lymphovascular invasion and submucosal invasion depth. The Akaike information criterion (AIC) using a multivariate logistic regression model was used to identify the combinatorial model with the highest predictive value for LNM.
The model consisting of BD density assessed on all slides containing any tumour front together with tumour grade, submucosal invasion depth and lymphovascular invasion was found to have the lowest AIC and therefore have the highest predictive value for LNM.

Parameters	Univariate Logistic Regression		*P*
	Odds Ratio	95% Confidence Interval	
BD number assessed on all slides	7.848	2.299-26.792	0.001
BD density assessed on all slides	12	1.529-94.186	0.001
BD number assessed on a single slide	5.821	1.548-21.892	0.004
BD density assessed on a single slide	4.632	1.234-17.392	0.013
BD number in hotspot	3.407	0.908-12.780	0.049

Univariate logistic regression results for all automated BD parameters.

Parameters	LN metastasis presence %	Multivariate Logistic Regression *P*
BD density assessed on all slides		**0.0003**
Low	1.08	
High	11.54	
Tumour Grade		**0.0004**
G1/2	6.1	
G3	100	
Submucosal Invasion Depth		**0.0436**
T1a	0	
T1b	8.3	
Lymphovascular Invasion		0.2854
No	2.3	
Yes	9.9	

Multivariate logistic regression comparing the most significant automated BD parameters to the currently used gold-standard features.

CONCLUSIONS

The automatic detection and quantification of BD on H&E images of T1 cases using a commercially available AI network (DenseNet v2) is feasible.
The use of deep learning algorithms shows promise for developing a standardised and reproducible BD quantification method in HE slides as well as for assisting pathologists in making treatment recommendations.
BD density assessed on all slides containing any tumour invasive front outweighs the predictive value of BD number in a hotspot region for LNM.

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