Deep learning enables fully automated mitotic density assessment in breast cancer histopathology

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No disclosures
Prognostic value of grading for breast cancer using deep learning techniques
Breast cancer grading

**Level of tubule formation**
- Score 1: > 75%
- Score 2: 10-75%
- Score 3: <10%

**Nuclear pleomorphism**
- Score 1: comparable to normal epithelium
- Score 2: enlarged, vesicular, small nucleoli
- Score 3: pleomorphic, vesicular, large nucleoli

**Mitotic activity**
- Score 1: 0 through 7 mitoses per 2 mm²
- Score 2: 8 through 12 mitoses per 2 mm²
- Score 3: 13 or more mitoses per 2 mm²

But....
Tellez et al. *Whole-Slide Mitosis Detection in H&E Breast Histology Using PHH3 as a Reference to Train Distilled Stain-Invariant Convolutional Networks.* Transactions on Medical Imaging
90 breast cancer cases from routine diagnostics
mitotic activity score 1 / 2 / 3 equally balanced in set
Algorithm

Observer 1

Observer 2

Balkenhol et al. *Deep learning assisted mitotic counting for breast cancer*. Laboratory Investigation, 2019

False negative detection of algorithm

Algorithm

False positive detection of algorithm

Balkenhol et al. *Deep learning assisted mitotic counting for breast cancer*. Laboratory Investigation, 2019
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<th>Comparison</th>
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<th>ICC</th>
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<td>0.808</td>
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<tr>
<td>Obs2-glass vs Obs2-hotspot</td>
<td>0.684</td>
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<td>Obs1-glass vs CNN</td>
<td>0.604</td>
<td>0.828</td>
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<tr>
<td>Obs2-glass vs CNN</td>
<td>0.609</td>
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We conclude that

- manual counting of mitotic figures in WSI is feasible
- manual mitosis counting is not affected by assessment modality (glass slides, WSI)
- using a predefined hotspot area considerably improves reproducibility
- fully automated assessment of mitotic score appears to be feasible without introducing additional bias or variability
More mitoses $\rightarrow$ worse prognosis

For all breast cancer patients?

Bult, P et al. *In primary breast cancer the mitotic activity yields similar prognostic information as the histological grade: a study with long-term follow-up*. Breast Cancer Res Treat. 122, 77-86 (2010)
Triple negative breast cancer (TNBC) prognosis

Distant recurrence

Survival after recurrence

Triple negative breast cancer cohort (n = 597)

Eastern Netherlands 2006 - 2014, stage I-III, non neo-adjuvant treated

• **Manual assessment mitotic count (on half of cohort)**

  2 pathologists & 1 pathologist in training, conventional mitotic counting on glass slides

• **Automatic assessment mitotic count (on total cohort)**

  Hotspot as 2 mm$^2$ circle

Average across 3 human observers: 1 mitosis per 2 mm$^2$

Deep learning algorithm: 5 mitoses per 2 mm$^2$
Average across 3 human observers: 187 mitosis per 2 mm²
Deep learning algorithm: 269 mitoses per 2 mm²
c-statistic values:

Relapse free survival: 0.739
Overall survival: 0.755
This is the first study

• in which the prognostic value of the mitotic count is evaluated for TNBC
• in which a deep learning network is used to assess the mitotic count

Our study suggests that

• the absolute number of mitotic count is not a prognostic factor for TNBC
• and that using a deep learning algorithm for mitosis counting is feasible

However, this should be validated in larger, independent cohorts.