Deep Learning-Based, Fully Automated Analysis of Whole Slide Images Can Detect Invasive Breast Carcinoma and Count Ki-67 Easily and Precisely

Akira I. Hida [1], Jeppe Thagaard [2], Takahiro Watanabe [3], Thomas Ramsing [2], Agnete Overgaard [2], Yumi Oshiro [4] and Takuya Moriya [5]
[1] Matsuyama Shimin Hospital, [2] Visiopharm A/S, [3] Hyogo College of Medicine, [4] Matsuyama Red Cross Hospital, [5] Kawasaki Medical School

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Abstract #888

Background:

- The basic treatment of hormone-receptor(HR) positive breast carcinoma(BC) is anti-hormonal therapy.
- Recently, **cyclin-dependent kinases 4/6 inhibitor** called abemaciclib, has been approved for **high risk** patients after surgery, together with **Ki-67** IHC MIB-1 pharmDx(Dako Omnis) for the patient selection.
- However, there remains concerns about reproducibility, and a development of automated image analysis is desired.

Conclusion:

- Here, we have created a fully automated software to analyze Ki-67, which includes **DL-based algorithm** to detect invasive BC nest and count a large amount of cells quickly.
- It has probed to have **concordant result** with experienced breast pathologists, although the prognostic value needs to be confirmed.
- As the software tend to have lower value than pathologists, we have to pay attention to **the cut-off value**.
- However, fully automated analysis can be performed by a technician or an engineer, and allow pathologists to focus on another task.
- This objective method would help clinicians and patients to select the optimal treatment based on the tumor biology.

Design:

- Random **100 cases** were collected from a previous study [Histopathology. 2020;77(3):471-480]. (**Figure 1**)

Figure 1

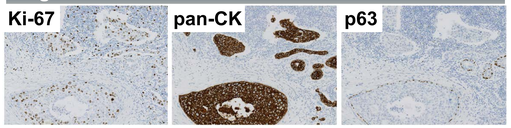
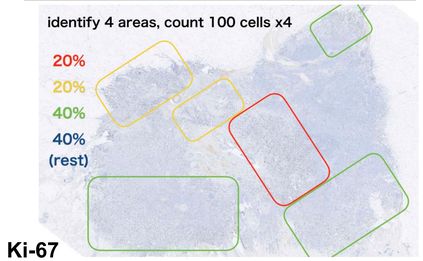


Figure 1. Three serial sections were aligned by virtual triple staining method by Visiopharm Oncotopix software.

- Resected specimen of primary breast invasive carcinoma (HR positive and HER2 negative) had been stained with **Ki-67**(MIB-1; Dako, Autostainer Link 48; Agilent), and digitized by NanoZoomer-XR (Hamamatsu Photonics K.K.).
- Two board-certified pathologists evaluated Ki-67 following the recommendations from the International Working Group.(JNCI. 2011;103(22):1656-64. **Figure 2**)

Figure 2



- We also performed original scoring using a **deep learning(DL)-based Ki-67**(Breast, AI APP, research use only; Visiopharm) **in a fully automated approach** with no manual input or review.
- We compared the continuous output score with Spearman's correlation analysis, and calculated agreement with the clinically relevant cut-off of 20% for treatment with adjuvant abemaciclib.

Results:

- Median/mean value of each pathologist and automated analysis were 11.7/15.1(AIH, Path 1), 8.4/12.0(TW, Path 2) and 6.5/9.4 respectively. Every pair showed **statistically positive correlations** of Ki-67(Figure 3), and the highest value was yielded by Path 1 and the software(AI-APP).
- Time needed for pathologist to evaluate 100 cases ranged from 328(Path 2) to 562 minutes(Path 1). The software counted 385,985 cells on average within the full-face slides. When we set the threshold of Ki-67 at 20% by pathologist 1 and calculated 13% by software, the sensitivity and specificity of our new algorithm is **88.9%** and **97.6%** respectively.

Figure 3

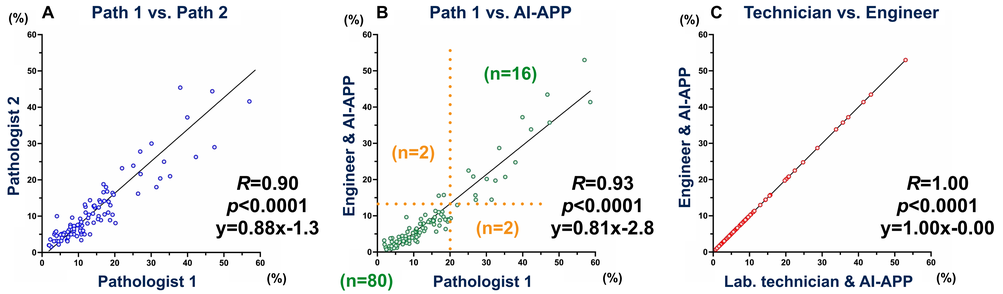


Figure 3. Each pair showed positive correlations, and AI-APP tend to yield lower value than pathologists(A-B). The threshold of 20% by Pathologist 1 was equivalent to 13.3% by AI-APP, which are indicated as orange dot line, and only four cases had a discordant result(B). When the same AI-APP was used by non-pathologists, the correlation was perfect(C).

Figure 4 & Table

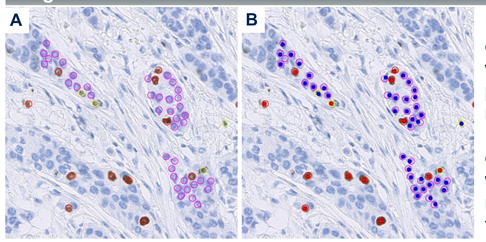


Figure 4. About 100 cells in each cases were annotated as positive/weak positive/ negative by the Pathologist 1(A: red circle; positive, yellow; weak positive, pink; negative), which were then compared with the result by the AI-APP(B: red dots; positive, blue dots; negative).

Out of total 7301 positive cells, the APP misses 330 cells (4.5% [2.9% among all 11187 cells]), and every single 3886 negative cells were judged as negative by the APP(Table).

	by APP		
by Path 1	negative	positive	Total
Negative	3886	0	3886
weak +	316	1544	1860
Positive	14	5427	5441
Total	4216	6971	11187

Figure 5

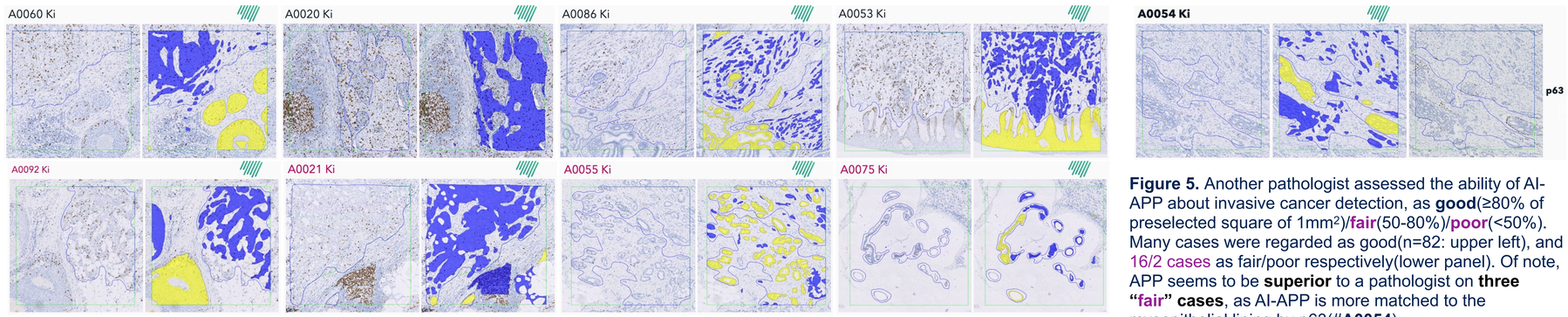


Figure 5. Another pathologist assessed the ability of AI-APP about invasive cancer detection, as **good**(≥80% of preselected square of 1mm²)/**fair**(50-80%)/**poor**(<50%). Many cases were regarded as good(n=82: upper left), and 16/2 cases as fair/poor respectively(lower panel). Of note, APP seems to be **superior** to a pathologist on **three "fair" cases**, as AI-APP is more matched to the myoepithelial lining by p63(#**A0054**).

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E-mail; ahida@matsuyama-shimin-hsp.or.jp / jth@visiopharm.com