Machine Learning Algorithms in Histology and Radiology for Cancer Drug Discovery and Development

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Disclosures

I am an employee of LPIXEL and own stock options of LPIXEL

Lung Cancer: significant unmet medical need

- About 14% of all new cancers are lung cancers, but 24% of all cancer deaths.
- About 234,030 new cases of lung cancer (121,680 in men and 112,350 in women) About 154,050 deaths from lung cancer (83,550 in men and 70,500 in women)
- One in 16 people in the US will be diagnosed with lung cancer in their lifetime.
- 10% to 15% of new lung cancer cases are among never-smokers.
- Only 19% of all people diagnosed with lung cancer survive 5 years or more, BUT if it's caught before it spreads, the chance for 5-year survival improves dramatically.
- About 80% to 85% of lung cancers are NSCLC. The main subtypes of NSCLC are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.

There is a significant need for improved diagnosis and drug therapies

Radiological detection of lung nodules

- X-ray
  - Chest x-ray usually is the first test that is done to look at abnormalities in the lung.
- CT
  - The American Cancer Society (ACS) has a lung cancer screening guideline for people with a higher risk of getting lung cancer
  - The ACS recommends yearly lung cancer screening with LDCT scans for people who are 55 to 74 years old in high risk category but, are in fairly good health.
- Lung-Rads score
  - Lung-RADS® is a tool designed to standardize lung cancer screening CT reporting and management recommendations, reduce confusion in lung cancer screening CT interpretations, and facilitate outcome monitoring.
- PET/CT
  - PET is used to distinguish between benign (noncancerous) and malignant (cancerous) masses. PET can also be used for staging.

Challenges with radiology detections

- Interpretation of CR has problems with overlooking.
- The reported error rates for missed lung cancer on CR are 20%-50% (Diagn Interv Radiol 2017;23:118-126; Am J Roentgenol2007; 188:1173-1178)
- In CT studies, reported sensitivities range from 30–97% with false positive counts of 0.6 – 2.1 per patient (G. Rubin, J Thorac Imaging. 2015 March ; 30(2): 130–138.)
- LDCT and subsequent Lung-Rads classification has high FP rates
  - Classified as Grade 4A : Solid nodules ≥ 8 to < 15 mm at baseline OR new 6 to < 8 mm Additional diagnostic testing and/or tissue sampling is recommended. Likelihood of finding cancer: 5-15%
  - Classified as Grade 4 B : solid nodule ≥ 15 mm OR new ≥ 8 mm. Additional diagnostic and tissue sampling is ordered. Likelihood of finding cancer: >15%

Deep learning techniques can potentially overcome performances of conventional reads. (Jpn J Radiol 2019; 37:15-33)

A deep convolutional neural network based software in a multicenter study involving 12 radiologists improved sensitivity by an average of 5.2%, 65.1 to 70.3 (Y. Sim, Radiol Nov12)

Drug therapy challenges in NSCLC

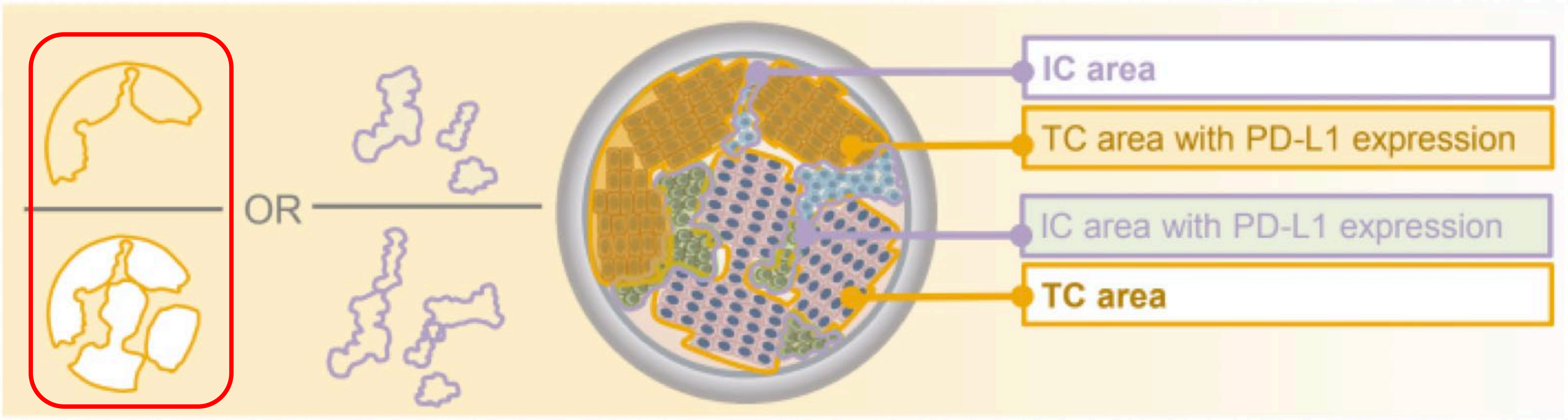
- Significant progress has been made in targeted and immunotherapies to treat NSCLC
- Therapies targeting angiogenesis, Epidermal growth factor receptor (EGFR), Anaplastic lymphoma kinase (ALK), ROS1 gene and NTRK gene fusion are available
- Immune checkpoint inhibitors blocking PD-1/PD-L1 pathways such as nivolumab (Opdivo), pemrolizumab (Keytruda), durvalumab (Imfinzi) and atezolimumab (Tecentriq) are standard treatment option for advanced NSCLC.
- A response rate of 14-23% is observed in unselected population with immunotherapies
- Response rate of 16-48% in patients in high PD-1 expression

PD-1/PD-L1 is an innovative therapy; however, it fails to work in many patients

Deep learning tool for accurate PD-L1 expression

- PD-L1 expression in the tumor microenvironment is one of the efficacy predictors of cancer treatment using immune checkpoint inhibitors.
- Tumor proportion score (the ratio of PD-L1 expressed area within the total tumor area) is often used as a measure to distinguish low and high PD-L1 expression
- However, due to difficulty in quantitative measurement of microscopic images, the proportion score is prone to be evaluated subjectively

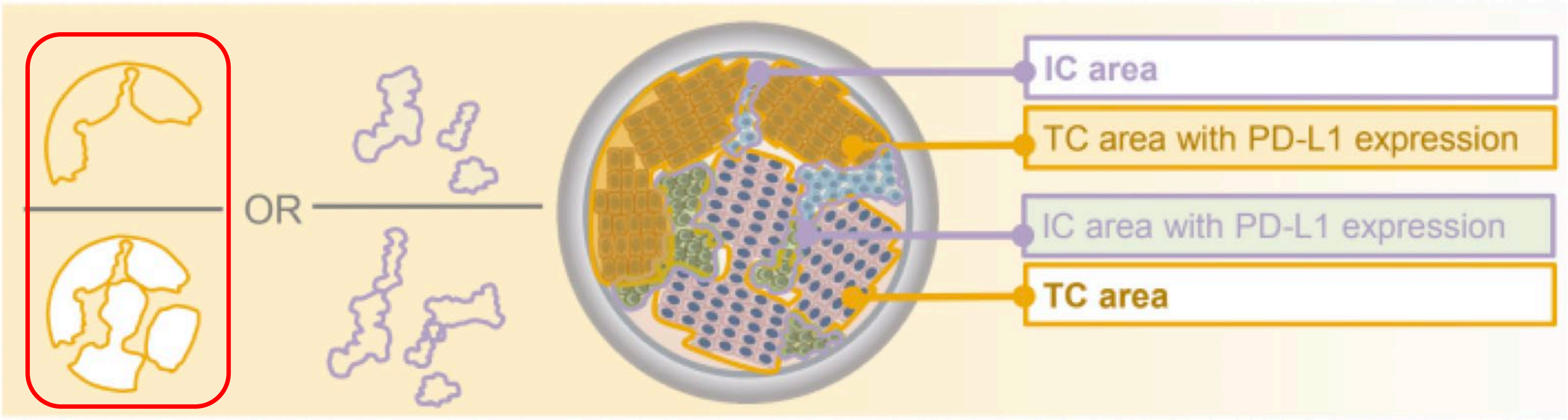
Ilustration of ”tumor proportion score”: Tumor area with PD-L1 expression / Total tumor area



Objective

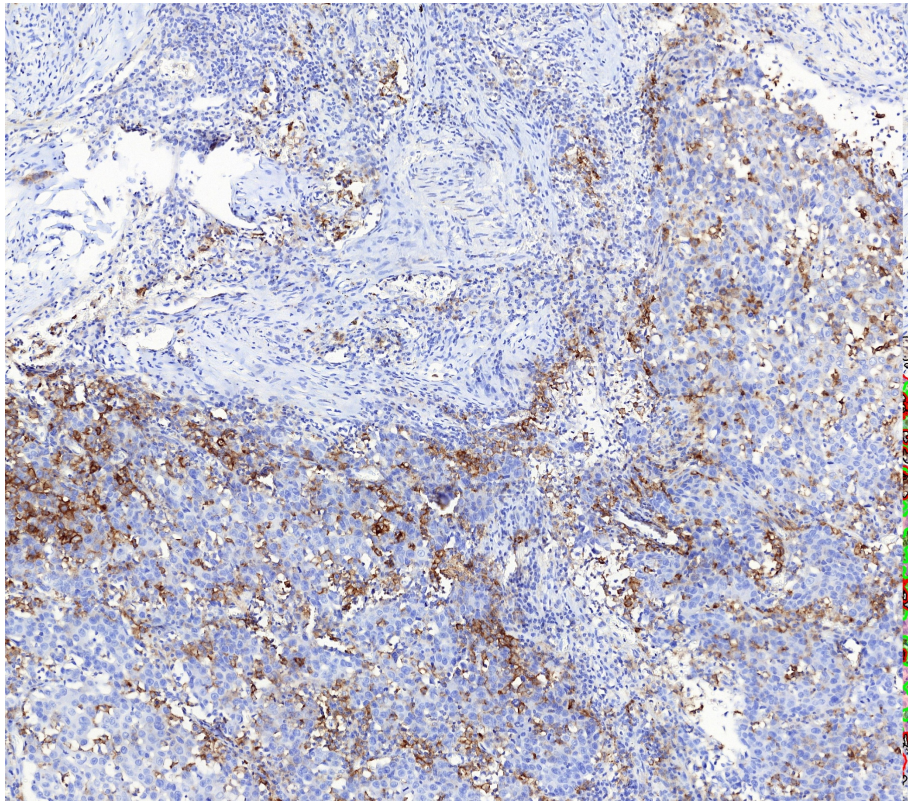
- Our objective is to create an image analysis system to automatically recognize the “total tumor area” and “tumor area with PD-L1 expression” in order to derive a quantitatively measured “tumor proportion score”

Ilustration of ”tumor proportion score”: Tumor area with PD-L1 expression / Total tumor area



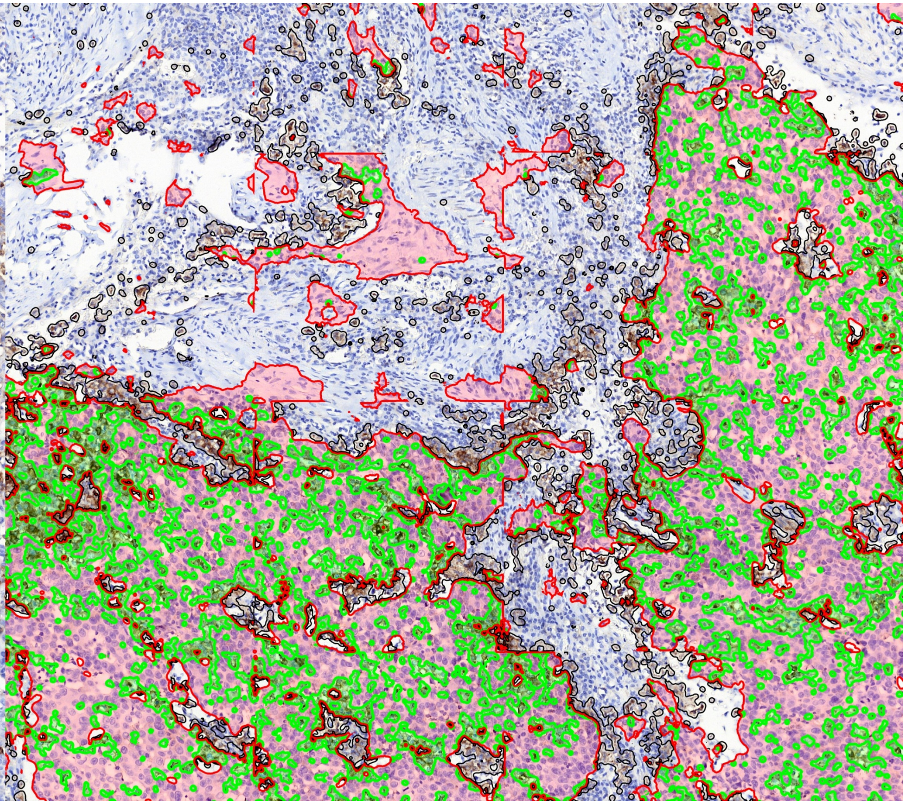
Segmentation result

Original image



~3600px

Segmentation result



Calculated ratio

Total-cancer to total-tissue ratio: 53.41%

PD-L1 cancer(green) to total-cancer(red+green) ratio: 39.21%

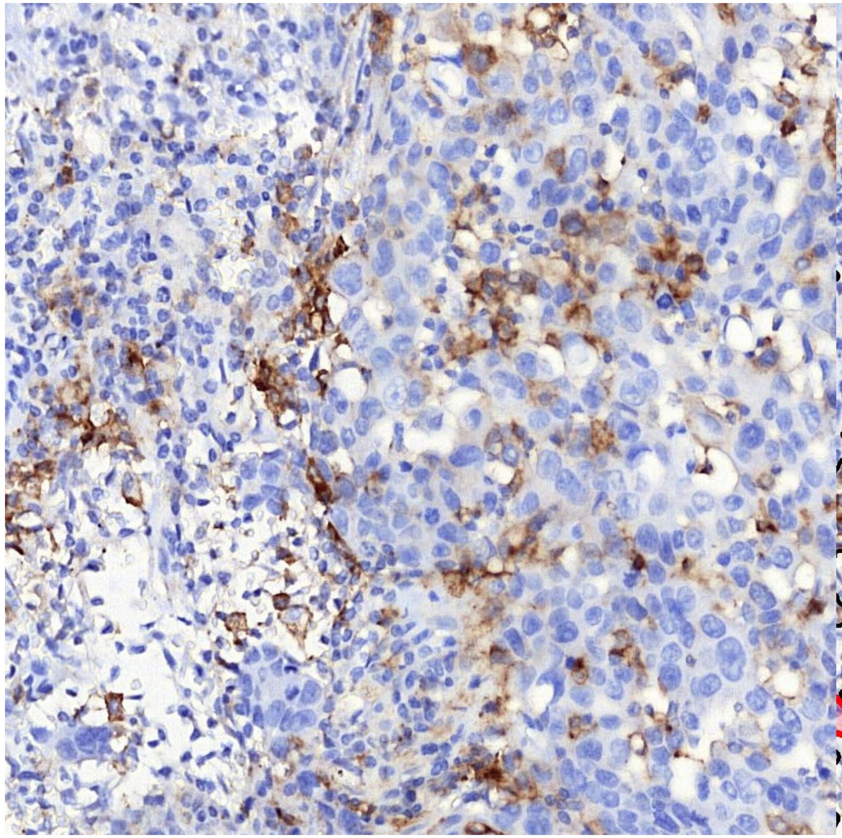
Red: TC area

Green: TC area with PD-L1 expression

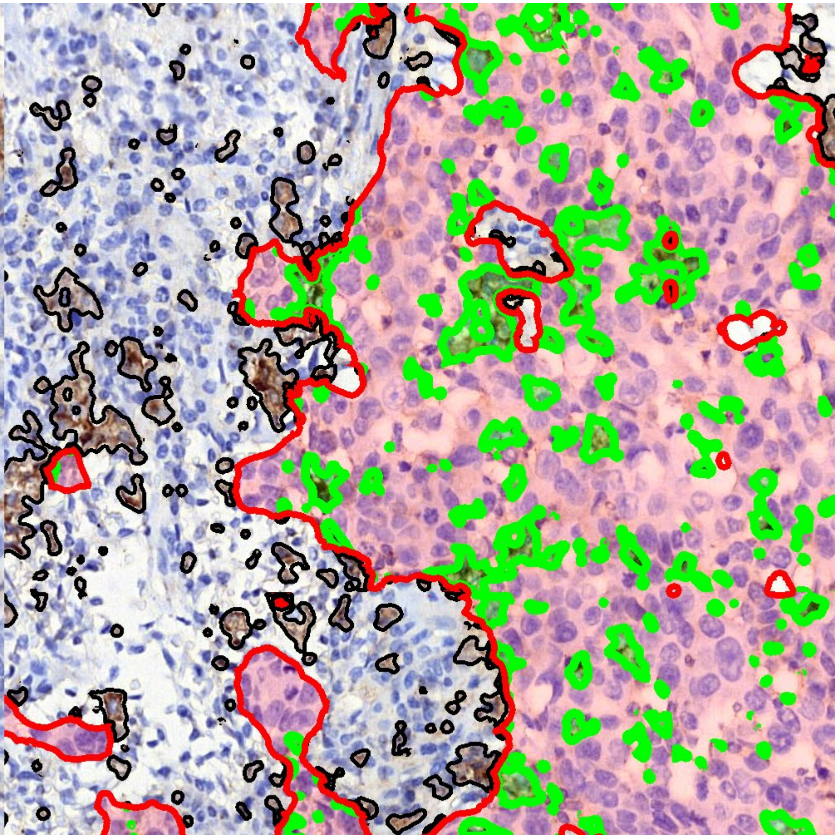
Black outline: non-TC area with PD-L1 expression

Segmentation results (magnified)

Original image



Segmentation result



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PD- L 1 specifically expressed in cancer cells can be quantified

Summary of PD – L1 analysis

We have demonstrated that application of deep learning to microscopic pathology images has potential in the following tasks

- Distinguishing cancerous regions from other tissue regions
- Segmentation of regions with PD-L1 expression
- Quantitative evaluation of tumor proportion score

Addressing the following limitations in data could further improve performance

- Quantity of training data
  - training has been done with only 34 patches of 1000 x 1000 pixel images
- Quality of training data
  - Annotations by a staff pathologist is needed
- Variation of training data
  - Training patches are extracted from slides from multiple institutions would help generalization ability of the model

Deep Learning Algorithm for Detecting Lung Cancers in Chest Radiographs

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- A training dataset was obtained between January 2006 and June 2017 in our institution.
- A test dataset was obtained between July 2017 and June 2018 in our institution.
- Patients who had surgery and pathologically proven lung cancers.
- CR had one or more malignant nodules or/and masses.
- CR was performed with an upright posterior-anterior view using a digital radiography.
- Chest CT was performed within a month of taking the CR.
- CRs with consolidation, atelectasis, or pleural effusion were excluded

Image segmentation and Algorithm development

- All malignant nodules and masses in CRs were manually segmentated by two radiologists with reference to CT images.
- Manual segmentations were made with ITK-SNAP version 3.6.0.

- The algorithm was developed by segmentation method with encoder-decoder architecture.
- The encoder used Inception-ResNet-v2 model as the backbone algorithm to extract features.
- The decoder was designed to compute upconvolution to detect lung nodule or mass with segmentation.

Statistical Analysis

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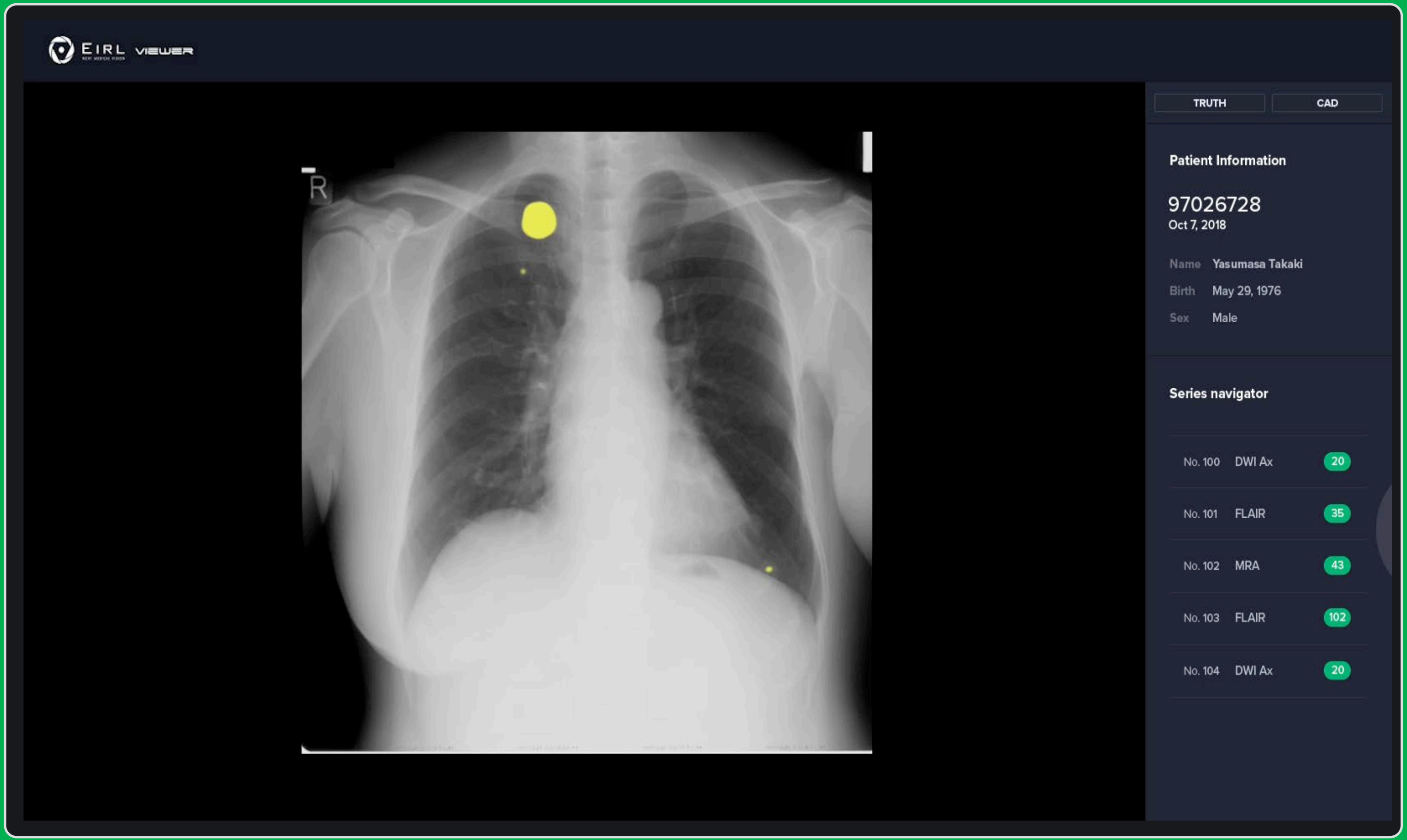
- The two radiologists determined true positive (TP) or false positive (FP) of the lesions which were segmentated by the algorithm.
- The algorithm was evaluated by its sensitivity, positive predictive value (PPV), false positive per image (FPI), and free-response receiver operating characteristic curve (FROC).
- The size, location, and shape of false negative(FN) candidates ware evaluated.

Characteristics Training dataset Test dataset

Characteristics	Training Dataset	Test Dataset
No. of chest radiographs	629	151
Men	408 (65%)	94 (62%)
Women	221 (35%)	57 (38%)
Mean age ±SD (year)	69±8.87	69±8.92
No. of malignant nodules and masses	652	160
Size (cm)		
<=1	5 (0.77%)	6 (3.8%)
1.1 – 1.5	45 (6.9%)	21 (13%)
1.6 – 2.0	68 (10%)	27 (17%)
2.1 – 2.5	87 (13%)	23 (14%)
2.6-3.0	111 (17%)	19 (12%)
3.1- 4.0	133 (20%)	25 (16%)
4.1 – 5.0	73 (11%)	13 (8.1%)
>5.0	130 (20%)	26 (16%)

Lung Nodule Detection in X-ray

Detection of lung nodules from chest X-rays using segmentation-based and object detection algorithms



Results

The sensitivity, PPV, and FPI were 73.0%, 85.3%, and 0.13, respectively.

Size	Number of Lung Cancer	No. of TPs	No. of FNs	Sensitivity (%)
Size (cm)				
<=1	6	0	6	0
1.1 – 1.5	21	8	13	38.1
1.6 – 2.0	27	14	13	51.9
2.1 – 2.5	23	19	4	82.6
2.6-3.0	19	15	4	78.9
3.1- 4.0	25	25	0	100
4.1 – 5.0	13	13	0	100
>5.0	26	22	4	84.6

Conclusion, limitations and future direction

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- In previous studies using deep learning techniques

  Sensitivity and FPI were 69.6-82.0% and 0.02-0.34, respectively (Radiology, 2019; 290:218-228)

  Sensitivity and FPI were 70.3% and 0.18, respectively (Radiology 2019, Nov 12, online)
- We could achieve high performance with few FPs using relatively small training data.
  - Sensitivity is poor for nodules <1.0 cm
  - Lung cancers larger than 5cm widely overlapped with the normal structures.
- Small dataset
- Further testing in other institutions is needed

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