Machine Learning in PDAC: Applications Analysis

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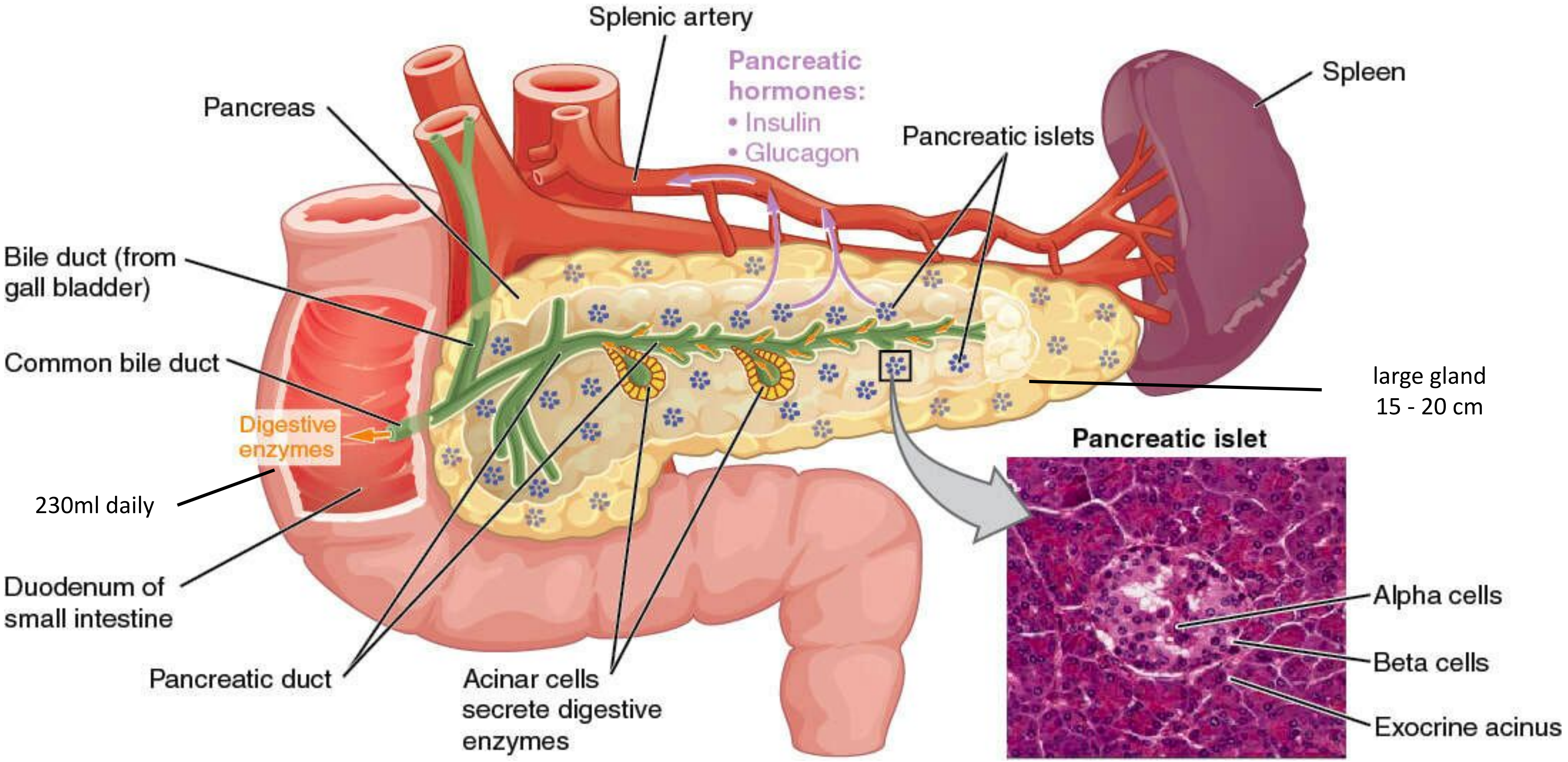
AGENDA

1 INTRODUCTION

PANCREAS



Source: The Olive Laboratory.

PANCREATIC CANCER

Two types of pancreatic cancer:

- Exocrine tumors in pancreatic ducts are also called adenocarcinomas.
- This cancer is based on its growth stage.

- Endocrine tumors are derived from a tumor, which impacts the cells of the hormone.
- Also known as the islet neuroendocrine cancer or cell cancer.

PANCREATIC CANCER

MORTALIDADE CONFORME A LOCALIZAÇÃO PRIMÁRIA DO TUMOR E SEXO

Em homens, Brasil, 2020

Localização Primária	Óbitos	%
Traqueia, Brônquios e Pulmões	16.009	13,6
Próstata	15.841	13,5
Cólon e Reto	9.889	8,4
Estômago	8.772	7,5
Esôfago	6.465	5,5
Fígado e Vias biliares intrahepáticas	6.093	5,2
Pâncreas	5.882	5,0
Sistema Nervoso Central	4.787	4,1
Cavidade oral	4.767	4,1
Laringe	3.896	3,3
Todas as neoplasias	**117.512**	**100,0**

Source: Instituto Nacional de Câncer - INCA

SCAN ME

PANCREATIC CANCER

Em mulheres, Brasil, 2020

Localização Primária	Óbitos	%
Mama	17.825	16,5
Traqueia, Brônquios e Pulmões	12.609	11,6
Cólon e Reto	10.356	9,6
Colo do útero	6.627	6,1
Pâncreas	6.011	5,5
Estômago	5.078	4,7
Fígado e Vias biliares intrahepáticas	4.670	4,3
Sistema Nervoso Central	4.567	4,2
Ovário	3.921	3,6
Leucemias	3.035	2,8
Todas neoplasias	**108.318**	**100,0**

Source: Instituto Nacional de Câncer - INCA

SCAN ME

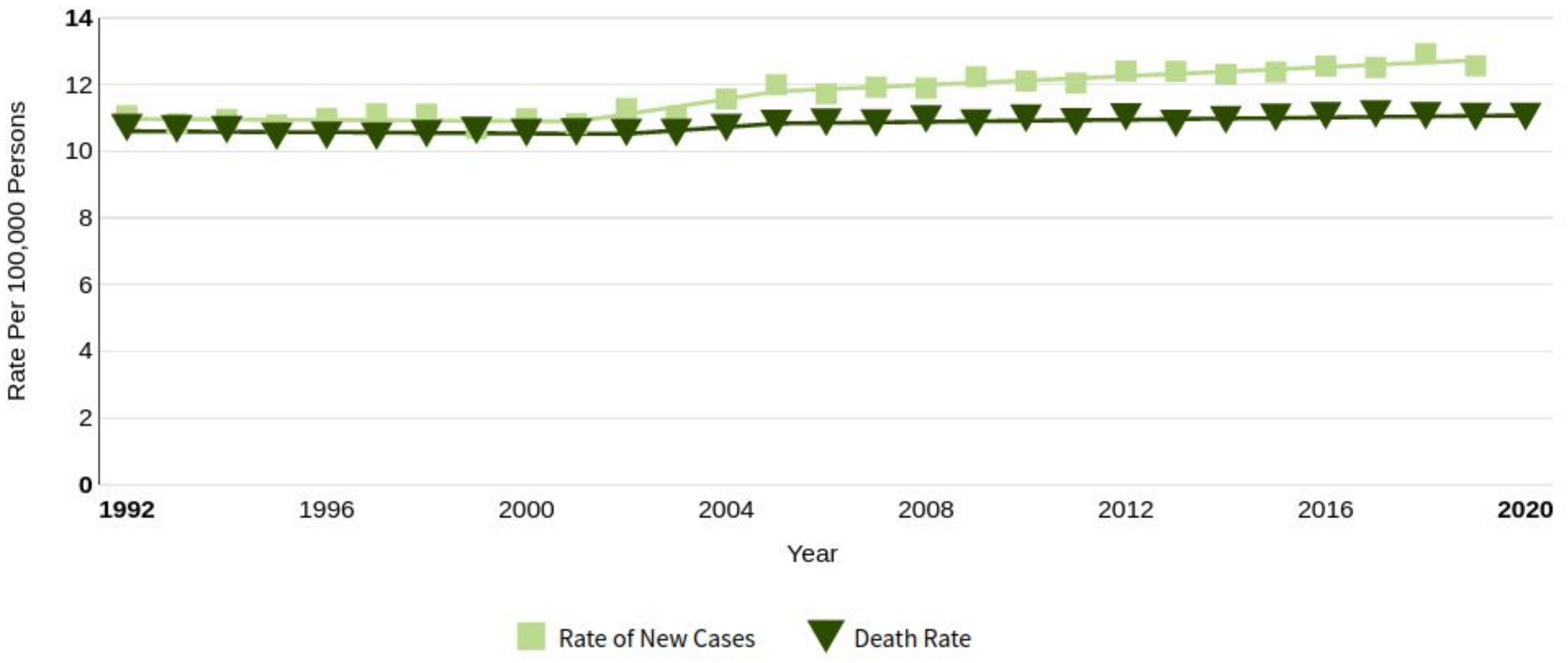
PANCREATIC CANCER

At a Glance

Estimated New Cases in 2022	62,210
% of All New Cancer Cases	3.2%

Estimated Deaths in 2022	49,830
% of All Cancer Deaths	8.2%

5-Year Relative Survival
11.5%
2012–2018

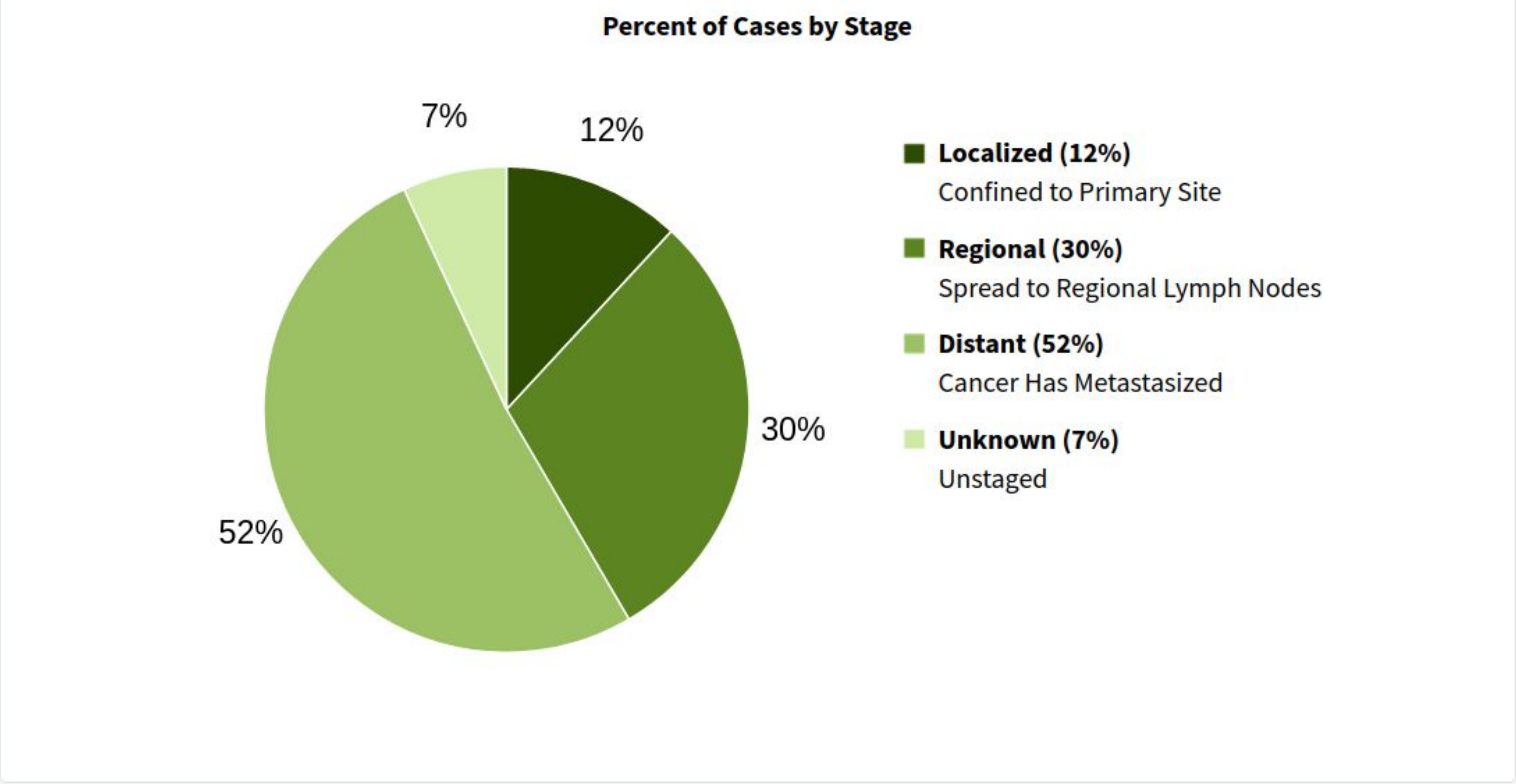


Source: Surveillance, Epidemiology, and End Results

SCAN ME

PANCREATIC CANCER

Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Pancreatic Cancer



Source: Surveillance, Epidemiology, and End Results

SCAN ME

How Common Is This Cancer?

Compared to other cancers, pancreatic cancer is fairly common.

	Common Types of Cancer	Estimated New Cases 2022	Estimated Deaths 2022
1.	Breast Cancer (Female)	287,850	43,250
2.	Prostate Cancer	268,490	34,500
3.	Lung and Bronchus Cancer	236,740	130,180
4.	Colorectal Cancer	151,030	52,580
5.	Melanoma of the Skin	99,780	7,650
6.	Bladder Cancer	81,180	17,100
7.	Non-Hodgkin Lymphoma	80,470	20,250
8.	Kidney and Renal Pelvis Cancer	79,000	13,920
9.	Uterine Cancer	65,950	12,550
10.	Pancreatic Cancer	62,210	49,830

Pancreatic cancer represents 3.2% of all new cancer cases in the U.S.

Source: Surveillance, Epidemiology, and End Results

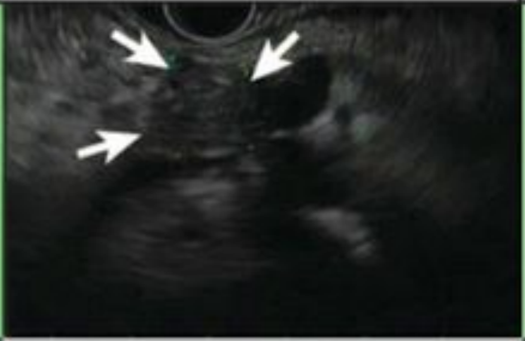
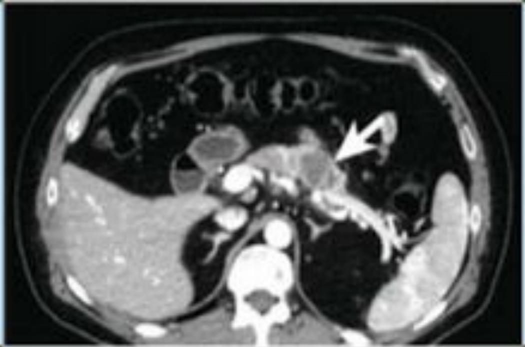
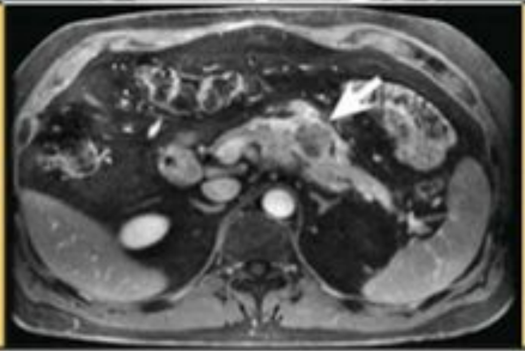
SCAN ME

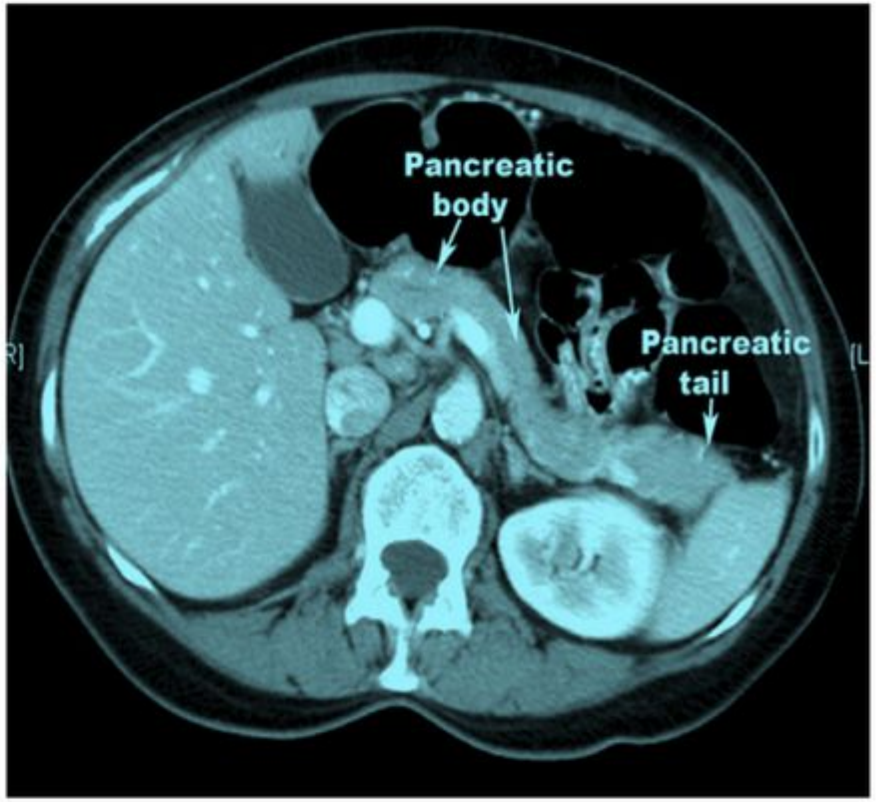
PANCREATIC CANCER

Pancreatic ductal adenocarcinoma (PDAC):

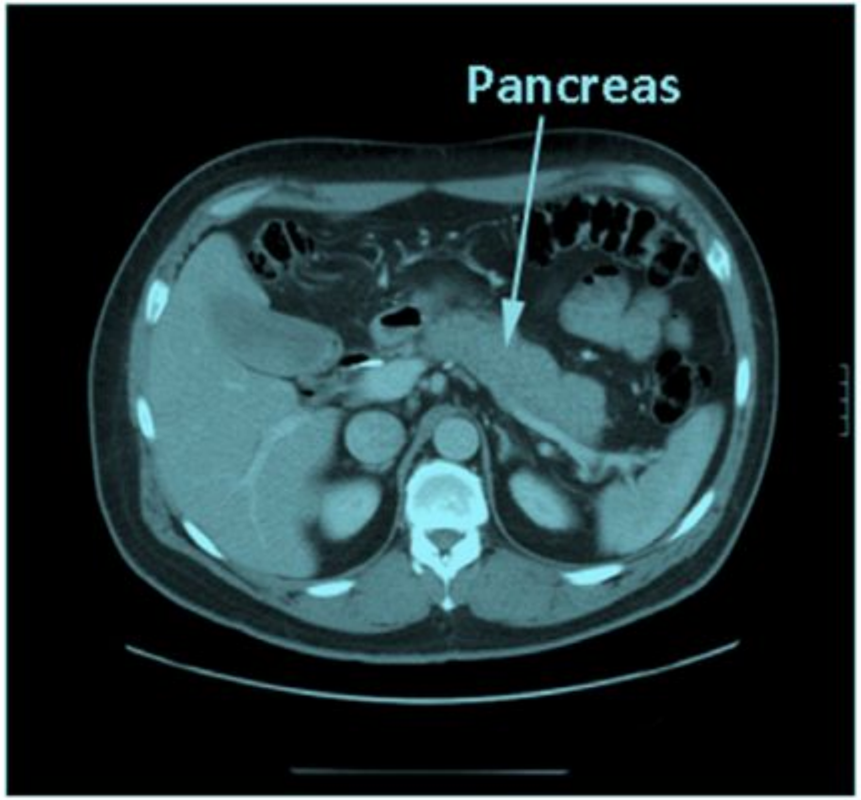
- 5-year relative survival 11.5%;
- The mortality rate for pancreatic cancer is high, as it is a difficult to diagnose and extremely aggressive disease;
- Symptoms typically occur late in the disease course;
- Screen may lead to an earlier interception and improved survival;
- The 5-year relative survival rate rises up to 39.4%.

MEDICAL IMAGING TECHNIQUES

		Advantages for early detection	Disadvantages for early detection
Endoscopic ultrasound (EUS)		• Highest sensitivity and specificity • Provides excellent resolution for small lesions • Can be used with FNA for diagnosis	• Not practical for routine screening • Can be dependent on technical expertise
Computed tomography (CT)		• High sensitivity and specificity • Generally standardized and available • Can be relatively easy to interpret	• Exposes patient to radiation • Requires iodine contrast, which can cause reaction in some patients
Magnetic resonance imaging (MRI)		• High sensitivity and specificity • Provides good soft tissue contrast • Does not expose patient to radiation	• Less standardized than CT • Can be difficult to do for patients with certain medical devices, claustrophobia, or allergies to gadolinium



(a) Image-1 CT Scan



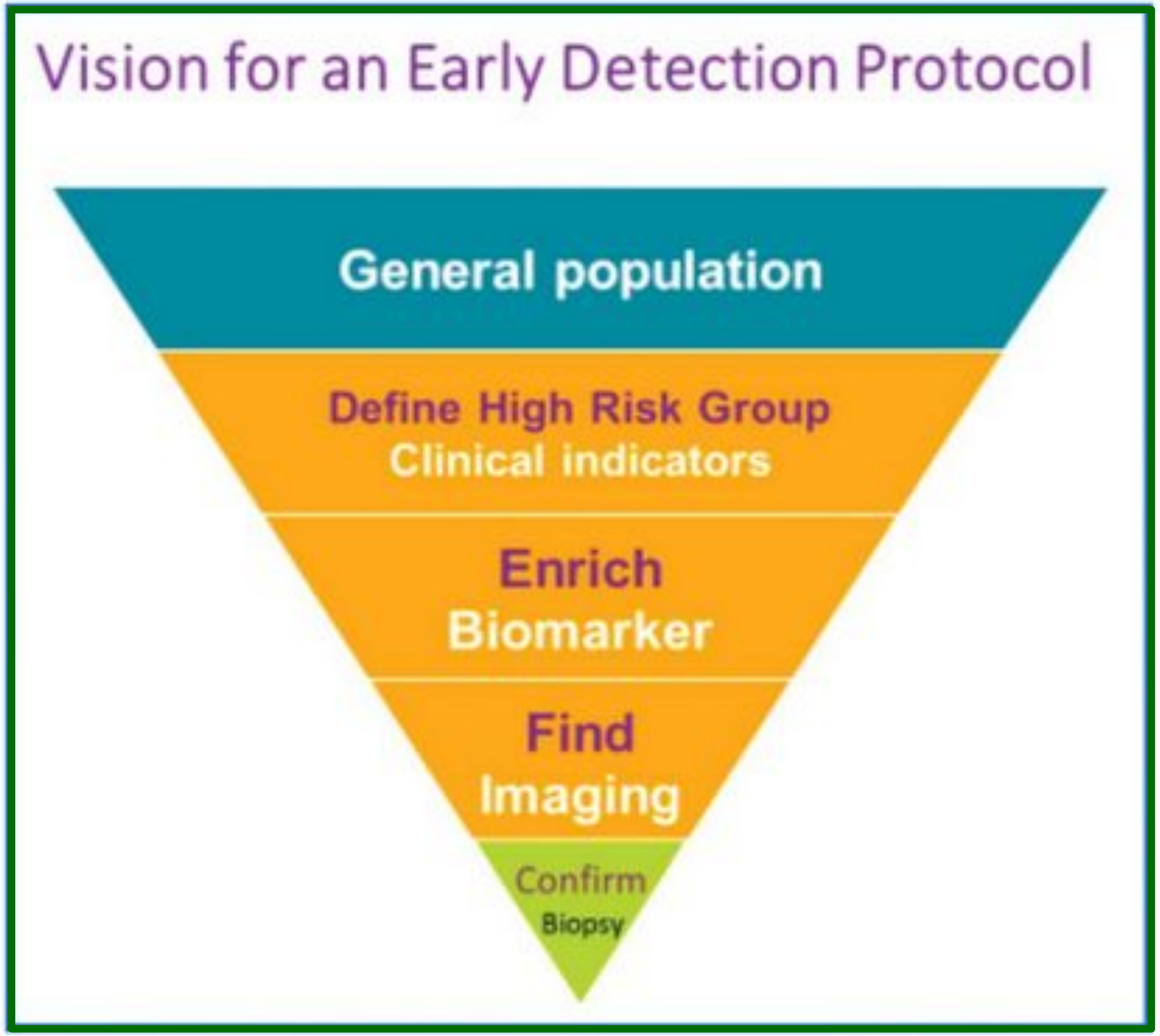
(b) Image-2 CT Scan

Source: W. Xuan and G. You, 2020.

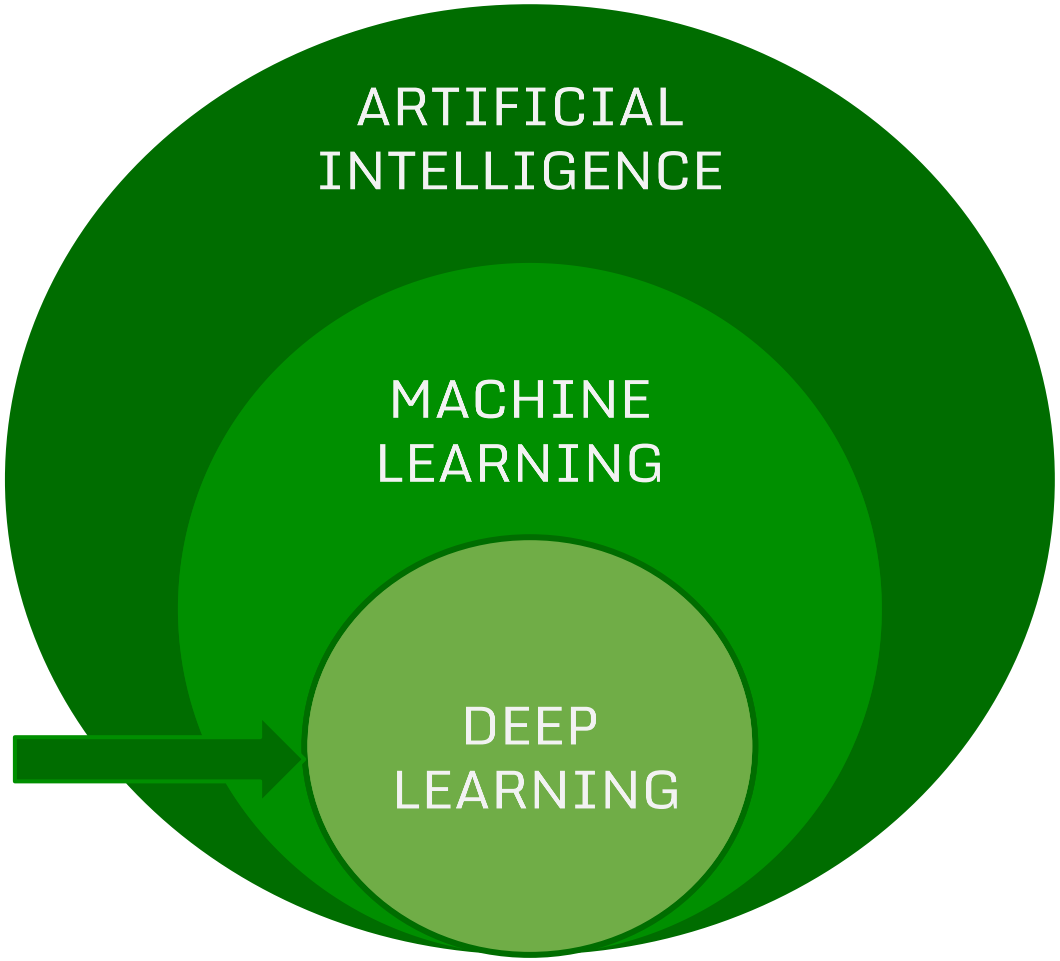
MEDICAL IMAGING TECHNIQUES

- Imaging techniques help screen for hidden features before visible symptoms;
- Tumor classification through these methods can also help to track, predict and endorse customized therapy as part of effective treatment, without cancer invasions;
- Blood and other laboratory tests usually determine the existence of PDAC;
- Computed tomography (CT) and magnetic resonance imaging (MRI) were used to help determine if the condition exists;

COMMON DIAGNOSIS WORKFLOW

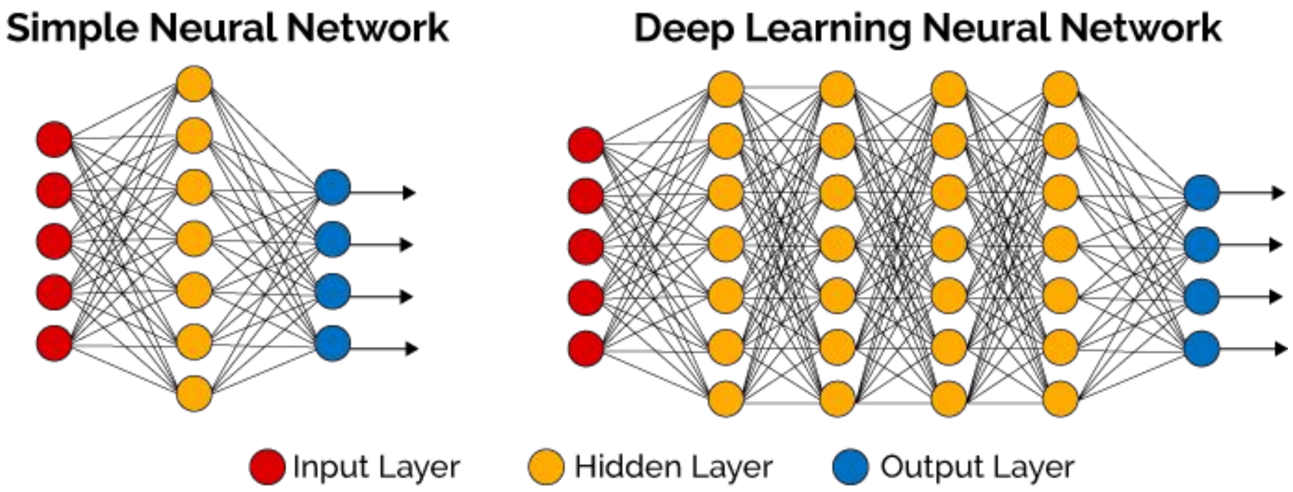


Source: Artificial Intelligence and Early Detection of Pancreatic Cancer. 2020



ARTIFICIAL NEURAL NETWORKS:

- Big data;
- Trained to perform a specific task;



Source: Instituto de Engenharia, 2019.

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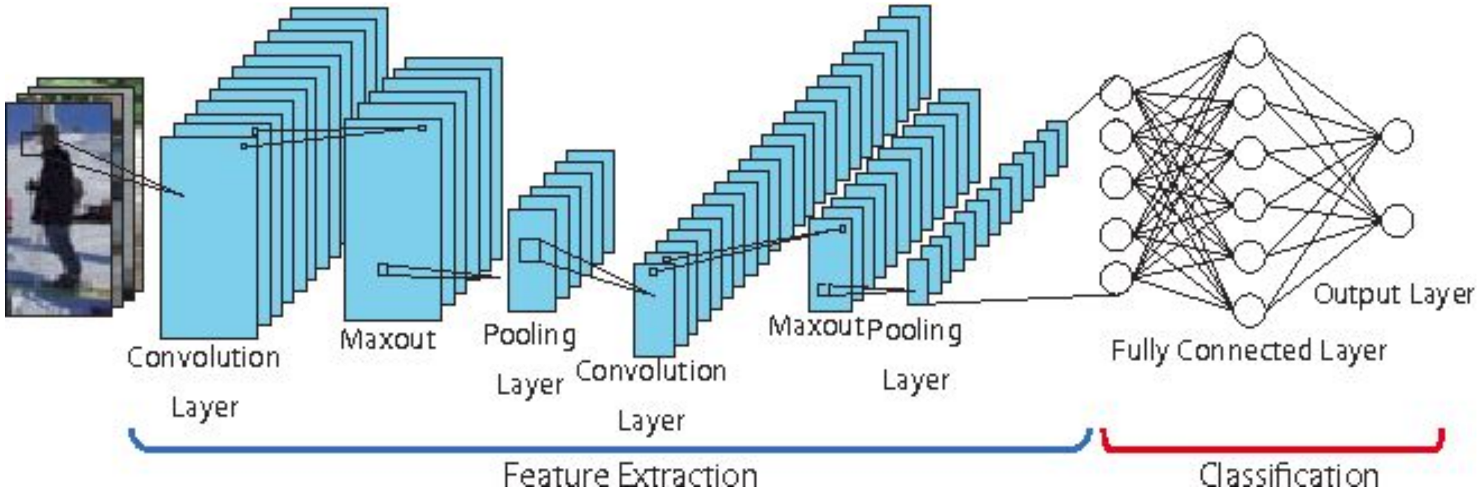
CONVOLUTIONAL NEURAL NETWORKS

- Filter application at the network entrance;
- Extract and map features;
- Semantic segmentation, imaging classification and image detection.



Source: IEEE Intelligent Vehicles Symposium (IV), 2015.

OBJECTIVE

Analyze articles and Deep Learning applications proposals, specifically CNNs, for the early detection of PDAC in CT images.

2 METHODOLOGY

METHODOLOGYS

1. Detection and diagnosis of pancreatic tumor using deep learning-based hierarchical convolutional neural network on the internet of medical things platform. (Wei Xuan, Guangqiang You. 2020);
2. Deep learning convolutional neural network with Gaussian mixture model for predicting pancreatic cancer. (Sekaran et al. 2019);
3. Deep learning to distinguish pancreatic cancer tissue from non-cancerous pancreatic tissue: a retrospective study with cross-racial external validation. (Liu et al. 2020);
4. Establishment and application of an artificial intelligence diagnosis system for pancreatic cancer with a faster region-based convolutional neural network. (Liu et al. 2019);
5. Construction of a convolutional neural network classifier developed by computed tomography images for pancreatic cancer diagnosis. (Ma et al. 2020);

Focus: CT images and CNN processing

- Xuan & You (2020):
  - Hierarchical Convolutional Neural Network (HCNN);
  - P-Net model adapted for 3D images, to segmentation of the tumor area;
  - Tested the model with datasets beginning from 10 to 50 CT datasets;
  - Validation was done by stabilized precision ratio, dice index, sensitivity, and specificity rates.
- Sekaran et al. (2019):
  - CNN model developed to classify tumor area (LFE + LR);
  - Gaussian Mixture Model (GMM) to segment and extract features from the area of interest;
  - 19,000 CT images to train and test the model;
  - Evaluation by recognition ratio versus the number of images on the training dataset.

Focus: CT images and CNN processing

- Liu et al. (2020):
  - CNN model derived from Visual Geometry Group (VGG) network;
  - Optimization done by weighted loss function and callback to avoid overfitting;
  - More than 14,000 CT images;
  - Success was evaluated by sensitivity, specificity, accuracy and area under ROC curve (AUC).
- Liu et al. (2019):
  - Faster region-based CNN model (Fast R-CNN);
  - VGG16 network for feature extraction;
  - More than 5,000 CT images, either from pancreatic cancer patients or not;
  - Model's performance measured by AUC.

METHODOLOGYS

Focus: CT images and CNN processing

- Ma et al. (2020):
  - CNN model composed by three convolutional layers and one fully connected, and then a batch normalization (BN), a rectified linear unit (ReLU), and a max-pooling layer;
  - More than 6,000 CT images, either from pancreatic cancer patients or not;
  - Model was evaluated using accuracy, specificity and sensitivity rates.

Between the chosen articles, there is some resemblance: they all used CT images as the data to develop the CNN models and the acquisition of these images was made with contrast application. Even so, all the studies had their parameters and forms of success evaluation, such as accuracy, the ROC curve, AUC, the Dice-performance ratio, and others.

3 MACHINE LEARNING APPLICATIONS ANALYSIS

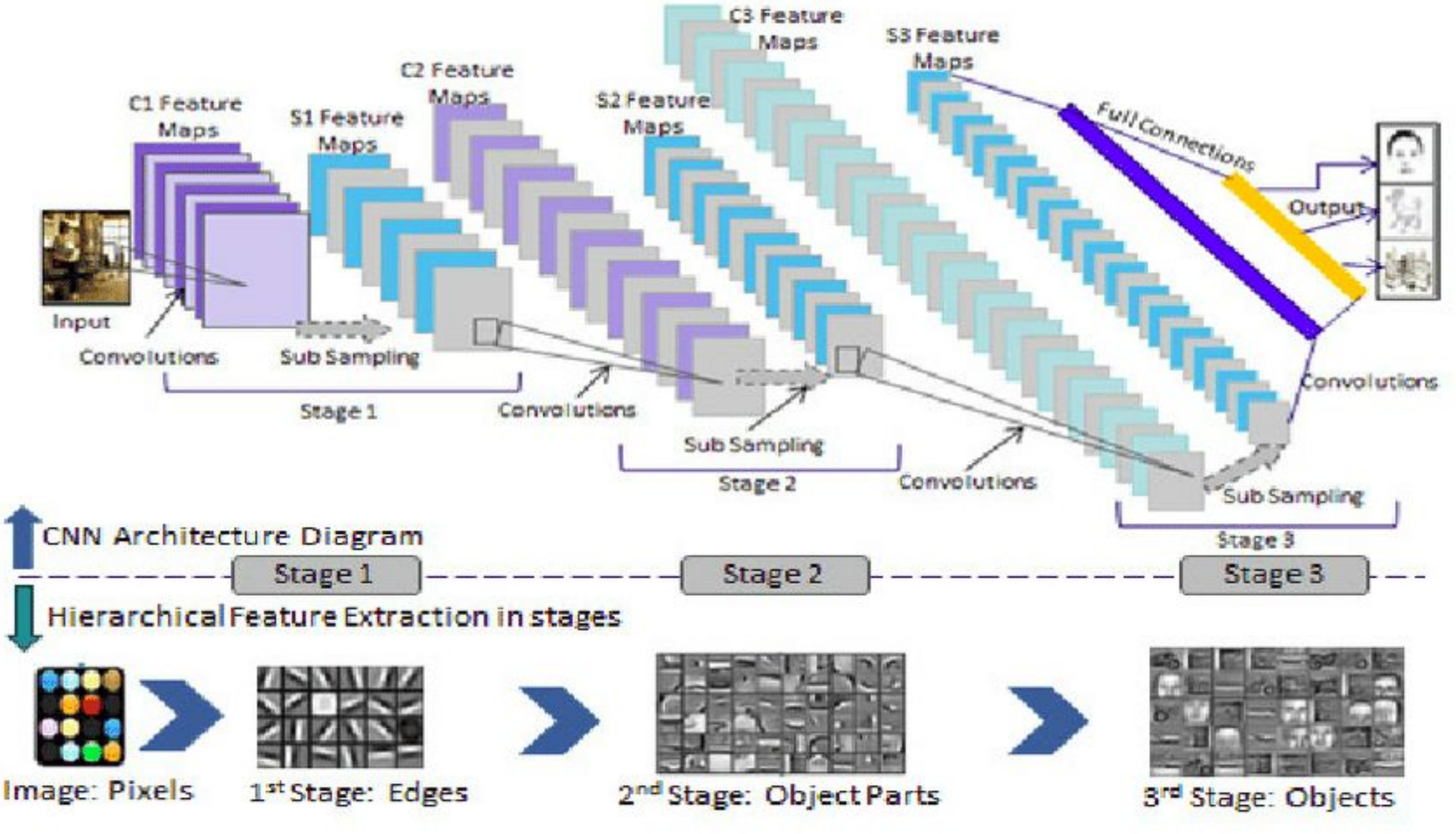
1. Detection and diagnosis of pancreatic tumor using deep learning-based hierarchical convolutional neural network on the internet of medical things platform.

(Wei Xuan, Guangqiang You. 2020)

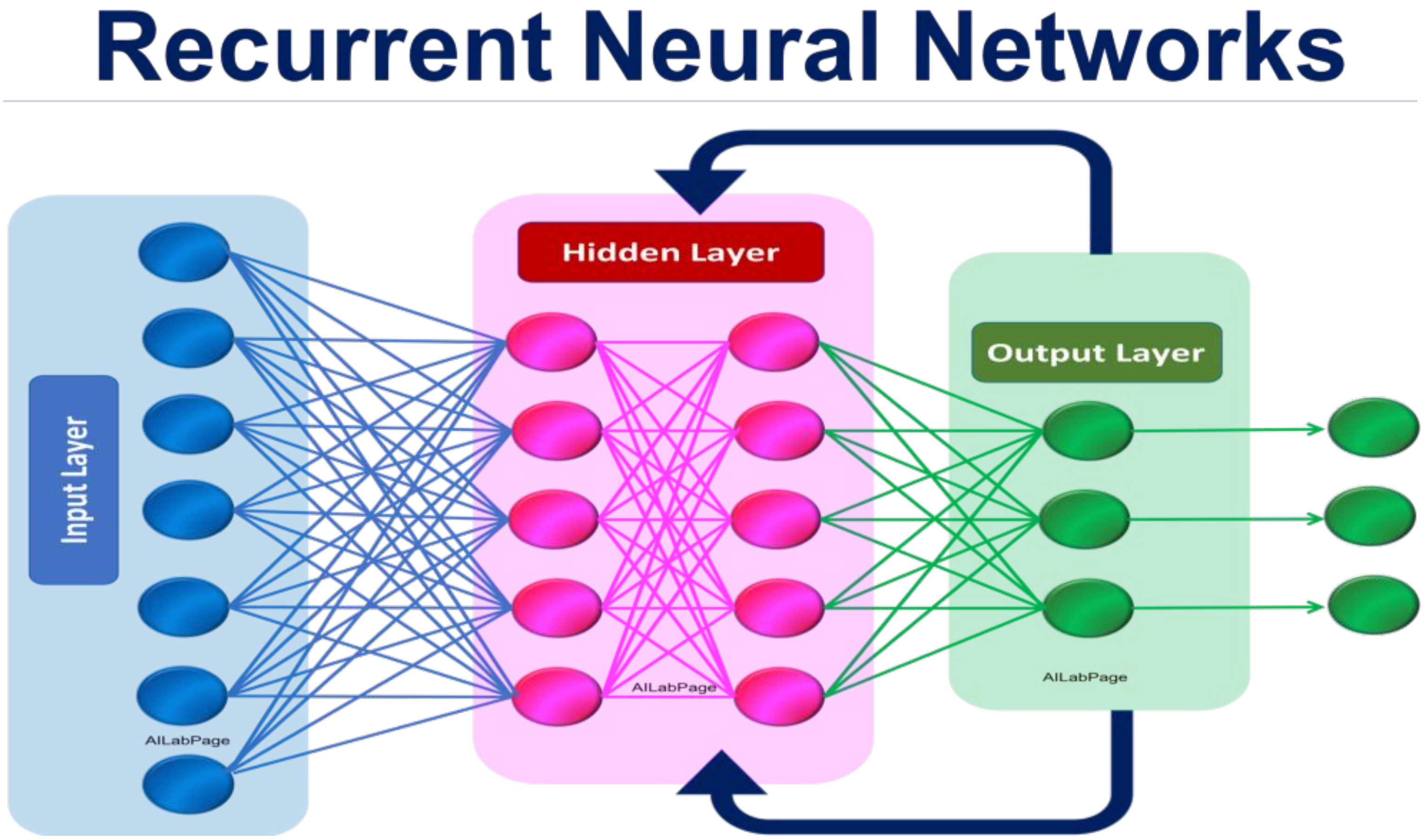
- Problem
  - The pancreas boundary is difficult to distinguish from its anatomies in CT scans, because of its complex visual appearance and vague curves.

- Objective:
  - Detection of the pancreatic tumor using the Hierarchical Convolutional Neural Network (HCNN);
  - Recurrent Neural Networks (RNN) to address the image segmentation spatial problem.

HCNN AND RNN - METHODOLOGY



Source: Siva Chaitanya Mynepalli, 2015.

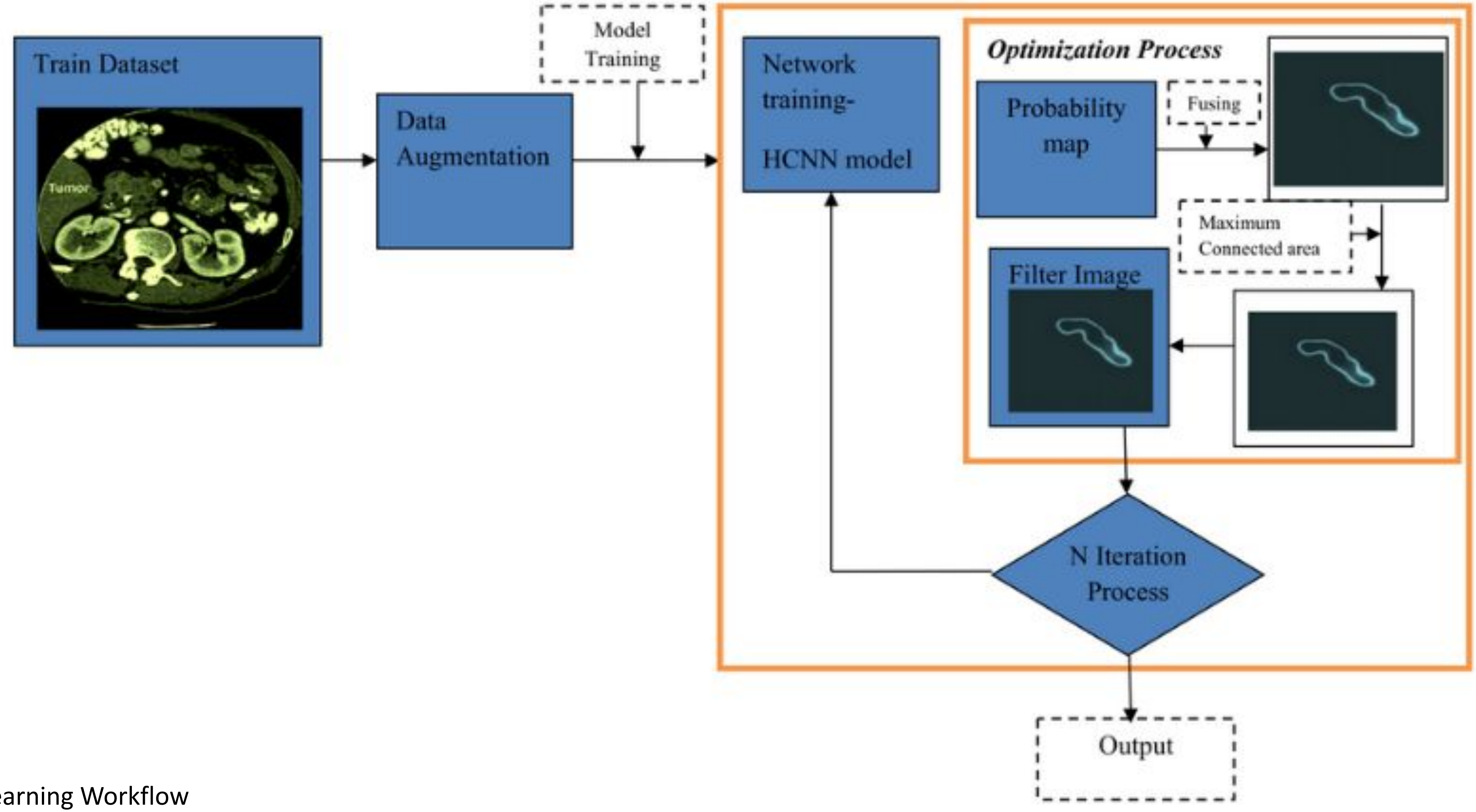


Source: Devanshi, 2021.

- P-net
  - Each layer produces its own output in addition to its connections to the subsequent layer;
  - Random forest with post-processing to refine the CNN output;
  - Each of these outputs are then averaged to each other to come up with a final prediction;
  - Upper layers of the network easily capture the pancreas hierarchy do not let the top layers of gradients (backpropagated by the training error) decrease quickly in the optimization process with filtered output based on iterations and probability map.

- Data:
  - Tested the model with datasets beginning from 10 to 50 CT dataset.
- Data augmentation:
  - The degree of deformation is selected such that the resulting distorted images represent realistic physical variations of the medical images;
  - Can help prevent over-configuration.

HCNN and CNN+RNN - METHODOLOGY



Machine Learning Workflow

- Statistical Stabilized Precision
  - Confidence intervals between impact estimates and the predictive potential of proposed indices.
- Sensitivity
  - Ratio between the correctly predicted non-malignant cases and all non-malignant cases
- Specificity
  - Correctly predicted malignant lesions over all images classified as malignant
- Dice Index

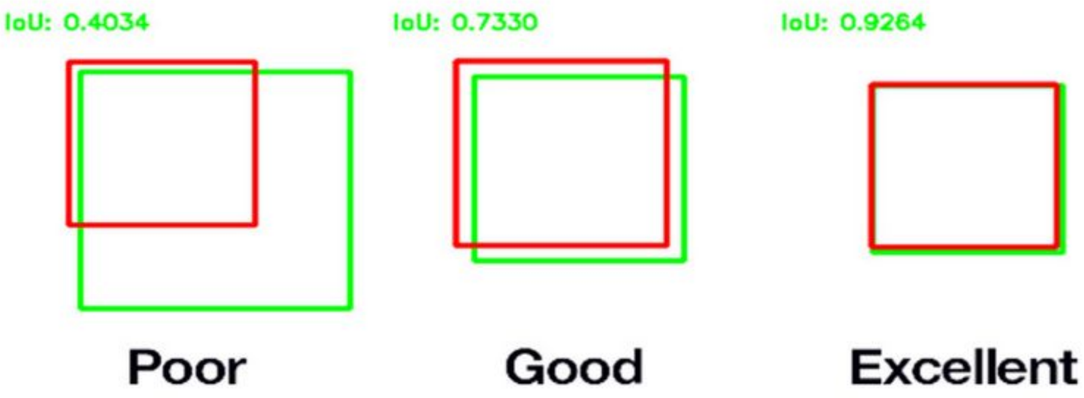


Fig. 3.1. Dice index IoU score for proper segmentation without loss.

HCNN and CNN+RNN - RESULTS

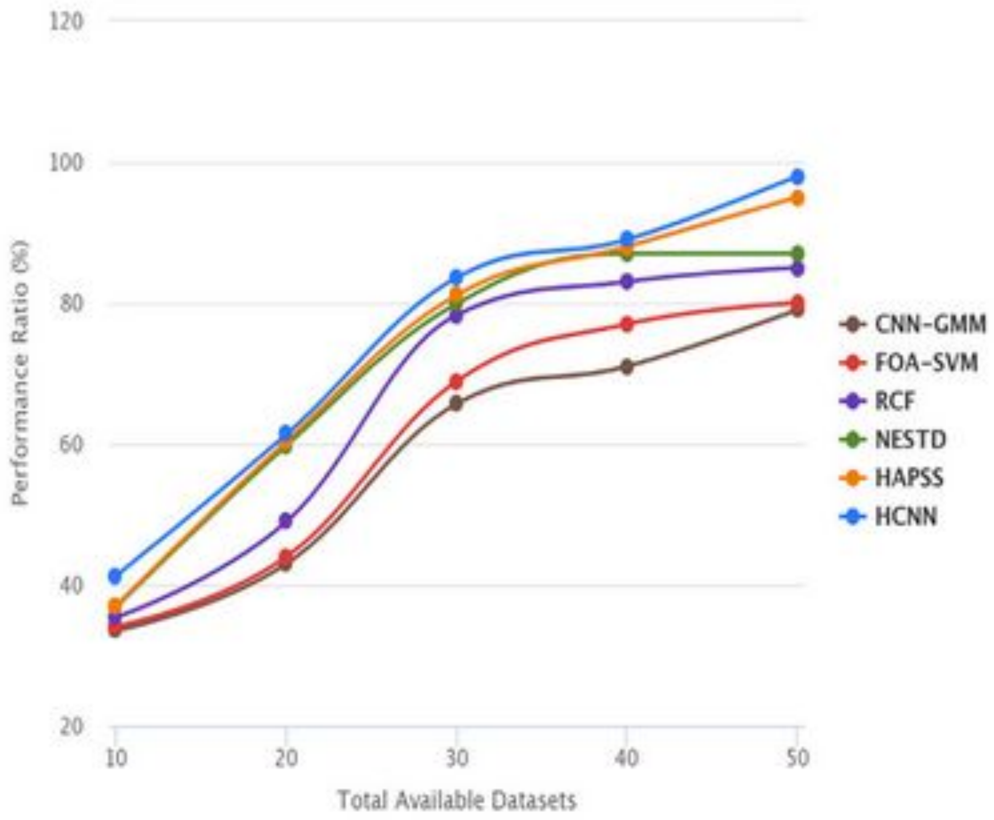
Table 1
Dice-performance index ratio.

Total available datasets	CNN-GMM	FOA-SVM	RCF	NESTD	HAPSS	HCNN
10	33.5	34.1	35.4	36.9	37.1	41.3
20	43.3	44.5	49.5	59.8	60.3	61.3
30	65.7	68.9	78.3	79.9	81.1	83.4
40	71.3	77.9	83.2	87.6	88.1	89.3
50	79.4	80.5	85.4	87.6	95.2	98.7

Table 2
Stabilized precision ratio.

Total available datasets	CNN-GMM	FOA-SVM	RCF	NESTD	HAPSS	HCNN
10	56.3	57.3	58.1	59.5	60.2	61.4
20	75.9	76.4	77.7	79.8	80.2	82.3
30	54.3	55.6	56.1	67.8	70.3	71.5
40	73.7	75.8	79.2	81.2	83.5	84.2
50	88.5	89.2	90.2	91.9	93.7	95.1

HCNN and CNN+RNN - RESULTS



(a): Dice Performance Index Ratio

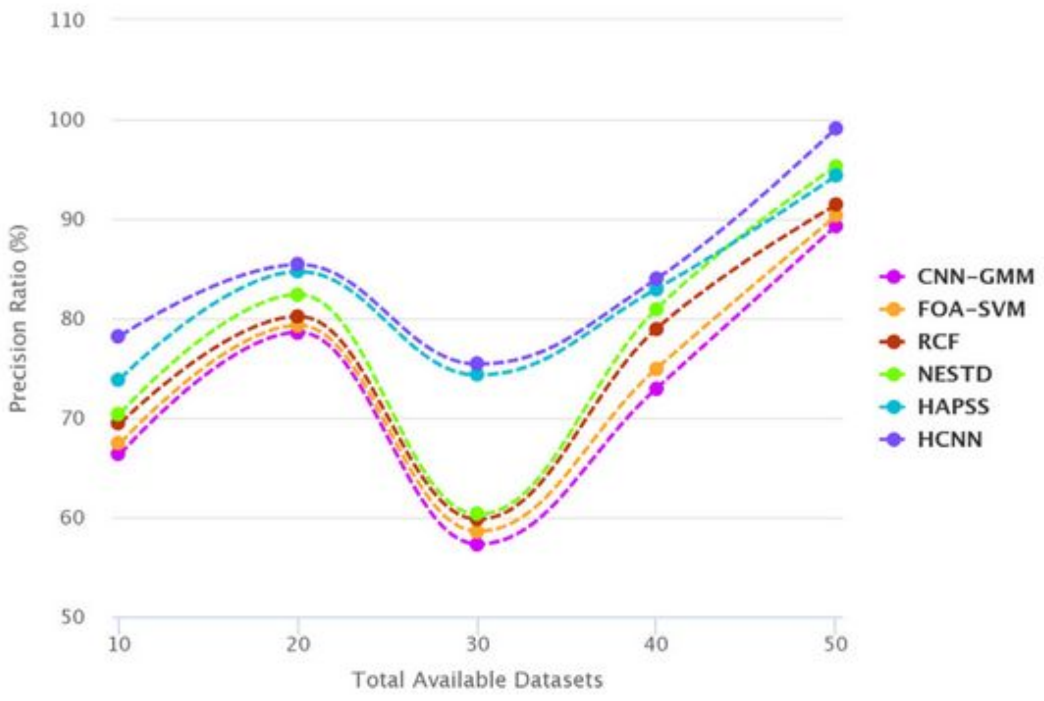
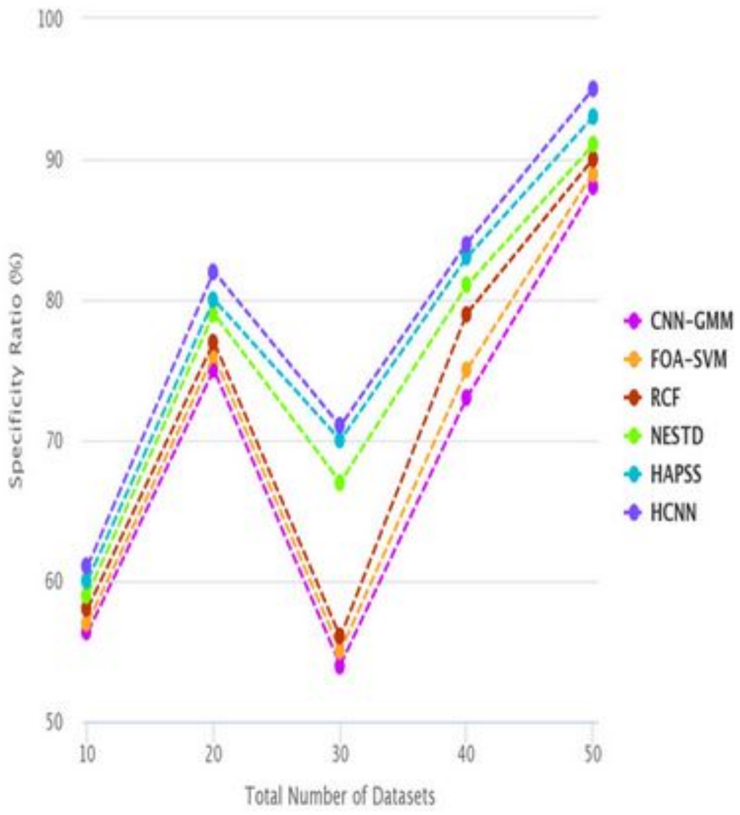
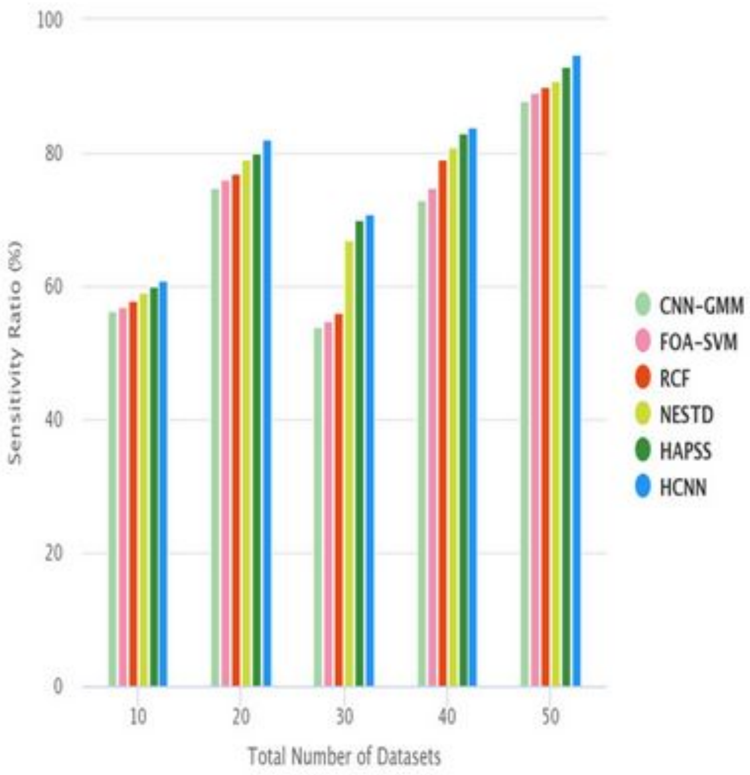


Fig. 9. Stabilized precision ratio analysis.

HCNN and CNN+RNN - RESULTS



(a): Dice Index Specificity Ratio



(b): Dice Index Sensitivity Ratio

Fig. 8.1. Dice index specificity vs. sensitivity.

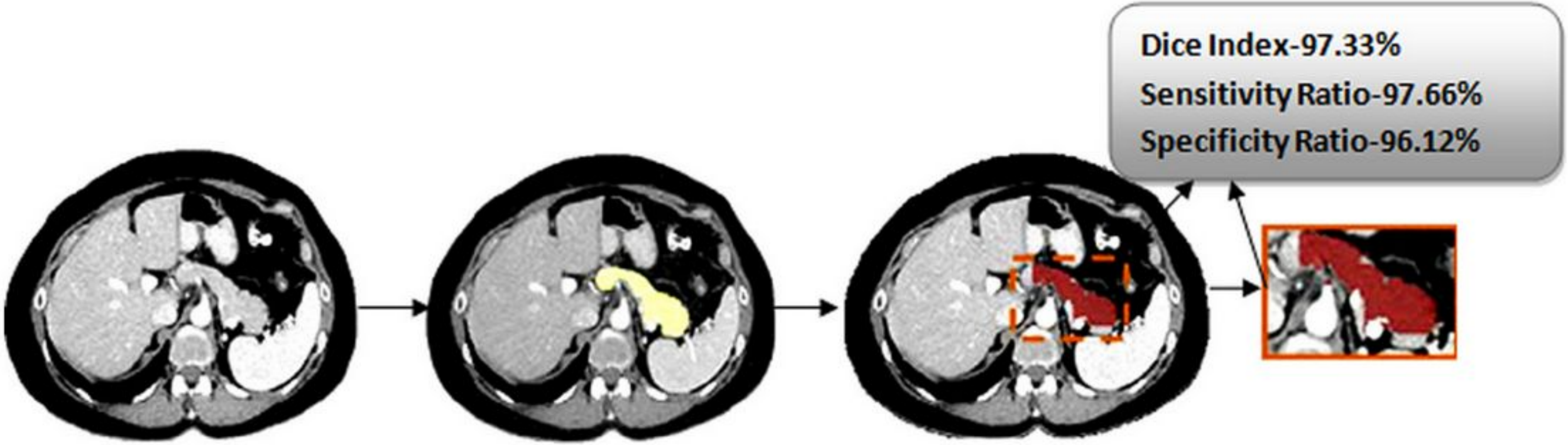


Fig. 8. Image dataset for dice index for specificity and sensitivity.

3 MACHINE LEARNING APPLICATIONS ANALYSIS

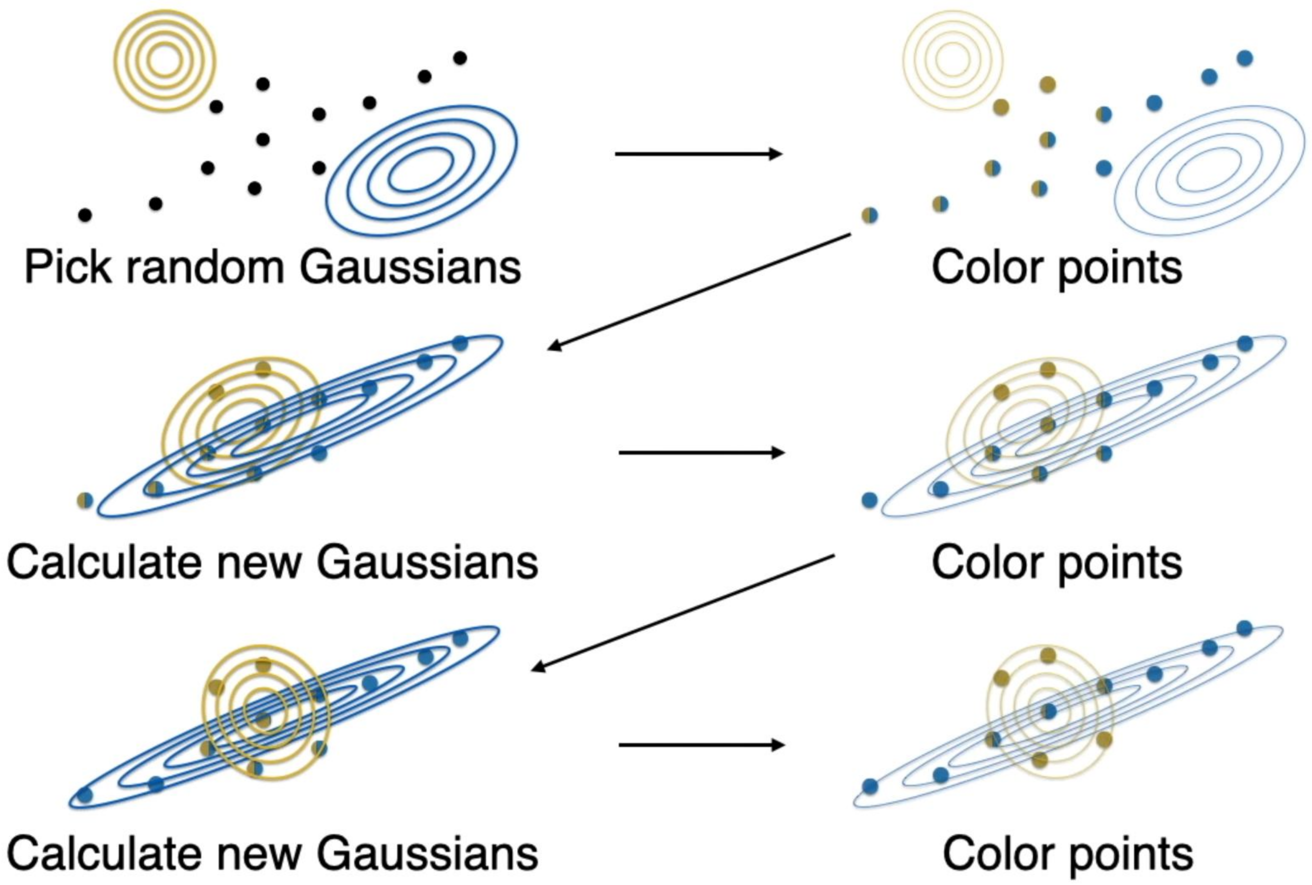
2. Deep learning convolutional neural network with Gaussian mixture model for predicting pancreatic cancer.

(Sekaran et al. 2019)

CNN-GMM - METHODOLOGY

- Objective:
  - Recognition of the pancreatic tumor using Artificial Intelligence Model based on CNN;
  - Feature and threshold extraction by Gaussian Mixture Model to segmentation of the area.

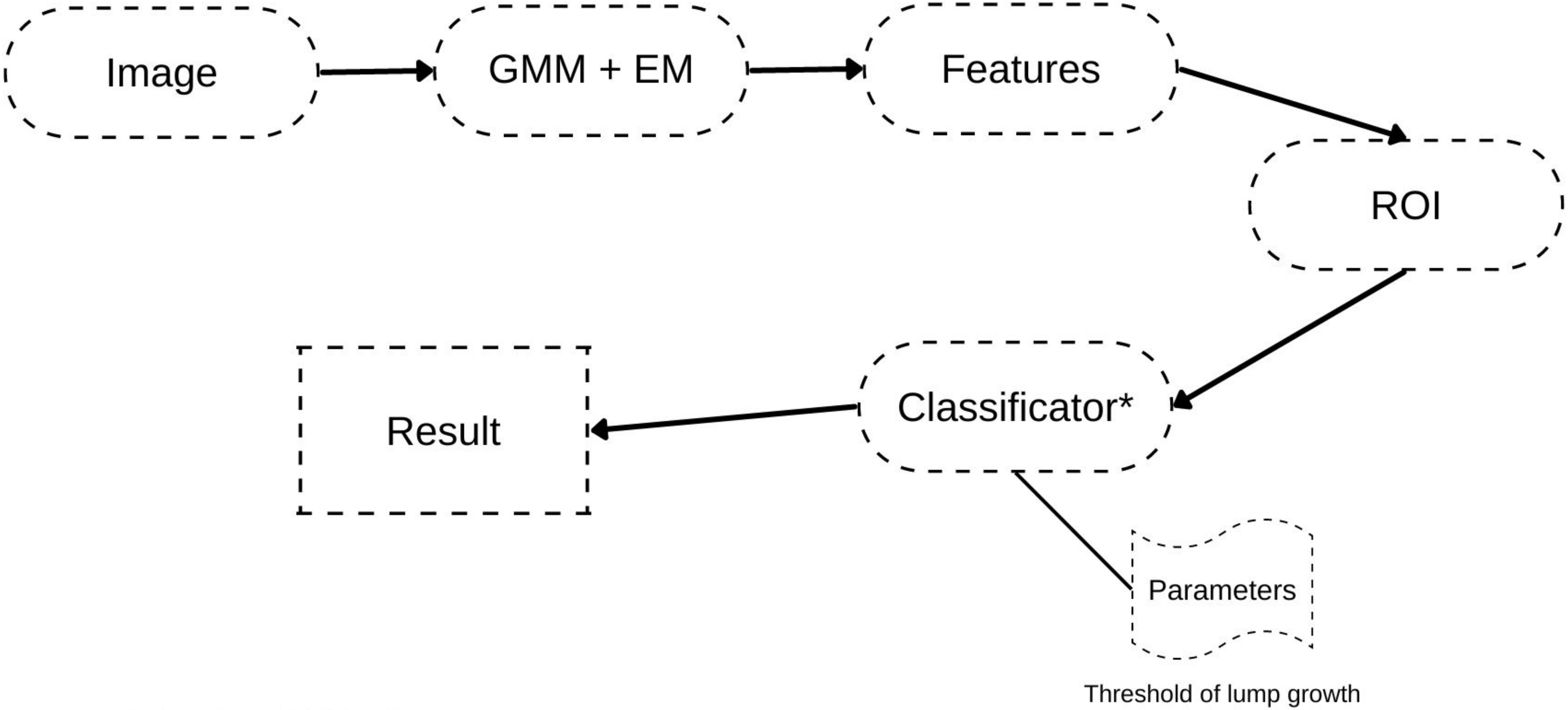
- Feature extraction with GMM-EM;
  - Soft clustering method based on Gaussian distribution;
  - Mixed data + random Gaussian -> correction until convergence -> the best segmentation:



Source: Serrano.Academy at YouTube (2020).

- Features feeding the CNN model, consisted of:
  - convolutional layers;
  - hidden layers;
  - sets to training and testing.
- Strategy:
  - Analysis of the lump of the pancreas by its size, shape, depth, length, and weight parameters;
  - LFE + LR (features + threshold parameters of lump growth).

CNN-GMM - METHODOLOGY



*Convolutional and hidden layers

CNN-GMM - METHODOLOGY

- Data:
  - National Institutes of Health Clinical Center - The Cancer Imaging Archive (TCIA);
  - 19,000 CT scan images.
  - The images were collected by Philips and Siemens MDCT Scanners, resulting in 512 x 512 pixels resolutions with a slice thickness of 1.5 – 2.5 millimeters.;
- Evaluation by recognition ratio versus the number of images on the training dataset.

Compared with other identification techniques, the pipeline utilized in this paper obtained a greater recognition rate of the PDAC located in the head section of the pancreas, as presented in Table 3 below:

Table 3. Recognition rate of images Vs Number of images, in the training dataset.

Images	K-Means	K-Mediods	GLCM	LBP	LFE + LR with GMM + CNN
50	45.5	55.2	78.3	65.1	88.3
100	46.6	56.3	79.4	66.4	89.5
200	47.3	57.5	79.4	68.3	97.4
300	47.8	58.4	79.7	69.3	97.7
400	48.5	59.4	80.1	70.1	98.3
500	49.3	60.2	81.7	73.7	98.6
600	49.1	61.8	83.8	74.8	98.9
700	49.5	63.2	87.3	76.3	99.3
800	49.8	63.7	88.5	77.5	99.5
900	50.5	64.2	89.7	76.7	99.7
1000	51.7	64.5	91.9	79.9	99.9

Source: Adapted from Sekaran et al. (2019).

3 MACHINE LEARNING APPLICATIONS ANALYSIS

3. Deep learning to distinguish pancreatic cancer tissue from non-cancerous pancreatic tissue: a retrospective study with cross-racial external validation.

(Liu et al. 2020)

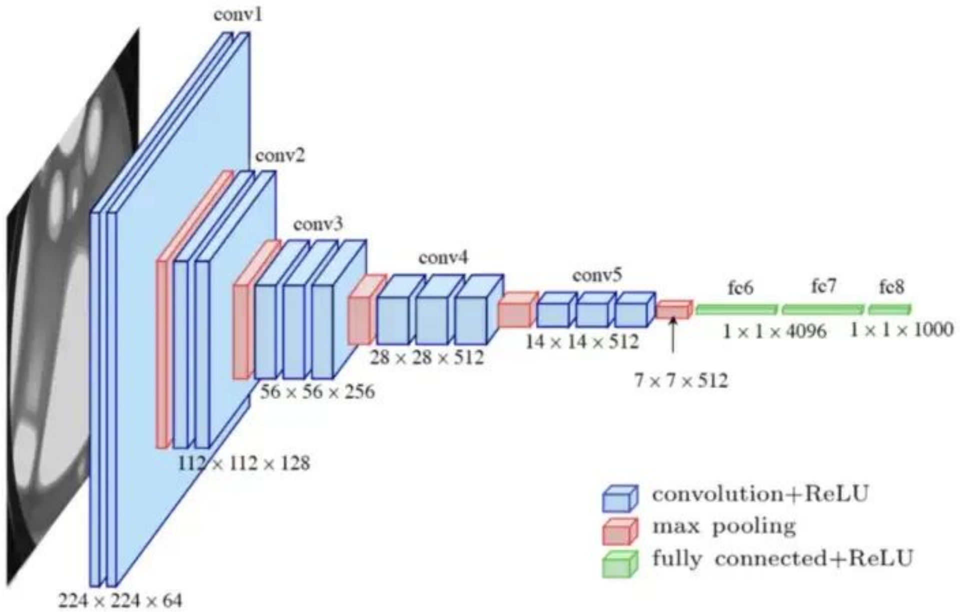
VGG NETWORK - METHODOLOGY

- Objective:
  - Differentiate cancerous pancreas and normal pancreas using Artificial Intelligence Model based on CNN model modification of VGG.

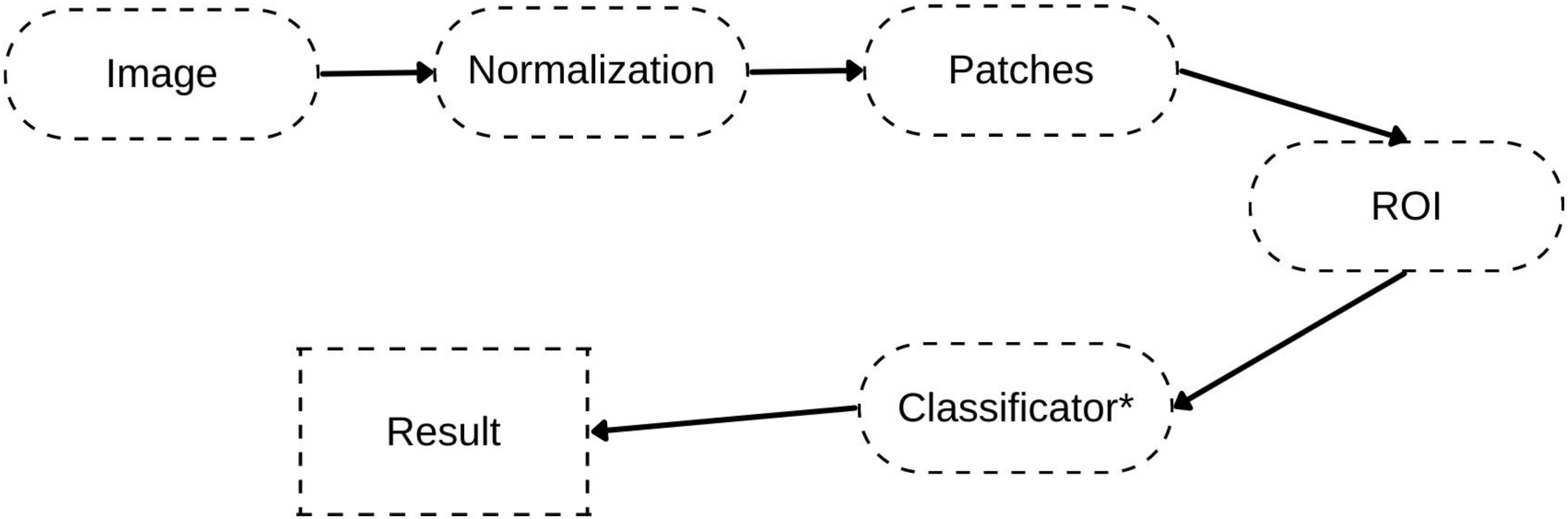
- Strategy:
  - Local and external datasets for validation;
  - Images were labeled and normalized and then cropped into patches with overlap;
  - CNN's results were compared with radiologists' diagnosis for the same set of samples.

VGG NETWORK - METHODOLOGY

- VGG network method modified:
  - Three convolutional blocks in which each block consisted of
    - Two convolutional layers;
    - Rectified linear unit;
    - Max-pooling layer at the end.
  - Flatten node was added to the last convolution block;
  - Three fully connected layers were attached at the end of the model.



Source: Researchgate.net.



*VGG Network: 3 convolutional blocks, which each has:
- 2 convolutional layers;
- a rectified linear unit
- a max-pooling layer.

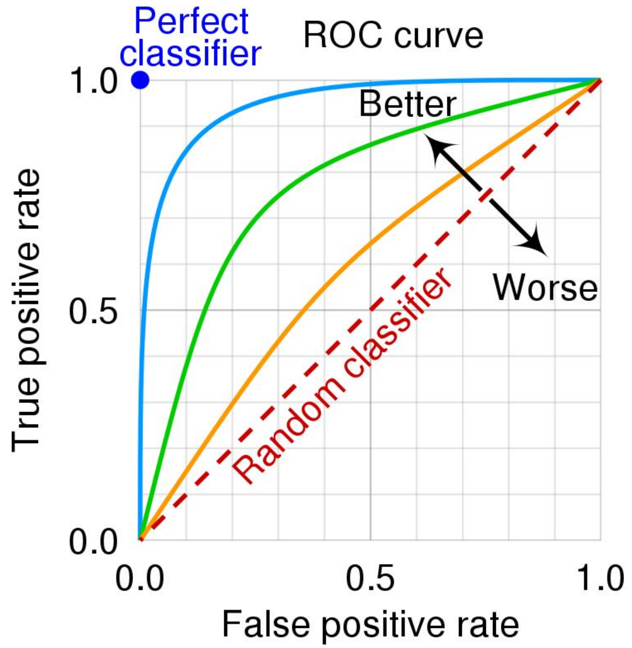
Added with flatten node to the last convolution block and 3 fully connected layers at the end of the model.

VGG NETWORK - METHODOLOGY

- Data:
  - National Taiwan University Hospital;
  - The Medical Segmentation Decathlon;
  - TCIA;
  - More than 14,000 CT images.
  - The images were done by six scanners, for example Philips and Siemens models, with slice thickness between 0.7-1.5 millimeters and image size 512 x 512 pixels;

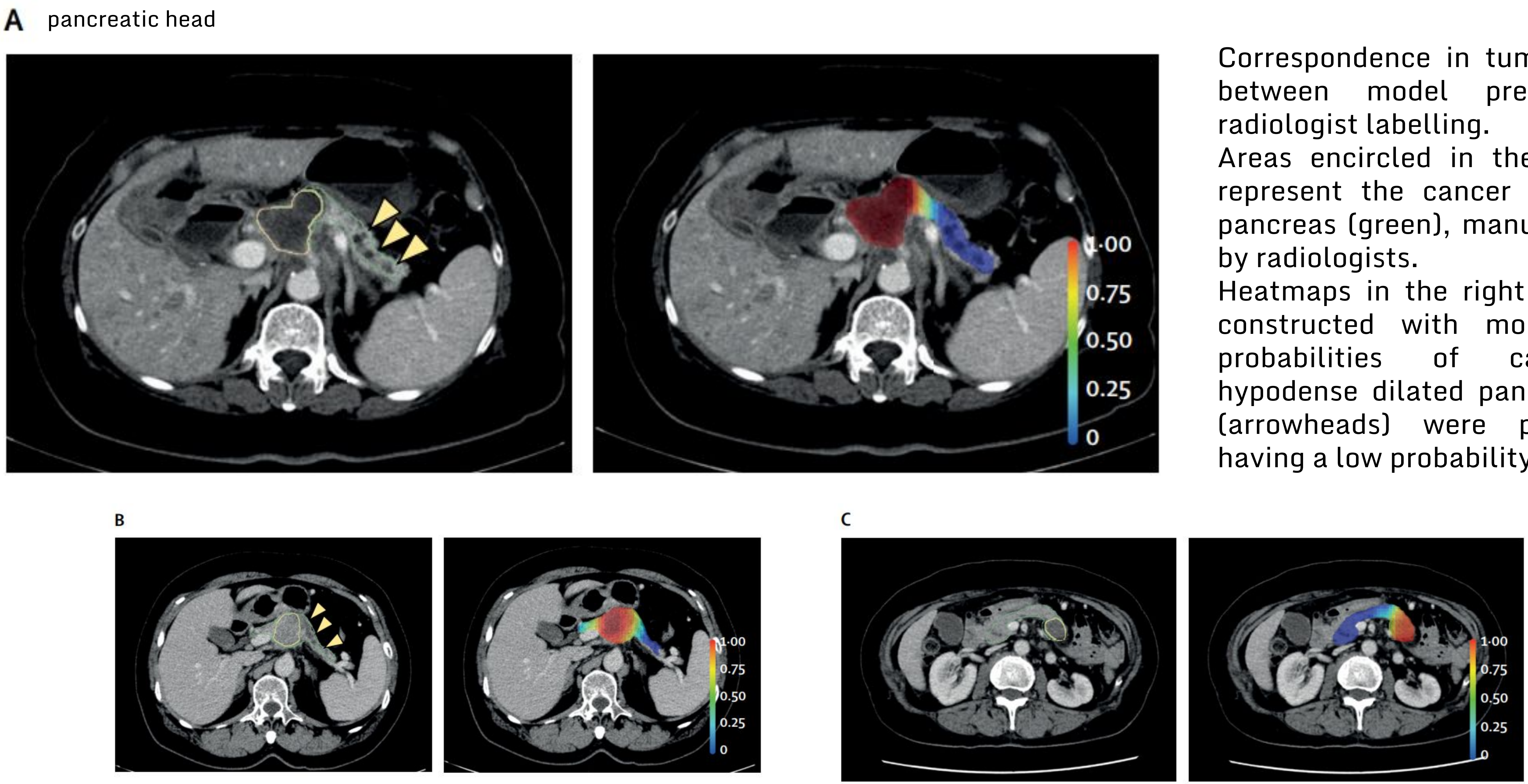
- Details:
  - For the process of classification been optimized, two callbacks were added in the model, based on the loss function;
- Evaluation:
  - (1) patch-based and (2) patient-based;
  - Success was evaluated by sensitivity, specificity, accuracy and area under ROC curve (AUC).

		Gold Standard	
		1	0
Model Predict / Test	1	True Positive	False Positive
	0	False Negative	True Negative



Source: Receiver operating characteristic. (2022, October 24). In *Wikipedia*.

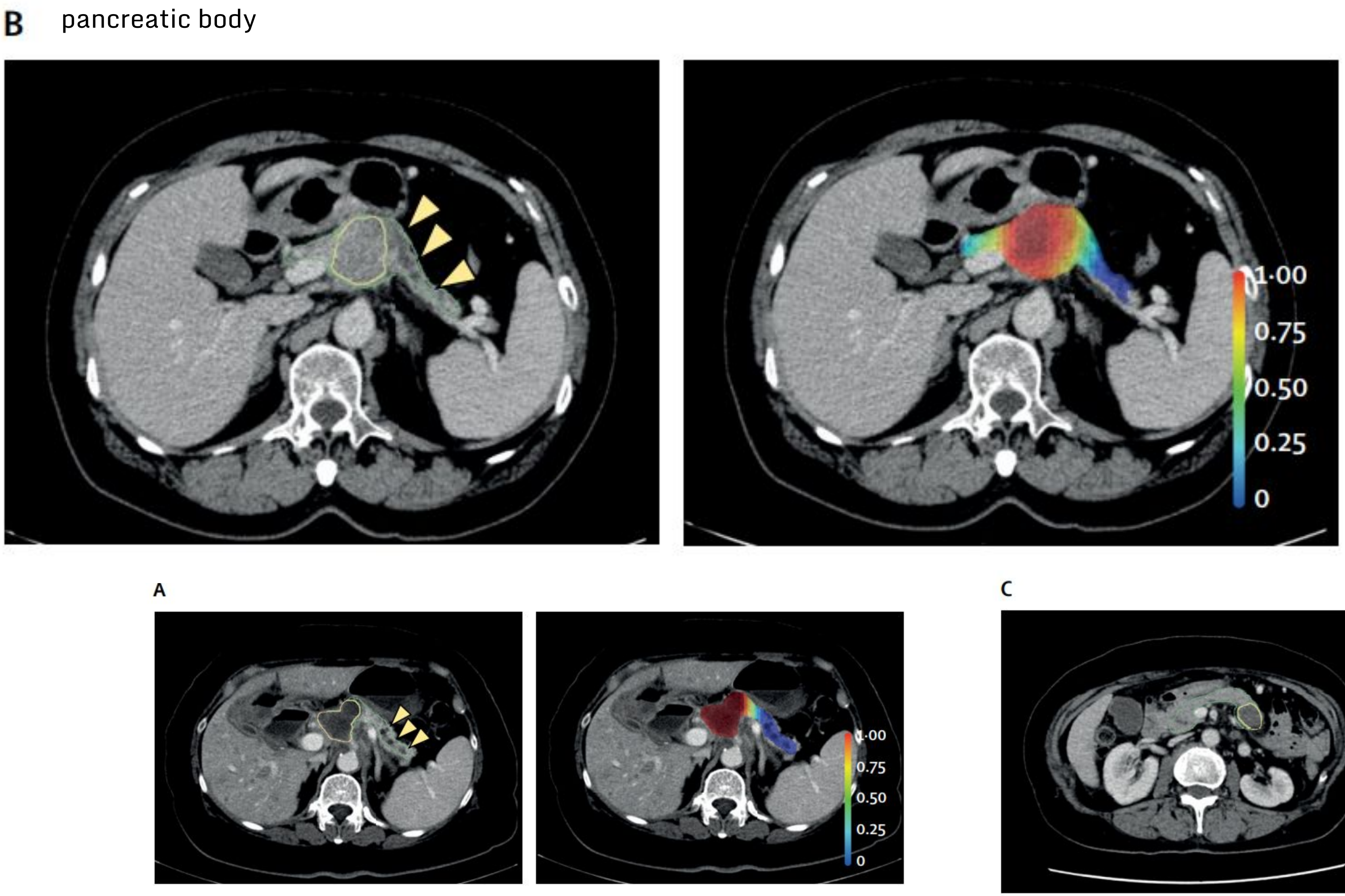
VGG NETWORK - RESULTS



Correspondence in tumour location between model prediction and radiologist labelling.
Areas encircled in the left panels represent the cancer (yellow) and pancreas (green), manually labelled by radiologists.
Heatmaps in the right panels were constructed with model-predicted probabilities of cancer. The hypodense dilated pancreatic ducts (arrowheads) were predicted as having a low probability of cancer.

Source: Adapted from Liu et al. (2020).

VGG NETWORK - RESULTS



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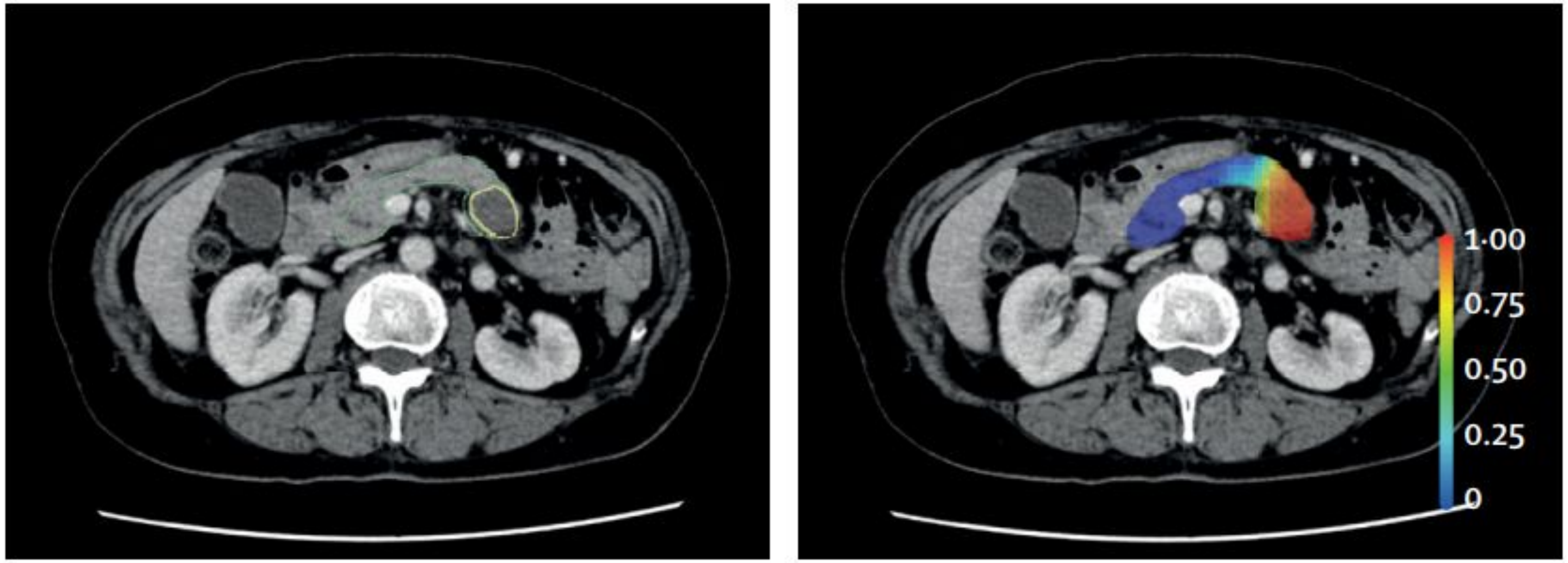
VGG NETWORK - RESULTS

C pancreatic tail



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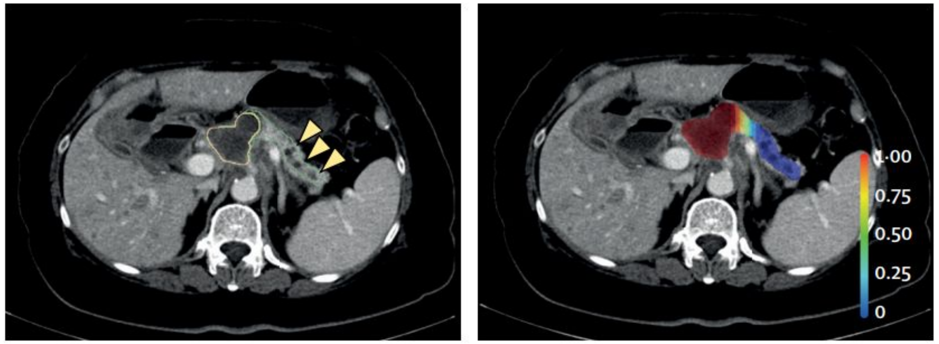
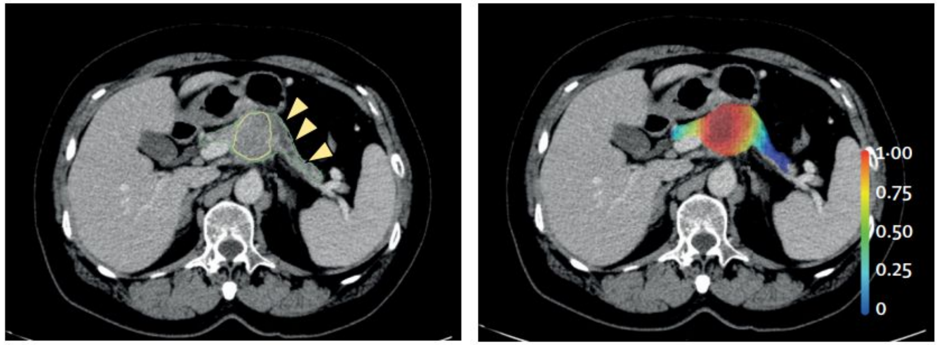
A



B



Source: Adapted from Liu et al. (2020).

VGG NETWORK - RESULTS

The rates of the CNN model are higher than the human performance of diagnosing the samples, achieving an sensitivity rate of nearly 98%. And between the (1) and (2) analysis, the second one has had greater results with 95% of confidence.

Table 4. Performance of trained CNN and radiologist.

	Sensitivity	Specificity	Balanced Accuracy	Area under the ROC curve	Sensitivity of Radiologist	Difference
Local training and validation set						
(1)	0.913	0.845	0.879	0.955	-	-
(2)	0.973	1.000	0.986	1.000	-	-
Local test set 1						
(1)	0.912	0.858	0.885	0.960	-	-
(2)	0.973	1.000	0.987	0.997	0.944	0.029
Local test set 2						
(1)	0.878	0.850	0.864	0.942	-	-
(2)	0.990	0.989	0.989	0.999	0.917	0.073
External test set						
(1)	0.613	0.768	0.690	0.750	-	-
(2)	0.790	0.976	0.883	0.920	-	-

Source: Adapted from Liu et al. (2020).

3 MACHINE LEARNING APPLICATIONS ANALYSIS

4. Establishment and application of an artificial intelligence diagnosis system for pancreatic cancer with a faster region-based convolutional neural network.

(Liu et al. 2019)

FASTER REGION CNN - METHODOLOGY

- 338 patients, 6084 images
- Split 70%-30% for training and test
- Three phases:
  - Feature extraction network, where a convolutional feature map of the image is generated using a VGG
  - Region Proposal Network (RPN): the feature map created above is used to generate regions of interest (ROI), which are the regions with a higher probability to find pancreatic malignancies
  - Proposal classification and regression network: coordinates and probability scores are assigned to regions of the image

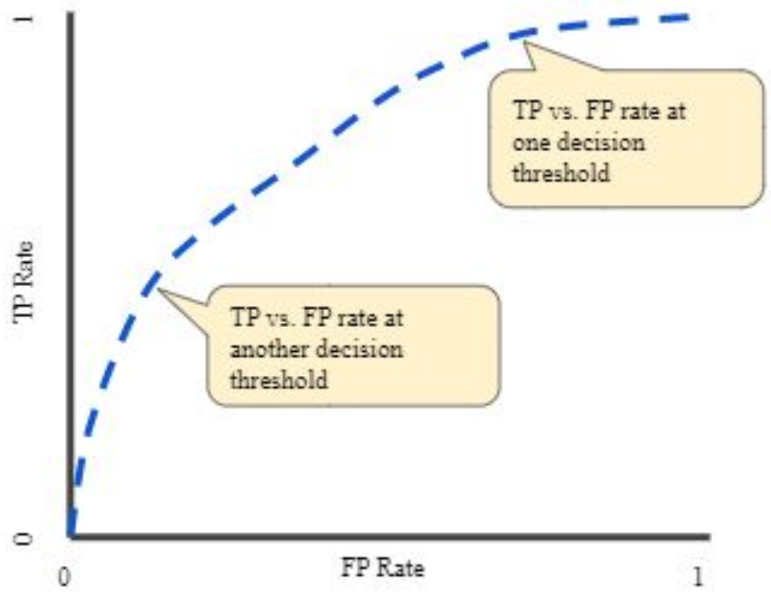
FASTER REGION CNN - METHODOLOGY

- Features used for the algorithm:
  - Age
  - Sex
  - Number of metastatic lymph nodes via CT
  - Number of metastatic lymph nodes via pathology
  - N stage (tells whether cancer has spread to the nearby lymph nodes)
  - Degree of tumor differentiation
  - Presence or absence of intravascular tumor thrombus
  - Presence or absence of nerve infiltration

FASTER REGION CNN - METHODOLOGY

- Images were analyzed by senior experienced radiologists (5 years of working experience)
- Labels for classification:
  - Pancreatic tumor
  - Normal pancreatic tissue
  - Chronic pancreatitis
  - Benign pancreatic tumor
- A clear advantage of the AI method was the time required for analysis, which was about 3 seconds rather than 8 minutes for imaging specialists

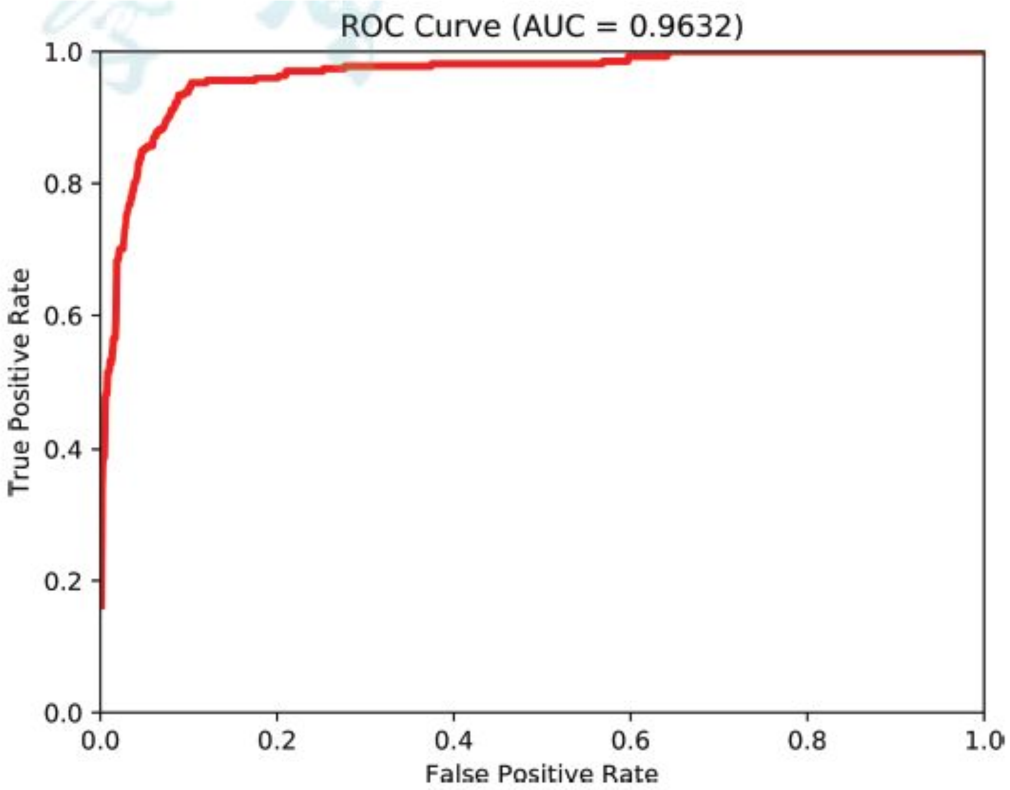
- Receiver Operating Curve (ROC)



$$TPR = \frac{TP}{TP + FN} = \frac{hits}{hits + misses}$$

$$FPR = \frac{FP}{FP + TN} = \frac{false\ alarms}{false\ alarms + correct\ rejections}$$

- As a measurement of its performance, the Area Under Curve (AUC) of the ROC resulted in a value of 0.9632
- We may conclude that the diagnostic capability of the trained Faster R-CNN AI system is quite high, as well as very effective since its maximum value is unity



Source: Liu et al. (2019)

FASTER REGION CNN - RESULTS

- Limitations of the verification process are
  - Only images of patients with pancreatic cancer were used
  - Data from only one clinical center

3 MACHINE LEARNING APPLICATIONS ANALYSIS

5. Construction of a convolutional neural network classifier developed by computed tomography images for pancreatic cancer diagnosis.

(Ma et al. 2020)

CONVOLUTIONAL LAYERS, BN, ReLU - METHODOLOGY

- 222 patients, 3494 images
- Split into training, verification and validation
  - 10-fold cross validation
- Plain scan
- Arterial phase
- Venous phase

Source:
towardsdatascience.com

CONVOLUTIONAL LAYERS, BN, ReLU - METHODOLOGY

- Binary classifiers
  - No cancer
  - Cancer
- Ternary classifiers
  - No cancer
  - Cancer at tail or body
  - Cancer at head or neck
- Surgical approach according to mass location

CONVOLUTIONAL LAYERS, BN, ReLU - METHODOLOGY

- Accuracy
  - Ratio between the number of correct predictions and all predictions
- Sensitivity
  - Ratio between the correctly predicted non-malignant cases and all non-malignant cases
  - Probability of a positive test given that the patient has the disease
- Specificity
  - Correctly predicted malignant lesions over all images classified as malignant
  - Probability of a negative test given that the patient is well

CONVOLUTIONAL LAYERS, BN, ReLU - RESULTS

- Binary classifier achieved high effectiveness, which can be seen when compared to the specialist's analysis

Dataset	Plain scan	Arterial phase	Venous phase	χ^2 value	p value
Accuracy	0.954747	0.957580	0.951549	0.346	0.841
Sensitivity	0.982710	0.975695	0.978692	0.149	0.928
Specificity	0.915758	0.940808	0.922756	0.914	0.633

Dataset	CNN	Gastroenterologists
Number of doctors	-	10
Accuracy	0.954747	0.922
Sensitivity	0.982710	0.923
Specificity	0.915758	0.921

Source: Ma et al. (2020)

CONVOLUTIONAL LAYERS, BN, ReLU - RESULTS

- Ternary classification, in turn, requires further studies, but can be used to localize the mass with moderate performance

Dataset	Plain scan	Arterial phase	Venous phase	χ^2 value	p value
Accuracy	0.820568	0.790633	0.788076	1.074	0.585
Sensitivity	0.985721	0.984770	0.990305	0.577	0.749
Specificity (tail/body)	0.520122	0.411098	0.360272	1.841	0.398
Specificity (head/neck)	0.462148	0.852390	0.728743	16.651	<0.001

Source: Ma et al. (2020)

4 RESULTS COMPARISON

Summarized Results of Literature

Article	Techniques	Results
Xuan & You, 2020.	HCNN for detection and CNN-RNN for segmentation.	- 95.10% Stabilized precision ratio; - 97.33% Dice index; - 97.66% Sensitivity Ratio; - 96.12% Specificity Ratio.
Sekaran et al., 2019.	Gaussian Mixture Model (GMM) with Expectation Maximization (EM) for feature extraction and a CNN model for classification.	The recognition ratio using 1,000 CT images to feature extraction on model training was 99.9%.
Liu et al., 2020.	CNN model derived from the Visual Geometry Group (VGG) network for classification.	Local Test set 1 - 97.3% Sensitivity Ratio; - 100% Specificity Ratio; - 98.7% Balanced Accuracy. Local Test set 2 - 99.0% Sensitivity Ratio; - 98.9% Specificity Ratio; - 98.9% Balanced Accuracy. External Test set - 79.0% Sensitivity Ratio; - 97.6% Specificity Ratio; - 88.3% Balanced Accuracy.
Liu et al., 2019.	Faster region CNN: feature extraction, region proposal network (RPN), proposal classification and regression network.	- AUC: 0.9632.
Ma et al., 2020.	Three convolutional layers and one fully connected, and then a batch normalization (BN), a rectified linear unit (ReLU), and a max-pooling layer.	Binary classifiers Accuracy: 95.4%; Sensitivity: 98.3%; Specificity: 91.6%. Ternary classifiers Accuracy: 82.1%; Sensitivity: 98.6%; Specificity (tail/body): 52.0%; Specificity (head/neck): 46.2%.

5 CONCLUSIONS

CONCLUSIONS AND DISCUSSIONS

- Deep Learning techniques are very promising in PDAC detection
- Measurements such as AUC of the ROC, accuracy, specificity, and sensitivity are high enough to believe and be enthusiastic about applying DL algorithms for pancreatic cancer detection purposes
- There are still many considerations to be taken if one desires to use it on a large scale
- Limitations
    - Concentrated population sampling
    - Short health history of patients
- No universal model could be achieved so far
- Demographic models

THANK YOU!

QUESTIONS?

References

SCAN ME