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# Lung and Pancreatic Tumor Characterization in the Deep Learning Era: Novel Supervised and Unsupervised Learning Approaches

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**Abstract**: *Through computer-aided diagnostic (CAD) technologies, it is possible to characterize cancers from radiological pictures more accurately and quickly. As part of precision medicine, tumor characterisation using these technologies can also facilitate non-invasive cancer staging, prognosis, and individualized therapy planning. In order to enhance tumor characterisation, we suggest both supervised and unsupervised machine learning techniques in this work. We show notable improvements using deep learning algorithms for our first method, which is based on supervised learning, especially when using a 3D Convolutional Neural Network with Transfer Learning. We then demonstrate how to integrate task-dependent feature representations into a CAD system using a graph-regularized sparse Multi-Task Learning (MTL) framework, which is inspired by the radiologists' interpretations of the scans. In the second method, we investigate an unsupervised learning technique to solve a prevalent issue in medical imaging applications: the scarcity of labeled training data. We suggest using proportion-SVM to characterize tumors, which is inspired by learning from label proportion (LLP) techniques in computer vision. Additionally, we look for the answer to the fundamental question of whether "deep features" are good for unsupervised tumor classification. We test the state-of-the-art sensitivity and specificity findings in both the lung and pancreas tumor diagnosis challenges using 1018 CT and 171 MRI scans, respectively, to assess our suggested supervised and unsupervised learning techniques.*

**Keywords***:* Unsupervised Learning, Lung cancer, 3D CNN, IPMN, Pancreatic cancer

## I. INTRODUCTION

Based on deaths from 2008 to 2012, the overall mortality rate for cancer is 171.2 per 100,000 people annually, meaning that about 40% of people will receive a cancer diagnosis at some point in their lives [1]. [1]. Lung and pancreatic cancers are two of the most common cancers. While lung cancer is the largest cause of cancer-related deaths in the world, pancreatic cancer has the poorest prognosis with a 5-year survival rate of only 7% in the United States [1]. With regards to pancreatic cancer, specifically in this work, we focus on the challenging prob- lem of automatic diagnosis of Intraductal Papillary Mucinous Neoplasms (IPMN). IPMN is a pre-malignant condition and if left untreated, it can progress to invasive cancer. IPMN is mucin-producing neoplasm that can be found in the main pancreatic duct and its branches. They are radiographically unsupervised learning and establish an upper bound on the classification performance using supervised learning methods. Finally, Section 6 states discussions and concluding remarks.

## II. STRUCTURE

A block diagram to represent different schemes, methods and experimental case studies presented in this pa- per. We develop both supervised and unsupervised learning algorithms to characterize tumors. For the supervised learning scheme, we propose a new 3D CNN architecture based on a Graph Regularized Sparse Multi-task learning and perform evaluations for lung nodule characterization from CT scans. For unsupervised learning scheme, we propose a new clus- tering algorithm, ∝SVM, and test it for the categorization of lung nodules from CT scans and pancreatic cysts (IPMN) from MRI scans. identifiable precursors to pancreatic cancer [2]. Detection and characterization of these lung and pancreatic tumors can aid in early diagnosis; hence, increased survival chance through appropriate treatment/surgery plans. Conventionally, the CAD systems are designed to assist radiologists in making accurate and fast decisions by reduc- ing the number of false positives and false negatives. For diagnostic decision making, a higher emphasis is laid on increased sensitivity: a false-flag is more tolerable than a tumor being missed or incorrectly classified as benign. In this regard, a computerized analysis of imaging features becomes a key instrument for radiologists to improve their diagnostic decisions. In the literature, automated detection and diagnosis methods had been developed for tumors in different organs such as breast, colon, brain, lung, liver, prostate, and others. As typical in such studies, a CAD includes preprocessing and feature engineering steps (including feature extraction and selection) followed by a classification step [3],[4],[5],[6]. However, with the success of deep learning, a transition from feature engineering to feature learning has been observed in medical image analysis literature. Those systems comprise Convolutional Neural Networks (CNN) as feature extractor followed by a conventional classifier such as Random Forest (RF) [7],[8]. In scenarios where a large number of labeled training examples are available, however, end-to-end trainable deep learning approaches can be employed [9].

This paper includes two main approaches for tumorcharac- terization from radiology scans: supervised and unsupervised learning algorithms. In the first part, we focus on novel supervised algorithms, which is a significant extension to our IPMI 2017 study [10]. Specifically, we first present a novel su- pervised learning strategy to perform risk-stratification of lung nodules from low-dose CT scans. For this strategy, we per- form a 3D CNN based discriminative feature extraction from radiology scans. We contend that 3D networks are important for the characterization of lung nodules in CT images which are inherently 3-dimensional. The use of conventional 2D CNN methods, whereas, leads to the loss of vital volumetric information which can be crucial for precise risk assessment of lung nodules. In the absence of a large number of labeled training examples, we utilize a pre-trained 3D CNN archi- tecture and fine-tune the network with lung nodules dataset. Also, inspired by the significance of lung nodule attributes for clinical determination of malignancy [11], we utilize the information about six high-level nodule attributes such as calcification, spiculation, sphericity, lobulation, margin, and texture (Figure 2-A) to improve automatic benign-malignant classification. Then, we integrate these high-level features into a novel graph regularized multi-task learning (MTL) frame- work to yield the final malignancy output. We analyze the impact of the aforementioned lung nodule attributes in-depth for malignancy determination and find these attributes to be complementary when obtaining the malignancy scores. From a technical perspective, we also exploit different regularizers and multi-task learning approaches such as trace-norm and graph regularized MTL for regression.

In the second part of the paper, inspired by the success- ful application of unsupervised learning methods in other domains, we explore the potential of unsupervised learning strategies in lung nodule and IPMN classification. First, we extract discriminative information from a large amount of unlabeled imaging data. We analyze both hand-crafted and deep learning features and assess how good those features are when applied to tumor characterization. In order to obtain an initial set of labels in an unsupervised fashion, we cluster the samples into different groups in the feature domain. We next propose to train Proportion-Support Vector Machine (∝SVM) algorithm using label proportions rather than instance labels. The trained model is then employed to learn malignant-benign categorization of the tumors. This paper is organized as follows. Section 2 describes re- lated work pertaining to supervised and unsupervised learning for the diagnosis of lung nodules and IPMN. We present our MTL based supervised learning algorithm we introduce an unsupervised learning method adapted for the diagnosis of lung nodules and IPMN from CT and MRI scans, respectively.

## III. RELATED WORK

The developments in machine learning as they relate to medical imaging and CAD systems created for the diagnosis of lung cancer are compiled in this section. Relevant works are primarily chosen from the clinical trials because the automatic characterization of IPMN from MRI scans has not been thoroughly investigated in the literature. In this sense, our work is the first.

Imaging Features and Classifiers: Traditionally, nodule segmentation, the computation and selection of low-level characteristics from the picture, and the application of a classifier/regressor may be necessary for the risk stratification

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(classification) of lung nodules. In the method by [12], class labels were produced using Artificial Neural Networks and other physical statistics, such as intensity measures, were recovered. In [3], spherical harmonics were used for shape analysis after appearance-based models were used to segment lung nodules. The final step was a classification based on k-nearest neighbors. Local Binary Patterns, Gabor, and Haralick are examples of 2D texture characteristics that were extended to 3D by another approach [4]. The last phase was classification using Support Vector Machines (SVM). Another study by Way et al. [5], implemented nod- ule segmentation via 3D active contours, and then applied rubber band straightening transform. A Linear Discriminant Analysis (LDA) classifier was applied to get class labels. Lee et al. [6] introduced a feature selection based approach utilizing both clinical and imaging data. Information content and feature relevance were measured using an ensemble of genetic algorithm and random subspace method. Lastly, LDA was applied to obtain final classification on the condensed feature set. In a recent work, spherical harmonics features were fused with deep learning features [8] and then RF classification was employed for lung nodule characterization. Hitherto, the application of CNN for nodule characterization has been limited to 2D space [13], thus falling short of incorporating vital contextual and volumetric information. In another approach, Shin et al. [14] employed CNN for the classification of lung nodules. Other than not completely 3D CNN, the approach didn't take into account high-level nodule attributes and required training an off-the-shelf classifier such as RF and SVM.

**Pancreatic Cysts (IPMN):** Even while automatic methods for segmenting the pancreas and associated cysts have evolved significantly [19], [20], there is little use of sophisticated machine learning algorithms for fully automatic risk-stratification of IPMNs. The method used by Hanania et al. [21] examined how 360-degree imaging characteristics, such as shape, texture, and intensity, may be used to categorize people as having low- or high-grade IPMN. In a another example, Gazit et al. [22] used a feature selection and classification strategy after extracting texture and characteristics from the solid component of segmented cysts. These two methods [21], [22] are only assessed on CT images and necessitated the segmentation of the pancreas or cysts.

**Unsupervised Learning:** Usually, labeled data (supervision) is used to handle the visual identification and classification tasks. However, the use of unsupervised learning techniques is very beneficial for applications where it is time-consuming and costly to manually generate labels matching to huge datasets. Problems in a variety of fields, including object classification [23], speech processing [24], and audio classification [25], have been resolved using unsupervised approaches. Traditionally, these techniques used supplementary information that was included with the data to enhance learning, which may not be accessible for a number of medical imaging classification problems. In medical imaging, there have been different approaches that used unsupervised learning for detection and diagnosis problems. The approach by Shin et al. [26] used stacked au- toencoders for multiple organ detection in MRI scans. Vaidhya et al. [27] presented a brain tumor segmentation method with stacked denoising autoencoder evaluated on multi-sequence MRI images. In a work by Sivakumar et al. [28], the segmenta- tion of lung nodules is performed with unsupervised clustering methods. In another study, Kumar et al. [7] used features from autoencoder for lung nodule classification. These auto-encoder approaches, however, did not yield satisfactory classification results. Other than these, unsupervised deep learning has also been explored for mammographic risk prediction and breast density segmentation [29].

**Our Contribution:**A block diagram representing different supervised and unsu- pervised schemes is presented in Figure 1. Overall, our main contributions in this work can be summarized as follows:

For lung nodule characterization, we present a 3D CNN based supervised learning approach to fully appreciate the anatomical information in 3D, which would be otherwise lost in the conventional 2D approaches. We use fine-tuning strategy to avoid the requirement for a large number of volumetric training examples for 3D CNN. For this purpose. we use a pre-trained network (which is trained on 1 million videos) and fine-tune it on the CT data.

We introduce a graph regularized sparse MTL platform to integrate the complementary features from lung nodule attributes so as to improve malignancy prediction. Figure 2- A shows high-level lung nodule attributes having varying levels of prominence.

We evaluate the proposed supervised and unsupervised learning algorithms to determine the characterization of lung nodules and IPMN cysts (Table I). In the era where the wave of deep learning has swept into almost all domains of

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visual analysis, we investigate the contribution of features extracted from different deep learning architectures. To the best of our knowledge, this is the first work to investigate the automatic diagnosis of IPMNs from MRI.

In the proposed unsupervised learning algorithm, instead of hard assigning labels, we estimate the label proportions in a data-driven manner. Additionally, to alleviate the effect of noisy labels (i.e. mislabels) obtained during clustering, we propose to employ ∝SVM, which is trained on label proportions only.

**TABLE I:** List and details of different experiments performed for supervised and unsupervised learning along with their evaluation sets.

| Experiments | Details | EvaluationSet |
|---|---|---|
| E1 | Supervisedlearning,3DCNNbased Multi-task learning with attributes, fine-tuning (C3D) network | 3Ddataset: Malignancy scoreregressionofLungnodules (CT) |
| E2 | Unsupervised learning, GIST features, Proportion-SVM | 2D dataset:Lung nodules(CT)andIPMN classification(MRI) |
| E3 | Unsupervisedlearning,featuresfrom differentlayersof2DVGGnetwork | |
| E4 | Supervisedlearningtoestablish classification upper-bound, GIST and VGGfeatures with SVM and RF | |

**TABLE II:** The comparison of the proposed approach with other methods using regression accuracy and mean absolute score difference for lung nodule characterization.

| Methods | Accuracy % | Mean Score Difference |
|---|---|---|
| GIST features + LASSO | 76.83 | 0.675 |
| GIST features + RR | 76.48 | 0.674 |
| 3D CNN features + LASSO (Pre-trained) | 86.02 | 0.530 |
| 3D CNN features + RR (Pre-trained) | 82.00 | 0.597 |
| 3D CNN features + LASSO (Fine-tuned) | 88.04 | 0.497 |
| 3D CNN features + RR (Fine-tuned) | 84.53 | 0.550 |
| 3D CNN MTL with Trace norm | 80.08 | 0.626 |
| Proposed (3D CNN with Multi-task Learning- Eq. 7) | 91.26 | 0.459 |

For computing structure matrix S, we calculate the corre- lation between different tasks by estimating the normalized coefficient matrix W via least square loss function with lasso followed by the calculation of correlation coefficient matrix [36]. In order to get a binary graph structure matrix, we thresholded the correlation coefficient matrix. As priors in Eq. (6) we used ρ1 and ρ2 as 1 and 10 respectively. Finally, to obtain the malignancy score for test images, the features from the network trained on malignancy were multiplied with the corresponding task coefficient vector W .

We evaluated our proposed approach using both classifi- cation and regression metrics. For classification, we consid- ered a nodule to be successfully classified if its predicted score lies in ±1 of the ground truth score. For regression, we calculated average absolute score difference between the predicted score and the true score. The comparison of our proposed MTL approach with approaches including GIST features [41], 3D CNN features from pre-trained network + LASSO, Ridge Regression (RR) and 3D CNN MTL+trace norm is tabulated in Table II. It can be observed that our proposed graph regularized MTL performs significantly better than other approaches both in terms of classification accuracy as well as the mean score difference. The gain in classification accuracy was found to be 15% and 11% for GIST and trace- norm respectively. In comparison with the pre-trained network, we obtain an improvement of 5% with proposed MTL. In addition, our proposed approach reduces the average absolute score difference for GIST by 32% and for trace-norm by 27%.

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**TABLE III:** Average classification accuracy, sensitivity, and specificity of the proposed unsupervised approach for IPMN and lung nodule classification with other methods

| Evaluation Set | Methods | Accuracy | Sensitivity | Specificity |
|---|---|---|---|---|
| *IPMN Classification* | Clustering | 49.18% | 45.34% | 62.83% |
| | Clustering+RF | 53.20% | 51.28% | **69.33%** |
| | Clustering+SVM | 52.03% | 51.96% | 50.5% |
| | **Proposed approach** | **58.04%** | **58.61%** | 41.67% |
| *Lung Nodule Classification* | Clustering | 54.83% | 48.69% | 60.04% |
| | Clustering+RF | 76.74% | 58.59% | **91.40%** |
| | Clustering+SVM | 76.04% | 57.08% | 91.28% |
| | **Proposed approach** | **78.06%** | **77.85%** | 78.28% |

## IV. DISCUSSION AND CONCLUDING REMARKS

In this study, we present a framework for the malignancy determination of lung nodules with 3D CNN based graph regularized sparse MTL. To the best of our knowledge, this is the first work where MTL and transfer learning are studied for 3D deep networks to improve risk stratification of lung nodules. Usually, the data sharing for medical imaging is highly regulated and the accessibility of experts (radiologists) to label these images is limited. As a consequence, the access to the crowdsourced and publicly gathered and annotated data such as videos may help in obtaining discriminative features for medical image analysis. We also analyzed the significance of different imaging attributes corresponding to lung nodules including spiculation, texture, calcification and others for risk assessment. Instead of manually modeling these attributes we utilized 3D CNN to learn rich feature representations associated with these attributes. The graph regularized sparse MTL framework was employed to integrate 3D CNN features from these attributes. We have found the features associated with these attributes complementary to those corresponding to malignancy.

Following up on the application of deep learning for almost all tasks in the visual domain, we studied the influence of dif- ferent pre-trained deep networks for lung nodule classification. For some instances, we found that commonly used imaging features such as GIST have comparable results as those obtained from pre-trained network features. This observation can be explained by the fact that the deep networks were trained on ImageNet classification tasks so the filters in CNN were more tuned to the nuances in natural images as compared to medical images To the best of our knowledge, this is one of the first and the largest evaluation of a CAD system for IPMN classification. CAD systems for IPMN classification are relatively newer research problems and there is a need to explore the use of dif- ferent imaging modalities to improve classification. Although MRI remains the most common modality to study pancreatic cysts, CT images can also be used as a complementary imaging modality due to its higher resolution and its ability to capture smaller cysts. Additionally, a combination of T2-weighted, contrast-enhanced and unenhanced T1-weighted sequences can help improve detection and diagnosis of IPMN [44]. In this regard, multi-modal deep learning architectures can be deemed useful [45]. The detection and segmentation of pancreas can also be useful to make a better prediction about the presence of IPMN and cysts. Due to its anatomy, the pancreas is a challenging organ to segment, particularly in MRI images. To address this challenge, other imaging modalities can be utilized for joint segmentation and diagnosis of pancreatic cysts and IPMN. Furthermore, visualization of activation maps can be quite useful for the clinicians to identify new imaging biomarkers that can be employed for diagnosis in the future.

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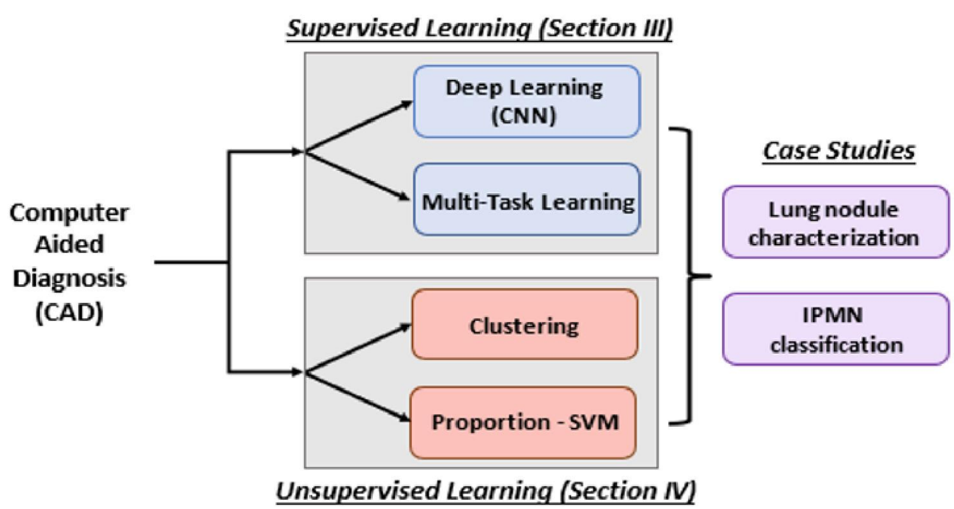
**TABLE IV:** Classification of IPMN and Lung Nodules using different features and supervised learning classifiers.

| Evaluation Set | Features | Classifiers | Accuracy(%) | Sensitivity(%) | Specificity(%) |
|---|---|---|---|---|---|
| *IPMN Classification* | GIST | SVM | 76.05 | 83.65 | **52.67** |
| | | RF | 81.9 | 93.69 | 43.0 |
| | VGG-fc7 | SVM | 84.18 | 96.91 | 44.83 |
| | | RF | 81.96 | 94.61 | 42.83 |
| | VGG-fc8 | SVM | **84.22** | **97.2** | 46.5 |
| | | RF | 80.82 | 93.4 | 45.67 |
| *LungNodule Classification* | GIST | SVM | 81.56 | 71.31 | 90.02 |
| | | RF | 81.64 | 76.47 | **85.97** |
| | VGG-fc7 | SVM | 77.97 | 75.2 | 80.6 |
| | | RF | **81.73** | **78.24** | 84.59 |
| | VGG-fc8 | SVM | 78.76 | 74.67 | 82.29 |
| | | RF | 80.51 | 76.03 | 84.24 |

Medical imaging has unique challenges associated with the scarcity of labeled examples. Moreover, unless corroborated by biopsy, there may exist a large variability in labeling from different radiologists. Although fine-tuning has helped to address the lack of annotated examples, the performance is limited due to large differences in domains. It is comparatively easier to obtain scan level labels than slice level labels. In this regard, weakly supervised approaches such as multiple instance learning (MIL) can be of great value. Active learning can be another solution to alleviate the difficulty in labeling. In addition to these directions, unsupervised learning approaches will surely be pursued to address unique medical imaging challenges.



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