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A Deep Multi-Task Network to Learn Tumor Pathological Representations for Lymph Node Metastasis Prediction

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Abstract. Lymph node metastasis is of paramount importance for patient treatment decision-making, prognosis evaluation, and clinical trial enrollment. However, accurate preoperative diagnosis remains challenging. In this study, we proposed a multi-task network to learn the primary tumor pathological features using the pT stage prediction task and leverage these features to facilitate lymph node metastasis prediction. We conducted experiments using electronic medical record data from 681 patients with non-small cell lung cancer. The proposed method achieved a 0.768 area under the receiver operating characteristic curve (AUC) value with a 0.073 standard deviation (SD) and a 0.448 average precision (AP) value with a 0.113 SD for lymph node metastasis prediction, which significantly outperformed the baseline models. Based on the results, we can conclude that the proposed multi-task method can effectively learn representations about tumor pathological conditions to support lymph node metastasis prediction.

Keywords. Multi-task learning, lymph node metastasis prediction, deep learning

1. Introduction

Lung cancer is the leading cause of cancer death worldwide. Lymph node metastasis (LNM) is critical for treatment decision-making and prognosis evaluation of lung cancer patients [1]. In clinical practice, clinicians usually use the Tumor-Node-Metastasis (TNM) stage system to evaluate the patient's disease progression from three aspects, i.e., tumor extent (T), lymph node metastasis (N), and distant metastasis (M) [2]. For the N stage, clinicians use the short axis of lymph node>10mm or the SUVmax of lymph node>2.5 as the criteria to determine the presence of LNM and group the patients into different N stages (N0/N1/N2/N3). However, these criteria cannot achieve accurate preoperative N staging, so many patients are misdiagnosed and receive suboptimal treatments [3].

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To achieve accurate LNM prediction for lung cancer patients, researchers first employed statistical analysis to find clinical features related to LNM to develop logistic regression (LR) models [4,5]. Besides, machine learning methods were also employed to train the LNM prediction models [6]. To fully exploit the image data, researchers applied radiomic methods to extract massive image features from the primary tumor regions to develop LNM prediction models [7]. However, annotating the regions of interest (ROI) on each image slice is extremely time-consuming and different annotators may have different annotation results.

With the great success of deep learning in computer vision, many researchers tried to develop deep learning models for LNM prediction [8]. Compared with radiomic methods, deep learning methods can learn the image features without ROI annotations and combine them with the clinical features to predict LNM in an end-to-end manner. Furthermore, some researchers proposed multi-task learning methods to simultaneously segment the primary tumor and predict the LNM to enforce the models to focus on the primary tumor regions, which contain wealthy information relevant to LNM [9, 10]. But, the annotations of ROI are still indispensable for training these multi-task models.

Although most studies tried to extract features from the images of the primary tumor region, note that the image appearance of the tumor may not reflect its actual condition. As reported in a recent study, only 65.4% of patients have clinical T stages consistent with their pathological T stages [3], which indicates the image findings are quite different from the actual pathological statuses. In this study, we assume that the pathological T (pT) stages of the primary tumors are useful for LNM prediction and propose a multi-task learning method to predict pT stages and LNM simultaneously. Using the pT stage prediction as an auxiliary task, our multi-task model can learn the tumor pathological representations to improve the LNM prediction performance. To the best of our knowledge, this is the first study to employ the pT stage prediction task to support the LNM prediction.

2. Methods

2.1. Data

We collected 681 patients' electronic medical record (EMR) data from the Department of Thoracic Surgery II of Peking University Cancer Hospital. All patients were diagnosed with non-small cell lung cancer (NSCLC) and underwent surgical resection with systematic mediastinal lymphadenectomy from 2010 to 2018. All patients did not receive preoperative chemotherapy or radiotherapy. The collected EMR data includes demographics, tumor biomarkers, disease histories, computerized tomography (CT) images, CT reports, and pathology reports.

2.2. Preprocessing

The demographics, tumor biomarkers, and disease histories are structured. For CT reports, we employed information extraction tools developed in our previous works[11, 12] to extract features about the primary tumor and lymph nodes. The extracted results were reviewed by the clinicians. For CT images, we first resized the image voxel to 0.7×0.7×5mm, clipped the voxel intensity in [-1000,400], and converted it to [-1,1]. And then, a 224×224×s voxel patch was cropped with the tumor at the center where 224 is

the height and width, and s is the number of slices the tumor appears. The clinicians manually annotated the pT and pathological N (pN) stages recorded in the pathology reports. We used 7-class labels, i.e., pT1a, pT1b, pT1c, pT2a, pT2b, pT3, pT4, for pT stage prediction. Because patients with N2 LNM are a heterogeneous group and may be offered chemoradiation therapy or surgery with preoperative chemotherapy. We used the pN2 or not as the labels for LNM prediction.

2.3. Multi-task Network

The architecture of the multi-task network is illustrated in Figure 1. We first used the ResNet50 as the backbone network to extract the features from each image slice. And then, two transformer encoder layers were employed to share the information between image slices. After that, an average pooling layer was applied to combine the information in different image slices. Finally, a fully connected (FC) layer was employed to reduce the image features to 8 dimensions.

After obtaining the image features, the pT stage prediction task used an FC layer to reflect these features to 7 outputs and a softmax layer to get the probabilities for each pT stage. The LNM prediction task concatenated the image features with clinical features and used another FC layer to reflect the vector to 2 outputs. A softmax layer was also employed to obtain the probability of pN2 LNM.

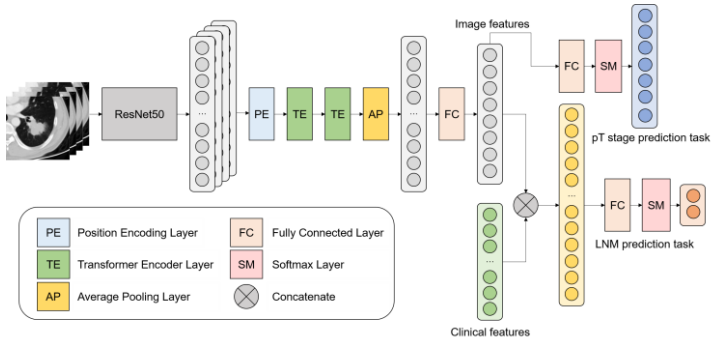

Figure 1. The architecture of the multi-task network for LNM prediction.

3. Results

3.1. Experimental Setup

In this study, we employed 10-fold cross-validation (CV) to test the model performance. In each iteration, 9-fold samples were used as the training data, the remaining 1-fold samples as the test set. When training, we employed another 5-fold CV on the training data for hyper-parameter tuning and early stopping. We saved the best model at each iteration of the 5-fold CV to fully exploit the training data and avoid overfitting the validation samples. When testing, we averaged the outputs of the 5 trained models as the final predicted results. We repeated the training and testing process 10 times with different random seeds to obtain more reliable results.

We removed the pT stage prediction task from the proposed model as the baseline model. Besides, we also train a logistic regression model with only clinical features. We selected the AUC and AP as the metrics. Moreover, we applied the paired t-test to compare the model performances. A p-value less than 0.05 was considered significant.

3.2. Experimental Results

Table 1 shows the performances of the proposed model and baseline models. The proposed multi-task model achieves better AUC and AP values with lower SD than the baseline models. The experimental results indicate that the LNM prediction task can benefit from the pT stage prediction task in the multi-task learning framework.

Table 1. The LNM prediction performances of the proposed model and baseline models.

Methods	AUC		AP	
	Mean	SD	Mean	SD
Logistic regression	0.760	0.073	0.433	0.116
Single-task model	0.760	0.079	0.448	0.118
Multi-task model	0.768	0.073	0.448	0.113

Table 2 shows the paired t-test results between the proposed model and baseline models. Based on the statistical analysis, the multi-task model obtains significant improvements in both AUC and AP values in comparison with the LR model and a significant improvement in AUC values in comparison with the single-task model.

Table 2. The paired t test of the performances of the proposed model and baseline models.

Methods	Pair t test of AUC	Pair t test of AP
Logistic regression vs Single-task model	0.99	<0.01
Logistic regression vs Multi-task model	<0.01	<0.01
Single-task model vs Multi-task model	<0.01	0.89

4. Discussion

In this study, we proposed a multi-task network to predict the LNM for lung cancer patients. Experimental results show that using the pT stage prediction as the auxiliary task can learn deep tumor pathological representations to facilitate the LNM prediction. Compared with using primary tumor segmentation, the proposed method does not require ROI annotations. And the pT labels are usually recorded in the pathology reports and easily obtained. As many types of cancer are evaluated by the TNM stage system, we can also extend this strategy to LNM prediction for other types of cancer.

The previous study [13] has proven that the primary tumor pathological features are significantly related to the LNM. In this study, we used a multi-task learning network to exploit the relations between pT stages and LNM. Note that we can also extract the pT stage representations separately and then integrate them with other clinical features like traditional radiomics methods, which may be more clinically acceptable.

Besides using clinical and image data, the plasma cell-free DNA (cfDNA) genome and methylation data also show potential for LNM prediction. In the future, we will try to combine the cfDNA features with clinical and image features to achieve more precise LNM prediction. Moreover, we will also explore how to predict the LNM in the lymph node station granularity to provide more detailed information for clinicians.

5. Conclusions

In this study, we proposed a deep multi-task network for LNM prediction. Experimental results show that the deep tumor pathological representations learned using the auxiliary task can significantly improve the LNM prediction performance.

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