Association between Tumor Heterogeneity and Progression-free Survival in Non-small Cell Lung Cancer Patients with EGFR Mutations Undergoing Tyrosine Kinase Inhibitors Therapy

Jiangdian Song[1,2], *Member, IEEE*, Di Dong[2], Yanqi Huang[3], Yali Zang[2*], Zaiyi Liu[3*], and Jie Tian[2*], *Fellow, IEEE*

***Abstract*—For non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (EGFR) mutations, current staging methods do not accurately predict the risk of disease recurrence after tyrosine kinase inhibitors (TKI) therapy. Developing a noninvasive method to predict whether individual could benefit from TKI therapy has great clinical significance. In this research, a radiomics approach was proposed to determine whether the tumor heterogeneity of NSCLC, which was measured by the texture on computed tomography (CT), could make an independent prediction of progression-free survival (PFS). A primary dataset contained 80 patients (median PFS, 9.5 months) with positive EGFR mutations and a validation dataset contained 72 NSCLC (median PFS, 10.2 months) patients were used for prognosis trial. The experiment results indicated that the features: "Cluster Prominence of Gray Level Co-occurrence" (hazard ratio [HR]: 2.13, 95% confidence interval [CI]: (1.33, 3.40), P = 0.010) and "Short Run High Gray Level Emphasis of Run Length" (HR: 2.43, 95%CI: (1.46, 4.05), P = 0.005) were significantly associated with PFS in the primary dataset, and these two texture features also make a consistent performance on the validation cohort. Our study further supported that the quantitative measurement of tumor heterogeneity can be associated with prognosis of NSCLC patients with EGFR mutation.**

I. Introduction

Lung cancer is the leading cause of cancer-related deaths in the United States, and its prevalence continues to increase worldwide [1]. Non small cell lung cancer (NSCLC) accounted for more than 80% of patients with lung cancer. Despite advances in modern therapies, however, the prognosis of NSCLC patients remains dismal [2], [3].

As an emerging therapy, the curative effect of targeted therapy for NSCLC was increasingly realized. In recent years, tyrosine kinase inhibitors (TKI) play an important role for the patients with positive expression for somatic mutations in kinase domain of epidermal growth factor receptor (EGFR). According to a survey found by NIH [4], more than 60% of NSCLC express EGFR. EGFR-TKIs are a group of inhibitors that target the activity of EGFR tyrosine kinase. Gefitinib and Erlotinib are two widely used EGFR-TKIs. These two inhibitors are selective EGFR tyrosine kinase inhibitors which have specific effects on cancer cell growth, metastasis, and angiogenesis by blocking EGFR tyrosine kinase phosphorylation [5]-[6]. As a metric to evaluate patient's survival, progression-free survival (PFS), which represents the time span from the start of treatment to the beginning of secondary tumor growth, is an important index to verify the therapeutic effect of targeted therapy in clinical [7].

Many researches have validated that EGFR mutational status with longer PFS after TKI therapy than conventional chemotherapy [8]-[10]. A research indicated that the PFS was improved among individuals with resected stages I–III lung adenocarcinomas harboring mutations in EGFR who received adjuvant TKI therapy [11]. In Noro's work, the authors proposed that MET gene may be useful to predict shortened PFS for the lung adenocarcinoma patients after Gefitinib treatment [12]. Another study proved that the lower expression of transglutaminase 2 may indicate longer survival in NSCLC patients who were treated with EGFR tyrosine kinase inhibitor [13].

However, to date the research based on medical imaging to predict which patients are likely to benefit from TKI treatment is rare. Although the identification of phenotypic characteristics with prognostic ability from pre-therapy CT images has been increasingly realized, these above researches do not clearly distinguish between patients who have a high or low risk of recurrence by medical images. The aim of our study is to elucidate the association of the cancer heterogeneity (assessed by texture features on pre-therapy CT images) with PFS of NSCLC patients with EGFR mutations undergoing TKI therapy.

II. Materials and Methods

A. Patients

The retrospective study included a primary dataset (80 patients) and a validation dataset (72 patients), with slice thickness of 2.5 mm for every CT scans. All the contrast-enhanced CT scans were performed within two weeks of the beginning of TKI treatment. With field of view: 390 mm; matrix: 512; reconstruction thickness: 2.5 mm. And all the patients were diagnosed as NSCLC with positive EGFR expression All the enrolled patients had no surgical resection,

*This work is financed by the National Natural Science Foundation of China under Grant No. and 81227901, 81501549, 61231004, 81501616, 81301346, the Guangdong Province-Chinese Academy of Science" comprehensive strategic cooperation program under 2012B090400039, the National Basic Research Program of China under Grant No. 61301002 and No. 61302025. *Asterisk indicates corresponding author.*

Corresponding Author: Jie Tian, (phone: +86-10-82618465; fax: +86-10-62527995; e-mail: tian@ieee.org)

[1]Sino-Dutch Biomedical and Information Engineering School, Northeastern University, Shenyang, 110819, China

[2]The Key Laboratory of Molecular Imaging, Institute of Automation, Chinese Academy of Sciences, Beijing 100190, China

[3]Department of Radiology, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou 510080, China

and the PFS of patients was strictly recorded by the radiologists.

B. ROI Delineation and Texture Extraction

An automatic lung lesion segmentation method was performed on all the pre-therapy contrast-enhanced CT images in our datasets [14]. Based on the region growing and multi-scale constraints, the automatic segmentation method had achieved better results on the Lung Image Database Consortium-Image Database Resource Initiative (LIDC-IDRI) dataset compared with other algorithms [15]. Manual segmentation was performed by clinicians when the automatic segmentation result was poor in the follow-up review stage.

Two phenotypic textural descriptors which express tumor heterogeneity are used in this study: one texture feature is extracted from run-length matrix, and the other texture feature is a descriptor from gray level co-occurrence matrix. Both of the two matrixes are transformed from the original CT tumor images.

1. Short Run High Gray Level Emphasis of Run-Length:

$$SRHGLE = \frac{\sum_{i=1}^{N(g)} \sum_{j=1}^{N(r)} \left[M(i,j \mid \theta) i^2 / j^2 \right]}{\sum_{i=1}^{N(g)} \sum_{j=1}^{N(r)} M(i,j \mid \theta)} \quad (1)$$

2. Cluster Prominence of Gray Level Co-occurrence:

$$CP = \sum_{i=1}^{N(g)} \sum_{j=1}^{N(g)} \left[i + j - \mu_x(i) - \mu_y(j) \right]^4 N(i,j \mid \theta) \quad (2)$$

Run-length is a metrics to quantify gray level runs in an image. Since the consecutive pixels that have the same gray level value in one direction could be measured, the gray level run is defined as the length in number of pixels. In a gray level run-length matrix $M(i,j \mid \theta)$, the (i,j) th element describes the number of times the gray level j appears i times consecutively in the direction specified by θ. The other definitions are described as follow:

$M(i,j \mid \theta)$ is the (i,j) th point in the run-length matrix which calculated on the original image with a direction θ,

$N(g)$ is the number of discrete intensity values in the image. It describes how many pixel intensities occur in the image,

$N(r)$ denotes the number of different run lengths. If the maximum in the run-length matrix is K, for example, $N(r) = K$.

Gray-level co-occurrence matrix is defined as $N(i,j,D,\theta)$, which is a matrix to describe the gray level distribution by a distance of D pixels in direction θ of an image with the size of $N(g) \times N(g)$, where the (i,j) th element represents the number of times the combination of intensity levels i and j occurs in two pixels in the image. The other definitions are described as follows:

$N(i,j \mid \theta)$ is the (i,j) th point in the co-occurrence matrix which calculated by the original image with a direction θ and a default distance of 1,

$\mu_x(i)$ and $\mu_y(j)$ are the means of marginal row probabilities and marginal column probabilities which calculated from the gray-level co-occurrence matrix, respectively.

C. Statistical Analysis

Descriptive statistics were expressed as numbers or percentages for categorical variables and "mean ± standard deviation" or medians for continuous variables.

Cox proportional hazards models [16] were used to assess the independent effects of the texture features on PFS. According to the ratio of a specific event occurrence calculated by several risk factors, the Cox proportional hazards regression allows analyzing the effect of the factors on overall survival or other events (such as recurrence). As the quantile is a common tool to distinguish high and low expression in the Cox model, we used the median value to bisect the features of all the patients for Cox survival analysis [17], in which 0 represented the lower texture expression group, and 1 represented the higher expression group [18]. Multivariate Cox model was adjusted for age, sex, smoke, metastasis, clinical stage and comparisons between groups which were performed by the log-rank test. PFS was defined as the time from the start of treatment to the beginning of secondary tumor growth. All the statistical analyses were performed by the PASW Statistics 18.0.0 (SPSS Company) and the results from Cox analysis were reported as hazard ratios (HRs), with 95% confidence intervals (CIs) and P values. Two-sided P values less than 0.05 were considered as a significant difference.

III. RESULTS

We first tested the prognostic ability of the features on the primary dataset, and the performance was then evaluated on the validation dataset. Patient demographics and clinicopathologic characteristics of the two datasets were listed in Table I. Cox model was adjusted for age, sex, tobacco use, TKI treatment type, metastasis and clinical stage. The results of prognostic trial on the two datasets were presented in Table II. In Table II, $^{+}$indicated a significant difference.

With the adjustment for age, sex, smoke, TKI treatment type, metastasis and clinical stage, the results from multivariate Cox model indicated the feature of "cluster prominence of gray level co-occurrence (CP)" was significantly associated with PFS. Cox model from the primary dataset indicated that the risk of patients with lower expression of CP increased more than two times compared with the higher expression patients (HR: 2.13; 95% CI: (1.33, 3.40) P = 0.010). Similarity, the results from "short run high gray level emphasis of run-length (SRHGLERL)" showed that, the risk of recurrence for a patient in the group with lower expression of SRHGLERL was 2.43 times higher than that for a patient with higher expression of SRHGLERL (HR: 2.43; 95% CI: (1.46, 4.05) P = 0.005).

And the results from validation data also indicated that the patients with lower expression of CP tended to be shorter survival (HR: 2.35; 95% CI: (1.39, 3.99) P = 0.002, compared with the higher group). From the comparison between

different expression groups of SRHGLERL, a similar conclusion could be summarized that better survival tended to be the patients with higher values (HR: 2.75; 95% CI: (1.60, 4.72) $P < 0.001$ for the lower expression vs. higher expression). Fig.1 and Fig.2 are the graphs which show the prognostic ability of the features for progression-free survival by multivariate Cox model on the different datasets.

TABLE I. PATIENT DEMOGRAPHICS AND CLINICOPATHOLOGIC CHARACTERISTICS OF THE PRIMARY SET (80 PATIENTS) AND THE VALIDATION SET (72 PATIENTS) FOR PROGNOSTIC ANALYSIS.

Demographics	Primary Set			Validation Set		
	No.	PFS (months)		No.	PFS (months)	
		%	Median		%	Median
Total	80	100	9.5	72	100	10.2
Sex						
Male	30	38	10.5	30	42	10.1
Female	50	62	8.6	42	58	7.5
Age, years						
<65	52	65	10.5	43	60	11.4
⩾65	28	35	9.2	29	40	9.1
N staging						
N0/N1	19	24	10.1	15	21	12.7
N2/N3	61	76	8.9	57	79	7.5
Location						
Left	38	48	10.2	31	43	10.1
Right	42	52	9.5	41	57	10.8
TKI type						
Gefitinib	64	80	9.1	53	74	9.0
Erlotinib	16	20	10.5	19	26	10.0
Tobacco use						
Smoker	14	18	10.1	16	22	9.7
Metastasis	46	58	9.6	43	60	8.9

TABLE II. PROGNOSIS RESULTS OF THE MULTIVARIATE COX-PROPORTIONAL HAZARDS REGRESSION ANALYSIS. DATA IN PARENTHESES ARE 95% CONFIDENCE INTERVALS.

Variable	Primary cohort		Validation cohort	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Age, ⩾65	1.09 (0.67, 1.79)	0.713	0.96 (0.61, 0.64)	0.995
Sex, men	0.94 (0.53. 1.68)	0.835	0.85 (0.47. 1.53)	0.586
Smoke, non	0.71 (0.65, 3.04)	0.393	0.52 (0.88, 4.18)	0.098
CP	2.13 (1.33, 3.40)	0.010^{+}	2.35 (1.39, 3.99)	0.002^{+}
SRHGLERL	2.43 (1.46, 4.05)	0.005^{+}	2.75 (1.60, 4.72)	$<0.001^{+}$
TKI	1.43 (0.78, 2.64)	0.245	1.16 (0.68, 1.98)	0.578
Metastasis	1.56 (0.96, 2.54)	0.072	0.80 (0.48, 1.33)	0.391
N Stage	1.56 (0.98, 2.76)	0.055	1.40 (0.79, 2.48)	0.062

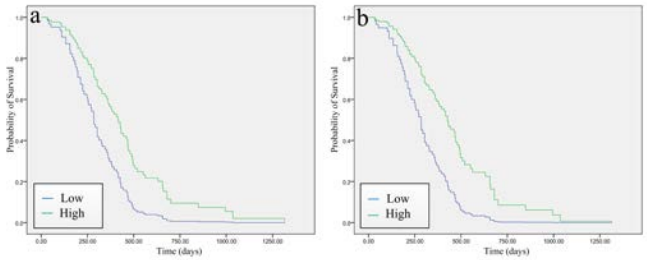

Figure 1. Graphs show survival functions from Cox model on the primary dataset for specified values of (a) Cluster prominence of gray level co-occurrence, (b) Short run high gray level emphasis of run-length.

IV. DISCUSSION

Our study presented that the tumor heterogeneity of NSCLC, which expressed by phenotypic texture from CT images, could be served as a potential prognostic biomarker for progression-free survival of EGFR mutational patients who undergoing TKI therapy. The multivariate Cox analysis on the pre-therapy CT images indicated that the texture features "cluster prominence of gray level co-occurrence" and "short run high gray level emphasis of run-length" were significantly associated with progression-free survival ($P < 0.05$), independent of the effects of age, sex, clinical stage and other society factors. Besides, the results were also evaluated on the validation dataset and showed consistent performance.

The radiomics method proposed in this paper provided a potential new way of clinical aided diagnosis for modern TKI therapy. We validated that the tumor phenotypic descriptors were significantly associated with EGFR mutational patients' progression-free survival. As a frontier research, the treatment effect of targeted therapy which evaluated by pre-therapy CT images can not only reduce unnecessary cost, but also be able to give a reliable and timely prediction of survival, so as to improve the accuracy of therapy.

Our study further supported the concept that quantitative measurement of tumor heterogeneity by texture analysis on the pre-therapy CT images can be used as a prognostic biomarker for lung cancer. This viewpoint was further strengthened by Coroller's study on the distant metastasis prediction of lung adenocarcinoma and Grove's study on the lung cancer prognosis by the descriptors of intratumor heterogeneity [19][20]. The features, "cluster prominence" and "short run high gray level emphasis", which revealing the distribution pattern of internal pixels of lung tumor, could be served as a descriptor of tumor heterogeneity to predict PFS. According to the results in this study, a conclusion could be summarized that the tumor heterogeneity described by phenotypic texture, which is extracted on the contrast-enhanced pre-therapy CT images were significantly associated with prognosis. We initially extracted thirty texture features in total. However, only the two features presented significant association with PFS. So we did not list other features. These features were only extracted in the cross section of CT image, the research related to features on the sagittal and coronal plane direction will be continued in the future studies.

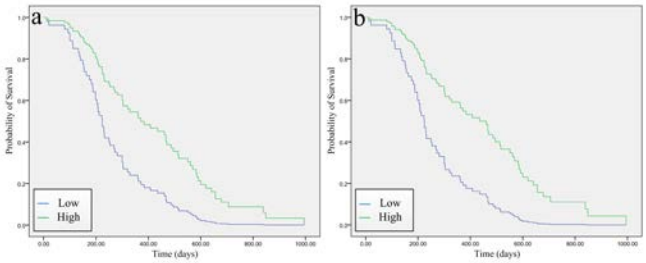

Figure 2. Graphs show survival functions from Cox model on the validation dataset for specified values of (a) Cluster prominence of gray level co-occurrence, (b) Short run high gray level emphasis of run-length.

There were several limitations of this study which should be addressed in the future. Firstly, the main object of this research is PFS, but the condition after recurrence has not been considered. Although the overall survival is much longer than PFS, the research was still helpful for future clinical analysis. Next, as the automatic tumor segmentation was the only way

for region of interest delineation, further studies exploring observer bias and variability of texture analysis arising from multiple readers should be evaluated. Finally, as the contrast-enhanced thin-slice CT images were only used, a comparative study of phenotypic texture analysis on the different modes of images should be developed in the future.

V. Conclusion

In conclusion, the tumor heterogeneity quantified by pre-therapy CT phenotypic descriptors indirectly reflects the efficacy of TKI therapy. Results in this study suggest that further research on quantitative imaging features is warranted, with more advanced applications of CT imaging used for treatment monitoring, outcome prediction or imaging biomarkers. Since effective and credible clinical aided diagnosis is important to plan subsequent definitive treatment, quantitative radiomics-related studies could provide better prognostic regimen for patients with NSCLC.

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