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DELTA-RADIOMICS SIGNATURE FOR PREDICTION OF SURVIVAL IN ADVANCED NSCLC PATIENTS TREATED WITH IMMUNOTHERAPY

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ABSTRACT

Lung cancer is the leading cause of cancer death in Europe with an approximate 5-years survival rate of 13% from diagnosis. The potential of computational image analysis to provide decision support in oncology and the importance of identifying predictive and non-invasive biomarkers of disease progression and response to therapy has led to Radiomics. The objective of this study was to develop a delta-radiomics signature to predict survival and treatment response in patients with advanced non-small cell lung cancer (NSCLC) undergoing immunotherapy. Pre-treatment and first follow-up CT images and intra-nodular and peri-nodular regions from 88 patients have been used to calculate delta-features. The delta-radiomics signature significantly stratified high- and low-risk patients ($p = 0.018$), it was significantly associated with Overall Survival ($p = 0.03$) and it predicted responders with an area under the receiver operating characteristic curve (ROC-AUC) of 0.76 in an independent test set. The results demonstrate the potential of delta-radiomics to be an early biomarker of immunotherapy response.

***Index Terms*—** Lung cancer, Immunotherapy, Radiomics, Biomarker, CT, Survival analysis

1. INTRODUCTION

Lung cancer is the most common cause of cancer-related deaths worldwide [1]. Despite recent efforts in lung cancer screening, 47% to 57% of new cases are diagnosed at an advanced stage [2]. Recent work with immune checkpoint inhibitors has changed the landscape of cancer treatment, leading to a rapid rise of immunotherapy treatments [3]. However, one of the challenges of immunotherapy, recently adopted as a new standard of care for stage III-IV NSCLC patients, is the ability of accurate and reproducible biomarkers that would allow a proper patient selection that are more likely to respond [4]. Different biomarkers have been introduced in clinical practice such as levels of PD-L1, presence of tumor-infiltrating lymphocytes or Tumor Mutational Burden (TMB), all of them with mixed results.

The potential of computational image analysis to provide decision support in oncology and the importance of identifying predictive and non-invasive biomarkers of disease progression and response to therapy has led to Radiomics [5]. These quantitative image features, extracted from radiological images, offer information on tumor radio-phenotype and microenvironment that differs from that provided by clinical reports, laboratory test results, and genomic or proteomic assays. Radiomics features could potentially aid cancer detection, diagnosis, assessment of prognosis, prediction of response to treatment, and monitoring of disease status. The key to success in applying radiomics to diagnosis, prognosis and treatment response monitoring is that most of the lung cancer patients will undergo multiple CT (Computed Tomography) and PET (Positron Emission Tomography) examinations during the treatment [6].

Therefore, there is a manifest clinical need to develop new radiologic response criteria given the unusual behavior of tumors with these new treatments. As immunotherapy has high cost and can bring toxicity, it is important to stratify patients who are more likely to benefit from therapy.

Previous studies have been proposed to predict treatment response using radiomics in NSCLC. Few studies have focused on the immunotherapy response and these consider only the pre-treatment CT or one of the possible types of immunotherapy treatment [7, 8, 9].

In this work, a delta-radiomics signature has been implemented to predict survival and treatment response in patients with advanced NSCLC undergoing immunotherapy as monotherapy, combination of immune-based agents or in combination with traditional treatments.

2. METHODS

2.1. Patients and endpoints

A total of 182 patients with pathologically confirmed stage IV NSCLC treated with immunotherapy from January 2013 to December 2019 at Hospital Universitario Fundación Jiménez Diaz (FJD) and Clínica Universidad de Navarra (CUN) were retrospectively collected.

Patient inclusion criteria were: 1) patients treated with immunotherapy as monotherapy, combination of immune-based agents or in combination with traditional treatments as chemotherapy or radiotherapy; 2) availability of clinical patient data; 3) for patients who underwent more than one line of treatment, only the last immunotherapy line was considered; 4) availability of both baseline and first follow-up CT image within two months from treatment start. Patients that had a primary tumor too complex to be isolated by an experienced radiologist on the CT image were excluded. This resulted in 88 patient datasets that were available for analysis.

Patients were divided in two complete independent cohorts, including a training cohort of 63 patients from FJD and a test cohort of 25 patients from CUN.

The primary endpoint in our study was the Overall Survival (OS), the gold standard endpoint in immunotherapy [10]. It was calculated as the time in months between the initiation of the immunotherapy treatment and the death or censored to last follow-up visit for survivors. The secondary endpoint was the patient response status based on patient survival. Patients who survived more than 12 months after the first cycle of treatment were classified as responders. If a patient was censored at 12 months, he was discarded. This resulted in 27 patients defined as responders and 35 as no responders.

2.2. CT acquisition and processing

All patients underwent a CT scan within 30 days before treatment and a follow-up CT scan within two months after treatment. CT images were acquired after contrast injection during the patient inspiration breath-hold, following the Contrast-enhanced CT chest protocol. Standard reconstruction algorithm was used. Since the CT images were acquired at different institutions, they were performed with different scanners from different manufacturers (Siemens, GE Medical System, Philips, Toshiba) and acquisition parameters.

Tumor segmentation was performed under the supervision of experienced radiologists on the CT images. Only the primary nodule for each patient was segmented. If a patient presented an ambiguous primary nodule, only one of the possible primary nodules was considered.

The segmented nodule mask was used to obtain the border mask (peri-nodular tumor region) through a morphological dilatation operation with a 3D spherical structural element, which radius was chosen depending on the Major Axis Length of the nodule. Subtracting the intra-nodular mask from this dilated mask enabled to extract a ring of lung parenchyma surrounding the nodule, that represents the peri-nodular mask. Air and mediastinal muscle pixels were removed from CT images and were replaced with the average pixel intensity of the 9x9 neighborhood surrounding the pixel; this is important to avoid edge artifacts during feature extraction [11]. An example of intra-nodular and peri-nodular regions from a baseline CT image is shown in Figure 1.

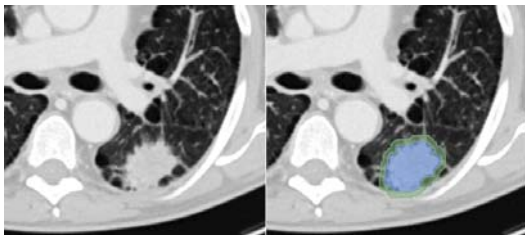

Fig. 1. Baseline CT image with intra-nodular (blue) and peri-nodular (green) regions.

Anisotropic image voxels were resampled to 1x1x1 mm^3 across the whole cohort and voxel intensity values were discretized using a bin width of 20 Hounsfield units.

2.3. Features extraction and selection

Radiomics features were extracted from primary nodules in both baseline and first follow-up CTs by using Pyradiomics [12]. Different features types were considered: first order statistics-based features, shape and size features and textural features. Features were extracted from both original and transformed images: many filters were used such as Wavelet, Laplacian of Gaussian, Local Binary Pattern, Square, Square Root, Logarithm and Exponential filters.

A total of 1925 Radiomics features were extracted from the intra-nodular and peri-nodular regions of the nodule, resulting in 3850 radiomics features at each time point.

Delta-radiomics features were calculated as the difference between first follow-up (post-treatment) and baseline (pre-treatment) features. This resulted in 1925 delta-radiomics features for each case, which were standardized based on a scaling transformation learned in the training set.

The features repeatability against segmentation was analyzed using two datasets: QIN Lung CT Segmentation dataset [13] and a subset of FJD dataset. In the first dataset, for each nodule two segmentations performed with two different automatic segmentation algorithms were considered. In the FJD subset, a radiologist performed the semi-automatic segmentation with two different modules of syngo®.via software. A total of 56 nodules were analyzed and the Lin's concordance correlation coefficient (CCC) for each feature was calculated. A cutoff value of 0.85 was chosen. Only repeatable features with CCC > 0.85 in both datasets were considered.

Feature reproducibility was also assessed. The test-retest scans from the Reference Image Database to Evaluate Therapy Response (RIDER) dataset were used [14]. This dataset includes 31 patients, each one underwent two chest CT scans within 15 minutes by using the same imaging protocol. Only reproducible features with CCC > 0.85 were considered.

Reproducible and repeatable features were considered stable and used for the subsequent analysis in our study.

2.4. Statistical analysis and signature construction

All the statistical analyses were performed with R software, version 3.6.2 (http://www.R-project.org). P-value < 0.05 was considered as significant. Regression model's performance was evaluated with the concordance index (C-index).

A univariate Cox proportional hazard regression analysis was implemented in the training set to study the relationship between delta-radiomics features and OS. Using a bootstrap approach, the CI of each feature was calculated 100 times: features found to be significantly correlated with OS (p-value < 0.5) and with C-index greater than 0.60 were considered predictive.

Among these selected delta-radiomics features, the least absolute shrinkage and selection operator (LASSO) was used to select the most useful predictive features in a multivariate Cox regression model. To avoid overfitting, 3-fold cross validation was performed in the training set to select features. A delta-radiomics score was calculated for each case as linear combination of the selected features weighted by their respective coefficients in the multivariate Cox model. The potential of delta-radiomics signature to predict OS was assessed by using the Kaplan-Meier survival analysis. Based on the median value of the delta-radiomics score in the training set, the patients were stratified in low- and high-risk groups. The statistical differences between the survival curves of these groups was calculated with log-rank test.

The ability of each selected delta-radiomics feature to stratify patients was also investigated.

Based on the delta-radiomics signature, a Logistic Regression model was implemented to predict responders to treatment. AUC and ROC curve analysis were performed. Youden's index was calculated to choose the appropriate cut-off point to discriminate patient outcome.

In addition, following the same method pre- and post-treatment signatures were also obtained.

3. RESULTS

3.1. Feature analysis and Delta-Radiomics signature

1925 radiomics features were extracted from each image. The feature repeatability against segmentations was achieved by 383 features (26% of features) and the reproducibility by 1068 features (57% of features). A total of 206 features remained after the stability filtering.

Features	C-index (95% CI)	HR (95% CI)	p-value
Pre-treatment	0.59 [0.43, 0.75]	0.89 [0.28, 2.78]	0.84
Post-treatment	0.52 [0.34, 0.70]	1.03 [0.65, 1.62]	0.91
Delta-radiomics	**0.69** [0.54, 0.84]	**2.06** [1.05, 4.06]	**0.03**

Table 1. Delta-radiomics signature performance in the test set compared to the signatures based on pre-treatment and post-treatment features.

Stable features were extracted from the intra-nodular and peri-nodular masks and merged to obtain a vector of 412 features for each case. Delta-radiomics features were calculated.

A univariate Cox regression analysis was performed. It resulted in 60 features significantly correlated with OS, 17 of which were extracted from peri-nodular regions. All features had a C-index > 0.60, with a maximum of 0.65 reached by Small Dependence Emphasis extracted from peri-nodular mask of the LoG image (C-index $= 0.65$, 95%CI = [0.54,0.77], HR $= 0.58$, P $= 0.04$). This feature explains the texture homogeneity of peri-nodular region, with a greater value indicative of less homogeneous texture.

From the LASSO multivariate Cox regression analysis (lambda $= 0.0218$), a total of 13 features with non-zero coefficient were selected in the training set, including 9 features from tumor and 4 features from peritumoral masks. The delta-radiomics signature achieved a C-index of 0.81 (95%CI $= [0.73, 0.89]$, HR = 3.66, 95%CI $= [2.31, 5.79]$, p < 0.0001) and significantly stratified low- and high- risk patients (p $<$ 0.0001) in the training set.

The Logistic regression model based on delta-radiomics signature achieved AUC of 0.88, ACC of 0.82, Sensitivity of 0.85 and Specificity of 0.79 in classifying responders to treatment.

3.2. Delta-Radiomics signature validation

Delta-radiomics signature was validated in a completely independent cohort of 25 patients from a different center (CUN). This signature was significantly correlated with OS (p-value = 0.03), as shown in Table 1. The results were compared to the ones obtained with the pre-treatment and post-treatment signatures.

The corresponding Kaplan-Meier analysis showed that the delta-radiomics signature was able to significantly stratify patients in low- and high- risk groups (p = 0.018). The median OS in the high-risk group was significantly shorter than that in the low-risk group (4.4 and 12.0, respectively) as well as the survival probability at 1 year (0.50 and 0.13, respectively). Kaplan-Meier survival curves are shown in Figure 2.

The association of each selected feature to predict OS was investigated. Only Inverse Variance from Wavelet image was significantly correlated with OS in the test set (C-index = 0.68, %CI = [0.53, 0.81]), HR = 2.27), but it could not stratify patients' risk (p = 0.16).

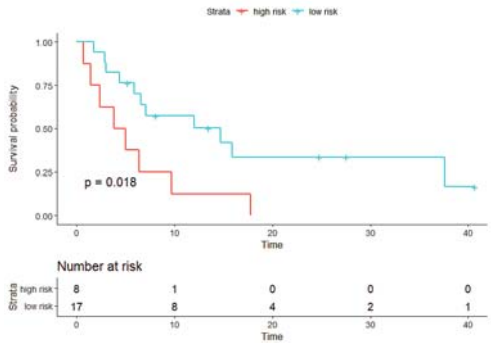

Fig. 2. Kaplan-Meier survival curves of low- and high- risk groups in the test set based on the delta-radiomics signature.

	AUC	ACC	SENS	SPEC
Pre-treatment	0.28	0.26	0.13	0.5
Post-treatment	0.54	0.3	0	**0.88**
Delta-radiomics	**0.76**	**0.70**	**0.67**	0.75

Table 2. Performance of Logistic Regression models using the delta-radiomics (red), pre-treatment (green) and post-treatment (blue) signatures.

The delta-radiomics signature was also predictive of treatment responders in the test set achieving an AUC of 0.76, as shown in Table 2. The results were compared to those obtained using only the pre- or post- treatment signatures independently. ROC curves are shown in Figure 3.

4. DISCUSSION AND CONCLUSION

Immunotherapy has recently been adopted as a new standard of care for advanced NSCLC patients. However, one of the challenges of immunotherapy is that an accurate and reproducible biomarker that would allow to predict patients that are more likely to respond has yet to be identified. In this study, a delta-radiomics signature has been developed to predict overall survival and response to treatment in patients treated with different combinations of immunotherapy and traditional treatments.

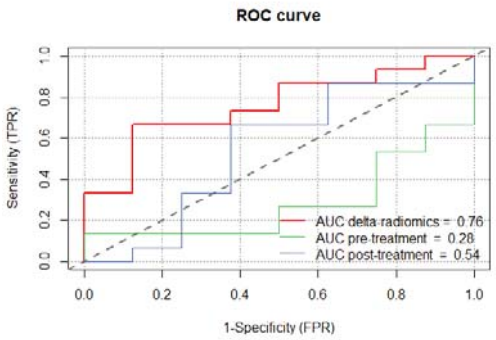

Fig. 3. ROC curves of Logistic Regression models using the delta-radiomics (red), pre-treatment (green) and post-treatment (blue) signatures.

The developed delta-radiomics signature comprised both intra-nodular and peri-nodular regions, highlighting the importance of the tumoral microenvironment to understand patient's response. Indeed, one of the selected features (Small Dependence Emphasis) suggests that more homogeneous peritumoral environment was related to a better prognosis in terms of survival. Since the delta features captured the changes over time, this means that a homogenization of the tumoral environment could be associated with a better prognosis. Morphological heterogeneity could be associated with infiltration, inflammation, neovascularization and necrosis of the tumor tissue and therefore a worse prognosis.

Kaplan-Meier analysis showed that proposed delta radiomics signature successfully stratified low- and high- risk patients. It works better compared to the signatures based only on pre- or post- treatment features, demonstrating the potential of delta-radiomics to capture the changes over time of tumor environment during immunotherapy treatments.

The Logistic regression model implemented for prediction of treatment responders with the delta-radiomics signature reached better results (AUC = 0.76) compared to the pre- and post-treatment signatures, suggesting that there is a significant association between changes in radiomics features and immunotherapy response.

In addition to the lack of data, the main limitation of this study was the heterogeneity of treatments provided to the patients of the institutions involved in this retrospective analysis. A homogenization of the dataset according to the patient treatment will be performed in future studies. Furthermore, the use of longitudinal data introduced the need of consider the temporal alterations not related to disease progression or response to therapy. An autocalibration of CT images may be useful.

In conclusion, the development of a delta-radiomics signature that could stratify low- and high- risk patient and predict response status can be very useful in the context of personalized medicine. Considering the relationship between delta-radiomics features and survival, more investigations are guaranteed to better understand the underlying biological insights of this observation.

5. COMPLIANCE WITH ETHICAL STANDARDS

This research study was conducted retrospectively using human subject data made available by Hospital Universitario Fundación Jiménez Diaz (FJD) and Clínica Universidad de Navarra (CUN) after the ethical approval of the institutional review boards (TRAIL I study).

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