論　文　内　容　の　要　旨
Synopsis of Thesis

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論文題名 Title	Three-dimensional iodine mapping quantified by dual-energy CT for predicting programmed death-ligand 1 expression in invasive pulmonary adenocarcinoma （デュアルエナジーCTを用いた3次元ヨードマップの解析による浸潤性肺腺癌のPD-L1発現の予測）

論文内容の要旨

〔目　的(Objective)〕

Lung cancer accounts for about 18% of all cancer-related mortalities worldwide, and adenocarcinoma is the most common type of pathology. Systemic therapy using chemotherapy or radiation therapy is the standard frontline treatment for advanced stage (IIIB-IV). Recently, an immune checkpoint inhibitor (ICI) has been offered to patients with programmed cell death 1- ligand 1 (PD-L1) expression and has shown impressive clinical performance. Therefore, it is important to prove or predict PD-L1 and PD-1 expression. In recent clinical practice, tissue biopsy is essential to evaluate gene expression within tumors. However, the tissue within tumors is heterogeneous. Tissue biopsy has problems with accuracy and reliability because only a portion of the tissue can be sampled. In addition, biopsy is invasive for patients and carries a risk of complications. On the other hand, CT is a non-invasive and widely used method. In addition, CT images cover the entire tumor and characterize it.

Previous studies using dual-energy CT have reported that quantitative values such as iodine concentration were helpful for predicting the gene expression level.

The extracellular volume (ECV) can also be obtained from the equilibrium phase of dual-energy CT. Many studies have shown that ECV is a useful quantitative imaging biomarker for fibrosis of organs such as the liver and myocardia. And lung adenocarcinoma cells are well known to interact with various cells of the surrounding microenvironment, such as fibroblasts. Activated fibroblasts within lung cancer, called cancer-associated fibroblasts (CAFs), have been reported to be associated with PD-L1 expression.

We hypothesized that dual-energy CT can predict the expression level of PD-L1 and texture features using 3D iodine density histogram texture analysis and ECV on dual-energy CT may correlate to the expression level of PD-L1. The purpose of this study was to examine the association between quantitative data measured by dual-energy CT and expression of PD-L1 using immunostaining methods.

〔方法ならびに成績(Methods/Results)〕

Consecutive 37 patients were scanned by DECT. Unenhanced and enhanced (3 min delay) images were obtained. 3D texture analysis was performed for each nodule to obtain 7 features (max, min, median, mean, standard deviation, skewness, and kurtosis) from iodine density mapping and extracellular volume (ECV). A pathologist evaluated a tumor proportion score (TPS, %) using PD-L1 immunostaining: PD-L1 high (TPS ≥ 50%) and low or negative expression (TPS < 50%). Associations between PD-L1 expression and each 8 parameter were evaluated using logistic regression analysis. The multivariate logistic regression analysis revealed that skewness and ECV were independent indicators associated with high PD-L1 expression (skewness: odds ratio [OR] 7.1 [95% CI 1.1, 45.6], p = 0.039; ECV: OR 6.6 [95% CI 1.1, 38.4], p = 0.037). In the receiver-operating characteristic analysis, the area under the curve of the combination of skewness and ECV was 0.83 (95% CI 0.67, 0.93) with sensitivity of 64% and specificity of 96%.

〔総　括(Conclusion)〕

Skewness from 3D iodine density histogram and ECV on dual energy CT were significant factors for predicting PD-L1 expression.

論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

本研究では、デュアルエナジーCTで撮影された画像の定量的解析から、浸潤性肺腺癌のPD-L1遺伝子の発現が予測できるかどうか検討した。37名の浸潤性肺腺癌の患者について、デュアルエナジーCTで撮影された画像から、造影後の腫瘍組織内のヨード密度分布を表すヨードマップを作成した。ヨードマップのヒストグラム解析を行い、7つの特徴量（最大値、最小値、中央値、平均値、標準偏差、歪度、尖度）を求めた。さらに、線維化を表す指標であるECVをヨード値を用いて算出した。統計解析により、これら8つの定量値とPD-L1の発現との関連を評価した。多変量ロジスティック回帰分析の結果、歪度とECVがPD-L1高発現を予測しうる独立した因子であることが明らかになった。また、ROC解析により、歪度とECVを組み合わせたものが特異度96%と高い診断能を示した。

本論文はデュアルエナジーCTから得られる定量値である歪度とECVが浸潤性肺腺癌におけるPD-L1の高発現を予測できる可能性を示したものであり、博士（医学）の学位授与に値する。