European Journal of Radiology 101 (2018) 118–123

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Research article

Predictive factors for treatment response using dual-energy computed tomography in patients with advanced lung adenocarcinoma

Sae Rom Hong[a], Jin Hur[a,*], Yong Wha Moon[b], Kyunghwa Han[c], Suyon Chang[a], Jin Young Kim[a], Dong Jin Im[a], Young Joo Suh[a], Yoo Jin Hong[a], Hye-Jeong Lee[a], Young Jin Kim[a], Byoung Wook Choi[a]

[a] Department of Radiology and Research Institute of Radiological Science, Severance Hospital, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, 120-752, Seoul, Korea, Korea

[b] Medical Oncology, Department of Internal Medicine, CHA Bundang Medical Center, CHA University, Seongnam, Korea

[c] Yonsei Biomedical Research Institute, Department of Radiology, Research Institute of Radiological Science, Severance Hospital, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, 120-752, Seoul, Korea

ARTICLE INFO

Keywords:
Dual-energy computed tomography (DECT)
Non-small cell lung cancer (NSCLC)
Adenocarcinoma
Chemotherapy
Therapeutic response

ABSTRACT

Purpose: This study aimed to investigate whether the quantitative parameters of dual-energy computed tomography (DECT) can predict the effects of chemotherapy in advanced adenocarcinoma based on the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.

Materials and methods: A total of 90 patients (59 males, 31 females, age 61.4 ± 12.3 (23–85)) with unresectable lung adenocarcinoma (TNM stage IIIB or IV) who underwent DECT before chemotherapy were prospectively included in this study. By comparing baseline studies with the best response achieved during 1 st line chemotherapy, patients were divided into two groups according to RECIST (version 1.1) guidelines as follows; responders (CR or PR) and non-responders (SD or PD). Quantitative measurements were performed on baseline DECT, and a logistic regression model was used to evaluate predictive factors for a response to chemotherapy.

Results: Among 90 patients, 38 were categorized as responders, while 52 patients were non-responders. The mean iodine concentration measurements were significantly higher in responders compared with non-responders (1.81 ± 0.51 vs 1.33 ± 0.76 mg/ml, $p < 0.001$). On multivariate analysis, EGFR mutation (odds ratio (OR): 3.116, 95% confidential interval (CI):1.182-8.213, $p = .019$) and iodine concentration (OR: 1.112, 95% CI:1.034-1.196, $p = .006$) were found to be significant for predicting a treatment response.

Conclusions: Dual-energy CT using a quantitative analytic method based on iodine concentration measurements can be used to predict the effects of chemotherapy in patients with advanced adenocarcinoma.

1. Introduction

Lung cancer is the most common cancer in the world and represents the leading cause of cancer-related death. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer and adenocarcinoma is the most common subtype of NSCLC in many countries. Despite improvements in therapeutic management, the prognosis for lung cancer remains poor with a 5-year survival rate of less than 15% [1]. One of the bright spots in lung cancer research has been the introduction of patient-centered chemotherapy based on that patient's specific tumor cell mutations in advanced stage [2]. Recently, molecular targeted drugs have been widely used for treating non-small cell lung cancer (NSCLC), especially for adenocarcinoma [3].

Quantitative image features as well as traditional qualitative features have shown some potential for precision medicine in oncology, and these features are continuously being refined and developed with evolving research [4,5]. A method for selecting patients who will have a better response could influence treatment decisions and potentially reduce therapeutic toxicity. Therefore, in addition to TNM staging, there is growing interest in developing and accessing the imaging biomarkers in NSCLC. To monitor treatment responses after chemotherapy or radiation therapy, computed tomography (CT) is generally used in accordance with the Response Evaluation Criteria in Solid Tumor (RECIST) guidelines [6]. However, because changes in tumor size can

Abbreviations: CI, confidential interval; CT, computed tomography; DECT, dual-energy computed tomography; GSI, gemstone spectral imaging; HU, hounsfield unit; NSCLC, non-small cell lung cancer; OR, odds ratio; RECIST, response evaluation criteria in solid tumors; ROC, receiver operating characteristic; VOI, Volume of interest

* Corresponding author.
E-mail address: khuhz@yuhs.ac (J. Hur).

https://doi.org/10.1016/j.ejrad.2018.02.019
Received 22 May 2017; Accepted 13 February 2018

be insignificant in the early follow-up stages especially with the use of targeted therapies or antiangiogenic drugs, conventional CT can be limited in the assessment of early treatment responses.

A recently introduced dual-energy computed tomography (DECT) technique enabled to differentiate contrast–enhanced structures from otherwise dense high-attenuation material in parenchymatous organs by applying different x-ray spectra that alter the contrast enhancement of iodine [7]. Few studies have reported that iodine-related attenuation on DECT is a reliable quantitative parameter in evaluating treatment responses to chemotherapy in patients with advanced lung cancer [8,9]. Therefore, we hypothesized that iodine concentration measurements along with DECT data would provide a more reliable quantitative parameter to indicate intratumoral changes and help predict early treatment responses to chemotherapy. The purpose of this study was to investigate whether the quantitative parameters of DECT could predict the effects of chemotherapy in patients with advanced adenocarcinoma based on the RECIST guidelines.

2. Materials and methods

2.1. Patient selection and treatment

This study was approved by our institutional review board, and all enrolled patients gave their written informed consent. Between February 2013 and June 2015, 109 patients [72 males, 37 females, age 62.3 ± 13.7 (23–85)] with advanced adenocarcinoma (TNM stage IIIB or IV) were prospectively enrolled in our study. Inclusion criteria were at least one measurable target lesion according to RECIST, age greater than 19 years, Eastern Cooperative Oncology Group (ECOG) performance status 0–2, adequate hematologic, liver and renal function, and no previous treatment with chemotherapy or radiation therapy. The exclusion criteria were as follows: no pathologically confirmed adenocarcinoma (n = 6), no history of treatment with chemotherapy (n = 2), and failure to provide informed consent (n = 11). Finally, a total of 90 patients (59 males, 31 females, age 61.4 ± 12.3 (23–85)) with advanced adenocarcinoma who underwent DECT before chemotherapy were included.

All eligible patients with EGFR mutation received daily administration of 250 mg gefitinib or 150 mg erlotinib, which was continued until disease progression or unacceptable toxicity was observed. Patients were re-evaluated every 4–8 weeks by CT and appropriate blood tests for evaluation of tumor response and toxicity, and short-term interval evaluation was done if rapid progression was suspected. All other patients received platinum-based doublet chemotherapy as first-line treatment. Chemotherapy was administered every 3 weeks for up to four cycles (unless there was evidence of disease progression or intolerance of the study treatment). Patients were re-evaluated every 2 cycles by DECT and appropriate blood tests for evaluation of tumor response and toxicity during the first-line treatment. Radiographic responses were evaluated on DECT scans after every two cycles of chemotherapy according to the RECIST (version 1.1) guidelines [6]. After the completion of four cycles of chemotherapy, further therapy was determined at the discretion of the physician and patient preference as follows: maintenance therapy with pemetrexed or erlotinib, two more cycles of the same chemotherapy, or observation.

2.2. Dual-energy computed tomography

DECT scans were performed using a 64-row multidetector CT scanner (Discovery CT750 HD; GE Healthcare, USA). Images were acquired during a single breath-hold from the lung apex to the costophrenic angles in the cranio-caudal direction. The scan delay was determined using a test bolus method. A test bolus was performed with an injection of 10 mL of a contrast agent, iopamidol (300 mg of iodine per milliliter; Radisense), followed by 30 mL of normal saline at 3 mL/sec. The time to peak enhancement in the main pulmonary artery (PA) was determined using the resultant time-enhancement curve. The scan started 90 s after peak enhancement of the main PA. For contrast enhancement, 80–120 mL (2 mL/kg) of iopamidol (300 mg of iodine per milliliter; Radisense) was injected at 3 mL/s, followed by a 20 mL saline chaser at 3 mL/s. We used a fast switching spectral CT in gemstone spectral imaging (GSI) mode (dual-energy CT mode), in which the energy of the x-ray beam rapidly changes. The scan parameters were as follows: detector collimation, 64 × 0.625 mm; gantry rotation time, 0.5 s; tube voltage, 140 and 80 kV; tube current, 630 mAs; and pitch, 1.375:1. All images were reconstructed with a slice thickness of 1.25 mm with a detail reconstruction kernel, and data were transferred to an off-line workstation (GE workstation, Volumeshare 5, GE Healthcare, USA).

2.3. Image analysis

In a blinded independent radiologic review, responses to treatment were assessed according to the RECIST (version 1.1) [6]. By comparing baseline studies with the best response achieved during 1 st line chemotherapy, patients were divided into two groups; including responders (complete response (CR) or partial response (PR) based on RECIST) and non-responders (stable disease (SD) or progressive disease (PD) based on RECIST).

For the assessment of DECT images, independent two radiologists who were blinded to patient identities and clinical histories, reviewed and analyzed all DECT studies. Decisions regarding CT findings were reached in consensus. Tumor size was defined by the longest diameter of the tumor on axial images. The TNM stage (7th edition) was determined according to the radiological findings, with the assistance of cytological results [10–12]. Lymph nodes with metastasis detected by endobronchial ultrasonography-guided transbronchial needle aspiration were regarded as metastatic lymph nodes. Tumor character was classified as being solid, consolidated, or of ground-glass opacity (GGO) [13]. Lesions with gas or fluid-filled areas were defined as having cavities or necrosis. Presence of pleural effusion and lung metastases was assessed on CT images. Presence of distant metastasis was evaluated using multiple imaging modalities.

For quantitative analysis, the whole volume of interest (VOI) of the target lesions was isolated by semi-automatic segmentation. If the segmented border of the target lesion was incorrect, the reviewers manually corrected the VOI according to the border of the target lesion on slices including the target lesion on axial monochromatic 70 keV images. After a VOI covering the entire target lesion was drawn, the segmented VOI of the entire target lesion was propagated to the other two modes of images to cover the same VOI of the target lesion across the three images. The mean CT attenuation densities of the whole target lesions in post-contrast CT images (monochromatic 70 keV images) were measured. The mean iodine concentration (mg/ml) for same VOI covering the whole target lesion was also measured in iodine (water) images. The mean of the measured values by two independent radiologists was used for the final analysis.

2.4. Statistical analysis

Categorical baseline characteristics were expressed as numbers and percentages, and were compared between responder and non-responder groups using Chi-square test or Fisher's exact tests. Continuous variables were expressed as means and standard deviations and were compared using Student's *t* tests or Mann-Whitney *U* tests. A logistic regression model was used to evaluate the predictive factors for responses to chemotherapy. Statistically significant findings on univariate analysis were subsequently included in multivariate analysis. Receiver operating characteristic (ROC) curves were constructed using the quantitative values of RECIST, and DECT variables. Agreement between the two radiologists regarding the mean Hounsfield unit (HU) and iodine concentration values was analyzed using the Bland-Altman