European Journal of Radiology 85 (2016) 176–186

Contents lists available at ScienceDirect

European Journal of Radiology

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

Dynamic contrast-enhanced perfusion area detector CT for non-small cell lung cancer patients: Influence of mathematical models on early prediction capabilities for treatment response and recurrence after chemoradiotherapy

Yoshiharu Ohno (MD, PhD)[a,b,*], Hisanobu Koyama (MD, PhD)[c], Yasuko Fujisawa (BS)[d], Takeshi Yoshikawa (MD, PhD)[a,b], Shinichiro Seki (MD, PhD)[c], Naoki Sugihara (MEng)[d], Kazuro Sugimura (MD)[c]

[a] Advanced Biomedical Imaging Research Center, Kobe University Graduate School of Medicine, Kobe, Japan
[b] Division of Functional and Diagnostic Imaging Research, Department of Radiology, Kobe University Graduate School of Medicine, Kobe, Japan
[c] Division of Radiology, Department of Radiology, Kobe University Graduate School of Medicine, Kobe, Japan
[d] Toshiba Medical Systems Corporation, Otawara, Japan

ARTICLE INFO

Article history:
Received 19 July 2015
Received in revised form 23 October 2015
Accepted 4 November 2015

Keywords:
CT
Perfusion
Non-small cell lung cancer
Chemoradiotherapy
Therapeutic effect

ABSTRACT

Purpose: To determine the capability and influence of the mathematical method on dynamic contrast-enhanced (CE-) perfusion area detector CT (ADCT) for early prediction of treatment response as well as progression free and overall survival (PFS and OS) of non-small cell lung cancer (NSCLC) patients treated with chemoradiotherapy.

Materials and methods: Sixty-six consecutive stage III NSCLC patients underwent dynamic CE-perfusion ADCT examinations, chemoradiotherapy and follow-up examinations. Response Evaluation Criteria in Solid Tumors (RECIST) criteria were used to divide all patients into responders and non-responders. Differences in each of the indices for all targeted lesions between measurements obtained 2 weeks prior to the first and the third course of chemotherapy were determined for all patients. ROC analyses were employed to determine the capability of perfusion indices as markers for distinguishing RECIST responders from non-responders. To evaluate their capability for early prediction of therapeutic effect, OS of perfusion index-based responders and non-responders were compared by using the Kaplan–Meier method followed by log-rank test.

Results: Area under the curve (Az) for total perfusion by means of the dual-input maximum slope method was significantly larger than that of pulmonary arterial perfusion using the same method ($p = 0.007$) and of perfusion with the single-input maximum slope method ($p = 0.007$). Mean OS demonstrated significantly difference between responder- and non-responder groups for total perfusion ($p = 0.02$).

Conclusion: Mathematical models have significant influence on assessment for early prediction of treatment response, disease progression and overall survival using dynamic CE-perfusion ADCT for NSCLC patients treated with chemoradiotherapy.

1. Introduction

Although early stage non-small cell lung cancer (NSCLC) cases can be curatively treated with surgery, advanced NSCLC cases are largely incurable. Combined modality therapy, consisting of chemotherapy and thoracic radiation therapy (i.e., chemoradiotherapy), is therefore the treatment of choice for patients with unresectable and/or locally advanced stage III NSCLC [1]. In addition, early prediction of therapeutic effect may make it possible to physicians and patients to consider treatment option for personalized medicine, and potential to improve quality of life during and after treatment in NSCLC patients. In the last few decades, several investigators have recommended two dynamic imaging techniques, dynamic contrast-enhanced (CE) perfusion multi-detector row computed tomography (CT) and dynamic CE-magnetic resonance (MR) imaging applied dynamic CE-perfusion MR method,

* Corresponding author at: Advanced Biomedical Imaging Research Center, Kobe University Graduate School of Medicine, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe, Hyogo 650-0017, Japan. Fax: +81 78 382 6129.
E-mail addresses: yosirad@kobe-u.ac.jp, yosirad@med.kobe-u.ac.jp, yoshiharuohno@aol.com (Y. Ohno).

http://dx.doi.org/10.1016/j.ejrad.2015.11.009
0720-048X/

as equally effective for treatment response assessment during or after chemotherapy, chemoradiotherapy and/or radiotherapy as positron emission tomography (PET) or PET combined with CT (PET/CT) using 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (FDG) [2–15]. The results reported by these investigators suggest that tumor perfusion parameters possess the capability to function as imaging based biomarkers as effectively as glucose metabolism evaluated by PET or PET/CT with FDG [2–15]. However, in these studies, multi-detector CT with a range of 4–64 detector rows was used with the helical scan technique employing various beam pitches and several software with mathematical models that were not fully detailed because different versions were provided by different vendors [5–7,11,12,15].

Since, 2011, 256- or 320-detector row CT systems with an area detector CT (ADCT) have been in clinical use to obtain isotropic volume data within a 160 mm area without helical scan and to perform dynamic first-pass CE-perfusion ADCT examination for quantitative evaluation of pulmonary nodule perfusion with high spatial resolution [16–18]. Moreover, compared with dynamic CE-MR imaging and/or PET/CT, dynamic CE-perfusion ADCT possesses equal or superior capability for distinguishing malignant from benign nodules as well as nodules requiring further intervention and/or treatment from nodules needing only follow-up examination [16–18]. Moreover, one of these studies has suggested that mathematical models can perform a key function in the improvement of diagnostic performance using dynamic CE-perfusion ADCT [17]. To the best of our knowledge, however, no studies have been reported regarding the capability of dynamic CE-perfusion ADCT for therapeutic effect prediction and the influence of mathematical models in this setting.

We hypothesized that dynamic CE-perfusion ADCT is capable of early prediction of therapeutic effect and recurrence in NSCLC patients treated with chemoradiotherapy. We further hypothesized that the applied mathematical models can have a significant effect on the potential of dynamic first-pass CE-perfusion ADCT in this setting. The purpose of this study was to determine the capability and influence of mathematical methods on the use of dynamic CE-perfusion ADCT for early prediction of treatment response, disease progression and overall survival of NSCLC patients treated with chemoradiotherapy.

2. Materials and methods

2.1. Subjects

This prospective study was approved by the institutional review board of Kobe University Graduate School of Medicine and written informed consent was obtained from all patients. It was financially and technically supported by Toshiba Medical Systems Corporation, and financially by Grants-in-Aid for Scientific Research from the Japanese Ministry of Education, Culture, Sports, Science and Technology (JSTS.KAKEN; No. 24591762), the Adaptive and Seamless Technology Transfer Program through Target Driven R & D from the Japan Science and Technology (JST) Agency and Bayer Pharma. Two of the authors (Y.F. and N.S.), who are employees of Toshiba Medical Systems Corporation, developed the software, but had no control over any data or information submitted for publication or any control over any parts of data and information included in this study.

A total of 79 patients, consecutively pathologically diagnosed with NSCLC and clinically diagnosed as stage III and comprising 55 men (mean age ± standard deviation [SD]: 69.5 ± 6.1 years) and 24 women (mean age ± SD: 70.5 ± 5.8 years) underwent dynamic CE-perfusion ADCT examinations. The diagnosis was based on the results of contrast-enhanced whole-body CT, FDG-PET/CT, contrast-enhanced brain MRI, body MR imaging including diffusion-weighted imaging (DWI), bone scintigraphy and pathological examination of specimens obtained by transbronchial and/or CT-guided biopsies according to the criteria for staging by the International Union against Cancer. All studies were performed in random order within 3 weeks of diagnosis and before treatment.

The patients included in this study were selected according to the following criteria: (a) tumor measuring 10 mm in diameter or more, (b) no prior history of chemotherapy or thoracic radiotherapy; Eastern Cooperative Oncology Group performance status ≤1, (c) age ≤75 years, (d) leukocytes ≥4000/μl, platelets ≥100,000/μl, hemoglobin ≥9.5 g/dL, serum creatinine ≤ normal institutional upper limit, 24-hour creatinine clearance ≥60 ml/min, bilirubin ≤1.5 mg/dL, AST and ALT ≤2.0 × normal upper limit, and partial pressure of arterial oxygen ≥70 mmHg. Patients were excluded if they had (1) pulmonary fibrosis, (2) other active, invasive malignancies in the 3 years leading up to protocol entry, (3) malignant effusion, (4) pyrexia of 38 °C or more at baseline, (5) infections, (6) significant cardiac disease, (7) uncontrolled diabetes mellitus, (8) paresis of the intestine ileus, or (9) regular use of corticosteroids.

The eventual study group comprised 66 consecutive patients, 49 males (mean age ± SD: 69.4 ± 5.2 years) and 17 females (mean age ± SD: 70.5 ± 5.4 years). On the basis of pathological examination results, 66 patients were diagnosed with 56 adenocarcinoma, eight with squamous cell carcinoma, and two with large cell carcinoma, while 30 cases were diagnosed as stage IIIA, and 36 as stage IIIB. All patients were treated with chemoradiotherapy consisting of concurrent administration of thoracic radiotherapy and chemotherapy. For platinum-based chemotherapy, cisplatin or carboplatin was used with other drugs such as docetaxel, paclitaxel, etoposide and videsine according to treatment guidelines provided by The Japan Lung Cancer Society. Radiotherapy was administered once daily with a daily fraction of 2.0 Gy, five days per week. The total dose ranged from 60 Gy to 66 Gy.

2.2. Evaluation of chemoradiotherapy response

All patients underwent chest radiography, complete blood count, and blood chemistry studies once a week during the treatment. The response was evaluated in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST ver.1.1) [14,19,20]. According to RECIST ver.1.1 criteria, all targeted and non-targeted lesions were decided by consensus of the radiologists, radiation oncologists, pulmonologists and oncologists who did not perform any of the image and/or statistical analyses for this study and had more than 10 years' experience in their respective specialty. After the treatment, chest radiographs or chest contrast-enhanced CTs were obtained every three months, and whole-body contrast-enhanced CT, brain contrast-enhanced MRI, bone scintigraphy and/or FDG-PET/CT every six months.

All patients were then divided into two groups (RECIST responders, consisting of the complete response (CR) and partial response (PR) groups, and RECIST non-responders), consisting of the stable disease (SD) and progressive disease (PD) groups. Overall survival (OS) and progression free survival (PFS) were also evaluated for each group. OS was defined as the time from diagnosis until death from any cause, and PFS as the time between assignment for treatment and disease progression, death, or last known follow-up. The follow-up ranged from 3 to 36 months.

2.3. Dynamic first-pass CE-perfusion ADCT examinations

All dynamic first-pass ADCT studies were performed on a 320-detector row CT scanner (Aquilion ONE; Toshiba Medical Systems, Otawara, Tochigi, Japan) by means of volumetric cine scan with-