Lung Cancer 121 (2018) 91–96

Contents lists available at ScienceDirect

Lung Cancer

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

Prognostic impact of the integration of volumetric quantification of the solid part of the tumor on 3DCT and FDG-PET imaging in clinical stage IA adenocarcinoma of the lung

Hideyuki Furumoto[a], Yoshihisa Shimada[a,*], Kentaro Imai[a], Sachio Maehara[a], Junichi Maeda[a], Masaru Hagiwara[a], Tetsuya Okano[a], Ryuhei Masuno[b], Masatoshi Kakihana[a], Naohiro Kajiwara[a], Tatsuo Ohira[a], Norihiko Ikeda[a]

[a] Department of Surgery, Tokyo Medical University, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo, 160-0023, Japan
[b] Department of Radiology, Tokyo Medical University, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo, 160-0023, Japan

ARTICLE INFO

Keywords:
Adenocarcinoma
Tumor volume
Three-dimensional CT
PET/CT
Stage IA

ABSTRACT

Objectives: The aim of this study was to conduct comparative analyses of the biological malignant potential of clinical stage IA adenocarcinoma using positron emission tomography/computed tomography (PET/CT), high-resolution CT (HRCT), and three-dimensional CT (3DCT). The predictive performance of these parameters was evaluated in terms of clinical outcomes and pathological invasiveness (positive lymphatic permeation, blood-vessel invasion, pleural invasion, and lymph-node metastasis).

Materials and methods: We enrolled 170 patients with c-IA adenocarcinoma who underwent PET/CT, HRCT, and 3D reconstruction of lung structures using the Synapse Vincent system (Fujifilm Corporation, Tokyo, Japan) followed by complete resection. Maximum standardized uptake values (SUV_{max}) of F^{18}-fluorodeoxyglucose and the size and volume of the solid part of the tumor were quantified and analyzed in relation to surgical outcomes.

Results: Univariate analysis demonstrated that all the three parameters and whole-tumor volume were associated with unfavorable disease-free survival (DFS), while the volume of the solid part was the independent predictor on multivariate analysis ($p < .001$). The receiver operating characteristic curves for pathological invasiveness, determined using the variables dichotomized at each cut-off level (SUV_{max} 2.4; solid-part size 1.23 cm; solid-part volume 779 mm^3), showed that all were significantly correlated with pathological invasiveness and prognosis, whereas the combination of SUV_{max} and the solid-part volume was the most powerful predictor of survival and pathological invasiveness compared to any other parameters: the 4-year DFS and proportion of pathological invasiveness in patients with $SUV_{max} > 2.4$ and solid-part volume > 779 mm^3 versus those with $SUV_{max} \leq 2.4$ or solid-part volume $\leq$779 mm^3 were 81.2% versus 98.3% ($p < .001$) and 84.3% versus 15.1% ($p < .001$), respectively.

Conclusion: In c-IA adenocarcinoma, the volume of the solid part of the tumor was the independent predictor for unfavorable DFS, and the integration of the volume of the solid part and SUV_{max} was highly beneficial for the prediction of survival and pathological invasiveness.

1. Introduction

Accumulating evidence suggests that a meticulous evaluation of preoperative features of lung tumor by thin-section computed tomography (CT) is highly beneficial for the preoperative estimation of pathological malignant grade and prognostic outcomes in patients with peripheral small-sized non-small-cell lung cancer (NSCLC) [1–5]. The size of the solid part of an adenocarcinoma of the lung, measured by CT, is reported to be a better prognostic factor than the size of the whole tumor [1–4,6,7]. Moreover, the effective use of combined maximum standardized uptake values (SUV_{max}) on F^{18}-fluorodeoxyglucose–positron emission tomography/CT (FDG-PET/CT) and solid-part size on high-resolution CT (HRCT) imaging provides exceptionally better accuracy in predicting pathological tumor invasiveness and survival compared with either modality used alone [4,5]. However, the shape of the solid part is often irregular, thus the measurement of its size can be difficult and in practice can cause intra- and inter-observer variations.

Preoperative three-dimensional (3D) imaging simulation is

* Corresponding author.
E-mail address: zenkyu@za3.so-net.ne.jp (N. Ikeda).

https://doi.org/10.1016/j.lungcan.2018.05.001
Received 25 December 2017; Received in revised form 11 February 2018; Accepted 3 May 2018

becoming increasingly common in daily practice for the safety and accuracy of surgical procedures in the field of lung cancer [8–12]. The latest progress in this technique has also allowed us to easily and precisely conduct volumetric quantification of the solid and non-solid parts of the tumor separately, and this may overcome a major disadvantage of the ambiguity of delineating solid-part size on HRCT [13].

Here we present comparative analysis of the predictive performance of FDG-PET/CT, HRCT, and 3DCT imaging, and the integration of two modalities in clinical stage IA adenocarcinoma patients with clinical outcomes and pathological tumor invasiveness.

2. Materials and methods

2.1. Patients

We enrolled 170 patients with clinical stage IA adenocarcinoma at our department between January 1, 2012 and December 31, 2015. Preoperative FDG-PET/CT, HRCT, and 3D reconstruction of lung structures using the Fujifilm Synapse Vincent system (Fujifilm Corporation, Tokyo, Japan) followed by curative R0 resection were performed for all patients. The TNM stage was determined in accordance with the 7th edition of the TNM classification of malignant tumors [14]. Preoperative evaluation included physical examination, chest radiography, CT of the chest and abdomen, blood examination, and FDG-PET/CT. Most patients were postoperatively evaluated to confirm relapse by physical examination, chest radiography, and CT of the chest and abdomen every 6 or 12 months. In some patients we conducted FDG-PET/CT, brain magnetic resonance imaging, or bone scintigraphy to detect recurrence. Data collection and analyses were approved, and the need to obtain written informed consent from each patient was waived by the Institutional Review Board of Tokyo Medical University.

2.2. HRCT and 3DCT assessment for the primary tumors

Patients underwent contrast-enhanced CT imaging with a 64-channel multi-detector CT (Light Speed VCT, GE Medical systems, Milwaukee, WI, USA) set at the following parameters: gantry rotation speed of 0.4 s per rotation, collimation of 0.625 mm, table incrementation speed of 39.37 mm/s with a helical pitch of 0.984, and tube voltage of 120 kV. Axial sections (1.25 mm thick) of the whole lung were reconstructed at intervals of 1.0 mm, and images were viewed on standard lung windows (level −600 HU; width 1500 HU) and mediastinal windows (level 30 HU; width 400 HU). Each CT image was acquired within one breath hold of about 5 s, after a delay of 70 s during which the contrast media injection took effect. HRCT scans were evaluated by two surgeons (H.F. and Y.S.) and a radiologist (R.M.) in consensus. We defined ground-glass opacities (GGOs) as hazy areas of increased attenuation in the lung.

The presented CT scan protocol has been used for both standard staging for lung cancer patients amenable to contrast radiography and 3D image conversion with the Synapse Vincent system. Digital imaging and communication in medicine data were transferred to a workstation with the software. After this, a surgeon spent approximately 3 min constructing 3D images and completing tumor volumetric analysis semi-automatically (Fig. 1). These results were interpreted by two surgeons (H.F. and Y.S.) in consensus since there was little variation in the observed numerical data. This 3D tumor analysis provided us with the volumes of the whole tumor, the solid part, and the non-solid part.

2.3. FDG-PET/CT assessment

The patients fasted for at least 4 h before being intravenously injected with 74–185 MBq FDG, and then rested for 1 h before evaluation. Blood glucose was measured before tracer injection to ensure a value of 150 mg/dL. Patients with blood glucose values of > 150 mg/dL during PET/CT image acquisition were excluded. All patients were assessed using a Biograph (Siemens Healthcare, Erlangen, Germany) PET/CT scanner. Unenhanced CT images of sections 2–4 mm thick that matched the PET images were acquired from the head to the pelvic floor of each patient using a standard protocol. Immediately after CT, PET covered the identical axial FOV for 2–4 min per table position depending on the condition of the patient and the scanner performance. Both PET and CT studies proceeded with the patient under normal tidal breathing. All PET images were reconstructed by an iterative algorithm with CT-derived attenuation correction using Fourier re-binning followed by ordered-subset expectation maximization (iteration number 5, subset number 16).

The SUV_{max} was established by drawing regions of interest (ROIs) around the primary tumor on attenuation-corrected FDG-PET images, and calculated using the software integrated within the PET/CT scanner based on the formula:

$$SUV_{max} = C(MBq/kg)/[ID(MBq)/w(kg)]$$

where C is defined as the maximal activity at a single pixel within the tissue identified by the ROI, and ID is defined as the injected dose/kg of body weight (w). The SUV_{max} was adopted because it is less variable than the mean SUV.

2.4. Statistical analysis

Factors with pathological invasiveness were defined as positive lymphatic permeation (Ly), blood-vessel invasion (V), pleural invasion (PL), and lymph-node metastasis (N). The receiver operating characteristic (ROC) curves of each parameter were used to predict any of the above-mentioned pathological factors. Overall survival (OS) was measured from the date of surgery to the date of death from any cause or the date on which the patients were last known to be alive. Disease-free survival (DFS) was measured from the date of the surgery until the first event (relapse or death from any cause) or the last follow-up visit. OS and DFS curves were plotted using the Kaplan–Meier method, and differences in variables were determined using the log-rank test. Categorical comparison was performed using the Pearson chi-squared test. Univariate analysis for DFS was performed using the Cox proportional hazards regression model, whereas the multivariate analysis was done with a stepwise variable selection for the Cox model. All tests were two-sided, and p values < .05 were considered to indicate a statistically significant difference. The SPSS statistical software package (version 24.0; DDR3 RDIMM, SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

3. Results

Patient characteristics in this study are shown in Table 1. The median follow-up time for survivors was 1246 days. During the study period, recurrences occurred in ten patients (5.9%), half of whom died from those relapses (n = 5, 2.9%). The mean sizes of the whole tumor and of the solid part on HR-CT were 1.92 ± 0.54 cm and 1.24 ± 0.74 cm, respectively, whereas the mean whole-tumor volume and solid-part volume on 3DCT were 2759 ± 2339 mm^3 and 1264 ± 1459 mm^3, respectively. The mean SUV_{max} on PET/CT was 3.13 ± 4.39. Pathological findings demonstrated that the numbers of patients with Ly, V, PL, and N were 47 (27.6%), 45 (26.5%), 23 (13.5%), and 20 (11.8%), respectively.

Univariate and multivariate analyses were performed to examine the association between DFS and preoperative clinical factors, including the above-mentioned radiological features (Table 2). SUV_{max} (p = .006), solid-part size (p = .007), whole-tumor volume (p = .015) and solid-part volume (p < .001) were identified as significant predictors of unfavorable DFS on univariate analysis. Multivariate analysis demonstrated that the solid-part volume was the only predictor for