Lung Cancer 95 (2016) 51–56

Contents lists available at ScienceDirect

Lung Cancer

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

Estimation of the pathological invasive size of pulmonary adenocarcinoma using high-resolution computed tomography of the chest: A consideration based on lung and mediastinal window settings

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ARTICLE INFO

Article history:
Received 4 December 2015
Received in revised form 23 February 2016
Accepted 28 February 2016

Keywords:
Pulmonary adenocarcinoma
Pathological invasive size
High-resolution computed tomography
Lung cancer staging

ABSTRACT

Objectives: Since the proposal of the new classification of pulmonary adenocarcinoma (PADC), the size of pathological invasion has become more important. We aimed to determine whether high-resolution computed tomography (HRCT) could be used to preoperatively evaluate PADC invasive size.
Methods: We investigated 360 complete resected cT1a–1b–2aN0 PADCs. We examined the correlation of pathological invasive size with three HRCT parameters [whole tumor *d*imension in the *l*ung window (LD), *c*onsolidation *d*imension in the lung window (CD), and tumor *d*imension in the *m*ediastinal window (MD)]. HRCT prediction of an invasive size of ≤5 mm was determined using receiver operating characteristic curve analysis.
Results: Pathological invasive size correlated well with both CD (r^2 = 0.710) and MD (r^2 = 0.743) comparably, and moderately with LD (r^2 = 0.514). CD and MD tended to be slightly larger and smaller, respectively, than the actual invasive size. Invasive size roughly approximated to MD + 3 mm, and an invasive size of ≤5 mm was best predicted by MD, followed by CD. MD of ≤2 mm and 0 mm predicted an invasive size of ≤5 mm with 64.1% and 47.4% sensitivity and 96.5% and 98.9% specificity, respectively. Lymphovascular invasion was best predicted by MD followed by CD. Pleural invasion and lymph node metastasis was predicted well by both MD and CD.
Conclusion: Preoperative estimation of the invasive size of PADC and evaluation of other parameters of invasiveness were possible using MD. This approach using HRCT may play a complementary role in more thorough clinical staging of PADC.

1. Introduction

The International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society have recently announced a new international multidisciplinary classification of pulmonary adenocarcinoma (PADC) [1,2]. In this classification, the following points are proposed: (1) the conventional term "bronchioloalveolar carcinoma" is no longer used; (2) adenocarcinoma of ≤3 cm in diameter with pure lepidic growth is defined as adenocarcinoma in situ (AIS) and is classified as a preinvasive lesion along with atypical adenomatous hyperplasia; (3) adenocarcinoma of ≤3 cm in diameter and ≤5 mm in pathological invasive size with lepidic growth is classified in the newly established category of minimally invasive adenocarcinoma (MIA); and (4) invasive adenocarcinoma (IAD) is not referred to as a mixed subtype, but as lepidic, acinar, papillary, micropapillary, or solid-predominant carcinoma, based on its predominant histologic subtype. MIA is a relatively new concept [3].

Since the introduction of thin-section high-resolution computed tomography (HRCT) of the chest, numerous studies have evalu-

Abbreviations: AIS, adenocarcinoma in situ; AUC, area under the curve; CD, consolidation dimension in the lung window setting; HRCT, high-resolution computed tomography; IAD, invasive adenocarcinoma; LD, whole-tumor dimension in the lung window setting; MD, tumor dimension in the mediastinal window setting; MIA, minimally invasive adenocarcinoma; PADC, pulmonary adenocarcinoma; ROC, receiver operating characteristic; TNM, tumor–node–metastasis.

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http://dx.doi.org/10.1016/j.lungcan.2016.02.017
0169-5002/

ated its use to preoperatively predict histopathological findings and disease prognosis. Some studies suggested that the degree of invasion and the prognosis after resection are correlated with the tumor disappearance ratio on chest HRCT, that is, the ratio of tumor dimension in the mediastinal window setting to the whole tumor dimension in the lung window setting [4–6]. Other studies suggested that the degree of invasion and the prognosis after resection are correlated with the solid part of the tumor in the lung window setting [7–10] or with absolute values of the whole-tumor dimension in the mediastinal window setting [11,12].

The pathological invasive size of PADC will become more important in the future because it is a key determinant of whether a lesion is MIA, less invasive, or IAD. The pathological invasive size can complement the pT factor of the tumor–node–metastasis (TNM) classification of lung cancer. Since the proposal of the new classification of PADC, there have only been a few reports on the preoperative measurement of invasive size using HRCT. In the present study, we investigated whether HRCT could be used to preoperatively assess the pathological invasive size and other parameters of invasiveness. Three HRCT parameters used were: whole-tumor *d*imension in the *l*ung window setting (LD), *c*onsolidation *d*imension in the lung window setting (CD), and tumor *d*imension in the *m*ediastinal window setting (MD).

2. Patients and methods

2.1. Study design and patients

This study was a retrospective review of the medical records of 357 consecutive patients who underwent complete resection of PADCs at the Aichi Cancer Center Hospital between October 2012 and June 2015. A total of 360 PADCs classified cT1a–1b–2aN0 of ≤5 cm in diameter, which had been assessed pathologically for invasive size, were reviewed. Three patients had two lesions that were confirmed to be clinically and pathologically independent of each other because, of the two lesions, at least one was AIS. The characteristics of the patients are shown in Table 1. The staging description was based on the 7th edition of the TNM classification system for lung cancer [13,14]. This study was approved by the institutional review board of the Aichi Cancer Center Hospital (approval No. 2014-1-083). Each patient was informed that his or her clinical data could be used for various studies, and consent was obtained on that basis.

2.2. Measurement of HRCT images

All HRCT images of the lesions were obtained using 8-, 64-, or 80-row multidetector CT scanners (Aquilion 8, Aquilion 64, Aquilion PRIME, respectively; Toshiba Medical Systems, Tokyo, Japan), with or without enhancement. Image reconstruction was performed using lung (FC52, FC81) and mediastinal (FC13) algorithms with a slice thickness of 0.5–2.0 mm (0.5 mm, 23 cases; 1.0 mm, 206 cases; 1.25 mm, 41 cases; 1.5 mm, 12 cases; and 2.0 mm, 75 cases). The images were displayed in lung (level, −600HU; width, 1500HU) and mediastinal (level, 35HU without enhancement or 75HU with enhancement; width, 320HU) window settings. Unenhanced HRCT was used only for patients with contrast medium allergy. LD, CD, and MD were measured on axial HRCT images by at least two staff members, and based on the reason of the measurement, all staff members and our radiologist discussed these measured values and determined the final value during preoperative departmental conferences. Measurement of the lesion on the HRCT images was performed with particular attention to following points: (1) images should be sufficiently magnified; (2) it was not necessary to measure LD, CD, and MD on the same image slice, but the maximum measured value was used; and (3) for lesions with more than one shadow on the mediastinal window setting, MD was measured using the diameter of the largest shadow. This was done considering that if multiple invasive areas were found in one tumor, the size of the invasion was not the summation of all such foci but the largest foci [1,2].

2.3. Pathological specimens

Pathological slides of the resected lung specimens were prepared using a standard procedure. In brief, the resected lung was inflated and fixed by injection with 10% formalin immediately after resection. Sliced tissues were embedded in paraffin, and the blocks were sectioned and stained with hematoxylin–eosin. Next, the blocks were sliced to match the HRCT axial image as closely as possible. The elastica van Gieson method and immunohistochemical staining were used as necessary. Pathological invasive size was defined on the basis of recent recommendations [1,2].

2.4. Statistical analysis

We evaluated the correlation of pathological invasive size with LD, CD, and MD based on the coefficient of determination, r^2. Furthermore, the diagnostic performance of LD, CD, and MD to identify an invasive size of ≤5 mm or >5 mm, the presence or absence of lymphatic (LY) and vascular (V) invasion, pleural invasion (PL), and lymph node (N) metastasis were analyzed using receiver operating characteristic (ROC) curves. Two areas under the ROC curves (AUCs) were compared using the DeLong, DeLong, and Clarke–Pearson method [15]. All statistical analyses were performed using JMP for Windows (version 9.0, SAS Institute, Cary, NC).

Practical meanings of calculated sensitivity, specificity, positive predictive value, negative predictive value, and accuracy in this study are as follows. Sensitivity refers to the probability that a lesion measured on the HRCT image is equal to or smaller than the cutoff value among PADCs with an invasive size of ≤5 mm (i.e., AIS and MIA). Specificity refers to the probability that a lesion measured on the HRCT image is larger than the cutoff value among PADCs with an invasive size of >5 mm (i.e., IAD). Positive predictive value refers to the probability that the invasive size of the lesion is ≤5 mm (i.e., AIS or MIA) when the lesion size on HRCT image is equal to or smaller than the cutoff value. Negative predictive value refers to the probability that the invasive size of the lesion is >5 mm (i.e., IAD) when the lesion size on the HRCT image is larger than the cutoff value. Accuracy refers to the proportion of correct HRCT estimations to the total number of lesions.

3. Results

Pathological invasive size correlated well with MD ($r^2 = 0.743$), followed by CD ($r^2 = 0.710$), and then LD ($r^2 = 0.514$; Fig. 1). The correlation of invasive size with MD and CD was comparable, whereas the correlation with LD was lower. As indicated in Fig. 1, measured CD tended to be slightly larger and measured MD tended to be slightly smaller than the invasive size. Linear regression analysis showed that the invasive size was roughly approximated by the following equation:

Invasive size ≈ MD + 3 mm

ROC analysis showed that an invasive size of ≤5 mm or >5 mm was best predicted by MD (AUC = 0.941), followed by CD (AUC = 0.897), and LD (AUC = 0.745; Fig. 2). Prediction by MD was significantly better than that by CD ($p = 0.001$), and prediction by CD was significantly better than that by LD ($p < 0.001$).

Table 2 is a numerical translation of Fig. 2. For example, when a cutoff of 2 mm was used, an MD of ≤2 mm predicted an invasive