Changes of Tumor Size and Tumor Contrast Enhancement during Radiotherapy for Non-small-cell Lung Cancer May Be Suggestive of Treatment Response

Hiroshi OKADA1,2*, Shigeto HONTSU2,4, Sachiko MIURA3, Isao ASAKAWA2, Tetsuro TAMAMOTO2, Emiko KATAYAMA2, Satoru IWASAKI1, Hiroshi KIMURA4, Kimihiko KICHIKAWA3 and Masatoshi HASEGAWA2

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We evaluated sequential dynamic contrast-enhanced CT (DCE-CT) scans to assess the possibility of early prediction of treatment responses by quantifying the tumor size reduction and the change in tumor enhancement during and after a course of radiotherapy (RT). Thirty-nine patients with non-small-cell lung cancer were treated with RT for initial treatment. DCE-CT scan was performed within one week before the beginning of treatment, after 17 or 18 fractions (34 or 36 Gy), and 1 week and 1 month after the end of RT. The correlation between the relative decrease in tumor diameter and that in the attenuation value was evaluated. Nineteen patients were evaluated in this study. The median tumor size was 39.5 mm at the start of treatment, 30.8 mm at 34–36 Gy, and 16.1 mm 1 month after the end of RT. The relative decrease in tumor diameter at 34–36 Gy well correlated with that 1 month after treatment (r = 0.85, r: Pearson’s correlation coefficient, p < 0.001). Relative change in the attenuation value at the rim of the tumor at 34–36 Gy did not significantly correlate with the change in tumor diameter 1 month after the completion of RT, but in the center of the tumor, the change of the attenuation value in the delayed phase correlated with the change in tumor diameter. The decrease of tumor diameter during RT may be predictive of treatment response. The relative change of tumor enhancement in the center of the tumor in the delayed phase correlated with tumor shrinkage 1 month after the completion of RT.

INTRODUCTION

Lung cancer is the most common cause of cancer mortality. Surgery is the first choice for locally resectable non-small-cell lung cancer (NSCLC), but about 80% of lung cancer patients are inoperable due to locoregional tumor extension, metastasis to other organs or poor physical condition. Radiotherapy (RT) is the definitive local treatment modality for unresectable locally advanced lung cancer patients and is often combined with chemotherapy. The current prognosis for NSCLC treated with RT is still poor, and treatment failure will occur in a significant number of patients. Early prediction of treatment response may allow therapy modification, such as increase of the total radiation dose and intensity of chemotherapy, and better local control. Recent data have often suggested that higher doses of radiation can improve local control and overall survival,1–3) however, delivering doses more than 70 Gy to traditionally defined target volumes is often impossible because of normal tissue damage, especially the risk of pneumonitis and lung fibrosis. If the radiation field is small, dose escalation may be possible and the toxicity of radiotherapy can be reduced. Many investigators have observed tumor volume shrinkage to varying degrees during the course of fractionated radiation therapy,4–8) and tumor volume shrinkage in a shorter period, specifically during the course of RT, is meaningful in clinical situations. Replanning for a shrinking field size to adapt to gross tumor volume (GTV) change will lead to greater normal tissue sparing without detrimental effects on the planned target volume (PTV) dose coverage. A recent study of head and neck cancer suggested that local blood supply increase, potentially a source of increased oxygenation, may be a positive indicator

*Corresponding author: Phone: +81-6-6781-5101,
Fax: +81-6-6787-2541,
E-mail: h-okad@kcn.ne.jp
1Department of Radiology, Higashiosaka City General Hospital, 3-4-5
Nishiwata, Higashiosaka 578-8588, Japan; 2Department of Radiation
Oncology; 3Department of Radiology; 4Second Department of Internal
Medicine, Nara Medical University, 840 Shijo-cho, Kashihara 634-8522,
Japan.
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of therapeutic response, however, a significant correlation between changes in local blood supply and therapeutic responses to RT for NSCLC has not been established yet.

Thus, we conducted a study of dynamic contrast-enhanced CT before, during, and after RT to assess the possibility of early prediction of treatment responses by quantifying the tumor size reduction and the change in tumor enhancement during and after a course of RT.

MATERIALS AND METHODS

Patients
Thirty-nine consecutive patients with NSCLC treated with RT as initial treatment for definitive therapy under the following protocol from January 2009 to April 2010 were involved. Each patient gave written informed consent, including information on radiation exposure from both CT examinations and RT and on the adverse effects of the treatment. The ECOG Performance Status Scale of all patients ranged from 0 to 2. This study was approved by the institutional ethics committee of Nara Medical University.

All patients were proven to have NSCLC histologically (median size, 39.5 mm; range, 11.0 to 72.9 mm) and all tumors were unresectable. All patients were treated with a course of RT delivering 60–70 Gy in 30–35 fractions with or without chemotherapy. Dynamic contrast-enhanced CT (DCE-CT) scan was performed within one week before beginning the treatment, after 17 or 18 fractions (34 or 36 Gy) of RT, and 1 week and 1 month after the end of RT.

Dynamic contrast-enhanced CT
Patients were scanned using a dual-source CT scanner (Somatom Definition; Siemens Medical Solutions, Forchheim, Germany). An initial non-contrast breath-hold scan encompassing the whole lung was performed. Using a dual-headed pump injector, 80 mL contrast media (300 mgI/mL (B.W. < 65 kg) or 370 mgI/mL (B.W. ≥ 65 kg)), was administered at 4 mL/s followed by 60 mL contrast media diluted 33% with saline. A contrast breath-hold scan was performed in dual mode (64 × 0.6 mm, 0.33 s rotation speed, 2 mm slice thickness, D30f kernel, 160 mAs at 140 kV, 532 mAs at 80 kV). A contrast medium bolus tracking scan was not used. Image acquisition was started 20 s after the beginning of bolus injection for the early phase, and 90 s after for the delayed phase.

The maximum tumor diameter was measured at the axial section in every series of serial DCE-CT study.

Additional analysis was carried out to assess the enhancement of the tumor center and tumor rim. The attenuation value of the tumor was measured by placing a separate ROI within the tumor rim and center at each point, respectively. All measurements in Hounsfield units were obtained from mediastinal window images to ensure that partial volume averaging was minimized. The tumor center was defined as the area more than 30% of the diameter from the edge, and the tumor rim was defined as the area less than 20% of the diameter from the tumor edge. Because of the difficulty in defining the rim and center, analysis was carried out at the maximum diameter of the axial section.

Statistical analysis
The correlation between the relative decrease in tumor diameter 1 month after the end of RT and that in the attenuation value during RT was evaluated. We did not analyze the relative change of tumor enhancement 1 week after the end of RT because, in this study, we evaluated the possibility of early prediction and modification of therapy during the course of RT. Standard statistical methods were used to assess correlations in univariate analysis. Pearson's χ² test was used for qualitative data. The correlation between the relative decrease in tumor diameter during and after the course of RT was also evaluated.

All statistical analyses were performed using StatMate version 4.0 (ATMS, Tokyo, Japan).

RESULTS

Of the 39 patients treated in this period, 2 died during the course of RT, and 2 aborted treatment because of adverse effects. In 4 patients, contrast-enhanced CT scans were not obtained because of renal dysfunction or poor general condition. In 1 patient with a 10 mm tumor, the attenuation value could not be measured in two regions. In 2 patients, CT scans were not obtained because of technical issues. In 8 patients, CT scans were not performed under this protocol. Two patients

| Table 1. Patient characteristics | Data |
|---------------------------------|------|
| Characteristics (n = 19)        | Data |
| Sex                             |      |
| Male                            | 18   |
| Female                          | 1    |
| Median age (range) (y)          | 70 (41–79) |
| Histology, n (%)                |      |
| Squamous cell carcinoma         | 12 (63.2) |
| Adenocarcinoma                  | 5 (26.3) |
| Mucoepidermoid carcinoma        | 1 (5.3)  |
| Others                          | 1 (5.3)  |
| Stage, n (%)                    |      |
| IIb                             | 3 (15.8) |
| IIIa                            | 9 (47.4) |
| IIb                             | 6 (31.6) |
| IV                              | 1 (5.3)  |
| Chemotherapy                    |      |
| Carboplatin + Paclitaxel        | 9    |
| Cisplatin + Docetaxel           | 7    |
| Total tumor dose [median (range)] (Gy) | 66 (60–70) |
were lost to follow-up. The other 19 patients were evaluated in this study. Characteristics of patients are shown in Table 1. The median age was 70 years (range: 41–79) and 1 patient was female. The median radiation dose was 66 Gy (range: 60–70). Chemotherapy was given to 16 patients. The chemotherapy regimens included carboplatin/paclitaxel (9 patients) and cisplatin/docetaxel (7 patients). The clinical stage was IIB in 3 patients, IIIA in 9 patients, IIIB in 6 patients and IV in 1 patient. Histology of tumors was 12 squamous cell carcinomas, 5 adenocarcinomas, 1 mucoepidermoid carcinoma, and 1 NSCLC could not be classified. The individual tumor size ranged from 11.0 to 72.9 mm at the start of treatment.

Tumor diameters and their percentage changes from before to after therapy are detailed in Fig. 1a and 1b. The median tumor size was 39.5 mm before treatment, 30.8 mm (mean regression rate (MRR): 0.74) at 34–36 Gy, 22.8 mm (MRR: 0.56) 1 week after the end of RT, and 16.1 mm (MRR: 0.5) 1 month after the end of RT, respectively. All but 3 tumors regressed at 34–36 Gy (more than 8%) and 1 month after the end of RT by more than 30%. Three tumors regressed less than 8% at 34–36 Gy. The relative decrease in tumor diameter at 34–36 Gy well correlated with that 1 month after treatment ($r = 0.85, r$: Pearson’s correlation coefficient, $p < 0.001$) (Fig. 2). Relative decrease of tumor diameter during and after the course of radiotherapy was not different between squamous cell carcinoma and adenocarcinoma in this study (data not shown). Relative change in the attenuation value in the center of the tumors at 34–36 Gy did not correlate with the change in tumor diameter 1 month after the completion of RT in the early phase ($r = -0.13, p = 0.60$), but in the delayed phase, it correlated with the change in tumor diameter ($r = -0.69, p < 0.01$) (Fig. 3). Relative change in the attenuation value at the rim of the tumors at 34–36 Gy did not correlate with the change in tumor diam-

![Fig. 1. Tumor diameters (1a) and tumor regression rate (1b) in all 19 patients included in this study from before to after therapy.](image)

![Fig. 2. Correlation between the relative decrease in tumor diameter at 34–36 Gy and that 1 month after the end of RT.](image)
eter 1 month after the completion of RT in the early phase ($r = 0.39$, $p = 0.22$) or in the delayed phase ($r = -0.07$, $p = 0.78$), respectively (Fig. 4).

Figure 5 shows a case of squamous cell carcinoma, that decreased in size gradually during and after treatment. Table 2 shows the characteristics of two groups when we divided all patients according to the median value of the relative change of tumor enhancement in the center of the tumor during RT.

**DISCUSSION**

Several trials have reported that dose escalation improved local control, leading to increased failure-free intervals and survival,\(^\text{1-3,11,12}\) however, dose escalation also leads to increased exposure of organs at risk, such as the lung, heart, esophagus, and spinal cord,\(^\text{16}\) and may have an increased probability of unacceptable normal tissue complications.

Generally, the tumor response to RT is believed to be a slow process.\(^\text{13}\) Wasik \textit{et al.} reported that tumors reached their maximum response (minimum volume) an average of 5–11 months after RT completion.\(^\text{14}\) Fox \textit{et al.} reported that GTV delineated on respiration-correlated four-dimensional CT scan fell 24.7% (range, –0.3% to 61.7%) during a course of RT at a dose of 30 Gy.\(^\text{7}\) In this study, tumor shrinkage was observed at an early stage of RT, and mean tumor regression was 26% (MRR 0.74) at 34–36 Gy and 44% (MRR 0.56) 1 week after the end of RT. Woodford \textit{et al.}
reported that average GTV reduction observed over 30 fractions (60 Gy) was 38%, and Kupelian et al. reported tumor regression rates with a range of 0.6% to 2.3% per day. In our results, the extent of tumor shrinkage was greater than in previous reports if the tumors had equivalent percentage reductions in the measures of length, width and height.

Tumor shrinkage was evident in most cases at an early stage of RT. We may be able to shrink the PTV at 40 Gy, but whether it is feasible to shrink the clinical target volume (CTV) is unclear in this study. Microscopic tumor extensions cannot be visualized with current imaging modalities. In addition, the required dose levels for microscopic cells beyond the visible gross tumor are unknown but might be lower than necessary for GTV. Further study is needed for adaptive radiotherapy planning to determine how and when to shrink CTV.

We evaluated the tumor size by the longest axis of the tumor in the present study. In the Response Evaluation Criteria In Solid Tumors (RECIST), tumor response was evaluated by the sum of the diameter of the tumors and it is suggested that measurement of the largest diameter of the tumor can be used as a reliable tool in assessing lung cancer response to nonoperative therapy, although tumor volume was calculated in most previous studies.

With the advent of image-guided RT, it has become possible to observe the shape, volume, and position changes of...

**Table 2.** Characteristics of two groups as a function of relative change in attenuation value

| Characteristics (n = 19) | RC ≥ 0.98 | RC < 0.98 |
|-------------------------|-----------|-----------|
| **Chemotherapy**         |           |           |
| Carboplatin + Paclitaxel | 4         | 5         |
| Cisplatin + Docetaxel    | 4         | 3         |
| none                     | 1         | 2         |
| **Histology**            |           |           |
| Squamous cell carcinoma  | 7         | 5         |
| Adenocarcinoma           | 1         | 4         |
| Mucoepidermoid carcinoma | 1         | 0         |
| Others                   | 0         | 1         |

RC: relative change in attenuation value
tumors during the treatment course in the treatment room.\textsuperscript{15} Currently, many investigators are using megavoltage computed tomography (MVCT) or kilovoltage CT (kVCT) scans or portal images in the treatment room to evaluate tumor volume changes during RT. In the present study, however, we used a dual-source CT scanner to perform multiple enhanced kVCT scans for two reasons: 1: to evaluate if the early change of tumor enhancement correlated with tumor shrinkage, 2: if the tumor has regressed, kVCT images during the course of RT may be used not only for assessment of tumor shrinkage, but also for treatment planning.

A recent study suggested that local blood supply increase may be a positive indicator of the therapeutic response of head and neck cancer.\textsuperscript{19} Microvessel density was reported to be a prognostic factor of survival in patients with lung cancer.\textsuperscript{17} Yamashita et al. suggested that maximum attenuation of lung carcinomas correlated with the number of small vessels (microvessels) (0.02–0.10 mm inner diameter) and distribution of elastic fibers in the tumoral interstitium.\textsuperscript{19} Peak enhancement is expected to be a good indicator of the extent of vascular endothelial growth factor expression and to have a potential role as a prognostic factor.\textsuperscript{17} If local blood supply is similarly a positive indicator of the therapeutic response of lung cancer, the extent of tumor enhancement of lung cancer may be correlated with the therapeutic response. It is generally known that many genes and signal transduction pathways play an important role in response to radiation damage and they affect tumor shrinkage by radiation therapy;\textsuperscript{18} however, it is impossible to evaluate genes and pathways related to radiation therapy in every case. Diagnostic imaging has been used recently for evaluating tumor response during the course of therapy in clinical practice.\textsuperscript{4–8}

In the present study, the relative change of tumor enhancement in the early phase during RT and tumor shrinkage 1 month after the end of RT was not correlated; however, the relatively delayed change of enhancement in the delayed phase in the center of the tumor showed a significant correlation with tumor shrinkage. The center of the tumor is often relatively avascular or hypovascular and is surrounded by a seminecrotic region.\textsuperscript{19} Increased tumor enhancement in the center of the tumor in the delayed phase may indicate a relative increase of vascularity and lead to better response of the tumor to RT. Furthermore, avascular necrotic areas may have shown a delayed response to RT, because it often takes more time for massive necrosis to disappear. Our data accorded with previous reports of head and neck cancer and cervical cancer.\textsuperscript{4,20} In this study, most cases were squamous cell carcinoma, and this might be a reason why our result accorded with previous reports. When we divided all cases into two groups based on relative changes of the attenuation value in the center of the tumor in the delayed phase, 4 of 5 cases of adenocarcinoma showed small changes of the attenuation value (Table 2). We need a larger study to confirm whether this finding holds true in adenocarcinoma. We did not analyze the difference in tumor enhancement with or without chemotherapy, because most cases (16 of 19 cases) were treated with RT and chemotherapy concomitantly.

The time-attenuation curve for lung carcinomas is reported to show gradual enhancement and to reach peak enhancement late.\textsuperscript{17} This may be why the correlation between tumor enhancement and tumor shrinkage was observed only in the delayed phase. The time course distribution of contrast medium in the normal lung and pulmonary cancer is not always equal.\textsuperscript{21} Washout mechanisms from the intravascular space or the interstitial space in lung cancer are suggested to be different from those in the normal lung. The tumor vascular effect of ionizing radiation is vasodilatation of vessels secondary to the release of inflammatory cytokines, neovessel formation due to upregulation of vascular endothelial growth factor, and the expression of endothelial nitric oxide.\textsuperscript{19} The greater the tumor perfusion, the better the tumor response expected through its effects on oxygenation, especially in an avascular area of the tumor center, which usually shows radiation resistance. Increased tumor enhancement in the delayed phase may indicate increased blood supply and reduced lymphatic flow from the interstitial space, which might lead to greater tumor shrinkage. Instead, when an early change of tumor enhancement is not observed at 36–38 Gy, tumor shrinkage will not be expected, and additional therapy such as boost irradiation and additional chemotherapy may be suggested.

Perfusion CT can measure tumor vascularity, including blood flow, blood volume, and permeability, and tumor vascularity has been shown to correlate with histologic markers of angiogenesis in lung cancer.\textsuperscript{17} A previous study reported that tumor vascularity increased during RT.\textsuperscript{19} We did not perform a perfusion study of the tumor in this study because we could not cover all tumors on current CT scanners, however, this might change with further technological improvements.

REFERENCES
1. Kong FM, et al (2005) High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: Long-term results of a radiation dose escalation study. Int J Radiat Oncol Biol Phys 63: 324–333.
2. Zhao L, et al (2007) High radiation dose may reduce the negative effect of large gross tumor volume in patients with medically inoperable early-stage non-small cell lung cancer. Int J Radiat Oncol Biol Phys 68: 103–110.
3. Rosenweig KE, et al (2005) Results of a phase I dose-escalation study using three-dimensional conformal radiotherapy in the treatment of inoperable nonsmall cell lung carcinoma. Cancer 103: 2118–2127.
4. Siker ML, Tomé WA and Mehta MP (2006) Tumor volume changes on serial imaging with megavoltage CT for non-small-cell lung cancer during intensity-modulated radiotherapy: How reliable, consistent, and meaningful is the effect? Int
5. Ramsey CR, et al (2006) A technique for adaptive image-guided helical tomotherapy for lung cancer. Int J Radiat Oncol Biol Phys 64: 1237–1244.
6. Bosmans G, et al (2006) Intra-patient variability of tumor volume and tumor motion during conventionally fractionated radiotherapy for locally advanced non-small-cell lung cancer: A prospective clinical study. Int J Radiat Oncol Biol Phys 66: 748–753.
7. Erridge SC, et al (2003) Portal imaging to assess set-up errors, tumor motion and tumor shrinkage during conformal radiotherapy of non-small cell lung cancer. Radiother Oncol 66: 75–85.
8. Fox J, et al (2009) Quantification of tumor volume changes during radiotherapy for non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 74: 341–348.
9. Cao Y, et al (2008) Early prediction of outcome in advanced head-and-neck cancer based on tumor blood volume alterations during therapy: a prospective study. Int J Radiat Oncol Biol Phys 72: 1287–1290.
10. Yamashita K, et al (1995) Small peripheral lung carcinoma evaluated with incremental dynamic CT: radiologic-pathologic correlation. Radiology 196: 401–408.
11. Metha M, et al (2001) A new approach to dose escalation in non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 49: 23–33.
12. Belderbos JS, et al (2006) Final results of a phase I/II dose escalation trial in non-small-cell lung cancer using three-dimensional conformal radiotherapy. Int J Radiat Oncol Biol Phys 66: 126–134.
13. Woodford C, et al (2007) Adaptive radiotherapy planning on decreasing gross tumor volumes as seen on megavoltage computed tomography images. Int J Radiat Oncol Biol Phys 69: 1316–1322.
14. Werner-Wasik M, et al (2001) Assessment of lung cancer response after nonoperative therapy: tumor diameter, bidimensional product, and volume. A serial CT scan-based study. Int J Radiat Oncol Biol Phys 51: 56–61.
15. Kupelian PA, et al (2005) Serial megavoltage CT imaging during external beam radiotherapy for non-small-cell lung cancer: Observations on tumor regression during treatment. Int J Radiat Oncol Biol Phys 63: 1024–1028.
16. Sonke JJ and Belderbos J (2010) Adaptive radiotherapy for lung cancer. Semin Radiat Oncol 20: 94–106.
17. Yi CA, et al (2004) Solitary pulmonary nodules: dynamic enhanced multi-detector row CT study and comparison with vascular endothelial growth factor and microvessel density. Radiology 233: 191–199.
18. Hall EJ and Giaccia AJ (2011) Radiobiology for the radiologist. 7th ed. pp. 45–50 and 273–299, Lippincott Williams and Wilkins; Philadelphia.
19. Ng QS, et al (2007) Acute tumor vascular effects following fractionated radiotherapy in human lung cancer: In vivo whole tumor assessment using volumetric perfusion computed tomography. Int J Radiat Oncol Biol Phys 67: 417–424.
20. Mayr NA, et al (2010) Ultra-early predictive assay for treatment failure using functional magnetic resonance imaging and clinical prognostic parameters in cervical cancer. Cancer 116: 903–912.
21. Yeon JJ, et al (2005) Solitary pulmonary nodule: characterization with combined wash-in and washout features at dynamic multi-detector row CT. Radiology 237: 675–683.

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