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Evaluation of intra-tumoral blood feeding to predict the effect of induction therapy in patients with locally advanced lung cancer

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ABSTRACT

There is little known about predictors of the effects of induction therapy in locally advanced lung cancer, including superior sulcus tumors. We analyzed whether intra-tumoral blood feeding could predict a pathologic complete response (pCR). Patients who underwent induction therapy followed by surgery for locally advanced lung cancer were retrospectively reviewed. The intra-tumoral blood feeding was defined by the CT value (HU, Hounsfield unit), which was calculated by subtracting the non-enhanced value from the contrast-enhanced value (divided into the early and delayed phase) at the maximum diameter of the tumor on dynamic CT. The cases were classified, according to the efficacy of induction therapy, into the pCR and residual tumor (pRT) group. There were 38 cases of T3 and 12 of T4; the induction therapy consisted of chemoradiotherapy in 39 patients, chemotherapy in 6, and radiotherapy in 5. A pCR was obtained in 15 (30%) patients. The mean CT values of the early and delayed phases in the pCR group were 14.8 and 30.7 HU, while those in the pRT were 15.3 and 32.2 HU, respectively. A logistic regression analysis revealed that a smaller tumor size (< 42 mm) was a non-significant predictor of a pCR ($p = 0.09$); the maximum standardized uptake value on FDG-PET and the CT values on the early and delayed phases of dynamic CT were not associated with the achievement of a pCR. In conclusion, intra-tumoral blood feeding of the locally advanced lung cancer did not predict the effects of induction therapy, whereas smaller sized tumors tended to show a better response.

Keywords: locally advanced lung cancer, induction therapy, blood supply, tumor vascularity, dynamic CT

INTRODUCTION

Induction therapy is a promising optional treatment for locally advanced lung cancer, including superior sulcus tumors. In the report of the Southwest Oncology Group Trial 9416, a pathologic complete response (pCR) or minimal microscopic disease was seen in 61 (56%) resection

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specimens.[1] Our prospective study also revealed that 26% of patients with lung cancer involving the chest wall experienced no residual tumor cells after the induction chemoradiotherapy.[2]

However, the predictors of the treatment effect and a pCR are not well-known. Antonoff et al[3] previously reported that a pCR was independently predicted by the extent of the reduction in the size of the tumor on imaging. However, this conclusion means that a pCR could not be predicted until the completion of induction therapy. If we could predict the effects of induction therapy, initial surgery could be recommended for patients with locally advanced lung cancer who will obtain little benefit from induction therapy.

On the other hand, tumor cells in hypoxic regions are generally resistant to both radiotherapy and chemotherapy.[4] Squamous cell carcinoma, a major histological type of locally advanced lung cancer, sometimes contains a necrotic area in the center of relatively large sized tumors. Thus, the inconsistency regarding low oxygen concentrations and a higher pCR rate after induction therapy in locally advanced lung cancer is still debatable.

Angiogenesis is a fundamental process in the development of tumors, whereby the growing malignancy appropriates its own blood supply from the adjacent tissues.[5,6] The prognostic influence of angiogenesis in lung cancer has been accepted secondary to evidence that an increased vascular density is associated with a higher incidence of metastasis and a worse prognosis in lung cancer patients. This theoretical concept would be applicable to the high incidence of brain metastasis after multimodal treatment for locally advanced lung cancer.

Thus, we hypothesized that the tumors invading neighboring structures would be more sensitive to induction therapy due to the richer blood supply from the involved organs as a result of angiogenesis. If the efficacy of induction therapy was dependent on the tumor vascularity, we could select cases for which induction therapy followed by surgery is an appropriate strategy. The purpose of this study was to evaluate the predictors of a pCR in patients undergoing induction therapy and to determine whether the volume of the blood supply to the tumor could be associated with the efficacy of induction therapy.

PATIENTS AND METHODS

After receiving institutional review board approval of 12 September 2012 (No 2012-0162), patients who underwent induction therapy followed by surgery for locally advanced lung cancer were retrospectively reviewed. To elucidate the relationship between tumor vascularity and the efficacy of induction therapy, clinical T3 and T4 tumors involving the neighboring structures were decided to be eligible. Patients who received induction therapy due to mediastinal lymph node metastasis were excluded from this study. Patients were also excluded if the tumor had not been histologically proven to be non-small cell lung cancer before induction therapy.

Imaging and calculation of blood supply

In our institution, dynamic CT was routinely performed for the preoperative evaluation of lung cancer.[7,8] All CT scans were performed with 16-row to 128-row MDCT scanners (Acquilion 16 and 64, Toshiba Medical, Tokyo, Japan; SOMATOM Definition Flash, Siemens Healthcare, Tokyo, Japan). After non-contrast CT, dual-phase dynamic contrast-enhanced CT was performed using a tube voltage of 120kV and automatic tube current modulation. Non-ionic contrast medium (80mL to 100mL) was administered intravenously through a vein in the cubitus or lower arm at a flow rate of 2.5mL/s to 4.0mL/s. The dose of contrast medium and a flow rate were decided based on patient's body weight, as previously described.[8,9] For the early phase, the scan delay was evaluated by an automatic bolus tracking system with a circular region of interest (ROI) localized

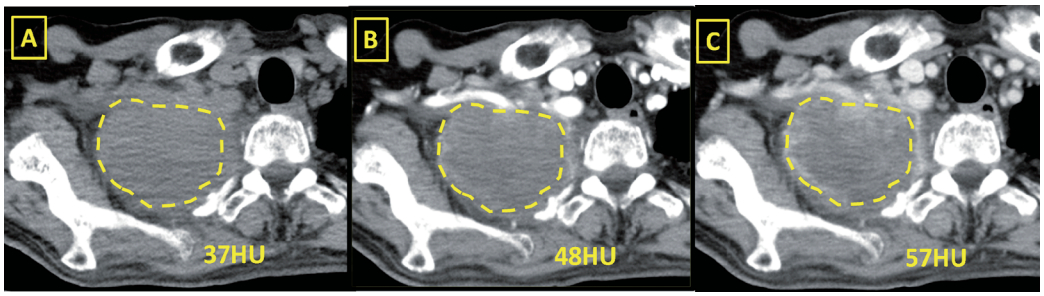

Fig. 1 The volume of blood supply to the tumor defined by the CT value (HU; Hounsfield Unit). The maximum dimension of tumor on dynamic CT ([A] non-enhanced, [B] early phase, and [C] delayed phase) were encircled by freehand with the disengagement of bony structures, and the CT values of the encircled area were measured using the syngo Dual Energy Lung Nodules accessory software program (Siemens Healthcare, Forchheim, Germany). The CT value, which was calculated by subtracting the non-enhanced value from the contrast-enhanced value (divided early phase and delayed phase) was considered to represent the blood supply to the tumor. The CT values of the early phase and delayed phase were 11 and 20 HU, respectively.

on the ascending aorta at the level of tracheal bifurcation. Scanning started automatically as the attenuation of the ROI reached 150 Hounsfield Unit (HU) before 2014, or as the attenuation of the ROI increased more than 70 HU from baseline since 2014 (about 25–30 s after initiation of contrast medium injection). For the delayed phase, the scan delay was 90 s after the end of the early-phase scan (about 2 min after the initiation of contrast medium injection). CT images were reconstructed with slice thickness of 1–5 mm using a standard algorithm and were displayed on a PACS viewer at the mediastinal window setting.

The volume of blood supply to the tumor was defined as the CT value (HU), which was calculated by subtracting the non-enhanced value from the contrast-enhanced value (divided into the early and delayed phases) at the maximum dimension of the tumor on dynamic CT. We decided to evaluate the CT values of both the early and delayed phases because dynamic CT may demonstrate differences by evaluating the wash-in and wash-out blood flow patterns and microvessel density.[10] As shown in the Figure 1, the measured areas of the tumor were encircled by freehand.[11] Two experienced chest surgeons (K.K. and M.G.) encircled the primary tumor with the disengagement of the bony structures or intra-tumoral cavity if needed, and the CT values were recorded twice for the early and delayed phases. The average of the two values was considered to represent the blood supply.

18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) was basically performed at pre- and post-induction therapy. The details of PET/CT have been described previously.[12] The maximum standardized uptake value (SUVmax) of the primary lesion on PET/CT was analyzed as a predictor of the effect of induction therapy.

The CT values on dynamic CT and the SUVmax on PET/CT were basically measured on the images obtained before induction therapy. In addition, the values were measured on CT and PET scans performed after induction therapy for the supplementary analyses.

Induction therapy, surgical treatment and pathologic evaluation

The standard strategy for locally advanced lung cancer in our institution was two cycles of cisplatin plus vinorelbine concurrent with 40 Gy of radiation followed by surgical resection. In a retrospective fashion, however, the radiation doses and chemotherapy regimens were not uniform, although most of the chemotherapy regimen were platinum doublets. After induction

therapy, every case was reassessed using physical examinations, dynamic CT of the chest and abdomen, and PET/CT to judge the clinical response and resectability. After the determination was made by our multidisciplinary team, surgical resection was performed at 3 to 6 weeks after the completion of the induction therapy. In principle, lobectomy or pneumonectomy that included the sites of invasion were required for curative resection, with mediastinal lymph node dissection. The surgical approach and the method of reconstruction were left to the discretion of the individual surgeon.

Information regarding the TNM classification was based on the 8th edition of the Union for International Cancer Control-TNM staging system. Histological typing was conducted according to the World Health Organization classification. The pathologic response was divided into two categories: a pathologic complete response (pCR; no residual microscopic tumor) and residual tumor (pRT; any viable cells detected).

Statistical analyses

All statistical analyses were performed using the SPSS 23.0 software program (SPSS, Inc., Chicago, IL, USA). For the categorical data, numbers and proportions were compared using a chi-squared test; for the continuous data, means were compared using a t-test. A multivariate analysis using a logistic regression model was performed to analyze the factors predicting a pathologic complete response. Survival was measured from the time of the operation until death or the last date of the follow-up. Survival curves were calculated by the Kaplan–Meier method, and comparisons among curves were made by means of the log-rank test. P values of <0.05 were considered to indicate statistical significance.

RESULTS

From April, 2005 to March, 2017, 50 patients (male, n = 43; female, n = 7; mean age, 60 years) were judged as eligible for inclusion in this study. The patient characteristics are shown in Table 1. The tumors consisted of 38 T3 lesions and 12 T4 lesions (chest wall, n = 36; mediastinum, n = 11; and vertebrae, n = 3). Squamous cell carcinoma was the most common histological type, followed by adenocarcinoma. Induction therapy included chemoradiotherapy in 39 patients, chemotherapy in 6, and radiotherapy in 5. The radiation doses were as follows: 40 Gy in 33 patients, 45 Gy in 1, 50 Gy in 6, and 60 Gy in 4, respectively. Forty-nine of the 50 patients underwent complete resection, and a pathologic complete response was obtained in 15 (30%).

In terms of the blood supply, the CT values of the tumor in the early and delayed phases of dynamic CT could be useful in most cases. The mean early and delayed phase CT values were 14.9 HU (range –2.0 to 37.0 HU) and 33.7 HU (range, –3.0 to 60.0 HU), respectively (Figure 2). With regard to the histological types, the mean CT values of squamous cell carcinoma and adenocarcinoma did not differ to a statistically significant extent (early phase, 15.4 HU vs 15.2 HU [p = 0.971]; delayed phase, 31.6 HU vs 36.1 HU [p = 0.54]).

Figure 3 shows the comparison of various clinical factors and pathologic responses. The mean CT values of the early and delayed phases in the pCR group were 14.8 ± 12 HU and 30.7 ± 14 HU, respectively, while those in the pRT group were 15.3 ± 13 HU and 32.2 ± 16 HU; the differences were not statistically significant. On the other hand, the pCR group tended to show lower of SUVmax values on PET in comparison to the pRT group (p = 0.07, Table 2). Figure 4 demonstrates the receiver operating characteristic (ROC) curve for predicting the pathologic complete responders according to the tumor size. The area under the curve (AUC) was 0.731

when the tumor size on CT was used. When the optimal cutoff point was set at 42 mm, the sensitivity and specificity were 93% and 60%, respectively. To elucidate the predictors of a pathologic complete response in a multivariate analysis, the CT values of the early and delayed phases on contrast-enhanced CT were divided into High and Low groups according using the mean values as cutoff (14.9 HU and 33.7 HU, respectively). The logistic regression analysis revealed that a smaller tumor size (< 42 mm) tended to predict a pCR ($p = 0.09$), whereas the SUVmax on PET and the CT values of the early and delayed phases on dynamic CT were not associated with the achievement of a pathologic complete response (Table 3).

Table 1 Patient characteristics

Gender	Male	43
	Female	7
Age	Mean (Range)	60 (38–77)
Histology	Squamous cell carcinoma	19
	Adenocarcinoma	18
	Others	13
Involved organs		
T3	Chest wall	36
	Mediastinum	2
T4	Great vessels	6
	Left atrium	1
	Mediastinal fat tissue	2
	Vertebrae	3
Induction therapy	Chemoradiotherapy	39
	Chemotherapy	6
	Radiotherapy	5
Pathologic responses	Complete response	15 (30%)
	Residual tumor	35 (70%)

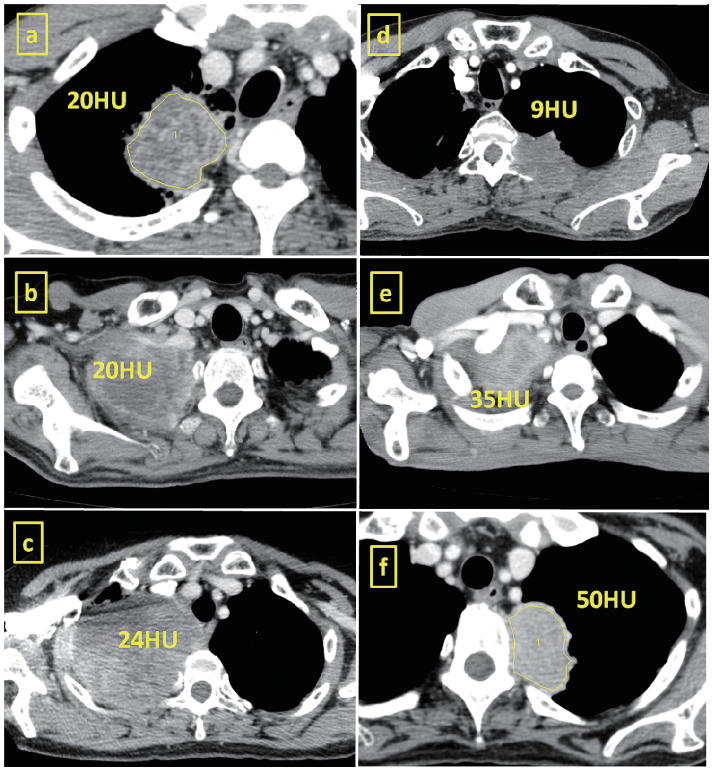

Fig. 2 The various CT values (HU; Hounsfield Unit) of the tumors on dynamic CT, encircled by freehand. c), d), and e) show CT values obtained in the early phase of dynamic CT; a), b), and f) show values obtained in the delayed phase.

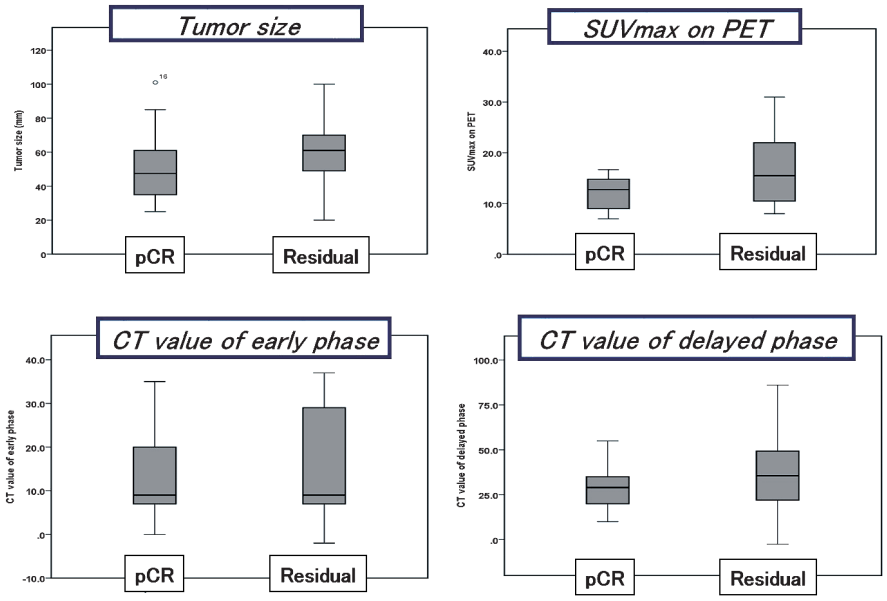

Fig. 3 The association between the clinical factors and the achievement of a pathologic CR. The pCR group tended to show a lower SUVmax on PET in comparison to the pRT group ($p = 0.07$), whereas no significant differences were seen in the mean early and delayed phases between the both groups.

Table 2 Comparison of the clinical factors and pathologic responses

		pCR (n = 15)	Residual (n = 35)	p value
Histology	SQ/AD/Others	6/5/4	13/13/9	0.63
Induction Tx	CRT/RT/CT	14/1/0	25/4/6	0.33
Tumor size	mean (mm)	51.6 ± 22.6	60.3 ± 18.1	0.18
CT value	Early phase (HU)	14.8 ± 12.1	15.3 ± 13.0	0.92
	Delayed phase (HU)	30.7 ± 14.1	32.2 ± 16.4	0.78
PET	SUVmax	12.1 ± 3.6	16.8 ± 6.8	0.07
Serum CEA	Mean (ng/ml)	57.0 ± 158.1	50.1 ± 133.7	0.88

pCR, pathologic complete response; SQ, squamous cell carcinoma; AD, adenocarcinoma; CRT, chemoradiotherapy; RT, radiotherapy; CT, chemotherapy

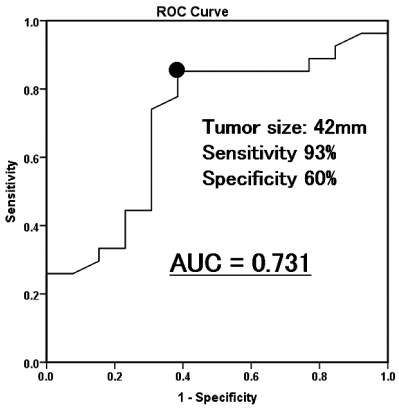

Fig. 4 A receiver operating characteristic curve for predicting a pathologic complete response according to the tumor size.
The area under the curve value was 0.731. The optimal cut-off tumor size was set at 42 mm. The sensitivity and specificity with this cut-off value were 93% and 60%, respectively.

Table 3 The logistic regression analysis to determine factors predicting a pathologic complete response

Factors	Reference	Odds	95%CI	p value
Histology	AD	1.81	0.10–33.33	0.69
Tumor size	> 42mm	12.99	0.66–250.0	0.09
CT value in early phase	Low	4.63	0.33–64.40	0.25
CT value in delayed phase	Low	2.17	0.12–39.03	0.60
SUVmax on PET	> 10	9.80	0.29–333.3	0.20
Serum CEA level	Normal	1.98	0.15–25.86	0.60

AD, adenocarcinoma; pCR, pathologic complete response; CEA, carcinoembryonic antigen

Table 4 Percentage of decrease in each factor after induction therapy

	pCR (n = 15)	Residual (n = 35)	p value
Tumor size	20.7 ± 13.0 %	23.6 ± 17.0 %	0.58
CT value in early phase	4.2 ± 28.5 %	16.2 ± 26.2 %	0.14
CT value in delayed phase	25.7 ± 24.8 %	20.3 ± 49.7 %	0.68
SUVmax on PET	70.0 ± 13.8 %	63.3 ± 21.6 %	0.45
Serum CEA level	36.5 ± 37.9 %	29.1 ± 37.2 %	0.55

pCR, pathologic complete response; CEA, carcinoembryonic antigen

The change in the values of each factor after induction therapy was also calculated (Table 4). The SUVmax of FDG-PET showed the largest reduction in both the pCR and pRT groups. The change in the CT value in the early phase was the smallest of all clinical factors. There were no significant differences in any of the factors of the two groups.

DISCUSSION

Lung cancer involving the chest wall, including the superior sulcus, is considered to be more sensitive to induction chemoradiotherapy in comparison to disease with mediastinal lymph node metastasis. In general, the radio-sensitivity is dependent on the cycle of cancer cell division, degree of differentiation of the cancer cells, and the oxygen concentration in the cancer cells.[4] We hypothesized that tumors invading neighboring structures would obtain an additional blood supply from the involved organs, and that the sensitivity to induction therapy would be affected by their richer blood supply. However, this preliminary study showed no significant correlation between the blood feeding and the sensitivity to induction therapy.

With the exception of small cell lung cancer, lung cancer is generally considered to show moderate to poor radio-sensitivity. However, radiotherapy is one of the main treatments for small sized or locally advanced lung cancer.[13] We previously conducted a phase II study of induction chemoradiotherapy and surgical resection for T3 lung cancer with chest wall invasion and reported an excellent effect of induction chemoradiation and preferable survival with a low mortality rate.[2] The study indicates that these tumors are good candidates for induction radiotherapy because of the peripheral location of the tumor and the fixation of their position during respiratory motion.

In addition to the small number of patients, the degree of malignancy was considered to be a possible reason for this outcome. Iwano et al reported that the intra-tumor iodine concentration was correlated with the degree of tumor differentiation, and that high-grade tumors tended to have lower iodine concentrations.[11] We also reported that the intra-tumor iodine concentration was continuously correlated with the locoregional invasiveness of non-small cell lung cancer.[8,14] However, high-grade malignant tumors are generally sensitive to radiotherapy. Thus, there would be a negative correlation between the tumor vascularity and the tumor differentiation, and a positive correlation between the degree of tumor differentiation and the radio-sensitivity (Figure 5). Contrary to our expectations, no significant association was seen between tumor vascularity and the effect of induction therapy in the method using the CT value of this study. Further research including pathologic tumor differentiation is needed in the future.

There have been several studies on the predictors of a pathologic complete response after the completion of induction therapy in patients with superior sulcus tumor. Cerfolio et al[15] reported

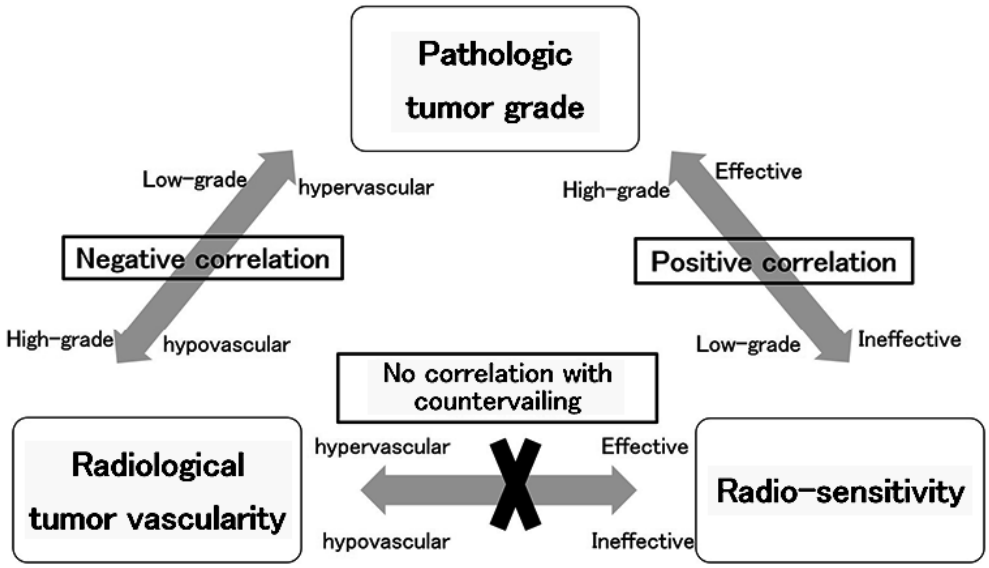

Fig. 5 The associations among tumor vascularity, tumor differentiation, and radio-sensitivity. Despite the hyper vascularity and lower differentiation of the tumor, the tumor vascularity was not significantly associated with the effect of induction therapy in this study.

that the change in the SUVmax on FDG-PET after neoadjuvant therapy was a more accurate predictor of a pathologic response than the size on CT.[15] In contrast, Antonoff et al[3] concluded that the extent of size reduction was an independent predictor of a pCR. Our study revealed that the reduction of the tumor vascularity was not associated with the achievement of a pathologic complete response. On the other hand, there are no reports of pretreatment clinical factors that can predict the efficacy of induction therapy. If we can predict the efficacy of induction therapy before it is initiated, other treatment strategies can be implemented and induction therapy can be avoided in cases in which it is predicted to be ineffective.

The present study is associated with several limitations. First, CT enhancement was substituted for the blood supply of tumors in this study. There were very few literatures in terms of the correlation between tumor vascularity and the CT enhancement.[16-18] We therefore decided to examine the CT values of both early and delayed phase of dynamic CT, and no significant difference was seen. Second, the radiation doses and chemotherapy regimens were not uniform, although the majority of cases received induction therapy consisted of two cycles of cisplatin plus vinorelbine concurrent with radiation, which was adopted in our previous phase II trial.[19] Third, the setting of the cases fell in various involved organs because of the small number of patients. There might be oncological differences between patients with tumor invading to the chest wall and others. In the preliminary analysis, however, there were no significant differences on the mean CT values between the chest wall and mediastinum (early phase, 16.1 HU vs 8.3 HU [p = 0.291]; delayed phase, 32.6 HU vs 26.6 HU [p = 0.407]). Fourth, the intra-tumoral blood flow was not uniform. There were several tumors that contained a cavity but no tumors with calcification in the present study. In addition, we considered the blood flow of the tumor to be associated with its oxygenation status, which was not confirmed. Several reports on head and neck cancer measured pretreatment tumor oxygenation using a computerized polarographic oxygen needle electrode.[20] Furthermore, some investigators reported molecular imaging of hypoxia

in non-small cell lung cancer.[21] These objective measurement tools could validate the outcomes of this study.[22]

Finally, this was a retrospective study; thus, the selection of patients for induction therapy and the timing of CT before and after induction therapy could not be described definitively. Further research is needed, however, we conclude that intra-tumoral blood feeding of locally advanced lung cancer was not associated with the effect of induction therapy in the method using the CT value, whereas smaller sized tumors tended to show a more effective response. Currently it is difficult to select patients with locally advanced lung cancer who can be expected to achieve a pathologic complete response with induction therapy.

CONFLICT OF INTEREST

The authors declare no conflicts of interest in association with the present study.

REFERENCES

1. Rusch VW, Giroux DJ, Kraut MJ, et al. Induction chemoradiation and surgical resection for superior sulcus non-small-cell lung carcinomas: long-term results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). *J Clin Oncol*. 2007;25:313–318.
2. Kawaguchi K, Yokoi K, Niwa H, et al. A prospective, multi-institutional phase II study of induction chemoradiotherapy followed by surgery in patients with non-small cell lung cancer involving the chest wall (CJLSG0801). *Lung Cancer*. 2017;104:79–84.
3. Antonoff MB, Hofstetter WL, Correa AM, et al. Clinical prediction of pathologic complete response in superior sulcus non-small cell lung cancer. *Ann Thorac Surg*. 2016;101:211–217.
4. Brown JM, Wilson WR. Exploiting tumour hypoxia in cancer treatment. *Nat Rev Cancer*. 2004;4:437–447.
5. Fontanini G, Vignati S, Boldrini L, et al. Vascular endothelial growth factor is associated with neovascularization and influences progression of non-small cell lung carcinoma. *Clin Cancer Re*. 1997;3:861–865.
6. Han H, Silverman JF, Santucci TS, et al. Vascular endothelial growth factor expression in stage I non-small cell lung cancer correlates with neoangiogenesis and a poor prognosis. *Ann Surg Oncol*. 2001;8:72–79.
7. Chae EJ, Song JW, Krauss B, et al. Dual-energy computed tomography characterization of solitary pulmonary nodules. *J Thorac Imaging*. 2010;25:301–310.
8. Shimamoto H, Iwano S, Umakoshi H, Kawaguchi K, Naganawa S. Evaluation of locoregional invasiveness of small-sized non-small cell lung cancers by enhanced dual-energy computed tomography. *Cancer Imaging*. 2016;16:18.
9. Iwano S, Koike W, Matsuo K, Okada T, Shimoyama Y, Naganawa S. Correlation between dual-phase dynamic multi-detector CT findings and fibrosis within lung adenocarcinoma tumors. *Eur J Radiol*. 2011;80:e470–475.
10. Jeong YJ, Lee KS, Jeong SY, et al. Solitary pulmonary nodule: characterization with combined wash-in and washout features at dynamic multi-detector row CT. *Radiology*. 2005;237:675–683.
11. Iwano S, Ito R, Umakoshi H, Ito S, Naganawa S. Evaluation of lung cancer by enhanced dual-energy CT: association between three-dimensional iodine concentration and tumour differentiation. *Br J Radiol.* 2015;88:20150224.
12. Fukumoto K, Fukui T, Okasaka T, et al. The Role of (18)F-fluorodeoxyglucose positron emission tomography-computed tomography for predicting pathologic response after induction therapy for thymic epithelial tumors. *World J Surg*. 2017;41:1828–1833.
13. McCloskey P, Balduyck B, Van Schil PE, Faivre-Finn C, O'Brien M. Radical treatment of non-small cell lung cancer during the last 5 years. *Eur J Cancer*. 2013;49:1555–1564.
14. Ito R, Iwano S, Shimamoto H, et al. A comparative analysis of dual-phase dual-energy CT and FDG-PET/CT for the prediction of histopathological invasiveness of non-small cell lung cancer. *Eur J Radiol*. 2017;95:186–191.
15. Cerfolio RJ, Bryant AS, Winokur TS, Ohja B, Bartolucci AA. Repeat FDG-PET after neoadjuvant therapy is a predictor of pathologic response in patients with non-small cell lung cancer. *Ann Thorac Surg*. 2004;78:1903–1909.

16. Kim HJ, Kim TK, Kim PN, et al. Assessment of the therapeutic response of hepatocellular carcinoma treated with transcatheter arterial chemoembolization: comparison of contrast-enhanced sonography and 3-phase computed tomography. *J Ultrasound Me*. 2006;25:477–486.
17. Han KS, Jung DC, Choi HJ, et al. Pretreatment assessment of tumor enhancement on contrast-enhanced computed tomography as a potential predictor of treatment outcome in metastatic renal cell carcinoma patients receiving antiangiogenic therapy. *Cancer*. 2010;116:2332–2342.
18. Chen X, Xu Y, Duan J, Li C, Sun H, Wang W. Correlation of iodine uptake and perfusion parameters between dual-energy CT imaging and first-pass dual-input perfusion CT in lung cancer. *Medicine (Baltimore)*. 2017;96:e7479.
19. Kawaguchi K, Yokoi K, Niwa H, et al. Trimodality therapy for lung cancer with chest wall invasion: initial results of a phase II study. *Ann Thorac Surg*. 2014;98:1184–1191.
20. Nordsmark M, Overgaard M, Overgaard J. Pretreatment oxygenation predicts radiation response in advanced squamous cell carcinoma of the head and neck. *Radiother Oncol*. 1996;41:31–39.
21. Yip C, Blower PJ, Goh V, Landau DB, Cook GJ. Molecular imaging of hypoxia in non-small-cell lung cancer. *Eur J Nucl Med Mol Imaging*. 2015;42:956–976.
22. Overgaard J. Hypoxic radiosensitization: adored and ignored. *J Clin Oncol*. 2007;25:4066–4074.