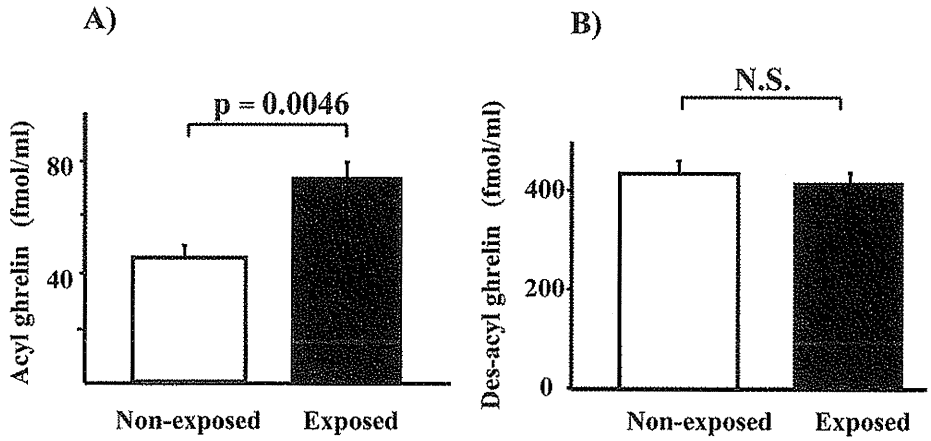

Fig. 3. Influences of cigarette smoke exposure on ghrelin levels in plasma. The outlined bars show the group not exposed to cigarette smoke, while the solid bars show those the smoke-exposed group. Each value indicates the mean ± S.D. of 10 animals. Data were analyzed by the Mann-Whitney U test. A) In acyl ghrelin levels the cigarette smoke-exposed group significantly differed from the cigarette smoke-unexposed group, p = 0.0046. B) in des-acyl ghrelin levels there was no significant difference in both groups.

was shown to cause a positive energy balance by reducing fat utilization through GH-independent mechanisms (Nakazato *et al.*, 2001). In addition, an administration of ghrelin has been shown to elicit the potency, namely, the long-lasting stimulation of food intake through stimulating NPY/AgRP and pro-opiomelanocortin (POMC) neurons in the hypothalamic arcuate nucleus in human and animals (Tschop *et al.*, 2000; Wren *et al.*, 2000; Shintani *et al.*, 2001). Ghrelin has been proved to circulate in both acylated and desacylated form. Of the circulating ghrelin forms, the acylated one (acyl ghrelin) is thought to be essential for ghrelin biological activity (Hosoda *et al.*, 2003), although the function of the desacylated one (des-acyl ghrelin) has not been fully elucidated. Leptin, one of the peptides derived from adipocytes, is produced in differentiated adipocytes and suppresses NPY neurons resulting in an inhibition of appetite (Halaas *et al.*, 1995). An enhancement of energy expenditure was shown to cause a negative energy balance (Collins *et al.*, 1996). Ghrelin and leptin have shown to antagonize each other on the hypothalamic NPY-Y1 receptor pathway in animal experiments (Shintani *et al.*, 2001).

Therefore, the present study suggests that during exposure to cigarette smoke, acyl ghrelin and leptin levels may change to compensate for negative energy balance caused by cigarette smoke. Additionally, the present study suggests that the plasma levels of both acyl ghrelin and leptin may change to stimulate the suppressed NPY pathway during exposure to cigarette smoke. Further investigation regarding the relationship of ghrelin and leptin in the regulation of food intake during exposure to cigarette smoke is needed.

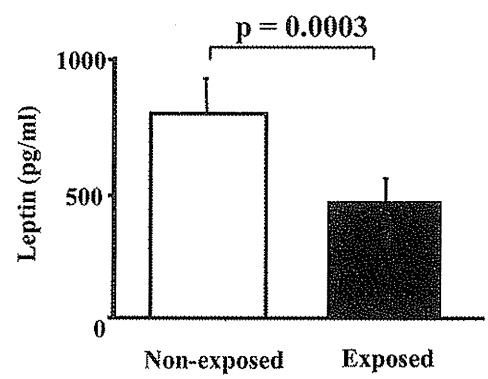

Fig. 4. Influences of cigarette smoke exposure on leptin level in plasma. The outlined bars show the group not exposed to cigarette smoke, while the solid bars show the smoke-exposed group. Each value indicates the mean ± S.D. of 10 animals. Data were analyzed by the Mann-Whitney U test. The cigarette smoke-exposed group significantly differed from the cigarette smoke-unexposed group, p = 0.0002.

Besides the negative energy balance cigarette smoke itself may contribute to the changes in plasma acyl ghrelin and leptin levels. In this study there may be only few direct effects of cigarette smoke because we measured the plasma levels 12 hr after final exposure when % CO-Hb returned to the baseline as shown at Table 1. However nicotine may possibly contribute to the changes in plasma

Table 2. Effects of cigarette smoke exposure on anti-oxidant/ oxidant balance in plasma.

	Non-exposed	Exposed
OXY (HCLO μmol/ml)	322 ± 9.1	359 ± 14.8
d-ROM (Carr unit)	356 ± 17.5	325 ± 18.6
OXY/d-ROM	0.91 ± 0.03	1.11 ± 0.06*

OXY: Oxy-adsorbent assay, index of anti-oxidant capacity. d-ROM: Diacron reactive oxygen metabolites, index of oxidative stress. : $p < 0.05$ vs. controls; Values are expressed as means ± S.D.. The oxidative status and total anti-oxidant capacity were determined by Oxy-absorbent test and d-ROMs test on fresh blood samples, taken from 10 rats, 12 hr after the final cigarette smoke exposure. Date given in the table are means ± S.D.. *$p < 0.05$ versus baseline values analyzed by the Mann-Whitney U test.

acyl ghrelin and leptin levels. The effect of nicotine on circulating leptin levels is controversial. Administration of nicotine to rats decreases plasma leptin levels (Li and Kane, 2003) while plasma leptin levels in long-term user of nicotine gum are elevated (Eliasson and Smith, 1991). The effects of nicotine on plasma ghrelin levels have not been studied yet. Further investigation about effects of nicotine on production of ghrelin and leptin is needed.

The function of des-acyl ghrelin has not been cleared, because it has been reported that des-acyl ghrelin might activate orexin and stimulate appetite (Toshinai *et al.*, 2006) while des-acyl ghrelin has been proved to not only enhance peristaltic movements but also suppress food intake (Asakawa *et al.*, 2005). The present study demonstrated that the des-acyl ghrelin levels were unchanged after the exposure to cigarette smoke. There was no significant relationship between the des-acyl ghrelin levels and food intake, suggesting that they are not related to changes in food intake during a 4-week exposure to cigarette smoke.

In underweight patients with COPD, anorexia nervosa, and cancer cachexia, plasma ghrelin levels increased (Itoh *et al.*, 2004; Otto *et al.*, 2001; Shimizu *et al.*, 2003), while plasma leptin levels decreased (Takabatake *et al.*, 1999; Schols *et al.*, 1999; Grinspoon *et al.*, 1996; Simons *et al.*, 1997). Malnutrition has been recognized as one of the systemic effects in COPD, because it has been proved to be not only related with clinical findings but also to be an independent prognostic factor (Agusti *et al.*, 2002). However while it has not been fully elucidated how malnutrition develops in COPD (Agusti *et al.*, 2002), the systemic effects by cigarette smoke are thought to partially contribute to the development of COPD and its systemic effects (Fabbri *et al.*, 2007). In present study emphysematous lesions have not been found after four weeks exposure of cigarette smoke (unpublished data). However negative energy balances with changes in plasma ghrelin and leptin levels were similar in those with underweight patients with COPD. These results may support the hypothesis that the systemic rather than only intrapulmonary effects of cigarette smoke may contribute to development of COPD and its systemic effects.

The present study did not clarify the effects of changes in plasma ghrelin and leptin, but after 4 weeks of exposure the ratio of antioxidant to oxidant increased. Some reports indicate that ant-oxidants in smokers might be enhanced compared with non-smokers, from the results of measuring the rates of accumulation of ascorbic acid and dehydroascorbate in alveolar macrophages (McGowan *et al.*, 1984) and contents of glutathione and catalase and protection endothelial cells from hydrogen peroxide in erythrocytes in smokers (Toth *et al.*, 1986). It has been not fully elucidated how anti-oxidant activities are increased in smokers. Recently ghrelin has been proved to have anti-inflammatory effects (Ersahin *et al.*, 2010). Elevated ghrelin levels may be related to an increased ratio of antioxidant to oxidant. Further investigations are needed to determine the relationship between ghrelin and systemic inflammation during exposure to cigarette smoke.

In summary, during 4 weeks of exposure to cigarette smoke in WKY rats, food intake and body weight gain were suppressed, while plasma acyl ghrelin levels increased and plasma leptin levels decreased. However, the plasma des-acyl ghrelin levels were not affected by cigarette smoke exposure. Acyl ghrelin and leptin levels may change to compensate for negative energy balance induced by cigarette smoke.

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ENVIRONMENTAL DETERMINANTS

Association between Episodes of Upper Respiratory Infection and Exacerbations in Adult Patients with Asthma

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Background. Asthma has several phenotypical features, including recurrent exacerbations and recurrent episodes of upper respiratory infection (URI). *Purpose.* A retrospective study was performed to identify the characteristics of adult patients with recurrent exacerbations of asthma, especially in association with recurrent episodes of URI. *Methods.* Information was collected using a self-administered questionnaire given to 7070 patients in autumn–winter 2006, 4859 patients in spring–summer 2007, and 4452 patients in autumn–winter 2007. The patients reported the degree of symptoms and the frequency of febrile episodes of URI and exacerbations. Severe exacerbations were defined as a self-report of asthma-related hospitalization, an emergency department visit, or a requirement for systemic corticosteroids. Recurrent febrile URI and exacerbations were defined as two or more episodes within the previous 6 months. A Poisson regression model was used to identify the factors that were predictors of a risk for exacerbations. *Results.* Of the 6266 patients who completed the questionnaire, the frequencies of febrile URI and episodes of severe exacerbations were 1.54 and 0.54 per subject per year, respectively. Logistic regression analysis showed that an older age [odds ratio (OR): 1.57; 95% confidence interval (CI): 1.15–2.13], female sex (OR: 1.58; 95% CI: 1.20–2.08), recurrent febrile episodes of URI (OR: 2.68; 95% CI: 1.47–4.91), a history of previous exacerbation within 1 year (OR: 1.74; 95% CI: 1.28–2.34), disuse of inhaled corticosteroids (ICSs) (OR: 2.63; 95% CI: 1.68–4.12), and disuse of add-on leukotriene receptor antagonists (LTRAs) (OR: 1.42; 95% CI: 1.06–1.74) were independently associated with moderate to severe symptom-severity. Poisson regression analysis showed that the independent factors that contributed to the frequency of recurrent severe exacerbations were female sex (regression coefficient $\beta = 0.62$, $p < .01$), an episode of sputum with coughing ($\beta = 1.23$, $p < .01$), nocturnal awakening ($\beta = 1.22$, $p < .01$), and severe exacerbation ($\beta = 0.78$, $p < .01$) within the previous 6 months. *Conclusion.* Symptom-severity of asthma and the frequency of severe exacerbations were associated with previous exacerbations and susceptibility to URI.

Keywords asthma, exacerbation, upper respiratory infection

INTRODUCTION

Asthma is a syndrome with heterogeneous phenotypes, including the recently proposed entity of "exacerbation-prone" asthma, which involves frequently occurring exacerbations (1). The characteristic features of exacerbation-prone patients include irreversible airflow limitation, a history of cigarette smoking, psychosocial dysfunction, medication noncompliance, and comorbidities including rhinosinusitis, obesity, gastroesophageal reflux, and intolerance to nonsteroidal anti-inflammatory medications (2, 3). Recent asthma exacerbations are a predictor of future exacerbations (4), but not all exacerbations are associated with severe disease.

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Periodic exacerbations are generally thought of as a worsening of asthma symptoms in response to a variety of triggers. Upper respiratory infection (URI) due to viral infection is recognized as a major trigger of acute exacerbation of asthma in children and adults and results in frequent outpatient visits and hospitalization (5–7). The frequency of URI is suspected to contribute to exacerbation-prone asthma, but the factors underlying the exacerbation-prone phenotype are incompletely understood.

Asthma guidelines recommend achieving and maintaining current control, as well as reducing the future risk of exacerbations (8, 9). We examined the prevalence of URI and exacerbations in patients with adult asthma using a self-administered questionnaire to determine the risk factors for severe exacerbations. We focused on the association between the episodes of URI and a deteriorated asthma status, such as that in patients with moderate to severe symptom-severity and severe exacerbations.

METHODS

Subjects and Study Design

The study was designed as a questionnaire-based retrospective study to capture all febrile episodes of URI, symptom-severity, and severe exacerbations that occurred in adult patients over a 6-month period. Adult patients with asthma that had been diagnosed by physicians were consecutively recruited during their regular visits to 446 centers, including the outpatient departments of 7 university hospitals, 24 general hospitals, and 315 clinics. The questionnaires were handed to the subjects in autumn–winter in 2006, spring–summer in 2007, and autumn–winter in 2007. Male and female asthma patients aged above 18 years were eligible for inclusion in the study if they had a diagnosis of moderate or severe persistent asthma confirmed by a chest physician, and the diagnosis had occurred at least 6 months before the beginning of the study. Each center's Institutional Review Board approved the protocol and all subjects gave signed informed consent.

Questionnaire

Questions to each patient concerning febrile episodes of URI, symptoms associated with asthma, and exacerbations were based on symptom-severity scores (10) and were modified to fit the design of this study (see Appendix). Another questionnaire was concurrently given to the physicians regarding the events of asthma-related hospitalization and treatment, based on chart review.

Definition of Symptom-Severity and Severe Exacerbations

The definition of moderate to severe symptom-severity was based on symptom-severity scores (10), as having at least one symptom of cough, sputum with coughing, and nocturnal awakening per week. Among the cold-severity indicators validated in the Wisconsin Upper Respiratory Symptom Survey (WURSS) (11), fever was one of the symptoms associated with acute exacerbations of asthma requiring hospitalization (12). To avoid inclusion of data for rhinitis and milder common colds, URIs were defined as self-reported episodes of nasal stuffiness and discharge, combined with sneezing, sore throat, or cough with fever. The American Thoracic Society/European Respiratory Society (ATS/ERS) Task Force on Asthma Control and Exacerbations defined exacerbations as events characterized by a change from the patient's previous status that prompts a need for a change in treatment (13). In this study, severe exacerbations were defined as self-reported episodes requiring systemic glucocorticosteroids, an emergency room (ER) visit, or asthma-related hospitalization. Recurrent events of exacerbations and URI were defined as two or more episodes within the previous 6 months. The primary outcomes were the rates of URI and severe exacerbations of asthma per patient per 6 months.

Statistical Analysis

SPSS version 18.0 (SPSS, Chicago, IL, USA) was used for all calculations. Factors associated with poor asthma control were evaluated by logistic regression analysis. The results are expressed as odds ratios (ORs) with 95% confidence intervals (CIs). The frequency of exacerbations was analyzed using a simple model assuming a Poisson distribution. The associations between recurrent severe exacerbations and clinical variables were initially explored by univariate regression. Multivariate regression models were then used to evaluate the relationship between recurrent severe exacerbations and variables found to be significant in univariate analysis, while adjusting for potential confounding factors that were also significant in univariate analysis.

RESULTS

Patient Characteristics

The self-administered questionnaire survey was given to a total of 16,381 adult patients with asthma in three separate periods (Table 1): 7070 subjects in autumn–winter 2006, 4859 subjects in spring–summer 2006, and 4452 subjects in autumn–winter 2007. A total of 11,573 completed questionnaires (70.6%) were received from 6266 patients (some patients completed questionnaires in two or all three of the periods). Of these patients, 42.7% were male. There were no significant differences in response rates among patients of different sex or age.

Incidence of URI

A total of 8876 URI episodes were documented in the 11,573 patients over 6 months, giving a rate of 1.54 episodes per patient per year. Recurrent febrile URI, which was defined as two or more episodes per 6 months, occurred in 17.4% of the patients. The incidence of febrile URI in autumn–winter was more frequent than that in spring–summer ($p < .05$) (Figure 1).

Independent Factors Associated with Asthma Symptom-Severity

A nested case–control study was performed to identify the characteristics of adult patients with poor asthma control, especially in those with a previous history of severe exacerbations. The nested study included the 1012 patients who answered the questionnaire in all three periods. Of these patients, 66% showed moderate to severe symptom-severity, which was defined as having at least one symptom of cough, sputum, and nocturnal awakening per week. The results of logistic regression analysis of covariate factors for symptom-severity are shown in Table 2. An older age (OR: 3.42; 95% CI: [1.75–8.06]; $p < .01$), female sex (OR [CI] = 1.59 [1.22–2.07]; $p < .01$), ≥3 episodes of febrile URI in the previous 6 months or an episode of sputum with coughing (OR = 3.83 [2.29–6.40], $p < .01$), previous exacerbations within 1 year (OR = 4.96 [1.75–14.0], $p < .01$), disuse of inhaled corticosteroids (ICSs) (OR = 2.70 [1.82–4.00], $p < .01$), and disuse of add-on leukotriene receptor antagonists (LTRAs) (OR = 1.58 [1.21–2.07], $p < .01$) contributed significantly to symptom-severity. In contrast, disuse of add-on long-acting β-agonists (LABAs) and add-on theophylline did not contribute to symptom-severity.

TABLE 1.—Characteristics of the patients.

	First questionnaire	Second questionnaire	Third questionnaire
Number of responses	7084	4858	4451
Responses with complete answers	4038 (57%)	3090 (64%)	2798 (63%)
Age (year)	54.5 (54.0–55.0)	56.2 (55.6–56.8)	56.8 (56.2–57.4)
Sex (male/female)	1784/2254	1331/1759	1272/1526
Frequency of URI per 6 months	0.79 (0.76–0.83)	0.80 (0.73–0.86)	0.60 (0.56–0.64)
Frequency of events using SABA per 6 months	10.0 (9.04–11.0)	9.50 (8.33–10.7)	11.9 (10.5–13.3)
Frequency of events using oral CS	1.64 (1.38–1.91)	1.90 (1.58–2.22)	1.83 (1.47–2.18)
Frequency of events of visiting ER	0.72 (0.56–0.90)	0.72 (0.60–0.84)	0.54 (0.47–0.62)
Coughing lasted over 1 week	2907 (72%)	2232 (72%)	2159 (77%)
None	0.90 (0.80–1.00)	0.74 (0.67–0.81)	0.65 (0.55–0.74)
Frequency per 6 months			
Sputum with coughing			
None	2027 (50%)	1621 (52%)	1584 (57%)
1–2 events per 6 months	928 (23%)	687 (22%)	622 (22%)
1–2 events per 1 month	500 (12%)	370 (12%)	291 (10%)
1–2 events per 1 week	339 (9%)	235 (8%)	183 (7%)
Almost every day	224 (6%)	177 (6%)	118 (4%)
Nocturnal awakening			
None	2549 (63%)	2135 (69%)	1965 (70%)
1–2 events per 6 months	864 (21%)	554 (18%)	523 (19%)
1–2 events per 1 month	366 (9%)	258 (8%)	209 (7%)
1–2 events per 1 week	189 (5%)	118 (4%)	75 (3%)
Almost every day	70 (2%)	25 (1%)	26 (1%)
Rhinitis symptoms			
None	1671 (41%)	1250 (40%)	1314 (47%)
Nasal obstruction	1394 (35%)	1077 (35%)	852 (30%)
Runny nose	1581 (39%)	1233 (40%)	973 (35%)
Sneeze	1187 (29%)	935 (30%)	703 (25%)
Treatment			
ICS[a]	5869 (83%)	4064 (84%)	3655 (82%)
Add-on LABA	2258 (32%)	1789 (36%)	1760 (38%)
Add-on LTRA	3061 (43%)	2246 (45%)	2059 (46%)
Add-on theophylline	2664 (38%)	1804 (37%)	1698 (38%)

Notes: Data are expressed as number (%) or mean (95% CIs) unless otherwise indicated.
CS, corticosteroid; ICS, inhaled corticosteroid; LABA, long-acting β_2 agonist; LTRA, leukotriene receptor antagonist; SABA; short-acting β_2 agonist, URI, upper respiratory infection; CI, confidence interval.
[a]Including ICS therapy alone and additional therapy with LABAs, LTRAs, and/or theophylline.

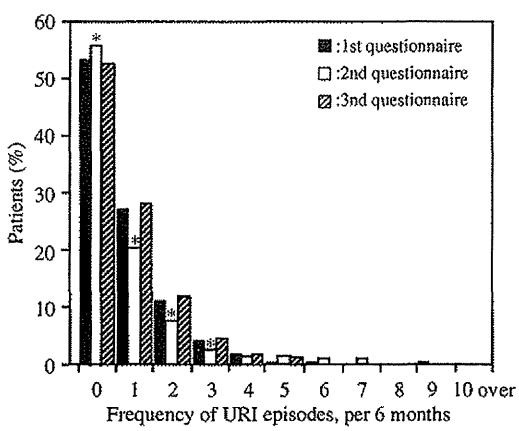

FIGURE 1.—Frequency of febrile URI episodes in adult patients with asthma in three periods. A self-administered questionnaire was given to 7070 patients in autumn–winter 2006 (1st questionnaire), 4859 patients in spring–summer 2007 (2nd questionnaire), and 4452 patients in autumn–winter 2007 (3rd questionnaire).
Note: *$p < .05$, compared with the first questionnaire.

Multivariate logistic regression analysis showed that recurrent febrile episodes of URI (OR = 2.68 [1.47–4.91]), disuse of ICS (OR = 2.63 [1.68–4.12]), a previous exacerbation within 1 year (OR = 1.74 [1.28–2.34]), female sex (OR = 1.58 [1.20–2.08]), older age (OR = 1.57 [1.15–2.13]), and disuse of add-on LTRAs (OR = 1.42 [1.06–1.74]) were independently associated with symptom-severity.

Independent Factors Associated with Frequency of Severe Exacerbations

To analyze previous episodes of severe exacerbations, we examined the responses of the 1012 patients who answered the questionnaire 3 times. In these patients, the frequency of severe exacerbations was 0.27 per subject per 6 months and 5.5% had ≥2 severe exacerbations. The results of univariate Poisson regression analysis are shown in Table 3. In a multivariate Poisson regression model, the independent factors that contributed to the frequency of severe exacerbations were a history of previous exacerbations within 1 year ($\beta = 0.99$, $p < .01$), an episode of sputum with coughing ($\beta = 0.97$, $p < .01$), an episode of nocturnal awakening ($\beta = 0.72$, $p < .01$), and female sex ($\beta = 0.59$, $p < .01$) (Table 4). The contributions of age ($\beta = 0.34$, $p = .26$), episodes of rhinitis symptoms ($\beta = -0.52$, $p = .88$), and any treatment were not significant. The

TABLE 2.—Univariate and multivariate logistic analysis of factors associated with moderate to severe symptom-severity.

	Univariate analysis OR (95% CI)	Multivariate analysis OR (95% CI)
Age		
< 65 years old	1	1
≥ 65 years old	3.42* (1.75–8.06)	1.57* (1.15–2.13)
Sex		
Male	1	1
Female	1.59* (1.22–2.07)	1.58* (1.20–2.08)
URI		
< 3 episodes in the past 6 months	1	1
≥ 3 episodes in the past 6 months	3.83* (2.29–6.40)	2.68* (1.47–4.91)
Previous exacerbation		
None	1	1
≥ One episode in the past year	4.96* (1.75–14.04)	1.74* (1.28–2.34)
ICS[a]		
Use	1	1
Disuse	2.70* (1.82–4.02)	2.63* (1.68–4.12)
Add-on LABA		
Use	1	1
Disuse	0.78 (0.60–1.02)	0.98 (0.73–1.30)
Add-on LTRA		
Use	1	1
Disuse	1.58* (1.21–2.07)	1.42* (1.06–1.74)
Add-on theophylline		
Use	1	1
Disuse	1.25 (0.96–1.62)	1.24 (0.82–1.90)

Notes: Poor asthma control is defined as having one or more symptom of cough, sputum with coughing and nocturnal wakening per week. ORs and 95% CIs of analyses using logistic regression models for associations between older age, female sex, recurrent URI, and a previous exacerbation are shown.
OR, odds ratio; CI, confidence interval; ICS, inhaled corticosteroid; LABA, long-acting β_2 agonist; LTRA, leukotriene receptor antagonist; URI, upper respiratory infection.
[a]ICS therapy alone and additional therapy with LABA and/or LTRA and/or theophylline were included.
*$p < .01$.

TABLE 3.—Univariate Poisson analysis of factors associated with the frequency of severe exacerbations.

	β (95% CI)	
Age		$p = .26$
<65 years old		
≥65 years old	0.34 (−0.26 to 0.94)	
Sex		$p < .01$
Male		
Female	0.62 (0.17–1.07)	
Episodes of URI		$p = .06$
<3 episodes in the past 6 months	−0.43 (−0.88 to 0.02)	
≥3 episodes in the past 6 months		
Episodes of rhinitis symptom		$p = .88$
None	−0.52 (−0.74 to 0.64)	
≥One episode in the past 6 months		
Episodes of sputum with coughing		$p < .01$
None	1.23 (0.77–1.68)	
≥One episode in the past 6 months		
Episodes of nocturnal awakening		$p < .01$
None	1.22 (0.61–1.82)	
≥One episode in the past 6 months		
Previous exacerbation		$p < .01$
none	0.78 (0.6–1.02)	
≥one episode in the past 6 months		
ICS[a]		$p = .08$
Disuse	0.16 (−0.08 to 0.52)	
Use		
Add-on LABA		$p = .12$
Disuse	0.24 (−0.14 to 0.52)	
Use		
Add-on LTRA		$p = .23$
Disuse	0.21 (−0.11 to 0.46)	
Use		
Add-on theophylline		$p = .66$
Disuse	−0.32 (−0.72 to 0.08)	
Use		

Notes: Severe exacerbations are defined as a self-report of an asthma-related hospitalization, an emergency department visit, or a requirement for systemic corticosteroids.
CI, confidence interval; ICS, inhaled corticosteroid; LABA, long-acting β_2 agonist; LTRA, leukotriene receptor antagonist; URI, upper respiratory infection.
[a]Including ICS therapy alone and additional therapy with LABAs, LTRAs, and/or theophylline.
β = regression coefficient.

Poisson regression model predicting the frequency of severe exacerbations from the four independent significant factors was statistically significant with a chi-square likelihood ratio = 171.503, df = 3 ($p < .0001$).

Analysis of the expected frequency of severe exacerbations showed that one or more previous exacerbations within 6 months had an expected log count of 0.99, indicating about 0.20 more events of severe exacerbations in patients with previous exacerbations, compared to those without exacerbations, with other factors held constant (Table 4).

DISCUSSION

To our knowledge, this study is the largest retroprospective study of URI and exacerbations in adult patients with asthma performed to date. The results indicate that the "exacerbation-prone" and "URI-prone" asthma phenotypes are common, with rates of 5.5% and 17.4%, respectively, and frequencies of severe exacerbations and febrile URI of 1.54 and 0.54 per subject per year, respectively. Recurrent URI and frequency of URI were associated with moderate to severe symptom-severity and severe exacerbation, respectively, and therefore our results support the hypothesis of an association between episodes of URI and a deteriorated asthma status.

The overall incidence of URI per subject per year of follow-up was 1.54, which is similar to the results of previous prospective reports (range 1.2–6.7) (14–19). To avoid overreporting of URI episodes, the subjects were specifically instructed not to report a URI if they were experiencing URI without fever. Severe exacerbations were defined as those requiring hospitalization or a course of antibiotics or oral corticosteroids, and this definition gave an overall rate of 0.54 exacerbations per patient per year. This frequency is in agreement with the previous reports showing that asthma leads to severe exacerbations with a frequency of 0.12–0.77 per patient per year (20–22).

Exacerbations are defined as events characterized by a change from the patient's previous status that prompts a need for a change in treatment (13). The ATS/ERS Task Force considered that episodes of "mild" exacerbations were only just outside the normal range of variation for

TABLE 4.—Multivariate Poisson analysis of factors associated with the frequency of severe exacerbations.

	β (95% CI)	Adjusted mean (95%CI)
Sex		
Male		0.11 (0.08–0.13)
Female	0.59* (0.16–1.01)	0.19 (0.13–0.26)
Episodes of sputum with coughing		
None		0.10 (0.08–0.12)
≥One episode in the past 6 months	0.97* (0.48–1.47)	0.26 (0.15–0.38)
Episodes of nocturnal awakening		
None		0.09 (0.05–0.12)
≥One episode in the past 6 months	0.72* (0.26–1.19)	0.18 (0.13–0.23)
Previous exacerbation		
None		0.12 (0.08–0.16)
≥One episode in the past 6 months	0.99* (0.34–1.65)	0.32 (0.20–0.42)

Notes: Severe exacerbations are defined as a self-report of an asthma-related hospitalization, an emergency department visit, or a requirement for systemic corticosteroids. Results are shown for an analysis using a Poisson regression model adjusted with covariates that were significant factors in univariate analysis. The adjusted mean is estimated as the arithmetic mean of the sample and the confidence interval is estimated using the relationship between the chi-square and Poisson distributions.
CI, confidence interval.
β = regression coefficient; *$p < .01$.

an individual patient and that current methods of analysis could not distinguish such exacerbations from a transient loss of asthma control. In the current study, we analyzed patients' experiences of a deteriorated status of asthma to identify "moderate to severe symptom-severity" and "severe exacerbations". The prevalence of moderate to severe symptom-severity is in concordance with that in a report by Soriano et al. (23), in which it was shown that 65% of adult asthma patients had moderate to severe symptom-severity. We assessed factors that contributed to poor asthma control, which was considered as a "mild" exacerbation by the ATS/ERS Task Force (10). Our findings were an agreement with those in Temprano et al. (24) showing that women were more likely to have poor asthma control, despite higher rates of ICS use, compared with men. Previous severe exacerbations and recurrent episodes of URI were also covariates for moderate to severe symptom-severity. Hermosa et al. (25) also found that the number of exacerbations during the previous year is the variable with the greatest effect on control in patients with severe asthma. Symptom-severity is also significantly affected by adherence to treatment, patient knowledge of the disease, body mass index (BMI), and the number of visits to a physician in the previous 6 months (25). Viral infection also contributes to deteriorated asthma control, and cold-severity within the first 2 days can be used to predict subsequent changes in asthma control in adult patients (11).

Many studies have demonstrated that URI is a trigger of acute exacerbations of asthma (5–7), but there is little information on the association of the frequency of exacerbations and the episodes of URI. The hypothesis of our study was that recurrent episodes of URI might contribute to loss of control, but not to severe exacerbations. The rates of severe exacerbations were analyzed using a Poisson regression model. In agreement with a previous study (26), our results showed that asthma exacerbations are more common in females than in males. Exacerbations also occurred most frequently in individuals with severe disease (27). Previous reports have also identified other risk factors, including a history of a recent exacerbation, comorbidities such as an increased BMI and psychological problems, as well as current smoking and lower socioeconomic status. A recent exacerbation within the last 3 months is associated with a markedly increased risk of a future exacerbation (2). The host response to viral infection is also likely to influence susceptibility to asthma exacerbation, and the association of a previous exacerbation with a risk for recurrent exacerbations suggests the presence of an "exacerbation-prone" subset of patients with asthma (1).

In the current study, we showed that drug intervention with ICSs and add-on LTRAs might improve symptoms, but severe exacerbations still occurred in some patients despite the use of these drugs. Many studies have described pharmacologic interventions in asthma exacerbations (28–30), and the exacerbations have been associated with poor asthma control (31). The Formoterol and Corticosteroids Establishing Therapy (FACET) study (32) revealed that a higher ICS dose had a marked beneficial effect on exacerbation frequency, but relatively less effect on symptoms and peak expiratory flow, whereas the opposite was true with the addition of LABAs (32, 33). Rosi et al. (34) also found that the asthma exacerbation frequency is not closely related to symptoms and measures of disrupted airway function. These reports and our results demonstrate that different strategies might be needed to reduce asthma exacerbations, as well as to optimize asthma control.

Leukotrienes produced in the airway in response to infection play important roles in the mechanism of exacerbation of asthma following viral infection (35). In a few studies, LTRAs have been shown to reduce asthma symptoms or exacerbations in children with colds (36–38). However, it has also been reported that LTRAs did not improve asthma control or cold symptom scores caused by experimental rhinovirus infection (39). Our results showing that add-on LTRAs with ICSs might lessen the symptoms of asthma in adults are consistent with the previous reports that add-on LTRAs are equivalent to add-on LABAs for control of asthma symptoms (40, 41). In the current study, discontinuing add-on LABAs was not associated with developing asthma symptoms, which might be due to low drug adherence.

The limitations of the study include the selection criteria, study design, and availability of data. Because we did not require evidence of bronchodilator reversibility, the enrolled patients may have had a combination of chronic obstructive pulmonary disease (COPD) and asthma. Therefore, the results cannot be generalized to all patients with asthma with the conditions described above. The questionnaire was incomplete due to missing data and distribution of the questionnaire to some patients after cold episodes. Second, microbiological specimens were not collected during the cold episodes and this prevented

determination of the role of viral or bacterial respiratory tract infections. However, because URI is self-limiting, a viral diagnosis is not clinically indicated. In children, viral URI has been associated with >80% of asthma exacerbations (42), but a recent study showed that the virus detection rate was only 36.7% in all unscheduled hospital visits in children (43). Third, we did not assess comorbidities and airway obstruction. Several comorbidities including severe nasal sinus disease, gastroesophageal reflex, recurrent respiratory infection, and obstructive sleep apnea (44), as well as current smokers (45) and increased BMI (2, 46), are associated with an increased risk for future exacerbations. Airway obstruction is also an important risk factor for multiple asthma exacerbations requiring hospital care or systemic corticosteroids (3, 47). Finally, the survey in the study was based on recall, and recall bias can distort the description of events. However, often a person recalls positive events more than negative events, and therefore it seems reasonable to assume that this recall bias did not skew our results.

In conclusion, our data suggest an association between episodes of URI and a deteriorated asthma status. These findings require confirmation in further studies in a larger number of affected individuals.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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APPENDIX

Questionnaire

Answer these questions and select the first answer that you think of.

1. During the past 6 months, have you had a bout of coughing that lasted over 1 week? If yes, how many events?
   ☐ No ☐ Yes (event(s))
2. During the past 6 months, have you had any sputum with coughing? If yes, how many events?
   ☐ No ☐ 1–2 events/6 months ☐ 1–2 events/a month
   ☐ 1–2 events/a week ☐ Almost every day
3. During the past 6 months, have you been woken up at night by an attack of asthma? If yes, how many events?
   ☐ No ☐ 1–2 events/6 months ☐ 1–2 events/a month
   ☐ 1–2 events/a week ☐ Almost every day
4. During the past 6 months, have you had any of these rhinitis symptoms?
   ☐ None ☐ Nasal obstruction ☐ Runny nose ☐ Sneeze
   If yes, what was the grade of the symptoms?
   ☐ Mild ☐ Intermittent ☐ Severe ☐ Extreme
5. During the past 6 months, have you had any episodes of common cold with fever (temperature >37.0°C)? If yes, how many episodes?
   ☐ No ☐ Yes (event(s))
6. During the past 6 months, how many times have you experienced the following events during an asthma attack?
   During these episodes, how many times did you use a reliever inhaler?
   (event(s))
   During these episodes, how many times did you use an oral steroid?
   (event(s))
   During these episodes, how many times did you visit an emergency room?
   (event(s))

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

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Non-small-cell lung cancer/Radiotherapy/Tumor enhancement/Tumor regression/Contrast-enhanced CT.

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

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of therapeutic response,[9] 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 χ^2 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

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)
IIIb	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-

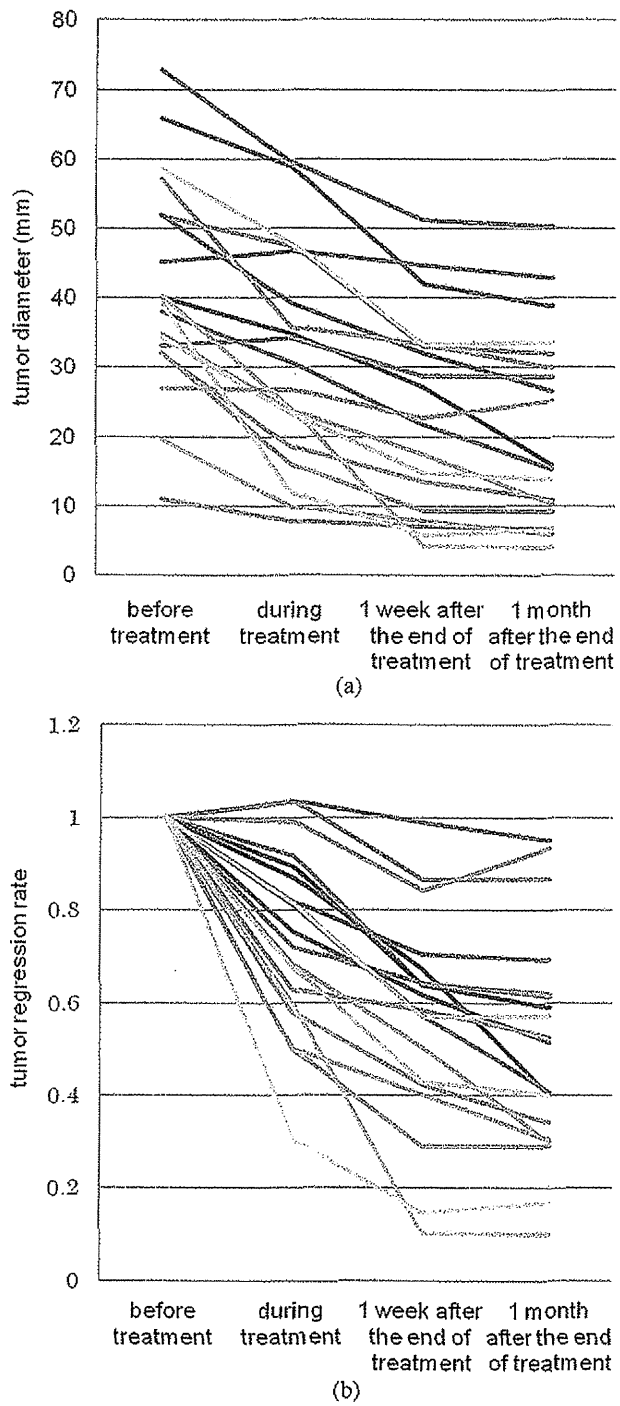

Fig. 1. Tumor diameters (1a) and tumor regression rate (1b) in all 19 patients included in this study from before to after therapy.

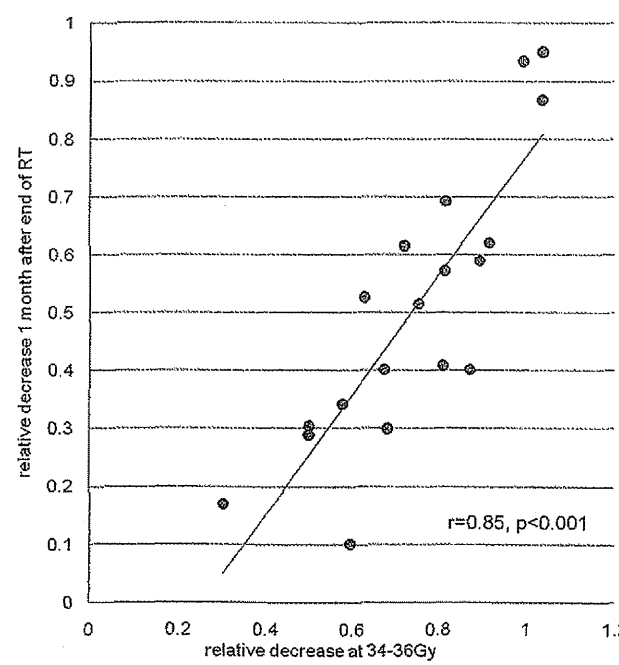

Fig. 2. Correlation between the relative decrease in tumor diameter at 34–36 Gy and that 1 month after the end of RT.

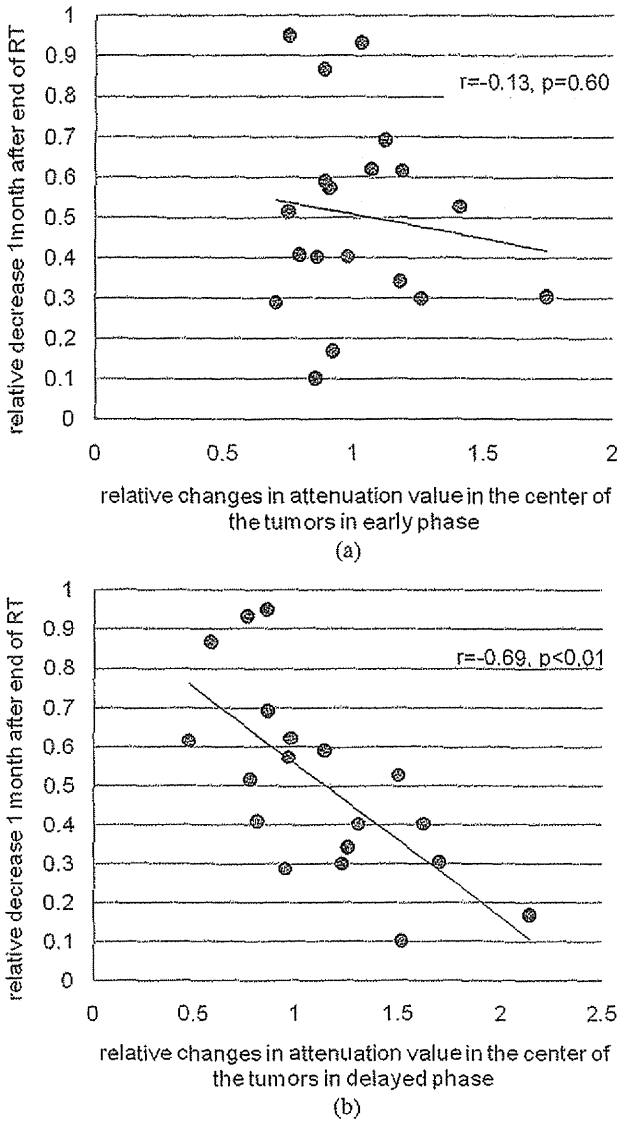

Fig. 3. Correlation between the change in tumor diameter 1 month after the end of RT and relative changes in the attenuation value in the early phase (Fig. 3a) and delayed phase (Fig. 3b) at 34–36 Gy in the center of the tumors.

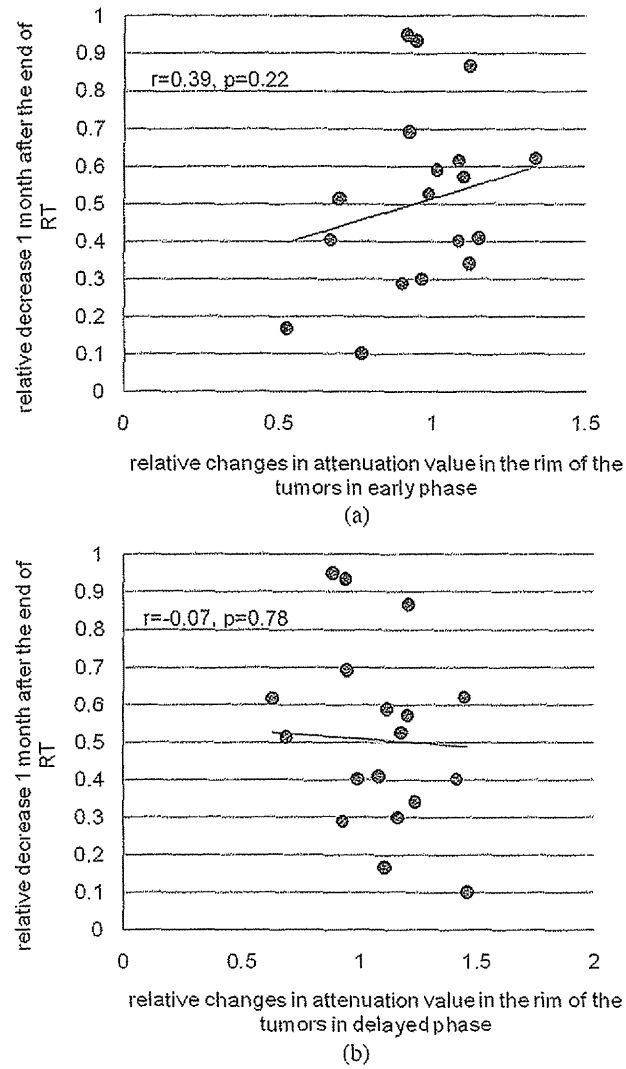

Fig. 4. Correlation between the change in tumor diameter 1 month after the end of RT and relative changes in the attenuation value in the early phase (Fig. 4a) and delayed phase (Fig. 4b) at 34–36 Gy in the rim of the tumors.

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,[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,[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.[13] Wasik *et al.* reported that tumors reached their maximum response (minimum volume) an average of 5–11 months after RT completion.[14] Fox *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.[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 *et al.*

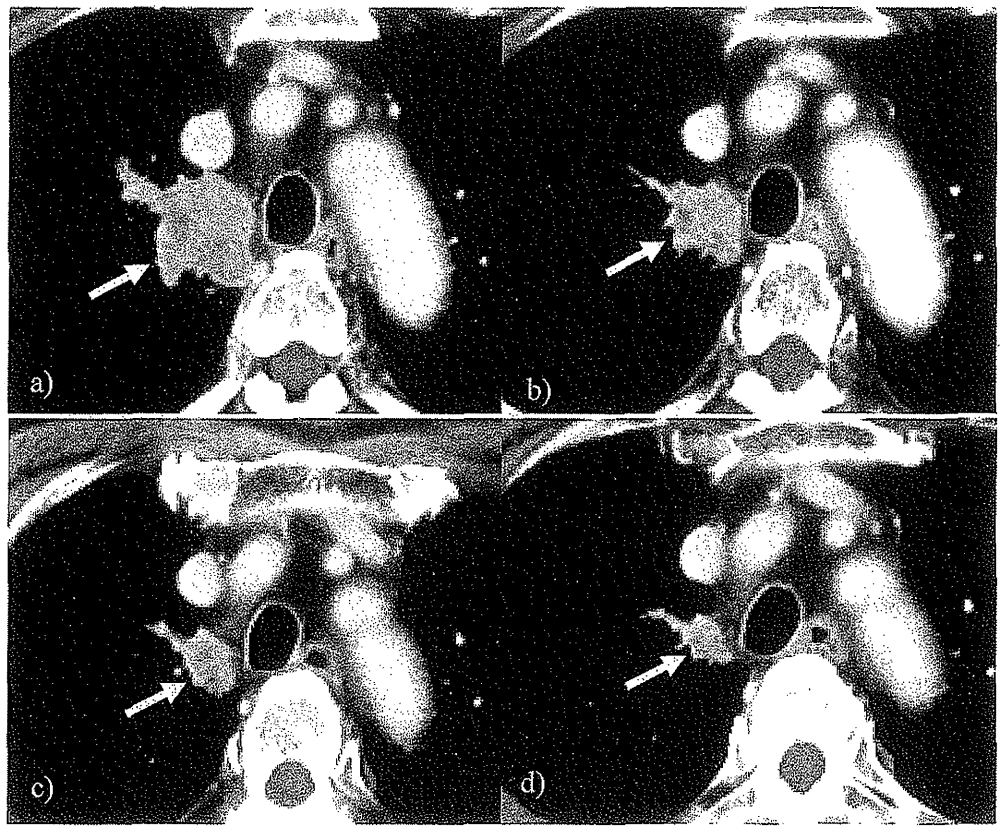

Fig. 5. Squamous cell carcinoma in a 76-year-old man (arrows). Dynamic contrast-enhanced CT in delayed phase before treatment a), during treatment b), 1 week after the end of RT c), 1 month after the end of RT d). The attenuation value of the center of the tumor was 78.88 before treatment, 63.97 at 34–36 Gy, 91.1 1 week after the end of RT, and 73.68 1 month after the end of RT, respectively.

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

reported that average GTV reduction observed over 30 fractions (60 Gy) was 38%,[13] and Kupelian *et al.* reported tumor regression rates with a range of 0.6% to 2.3% per day.[15] 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.[16] 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,[13] 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

tumors during the treatment course in the treatment room.[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.[9] Microvessel density was reported to be a prognostic factor of survival in patients with lung cancer.[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.[10] 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.[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;[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.[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.[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.[9,20] 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.[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.[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.[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.[17] A previous study reported that tumor vascularity increased during RT.[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.

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Review Article

Tobacco, Cardiopulmonary Vascular Disease, and Aging

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Abstract

Smoking causes disease through oxidative stress, which accelerates aging. Recently, chronic obstructive pulmonary disease (COPD), emblematic of tobacco-related diseases, has come to be viewed as a systemic inflammatory disease. COPD is regarded as contributory to cardiovascular events stemming from vascular inflammation. As an independent risk factor for cardiovascular disease, COPD in combination with smoking also raises cardiovascular risk synergistically. Vascular endotheliopathy caused by tobacco is also closely related to decreases in endothelial progenitor cells (EPC) and elevated cardiovascular risk. α1-antitrypsin-LDL (AT-LDL), an oxidized/modified LDL that contributes to development of arteriosclerosis, is also elevated in smokers.

Tobacco-induced cardiopulmonary vascular disease entities are in this way interrelated and deemed to create a vicious circle. The EPC reduced in smokers recovers rapidly after smoking cessation, and increased AT-LDL also decreases after smoking cessation. Smoking cessation is thus essential to breaking this vicious circle. In the interest of arresting and preventing aging and disease, we hope to deepen understanding of smoking cessation among smokers through patient-based awareness.

KEY WORDS: chronic obstructive pulmonary disease (COPD), cardiovascular disease, oxidative stress, vascular endotheliopathy, smoking cessation therapy

Introduction

Smoking is a cause of cancer, stroke, myocardial infarction, and chronic obstructive pulmonary disease(COPD) and is also involved in aspects of aging such as increased wrinkles and gray hair. Oxidative stress is one important mechanism that causes these changes. Smoking causes disease through oxidative stress, which accelerates aging.

Regulatory measures to prevent passive smoke exposure have been enacted recently in Japan; an anti-smoking policy in the form of higher tobacco taxes has also been promoted, and the creation of a standard smoking cessation protocol has broadened use of smoking cessation therapy. At the same time, measures in Japan remain insufficient compared to those in the developed countries of the EU and US, and health care providers still require a deeper understanding and awareness of tobacco-induced health injuries and nicotine dependence.

To deepen understanding of tobacco-induced health injuries, our review first presents an overview of COPD, a representative tobacco-related disease, by Professor Hiroshi Kimura. Dr. Yasuko K Bando then surveys the mechanisms leading from smoking to arteriosclerotic vascular disease. Dr. Hiromichi Wada describes the relation of a new arteriosclerosis marker, α1-antitrypsin-LDL, to cigarette smoking. Finally, to deepen understanding of smoking cessation among smokers based on the idea that smokers are patients, Professor Yuko Takahashi describes smoking cessation support and recent smoking cessation therapy for rejuvenation and disease prevention.

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