Retrospective study of the predictors of mortality and radiographic deterioration in 782 patients with nodular/bronchiectatic *Mycobacterium avium* complex lung disease

Mina Gochi, Noboru Takayanagi, Tetsu Kanauchi, Takashi Ishiguro, Tsutomu Yanagisawa, Yutaka Sugita

ABSTRACT

**Objectives:** Some patients with nodular/bronchiectatic *Mycobacterium avium* complex lung disease (NB MAC-LD) deteriorate and die. The main aim of the study is to evaluate the prognostic factors and radiographic outcomes in patients with NB MAC-LD.

**Setting:** Retrospective single-centre review.

**Participants:** 782 HIV-negative patients with NB MAC-LD treated at our institution in Japan.

**Primary and secondary outcome measures:** All-cause and MAC-LD progression mortality rates and the prognostic factors, and radiographic deterioration rates and the prognostic factors.

**Results:** Mean age was 68.1 years, and median follow-up period was 4.3 years. Death from any cause and progression of MAC lung disease (MAC-LD) occurred in 130 (16.6%), and 19 (2.4%) patients, respectively. All-cause and MAC-LD progression 10-year mortality rates were 27.4% and 4.8%, respectively. In 536 patients with MAC-LD who were followed-up for more than 1 year, radiographic deterioration occurred in 221 (41.2%) patients and median time-to-radiographic deterioration was 9 years. A multivariate Cox proportional hazard model showed male sex, older age, body mass index <18.5 kg/m², absence of bloody sputum, hypoalbuminaemia and erythrocyte sedimentation rate >40 mm/h to be negative prognostic factors for all-cause mortality, and the presence of idiopathic pulmonary fibrosis, haemoglobin <11.3 mg/dL, C reactive protein >1.0 mg/dL and the presence of cavity to be negative prognostic factors for radiographic deterioration.

**Conclusions:** Only 2.4% of patients with NB MAC-LD died from MAC-LD progression. As clinical trials testing the effectiveness of drug therapy in patients with NB MAC-LD are being designed and implemented, the primary end point could be time-to-radiographic deterioration, and trial patients need to be stratified according to these prognostic factors before randomisation.

INTRODUCTION

*Mycobacterium avium* complex (MAC) comprises the species most frequently associated with non-tuberculous mycobacterial (NTM) lung disease in most of the world. MAC lung disease (MAC-LD) is an important cause
of morbidity and mortality, and is increasing in the USA, Canada and Japan. It comprises five clinical diseases: nodular/bronchiectatic (NB) disease, fibrocavitary (FC) disease, solitary pulmonary nodule, disseminated disease and hypersensitivity-like disease. We previously reported the prognostic factors of MAC-LD and showed that nodular/bronchiectatic Mycobacterium avium complex lung disease (NB MAC-LD) was the most frequent disease type (76%) and showed the most favourable outcome. However, some patients with NB MAC-LD progressively deteriorate and die.

Meta-analysis showed that the estimated pooled treatment success rate, rates of failure, relapse and death for patients with MAC disease were 39%, 27%, 6% and 17%, respectively. To evaluate the efficacy of treatment for patients with NB MAC-LD, which parameter should we use? One recent study indicated that sputum conversion would be achieved by therapy in more than two-thirds of patients with NB MAC-LD, but microbiological recurrences are common due to reinfection by MAC genotypes. Another study indicated that long-term survival is not poor, but more than half of the patients deteriorate radiographically after 10 years. Thus, when evaluating the efficacy of treatment of patients with NB MAC-LD, not only short-term, but also long-term outcomes are needed. For long-term outcome, all-cause mortality and rate of radiographic deterioration (time-to-radiographic deterioration) would be useful markers.

The American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) guidelines state that “making the diagnosis of NTM lung disease does not, per se, necessitate the institution of therapy...”. If deciding to treat patients with MAC-LD, patients with negative prognostic factors (eg, FC disease, symptomatic patients and patients with cavity) should be included first. Then, should all patients with NB MAC-LD be treated immediately after diagnosis? To answer these questions, we examined the data on predictors of mortality and radiographic deterioration and time-to-radiographic deterioration, in patients with NB MAC-LD.

METHODS

Patients

All patients who fulfilled the 2007 ATS/IDSA diagnostic criteria were classified according to five disease patterns based on chest high-resolution CT (HRCT) scanning: NB, FC, NB+FC, disseminated and unclassifiable. We studied 782 patients with NB MAC-LD aged >18 years who were newly diagnosed over a 12-year period from 1999 through 2010, and treated at the Saitama Cardiovascular and Respiratory Center, Saitama, Japan.

Study design

This was a retrospective cohort study. Clinical, radiographic and microbiological data, treatments and outcomes were collected from medical records. If drug administration was initiated within 6 months after diagnosis and this therapy was continued for more than 3 months, it was considered the first-line treatment. If the patients were followed more than 6 months after diagnosis without any drugs, the first-line treatment was considered to be observation. Patients were followed through June 2012. Survival status was obtained from medical records and/or telephone interviews. The study was conducted with the approval of ethical committees at Saitama Cardiovascular and Respiratory Center.

If the chest radiography was performed each year, assessment of radiographic change was independently performed by two pulmonologists and classified as improvement, no change, or deterioration. To quantify observer variation, k coefficients of agreement (k) were calculated for assessment of radiographic changes. Time-to-radiographic deterioration was evaluated for the period from the date of the first radiograph to the date when deterioration was first observed.

Statistical analysis

Categorical baseline characteristics are summarised by frequency and per cent, and continuous characteristics are reported as the mean±SD. To investigate potential risk factors of mortality, we compared baseline characteristics for with or without bloody sputum, with or without cavity and for number of first-treatment drug regimens by Fisher’s exact test or Wilcoxon test in accordance with nominal and continuous variables, respectively. We chose the following variables from these results that showed significant difference or that had previously recognised clinical significance for entry into univariate Cox regression analysis and estimation of crude HR: sex, age, smoking history, respiratory comorbidity (none, old pulmonary tuberculosis, emphysema, idiopathic pulmonary fibrosis or others), diabetes mellitus, heart disease, rheumatoid arthritis, liver disease, cerebrovascular disease, postgastrointestinal tract surgery, radiographic feature (NB, FC/FC+Nb, others), body temperature, body mass index (BMI), bloody sputum, peripheral oxygen saturation, white cell count, lymphocyte count, haemoglobin (Hb), erythrocyte sedimentation rate (ESR), C reactive protein (CRP), serum albumin, cavity on HRCT and the number of first-line treatment drugs received (0 or 1, or 2–4). We performed multivariate Cox regression analysis with backward selection to estimate the adjusted HR for mortality of all-cause and MAC-LD disease progression.

Survival in each patient group was estimated by Kaplan-Meier analysis. Mortality rates and time-to-radiographic deterioration were compared with a log-lank test. A p value of <0.05 was considered to be statistically significant in all analyses. For time-to-radiographic deterioration analysis, data from patients without deterioration were censored at the last assessment. All data were analysed with SAS V.9.1.3 (SAS Institute Inc, Cary, North Carolina, USA).
RESULTS
Baseline patient characteristics
Of the 782 patients in the study, 536 (68.5%) were female. Mean patient age was 68.1 years. No patients were infected with HIV. Pulmonary comorbidities were found in 215 (27.5%) patients. Symptoms included bloody sputum in 98 (15.5%) and fever of ≥37°C in 135 (17.3%) patients (table 1).

Presence of bloody sputum
Respective 5-year and 10-year all-cause mortality rates in the patients without bloody sputum were 14% and 29%, vs 5.9% and 19.9% in those with bloody sputum (p=0.018; figure 1). Since bloody sputum was a risk factor of mortality, we compared baseline characteristics of the patients with and without bloody sputum. As a result, compared with patients without bloody sputum, the patients with bloody sputum were significantly more frequently female (76.4% vs 66.8%, p=0.027), had higher serum albumin (4.1±0.4 vs 4.0±0.5 mg/dL, p=0.026) and lower CRP (0.5±1.1 vs 1.6±3.8 mg/dL, p=0.026) and had less frequently associated pulmonary comorbidity (17.9% vs 29.6%, p=0.002).

Presence of cavity on HRCT
Compared with patients without cavity, associated pulmonary comorbidity (32.6% vs 25.7%, p=0.041), low BMI (18.0±2.7 vs 20.1±2.9 kg/m², p<0.001), lower lymphocyte counts (1383±502 vs 1547±522/µL, p=0.002), hypoalbuminaemia (3.8±0.6 vs 4.0±0.4 mg/dL, p=0.010) and elevation of inflammatory markers (ESR: 68.1±37.6 vs 46.4±32.6 mm/h, p<0.001; CRP: 2.6±5.1 vs 1.2±3.2 mg/dL, p<0.001), were significantly more frequent in patients with cavity.

Therapy
Treatments undergone are shown in table 2. First-line treatment regimens included observation in 629 (80.4%) patients, 1 drug in 51 (6.5%), 2 drugs in 27 (3.5%), 3 drugs in 47 (6%) and 4 drugs in 28 (3.6%). Of the 629 patients whose first-line treatment was observation, 541 (69.2%) ultimately underwent observation only. Patients whose first-line treatment regimens

Table 1 Baseline characteristics of the 782 study patients with nodular/bronchiectatic MAC-LD, according to number of first-line treatment drugs

| Characteristics | Total | Number of first-line treatment drugs | 0 or 1 | 2–4 | p Value |
|-----------------|-------|-------------------------------------|-------|-----|---------|
| Number of patients | 782 (100) | 680 (100) | 102 (100) | | |
| Female | 536 (68.5) | 466 (68.5) | 70 (68.6) | | |
| Age, mean years±SD | 68.1±11.1 | 68.2±11.2 | 67.9±10.7 | | |
| Smoker | 197 (25.2) | 177 (26.0) | 20 (19.6) | | |
| Diabetes mellitus | 49 (6.3) | 41 (6.0) | 8 (7.8) | | |
| Heart disease | 81 (10.4) | 74 (10.9) | 7 (6.9) | | |
| Rheumatoid arthritis | 40 (5.1) | 33 (4.9) | 7 (6.9) | | |
| Liver disease | 32 (4.1) | 27 (4.0) | 5 (4.9) | | |
| Cerebrovascular disease | 37 (4.7) | 34 (5.0) | 3 (2.9) | | |
| Postgastrointestinal tract surgery | 30 (3.8) | 24 (3.5) | 6 (5.9) | | |
| Respiratory disease | 215 (27.5) | 180 (26.5) | 35 (34.3) | | |
| Old pulmonary tuberculosis | 91 (11.6) | 73 (10.7) | 18 (17.4) | | |
| Pulmonary emphysema | 34 (4.3) | 30 (4.4) | 4 (3.9) | | |
| Idiopathic pulmonary fibrosis | 27 (3.5) | 20 (2.9) | 7 (6.9) | | |
| Others | 63 (8.1) | 57 (8.4) | 6 (5.9) | | |
| Body mass index, kg/m² | 19.8±3.1 | 19.9±3.0 | 19.2±3.0 | | |
| Bloody sputum | 140 (17.9) | 123 (18.1) | 17 (16.7) | | |
| Peripheral oxygen saturation, <95% | 33 (4.2) | 29 (4.3) | 4 (3.9) | | |
| Body temperature | 36.6±0.5 | 36.6±0.5 | 36.7±0.5 | | |
| White cell count, µL | 6245±2238 | 6215±2236 | 6440±2257 | | |
| Lymphocytes, µL | 1524±522 | 1551±529 | 1333±427 | | |
| Haemoglobin, g/dL | 12.8±1.5 | 12.9±1.5 | 12.5±1.4 | | |
| Albumin, g/dL | 4.0±0.5 | 4.0±0.5 | 3.9±0.5 | | |
| ESR, mm/h | 49.5±34.2 | 48.3±33.4 | 57.5±38.5 | | |
| CRP, mg/dL | 1.4±3.5 | 1.2±3.4 | 2.4±4.2 | | |
| Cavity | 117 (15.0) | 88 (12.9) | 29 (28.4) | | |
| Cause of death | | | | | |
| Progression of MAC-LD | 19 (2.4) | 10 (1.5) | 9 (8.8) | | |
| Other pulmonary disease | 41 (5.2) | 33 (4.9) | 8 (7.8) | | |
| Non-pulmonary disease | 70 (9.0) | 59 (8.7) | 11 (10.8) | | |

Data are number (%) of patients, unless otherwise indicated.
CRP, C reactive protein; ESR, erythrocyte sedimentation rate; Liver disease, chronic hepatitis or liver cirrhosis; MAC-LD, Mycobacterium avium complex lung disease.

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included treatment with 2–4 drugs more frequently had cavity on HRCT, low lymphocyte count, anaemia and a high-CRP value (table 1).

**Mortality**

Death from any cause occurred in 130 (16.6%) patients over a median follow-up period of 4.3 years (range, 0.003–29.5 years). Patients died from progression of the MAC-LD (14.6%), other pulmonary diseases (31.5%) and non-pulmonary diseases (53.8%; table 1).

**Prognostic factors of all-cause mortality**

Overall cumulative 5-year and 10-year mortality rates were 12.5% and 27.4%, respectively (figure 1). Respective 5-year and 10-year all-cause mortality rates in the patients without bloody sputum were 14% and 29%, vs 5.9% and 19.9% in those with bloody sputum (p=0.018), respectively.

**Prognostic factors of MAC-LD progression mortality**

Five-year and 10-year mortality rates from MAC-LD progression were 2% and 4.8%, respectively (figure 2). Respective 5-year and 10-year mortality rates from MAC-LD progression in the patients with cavity were 8.5% and 25.1%, vs 0.8% for each in those without cavity.

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**Table 2** Treatments in the study patients

| First-line treatment regimen | Number of patients (%) | After first-line therapy |
|------------------------------|------------------------|--------------------------|
| Observation                  | 629 (80.4)             | Observation: 541 (69.2)  |
| One drug                     |                        | Some drug therapy: 88 (11.3) |
| CAM                          | 43 (5.5)               | First-line drug continued*: 29 (3.7) |
| FQ                           | 3 (0.4)                | Observation: 13 (1.7)    |
| EM                           | 1 (0.1)                | Some other drug therapy: 9 (1.2) |
| INH                          | 1 (0.1)                |                          |
| Two drugs                    |                        | First-line drugs continued*: 10 (1.3) |
| CAM+FQ                       | 18 (2.3)               | Observation: 10 (1.3)    |
| CAM+EB                       | 2 (0.3)                | Some other drug therapy: 7 (0.9) |
| CAM+RIF                      | 2 (0.3)                |                          |
| EB+RIF                       | 2 (0.3)                |                          |
| RIF+INH                      | 3 (0.4)                |                          |
| Three drugs                  |                        | First-line drugs continued*: 16 (2.0) |
| RIF+INH+EB                   | 20 (2.6)               | Observation: 21 (2.7)    |
| CAM+RIF+EB                   | 19 (2.4)               | Some other drug therapy: 10 (1.3) |
| CAM+INH+EB                   | 2 (0.3)                |                          |
| CAM+RIF+FQ                   | 2 (0.3)                |                          |
| Other combination            | 4 (0.5)                |                          |
| Four drugs                   |                        | First-line drugs continued*: 16 (2.0) |
| CAM+EB+RIF+SM               | 12 (1.5)               | Observation: 4 (0.5)     |
| CAM+EB+RIF+FQ               | 12 (1.5)               | Some other drug therapy: 9 (1.2) |
| Other combination           | 4 (0.5)                |                          |

*First-line drug(s) continued indicates that the first-line treatment regimen was continued throughout the follow-up period.

CAM, clarithromycin; EB, ethambutol; FQ, fluoroquinolone; INH, isoniazid; RIF, rifampin; SM, streptomycin.
cavity (p<0.001; figure 2). A multivariate Cox proportional hazard model showed older age, presence of cavity and therapy of 2–4 drugs to be negative prognostic factors (table 3).

Risk factors of radiographic deterioration

Interobserver agreement regarding radiographic changes was good (κ, 0.862; 95%CI, 0.733 to 0.990). In 536 patients with MAC-LD whose follow-up was more than 1 year, radiographic deterioration occurred in 221 (41.2%) patients over a median follow-up period of 5 years (range, 1–30 years). Patients with cavity more frequently had lower BMI and elevation of inflammatory markers, and were more frequently treated with a regimen of 2–4 first-line drugs (table 4). Cumulative median time-to-radiographic deterioration was 9 years, and 5-year and 10-year rates of radiographic deterioration were 39.1% and 54%, respectively (figure 3). Median time-to-radiographic deterioration and 5-year and 10-year rates of radiographic deterioration in the patients with cavity were 3 years, and 66.7% and 70.4%, versus 10 years, and 34.6% and 51.7%, in those without cavity (p<0.001; figure 3). A multivariate Cox proportional hazard model showed the presence of idiopathic pulmonary fibrosis, Hb <11.3 g/dL, CRP >1.0 mg/dL and the presence of cavity to be negative prognostic factors of radiographic deterioration (table 3).

DISCUSSION

We investigated NB MAC-LD to assess the predictors of all-cause and MAC-LD progression mortality, and radiographic deterioration. Overall, 10-year mortality rates from all causes and MAC-LD progression were 27.4% and 4.8%, respectively. Although only observation was

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### Table 3 The risk of all-cause mortality, MAC-LD progression mortality and radiographic deterioration in multivariate Cox regression models

| Variable                                      | Multivariate Cox regression Final model | Adjusted HR | 95% CI    | p Value |
|-----------------------------------------------|----------------------------------------|-------------|-----------|---------|
| All-cause mortality (n=782)                   |                                        |             |           |         |
| Male (vs female)                              |                                        | 1.958       | 1.357 to 2.823 | <0.001  |
| Age ≥70 years (vs <70 years)                  |                                        | 4.232       | 2.746 to 6.523 | <0.001  |
| Body mass index <18.5 kg/m² (vs ≥18.5 kg/m²)  |                                        | 1.725       | 1.093 to 2.723 | 0.019   |
| Some bloody sputum (vs none)                  |                                        | 0.542       | 0.542 to 0.927 | 0.025   |
| ESR ≥40 mm/h (vs <40 mm/h)                    |                                        | 1.849       | 1.140 to 2.999 | 0.013   |
| Alb <3.5 g/dL (vs ≥3.5 g/dL)                  |                                        | 3.159       | 1.708 to 5.844 | <0.001  |
| MAC-LD progression mortality (n=782)          |                                        |             |           |         |
| Age ≥70 years (vs <70 years)                  |                                        | 3.369       | 1.257 to 9.027 | 0.016   |
| Some cavity (vs none)                         |                                        | 11.911      | 4.512 to 31.444 | <0.001  |
| 2–4 drugs in first-line treatment (vs 0 or 1) |                                        | 4.135       | 1.671 to 10.235 | 0.002   |
| Radiographic progression (n=536)              |                                        |             |           |         |
| Underlying IPF (vs none)                      |                                        | 2.191       | 1.325 to 3.624 | 0.002   |
| Haemoglobin <11.3 g/dL (vs ≥11.3 g/dL)        |                                        | 1.852       | 1.265 to 2.713 | 0.002   |
| CRP ≥1.0 mg/dL (vs <1.0 mg/dL)                |                                        | 1.520       | 1.081 to 2.136 | 0.016   |
| Some cavity (vs none)                         |                                        | 1.651       | 1.181 to 2.307 | 0.003   |

Alb, albumin; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; IPF, idiopathic pulmonary fibrosis; MAC-LD, *Mycobacterium avium* complex lung disease.
the first-line treatment regim in 629 (80.4%) patients and ultimately 541 (69.2%) underwent observation only, long-term prognosis was not poor in the patients with NB MAC-LD. However, more than half of the patients had deteriorated radiographically at 10 years. Negative prognostic factors of radiographic deterioration included the presence of idiopathic pulmonary fibrosis, Hb <11.3 mg/dL, CRP >1.0 mg/dL and the presence of cavity. The presence of bloody sputum was found to be a positive prognostic factor. Compared with patients without bloody sputum, those with bloody sputum were significantly more frequently female, and had higher serum albumin and lower CRP values, which were positive prognostic factors of either all-cause mortality or radiographic deterioration.

A most important and unresolved question in MAC-LD is whether treatment must begin immediately or can be delayed. Marras and coworkers surveyed respirologists and experts from NTM disease centres of excellence. One question asked was, “In what percentage of new cases of disease do you use: intensive therapy, less-intensive therapy and no antimycobacterials?”. Respirologists answered that intensive therapy would be used in 50% of the patients and no antimycobacterials in 37.5%, whereas experts answered 79% and 10%, respectively. In a recent study, antibiotic therapy was administered to <20% of patients in the USA and about 53% of patients in Canada after being given a diagnosis of NTM or MAC-LD. Koh et al reported the outcome of 590 patients with MAC-LD. An observation period without antibiotic treatment was usually implemented. When the disease was clearly recognised as being progressive, the patients received antibiotic therapy and during the follow-up period, antibiotic therapy was initiated in 330 (55.9%) patients. In three recent reports, 32.4–61.1% of patients with NB MAC-LD were treated, whereas in the present study, 30.8%
of the patients were treated initially or in follow-up periods.

Yamazaki et al reported the natural history of 57 patients with NB MAC-LD and found that more than 40% of the patients had not deteriorated radiographically after 2 years without therapy. In the report by Kitada et al, 2 of 72 patients with NB MAC-LD died due to progression of MAC-LD, and 5-year and 10-year radiographic deterioration rates were 22.2% and 53.3%, respectively. In the present study, the 10-year mortality rate for the progression of MAC-LD was 4.8%, and 5-year and 10-year deterioration rates were 39.1% and 54.0%, respectively. Although the present study includes patients more frequently treated with observation only than those in the Kitada et al report, the prognosis and 10-year radiographic deterioration rates were very similar. However, the 5-year radiographic deterioration rate was higher in this study than in that of Kitada et al. One reason might be that patients with underlying structural lung disease were excluded in the Kitada et al study but were included in our study. Kim et al reported that 34 (50.7%) of 67 patients with NB MAC-LD, of whom 52.2% received anti-MAC treatment, had deteriorated on chest CT after a median follow-up of 80 months. This rate of deterioration was similar to our result.

What primary end points should be used to evaluate the efficacy of NB MAC-LD therapy? In the Research Committee of the British Thoracic Society trial, primary end points were death due to mycobacterial disease, failure of treatment and relapse. Since patients who die due to mycobacterial disease are so few, and relapse and reinfection occur frequently, these two primary end points might not be suited to evaluation of the efficacy of NB MAC-LD treatment. We think that time-to-radiographic deterioration could be one of the primary end points.

We found that therapy of 2–4 drugs was a negative prognostic factor of MAC-LD progression mortality. One reason might be that the patients whose first-line treatment regimens included treatment with 2–4 drugs more frequently had negative prognostic factors of either MAC-LD progression mortality or of radiographic deterioration. Kim et al reported that a significantly higher number of patients with NB MAC-LD were treated in the deteriorated group than in the non-deteriorated group. This and the Kim et al study might indicate that patients at high risk for deterioration tend to be treated.

There are several limitations in this study. First, the extent of the HRCT findings is reported to be one of the prognostic factors of MAC-LD. Since we did not evaluate these findings, we could not include them into the Cox regression analysis. Second, macrolide resistance affects the sputum conversion rate. Macrolide resistance was also not evaluated; thus, we could not verify the relation between macrolide resistance and outcome. Third, because treatment decisions were made by individual physicians, we could not assess which patients should have been treated or which patients should only have been evaluated. Finally, our conclusions are limited by this study being a single-centre review and by the retrospective nature of the analysis.

Despite these limitations, the present study clarified the following points: male sex, older age, BMI <18.5 kg/m², absence of bloody sputum, hypoalbuminaemia and ESR >40 mm/h were negative prognostic factors for all-cause mortality, whereas the presence of idiopathic pulmonary fibrosis, Hb <11.3 mg/dL, CRP >1.0 mg/dL and the presence of cavity were negative prognostic factors for radiographic deterioration of the patients with NB MAC-LD. In conclusion, as clinical trials testing the effectiveness of drug therapy in patients with NB MAC-LD are being designed and implemented, the trial patients need to be stratified according to these prognostic factors before randomisation and time-to-radiographic deterioration could be one of the primary end points.

Figure 3 Kaplan-Meier curves of the probability of no radiographic deterioration of patients with nodular/bronchiectatic Mycobacterium avium complex lung disease with or without cavity. Cumulative median time-to-radiographic deterioration was 9 years, and 5-year and 10-year radiographic deterioration rates were 39.1% and 54%, respectively. Median time-to-radiographic deterioration and 5-year and 10-year radiographic deterioration rate in the patients with cavity were 30 years, and 66.7% and 70.4%, versus 10 years, and 34.6% and 51.7%, in those without cavity, respectively (p<0.001).
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