Prognostic Value of Serum Tumor Markers in Patients With Stage III NSCLC Treated With Chemoradiotherapy

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Abstract. Background/Aim: Serum tumor markers such as carcinoembryonic antigen and cytokeratin subunit 19 fragment are generally monitored in non-small cell lung cancer (NSCLC) patients in the clinical practice. However, their clinical relevance in stage III NSCLC treated with concurrent chemoradiotherapy (CCRT) remains unclear. Herein, we examined the clinical relevance of tumor markers in those patients. Patients and Methods: We retrospectively reviewed 62 consecutive patients with stage III NSCLC who received CCRT. We examined the associations of tumor marker levels with their prognosis. Results: There was no correlation between pretreatment tumor marker levels and prognosis. Normal tumor marker levels post-CCRT were significantly associated with favorable progression-free survival (54.8 versus 14.5 months, p=0.02) and overall survival (71.7 versus 40.4 months, p=0.06) compared with high tumor marker levels post-CCRT. Conclusion: We revealed that normal tumor markers levels post-CCRT in stage III NSCLC might be a useful surrogate marker for curing those patients.

Lung cancer is the leading cause of cancer-related death worldwide (1). Non-small cell lung cancer (NSCLC) accounts for 80% of all lung cancer cases and approximately 30% of NSCLC patients present with stage III disease (2-3). Concurrent chemoradiotherapy (CCRT) is the standard of care for these patients (4-5). Despite extensive research into the treatment of NSCLC, the prognosis of patients with stage III disease remains poor, with a median survival of approximately 20 months (6-8).

Several researchers have investigated the predictive value of 18F-fluorodeoxyglucose uptake on positron emission tomography, tumor volume, and clinical tumor response in patients with stage III NSCLC treated with CCRT (9-15). However, these studies were unable to clarify the predictive value of these factors because of various heterogeneities in the tumors and among patients with stage III NSCLC.

Serum tumor biomarkers, such as carcinoembryonic antigen (CEA) and cytokeratin subunit 19 fragment (CYFRA) are generally used to evaluate NSCLC in clinical practice in Japan. However, their clinical relevance in stage III NSCLC remains unclear. Therefore, in the present study, we investigated the associations between tumor markers and clinical outcomes.

Patients and Methods

Patients. We retrospectively screened consecutive patients who had been diagnosed with stage III NSCLC at the Kurume University Hospital, Japan, between 2009 and 2014. Patients who had been diagnosed pathologically with NSCLC had received CCRT with platinum-containing chemotherapy and underwent tumor marker testing, before treatment or at CCRT completion were eligible for inclusion. The present study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Review Boards of Kurume University Hospital.

Statistical analyses. We evaluated the parameters associated with the survival of patients with stage III NSCLC who had received CCRT. We assessed tumor shrinkage according to the response evaluation criteria in solid tumours (version 1.1) (16). We analyzed the associations of pretreatment levels of serum CEA and CYFRA with progression-free survival (PFS) and overall survival (OS) using Pearson’s chi-squared test. PFS was defined from the date of initiation of first-line treatment to the date of disease progression or death from any cause. OS was measured from the initiation of the treatment or the initial diagnosis to the date of death or last follow-up. The Kaplan–Meier method was used to generate survival curves, and significant differences in the curves between the two groups

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were evaluated by the log-rank test. Multivariate regression analysis was performed using the Cox proportional hazards model. All variables with \( p \)-values <0.05 were included in the Cox model. All tests were two-sided, and differences were considered statistically significant at \( p<0.05 \). All statistical analyses were conducted using JMP version 11 (SAS Institute Inc., Cary, NC, USA).

**Results**

**Patient characteristics.** Table I lists the clinical characteristics of the 62 patients who were eligible for inclusion in the study. The median age of the patients at diagnosis was 63 (range, 43-75) years. Forty-five (73%) patients were male, and 51 (82%) had a performance status (PS) of 0. The most predominant histological type was adenocarcinoma (35 patients), followed by squamous cell carcinoma (21 patients). At the time of diagnosis, 37 (60%) and 25 (40%) patients had stage IIIA and IIIB disease, respectively. All patients received CCRT containing platinum-based agents as first-line treatment. At the time of analysis, the median follow-up duration was 45 months.

**Tumor shrinkage.** According to tumor shrinkage, 3 (5%) patients achieved a complete response and 26 (42%) a partial response. We analyzed PFS and OS between patients who achieved a complete or partial response and those with stable disease. There were no correlations with PFS or OS in these two patient groups (median PFS: 16.5 versus 20.6 months, median OS: 58.4 months versus not reached, Figure 1).

**Tumor markers.** Before treatment, the median serum level of CEA was 7.6 ng/ml (range, 1.0-220 ng/ml, normal <5.0 ng/ml), and that of CYFRA was 3.9 ng/ml (range, 0.8-47.4 ng/ml, normal <3.5 ng/ml). Figure 2 shows the correlations between the levels of pretreatment tumor markers and the clinical outcomes. There was no correlation between the pretreatment serum CEA level and the survival outcome (\( R^2<0.01 \)). Similarly, the pretreatment serum level of CYFRA was not associated with either PFS (\( R^2=0.12 \)) or OS (\( R^2=0.17 \)).

Furthermore, we examined the associations of normal versus high tumor marker levels at CCRT completion with the clinical outcome. We stratified the patients into two groups, depending on whether they had normal or high levels of the tumor markers at the time of CCRT completion. There were no differences between the groups in terms of patient characteristics such as age (\( p=0.79 \)), sex (\( p=0.78 \)), smoking status (\( p=0.40 \)), PS (\( p=0.52 \)), histology (\( p=0.72 \)), clinical stage (\( p=0.79 \)), and having received chemoradiotherapy (CRT) (\( p=0.52 \)) (Table II). Fourteen patients did not receive CRT because of adverse events (n=10), undergoing surgery (n=2), a decreased PS (n=1), or progressive disease (n=1).

Univariate analysis revealed that having normal tumor marker levels at CCRT completion was significantly associated with a favorable PFS (median 54.8 months, Figure 3A), whereas none of the other factors examined was significantly associated with PFS (Table III). Multivariate analysis demonstrated that having normal levels of the tumor markers at CCRT completion was an independent and significant predictive factor for PFS (Table III).

Univariate analysis revealed that having normal tumor marker levels at CCRT completion trended towards a favorable OS (71.7 months, Figure 3B). Multivariate analysis demonstrated that normal tumor marker levels at CCRT completion was an independent and significant predictive factor for OS (Table III).

**Discussion**

In the present study, we examined tumor markers pre- and post-CCRT in patients with stage III NSCLC and found that patients with normal levels of tumor markers post-CCRT had a better PFS and OS compared to patients with high levels. However, pretreatment tumor markers and tumor shrinkage were not associated with PFS and OS.

Tumor biomarkers are useful for evaluating cancer in clinical practice regardless of the disease stage (17-21). Several studies have reported a relationship between high levels of pretreatment tumor markers and the clinical
Figure 1. Kaplan–Meier curves for progression-free survival (A) and overall survival (B) of patients with stage III NSCLC who had tumor response.

Figure 2. Relationship between pretreatment tumor marker levels and survival.
outcome (17–20). Only one report described that a change in tumor marker levels from before treatment to 1 month after treatment using chemotherapy was significantly correlated with clinical outcome in patients with advanced NSCLC (21). Our results also indicate that normalization of tumor marker levels at CCRT completion, regardless of the pretreatment levels, is associated with better clinical outcomes in patients with stage III NSCLC.

A 5-year OS rate of 15% in stage III NSCLC patients receiving CCRT has been reported (22, 23). Akamatsu et al. suggested that the 2-year PFS rate may be a reliable surrogate marker for cure, instead of 5-year OS rate, in patients with stage III NSCLC treated with CCRT (24). In the present study, the 2-year PFS rate in patients with normal tumor marker levels was 56%, and the 5-year OS rate was 67% (Figure 3). In contrast, the respective rates in the group with high tumor marker levels were 33% and 41%. Therefore, normal levels of tumor markers at completion of CCRT may be a surrogate marker indicating successful CCRT treatment of stage III NSCLC.

Several investigators have demonstrated a significant association between the clinical tumor response and OS in patients with stage III NSCLC treated with CCRT (12–14). However, in the report by McAleer et al., Kaplan–Meier OS curves revealed that 90% of the responders died within 4 years (12), while the study by Kim et al. used an insufficient follow-up (median follow-up: 16 months) (13). Furthermore, only 28 patients were eligible for enrollment in the study by Lee et al. (14). Our study found no relationship between tumor shrinkage and PFS or OS after

Table II. Patient characteristics categorized by serum tumor marker (CEA and CYFRA) levels at completion of CCRT.

| Characteristic                  | N  | Normal | High | p-Valuea |
|--------------------------------|----|--------|------|----------|
| Age (years)                    |    |        |      |          |
| ≤63                            | 13 | 16     |      | 0.79     |
| >63                            | 12 | 17     |      |          |
| Gender                         |    |        |      |          |
| Male                           | 19 | 24     |      | 0.78     |
| Female                         | 6  | 9      |      |          |
| Smoking status                 |    |        |      | 0.40     |
| Never-smoker                   | 6  | 5      |      |          |
| Smoker                         | 19 | 28     |      |          |
| Performance status             |    |        |      | 0.52     |
| 0                              | 22 | 27     |      |          |
| 1 or 2                         | 3  | 6      |      |          |
| Histology                      |    |        |      | 0.72     |
| Adenocarcinoma                 | 14 | 20     |      |          |
| Squamous cell carcinoma        | 7  | 11     |      |          |
| Other                          | 4  | 2      |      |          |
| Stage                          |    |        |      | 0.79     |
| IIBA                           | 16 | 20     |      |          |
| IIIB                           | 9  | 13     |      |          |
| Consolidation chemotherapy     |    |        |      | 0.52     |
| Yes                            | 20 | 24     |      |          |
| No                             | 5  | 9      |      |          |

*aDetermined by Fisher’s exact test. CCRT, Concurrent chemoradiotherapy.
a median follow-up duration of 45 months. We consider that this may be because patients with stage III NSCLC have heterogeneous characteristics, such as tumor size, tumor invasive capacity, and number of lymph node metastases.

Our retrospective study had several limitations. First, the sample size was relatively small. Second, several confounding biases were potentially introduced in this non-randomized study. Further studies in larger cohorts are warranted.

In conclusion, we demonstrated that pretreatment tumor marker levels and tumor shrinkage were not associated with the prognosis of patients with stage III NSCLC treated with CCRT. Furthermore, we revealed that normal levels of tumor markers post-CCRT may be a useful surrogate marker indicating successful treatment of stage III NSCLC.

Conflicts of Interest

The Authors have no conflicts of interest to declare. No funding source was associated with this study.

Table III. Univariate and multivariate analyses of clinicopathological factors associated with PFS and OS.

| Factor                                | PFS                  | OS                      |
|---------------------------------------|----------------------|-------------------------|
|                                       | Univariate           | Multivariate            | Univariate           | Multivariate            |
|                                       | Median (months)      | p-Valuea                | p-Valuea              | HR                      | Median (months)      | p-Valuea              | p-Valuea              | HR                      |
| Age (years)                           |                      |                        |                       |                        |                        |                        |                       |                        |
| ≤63                                   | 17.7                 | 0.85                    | 0.57                  | 65.3                   | 0.99                    | 0.81                   |
| >63                                   | 18.4                 | 1.21                    | 1.11                  | 58.4                   | 1.11                    |
| Gender                                |                      |                        |                       |                        |                        |                        |                       |                        |
| Male                                  | 45                   | 17.9                    | 0.65                  | 58.4                   | 0.29                    | 0.26                   |
| Female                                | 17                   | 18.9                    | 0.85                  | 71.7                   | 1.85                    |
| Smoking                               |                      |                        |                       |                        |                        |                        |                       |                        |
| Never-smoker                          | 18                   | 19.5                    | 0.94                  | -                      | 65.3                   | 0.32                   | -                      |
| Smoker                                | 44                   | 17.2                    | -                     | NR                     | -                      | -                      |
| PS                                     |                      |                        |                       |                        |                        |                        |                       |                        |
| ≤63                                   | 51                   | 20.1                    | 0.15                  | 58.4                   | 0.78                    | 0.54                   |
| ≥63                                   | 11                   | 15.9                    | 0.59                  | NR                     | 1.45                    |
| Histology                             |                      |                        |                       |                        |                        |                        |                       |                        |
| Adeno                                 | 35                   | 21.9                    | 0.55                  | -                      | 65.3                   | 0.26                   | -                      |
| Squamous                              | 21                   | 12.0                    | -                     | 26.7                   | 1.11                    |
| Other                                 | 6                    | 26.0                    | -                     | NR                     | -                      |
| Tumor marker (CEA and CYFRA) level at CCRT completion |            |                        |                       |                        |                        |                        |                       |                        |
| Normal                                | 25                   | 54.8                    | 0.02                  | 71.7                   | 0.06                    | 0.04                   |
| High                                  | 33                   | 14.5                    | 0.44                  | 40.4                   | 0.40                    |
| CCT                                   |                      |                        |                       |                        |                        |                        |                       |                        |
| Yes                                   | 44                   | 20.6                    | 0.39                  | 65.3                   | 0.04                    | 0.15                   |
| No                                    | 14                   | 6.4                     | 0.69                  | 15.2                   | 0.48                    |

*aDetermined by log-rank test. PFS: Progression-free survival; OS: overall survival; CI: confidence interval; PS: performance status; Adeno: adenocarcinoma; Squamous: squamous cell carcinoma; CCRT: concurrent chemoradiotherapy; CCT: consolidation chemotherapy.

Authors’ Contributions

Study concept: Takaaki Tokito; Study design: Takaaki Tokito, Koichi Azuma; Data acquisition: Yoshiko Naito, Hiroki Natori; Quality control of data and algorithms: Norikazu Matsu, Takashi Kinoshita; Data analysis and interpretation: Hidenobu Ishii, Kazuhiro Yamada; Statistical analysis: Tomoaki Hoshino; Manuscript preparation: Takaaki Tokito; Manuscript editing: Koichi Azuma, Kazuhiro Yamada; Manuscript review: All authors.

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