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Complex fasciculation potentials and survival in amyotrophic lateral sclerosis
Complex fasciculation potentials and survival in amyotrophic lateral sclerosis

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HIGHLIGHTS

• Complex fasciculation potentials (FPs) in ALS are more frequently observed in muscles with normal strength or mild weakness.

• ALS patients with complex FPs have poorer survival periods than those without complex FPs.

• Wide distribution of complex FPs predicts shorter survival in ALS.

ABSTRACT

Objective: We investigated the relationship between fasciculation potentials (FPs) and survival in patients with ALS.

Methods: In 85 ALS patients, we prospectively performed needle EMG in five to seven muscles of each patient. The shape of the detected FPs was analyzed by inspection, and FPs with > 4 phases were judged as complex FPs. We analyzed the correlation between complex FPs and survival period using the Cox proportional hazard model.

Results: Complex FPs were observed in 47 patients, more frequently in the muscles with normal strength or mild weakness. The presence of complex FPs was associated with shorter survival (hazard ratio 3.055; p = 0.004). The greater the number of muscles with complex FPs, the shorter the survival and the faster the progression speed.

Conclusion: Wide distribution of complex FPs is associated with shorter survival in ALS.

Significance: Complex FPs are useful to predict prognosis of ALS patients and should be evaluated in the EMG examination.

Keywords: amyotrophic lateral sclerosis; electromyography; complex fasciculation potential;
survival prognosis

*Abbreviations:* ALS = amyotrophic lateral sclerosis; CFP = complex fasciculation potential;

fib-psw = fibrillation potential and positive sharp wave; FP = fasciculation potential; FVC =

forced vital capacity; MUP = motor unit potential; PMA = progressive muscular atrophy
1. Introduction

Fasciculations, often emerging across a wide range of body regions, are a clinical and electromyographic hallmark of amyotrophic lateral sclerosis (ALS). The Awaji criteria proposed in 2008 re-evaluated electrophysiological findings and emphasized the diagnostic significance of fasciculation potentials (FPs) in ALS (de Carvalho et al., 2008). FPs were regarded to be equivalent to fibrillation potentials and positive sharp waves (fib-psw) in terms of clinical significance. The implication is that FPs are closely related to the progressive denervation process of muscles in ALS.

The characteristic features of FP in ALS are complexity and instability. Complex FP (CFP) is defined as FP with > 4 phases, increased duration, or increased amplitude (de Carvalho et al., 2008). De Carvalho et al. proposed that simple and stable FPs arise proximally, related to axonal hyperexcitability, whereas CFPs originate in distal axonal sprouts, associated with the reinnervation process (de Carvalho and Swash, 1998; de Carvalho, 2000). Although CFP might be directly connected to the pathogenesis of ALS, its significance in disease progression and survival prognosis remains to be elucidated. Mills reported that FPs in ALS and benign fasciculation syndrome were morphologically indistinguishable, and doubted the prognostic significance of FPs (Mills, 2010). Krarup, on the other hand, recently suggested a correlation between the number of FPs and survival prognosis in ALS (Krarup, 2011). In addition, recent studies have reported apparent morphological differences of FPs between ALS and other benign disorders, contrary to Mills’s observation (de Carvalho and Swash, 2013; Simon and Kiernan, 2013). The recent report disclosed that FPs were earliest findings in ALS and changed to more complex forms with disease progression, suggesting that the complexity of FPs was closely related to morphological changes of motor unit potentials.
This report suggests a close relationship between the complexity of FPs and the mode of disease progression. Our aim of this study was to investigate the relationship between FPs and clinical features, and whether FPs predict survival prognosis in ALS.

2. Methods

2.1. Subjects

Ninety-two consecutive patients suspected of having ALS were referred to the EMG laboratories of Tokyo Metropolitan Neurological Hospital and Fukushima Medical University Hospital from January 2010 to August 2012. We excluded patients with a family history of ALS (three patients) and patients with disease duration > 10 years (four patients). Eighty-five patients with sporadic ALS were prospectively enrolled (41 men and 44 women). They fulfilled the revised El Escorial criteria for ‘definite’ (n = 12), ‘probable’ (n = 25), ‘probable-laboratory supported’ (n = 22) and ‘possible’ (n = 5) ALS at the time of EMG examination (Brooks et al., 2000). We also included patients with progressive muscular atrophy (PMA) (n = 21), since PMA has been considered to share a common pathophysiology with ALS although patients with PMA showed no upper motor neuron signs (Kim et al., 2009; Sonoo et al., 2009). All patients showed relentless progressive courses, and no other causative disorders other than ALS or PMA were found during the follow-up. There were no patients with systemic diseases such as malignancy or diabetic complications. The age of the enrolled patients was 39–88 (median 68) years at the EMG examination. Onset was defined as the time (month) when the first motor symptom related to ALS was noticed by patients. The body regions affected at onset were bulbar (n = 23), upper limb (n = 36), lower limb (n = 24),
respiratory (n = 1), and axial (n = 1).

From the patients’ history and follow-up, the second body region affected was evaluated (Fujimura-Kiyono et al., 2011). We calculated the duration from the onset to the appearance of the second region symptom. The endpoint for follow-up was defined as the time when patients died, were tracheotomized, or were placed on a ventilator permanently, since tracheostomy or initiation of artificial ventilation was considered to be equivalent to death for the study of survival prognosis in ALS. The survival period was calculated as the disease duration between the onset and endpoints, and we also calculated the duration from the time of EMG examination to the endpoints. The censored time of the study was the end of December 2012. The follow-up of seven patients was suspended because of a referral to other hospitals, and their data were treated as ‘censored at the day of the referral’.

2.2. Electromyography

All needle EMG examinations were carried out by one of the authors (T.S.), using concentric needles and Neuropack 8 (NIHON KOHDEN, Co. Ltd., Tokyo). The standard filter setting was used (10–5kHz). Five to seven muscles were examined for each patient: upper trapezius, biceps brachii, extensor carpi radialis, first dorsal interosseous, 10th thoracic paraspinal, vastus medialis, and tibialis anterior muscles. The number of muscles examined was determined by diagnostic implication. The examination was done unilaterally in a more affected side in individual patients.

For each muscle, fib-psw was explored in at least 10 different sites within a muscle. The definition of fib-psw was the same as the description in the Awaji criteria (de Carvalho et al., 2008). Only regularly firing potentials that lasted more than 3 s were accepted as fib-psw. FPs
were defined as motor unit potential-shaped potentials that fired in a highly irregular pattern (de Carvalho et al., 2008; Sonoo et al., 2009; Higashihara et al., 2012). We avoided any persistent voluntary EMG discharges, and performed observations for 60 to 90 s for each relaxed muscle to determine FPs after searching fib-psw (Mills, 2011). We discarded from the analysis spontaneous potentials that discharged only once during the observation period, since these potentials could not be completely distinguished from potentials evoked by voluntary contraction or slight needle movements. FPs were defined as having the amplitude of more than 100 µV in peak-to-peak measurement. ‘Complex’ and ‘simple’ FPs were simply defined as FPs of > 4 and ≤ 4 phases, respectively, according to the description in the Awaji criteria (de Carvalho et al., 2008). Since the morphology of FPs is variable according to the needle position in the muscle, hand manipulation of the needle was avoided during the observation period in order to make the needle be immobilized. Slight changes of the needle position might induce changes in the turns to the phases of FP waveforms and vice versa, and, therefore, we adopted the simple way of detecting complex FPs by focusing only on the phases of FPs. The size, instability, firing frequency, and the number of FPs in each muscle were not evaluated in this study. When the same muscle showed both complex and simple FPs, we judged the muscle as having CFPs. In this study, we did not take combined FPs into account.

2.3. Analysis

To investigate the relationship between FPs and muscle strength, we evaluated the MRC grading of muscle strength for the biceps brachii (elbow flexion), extensor carpi radialis (wrist extension), vastus medialis (knee extension), and tibialis anterior (ankle dorsiflexion) muscles.
To minimize the variability of results, we classified the muscle strength into three categories. ‘Normal’, ‘moderate’ and ‘severe’ strengths represent MRC grades ‘5’, ‘4’, and ‘< 3’, respectively. The relationships between muscle strength and the frequency of fib-psw, FPs, or CFPs were analyzed using Chi-square test.

For survival analysis, we first classified the patients into two subgroups according to sex (men or women), onset age (< or ≥ 65 years), onset region (bulbar or non-bulbar), percent forced vital capacity (FVC; > or ≤ 60%), and CFPs (absence or presence). We screened the survival function for each parameter using Kaplan-Meier survival analysis and log-rank test. Similarly, the progression rate to the appearance of the second region symptom was also analyzed. Then, we performed uni- or multivariate analyses for survival using the Cox proportional hazard model. Thereafter, the clinical parameters (sex, onset age, onset region, FVC, the number of patients reaching an endpoint, and survival period of patients with an endpoint) were compared between the patient groups with CFP = 0 and ≥ 1 muscle (Chi-square test for categorical variables or Mann-Whitney U test for continuous variables). P < 0.05 was considered significant. All statistical analyses were performed using JMP 9.0.0 for Macintosh.

The study was approved by the ethical committees of Tokyo Metropolitan Neurological Hospital and Fukushima Medical University Hospital, and all patients gave their informed consent for the procedure.

3. Results

The median period of the follow-up in all 85 patients was 2.25 years (IQR 1.36–3.42). During the follow-up, 39 patients reached the endpoints (death, tracheostomy, or ventilator
use). The median survival length of these 39 patients was 1.98 years (IQR 1.22–3.29). These values were compatible with standard data of ALS patients from other reports, indicating the patient population of the study was not biased.

Of the 85 patients, CFP was detected in 47 patients (55.3%) in at least one muscle. Eight patients (9.4%) showed no FPs, and 30 patients (35.3%) showed only simple FPs. There were no statistically significant correlations between the duration from onset to the examination time and the number of muscles with FPs or CFPs. There were also no significant correlations between the number of examined muscles and the number of muscles with FPs or CFPs. Figure 1 shows the relationship between muscle strength and the occurrence of fib-psw or FPs for each muscle. The occurrence of fib-psw was correlated with the severity of muscle weakness; the severely weak muscles showed the highest occurrence of fib-psw for all muscles. As for FPs, however, the muscles with ‘normal’ or ‘moderate’ strength showed higher occurrences of FPs and CFPs than those with ‘severe’ weakness. These differences were relatively constant, and the differences between fib-psw and FPs were statistically significant for all muscles (Chi-square test; Fig. 1).

Comparison of the survival curves after disease onset between patients with (n = 77) and without any FPs (n = 8) showed no difference (log-rank test, p = 0.4991). Meanwhile, there was a difference in the survival curves after onset between patients with (CFP ≥ 1; n = 47) and without CFPs (CFP = 0; n = 38) (log-rank test, p = 0.0017; Fig. 2A). When the patients were re-classified into subgroups having ≥ 2 and < 2 muscles with CFPs (n = 33 and 52, respectively), the survival curves also showed a higher level of significance (log-rank test, p < 0.0001; Fig. 2B). As for the other parameters, the log-rank test showed only a significant effect of the onset age (p = 0.011). The results of the log-rank test were the same when we
excluded the patients without FPs (n = 8) and compared the patients with only simple FPs (n = 30) to those with one or more complex FPs (n = 47) (data not shown).

Analysis for the duration from the time of EMG examination to the endpoints showed shorter survival in the patient group having ≥ 2 muscles with CFPs (log-rank test, p < 0.0090; Fig. 2D). There was a tendency toward shorter survival in the patient group with CFP ≥ 1 than that with CFP = 0, although not statistically significant (log-rank test, p = 0.1145; Fig. 2C). As for the other parameters, the log-rank test showed significant effects of the onset age and FVC (p = 0.0044 and 0.0023, respectively).

Analysis of the duration from onset to the appearance of the second region symptom indicated that patients with CFPs showed faster progression than patients without CFPs (log-rank test, p = 0.0147; Fig. 2E). A similar difference was also observed in the comparison between patient groups having < 2 and ≥ 2 muscles with CFPs (log-rank test, p < 0.0001; Fig. 2F).

Multivariate analysis of survival by the Cox proportional hazard model revealed the onset age and presence of CFP showed significant effects on survival after disease onset (p = 0.024 for the onset age, and p = 0.004 for CFP; Table 1A). Multivariate analysis of survival after EMG examination time revealed that sex, FVC, and the presence of CFP showed significant effects on survival (Table 1B).

Univariate analyses by the Cox model revealed that the number of muscles with FPs (= simple + complex) or CFPs (n = 1 to 6) showed significant effects on survival periods both after disease onset (p = 0.0085 for total FPs, and p < 0.0001 for CFPs) (Table 1C) and after EMG examination time (p = 0.0488 for total FPs, and p = 0.0019 for CFPs) (Table 1D). However, when we focused on only simple FPs, univariate analyses showed no significant
effect on survival periods either after disease onset (p = 0.1737) or after EMG examination (p = 0.0687). These results indicate that the greater the number of muscles with CFPs, the shorter the survival.

In a comparison of the clinical parameters between patient groups with CFP = 0 and ≥ 1 muscle, there were no differences in sex, onset region, onset age, and FVC. The number of patients who reached the endpoints (death, tracheostomy, or ventilator use) was 15 in the group with CFP = 0 and 24 in the group with CFP ≥ 1, and the median values of the survival period were significantly different between them (3.1 [IQR 2.1–3.6] and 1.5 [1.2–2.6] years for the groups with CFP = 0 and ≥ 1 muscle, respectively; p = 0.0017). The median values of the time to the appearance of the second region symptom were also significantly different between the groups with CFP = 0 and ≥ 1 muscle (1.3 [0.5–2.0] and 0.7 [0.3–1.1] years, respectively; p = 0.0149).

4. Discussion

This study disclosed the clinical significance of FPs in ALS. FPs were frequently observed in normal or less weak muscles in contrast to fib-psw, and CFPs showed significant effects on survival prognosis. The wide distribution of CFPs predicted shorter survival in ALS.

The complexity of FPs in ALS has recently drawn attention, especially since the release of the Awaji criteria (de Carvalho et al., 2008). The pathophysiology behind the complexity is yet to be clarified, but several pathomechanisms have been proposed: variability or slowing in axonal conduction velocity at the distal motor axons, multifocal and intermittent distal axonal firing, firing propagation within distal axonal arborization leading to temporal dispersion of muscle fiber contraction, and phase dispersion associated with reinnervation (de Carvalho,
If the firing propagation within distal axonal arborization is the main mechanism, FPs will have more complex forms when spontaneous firing sites are more distal, and when turning points of backward conduction from fasciculating points are more proximal. If the axonal membrane excitability is relatively low, and if firing signals would propagate only forward, they would induce only synchronous contraction of several muscle fibers, resulting in a simple FP morphology. In addition, incomplete reinnervation process might be important for the complexity of FPs (de Carvalho and Swash, 2013). Those mechanisms of CFPs might strongly relate to the specific pathophysiology of ALS, and therefore a prognostic significance.

Our observations apparently refute the report by Mateen et al., who reported that FP frequency in the forearm muscles was not associated with the disease duration of ALS (Mateen et al., 2008). Also in our study, however, there was no significant correlation between the number of muscles with FPs and disease duration after onset, indicating that in any stages muscle fibers could fasciculate under relentless degenerative process. Mateen et al. described that FPs had no prognostic utility in ALS (Mateen et al., 2008), but this conclusion should be further open to debate (Kraráp, 2011). They analyzed the FP frequency only from the forearm muscles using surface electrodes, and did not evaluate the complexity of FPs.

In this study, the prognostic effect of CFPs was observed also in the survival analysis after the time of EMG examination. This indicates that even if there were some variations of the EMG examination time across patients, the wide distribution of CFPs predicted a poor prognosis after the examination. Unless patients show generalized severe muscle wasting, detection of CFPs in multiple muscles would inform us of survival prognosis after the EMG examination.
diagnosis as well as after disease onset.

Axonal excitability tests have elucidated peripheral axonal hyperexcitability in ALS (Bostock et al., 1995; Kanai et al., 2006). Two kinds of axonal ion channel abnormality have been reported: increased persistent sodium currents and reduced potassium currents, both of which might increase axonal excitability and induce fasciculation (Kanai et al., 2006). Kanai et al. reported that the increase in axonal persistent sodium currents in early stage of disease was a strong predictor of shorter survival in ALS (Kanai et al., 2012). When hypothesizing that FPs arise from hyperexcitable motor axons, our results are well consistent with their report. Although Kanai et al. studied only median nerve excitability, this functional alteration must be present in generalized body regions, and the extent of the excitability abnormalities may be deeply associated with survival prognosis. Presumably, more generalized axonal hyperexcitability would produce more frequent occurrence of FPs, and resultant fast progression and poor survival.

The limitation of this study is a lack of quantitative analysis of FPs in individual muscles. The amplitude, duration, and instability of FPs should be analyzed to elucidate their clinical significance in detail. Furthermore, the morphology of MUPs should be also analyzed in relation to that of FPs. FP morphology might vary in association with changes of MUP morphology. The amplitude and phases of FPs were reported to be larger in muscles with neurogenic MUPs than in muscles with normal MUPs, and conversely in advanced stages FPs would be infrequently elicited even in the presence of highly neurogenic MUP (de Carvalho and Swash, 2013). We imagine that the effect of CFP distribution on survival in our study will be closely related to the effect of distribution of neurogenic MUPs on survival. Further study would be needed to elucidate whether the complexity and instability of MUPs in early stage
and their distribution would predict survival prognosis.

Acknowledgment

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Figure legends

Fig. 1. Frequency of the fibrillation potential and positive sharp waves (fib-psw; white columns), any fasciculation potentials (FP; light grey columns), and complex fasciculation potentials (CFP; dark grey columns) relative to muscle power in the biceps brachii (A), extensor carpi radialis (B), vastus medialis (C), and tibialis anterior (D) muscles. ‘Normal’, ‘moderate’, and ‘severe’ indicate 5, 4, and < 3 by MRC grading of muscle strength, respectively. The frequency patterns relative to the muscle strength were significantly different between fib-psw and both FP and CFP for all the muscles (Chi-square test).

Fig. 2. Comparison of the survival rate between the patients with (CFP ≥ 1; thick line) and without complex fasciculation potentials (CFP = 0; thin line) (A and C), and between the patients having ≥ 2 (CFP ≥ 2; thick line) and < 2 (CFP < 2; thin line) muscles with complex fasciculation potentials (B and D). Figures A and B indicate the survival rate after disease onset, whereas figures C and D indicate the survival rate after the time of EMG examination. Figures A, B, and D show statistically significant differences between the patient subgroups (Kaplan-Meier survival analysis and log-rank test). Figures E and F show the comparison of the progression rate to the appearance of the second region symptom between the patients with (CFP ≥ 1; thick line) and without complex fasciculation potentials (CFP = 0; thin line)
(E), and between the patients with CFP ≥ 2 (thick line) and CFP < 2 (thin line) muscles (F).

For both categorizations, there were significant differences between the patient subgroups (Kaplan-Meier survival analysis and log-rank test).
References


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### Table 1.
Analysis of survival by the Cox proportional hazard model

#### A. Multivariate analysis of survival after disease onset

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<th>Hazard ratio</th>
<th>95% CI</th>
<th>p value</th>
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<tr>
<td><strong>Sex</strong></td>
<td>male vs. female</td>
<td>2.102</td>
<td>0.991 – 4.765</td>
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<td><strong>Onset age</strong></td>
<td>lower vs. higher than 65</td>
<td>2.493</td>
<td>1.124 – 6.117</td>
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<td><strong>Onset region</strong></td>
<td>bulbar vs. non-bulbar</td>
<td>1.095</td>
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<td><strong>FVC</strong></td>
<td>higher vs. lower than 60%</td>
<td>1.594</td>
<td>0.748 – 3.409</td>
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<tr>
<td><strong>CFP</strong></td>
<td>0 vs. ≥ 1 muscle</td>
<td>3.055</td>
<td>1.417 – 7.406</td>
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#### B. Multivariate analysis of survival after EMG examination

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<td><strong>Sex</strong></td>
<td>male vs. female</td>
<td>3.168</td>
<td>1.287 – 8.689</td>
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<td><strong>Onset age</strong></td>
<td>lower vs. higher than 65</td>
<td>2.123</td>
<td>0.956 – 5.067</td>
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<td><strong>Onset region</strong></td>
<td>bulbar vs. non-bulbar</td>
<td>0.721</td>
<td>0.260 – 1.863</td>
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<td><strong>FVC</strong></td>
<td>higher vs. lower than 60%</td>
<td>6.195</td>
<td>2.441 – 16.260</td>
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<td><strong>CFP</strong></td>
<td>0 vs. ≥ 1 muscle</td>
<td>2.39</td>
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#### C. Univariate analysis of survival after disease onset

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<tr>
<td>(a) Total FP</td>
<td>per 1 muscle with any FP</td>
<td>1.310</td>
<td>1.071 – 1.607</td>
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<tr>
<td>(b) Simple FP</td>
<td>per 1 muscle with simple FP</td>
<td>0.831</td>
<td>0.621 – 1.082</td>
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<tr>
<td>(c) CFP</td>
<td>per 1 muscle with CFP</td>
<td>1.594</td>
<td>1.284 – 1.961</td>
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#### D. Univariate analysis of survival after EMG examination

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<th>p value</th>
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<tr>
<td>(a) Total FP</td>
<td>per 1 muscle with any FP</td>
<td>1.226</td>
<td>1.001 – 1.502</td>
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<tr>
<td>(b) Simple FP</td>
<td>per 1 muscle with simple FP</td>
<td>0.756</td>
<td>0.545 – 1.021</td>
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<tr>
<td>(b) CFP</td>
<td>per 1 muscle with CFP</td>
<td>1.421</td>
<td>1.145 – 1.739</td>
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**CFP**: complex fasciculation potential; **FP**: fasciculation potential; **FVC**: forced vital capacity;
(a) Biceps brachii

Fib-psw vs FP; p<0.0001
Fib-psw vs CFP; p=0.0003

(b) Extensor carpi radialis

Fib-psw vs FP; p=0.0011
Fib-psw vs CFP; p=0.0117

(c) Vastus medialis

Fib-psw vs FP; p<0.0001
Fib-psw vs CFP; p=0.0002

(d) Tibialis anterior

Fib-psw vs FP; p<0.0001
Fib-psw vs CFP; p=0.0013

- Fib-psw
- Any FPs
- Complex FPs
Figure 2

(a) Survival rate vs. Total disease duration (y)
- CFP=0 (n=38)
- CFP≥1 (n=47)
  p=0.0071

(b) Survival rate vs. Total disease duration (y)
- CFP<2 (n=52)
- CFP≥2 (n=33)
  p<0.0001

(c) Survival rate vs. Duration from EMG exam to endpoint (y)
- CFP=0 (n=38)
- CFP≥1 (n=47)
  p=0.1145

(d) Survival rate vs. Duration from EMG exam to endpoint (y)
- CFP<2 (n=52)
- CFP≥2 (n=33)
  p=0.0090

(e) Non-progression rate vs. Progression time to 2nd region (y)
- CFP=0 (n=38)
- CFP≥1 (n=47)
  p=0.0147

(f) Non-progression rate vs. Progression time to 2nd region (y)
- CFP<2 (n=52)
- CFP≥2 (n=33)
  p<0.0001