The role of cranial and thoracic EMG within diagnostic criteria for ALS

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Abstract

Introduction: The contribution of cranial and thoracic region electromyography (EMG) to diagnostic criteria for amyotrophic lateral sclerosis (ALS) has not been evaluated.

Methods: Clinical and EMG data from each craniospinal region were retrospectively assessed in 470 patients; 214 had ALS. Changes to diagnostic classification in Awaji-Shima and revised El Escorial criteria following withdrawal of cranial/thoracic EMG data were ascertained.

Results: Sensitivity for lower motor neuron involvement in ALS was highest in cervical/lumbar regions; specificity was highest in cranial/thoracic regions. Cranial EMG contributed to definite/probable Awaji-Shima categorization in 1.4% of patients. Thoracic EMG made no contribution. For revised El Escorial criteria, cranial and thoracic data reclassified 1% and 5% of patients, respectively.

Conclusion: Cranial EMG data make small contributions to both criteria, thoracic data contribute only to the revised El Escorial criteria. However, cranial and thoracic region abnormalities are specific in ALS. Consideration should be given to allowing greater diagnostic contribution from thoracic EMG.

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Introduction

Early diagnosis of amyotrophic lateral sclerosis (ALS) is important for patients, since time is a limited commodity. There is also a need for early recruitment into clinical trials of new agents while a viable pool of motor neurons still remains. To facilitate diagnosis, the El Escorial,[1] revised El Escorial,[2] and subsequent Awaji-Shima[3] criteria all combine patterns of upper motor neuron (UMN) and lower motor neuron (LMN) abnormalities derived from the cranial, cervical, thoracic, and lumbar anatomical regions into a diagnostic algorithm. The El Escorial criteria maintain a clinical emphasis on diagnosis, with electromyography (EMG) data only able to contribute towards entry into a "laboratory-supported probable" category. The more recent Awaji-Shima criteria refer to the El Escorial criteria for detection of UMN signs but allocate equal value to EMG and the clinical examination for detection of LMN signs and also allow electrophysiological fasciculation potentials to serve as evidence of active denervation. This renders the laboratory-supported category of the El Escorial criteria obsolete, and has been shown to improve overall diagnostic sensitivity without compromising specificity.[4-6]

A practical difficulty with these classification systems is that the ease of identification of signs of pathology, both through clinical and EMG examination, differs between anatomical regions. For example, in the thoracic region, the only available UMN sign is the absence of abdominal reflexes, which may be subject to a degree of modulation by higher centers not seen in limb reflexes; with training the response can be either extinguished or enhanced[7]. In addition, EMG of cranial and thoracic innervated muscles (in practice, usually the tongue and thoracic paraspinal muscles) is often more challenging than limb muscles, particularly with respect to achieving muscle relaxation. As a consequence, studies of their use vary in the reported diagnostic utility.[8-11] While previous studies have examined the distribution of EMG changes[12] and the frequency of acute and chronic

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neurogenic abnormalities in ALS,[13] the contribution of the cranial and thoracic regions to diagnostic categorization has not been evaluated systematically.

In this study, we aimed to determine whether such data (obtained in a routine clinical setting) were worthwhile, in terms of achieving an earlier diagnosis of clinically probable/definite ALS. We sought to address this issue through a large retrospective review of clinical and EMG data obtained at the time of referral to our tertiary referral ALS center. We hypothesized that cranial EMG would regularly contribute to diagnosis by current criteria, while thoracic EMG would not because of the lack of a reliable clinical UMN sign.

Methods

Study design and approval

A retrospective review of clinical and EMG data obtained through routine clinical contact in a tertiary neuromuscular center in England was performed. The study was approved by the local institutional Review Board (project number 5250). Informed consent was not required by the review board.

Subjects

The EMG database at the Department of Clinical Neurophysiology, Royal Hallamshire Hospital, Sheffield, England, was interrogated for all patients referred between 2006-2011 for assessment of possible motor neuron disease/ALS. Neurophysiological investigations were carried out by 5 experienced consultant clinical neurophysiologists as part of standard clinical care. Five hundred consecutive patients were identified, and all subjects with sufficient available clinical and EMG information were included.

Initial classification and clinical outcomes

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Clinical data were obtained from the first tertiary Neuromuscular Clinic letter; if such a letter was not available, then General Neurology Clinic findings were used. Demographic and EMG data from the first examination performed at our institution were analyzed. Clinical course and outcome were determined from case notes. In the absence of post-mortem data, ALS patients were defined by clinical diagnosis and confirmed by death or consistent, deteriorating clinical course on follow-up of 2-7 years duration. Patients were first allocated into the following diagnostic categories: ALS (defined as motor neuron disease with presence of both UMN and LMN signs), primary lateral sclerosis (UMN only; PLS), progressive muscular atrophy (LMN only; PMA), and non-motor neuron disease (non-MND).

ALS patients: clinical examination findings

The presence of UMN signs, LMN signs, combined signs, or no signs was recorded for each of 4 craniospinal regions: cranial, cervical, thoracic, and lumbar. Spasticity, clonus, hyper-reflexia, preserved reflexes in a wasted limb, spreading of reflexes outside of the stimulated territory, frontal release signs (e.g. positive snouting reflex), pyramidal pattern weakness and/or extensor plantar responses were considered UMN signs. Flaccidity, fasciculations, wasting, and/or areflexia were considered LMN signs. For each region examined, findings were recorded as present, absent, or not documented. This allowed "clinical only" diagnostic categorization.

ALS patients: EMG examination findings

The presence of fibrillation potentials, positive sharp waves and/or fasciculation potentials (the latter only for Awaji-Shima criteria assessment)[3] were considered evidence of active denervation and were recorded for each of the 4 craniospinal regions. Reinnervation changes were defined as any of the following: long duration motor unit potentials (MUPs), high amplitude MUPs, increased

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polyphasia, reduced recruitment pattern, instability of MUPs, and/or jiggle. Judgements on the presence/absence of such findings were made in line with standard convention.[14] Regions were classified as abnormal according to standard electrophysiological diagnostic criteria[3,2,15]. The muscles examined, number of areas sampled in each muscle, time spent sampling at each insertion and quantification were at the discretion of the investigating consultant neurophysiologist. Paraspinal muscle data were taken only from thoracic region examinations. All data presented from the cranial region evaluation were from the tongue.

ALS patients: sensitivity of clinical and EMG examinations by body region

In this study, as in routine clinical practice, no "gold standard" to confirm the presence or absence of denervation in patients was available. The percentage of ALS patients with clinical LMN signs in each craniospinal region was reported as "sensitivity", accepting the limitations of the term in this context; not all ALS patients necessarily have denervation in all anatomical segments at the time of diagnosis. This nomenclature is consistent with previous studies.[15]

The percentage of ALS patients with EMG findings of both active and chronic denervation satisfying Awaji-Shima criteria was reported for each craniospinal region in the same manner.

Specificity of EMG examination by body region

The percentage of patients with EMG findings of both active and chronic denervation satisfying Awaji-Shima criteria in the non-MND group was calculated for each craniospinal region, subtracted from 100% and designated estimates of EMG "specificity".

ALS patients: diagnosis by Awaji-Shima criteria

The percentage of ALS patients fulfilling definite/probable diagnostic criteria solely on clinical grounds was reported.

The percentage of ALS patients fulfilling definite/probable diagnostic criteria after pooling clinical and electrophysiological data was reported.

ALS patients: diagnosis by revised El Escorial criteria

The percentage of ALS patients fulfilling the different classes of the El Escorial diagnostic criteria was reported. EMG data in this analysis did not include fasciculation potentials as evidence for denervation[2].

ALS patients: concordance of clinical and Awaji-Shima EMG examinations

Concordance of clinical and EMG findings in ALS patients was examined for each craniospinal region. For each patient and each region, concordance was defined as any of the following: i) presence of clinical LMN signs (no clinical UMN signs) and EMG changes satisfying Awaji-Shima criteria ("positive EMG"), i.e. both clinical and EMG evidence of LMN involvement; ii) clinical mixed UMN/LMN signs and positive EMG, i.e. both clinical and EMG evidence of LMN involvement; iii) normal clinical examination and Awaji-Shima EMG criteria not fulfilled ("negative EMG"), i.e. neither clinical nor EMG evidence of LMN involvement; iv) clinical UMN signs only and negative EMG, i.e. neither clinical nor EMG evidence of LMN involvement. Discordant findings were allocated to the following 3 categories: i) clinical LMN signs but negative EMG; ii) normal clinical examination but positive EMG; or iii) clinical UMN signs only but positive EMG.

ALS patients: contribution of cranial and thoracic EMG to diagnosis

The relative contribution of cranial and thoracic EMG was assessed by removing the relevant EMG data, each in turn, from the dataset, reassessing the percentage of patients with ALS classified as having definite/probable ALS by Awaji-Shima criteria, and reporting the difference. This analysis was then repeated applying the revised El Escorial criteria and reassessing laboratory-supported probable diagnostic categorization.

ALS patients: counting cranial or thoracic EMG changes alone towards Awaji-Shima diagnostic criteria

Following our initial results, 2 additional *post-hoc* analyses were performed. The percentage of patients with definite/probable ALS by Awaji-Shima criteria was re-estimated, this time allowing EMG changes of both active and chronic denervation to contribute alone *without the necessity for associated clinical UMN signs.* This was performed for the cranial and thoracic regions, each in turn.

Results

Subjects

From the initial 500 patients, 470 had sufficient clinical and EMG data available for inclusion. Case notes were unobtainable for the remainder.

Initial classification and clinical outcomes

Of the 470 patients, 214 were diagnosed with ALS and followed a consistent clinical course. Of the 214 patients, 76% had died of ALS by the time of case notes review. A further 10% were alive and following a deteriorating course consistent with ALS. The remaining 14% were following a

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deteriorating course consistent with ALS at last assessment, and the diagnosis appeared secure, but did not undergo long-term follow-up care at our institution. The proportion of patients allocated to the ALS, PLS, PMA, and non-MND groups, together with relevant demographic data are reported in Figure 1a. Alternative diagnoses made in the non-MND group are reported in Figure 1b.

ALS patients: sensitivity of clinical and EMG examinations by body region

Sensitivity estimates for clinical and EMG examinations in each craniospinal region in the ALS group are reported in Table 1.

Specificity of EMG examination by body region

Specificity estimates for EMG examination in each craniospinal region, derived from the non-MND group, are reported in Table 2.

ALS patients: diagnosis by Awaji-Shima criteria

The percentage of patients in the ALS group fulfilling each diagnostic category with and without EMG data is illustrated in Figure 2. Overall, the percentage of patients diagnosable with definite/probable ALS at presentation increased from 54.2% to 70.1% by adding EMG to clinical data.

ALS patients: concordance of clinical and Awaji-Shima EMG examinations

Concordance of clinical and EMG examination findings in the ALS group is reported in Figure 3. Concordance was generally high in the cervical and lumbar regions. There were important differences in the sensitivity of clinical and EMG assessment in the cranial and thoracic regions.

ALS patients: contribution of cranial and thoracic EMG to diagnosis: Awaji-Shima

Using Awaji-Shima criteria following withdrawal of cranial EMG data, 1.4% of patients were reallocated from probable/definite ALS to lower diagnostic categories. On withdrawal of thoracic EMG data, no patient changed diagnostic category. The detail of this analysis, summarizing shifts across each diagnostic category is shown in figure 4a.

ALS patients: counting cranial or thoracic EMG changes alone for Awaji-Shima criteria

In the thoracic region, eschewing clinical data and instead allowing only EMG data to count towards diagnostic criteria would result in re-categorization with greater confidence in 39% of patients who underwent thoracic EMG (67 of 170; figure 4b). In 28 of these 170 patients (16.5%), this maneuver led to reclassification into the probable/definite diagnostic categories. This compares to the contribution of thoracic EMG by current Awaji-Shima criteria of zero.

In the cranial region, eschewing clinical data and instead allowing only EMG data to count towards diagnostic criteria resulted in re-categorization with greater confidence in 4% of patients who underwent cranial EMG (7 of 183). In 2 of these 183 patients (1.1%), this maneuver led to reclassification into the probable/definite categories. This percentage would be added to the contribution of cranial EMG by current Awaji-Shima criteria of 1.4%.

Using the same EMG-only criteria for the non-MND cohort, 4/91 (4.4%) of patients examined with thoracic EMG had false positive changes fulfilling Awaji-Shima criteria. In 2 of these patients (2.2% of the tested cohort; figure 4c), these changes resulted in erroneous re-categorization as

probable/definite ALS. However, in both patients, additional clinical and imaging findings facilitated the final diagnoses of multi-level radiculopathy and camptocormia of uncertain etiology.

In the non-MND cohort, 3/137 (2.2%) patients examined with cranial EMG had false positive changes fulfilling Awaji-Shima criteria. In 1 patient (0.7% of the tested cohort), these changes resulted in erroneous re-categorization as probable/definite ALS (figure 4c). The final diagnosis in this patient, who had a history of rheumatoid arthritis, remained unclear, but did not appear consistent with ALS.

ALS patients: contribution of cranial and thoracic EMG to diagnosis: revised El Escorial

Diagnostic categorization of the ALS patients by revised El Escorial criteria is shown in figure 5. By these criteria, EMG data can only contribute to classification in the "laboratory-supported" category. Cranial and thoracic EMG data resulted in a shift from possible to laboratory-supported classification in 1% and 5% of patients, respectively.

Discussion

The key finding from this study is that neurophysiological examination of the thoracic region did not contribute to the Awaji-Shima classification of a single ALS patient in our large cohort. If the revised El Escorial criteria were used, a small number of patients moved from the possible into the "laboratory supported" classification as a result of thoracic EMG data. Cranial EMG data changed diagnostic classification for a small number of patients in both criteria. Thus, the most specific craniospinal segments in the EMG examination appear to make only a modest impact on the diagnostic stratification of patients.

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The patients in our cohort seem to be representative of the general MND population. PLS and PMA patients represented 2% and 6% of our MND patient population, respectively, which is similar to previous reports [16,17]. The percentage of patients with clinically probable/definite disease and the improvements in diagnostic sensitivity achieved by adding EMG to clinical data are comparable with previous studies [4,18]. Most of the increase in diagnostic confidence by the Awaji-Shima classification was derived from EMG examination of the limbs, perhaps because limb-onset ALS is the most common form of disease presentation,[19] or because clinical detection of UMN-only pathology together with EMG-only detection of LMN pathology occurs most frequently in the limbs (figure 3). Although cranial and thoracic EMG abnormalities were highly specific for ALS, these examinations rarely increased the certainty of diagnostic classification, which may in part be due to difficulties in objective clinical assessment of these regions.

The difficulty of clinically assessing the thoracic region is well recognized by clinicians but not acknowledged by any of the diagnostic criteria. Identification of UMN pathology in the thoracic region relies on the absence of abdominal reflexes, which some clinicians consider unreliable and have been reported by some authorities to be absent in up to 15% of healthy individuals.[20] There are some fundamental differences between the abdominal reflexes and the limb stretch reflexes; as an UMN sign it is notable by its absence, and previous work has demonstrated that the response can be altered with conditioning stimuli , a phenomenon not seen in limb reflexes[7], potentially complicating interpretation. There are few studies on the sensitivity and specificity of this clinical sign in ALS. One such study reported absent abdominal reflexes in only 5% of prospectively recruited ALS patients[21]. To our knowledge specificity has not been studied. Additionally, fasciculations may also be difficult to appreciate clinically in thoracic muscles and would appear to be identified less often by clinicians than in the other regions.

Such limitations, together with the specificity of thoracic EMG abnormalities, heighten the importance of EMG in this region. Previous data on the utility of thoracic EMG in diagnosis of ALS are conflicting. While limb muscles may demonstrate denervation changes more frequently than their thoracic counterparts,[22] frequent detection of abnormalities in thoracic muscles has been reported in small cohorts.[8] Thoracic EMG has been proposed as being useful in differentiating ALS from other motor syndromes.[11] While there is documentation of spontaneous activity in the cervical[23,24] and lumbar[25] regions in healthy subjects, little has been reported for thoracic paraspinal muscles. A study of paraspinal motor units across all three spinal regions found spontaneous activity in under 1% of paraspinal levels examined, although the levels at which these observations were made was not explicitly stated[26]. Our data, derived from ALS and non-MND cohorts of very similar demographics, suggest that thoracic EMG identifies subclinical LMN pathology in a large proportion of ALS patients and only rarely in non-MND cases. We conclude that thoracic EMG data have real clinical value as a distinguishing feature between ALS and other neuromuscular conditions.

As abdominal reflexes appear to be considered non-specific and were not assessed by the clinicians in this study then, by Awaji-Shima conditions, there is only one scenario in which thoracic EMG could potentially increase diagnostic categorization, by identifying subclinical LMN signs below clinical UMN signs. In this instance thoracic EMG abnormalities could alter categorization from "does not meet criteria" to "possible ALS". Such a scenario did not occur in any of our 470 patients; there was always sufficient clinical or electrophysiological evidence of denervation in other regions to result in categorization with higher certainty. Using the revised El Escorial standards, thoracic EMG made a small diagnostic contribution by revealing LMN pathology not identified on clinical grounds alone, which contributed to recategorization of a small number of patients from possible to laboratory-supported. These observations may help explain the findings of a recent meta-analysis which found

that the Awaji-Shima criteria downgraded a minority of patients when compared directly against the revised El Escorial guidelines due to the requirement for UMN signs in 2 regions[6].

In our analysis, we explored a new approach to improve the utility of thoracic EMG by altering the Awaji-Shima thoracic region criteria to give the presence of EMG changes alone equal weighting to mixed UMN/LMN signs in the other 3 body regions. We recognize that this proposal is imperfect. In our analysis, sensitivity to categorize as definite/probable ALS increased by 16.5%, however, a small number of non-MND cases fell into higher diagnostic categories. In these cases, additional clinical and/or imaging features helped avoid misdiagnosis, emphasising that ALS remains a clinical diagnosis. Further work is required to determine the reproducibility of our results in other centers and also to determine whether thoracic UMN involvement can be demonstrated by other means in order to enable thoracic region EMG to make a significant diagnostic contribution by current criteria. By contrast, considering cranial EMG data alone added little diagnostic sensitivity. This is most likely due to the availability of reliable clinical UMN signs and also because of the discordance identified in clinical and electrophysiological examination in this region.

In our dataset LMN abnormalities in the cranial region were more frequently identified clinically than with EMG. As our cranial region EMG data were obtained through examination of the tongue, this may relate to technical difficulties, such as the difficulty in achieving tongue relaxation. Reported detection rates for tongue EMG abnormalities in ALS vary,[27,9,10] and such observations may depend upon the number/location of needle insertion sites. Conversely, clinical examination of the tongue may be prone to over-diagnosis of fasciculations, again due to incomplete muscle relaxation. A limitation of this study is that we are unable to determine which of these potential explanations was responsible for the discordance, as we lacked a "gold standard" for presence of denervation. From a

practical perspective, we conclude that clinical examination of the cranial region appears to offer sensitivity, and EMG adds value in specificity.

The retrospective and observational nature of our study has several limitations. For example, while virtually all patients had a clinical assessment and cervical/lumbar EMG, cranial and thoracic EMG were performed in only 86% and 79% of ALS patients, respectively (Table 1). This could have biased the estimated frequencies of cranial and thoracic EMG abnormalities. In addition, the study did not involve a standardized clinical or EMG protocol. This meant that EMG data were taken from different muscles, with different numbers of sites sampled, and potentially different durations of sampling. We cannot exclude the possibility that such inter-operator differences could influence the reported frequency of spontaneous activity[9]. We also did not assess if EMG was undertaken in clinically normal/ abnormal muscles; however, a comparison of this nature is already available[13]. Instead, our analysis was concerned with the value of findings in different craniospinal regions. While the lack of a protocol-driven assessment of the type associated with prospective research studies must be taken into account when interpreting the data, we consider our findings more representative of routine practice, and thus they are especially valid to the everyday clinical setting.

In summary, our data indicate that cranial and thoracic EMG abnormalities are highly specific in ALS. However, they rarely contribute to increased diagnostic categorization using established criteria in a routine clinical setting. In particular, thoracic EMG appears to be restricted to improving diagnostic confidence outside of the Awaji-Shima criteria. In the future, new technologies may facilitate use of EMG data; for example, assessment of UMN involvement through threshold tracking transcranial magnetic stimulation[28] could improve the diagnostic contribution of the thoracic region. In the meantime, in order to permit use of thoracic EMG abnormalities there are 2 options: either pay close attention to the abdominal reflexes (accepting that specificity is unknown) or, alternatively,

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allow thoracic EMG data equivalence with combined UMN/LMN signs within diagnostic criteria until

more effective means of identifying thoracic UMN pathology become available.

Acknowledgements

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Figure legends

Figure 1. Subject categorization by diagnosis. a) Demographic profile of each patient group. b) Breakdown of the alternative diagnoses in the non-MND group.

Figure 2. Awaji-Shima diagnostic category at time of presentation.

The percentage of ALS patients in each Awaji-Shima diagnostic category at presentation, taking into account only clinical data (left hand columns, black) and following pooling of both clinical and EMG data (right hand columns, grey).

Figure 3. Concordance between clinical and Awaji-Shima electrophysiological examination findings in the ALS group. a) Table of all concordance data. Concordance was generally high in the cervical and lumbar regions. There were larger differences in the sensitivity of clinical and EMG assessment in the cranial and thoracic regions. Discordant data characterized by clinical UMN signs only (i.e without clinical LMN signs) but positive EMG were responsible for the observed increase in diagnostic yield compared to clinical examination alone, by Awaji-Shima criteria (see Figure 2). b) Graph of differences in concordance between clinical and EMG assessment, in terms of sensitivity to detect LMN pathology. EMG appeared superior to clinical examination in the thoracic region, whereas clinical examination appeared superior to EMG examination in the cranial region.

Figure 4. Effects of altering the contribution of cranial and thoracic EMG in the Awaji-Shima system.

a) Percentage of ALS patients at the time of diagnosis allocated to different Awaji-Shima categories (black columns). Removing cranial EMG from the criteria reduced a small number of patients in the probable and definite groups into lower categories (white columns). Removing thoracic EMG data had no effect on categorization in any patient (grey columns). b). Removing clinical data and allowing EMG data alone to count toward categorization in the cranial region (black columns) or thoracic

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region (grey columns) improved diagnostic confidence, most notably for the thoracic EMG group (left columns). A proportion of these patients now entered the definite/probable categories (right columns). c). Applying EMG-only diagnostic paradigms to non-MND patients resulted in a small number of false positive placements into probable/definite categories. The black column indicates the number of additional false positives incurred by allowing cranial EMG data alone and the grey column thoracic EMG data alone.

Figure 5. Contribution of thoracic and cranial EMG data to revised El Escorial classification.

a) Diagnostic classification by revised El Escorial criteria in ALS patients. b) The percentage of patients moving from clinically possible to laboratory-supported categories as a result of thoracic (left column) and cranial region (right column) EMG data.

Abbreviations

Electromyography – EMG

Motor neuron disease - MND

Amyotrophic lateral sclerosis – ALS

Upper motor neuron – UMN

Lower motor neuron – LMN

Motor unit potentials – MUPs

Primary lateral sclerosis – PLS

Progressive muscular atrophy - PMA

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Table 1. Sensitivity estimates for clinical and EMG examinations in the ALS group, by craniospinal region (n=214).

Body region	% patients with clinical LMN signs	% patients with positive EMG fulfilling Awaji-Shima criteria	Number of patients with both clinical and EMG data available
Cranial	49.8	24.6	183
Cervical	84.6	83.2	214
Thoracic	4.7	51.8	170
Lumbar	67.6	77.0	213

Table 2. Specificity estimates for EMG examination in the non-MND group, by craniospinal region (n=238).

Body region	Specificity of EMG changes fulfilling Awaji-Shima criteria (%)	Number examined
Cranial	97.8	137
Cervical	89.2	238
Thoracic	95.6	91
Lumbar	81.0	226