

THE PALLIATION OF AMYOTROPHIC LATERAL SCLEROSIS

Objectives

1. Review the clinical features, epidemiology, pathophysiology, and prognostic factors associated with ALS.
2. Discuss the management of ALS throughout disease progression.
3. Consider the end-of-life care for the ALS patient.

Amyotrophic Lateral Sclerosis

- Landmark series of lectures by Jean-Martin Charcot in Paris in 1874
 - ▣ 20 clinical cases
 - ▣ 5 autopsies
- Clinical observations:
 - ▣ Atrophic muscular weakness (amyotrophy)
 - ▣ spasticity
- Pathological findings:
 - ▣ Hardening of the lateral columns of the spinal cord (lateral sclerosis)
 - ▣ Lesions of the anterior horn

Amyotrophic Lateral Sclerosis (ALS)

- Neurological deterioration involving the corticospinal tract, brainstem, and anterior horn cells
 - ▣ Leads to limb paralysis, dysarthria, dysphagia, and respiratory failure
- Median survival of 3 years
 - ▣ Up to 10% of patients survive for more than 8 years
 - ▣ With mechanical ventilation, survival can be 15 years or greater

ALS: Clinical Features

- Disease phenotype often is classified by site of onset:
 - ▣ Limb symptoms: 65%
 - ▣ Bulbar dysfunction: 30%
 - ▣ Respiratory: 5%
- Extraocular and sphincter muscles spared
- Sensory neurons intact

ALS and Related Phenotypes

Table 1 | ALS and related phenotypes

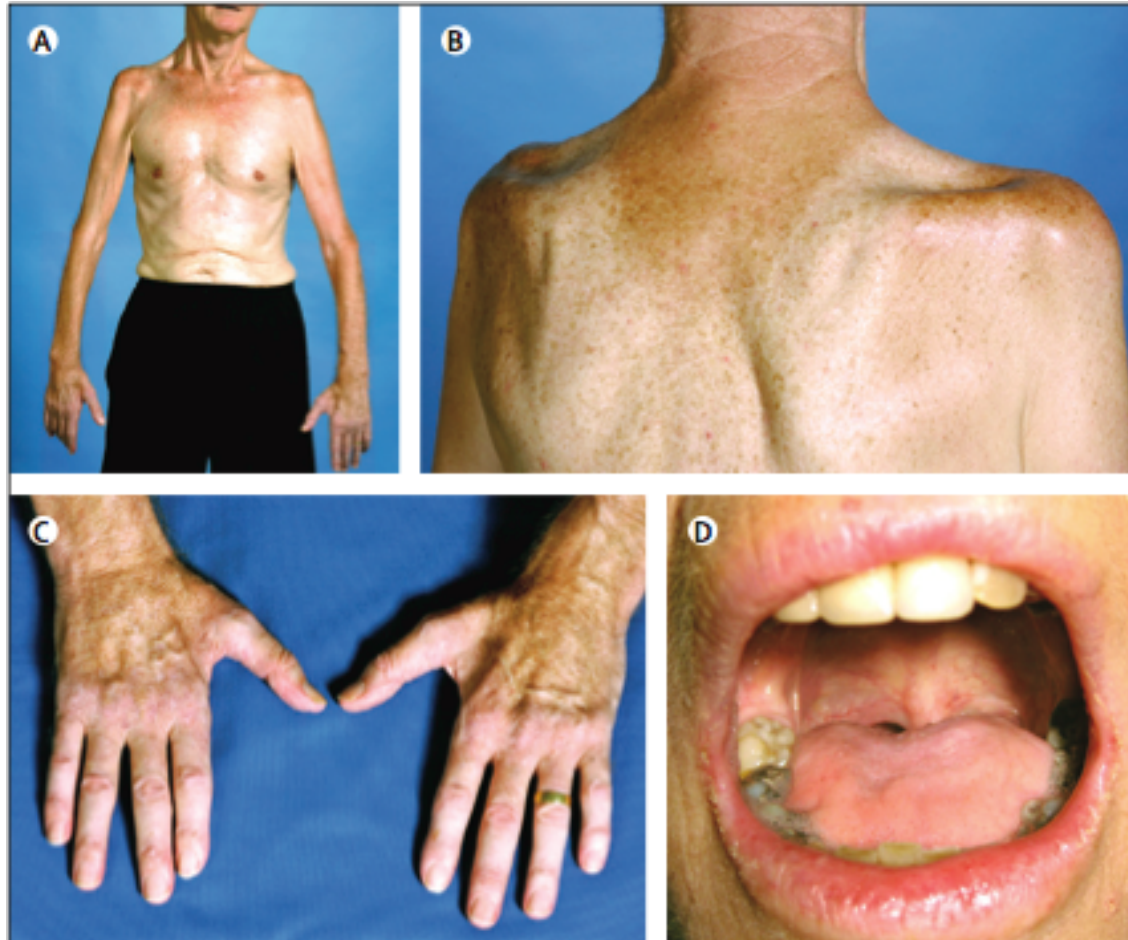
Disease	Clinical features	Comments	Median survival
ALS	Multiple spinal segments affected with both upper and lower motor neuron signs	Most common adult-onset form of motor neuron disease	3–5 years
Primary lateral sclerosis	Upper motor neuron signs only	Many patients eventually develop clinical or electrophysiological signs of lower motor neuron involvement; ALS develops in up to 77% of patients within 3–4 years	≥20 years for patients who do not progress to ALS
Progressive muscular atrophy	Lower motor neuron signs only	Variable evolution to ALS	Typically 5 years, but a subset survive for ≥20 years
Progressive bulbar palsy	Speech and swallowing initially affected, owing to lower motor neuron involvement of cranial nerves IX, X and XII	Symptoms include dysarthria, dysphagia and dysphonia; aspiration pneumonia is usually the cause of death	2–3 years

Abbreviation: ALS, amyotrophic lateral sclerosis.

Table 1 Clinical manifestations of ALS

Bulbar	Upper motor neuron	Lower motor neuron
● Dysphagia ● Dysarthria ● Sialorrhea ● Tongue atrophy ● Tongue fasciculation	● Hyperreflexia ● Spasticity ● Babinski signs ● Jaw jerk ● Snout reflexes ● Spread of reflexes ● Incoordination ● Weakness	● Weakness ● Muscle atrophy ● Fasciculations

ALS: Clinical Features



ALS: Associated Cognitive Dysfunction

- Frequent feature of ALS
- Frontotemporal dementia (FTD) occurs in up to 15%
 - ▣ Personality change
 - ▣ Irritability
 - ▣ Poor insight
 - ▣ Pervasive deficits on frontal executive tests
- Mild form of executive impairment in approximately 20%
 - ▣ Impaired judgement, impulsivity
- Cognitive or behavioural changes may precede or follow motor symptoms
- No definitive screening test

ALS: Epidemiology

- Incidence: 2-3 people per 100 000
- Caucasians more frequently affected than other ethnic groups
- Men more than women (1.2-1.5:1)
- Risk peaks between ages of 50-75 years, then declines
- Not increasing
- Both sporadic and inherited forms of the disease

ALS: Familial Form

- 90% of ALS is sporadic
- 5-10% inherited
- 13 genes and loci identified:

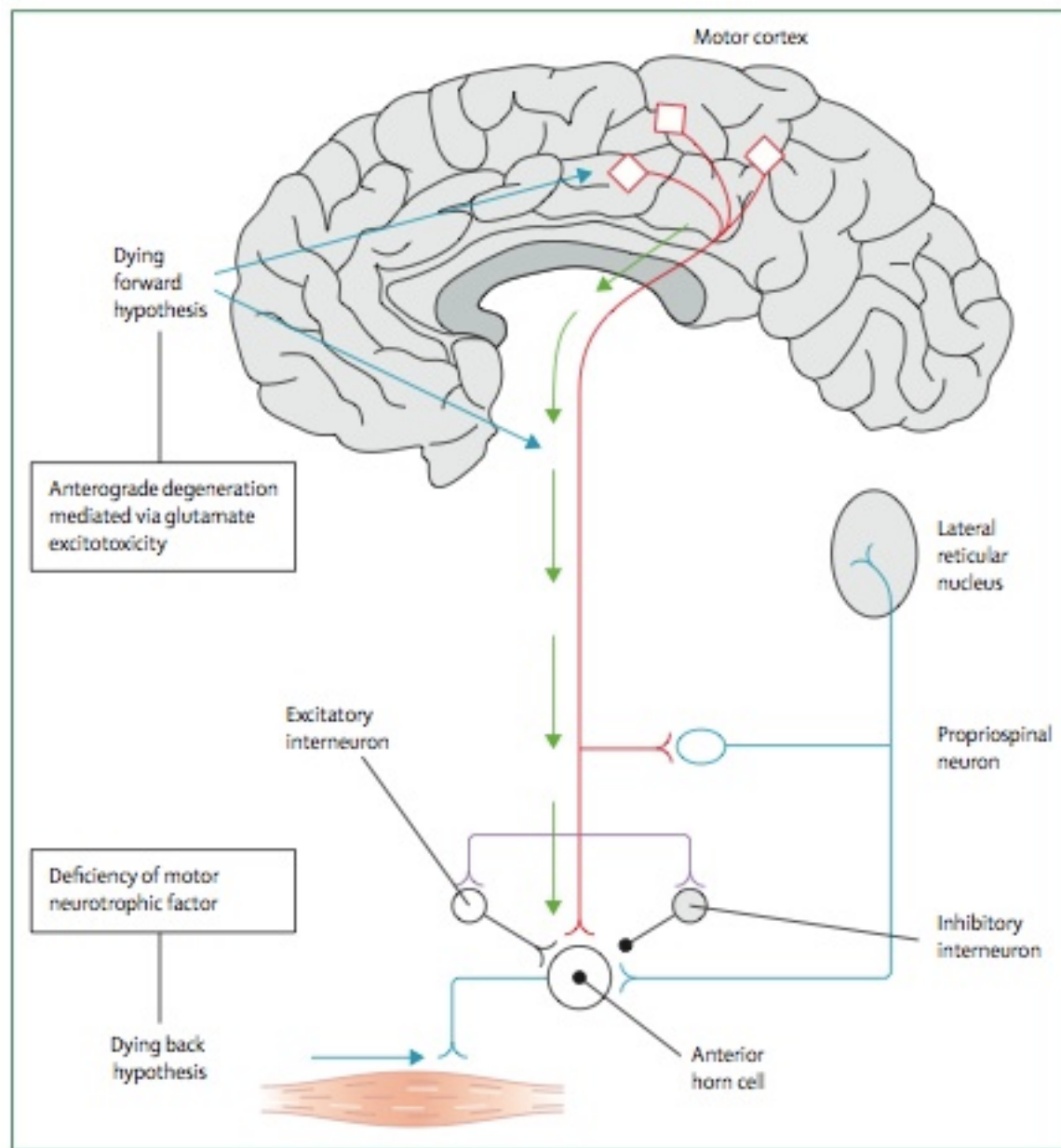
GENE	Percentage of Familial ALS
<i>SOD1</i>	20%
<i>TARDP</i>	5-10%
<i>FUS</i>	5%
<i>OPTN</i>	?
<i>ANG</i>	1%

ALS: Epidemiology

- Geographical disease clusters identified:
 - ▣ Chamorro tribe of Guam (1945)
 - ▣ Honshu Island, Japan
- Occupational clusters identified:
 - ▣ Italian soccer players
 - ▣ Military service
- Possible environmental factors:
 - ▣ Smoking
 - ▣ Pesticides
 - ▣ Lead
 - ▣ Organic toxins
 - ▣ Electromagnetic radiation

ALS: Etiology

- Currently unknown
- Possible mechanisms:
 - ▣ Mitochondrial dysfunction
 - ▣ Protein aggregation
 - ▣ Free radical generation
 - ▣ Excitotoxicity
 - ▣ Inflammation and apoptosis
- Multifactorial → contributions from multiple genes and environmental exposures



Box 1 | Differential diagnoses of ALS**Hereditary conditions**

- Spinobulbar muscular atrophy (Kennedy disease)
- Hereditary spastic paraparesis
- Acid maltase deficiency
- Facioscapulohumeral muscular dystrophy
- Adrenomyeloneuropathy
- Huntington disease
- Hexosaminidase deficiency

Metabolic conditions and toxic effects

- Hyperthyroidism
- Hyperparathyroidism
- Heavy metal intoxication
- Lathyrism
- Organophosphate toxic effects

Immune and/or inflammatory conditions

- Multifocal motor neuropathy with conduction block
- Chronic inflammatory demyelinating polyneuropathy
- Myasthenia gravis
- Inclusion body myositis
- Polymyositis
- Multiple sclerosis
- Paraneoplastic disorders

Structural disorders

- Cervical spondylotic myelopathy
- Syringomyelia or syringobulbia
- Postirradiation myelopathy and/or plexopathy
- Tumor
- Cerebrovascular disease

Other neurodegenerative diseases

- Corticobasal degeneration
- Multiple system atrophy
- Progressive supranuclear palsy
- Parkinson disease
- Huntington disease

Other motor neuron diseases

- Primary lateral sclerosis
- Progressive muscular atrophy
- Spinal muscular atrophy
- Post-polio spinal muscle atrophy
- Benign fasciculation syndrome
- Hirayama disease

Abbreviation: ALS, amyotrophic lateral sclerosis.

ALS: Diagnosis

- Up to 14 months from onset of symptoms until diagnosis
- Based primarily on clinical exam
- No definitive diagnostic test → may involve:
 - ▣ Laboratory testing
 - ▣ Electromyography (fasciculation, denervation discharges, polyphasic units)
 - ▣ Genetic testing
 - ▣ Neuroimaging (MRI)
- El Escorial criteria in 1994 → multiple revisions
- Definite diagnosis requires:
 - ▣ LMN degeneration on clinical, electrophysiological, or neuropathological exam
 - ▣ UMN degeneration on clinical exam
 - ▣ Progression of motor syndrome within a region or to other regions
 - ▣ Absence of evidence of other disease processes that may explain the symptoms

ALS Treatment: Riluzole

- Only drug approved by the FDA
- First developed as an antiepileptic drug
- Inhibit the synaptic release of glutamate, but mechanism in ALS is unknown
- Common side effects: fatigue, somnolence, nausea, diarrhea, dizziness
- Miller, R.G., *et al.* 2012 Cochrane Database of Systematic Review, Issue 3:
 - ▣ 4 RCTs involving 1477 ALS patients
 - ▣ 100 mg daily: median survival benefit of 2-3 months
 - ▣ Reasonably safe, very modest effect, expensive

ALS: Prognostic Factors

- Age
- Site of disease onset
- Type of disease
- Diagnostic delay
- Psychological well-being
- Marital status
- Presence of FTD
- Low BMI and weight loss
- Interdisciplinary care
- * lower predicted forced vital capacity (FVC)



“The palliation of ALS begins with breaking the news and ends only at the end of life.”

McCluskey, L. 2007 NeuroRehabilitation 22: 463-472

ALS: Practice Guidelines

- Published by the American Academy of Neurology (AAN) and European ALS Consortium (EALSC)
- Evidence-based guidelines → mostly level B and C evidence (small numbers, lack of RCTs)
 - ▣ Expert consensus
- Recommendations:
 - ▣ Delivery of diagnosis
 - ▣ Use of multidisciplinary care team
 - ▣ Use of riluzole
 - ▣ Specific symptom management
 - ▣ End-of-life care

ALS: Multidisciplinary Care Team

- Neurologist
- Specialized nurse
- Physical therapist
- Occupational therapist
- Respiriologist
- Respiratory therapist
- Speech pathologist
- Gastroenterologist
- Dietician
- Social worker
- Psychologist
- Family physician
- Palliative Medicine physician

ALS: Symptom Management

- Sialorrhea: socially disabling, impaired handling of secretions
 - ▣ Medications: antimuscarinic agents, TCA
 - ▣ Home suction device
 - ▣ Botulinum toxin, radiotherapy
- Bronchial secretions:
 - ▣ Mucolytics
 - ▣ Manual assisted cough
 - ▣ Suction, insufflator-exsufflator
- Pseudobulbar emotional lability: pathological weeping/laughing/yawning, occurs in 20-50%, not a mood disorder (brain lesion)
 - ▣ Antidepressants, dextromethorphan/quinidine

ALS: Symptom Management

- Cramps:
 - ▣ Massage, PT, exercise, hydrotherapy
 - ▣ Medications: quinine, anticonvulsants, benzodiazepenes → efficacy in ALS?
- Spasticity:
 - ▣ PT, hydrotherapy, ultrasound, TENS
 - ▣ Medications: baclofen, benzodiazepenes, dantrolene, tizanidine, anticonvulsants → Efficacy in ALS?
- Depression/anxiety/insomnia: occur frequently at all stages of disease
 - ▣ Medications: SSRIs, TCAs, benzodiazepines, zopiclone, Benadryl

ALS: Symptom Management

- DVT prophylaxis: increased risk in paralysis, but incidence in ALS is unknown
 - ▣ Insufficient evidence to recommend prophylaxis
- Pain: occurs frequently (up to 80%), may involve neuropathic component, typically increases with disease progression
 - ▣ Medications: according to WHO analgesic ladder
 - ▣ Brettschneider, J. *et al.* 2010 Cochrane Database of Systematic Reviews Issue 11:
 - No RCTs on drug therapy for pain in ALS

ALS: Management of Nutrition

- Functional consequences of bulbar symptoms: choking, aspiration, weight loss, dehydration
- Hypermetabolic state in 50-60% of patients → independent of increased WOB, ? Mitochondrial dysfunction
- Social impact
- Interventions:
 - ▣ Texture modification
 - ▣ Nutritional supplements
 - ▣ Modified feeding aids
 - ▣ Percutaneous endoscopic gastrostomy tube (PEG)

ALS: Feeding via PEG Tube

- Recommended in patients with difficulty maintaining good nutrition
- Increased mortality if placed once the FVC is less than 50% predicted
 - ▣ Procedure: 1.8%
 - ▣ 24 hour: 3.6%
 - ▣ 30-day: 11.5%
- Associated complications:
 - ▣ Laryngospasm
 - ▣ Localized infection
 - ▣ Gastric hemorrhage
 - ▣ Failure to place PEG due to technical difficulties
 - ▣ Death due to respiratory arrest

ALS: Feeding via PEG TUBE

- Probably effective in stabilizing body weight
- Currently, no evidence of survival benefit
- Lou, J. *et al.* 2010 Amyotroph Lateral Scler 11: 116-121
 - ▣ 412 ALS patients enrolled in clinical trial (minocycline)
 - ▣ Analyzed how PEG affects QoL → used McGill Quality of Life Scale to assess 52 patients with PEGs placed during the study period
 - ▣ Rate of decline on QoL scale slowed after initiation of PEG
 - ▣ Reasons for suspected improvement in QoL unknown

Management of Respiratory Symptoms

- Respiratory muscle weakness: inability of respiratory muscles to generate normal levels of pressure and airflow during inspiration and expiration
- Respiratory insufficiency: inadequate pulmonary ventilation to the point where gas exchange is impaired, resulting in carbon dioxide retention, hypoxemia, and frank respiratory failure
- Respiratory failure (with or without pneumonia) is the most common cause of death in ALS patients

Table 1 Clinical Symptoms and signs of respiratory impairment in ALS

Symptoms of respiratory dysfunction in ALS

Dyspnoea on minor exertion or talking

Frequent nocturnal awakenings

Excessive daytime sleepiness

Daytime fatigue

Morning headache

Hallucinations

Poor appetite

Poor concentration and/or memory

Mouth dryness

Signs of respiratory dysfunction in ALS

Tachypnoea

Orthopnoea

Use of auxiliary respiratory muscles

Paradoxical movement of the abdomen

Decreased chest wall movement

Weak cough

Sweating

Difficulty clearing secretions

Weight loss

Noninvasive Positive Pressure Ventilation (NIPPV)

- Provided via BiPAP → enough support to offload work of breathing
- Recommended by the AAN, EALSC, and the American College of Chest Physicians
 - ▣ Not widely used in USA and Europe
 - ▣ Poor compliance in patients with bulbar symptoms and FTD
- Debate about which test optimally detects impending respiratory muscle insufficiency:
 - ▣ Vital capacity
 - ▣ Maximum inspiratory and expiratory pressure (MIP/MEP)
 - ▣ Maximum sniff nasal pressure (SNIP)
- No guidelines in literature for initiation of NIPPV → respiratory symptoms and/or evidence of respiratory muscle weakness
 - ▣ Polysomnography plays no significant role in determining when to start
 - ▣ No RCTs that address whether initiating before the onset of symptoms or hypercapnia prolongs time to respiratory failure or death

ALS: RCTs for NIPPV

- Radunovic, A. *et al.* 2009 Cochrane Database of Systematic Reviews Issue 4:
 - ▣ Examine the efficacy of mechanical ventilation in improving survival, on disease progression, and quality of life in ALS
 - ▣ Only one study judged to be of adequate methodological quality → no meta-analysis

ALS: RCT for NIPPV

- Bourke, S.C. *et al.* 2006 Lancet Neurol 5: 140-147:
 - ▣ Effect of NIPPV on quality of life and survival
 - ▣ 92 patients at a single centre were assessed every 2 months → randomised to NIPPV (n=22) or standard care (n=19) when they developed either orthopnea with MIP less than 60% predicted or symptomatic hypercapnia
 - ▣ QoL measured with Mental Component Summary and Sleep Apnea Quality-of-life Index → time maintained above 75% of baseline and mean improvement

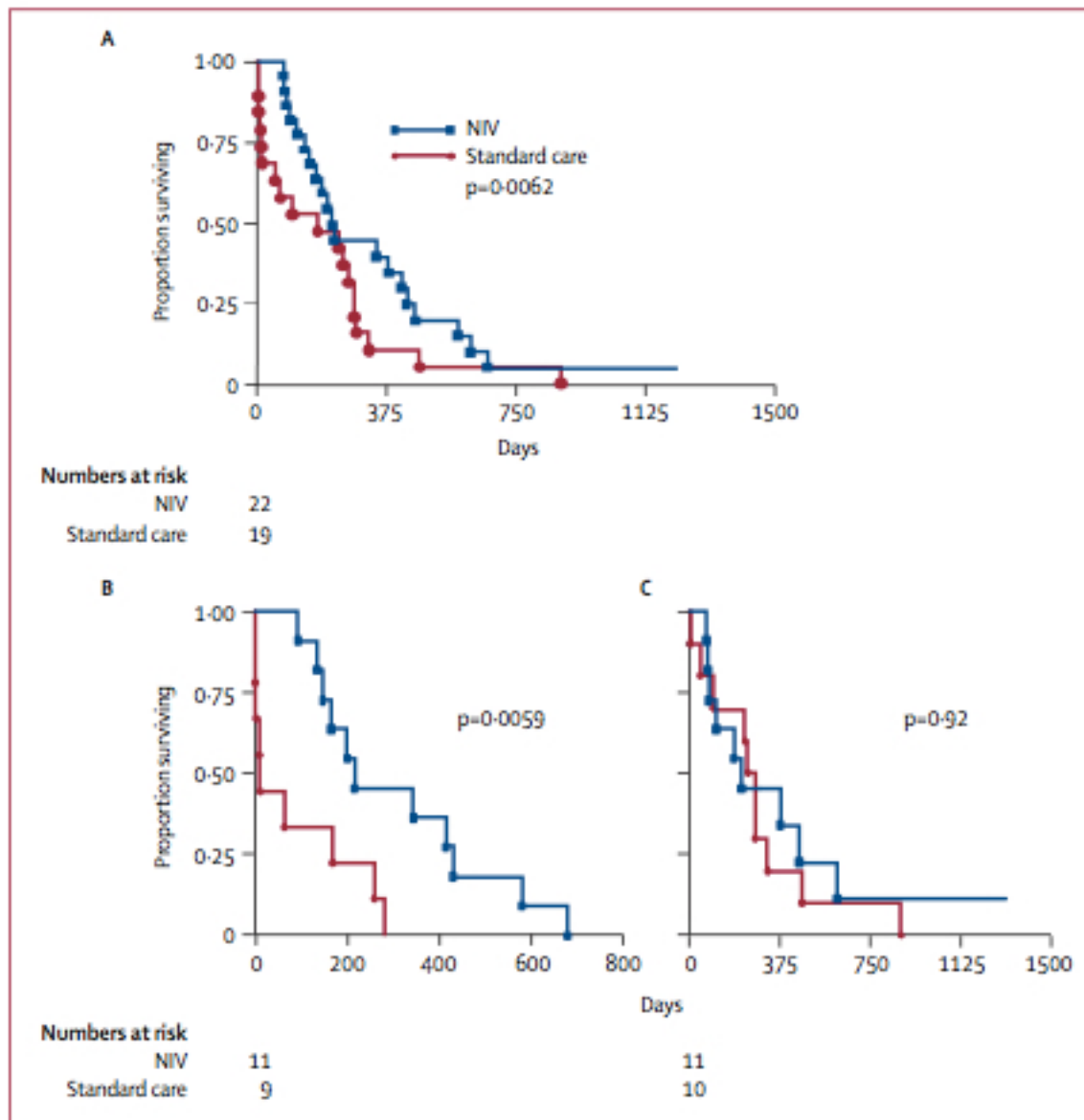


Figure 2: Survival from randomisation

A: all patients; B: patients with normal or moderately impaired bulbar function; C: patients with severe bulbar impairment.

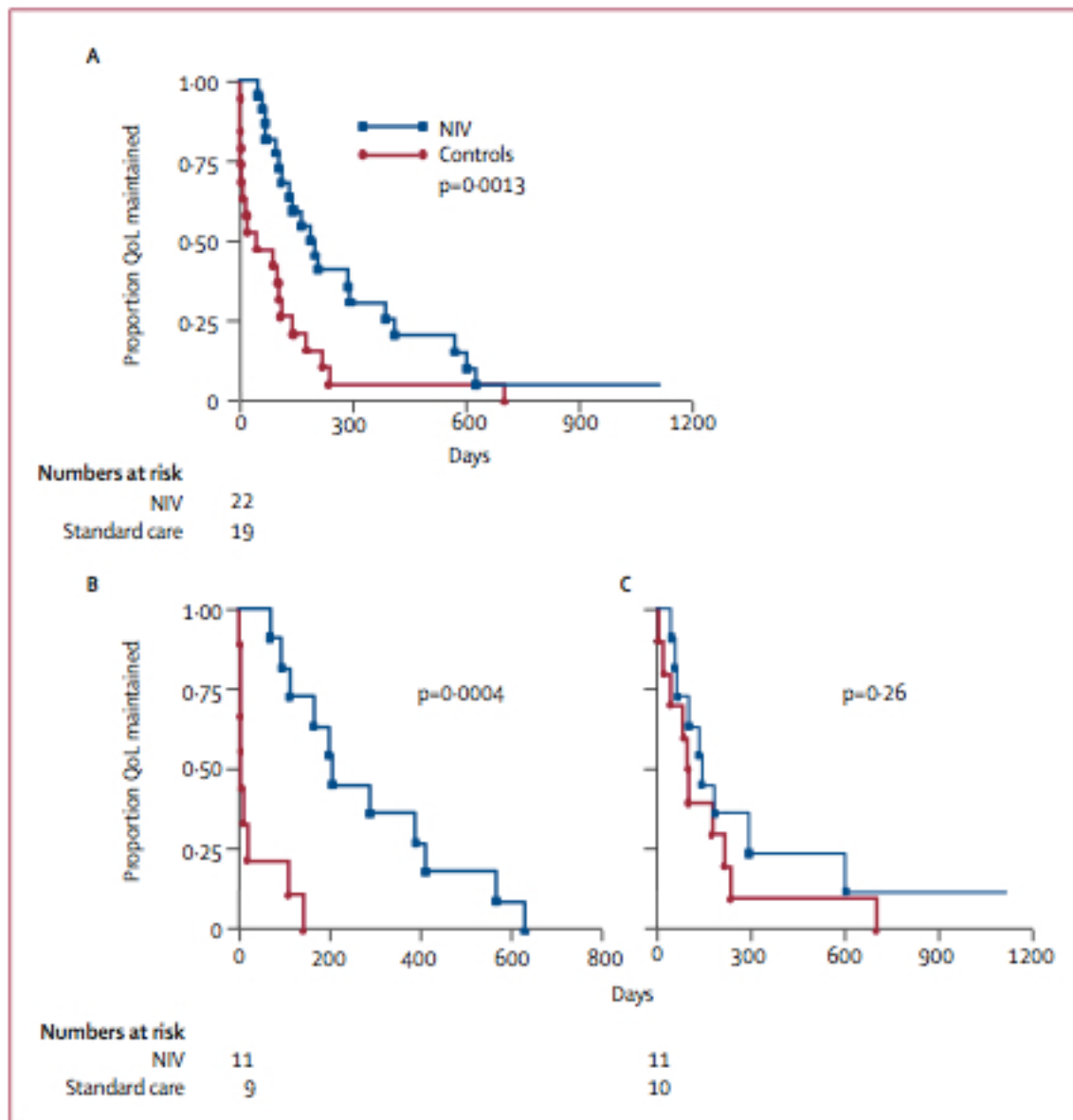


Figure 3: Time SAQLI symptoms domain maintained above 75% of prerandomisation assessment
 A: all patients; B: patients with normal or moderately impaired bulbar function; C: patients with severe bulbar impairment. QoL=quality of life.

ALS: RCT for NIPPV

- Bourke, S.C. *et al.* 2006 Lancet Neurol 5: 140-147:
 - ▣ NIPPV improved QoL and survival (median of 205 days) in ALS patients without severe bulbar dysfunction
 - ▣ Survival benefit greater than available drug treatment
 - ▣ Reason for lack of survival benefit in patients with severe bulbar function unclear → NIPPV may not be effective in this subgroup or may be related to intolerance
 - Cannot comment on use of NIPPV in this subgroup

Long Term Mechanical Ventilation (LTMV)

- Generally considered for symptoms of respiratory failure: intolerance of NIPPV or failure of NIPPV → Often initiated in emergent situation
 - Secures airway
 - Prevents/reduces aspiration pneumonia
 - Prolongs life
- Patient factors associated with tracheostomy:
 - Male gender
 - Younger
 - Higher income
 - Young children
 - Belief in future cure
- Varying tracheostomy rate between countries:
 - USA: 3%
 - Germany: 3%
 - United Kingdom: 0%
 - Japan: 27-45%

ALS: LTMV

- Median survival: 12-37 months
- Most common cause of death: respiratory tract infection
- Controversial:
 - ▣ 50-70% of patients with tracheostomy will have minimal ability to communicate or locked-in
 - ▣ Expensive
 - ▣ Increased caregiver burden
 - ▣ Very limited data, re: survival, QoL

ALS: LTMV

- Vianello, A. *et al.* 2011 J Crit Care 26: 329e.7-14:
 - ▣ Retrospective chart review and prospective evaluation of QoL, degree of depression, and survival
 - ▣ 60 ALS patients who underwent unplanned tracheostomy for acute respiratory failure (1995-2008)
 - ▣ Mean survival after tracheostomy: 30.3 months → shorter in patients older than 60 years of age
 - Cause of death: pneumonia (46%), sudden death (26%), unknown (19%), cardiac failure (9%)
 - ▣ 13 patients surveyed using Beck Depression Inventory and Life Satisfaction Index and compared to 14 ALS patients on NIPPV, with no significant effect of receiving tracheostomy
 - ▣ 11/13 patients reported positive view of LTMV and would choose tracheostomy again

ALS: Respiratory Symptoms

- Dyspnea: opioids, benzodiazepines
- Diaphragmatic pacing stimulators: intramuscular implantation of electrodes, with goal of postponing need for invasive mechanical ventilation
 - ▣ Very small, nonrandomized trial showed slowing of FVC rate of decline
 - ▣ Unable to assess effect, harm, or benefit
- Oxygen therapy has been demonstrated to worsen respiratory symptoms and carbon dioxide retention in patients with neuromuscular respiratory insufficiency
 - ▣ May lead to hypercapnic coma or respiratory arrest
 - ▣ Oxygen can be used for non-ALS disease in conjunction with NIPPV

ALS: End-of Life Care

- Currently unclear from international guidelines when Palliative Care should become involved in patient care → suggestion of early on in disease
 - ▣ To develop rapport
 - ▣ To introduce end-of-life planning prior to onset significant cognitive or communication issues
- Suggested triggers for end-of-life discussions:
 - ▣ Patient initiated
 - ▣ Presence of severe psychological, social, or spiritual distress or suffering
 - ▣ Presence of pain requiring high-dose analgesic medications
 - ▣ Dysphagia requiring feeding tube
 - ▣ Presence of dyspnea, symptoms of hypoventilation, or FVC <50%
 - ▣ Loss of body function in two regions (bulbar, arms, or legs)
- UK study:
 - ▣ Only 30 % of PC units provide ALS care
 - ▣ Only 8% involved from time of diagnosis

ALS: End-of-Life Management

- Palliative Medicine consultant generally involved only during terminal phase of disease
 - ▣ Hospice/PC unit admission
 - ▣ Withdrawal of LTMV
- Majority of patients die at home → may have difficulty accessing community PC programs
- Common barriers to palliative care intervention:
 - ▣ Unpredictable non-cancer disease trajectory
 - ▣ Lack of defined referral criteria for non-malignant conditions
 - ▣ Lack of non-cancer disease specific expertise
 - ▣ Limited resources

ALS: End-of-Life Management

- Anxiety surrounding final stages of disease → dyspnea, choking, and pain
- Mandler, R.N. *et al.* 2001 Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders 2: 203-208:
 - ▣ Observational registry of 1014 American and Canadian ALS patients who died during 4 year period
 - ▣ Questionnaire filled out by caregiver or family member
 - ▣ Mean age at death: 62 years
 - ▣ 64.1% of patients died at home, 20.7% in hospital, 7.7% in skilled nursing facility, 6.9% in hospice
 - ▣ >90% of patients were followed at a tertiary care centre with ALS expertise and multidisciplinary approach

ALS: End-of-Life Management

- Mandler, R.N. *et al.* 2001 Amyotrophic Lateral Sclerosis Other Motor Neuron Disorders 2: 203-208:
 - ▣ 88.9% had advance care directives in place
 - ▣ 90.7% of patients died peacefully
 - ▣ 9.3% with distress during dying process:
 - Breathing difficulties: 82.1%
 - Fear/anxiety: 55.2%
 - Pain: 23.9%
 - Insomnia: 14.9%
 - Choking: 14.9%
 - ▣ Palliative care relatively well-managed and interventions effective

ALS: The Netherlands Experience

- Euthanasia and physician-assisted suicide (PAS) legalized with Euthanasia Act of 2002
 - ▣ Voluntary request from patient
 - ▣ Unbearable and hopeless suffering
 - ▣ Absence of realistic alternatives for treatment
 - ▣ Consult from second independent physician
 - ▣ Due medical care
 - ▣ Cause of death reported as non-natural
- Maessen, M. *et al.* 2009 *Neurology* 73: 954-961:
 - ▣ Identified all ALS patients at a single centre, surveyed physicians and caregivers of 412 ALS patients
 - ▣ Compared data from 1994-1998 and 2000-2005
 - ▣ Unclear if quality of palliative care or other factors were associated with choice of euthanasia/PAS or if rates of euthanasia/PAS were increasing

ALS: The Netherlands Experience

- Maessen, M. *et al.* 2009 *Neurology* 73: 954-961:
 - ▣ Rates of euthanasia/PAS in ALS have remained stable
 - Approximately 16% of patients chose euthanasia, 2% chose PAS
 - ▣ Patients choosing euthanasia/PAS: higher level of education, religion not important, hopelessness (but not depression)
 - ▣ Reasons for hastening death: fear of choking, no chance for improvement, loss of dignity, fatigue, dependence on others
 - ▣ Euthanasia/PAS performed at end stage of disease, median disease duration of 2.2 years
 - ▣ No association between choosing euthanasia/PAS and lack of palliative care

Conclusions

- Complex, progressive disease with very limited treatment options
 - ▣ No evidence of change in median survival
- Very few well-designed trials to guide symptom management → reliant on expert consensus and clinical experience
- Ongoing loss of function, including cognition and communication → early Palliative Care and end-of-life planning is essential