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## Chapter X

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# COMPARATIVE STUDY ON APPLICATION OF INVASIVE AND NON-INVASIVE VENTILATION TO ALS PATIENTS IN JAPAN, THE USA AND EUROPE

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## ABSTRACT

We reviewed the published documents on application of mechanical ventilation to amyotrophic lateral sclerosis (ALS) patients and analyzed the influential factors of decision making for applying mechanical ventilation by looking into how it is practiced in Japan, the USA, and Europe. In Japan, 29.3% of ALS patients were on invasive ventilation via tracheostomy (TV), 7.2% on non-invasive ventilation (NIV) in 2005. The significant difference in the prevalence of mechanical ventilation was observed among prefectures or hospitals. In the USA, the prevalence rates of TV and NIV were reported to be 3% and 36.2%, respectively, in 2006. NIV is less applied in European nations compared with its usage in Japan and the USA. It is confirmed that the number of patients who choose TV is gradually growing, yet relatively small, in European nations, where an inconsistency in the introduction rate of mechanical ventilation to ALS patients was also observed in accordance with the national, regional and hospital levels. According to the analysis of influential factors in the introduction of mechanical ventilation, it seems that the heavy economic burden is the main factor to decrease the usage rate of mechanical ventilation for ALS patients.

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**Keywords:** amyotrophic lateral sclerosis (ALS), decision making, invasive ventilation via tracheostomy (TV), non-invasive ventilation (NIV), mechanical ventilation

## I. INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by degeneration of motor neurons in the cerebral cortex, brainstem and spinal cord, and is also known as “Lou Gehrig’s disease” in the USA and as “Maladie de Charcot” in France. A combination of upper and lower motor neuron dysfunction produces progressive weakness of voluntary muscles. ALS patients gradually lose their ability to work, walk, speak, and swallow, so they need to be assisted in daily living activities, with equipments, such as wheelchairs and communication aids, life-sustaining therapy, such as percutaneous endoscopic gastrostomy (PEG), and mechanical ventilation. Respiratory failure, mainly due to respiratory muscle dysfunction, is the most common cause of death of ALS patients within five years from the onset of disease. Invasive ventilation via tracheostomy (TV) was the only life-sustaining therapy known to support ALS patients for a long period of time. Recently, some studies have reported that non-invasive ventilation (NIV) improved survival and quality of life of ALS patients almost as much as TV did. ALS does not deprive its patients of their sensation, cognitive faculty and consciousness, so that the patients must decide their own treatment at some stages of the disease. We attempt in this chapter to review the published documents and analyze the influential factors of decision making in applying NIV and TV to ALS patients by looking into how it is practiced in Japan, the USA and Europe.

## II. THE EFFICACY OF TV AND NIV ON ALS PATIENTS

TV began to be used, worldwide, for treating the respiratory muscle paralysis by the poliomyelitis in 1950's, and for neuromuscular diseases in 1960's. NIV has carried out for neuromuscular diseases since 1987 in USA. In Japan, initially TV began to be used for neuromuscular diseases in 1970's, and for ALS patients in the latter half of 1980's. NIV began to be used for patients of Duchenne muscular dystrophy (DMD) in 1988. The number of ALS patients with NIV has increased slowly since 1990. As the efficacy of NIV became apparent, some guidelines had already become open to public, which includes “Practice Parameter” updated by the American Academy of Neurology (AAN) in 2009 [1], “Good Practice in the Management of ALS” by the EALSC Working Group in 2007 [2], and “ALS Care Guideline” by the Societas Neurologica Japonica in 2002 [3] for managing respiratory insufficiency of ALS patients at advanced stages.

The content which is common in these guidelines is as follows.

1. NIV and TV are used to relieve respiratory symptoms, improve quality of life and prolong survival.
2. There is no verified timing and criteria of introduction of NIV and TV in ALS patients.

3. Physicians and patients should discuss, in advance, the end of life issues, palliative care, and advance directives, so that they can avoid unplanned TV.
4. NIV should be applied to relieve respiratory symptoms before TV.
5. TV may be proposed in a case that NIV is not effective, which is caused by the difficulty to secure the upper airway due to worsen bulbar palsy or increased secretion.

#### i. The Survival of ALS Patients with Mechanical Ventilation

There are 2 studies that adopted survival as an endpoint, both of which reported prolonged survival of ALS patients with TV. Cazzolli PA *et al.* reported survival rate of 50 patients with TV. They described that 4 of 23 deceased lived for 9-12 years after starting TV, 2 of 27 alive lived after 7-8 years, and 3 were alive after 11-14 years of TV. Most of them were provided with tracheostomy care by family members, as skillfully as trained respiratory care practitioners and registered nurses. TV might extend survival for up to more than 10 years despite significant bulbar impairment when effective respiratory care is given [4]. Lo Coco D *et al.* reported that ALS patients with TV had a high chance of long-term survival; the mean survival time was 37 months [5].

Of ALS patients with NIV, 6 studies used survival as an endpoint and all reported prolonged survival. Bach JR *et al.* showed that 14-17 months prolonged survival in ALS patients who succeeded in use of NIV for 24 hours [6]. Aboussouan LS *et al.* showed that ALS patients who are tolerant of NIV have better survival than those who are intolerant in an observational cohort study [7]. Although NIV has no impact on the rate of decline of lung function, median survivals in ALS patients intolerant and tolerant of NIV were 5 and 20 months, respectively [8]. Kleopa KA *et al.* showed that ALS patients using NIV more than 4hr / day had longer survival and slower decline in vital capacity in a retrospective chart review [9]. Pinto AC *et al.* showed that ALS patients using NIV had longer survival and later appearance of gas exchanges disorders in a prospective, controlled study [10]. Moreover, Bourke SC *et al.* showed that ALS patients using NIV experienced, in a randomized controlled study, a median survival benefit of 205 days with maintained quality of life, but without effect on rate of decline of respiratory function [11].

#### ii. The Quality of Life in ALS Patients with Mechanical Ventilation

The quality of life in ALS patients with mechanical ventilation was assessed in 6 studies using questionnaires, and all reported positive effect. Kaub-Wittemer D *et al.* described that there was no difference in quality of life between patients using NIV and patients with TV [12]. Gelinas DF *et al.* reported that most patients using either NIV or TV would choose mechanical ventilation again, being satisfied with their decisions [13]. Lyall RA *et al.* [14] and Aboussouan LS *et al.* [8] concluded that NIV improved quality of life of ALS patients despite their increasing disabilities. Bourke SC *et al.* [15] and Jackson CE *et al.* [16] reported that NIV improved the scores in the subscale of vitality and mental health in the Short Form 36 Health Survey (SF-36) that is a self-assessment measure of the quality of life.

### III. THE PREVALENCE OF TV AND NIV ON ALS PATIENTS

These evidences given above thus have come to prove the utility of NIV and TV. Although some guidelines recommended mechanical ventilation for management of respiratory insufficiency in ALS patients, the prevalence of NIV and TV has not actually increased.

#### i. The Prevalence in Japan

In Japan, 7.2% of 4202 ALS patients were on NIV, 29.3% on TV according to the report from the Ministry of Health, Labour and Welfare in 2005. In the report, the significant difference in the prevalence of mechanical ventilation was observed in relation with where it is practiced. Some prefectures, such as Aomori, Yamagata, Kagawa and Oita had a quite high rate, as much as 60%, whereas Yamanashi, Nara and Hiroshima had only 10~15%. In Hokkaido, the prevalence rates of NIV and TV were expected to be 20% and 20%, respectively, in 2010. Many patients on NIV receive medical treatment as outpatients, and nearly half of patients on TV are hospitalized.

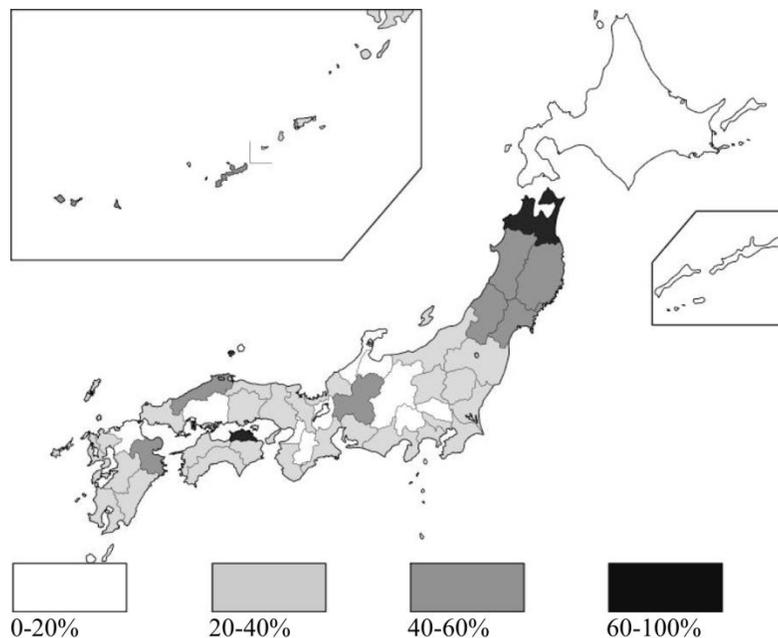


Figure 1. The prevalence of mechanical ventilation by prefecture in Japan.

The prevalence of whole mechanical ventilation is uneven at each prefecture, and there is no tendency according to the district and the population.

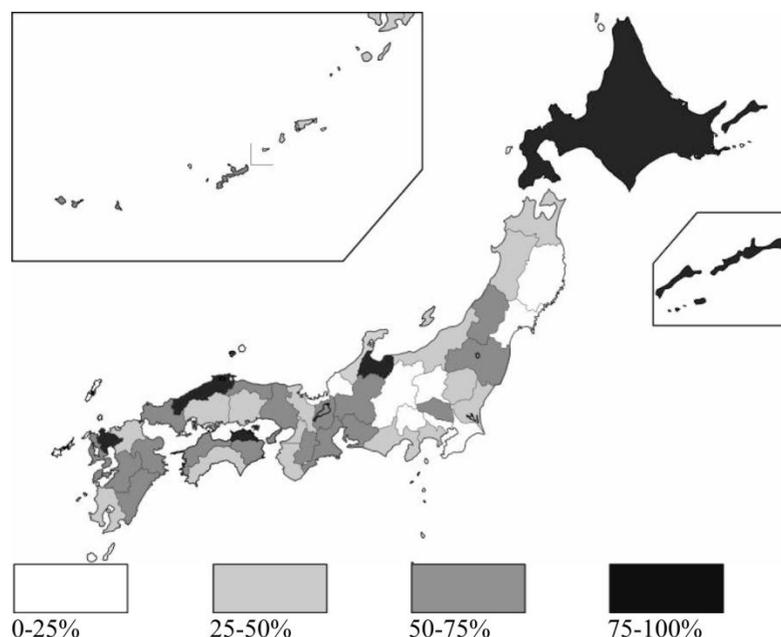


Figure 2. The ratio of hospitalization of the ALS patients with mechanical ventilation by prefectures in Japan.

Among the prefectures where the prevalence of mechanical ventilation is high, some prefectures have high ratios of hospitalization and the other have high ratios of home medical care.

Similarly, the same kind of inconsistency was also observed among hospitals. The investigation on the prevalence of NIV and TV at individual medical institutions has not yet been done throughout Japan. So far, 22 reports from hospitals and visiting nurse stations have been published in Japan, which describe the usage rate of both NIV and/or TV. 9 of these described the usage rate of both NIV and TV all of which was reported between 2003 and 2007. These institutions would be divided into three groups as follows.

1. Institutions where TV is provided for most ALS patients. The usage rates of NIV and TV were 0%-5% vs. 25%-80%, respectively.
2. Institutions where TV is more provided for ALS patients than NIV. The usage rates of NIV and TV were 20%-25% vs. 40%-50%, respectively.
3. Institutions where NIV is more provided for ALS patients than TV. The usage rate of NIV was slightly higher than TV.

The deflection of the usage rate was not seen among districts or prefectures. The following table shows details [17-25].

The majority of institutions seem to have reluctance toward NIV and/or TV. As shown above, even among a few institutions which deal with the management of respiratory insufficiency of patients with neuromuscular disorders such as ALS, there is a wide gap in the usage rate of TV and NIV.

**Table 1. The usage rate of NIV and TV in Japan**

	Author	Prefecture	Year	Cases	NIV	TV
TV >> NIV	Kimura et al. [17]	Osaka	2003	92	5.4%	29.3%
	Kataoka et al. [18]	Tokyo	2006	12	0.0%	83.3%
	Yoshida et al. [19]	Nagano	2006	136	5.1%	25.0%
	Kondo et al. [20]	Hyogo	2007	59	6.8%	81.4%
TV > NIV	Uehara et al. [21]	Osaka	2003	21	23.8%	47.0%
	Yamamoto et al. [22]	Oita	2003	20	20.0%	65.0%
	Nagahama et al. [23]	Osaka	2004	17	23.5%	41.2%
TV < NIV	Nanba et al. [24]	Okayama	2005	45	33.3%	31.1%
	Kasahara et al. [25]	Tokyo	2005	35	28.6%	25.7%
Total				437	12.4%	39.4%

Some institutions have a lot of ALS patients with TV, other institutions have ALS patients with NIV as many as ALS patients with TV regardless of time, prefectures in Japan.

## ii. The Prevalence in the USA

According to ALS CARE database, in the USA, the prevalence rates of NIV and TV were reported to be 15.6% and 2.1%, respectively, in 2004. Though the usage rate of NIV gradually increased to 36.2%, that of TV stayed at 3% from the same database in 2006 [26-28]. The ALS CARE database collected information on 2,500-4,000 ALS patients, of which white prevailed as of 90%. It was estimated that the number of ALS patients in the USA rises up to around 30,000 people. Based on the USA population's distribution in 2009, the total population was 307 million in 2009, white alone was 229.8 million (74.8%), black or African American 38.1 million (12.4%). There was discrepancy between demographic data and ALS CARE database. There was uncertainty as to whether these patients were representative of the ALS patient population at large, and whether the conclusions can be generalized. It could be the tendency in the whole USA, but the selective bias could not be excluded completely.

From those institutions, 9 reports reported the usage rate of both NIV and TV. All was reported between 1997 and 2010, when NIV had begun to infiltrate among developed nations. The number of ALS patients with NIV is reported as about 20-60%. At only two institutions, the number of ALS patients with TV came to around 20%; the number of ALS patients with TV came to a little less than 5% at the other institutions. The following table shows details [6-8, 26, 27, 29-32].

**Table 2. The usage rate of NIV and TV in the USA**

	Author	State	Year	Cases	NIV	TV
TV = NIV	Sivak ED et al. [29]	NY	2001	27	18.5%	18.5%
	Bach JR et al. [6]	NJ	2002	166	22.3%	23.5%
TV < NIV	Aboussouan LS et al. [7]	OH	1997	66	59.0%	3.0%
	Melo J et al. [30]	All	1999	2537	15.7%	2.8%
	Albert SM et al. [31]	NY	1999	93	19.4%	4.3%
	Aboussouan LS et al. [8]	OH	2000	60	38.3%	5.0%
	Bradley WG et al. [26]	All	2001	2018	28.0%	3.2%
	Cedarbaum JM et al. [32]	All	2001	387	7.0%	2.0%
	Lechtzin N et al. [27]	All	2004	1458	15.6%	2.1%

Most institutions have a few ALS patients with TV regardless of time or place in USA.

### iii. The Prevalence in Europe

The NIV is less applied to ALS patients in European nations compared with its usage in the USA and Japan. It is confirmed that there are few patients who choose TV in the continent. In EU survey [33], 1.9 patients (2.6%) selected TV and 7.6 patients (10.3%) selected NIV out of 74 mean patients within a year. From these institutions in UK, Germany, Italy, Portugal, Denmark, 6 reported the usage rate of both NIV and TV. All was reported between 1995 and 2009. It cannot be said that the number of ALS patients with NIV and TV had increased progressively in the period. The numbers of ALS patients with NIV were inconsistent, 5-50%. The ALS patients with TV were around 10% at the only one institution, the ALS patients with TV were 0%-5% at the other institutions. Thus, inconsistency in the introduction rate of NIV and TV was also observed in accordance with the national, prefectural and hospital levels in European nations. The following table shows details [10, 34-39].

**Table 3. The usage rate of NIV and TV in Europe**

	Author	Nation	Year	Cases	NIV	TV
TV>NIV	Mandrioli J et al. [34]	ITA	2006	123	1.6%	5.7%
TV<NIV	Pinto AC et al. [10]	POR	1995	20	45.0%	5.0%
	Borasio GD et al. [35]	18 nations	2001	74	10.3%	2.6%
	Bourke SC et al. [36]	UK	2002	2280	5.5%	0.4%
	Kuhnlein P et al. [37]	GER	2008	29	93.0%	0.0%
	Nonnenmacher S et al. [38]	GER	2009	65	35.0%	6.0%
	Lorenzen CK et al. [39]	DEN	2009	301	53.5%	11.6%

Most institutions have very few ALS patients with TV regardless of time or nations.

## IV. Factors of Difference in Each Nation, Region and Hospital

The prevalence of NIV and TV varies substantially both within and between nations. It is worth analyzing the factors to study the difference of usage rate at each hospital, in the region and the nation. At the national level, the difference in the medical system, the legal system, the state religion and the national traits will be enumerated. At the regional level, the difference in the regional economy, the regional medical service, the trait of the residents will be given as examples. At the institutional level, problems such as the lack of the facilities and trained medical staff that each hospital has, and the difference in physicians' attitudes, experience and training will be enumerated, also.

### i. The Difference of the Medical Systems

Firstly, we attempt to consider the difference within the medical systems. Regardless of the use of mechanical ventilator, it became clear in some precedent studies that medical treatment of the ALS patients costs a large amount of expenses [33, 40-43]. Home mechanical ventilation can be expensive. The home health care of 24 hours, which is necessary for ALS patients who choose home mechanical ventilation, costs a lot.

In Japan, the public health insurance system has provided all those living in Japan with tracheostomy and home oxygen therapy since 1985, and with home mechanical ventilation since 1990. Patients pay 0-30% of the medical expense according to age, disability and income. Nitta S *et al.* reported that yearly expenses of 4 ALS patients with TV at home were ¥334,000, ¥350,000, ¥411,000, and ¥872,000, respectively [44]. Uchida T *et al.* reported also that mean monthly medical costs of ALS patients with TV at home was ¥746,219±253,581, at institution was ¥1,049,923±71,147, and the mean monthly out-of pocket expense to families at home was 10%, at institution was 0% [45].

The USA alone, among developed nations, does not have a universal health care system, which will be developed by 2014. The Tax-financed Medicare and Medicaid cover 27.8% of the population. A little over 59% of Americans receive health insurance through employers, leaving a significant number of people without health insurance. As a result, most patients are led to pay all the expense for their own NIV and TV. The average yearly cost of home mechanical ventilation in the USA has been placed at more than \$150,000. Some items, such as communication aids, may not be covered. Out-of-pocket expenses borne by families can be amount to \$7,200 a month. Moss AH *et al.* also reported that the mean yearly expense of TV was \$180,120 (\$696-\$1,080,000), 91% of patient expenses were covered by insurance, and so the mean yearly out-of pocket expense to families was \$10,356 (\$0-\$240000) [33, 46]. The burden on the patient and their family is large even if some of the expense was covered by insurance. Klein and Forsheew also estimated that patients' care with mechanical ventilator cost \$16,625 per month, approximately 90% of which was resulted from the intensive nursing care needed by these patients [43]. Most of the expense seems to arise from the part related to the maintenance of the recuperation environment, such as nursing and care, *etc.*

In England, the public health system known as the National Health Service (NHS) has provided free healthcare to all the UK residents since 1948. It has covered NIV from general taxation, but not covered home mechanical ventilation. The ALS patients with TV were forced to spend the whole life in the hospital, which may be the reason that the usage rate of TV does not increase. In France and Germany, the public or private health insurance system has covered all the residents. They provide for NIV, and for some of the home mechanical ventilation, but not entirely. The financial cost of home mechanical ventilation is a less significant factor in nations with national health insurance. There are some reports from European nations on the costs for ALS patients and home mechanical ventilation. In Spain, Lopez-Bastida J *et al.* reported that the annual cost for ALS patients was estimated to be €36,194, and ALS patients have higher mean annual costs compared to other chronic illness such as Parkinson disease (PD), stroke, ataxia and Alzheimer disease (AD) [47]. In the Netherlands, van der Steen I *et al.* reported that the mean monthly expense was €1,336 for ALS patients receiving multidisciplinary care and €1,271 for those receiving general care. It showed that the costs of multi disciplinary ALS care were practically identical to the costs of general care [42]. In Germany, Kaub-Witteimer D *et al.* estimated also the monthly expense of NIV was €230-€1,900, and that of TV was €200-€5,000 [12].

## ii. The Advance Directive and the Patient's Autonomy

Next, we attempt to consider the difference within the legal systems. Modern medical ethics are based on "The Hippocratic Oath". Four principles, autonomy, beneficence, non-

maleficence, and justice, are respected throughout the decision making process in the medical treatment. In 1949, "International Code of Medical Ethics" was enacted, which was based on "Declaration of Geneva" in 1948. The new ethics was a revised version of the Hippocratic Oath to make it suitable for the 20th century. "Lisbon declaration" concerning the patients' right was enacted in 1981.

In Japan, the paternalism was the main current in the medical treatment for a long time. The occupation ethics indicator issued by the Japan Medical Association was revised in 2004. Since then, patients' autonomy has been regarded as one of the most important things in the medical treatment.

In the USA, The patients' right movement started in the 1960's in a series of right movement, such as the antidiscrimination movement, the women's liberation movement, and the student movement. "Patient's Bill of Rights" by American Hospital Association was enacted in 1973.

In Europe, the Council of Europe recommended the patients' right several times between the 1970's and the 80's. Movement to enact the law concerning the patients' right had come out after the 1980's.

The advance directives are legally effective in some nations, where people can perform them as they wish. In Japan, the law has not yet come to embrace the concept of advance directives. While several types of advance directive document models were issued by voluntary associations, and the medical workers often follow the documents, they were not authorized legally.

The first law concerning the advance directive was enacted by the state of California, the USA, in 1976. All the 50 states and the District of Columbia now have the law that gives individuals the right to issue advance directive documents and to exercise their will to refuse treatment in certain situations.

In Japan, traditionally, the medical care was offered to patients based on the judgment and the ability of doctor. Patients' own decision making has been given the top priority in the treatment policy since 1980's, just as the USA and European nations. As in the case of ALS, its paternalistic approach, with regards to decisions to start or not to start, or to discontinue the treatment, came to be criticized. Simultaneously, the discussion on how to end one's life gathered a lot of attention in the society. In such public atmosphere, the guideline for patients' own decision making process in the terminal care was issued in 2007 by the Ministry of Health, Labour and Welfare.

1. It is the most important principle to proceed with the terminal care in accordance with decisions made by the patient's oneself. Every decision made by the patient should be based on the appropriate treatment and information provided by medical staff, such as physicians, and the discussion between the patient and the staff.
2. It should be deliberately judged, based on the medical validity, adequacy and the discussions by the medical team which involves multidisciplinary expertise, to start or not to start, modify, and terminate the treatment.
3. It is necessary to provide a patient with the holistic medical treatment, which includes mental and social support for the patient and family, to remove or alleviate, as much as possible, pain and discomfort.
4. This guideline does not concern with the positive euthanasia with the intension to shorten one's life.

In the USA, the prevalence of advance directives is estimated to range from 5%-20% of the population. Moss showed that 79% of ALS patients had completed an advance directive. Only 6% had directives before the ALS diagnosis, while 34% completed directives after diagnosis but before starting mechanical ventilation. 36% completed an advance directive after beginning ventilator support. Only 8% of the patient population did not want to issue an advance directive [46]. Moss AH *et al.* also found that 58% of physicians favored early discussion of the home ventilation option. 24% felt, however, this issue should not be discussed before respiratory failure occurred. On the other hand, only 75% of ALS patients were aware of the likely development of respiratory failure, fewer than 50% of ALS patients reported that they had discussed this information with their physician. These data suggest that most patients are not well prepared to decide on mechanical ventilation [33].

In EU, the legal significance of autonomy is much less developed than in the USA. Advance directives, however, are believed to be useful at 78% of hospitals. 55% discuss them regularly with their patients, and 30% of patients complete them. The prevalence of advance directives in EU is estimated at less than 5% of the population.

In the scene of the palliative care, most of medical workers feel necessity of the advance directive, there was not the difference of the thought by the international comparison [48]. In EU and Japan, the autonomy of medical therapy is gradually gaining acceptance among ALS patients, their families and treating physicians.

### iii. Legal Aspect of Withdrawing and Withholding of TV

Withdrawing of TV means death for ALS patients. In general, it is thought to correspond to passive euthanasia, which is known as accelerating the death of a patient by altering some form of treatment and letting nature take its course. "Active euthanasia" involves causing the death of a patient through a direct action, in response to a request issued by that patient. "Physician-assisted suicide (PAS)" involves supplying information and/or the means of committing suicide to patients, so that the patients can successfully terminate their own lives. PAS is regarded as being in the middle of active and passive euthanasia.

In the USA and European nations where patients' own decision making is given the top priority in shaping the treatment policy, withholding or withdrawing of mechanical ventilation with patient consent (voluntary) is almost unanimously considered to be legal. Although some governments around the world have legalized voluntary euthanasia, generally it remains as a criminal homicide. In the Netherlands and Belgium, where euthanasia has been legalized, it still remains as homicide although it is not prosecuted and not punishable if the doctor meets certain legal exceptions. In 2002, the Netherlands passed a law legalizing euthanasia including physician-assisted suicide. The mandatory conditions of euthanasia in Dutch law consist of four points as follows; (1) The patient has the voluntary intention of euthanasia; (2) The patient has an unbearable pain; (3) The outlook of disease is hopeless; and (4) The treating physician of the patient has consulted the Support and Consultation in Euthanasia in the Netherlands (SCEN) physicians for a second opinion. Maessen M *et al.* reported that 20% of ALS patients die due to euthanasia or EAS, compared with 5% of cancer patients or 0.5% of cardiac patients [49].

In Japan, euthanasia is illegal, and the application of euthanasia to ALS is not allowed.

The mandatory conditions of euthanasia in Japanese judicial precedents were set nearly half century before; “The Nagoya High Court Decision of 1962” consists of the following six points; (1) The patient’s condition is incurable with no hope of recovery, and death should be imminent; (2) The patient suffers from unbearable and severe pain that cannot be relieved; (3) The act of killing is undertaken with the intention of alleviating the patient’s pain; (4) The patient himself or herself has made an explicit request of euthanasia; (5) Except for special cases where some other assistances are admitted, in principle the euthanasia must be carried out by a physician; and (6) The euthanasia must be carried out by ethically acceptable methods. These are, however, only a judicial precedent, which cannot be exercised as laws. A constant opinion on the mandatory conditions of euthanasia is still not obtainable today.

The withdrawing of ventilation is not, also, accepted legally. No constant opinions are given on the withholding of ventilation either. The argument on advance directives and palliative care is ongoing even today in the Ministry of Health, Labour and Welfare.

In the USA, while active euthanasia is illegal throughout the USA, Physician-assisted suicide is legal in the three states: Oregon, Washington and Montana. The use of analgesic in order to relieve suffering, even if it hastens death, has been held as legal in several court decisions.

In the UK, euthanasia is illegal. Any person found to be assisting suicide is breaking the law and can be convicted of assisting suicide or attempting to do so.

#### iv. Attitudes, Beliefs and Opinions of Physicians

It is reported that the doctor who has put on ventilator to a patient tends to put on ventilator to the next patient in Japan, the USA and UK [36, 41, 50]. Bourke SC *et al.* reported also that the majority of UK consultant neurologists did not suggest using NIV to any patients in the preceding 12 months, while only 3 neurologists made as much as 30% of all referrals nationally [36]. Although the guideline recommends NIV and TV, the prevalence of them does not seem to have increased. Neurologists and supporting healthcare professionals can greatly influence patients and their families. Even if physicians do not express their opinions specifically, the attitudes, beliefs, and opinions are conveyed to patients and their families [51]. The indifferent attitude of the neurologists towards application of mechanical ventilation to ALS patients might be one of the reasons that the number of ALS patients with NIV or TV have not increased even after the publication of clinical guidelines on the mechanical ventilation. To our knowledge, there was no research reporting the difficulty in the management of the ALS patient with NIV or TV.

#### v. The Characteristics of ALS Patients Living with Mechanical Ventilator

Here we report the characteristics of ALS patients living with mechanical ventilator.

In the USA, NIV users were more likely to be male. The evidence suggested that patients receiving NIV were more likely to have a higher income. There was no correlation between age, race, and types of insurance. A higher proportion of patients receiving NIV were using other life-sustaining interventions such as PEG and speech devices [52]. Those who choose TV were younger, more had young children, and had more education and higher incomes than

average [41]. The choice of TV was not made from desperation, ignorance, or inability to make wishes clear during a chaotic dying period. Rather, TV choice was consistent with a sustained sense that life was worth living in any way possible, at least for some time and to certain extent [41]. Atkins L *et al.* said that quality of the pre-illness marital relationship is a significant predictor of ongoing marital relationship in both ALS patients and their spouse caregivers. Additionally, social and psychological symptoms rather than disease symptoms are important predictors of marital relationship quality after ALS diagnosis [53]. Murphy PL *et al.* described ALS patients who were more likely to use NIV were more religious and more affected with mobility. Tracheostomy was not correlated with either religiousness or spirituality [54]. Rabkin JG *et al.* also reported that there was no evidence of contribution to the decision on TV for religious and spiritual faith [41].

## V. CAREGIVER'S DEPRESSION

The great burden is imposed upon their spouses and their children with the care of the ALS patients. This burden can become one of the causes to hesitate before mechanical ventilation.

In Japan, Miyashita M *et al.* showed that the care burden of caregivers was mainly explained by the intensity of the care and hours spent for giving care per day. The existential and physical burden tended to be higher for the caregivers of ALS compared to those of other neurodegenerative diseases, such as PD and spinocerebellar degeneration (SCD) [55].

In German, Kaub-Wittmer D *et al.* reported that the quality of life evaluated with the Profile of Mood State (POMS) and the Munich Quality of Life Dimensions List (MLDL) in ALS patients did not show any differences between those with NIV and those with TV. The quality of life in their caregivers, on the other hand, showed differences between those with NIV and those with TV. When asked directly, 94% of ALS patients with NIV and 81% of ALS patients with TV would go for the same choice if they went back to the time when they had made a decision to put on the mechanical ventilation, and there was no difference in both groups. However, 94% of the caregivers of ALS patients with NIV and 50% of the caregivers of ALS patients with TV would advise their patients to choose the ventilation again if they returned to that time of the decision, showing that there was difference between two groups. The POMS assessed feeling and emotional states of ALS patients and their caregivers, when applied with mechanical ventilation and summarized the assessment into 4 modes. Not only the patients but also their caregivers felt more fatigue and vigor than depression and anger [12]. In addition, in the UK, Mustfa N *et al.* compared the quality of life of caregivers of patients with NIV with that of caregivers of patients with similar disabilities; the ALS Functional Rating Score (ALSFRS) and the Norris Bulbar Score (NBS), but without ventilation, there was a slight increase of anxiety, but not stress or depression [56]. Contrary to these results, Goldstein LH *et al.* from the UK, Hecht MJ *et al.* from German and Chio A *et al.* from Italy did find an association between greater patients' functional impairment and higher caregivers' depression score [57-59].

## VI. THE TOTALLY LOCKED-IN STATE (TLS)

ALS patients progressively lose their ability to control voluntary movements and occasionally enter the totally locked-in state (TLS), in which they cannot move any part of their bodies including the eyes. Majority of ALS patients without TV die of respiratory failure or aspiration pneumonia. Most ALS patients with TV also die of pneumonia, while some ALS patients with TV progress to TLS if the mechanical ventilation could succeed in extending patients' life. It is thought that one of the reasons why many ALS patients do not choose mechanical ventilation is the TLS. Though case reports have occasionally appeared since around 1989, there are no reports on the TLS.

In Japan, Hayashi H *et al.* reported that 47 of 70 ALS patients with TV (67.1%) died within 20 years of the observation, and 27 of those (57.4%) died of pneumonia, 11 of cardiac disease, 2 of chronic renal failure, 2 owing to a ventilator accident, 1 of ischemic colitis, and three of unknown causes. TLS occurred in 8 of 70 ALS patients with TV (11.4%). Of the 33 on TV for more than 5 years, 6 (18.2%) developed TLS, and 11 (33.1%) developed Minimal communication state [60]. To our knowledge, there is no report on the frequency of TLS in the USA and Europe.

Recently, it is reported that cognitive functions and brainstem functions could be preserved in ALS patients in the TLS [61, 62]. Given that, for the patients to use the function to express their thought, there are two kinds of the Brain-Machine Interface (BMI) that utilizes the brain wave. One is invasive type, whose electrodes are buried within the scalp. The other one is non-invasive type, whose electrodes are pasted on the scalp. The devices enable ALS patients to use of a mouse pointer, inputting the letters on the computer screen, and switching on the electric care bed, the light of the room.

## VII. DISCUSSION

Decision making on the matters of one's life and death reflects universal value, being, at the same time, extremely personal. Withholding treatment with mechanical ventilation, even if it was requested by the patient who wishes to keep his/her own dignity, might be regarded as a homicide. Even when the mechanical ventilation is available, many patients with ALS do not select life with the mechanical ventilation. If a kind of guilt prevents patients to choose to be supported with mechanical ventilators, it should not be the case. It is ideal if the patients can be assured to be safe and comfortable with the mechanical ventilators. On the other hand, the patients suffering from dyspnea who decide not to receive mechanical ventilation should be treated with utmost palliative therapy. It should be noted that the line between palliative care and euthanasia is a very vague one.

Bach JR warns us that healthcare professionals universally rate a patient's quality of life much lower than the patients rate their own quality of life [63]. Earlier and better communication between physician and patient is needed so that ALS patients can deliberate on mechanical ventilation in advance. In this communication process, information on the patient's expected course, the burdens on the family caregiver, the major expense and the limits to mechanical ventilation need to be disclosed to patients. Neurologist should start to perform and discuss the evaluation with patients and their families, so that patients will be

able to make a better choice for their own good. Though physicians must attend each patient and family as individuals, physicians must also endeavor to be objective in evaluating the patient's condition because it can affect patient's outlook.

Though the guidelines are made, the prevalence of NIV has not increased as expected.

The reasons on the patients' side, which impede their willingness for NIV and TV, are the load on the family, the loss of dignity, and depression. The reason on the doctors' side is the lack of experience with NIV. Regarding the present state of the medical care system, the insufficiency of the home care system, such as the house call doctor and the home care service, should be urgently addressed.

It is a well known fact that, just like the prevalence of the mechanical ventilation for the ALS patients, the rate of dialysis for the patients with chronic kidney failure is different from nation to nation as a reflection of the difference in the medical care systems. The dialysis population is 1,230 per 1,000,000 in Japan, but it is 738 in the USA and 229 in the UK [64]. The international comparative cost study has advanced recently because the chronic renal failure has a high morbidity rate. The costs of dialysis per patient a year in Japan was \$57,621, while it was \$46,000 in the USA and \$44,625 in the UK [64]. In Japan, the renal failure requiring hemodialysis is specified as one of "specified diseases", and all of the medical expense that exceeds ¥10,000 within a month is supplied from insurance. In the USA, Medicare covers the patient with chronic renal failure. Although 80% of medical expense is paid by Medicare, 20% of that is covered by the second insurance or is paid individually, which amounts to several thousand dollars per year. It is thought the dialysis is directly leading to the kidney transplant. In the UK, The acceptance of dialysis is severely limited though it is covered with NHS. Although the annual cost is hardly different, the numbers of dialysis population are different among Japan, the USA, and the UK. Small amount of out-of-pocket expenses is needed in Japan and the UK [65]. In addition, the rate of consultation with the specialist in dialysis from general practitioner is low in the present condition in the USA and the UK.

The main reasons that ALS patients with mechanical ventilation did not increase are the large amount of out-of-pocket expenses and the uneasy access to the specialist. It is likely that ALS patients are placed in the similar situation as dialysis patients. Even though some autonomy is given to patients, their treatment is actually very limited in the whole medical care system. Several evidences show that patients' decision making are greatly influenced not by their culture or own value towards life and death, but the medical care system. The economic burdens on the ALS patients force them to give up survival, which causes a lot of difficulties on the medical treatment, and a criticism from ethical point of view. A public policy that will relieve ALS patients of the burden is urgently required.

The report on ALS patients with NIV and TV from Japan is a few. It is perhaps due to its very sensitive nature. A survey at the national level on this matter is essential for shaping a better policy against rare and intractable diseases such as ALS.

## **VIII. CONCLUSIONS**

Each nation has its own medical system and the legislation. Each patient has his/her own lifestyle and values towards life and death, which of course varies from one person to another.

It thus seems difficult to establish standardized systems for decision making in the process of applying mechanical ventilation to ALS patients even at institution or prefectural level, and it is almost impossible to establish the system to function globally that would go beyond the difference in socio-medical, cultural, and religious backgrounds. Such inequality of critical medical service may bear problematic ethical issues. As reviewed in this chapter analysis of influential factors in the introduction of mechanical ventilation would facilitate neurologists and supporting healthcare professionals to avoid paternalistic approach and help ALS patients to make the better decision for their benefit.

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## CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

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