博士論文

Intervention study for the prevention of aspiration pneumonia by recommendation of swallowing care based on the results of ultrasound examination

(超音波検査の結果に基づいた摂食嚥下ケアの推奨による誤嚥性肺炎予防のための介入研究)

三浦　由佳

CONTENTS:

LIST OF ABBREVIATIONS

AP	aspiration pneumonia
BMI	body mass index
FEES	fiberoptic endoscopic evaluation of swallowing
US	ultrasonography
VFSS	videofluoroscopic swallowing study

ABSTRACT

Background: Aspiration pneumonia is a great concern in the era of global population aging. The aim of this study was to investigate the effectiveness of recommendations for swallowing care guided by ultrasound examination during mealtimes for preventing aspiration pneumonia.

Methods: This study consists of three steps: a cross-sectional study for development of method to detect pharyngeal post-swallow residue by ultrasound examination in a dysphagia outpatient clinic; a feasibility study of eight participants in a special elderly nursing home to clarify acceptability and usefulness of ultrasound examination which detects aspiration and pharyngeal post-swallow residue during mealtimes; an open-labeled randomized controlled trial of 54 participants in the same facility to investigate the effectiveness for reduction of the frequency of aspiration and residue by ultrasound examination and recommendations for swallowing care within 8-week follow-up period.

Results: The sensitivity and specificity of detection of pharyngeal post-swallow residue by ultrasound examination were 67% and 75% using fiberoptic endoscopic evaluation of swallowing as a reference method. Ultrasound examination during mealtimes was accepted without interruption of mealtime, and aspiration and pharyngeal post-swallow residue that were detected using ultrasound examination during mealtimes showed an association with development of aspiration pneumonia. Swallowing care guided by ultrasound examination during mealtimes effectively reduced frequency of aspiration and residue in the individuals with

severe dysphagia as compared with standard care

Conclusion: Detection of aspiration and pharyngeal post-swallow residue using ultrasound examination is a promising method to reduce aspiration pneumonia which comes from frequent aspiration during mealtimes.

KEY WORDS: Aspiration pneumonia, deglutition disorders, randomized controlled trial, ultrasound

INTRODUCTION

In this era of global population aging, pneumonia in adults is a greater concern than it has been in the past. The risks of pneumonia and pneumonia-related death are known to increase with age, and the incidence of pneumonia in people aged ≥85 years is 10-fold higher than in people aged 15–64 years [1]. In Japan, which has the fastest growing aged population, pneumonia is the third leading cause of death [2]. Most community-onset pneumonia in elderly people, which includes both community-acquired pneumonia and health care-associated pneumonia, is related to aspiration pneumonia [1]. The estimated annual number of cases of aspiration pneumonia in Japan were 630,000 in 2013 [1]. Strategies are required to prevent aspiration pneumonia in active aging society.

Prevention of aspiration pneumonia includes pneumococcal vaccination and enteral tube feeding. Pneumococcal vaccination is recommended for the prevention of aspiration pneumonia among elderly people [3]; however, gram-negative enteric bacilli, anaerobic bacteria, and *Staphylococcus aureus*, which exist in oropharyngeal cavity and often cause aspiration pneumonia, are not the target of pneumococcal vaccination [4]. Considering this fact, pneumococcal vaccination is insufficient for the prevention of aspiration pneumonia. Enteral nutrition is sometimes provided for patients with dysphagia for the prevention of aspiration pneumonia; however, a previous cohort study among people with dysphagia and advanced dementia showed that the incidence of aspiration pneumonia was higher in the enteral nutrition

group than in the oral nutrition group [5]. Introducing enteral tube feeding promotes oropharyngeal secretion and deteriorates swallowing function, and then it increases the risk of aspiration. Therefore, providing enteral nutrition is not an effective strategy for the prevention of aspiration pneumonia. Because aspiration that causes aspiration pneumonia often occurs during the mealtimes, prevention of aspiration during mealtimes requires the assessment of the swallowing problems and appropriate swallowing care [6 7].

Aspiration is the passage of food or liquid through the vocal folds that sometimes occurs during the pharyngeal phase in people with dysphagia [8]. People with impaired swallowing ability allow the passage of aspirated boluses, which contain bacteria flow into lower respiratory tract without effective cough reflex. Moreover, people with impaired swallowing ability often show pharyngeal post-swallow residue, which is the presence of food or liquid in the pharynx after swallowing [9]. These swallowing abnormalities are crucial issues because they increase the risk of aspiration pneumonia. Aging itself deteriorates swallowing ability [10], and elderly people with neurological diseases including stroke, Parkinson's disease, and dementia often experience aspiration, pharyngeal post-swallow residue, and ultimately aspiration pneumonia [6 10 11]. Therefore, healthcare providers try to provide appropriate swallowing care and prevent aspiration pneumonia in elderly people.

LITERATURE REVIEW

This literature review section will describe following two points to justify the purpose of this dissertation: 1) the problem of existing swallowing care to prevent aspiration pneumonia; and 2) a proposal for new swallowing care.

1) The problem of existing swallowing care to prevent aspiration pneumonia

A major problem of existing swallowing care to prevent aspiration pneumonia is the lack of a bedside assessment to detect swallowing problems using an imaging method. Previous studies have suggested that the frequency of aspiration during mealtimes can be reduced by modifying the viscosity of food and liquid, posture during eating, and introducing swallowing rehabilitation [12-14]. These swallowing care provisions thus effectively prevent aspiration pneumonia in the clinical setting when it is based on an appropriate swallowing assessment. However there are no noninvasive imaging methods to detect aspiration and pharyngeal post-swallow residue.

Visualization of swallowing problems for elderly people is important because they sometimes aspirate without coughing owing to a deteriorated cough reflex caused by neurologic diseases or aging itself [15]. This feature is called silent aspiration. A previous report showed that over half of aspiration cases detected by videofluoroscopic swallowing studies (VFSS) were, in fact, silent aspiration [16]. Silent aspiration is, therefore, detected only by such imaging methods. The pharyngeal post-swallow residue is also difficult to detect without an imaging

method that can visualize the hypopharyngeal area. VFSS and fiberoptic endoscopic evaluation of swallowing (FEES) are considered gold standards to detect aspiration and pharyngeal post-swallow residue. VFSS uses barium to visualize the food and liquid on radiographs, thus aspirated boluses or boluses remaining in the hypopharyngeal area can be detected [17]. FEES uses a video endoscope that is passed through the nose and then directly visualizes the pharyngeal area during the swallowing of food and liquid [18]. VFSS exposes participants to ionizing radiation, and FEES requires insertion of an endoscope into the participant's nose. Therefore, these invasive assessment methods are not appropriate to use as a daily assessment during mealtime. Daily assessments for swallowing problems are important because the swallowing conditions of elderly people will be affected by the kinds of food and liquid they ingest and by the small changes in their physical and cognitive status [19-21].

Although there are some less invasive bedside swallowing assessments, they do not discern aspiration or pharyngeal post-swallow residue during mealtime. A repetitive saliva swallowing test checks the participant's ability to voluntarily swallow repeatedly, which is correlated to aspiration [22]. The test had a sensitivity of 98% and a specificity of 66%, predicting aspiration detected by VFSS. Although the sensitivity is high, some elderly people with cognitive impairment find it difficult to understand the instructions of the test and participate in the test. The water swallowing test [23] and food test [24] check the participant's swallowing behavior and whether a cough or abnormal voice is present after swallowing. The water

swallowing test had a sensitivity of 48% and a specificity of 92%. The food test had a sensitivity of 72% and a specificity of 62%. These existing assessments may overlook aspiration and residue because the evaluation depends on clinical features. They cannot visualize aspirated boluses in the trachea and boluses remaining in the pharyngeal area and, therefore, cannot be used to detect silent aspiration and pharyngeal post-swallow residue. The cough test, which is reported to have high sensitivity and specificity to detect silent aspiration, checks the participant's cough reflex induced by citric acid inhalation [25]. However, clinicians cannot obtain information from the cough test about the types of food, liquid or postures that cause aspiration and residue. Therefore, it is difficult for clinicians to use the results of a cough test to guide their daily swallowing care during mealtimes. The 10-item eating assessment tool was reported to detect aspiration episodes during participants' daily eating and swallowing, but as the assessment is based on a participants' self-report [26], it is difficult to apply in facilities where many people have cognitive impairments.

2) Proposal of new swallowing care

To overcome these issues, I first introduced an ultrasound (US) imaging method to detect aspiration noninvasively. Because the US has the advantages of noninvasiveness and portability as an imaging method, it is useful as a daily assessment tool for swallowing problems. Currently, the US is widely used as a bedside assessment tool for central line catheterization [27], measurement of postpartum urinary bladder volume [28], and detection of deep skin-tissue

injuries [29]. With a US examination, a real-time assessment, can be performed to yield results such that the appropriate treatment and care that can be provided before the problems become more severe. If clinicians who evaluate elderly people's daily swallowing ability assess aspiration and residue by US examination, the opportunity to provide precise swallowing care will increase and elderly people can receive appropriate swallowing care to prevent aspiration pneumonia.

Based on the advantages of the US method, several studies have developed methods to evaluate swallowing abilities [30-32]. These studies measured the movement of the hyoid bone or pharyngeal muscles to estimate aspiration as indirect methods. In other words, there were no methods to visualize aspiration by US examination. US examination was previously considered inadequate to observe the oral cavity and pharyngeal cavity where a lot of air reflects the US beam. However, recent advances in US resolution have enabled clinicians to obtain clear images of the anatomy of the oropharyngeal area [33 34]. There are some reports of visualization of the liquid in the oropharyngeal area by US [35 36]. Moreover our group recently succeeded in visualizing aspirated boluses in the trachea during swallowing by US [37 38]. Both aspirated boluses and surrounding tissues were observed as hyperechoic narrow moving objects during swallowing. When a transducer was attached in the sagittal plane in the cervical area above the thyroid cartilage (Figure 1a), US images revealed the vocal folds as a hyperechoic object that vibrated during speaking (Figure 1b). Therefore, the region was used as a landmark to detect

aspirated boluses during the US examination. Aspirated boluses (Figure 1c) during swallowing appeared as a hyperechoic line along the tracheal wall that passed through the vocal folds (Figure 1d) in the cases in which aspiration of barium liquid was detected by VFSS [37]. One of the participants had silent aspiration. Because US findings of aspirated boluses were defined in these case reports, the performance of US to detect aspiration during swallowing was evaluated [38]. Simultaneously performed VFSS or FEES was used as a reference. Forty-two US measurements of swallowing movies within 6–30 s were obtained from 17 participants in a dysphagia outpatient clinic. The sensitivity of aspiration detection during swallowing was 64%, and the specificity was 84%, which were relatively low figures. To increase the sensitivity and specificity, an image processing method based on the movement of the aspirated boluses, which was different from the movement of the surrounding tissue caused by swallowing, was applied [39]. This image processing method focused on the characteristic region related to aspirated boluses and tracheal walls and colored them red and blue, respectively. The correlation coefficient between current and previous images was used to emphasize the characteristic movement of aspirated boluses. As expected, this method assisted detection of the aspirated boluses from complex US images, improving the sensitivity and specificity to 91% and 94%, respectively.

The final goal of this research was to prevent aspiration pneumonia by introducing US examinations during mealtimes. Although a method to detect aspiration by US examination was

established, there were no methods to detect pharyngeal post-swallow residue, which is also related to aspiration pneumonia. Moreover there are no studies that used US examination to detect swallowing problems during mealtimes and investigated its effectiveness for preventing aspiration pneumonia. Firstly, the establishment of a visualization method to detect pharyngeal post-swallow residue, based on a US method is required. Secondly, the feasibility of performing US examinations during mealtimes should be clarified. Finally, the effectiveness of US examinations for preventing aspiration pneumonia compared with standard care should be verified.

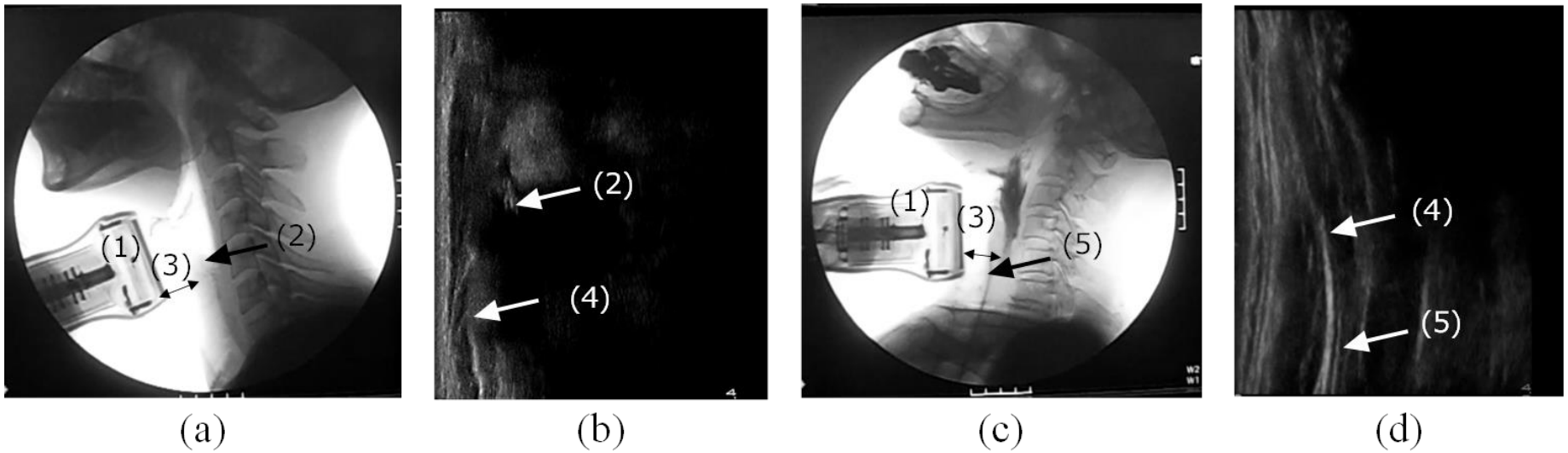


Figure 1. The scanning method of US examination for the detection of aspiration.

a US transducer was attached in the sagittal plane above the thyroid cartilage.

b The vocal folds that were depicted as a vibrated hyperechoic objects were used as a landmark during US examination for detecting aspiration.

c Aspirated boluses were observed in the trachea.

d Aspirated boluses appeared as a hyperechoic narrow object along the tracheal wall.

(1) The US transducer, (2) vocal folds, (3) tracheas, (4) tracheal walls, and (5) aspirated boluses.

Upper side of the images represented cranial side. Left side of the US images were skin surface, where, transducers were attached.

US: ultrasound.

OBJECTIVES

I planned the following three steps to verify the effectiveness of US examination during mealtimes for preventing aspiration pneumonia. Step 1 was a cross-sectional study to develop a method to detect pharyngeal post-swallow residue using a US method (Chapter 1). Step 2 was a feasibility study to clarify the feasibility of US examinations during mealtimes (Chapter 2). Step 3 was a randomized controlled trial to investigate the effectiveness of preventing aspiration pneumonia using swallowing care guided by the US examination during mealtimes (Chapter 3).

CHAPTER 1

Development of a method to detect pharyngeal post-swallow residue using an ultrasound examination

Background

Visualization of pharyngeal post-swallow residue will be effective to prevent aspiration pneumonia [40]. The pharyngeal post-swallow residue is the presence of food or liquid in the hypopharynx that is not entirely eliminated by swallowing [9]. Although a method for detecting aspiration by US examination was established in the previous studies, aspiration pneumonia is not prevented only by the assessment of and care for aspiration. The pharyngeal post-swallow residue is a predictor of aspiration that causes aspiration pneumonia because the residue suggests impairment of the driving forces of the oropharyngeal bolus and reduced swallowing efficiency [41]. The accumulated pharyngeal post-swallow residue sometimes flow into airway without cough reflex in people with dysphagia. Therefore, the presence of pharyngeal post-swallow residue increases the risk of aspiration more than 2.75 times compared with the absence of residue [42]. The pharyngeal post-swallow residue is regarded as a risk factor of aspiration pneumonia but it often occurs independently from aspiration. Therefore assessing pharyngeal post-swallow residue in addition to aspiration is important to provide appropriate swallowing care to prevent aspiration pneumonia.

Many healthcare providers have tried to reduce residue in clinical settings. The

viscosity of the food and liquid is known to influence the amount of oropharyngeal residue [43]. Therefore, healthcare providers often modify the viscosity of food and liquid to reduce pharyngeal post-swallow residue when the residue was detected by VFSS or FEES. Moreover, some types of swallowing exercises were reported to be effective for reducing the amount of pharyngeal post-swallow residue [44 45]. The important point is that these strategies to reduce pharyngeal post-swallow residue are different from those to reduce aspiration. Food and liquid with high viscosity prevents aspiration; however, they tend to remain in the hypopharynx in people with impaired driving forces of the oropharyngeal boluses. The type of the swallowing exercise for reducing the amount of pharyngeal post-swallow residue is different from that of the exercise for reducing the amount of aspiration. The exercises for reducing the amount of pharyngeal post-swallow residue focus on the movement of the pharyngeal constrictor [44 45]. On the other hand, the reduction of the amount of aspiration focuses on the glottal closure [46]. Therefore, if US detects both pharyngeal post-swallow residue and aspiration during mealtime, healthcare providers can prevent aspiration pneumonia by providing appropriate swallowing care before these problems become more severe.

Clinicians have tried to assess pharyngeal post-swallow residue as an abnormal swallowing condition. Pharyngeal post-swallow residue often occurs in either the vallecular space or the pyriform sinuses [47]. The vallecular space is the space between the epiglottis and base of the tongue. The pyriform sinuses are the spaces situated to either side of the opening to

the larynx. Residue in both areas is difficult to detect just by visual examination. Clinicians usually perform VFSS or FEES to assess pharyngeal post-swallow residue [42 48]. With VFSS, the pharyngeal residue is visualized as a shadow in the pharynx after the participant swallows a contrast agent such as barium sulfate. With FEES, food and liquid in the pharynx can be observed directly through an endoscope.

A few researchers have tried to detect pharyngeal post-swallow residue using acoustic measurements [49 50]. They tried to assess pharyngeal post-swallow residue that was detected through VFSS or FEES from the voice or breath sounds after swallowing. These studies reported that it was difficult to achieve both good sensitivity and specificity. It was difficult to classify normal and abnormal status in the hypopharynx based on acoustic measurements as many noises interfere with the evaluation. These methods required acoustic analysis; thus, they were not real-time assessment methods of residue. Visualization of the internal hypopharynx will provide sufficient real-time information and will improve sensitivity and specificity for detecting pharyngeal post-swallow residue.

US appears to be an ideal imaging method for detecting pharyngeal post-swallow residue because it is noninvasive and can be performed at the bedside. In our previous study, it was possible to distinguish aspirated boluses from surrounding tissues, and an image-processing method succeeded in enhancing the difference to improve the performance of US for detecting aspiration [39]. This image processing method focused on the characteristic region

related to aspirated boluses and tracheal walls. The correlation coefficient between current and previous images was used to emphasize the characteristic movement of aspirated boluses. The aspirated boluses and the tracheal walls were colored by red and blue, respectively. Distinguishing pharyngeal post-swallow residue from the surrounding tissues will be more difficult than distinguishing aspirated boluses from the surrounding tissues because there are no differences between remaining food and liquid boluses and surrounding tissues with respect to the characteristics of their movement. However, the acoustic impedance of food and liquid will be different from that of surrounding tissues. Therefore, I hypothesized that pharyngeal post-swallow residue can be detected as the region with a different brightness from the surrounding tissues, especially the vocal folds and pharyngeal muscles. The aim of this study was to develop a method for detecting pharyngeal post-swallow residue using US examination and to evaluate its performance by comparing the results obtained using an US with those using FEES, which was used as a gold standard.

Methods

1) Study design

All the data were obtained from a cross-sectional study that was conducted from August to November in 2012. This study used US images that were obtained in the previous study to develop a method to detect aspiration by US examination [38].

2) Participants and setting

The data were collected at a dysphagia outpatient clinic of a general hospital in Chiba Prefecture, Japan. Participants who underwent US examination simultaneously with FEES were included in this study. Participants with conditions that made it difficult to attach a transducer in the appropriate position were excluded from the study. The study protocol was approved by the Ethics Committee of the Graduate School of Medicine, The University of Tokyo [#3260-(1)]. Written informed consent was obtained from all participants or their proxies.

3) Ultrasound examination

The US examinations were performed simultaneously with a FEES. The type of the test boluses, the number of the measurements and the order of the measurements were determined based on each participant's swallowing ability assessed before the examinations by the experienced dentists who performed FEES. The test bolus included food and liquid with different viscosities. A portable ultrasound (M-Turbo; Sonosite, Bothwell, WA, USA) with a 6-to 15-MHz (HFL509) linear array transducer was used for the examination. US movies of 6–30 s of swallowing were obtained. The head and neck positions of the participants were not fixed so that they could swallow boluses in a way that was most comfortable for them. A transducer was attached to the thyroid cartilage to visualize the vocal folds in the sagittal plane. A US operator controlled the pressure exerted by the transducer in order to not disturb the participants' swallowing during the examination. The depth of the visualization was kept at 40 mm from the skin surface to include the vocal folds as a landmark and the hypopharyngeal and tracheal area. The echo gain

and dynamic range were adjusted to a proper level for each measurement to clearly visualize the target area. Other settings including focus, frequency, and zoom were predetermined and maintained at a constant value during the examination. The pharyngeal post-swallow residue was interpreted as a misty hyperechoic area above the vocal folds that remained after swallowing. A researcher who was blinded to the information of the participants and the examinations evaluated the presence or absence of pharyngeal post-swallow residue from the US movies.

4) Fiberoptic endoscopic evaluation of swallowing

FEES was performed by experienced dentists, and the results were used as a reference in this study. A fiber-optic fluorescence imaging system (FNL-10RBS; PENTAX Medical, Ontario, Canada) was used for the FEES. A coloring agent was introduced to enhance the visualization of liquid in the FEES. An experienced dentist who was blinded to the results of the US examination evaluated the presence or absence of the pharyngeal post-swallow residue in the vallecular space on the FEES images. He was also blinded to the information of the participants and the examinations.

5) Statistical analyses

The FEES results were used as a reference for calculating the sensitivity and specificity of the US examination for detecting pharyngeal post-swallow residue. The evaluation was performed for each measurement, not for each participant as most of the participants underwent multiple

measurements that included different types of test boluses. To investigate the performance for detecting different viscosities of the test food and liquid, test boluses were categorized as low or high viscosity. Liquids without any thickening agent or solid food were categorized as low viscosity, and liquids with a thickening agent or paste food were categorized as high viscosity. Fisher's exact test was used for the analysis. The P-value was set at 0.05 for statistical significance. All analyses were conducted using STATA, version 14 (STATA Corp., College Station, TX, USA).

Results

Twenty-five US and 25 FEES images were simultaneously obtained. Owing to poor image quality, two FEES images were difficult to evaluate and thus, excluded from the analysis. Finally, 23 images from nine participants (eight men) with a median age of 70 years were analyzed. Six of the nine participants had swallowing problems caused by a stroke (Table 1). The residue was found in eight participants and aspiration was found in four participants by FEES.

The sensitivity for detecting pharyngeal post-swallow residue of 23 images from nine participants by US examination was 67%, and the specificity was 75% (Table 2-1). Disagreement between the US examination and FEES occurred for seven measurements of 19 low-viscosity boluses, and there were no disagreements for four high-viscosity boluses (Table 2-2). There were no significant differences in detection performance by US examination

between the two viscosity levels (P = 0.273). Two typical cases for which US examination detected pharyngeal post-swallow residue are described below. The first was a case in which only residue was detected, and the second was a case in which both residue and aspiration were detected.

Case 1: Only residue detected.

A 75-year-old man with a history of aspiration pneumonia underwent FEES. His usual meals consisted of soft food, and he stated that he did not have a cough during mealtime. The participant was asked to swallow a colored liquid with low viscosity with his head oriented up in a 90° angle. US images depicted the vocal folds as a hyperechoic spot before swallowing (Figure 2a). After the swallowing reflex occurred, a misty hyperechoic area was observed above the vocal folds (Figure 2b). Before the swallowing reflex, FEES images showed no residue of green liquid with a coloring agent in the vallecular space (Figure 2c). FEES images showed a residue of colored liquid in the vallecular space after swallowing (Figure 2d). Aspiration was not detected in the FEES images.

Case 2: Both residue and aspiration detected.

A 76-year-old man with a history of Parkinson's disease and stroke underwent FEES to evaluate changes in his swallowing ability. He complained of increased sputum after he had a fever 2 weeks earlier. He was eating a low-viscosity diet. He used a thickening agent to prevent aspiration when he was drinking liquid.

The participant was asked to swallow rice and vegetables with low viscosity with his head oriented up in a 90° angle. Aspirated rice grains were observed as hyperechoic narrow objects along the tracheal wall moving into the trachea in the US examination (Figure 3a). The US images also showed the vocal folds with a hyperechoic misty area after he swallowed rice porridge and minced vegetables (Figure 3b). The FEES images showed aspiration of rice during the swallowing (Figure 3c) and remaining boluses of rice and vegetables in the vallecular space after the swallowing (Figure 3d).

Discussion

To the best of my knowledge, this is the first study showing that pharyngeal post-swallow residue can be detected by US examination. In addition, the performance of US examination in detecting pharyngeal post-swallow residue was evaluated in comparison with FEES.

Based on previous studies that clearly visualized the oropharyngeal anatomy including vocal folds and boluses in the oropharyngeal area by US examination [33-36], I hypothesized that pharyngeal post-swallow residue can also be visualized by US examination. The pharyngeal residue was detected as a misty hyperechoic area above the vocal folds in US images that could be distinguished from the soft tissues around the vocal folds. Pharyngeal residue seems to be more difficult to detect by US examination than aspiration in the tracheal area because residue does not show any characteristic movement during swallowing. In this study we focused on the vocal folds, which is close to the vallecular space to detect pharyngeal post-swallow residue.

The vallecular space is one of the most common hypopharyngeal areas where boluses remain after swallowing. Thus, we succeeded in detecting pharyngeal post-swallow residue as a misty hyperechoic area above the vocal folds in US images.

The advantage of detection of pharyngeal post-swallow residue using US examination is that the real-time assessment of various types of food and liquid is possible with acceptable sensitivity and specificity based on the imaging method. The sensitivity and specificity of US for detecting residue were higher than some results of previous methods [49 50] that aimed to detect dysphagia including pharyngeal post-swallow residue by voice or breath sounds after the swallowing (67% vs. 8%–92%, 75% vs. 59%–86%). Because previous methods only detected residue from liquids, the sensitivity and specificity of residue from various types of foods were not verified. US examination indicated the possibility of usefulness for applying it to mealtimes for the detection of pharyngeal post-swallow residue.

Although there were no significant differences in performance for detecting boluses of different viscosities, all the disagreements between US examination and FEES were caused by low-viscosity boluses. In our previous study, which aimed to detect aspiration, I also found a higher disagreement between US examination and FEES for low-viscosity boluses [38]. The size of the boluses may affect the visualization of pharyngeal post-swallow residue. The amount of residue of low-viscosity boluses will be small because they spread fast, and thus, it is difficult to visualize as well as aspirated boluses by US examination. The sensitivity and specificity of

an US examination for detecting pharyngeal post-swallow residue were lower than those for detecting aspirated boluses. Because the information of movement was not available for detecting residue, the evaluation of residue would be more difficult than that of aspiration, which showed characteristic movement of aspirated boluses for evaluation.

In conclusion, in US images, the pharyngeal post-swallow residue is defined as a misty hyperechoic object above the vocal folds after swallowing. The sensitivity and specificity of US examination for detecting pharyngeal post-swallow residue are 67% and 75%, respectively. Since both pharyngeal post-swallow residue and aspiration can be risk factors of aspiration pneumonia, the detection method based on US examination will be able to propose a comprehensive US assessment-based swallowing care recommendation to prevent aspiration pneumonia.

Table 1. Characteristics of the participants.

Case	Age/ sex	Diseases	Types of test foods and liquids	Aspiration detected by FEES	Residue detected by FEES
1	70/ M	Stroke	Low viscosity	–	+
2	60/ M	Stroke	High and low viscosity	–	+
3	60/ M	Stroke	Low viscosity	+	+
4	80/ M	Amyotrophic lateral sclerosis	High and low viscosity	+	+
5	60/ M	Stroke	High and low viscosity	+	+
6	62/ F	No diseases	Low viscosity	–	–
7	75/ M	Pneumonia	Low viscosity	–	+
8	76/ M	Parkinson’s disease, stroke	Low viscosity	+	+
9	70/ M	Stroke	Low viscosity	–	+

FEES: fiberoptic endoscopic evaluation of swallowing; F: female; M: male.

Table 2-1. Results of the detection of pharyngeal post-swallow residue.

N = 23		FEES	
		Presence	Absence
US	Detected	10	2
	Not detected	5	6

Sensitivity = 68%, specificity = 75%.

Twenty-three images from nine participants were analyzed.

FEES: fiberoptic endoscopic evaluation of swallowing; US: ultrasound.

Table 2-2. Detection performances of pharyngeal post-swallow residue by US in different viscosities.

N = 23		Types of test food and liquid	
		Low viscosity	High viscosity
Results of US	Agreement with FEES	12	4
	Disagreement with FEES	7	0

Twenty-three images from nine participants were analyzed.

FEES: fiberoptic endoscopic evaluation of swallowing; US: ultrasound.

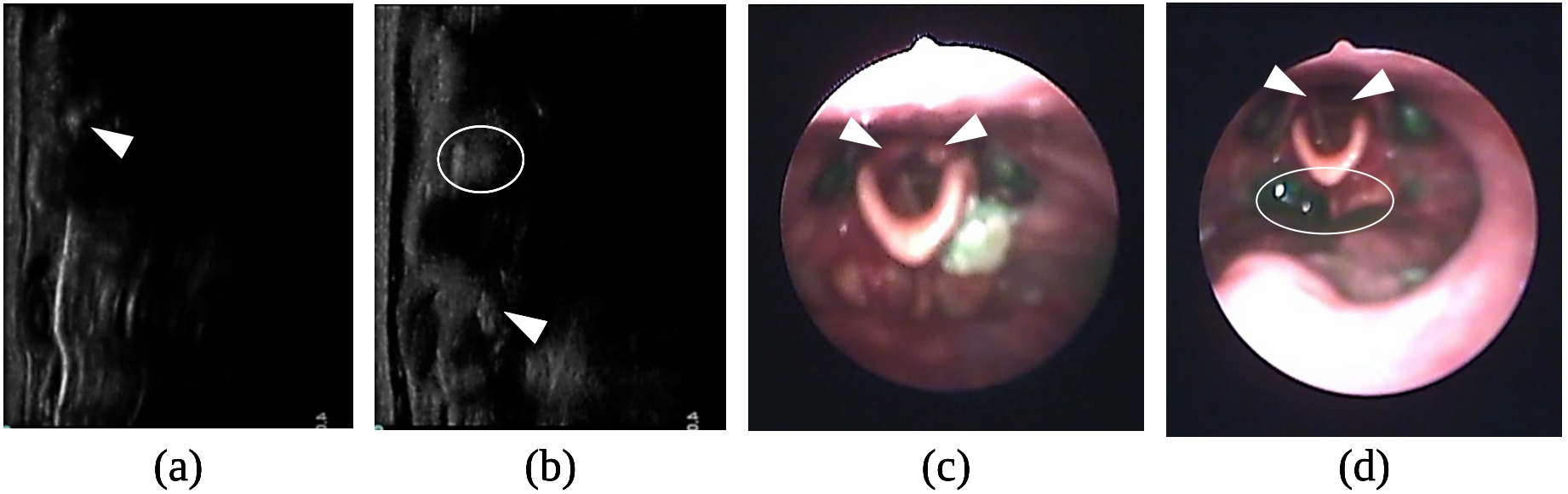


Figure 3. Only residue detected. A 75-year-old male.

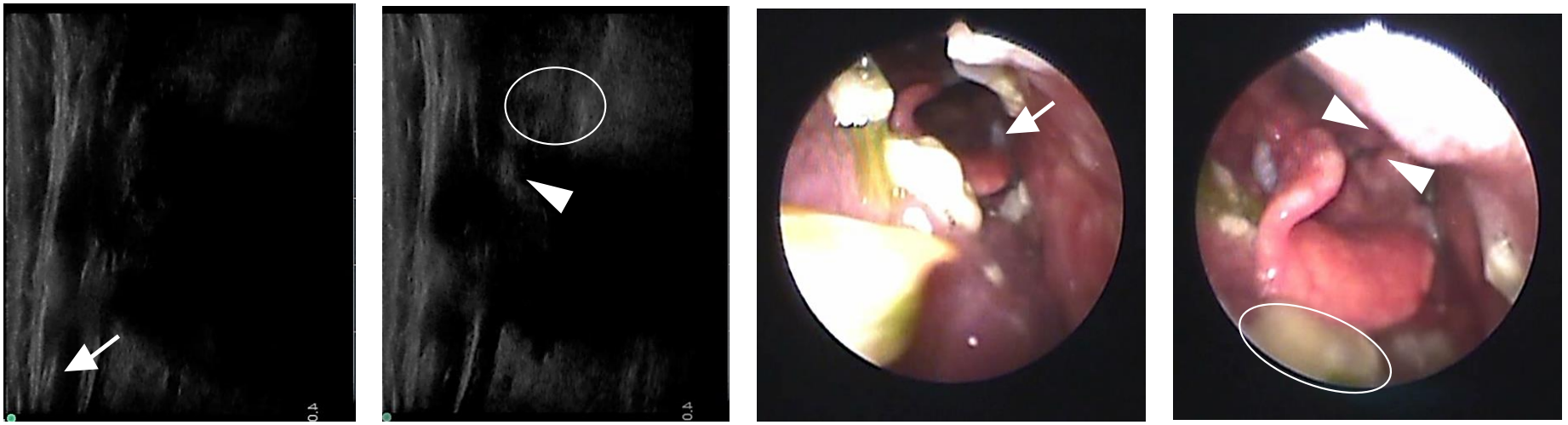
a The vocal folds were observed as a hyperechoic spot before swallowing.

b The misty hyperechoic area was observed above the vocal folds after swallowing.

c There was no residue of colored liquid in the vallecular before swallowing.

d There was a residue of colored liquid in the vallecular after swallowing.

Arrow heads represent vocal folds. Circles represent pharyngeal post-swallow residue of liquid.



(a) (b) (c) (d)

Figure 4. Both aspiration and residue detected. A 76-year-old male.

a Hyperechoic narrow objects appeared along with the tracheal wall.

b After swallowing, the hyperechoic misty area appeared above the vocal folds.

c Some grain of rice flew into the trachea.

d After swallowing, boluses of rice and vegetables remained in the vallecular.

Arrows represent aspirated boluses. Arrow heads represent vocal folds. Circles represent pharyngeal post-swallow residue.

Chapter 2

A feasibility study to clarify acceptability and usefulness of ultrasound examination during mealtimes

Background

US examination to detect aspiration and pharyngeal post-swallow residue was established in previous studies [37-39] and Chapter 1. According to previous studies, US examination does not require any special foods or equipment; therefore, the examination will show the usual swallowing pattern during mealtimes. US examination for usual swallowing is needed because differences in bolus type, volume, and delivery method of food alter the risk of aspiration [51]. Repeated aspiration of foods or saliva with bacteria into the airway causes aspiration pneumonia [6]. Therefore timely assessments of aspiration and pharyngeal post-swallow residue during mealtimes are required for appropriate swallowing care such as food and liquid modification, change of posture, and change of delivery method before swallowing problems become severe and cause aspiration pneumonia.

Previous studies that aimed to detect aspiration and pharyngeal post-swallow residue have been conducted in laboratory settings; therefore, the acceptability of this method for participants and care staff during mealtimes in a residential setting has not been elucidated. Although US examination is less invasive compared with VFSS and FEES, the examination requires attachment of a transducer during swallowing which might interrupt the participants'

mealtimes. If participants and care staff feel uncomfortable with the attachment of a transducer, the participants cannot continue their usual eating and US examination cannot detect aspiration and pharyngeal post-swallow residue during mealtimes.

There have been no studies to detect aspiration and pharyngeal post-swallow residue during mealtimes; thus, a study needed to demonstrate the possible positive outcomes of this new US examination method. Previous studies showed an association between aspiration detected by VFSS or FEES and aspiration pneumonia [52 53]. Likewise, if US examination during mealtimes showed an association between aspiration and pharyngeal post-swallow residue, and aspiration pneumonia, healthcare providers would be able to provide appropriate swallowing care based on the examination results.

To the best of my knowledge, US examination during mealtimes has not been applied together with swallowing care in a clinical setting. Therefore, I needed to conduct a feasibility study [54] of US examination during mealtimes before investigating the effectiveness of US in reducing the frequency of aspiration and pharyngeal post-swallow residue, which would help prevent aspiration pneumonia. In terms of clinical feasibility, investigation of inter-rater reliability of US examination and external validity were also required. However, I focused on the acceptability and usefulness which were the most important concepts for conducting the intervention study in step 3. The feasibility study aimed to investigate the acceptability and usefulness of US examination during mealtimes.

Methods

1) Study design

This was a feasibility study conducted from October 2013 to September 2014.

2) Setting and participants

The study was performed in a special elderly nursing home with 80 residents in the Tokyo metropolitan area, Japan. The study included nine participants who were consuming modified food, which was defined as soft, or mousse-type food, or jelly, because of suspected dysphagia. People consuming modified food tend to have more severe swallowing difficulty and a higher risk of aspiration pneumonia than those without food modification. Participants who were unable to participate in the study for over 4 weeks were excluded. The study protocol was approved by the Ethics Committee of the Graduate School of Medicine, The University of Tokyo (#10687). Written informed consent was obtained from all participants or their proxies.

3) Outcomes

The study aimed to assess the acceptability and usefulness of US examination during mealtimes. Acceptability for participants and care staff was assessed by interruption of mealtimes, which was defined as participants stopping eating or swallowing for ≥5 minutes continuously, even though they were awake. No interruption of US examinations during mealtimes was defined as the absence of interruption, and more than once interruption was defined as the presence of interruption. The participation period of this study and the number of US examinations were

also recorded so as to evaluate acceptability. A research nurse who was supervised by an experienced sonographer performed US examination during mealtimes in the dining rooms (Figure 4). For 5 months before preforming US examination, the nurse researcher acquired knowledge of the anatomy of the scanning area and was trained in the scanning method and interpretation of US images. The equipment and scanning method were the same as described in previous studies [37] [38] and Chapter 1. US movies of swallowing were obtained during 10 seconds in each measurement. The transducer was replaced for each measurement and the duration of the US examination was <10 minutes. The participants' usual food and liquid were used as the test boluses and no specialized test materials were prepared for this US examination. Care staffs were asked to provide usual assistance for the participants and to tell any difficulty for assistance if they feel it during mealtimes. Participants and care staffs were allowed to cancel the US examination anytime if they preferred. The examination was conducted at least once monthly because the frequency of the FEES, which was performed to recommend some swallowing care for preventing aspiration pneumonia, was at most once monthly performed for some residents in this facility. If the frequency of US examination was less than that of FEES, the effectiveness of US examination would be masked by FEES.

The incidence of aspiration pneumonia after baseline US examination was recorded as a measure of usefulness. The association between aspiration and pharyngeal post-swallow residue detected by US examination during mealtimes, and aspiration pneumonia indicated the

potential usefulness of this method for preventing aspiration pneumonia. Aspiration pneumonia was diagnosed by physicians at the hospitals where participants were admitted for treatment of pneumonia. These physicians were blinded to the results of US examinations. Participants were diagnosed with aspiration pneumonia if aspiration or aspirated bolus, or swallowing disorders were observed [55]. The diagnostic criteria for pneumonia were a new pulmonary infiltrate seen on chest X-ray or computed tomography and one of the following features: temperature ≥37.5°C, excessive C-reactive protein, peripheral blood leukocyte count ≥9000/μL, and respiratory tract symptoms such as sputum [55]. Participants who developed aspiration pneumonia withdrew from follow-up. Additional swallowing care after baseline US examination including modification of food or liquid, change of posture, feeding assistance, and FEES were recorded every week to consider which factors caused or prevented aspiration pneumonia. Data regarding age, sex, body mass index, and disease history were collected from the medical records.

Results

One participant was excluded after the baseline US examination because he developed aspiration pneumonia and was hospitalized 10 days later. Finally eight participants (seven women) with a median age of 83 years (range: 69–91 years) were included (Table 3). One participant received tube feeding as her main nutritional intake route, and the other seven received only oral feeding. Five participants were taking mousse-type food that did not require chewing and the remaining two were taking soft food that required less chewing than the usual

diet. Six participants required assistance with eating. All had a history of cerebrovascular diseases and four had dementia. Five had a history of aspiration pneumonia.

In terms of the acceptability of US examination, mealtime was interrupted for one of the eight participants (Case 8; Table 4). She stored jelly in her oral cavity and stopped chewing and swallowing even though the US operator removed the transducer from her cervical area. She did not show any cough reflex or difficulty in breathing. The US operator and a healthcare worker decided to stop US examination for her safety. US examinations during mealtimes were conducted again twice after that day, with her consent and she did not experience any interruption during the examination. The median duration of observation of the eight participants was 169.5 days (range: 32–347 days) and the median number of US examinations for each participant was 7.5 times (range: 1–21 times).

In terms of the usefulness of US examination, two of five participants in whom aspiration and pharyngeal post-swallow residue were detected developed aspiration pneumonia (Table 4). Two of the three participants in whom aspiration and residue were not detected did not develop aspiration pneumonia. Participants in whom aspiration was detected but who did not develop aspiration pneumonia received additional swallowing care, including change of posture, modification of liquid viscosity, and assistance with feeding during observation (Table 5). Participants who developed aspiration pneumonia showed a higher median frequency of aspiration and residue (0.60 and 0.90, respectively) at the first detection than participants who

did not developed aspiration pneumonia (0.40 and 0.50, respectively).

Discussion

To the best of my knowledge, this is the first study to show the feasibility of US examination during mealtimes for residents in a nursing home. The finding that US examination was conducted without interruption of mealtime showed the acceptability of this method. The association between aspiration and pharyngeal post-swallow residue detection by US examination during mealtimes and the development of aspiration pneumonia indicated the potential preventive usefulness of this method.

The most important determinant of the acceptability of US examination during mealtimes was the lack of interruption of eating and swallowing during attachment of the transducer to the cervical area. The US operator carefully controlled the transducer pressure and observed the participants' swallowing during the examination so as to avoid swallowing difficulty. This study found it was possible to apply US examination during usual mealtimes. The US examination during mealtimes in the present study differed from previous studies [37 38] and that described in Chapter 1, in which it was performed in a laboratory setting, with the participants' posture and body motion limited. VFSS or FEES sometimes requires participants to fix their head and neck position for good visualization of images and for safety. A US operator used vocal folds as a land mark to detect aspiration and residue in the US images, thus; the US operator did not have to limit the participants' posture and body motion. Therefore, the

participants were able to continue their mealtime in comfort during US examination. Although one participant stopped swallowing and the examination was halted, this seemed to be a temporary event. US examination was accepted on the next occasion.

The association between US detection of aspiration and pharyngeal post-swallow residue during mealtimes, and aspiration pneumonia suggest the usefulness of this method. All participants with aspiration and residue who did not develop aspiration pneumonia had received additional swallowing care to prevent aspiration pneumonia. In contrast, all participants with aspiration and residue who developed aspiration pneumonia had not received additional swallowing care. These results suggest that detection of aspiration and residue by US examination could have a role in predicting development of aspiration pneumonia and the administration of preventive care. Based on the results of US examination during mealtimes, healthcare providers can suggest appropriate swallowing care to prevent aspiration pneumonia.

There was one person in whom aspiration was not detected by US examination but aspiration pneumonia developed after the examination. FEES also did not detect aspiration or pharyngeal post-swallow residue in this participant, who developed aspiration pneumonia 5 days after undergoing FEES. Her aspiration pneumonia was difficult to predict using imaging methods for detection of aspiration and pharyngeal post-swallow residue during mealtimes.

Aspiration and pharyngeal post-swallow residue detected by US examination were associated with development of aspiration pneumonia. However, this feasibility study does not

confirm that US examination contributes to the prevention of aspiration pneumonia. There are two main possibilities for how bias affected the relationship between US examination and development of aspiration pneumonia. One is that FEES affected swallowing care and contributed to preventing aspiration pneumonia. FEES as well as US examination, could have a role in preventive care for aspiration pneumonia because all three participants who had a change of swallowing care underwent FEES, which showed aspiration or pharyngeal post-swallow residue (Table 4). There was no control group that did not undergo US examination; thus, an effect of FEES cannot be excluded. The other possibility is that differences in the onset of dysphagia may have affected the development of aspiration pneumonia. There was a large difference in the follow-up period between participants who developed aspiration pneumonia and those who did not. It is difficult to investigate the onset of dysphagia within nursing homes, so statistical adjustment after data collection was impossible. Randomization would resolve this problem and adjust for other unavoidable confounding factors. Therefore, to show the direct effectiveness of US examination for prevention of aspiration pneumonia, a randomized controlled trial is needed.

In conclusion, this feasibility study in a nursing home showed that US examination during mealtimes was acceptable for the residents and useful in predicting and preventing aspiration pneumonia. Regular US examinations did not cause interruption of eating and swallowing. Aspiration and pharyngeal post-swallow residue detected by US examination

during mealtimes were associated with development of aspiration pneumonia. In the next study, the effectiveness of intervention guided by US examination will be confirmed by a randomized controlled trial.

Figure 4. How to attach a transducer in US examination during mealtimes.

The transducer was attached to the participant's cervical area above the thyroid cartridge in a sagittal plane with sufficient echo jelly. The US operator controlled the pressure of the transducer so as not to disturb the participant's swallowing.

US: ultrasound.

Table 3. Characteristics of the eight participants who underwent US examinations during mealtimes.

Case	Age (year)/ sex	BMI	Barthel Index	Type of food	Feeding method	Main diseases	History of AP	Development of AP
1	70/M	14.5	5	Mousse	Assisted	Stroke	+	+
2	90/F	17.6	25	Soft	Self	Stroke, dementia	−	+
3	90/F	20.6	5	Mousse	Assisted	Stroke, dementia	+	−
4	69/F	21.6	10	Mousse	Assisted	Stroke, dementia, Chronic obstructive pulmonary disease	+	−
5	75/F	16.8	10	Mousse	Self	Stroke	−	−
6	76/F	16.1	5	Mousse	Assisted	Stroke	+	+
7	90/F	26.9	5	Soft	Assisted	Chronic subdural hematoma, dementia	−	−
8	91/F	20.8	5	Tube feeding, jelly	Assisted	Stroke	+	−

AP: aspiration pneumonia; BMI: body mass index; F: female; M: male; US: ultrasound.

Table 4. Feasibility of US examination during mealtimes.

Case	Acceptability			Usefulness				
	Follow up (days)	No. of US examinations	Interruption of mealtime	Aspiration	Residue	Development of AP	Swallowing care	FEES after US examinations (Results)
1	36	2	Absence	Presence	Presence	+	No change	−
2	32	1	Absence	Presence	Presence	+	No change	−
3	347	21	Absence	Presence	Presence	−	Changed	+ (Aspiration)
4	346	20	Absence	Presence	Presence	−	Changed	+ (Residue)
5	235	12	Absence	Presence	Presence	−	Changed	+ (Aspiration)
6	68	5	Absence	Absence	Absence	+	No change	+ (No detection)
7	189	9	Absence	Absence	Absence	−	No change	−
8	150	5	Presence	Absence	Absence	−	No change	+ (No detection)

AP: aspiration pneumonia; FEES: fiberoptic endoscopic evaluation of swallowing; US: ultrasound

Table 5. Details of the US examination and swallowing care.

Case	Follow up (days)	No. of US examinations	AP	Aspiration				Residue			Swallowing care (day)†
				Day†	Frequency	Type	Silent	Day†	Frequency	Type	
1	36	2	+	0 14	1/5 3/3	Mousse Mousse	1/1 2/3	0 14	4/5 3/3	Mousse Mousse	No change
2	32	1	+	0	3/3	Porridge, Soft	0/3	0	3/3	Porridge, Soft	No change
3	347	21	−	105	2/5	Mousse	2/2	14 127 168 203 248 304 332	2/3 3/4 2/4 2/4 5/7 3/5 1/2	Jelly Mousse, soup Jelly Mousse, jelly Mousse, jelly, soup Mousse, jelly Mousse	Changed degree of reclining (231)
4	346	20	−	0 331	1/3 1/2	Mousse Mousse	1/1 1/1	41 55 70 132 142 188 247 258 314 331	3/6 1/5 1/6 2/6 4/6 2/5 5/6 3/8 1/3 1/2	Mousse, jelly Mousse Mousse Thickened water Mousse, jelly, soup Soup, jelly Mousse, soup, jelly Mousse, soup Mousse Mousse	Changed viscosity of liquid (132)
5	235	12	−	0 15 45 136	1/1 1/3 1/3 1/3	Jelly Mousse Soup Jelly	1/1 0/1 1/1 1/1	220	1/3	Jelly	Changed self-feeding to assisted feeding (4)
6	68	5	+	−	−	−	−	−	−	−	No change
7	189	9	−	−	−	−	−	−	−	−	No change
8	150	5	−	−	−	−	−	−	−	−	No change

†Days after baseline US examination.

AP: aspiration pneumonia; US: ultrasound

Chapter 3

A randomized controlled trial to investigate the effectiveness of the prevention of aspiration pneumonia using recommendations for swallowing care guided by ultrasound examination

Background

The feasibility study that included eight residents in a special elderly nursing home showed that US examination during mealtimes could be safely continued for 32–347 days. Moreover, there was an association between aspiration and pharyngeal post-swallow residue detected using US examination during mealtimes and the development of aspiration pneumonia. Participants in whom aspiration and pharyngeal post-swallow residue were detected developed aspiration pneumonia where no additional swallowing care was received. These findings indicated the acceptability and usefulness of US examination during mealtimes. However, it is not possible to reach a definitive conclusion regarding the effectiveness of the introduction of US examination during mealtimes, and to make recommendations concerning swallowing care for the prevention of aspiration pneumonia, because of the limitations of the study design presented in Chapter 2. This feasibility study did not have a parallel control group that did not undergo US examination and receive recommendations for swallowing care. Other types of swallowing care that were not related to US examination and the severity of swallowing disorders of the participants might have affected the development of aspiration pneumonia. A control group and

randomization are needed to exclude biases.

A previous randomized controlled trial demonstrated the effectiveness of higher frequency VFSS in preventing aspiration pneumonia relative to lower frequency VFSS in an acute care setting [56]. In this trial, advice on safe swallowing and dietary modification were conducted based on VFSS and clinical observation. Daily swallowing assessment and appropriate swallowing care will be crucial in preventing aspiration pneumonia; however, swallowing examination involving the frequent use of imaging methods with VFSS was only possible in this trial in an acute care hospital. Given that the medical conditions of patients in acute care settings are unstable, frequent VFSSs were considered to be useful in the detection of changes in swallowing ability even if these examinations involved invasive methods. It is considered that frequent VFSSs in a nursing home, where the medical conditions of the residents are usually stable, is not beneficial. However, less invasive US examinations during mealtimes for the detection of aspiration and pharyngeal post-swallow residue are considered to be beneficial. US examinations can provide appropriate guidance regarding safe swallowing and dietary modification as well as VFSS before the swallowing problems become severe and cause aspiration pneumonia.

I hypothesized that frequent swallowing examinations using the US method with recommendations for swallowing care reduces aspiration and pharyngeal residue, which are risk factors for aspiration pneumonia. The aim of this study was to investigate the effectiveness

of US examination and recommendations for swallowing care for the reduction of aspiration and pharyngeal post-swallow residue as compared with standard swallowing care.

Methods

1) Study design

The study was a prospective open randomized-controlled, parallel design trial, with one-to one allocation ratio. It is registered with the UMIN Clinical Trials Registry, number UMIN000016002. The full trial protocol is available at https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&recptno=R000018600&type=summary&language=E. The study has been conducted in accordance with the CONSORT Statement (Appendix 1) [57].

2) Setting and participants

The study was conducted in a special elderly nursing home in the Tokyo metropolitan area, where I performed the feasibility study described in Chapter 2, from December 2014 to September 2015. Recruitment of the participants was conducted from December 2014 to June 2015. Residents received written and oral explanations regarding the study. If a resident was assessed who had difficulty understanding the explanation of the study given by the ward manager, written or oral explanation was provided for their proxies via mail or during their visitation. All residents who underwent oral feeding were assessed for eligibility. Residents that did not provide consent, or consent was not given by their proxies, were excluded from the

study. The study protocol was approved by the Ethics Committee of the Graduate School of Medicine, The University of Tokyo (#10707). Written informed consent was obtained from all residents or their proxies.

3) Randomization and blinding

A stratified randomization was introduced in this study. The risk of aspiration pneumonia is related to the severity of swallowing disorders [58]; therefore, if many of the individuals with severe swallowing disorders are allocated to either group, the outcome of that group will be biased. To reduce such bias, stratified randomization method was adopted. Participants who satisfied at least the following three criteria were labeled as the "intensive-care group". The other participants were labeled as the "none intensive-care group". The criteria were as follows: 1) underwent FEES within the past 6 months or had a scheduled FEES during the study period; 2) underwent diet modification to mousse type food or mixer type food; 3) had already been introduced to alternate swallowing based on FEES or clinical observation. The intensive-care group was considered to have more severe swallowing disorders than the none-intensive-care group.

Participants were randomly assigned to the intervention group or the control group based on a randomization procedure using a single computer-generated random numbers list, held in the research office remote from the study environment. After informed consent was provided, a researcher assessed whether a participant should be included in the intensive-care

group or none-intensive-care group. Then the information was provided to another researcher who performed the randomization. Other characteristics of the participants were not provided to the researcher to avoid bias involving the randomization. Blinding was not possible for participants, health care providers, and the researcher who performed US examinations; this was because it was clear to these groups that the participants underwent US examination during mealtimes.

4) Algorithm of recommendations for swallowing care

An algorithm regarding recommendations for swallowing care was introduced in this study (Figure 5). When aspiration was detected during US examination at mealtimes, modification of the food type and FEES were recommended. Based on previous studies, modification of the viscosity of food is one of the most effective intervention approaches in preventing aspiration pneumonia [14 59]. Aspiration involves the unintentional flow of foods or liquids boluses into the trachea that occurs in individuals with an impaired swallowing reflex. It is more difficult for these individuals to safely swallow a chopped meal or a low viscosity liquid because it scatters in the oral and pharyngeal cavity. It is difficult to detect the appropriate timing of the swallowing of scattered boluses. Increasing the viscosity of the food and liquid improves bolus formation before swallowing so the level of aspiration can be reduced [60]. FEES can visualize structural abnormalities of the pharynx and larynx, which sometimes cause swallowing disorders. A method for the detection of structural disorders using US examination has not yet been

established; thus, FEES was added to the recommendations for cases with aspiration to investigate the causes of aspiration.

When pharyngeal post-swallow residue was detected during US examination at mealtimes, alternate swallowing was recommended. Preventing pharyngeal post-swallow residue is also indispensable for the prevention of aspiration pneumonia. Alternate swallowing is one of the common strategies that are used to reduce pharyngeal post-swallow residue, because alternate solids and liquids can wash down the remaining boluses from the pharynx [61].

5) Intervention

The intervention consisted of four times US examinations during mealtimes and recommendations for swallowing care based on the algorithm, every 2 weeks during an 8 week period. FEES for providing preventive swallowing care for aspiration pneumonia was performed once monthly for some participants. Therefore, a study period that was >1 month was required to compare the effectiveness of the intervention to usual swallowing care. The participants in whom aspiration or residue from US examination was detected, and who did not undergo a change in swallowing care, developed aspiration pneumonia in <2 months in the study conducted in Chapter 2; therefore, the follow-up period for investigation of the effectiveness of the intervention was 8 weeks. The flow of the US examinations and recommendations for swallowing care during mealtimes are summarized in Figure 6. US examinations during mealtimes were performed by a research nurse using the same equipment

as that detailed in Chapters 1 and 2. Baseline and follow-up examinations were performed twice over a 2 day period to avoid random error regarding the outcome, as a result of the participants' condition and preferences concerning the contents of the meal. Because the US examinations needed to detect constant aspiration and pharyngeal post-swallow residue during mealtimes that were related to the development of aspiration pneumonia, the occurrence of a single aspiration or residue during a 2 day period was regarded as an error. If more than two detections of aspiration or residue were obtained, it was considered that the participant had a swallowing disorder that would cause aspiration pneumonia. The US examination consisted of multiple measurements involving different viscosities of food and liquid, and the presence or absence of aspiration and pharyngeal post-swallow residue at each measurement were recorded. One US examination basically consisted of nine measurements (staple diet, three measurements; side dishes, three measurements; liquids, three measurements) unless there were any difficulties encountered in collecting the images. One measurement involved a US movie of swallowing over a period of 10 seconds; the US examination during mealtime was completed within 10 minutes. Aspiration during swallowing on a US image was interpreted as the passage of a hyperechoic object through the vocal folds along the tracheal wall, involving movement that differed from that of the surrounding tissue [37]. Pharyngeal post-swallow residue was defined as the remaining hyperechoic misty area above the vocal folds after swallowing (Chapter 1). Recommendations to health care providers regarding swallowing care using US images were

provided by a US operator through a full-time dietitian.

No recommendations concerning swallowing care were provided to the control group by a US operator. They undertook US examinations at the baseline and follow-up regarding the evaluation of the outcome. Swallowing care based on the usual observation and standard examinations including scheduled FEES were undertaken in the control group.

6) Outcome measures

The primary outcome was the frequency of aspiration and residue. The frequency of aspiration or residue was defined as x / y × 100 % when aspiration or residue were detected x times from y times concerning the total US measurements. The secondary outcomes were the changes in swallowing care in accordance with the algorithm and the incidence of aspiration pneumonia. The changes in swallowing care were unscheduled FEES, the introduction of alternate swallowing, and modification of food type. These changes were evaluated every week by a dietitian. The definition of aspiration pneumonia was the same as those used in Chapter 2. Data regarding age, sex, body mass index, and experience of VFSS and FEES after admission to the nursing home were collected from the medical records.

7) Statistical analyses

Calculation of the study sample size was based on the feasibility study finding (Chapter 2) that three participants out of the eight (38%) showed a reduction in the frequency of aspiration. Consequently, the calculation applied 40% of the reduction of the frequency of aspiration in the

intervention group, and 10% of the reduction of the frequency of aspiration in the control group, over a period of 2 months for the estimation of sample size. To achieve 80% power at the 5% (two-tailed) significance level for the reliable identification of treatment effect, the sample size required was estimated to be 32 in each group. Assuming a 10% drop out rate from the study in each group, the required sample size needed was 72 in total.

Analyses were conducted by intention to treat; therefore, all 54 participants who undertook randomization were included in the analyses. Participants were categorized into four groups (severe dysphagia, moderate dysphagia, normal, and unknown) based on the frequency of aspiration and residue at the baseline US examination, to confirm the equality of random allocation in terms of the severity of swallowing disorders. The severe dysphagia group was defined as the participants whose baseline frequency of aspiration or residue was ≥50%. The moderate dysphagia group was defined as the participants whose baseline frequency of aspiration or residue was <50%, and who showed aspiration or residue more than twice. The normal group was defined as the individuals whose baseline numbers of aspirations and residues were <1. Individuals who dropped out of the trial before baseline US examinations were defined as the unknown group. Then I investigated the outcomes of participants based on the follow-up US examinations. For the severe and moderate dysphagia groups, when the frequency of aspiration and residue were reduced relative to the baseline US examinations, the participant was regarded as “reduced”, and the remaining participants were regarded as

“increased”. For the normal group, when the number of aspirations and residues were ≤1, the participant was regarded as “maintained”, and the remaining participants were regarded as “increased”. Where there was a reduction, the differences in the frequency of aspiration and residue from baseline to follow-up were calculated for each participant. For the participants whose evaluation of the comparison was inconsistent between aspiration and residue, only those who exhibited a reduction in both aspiration and residue were defined as reduced and the others were defined as increased or maintained.

The Wilcoxon rank sum test was used for the evaluation of continuous variables and Fisher’s exact test or chi-square test were used for categorical variables. Differences in the Kaplan–Meier curves were analyzed using the log rank test. All analyses were conducted using STATA, version 14 (STATA Corp., College Station, TX, USA).

Results

Seventy-five residents in total, who were capable of oral feeding in a special elderly nursing home, were assessed for eligibility before recruitment to this study. Written informed consent was obtained from 54 (72%) of the 75 eligible residents or their proxies between December 19, 2014 and June 30, 2015 (Figure 7). Follow-up was continued until September 3, 2015. Twenty-eight participants were randomized to the intervention group and 26 to the control group. In the intervention group, nine participants could not complete the 8-week follow-up period. Prior to the baseline US examinations, five participants withdrew from the study; three participants

declined to join the study, one participant died, and in one participant it was judged that the attachment of the transducer was impossible because of the presence of a severe cavity in the cervical area. After the baseline US examinations, one participant refused to continue with the study, and three participants were hospitalized. In the control group, three participants could not complete follow-up. In two participants, it was considered that the attachment of the transducers was impossible because of a severely humped back or the excessive thickness of fat in the cervical area; one participant died before the baseline US examination. One participant was hospitalized after the baseline US examination. There were no cases where interruption of mealtime reported in Chapter 2 was observed.

Table 6 details the baseline characteristics of the participants. The intervention group included seven participants and the control group included six participants allocated to the intensive-care group. There were no significant differences in characteristics between the two groups including age, sex, body mass index, history of aspiration pneumonia, types of meal ingested, and the number of participants in whom aspiration and residue were detected at the baseline US examination. The distribution of the grade of severity of swallowing disorder differed significantly between the two groups ($P = 0.046$). In the intervention group, the severe dysphagia group included three (10.7%) participants and the moderate dysphagia group included one (3.6%). In the control group, the severe dysphagia group included one (3.9%) participant and the moderate dysphagia group included eight (30.8%).

In terms of the frequency of aspiration and residue at the follow-up US examinations in the severe dysphagia group, two of the three participants exhibited a reduction in the frequency in the intervention group (Table 7). However, one participant in the severe dysphagia group developed aspiration pneumonia in the control group.

In the intervention group, all of the participants with aspiration or residue at the baseline examination showed a reduction in the frequency of the aspiration and residue at the follow-up US examination (Table 8). There were five participants in whom aspirations or residues were not detected at the baseline US examinations; they were detected at the follow-up US examinations. Any participants in the control group with aspiration at the baseline examinations did not show a reduction in the frequency of the aspiration (Table 9). Three of the participants in the control group, in whom residue was detected at the baseline examinations, exhibited a reduction in the frequency of residue. Among those participants who showed a reduction in the frequency of aspiration or residue, the difference in baseline and follow-up frequency of aspiration or residue tended to be higher in the intervention group than in the control group. The median reduction in the frequency of aspiration and residue in the intervention group was 31%, and that in the control group was 11%.

In the intervention group, one participant underwent FEES and one participant underwent alternate swallowing based on the recommendations for swallowing care. Both showed a reduction in aspiration and residue after 8 weeks. One participant in the control group

received a modification of food type even though there was no recommendation for swallowing care by the US operator. She did not exhibit a reduction in aspiration and residue after 8 weeks. Any scheduled FEES was not performed for participants in the intervention group or in the control group.

Two of the 28 (7.1%) participants allocated to the intervention group developed aspiration pneumonia. One of the 26 (3.8%) participants allocated to the control group developed aspiration pneumonia. There was no significant difference between the intervention and control groups regarding the time required to develop aspiration pneumonia ($F = 3.0$; $P = 0.450$).

Discussion

To the best of our knowledge, this is the first randomized controlled trial that has investigated the effectiveness of swallowing care guided by US examination during mealtimes as compared with standard care. The new finding was that swallowing care guided by US examination effectively reduced the frequency of aspiration and residue.

The results suggested that swallowing care guided by US examination during mealtimes effectively reduced the frequency of aspiration and pharyngeal post-swallow residue in individuals with severe dysphagia. Two participants out of the three in the severe group experienced a reduction in the frequency of aspiration and pharyngeal post-swallow residue in the intervention group (Table 7). Moreover, this reduction in frequency was relatively higher in

the intervention group than in the control group (Tables 8 and 9). This finding is consistent with that of a previous randomized controlled trial [56], where participants who undertook frequent VFSS were effectively prevented from developing aspiration pneumonia in an acute care setting. Although it is difficult to compare the effectiveness of the intervention involving usual care among the severe dysphagia group, the participants with severe dysphagia in the intervention group had not undertaken any swallowing assessments before the study, such as VFSS or FEES; therefore, there was a possibility that their dysphagia could have become worse, and that they could have developed aspiration pneumonia if they had not undertaken US examination during mealtimes.

Five participants in the intervention group experienced an increase in the frequency of aspiration or residue even though they did not show aspiration or residue at the baseline examination. Based on an algorithm for swallowing care guided by US examinations every 2 weeks, the US operator recommended continuation of usual care for the participants in whom aspiration and residue were not detected. The increased frequency of aspiration or residue in the intervention group indicated that the frequency of the US examinations every 2 weeks was insufficient, because there was a possibility that some deterioration in swallowing ability occurred during the 2 weeks period. The frequency of the US examination during mealtimes could be increased to detect changes in swallowing ability for more effective prevention of aspiration pneumonia.

For clinical implementation, noninvasive US examination during mealtimes will be effective in reducing the frequency of aspiration and pharyngeal post-swallow residue without causing harm. In this study, no adverse events including the interruption of mealtimes were observed in both the intervention and control groups. Twenty-three (82.1%) participants were taking modified food and eight (28.6%) required some assistance for eating in the intervention group who undertook US examination during mealtimes (every 2 weeks over an 8-week period). Nineteen of the 28 (67.9%) participants in the intervention group completed the 8-week follow-up period, indicating that the frequency and duration of the US examination were generally acceptable for the participants and care staff. Two participants were excluded from this study because the transducer could not be fully attached. They had a severe cavity or excess fat in the scan area, which prevented appropriate attachment of the transducer. These participants might have had severe dysphagia caused by pharyngeal muscle atrophy [62 63]. If US operators detect participants with insufficient attachment of the transducer, the recommendation of other imaging examinations for the detection of swallowing problems for early intervention will be needed.

The strength of this study was that I recruited all residents in a special elderly nursing home. Fifty-four (72%) participants of 75 accepted an invitation to join the study. In terms of generalizability, this facility is a typical nursing home in Japan. The mean age of the participants was ≥80 years; approximately 80% were women, and most undertook some food modifications

[64 65]. The finding that swallowing care guided by frequent US examination contributed to a reduction in the frequency of aspiration and pharyngeal-residue may be applied to other nursing homes in Japan.

This study had two limitations. The first was that an imbalance concerning the distribution of severity of dysphagia between the intervention and the control group occurred as a result of randomization. I used stratified randomization based on the application of swallowing care, which was considered to indicate the severity of dysphagia; however, this approach was not sufficient. The introduction of swallowing assessment for the evaluation of aspiration and pharyngeal post-swallow residue before randomization might be a better approach in avoiding an imbalance in distribution. However it was difficult to perform US examination before randomization for all participants because of the lack of a sufficient number of US operators. The application of other imaging assessments such as VFSS and FEES for all participants was ethically difficult.

The second limitation was that there was no significant difference in the incidence of aspiration pneumonia between the intervention and control groups because of the low incidence of aspiration pneumonia. In the current study, three participants of the 54 (5.6%) developed aspiration pneumonia; however, three participants out of eight (37.5%) developed aspiration pneumonia in the study described in Chapter 2. The reduction in the development of aspiration pneumonia indicates the possibility that the introduction of US examination during mealtimes

affected swallowing care in this facility. The frequency of US examination and the number of residents who undertook US examination largely increased relative to the study reported in Chapter 2. Therefore, awareness in preventing aspiration pneumonia and the promotion of swallowing care might have occurred overall in this facility, and this could have influenced the reduction in the number of residents with aspiration pneumonia. The selection of other facilities for the intervention study might have avoided the effect of the US examination and visits of a researcher, and reduced the incidence of aspiration pneumonia. Since this was the first intervention study for the investigation of the effectiveness of US examination during mealtimes, a trusting relationship between the researcher and care staff was needed. For this reason, I conducted the intervention study in the same facility as the feasibility study reported in Chapter 2. A randomized controlled trial with a larger sample size involving multiple facilities is needed to avoid inequality concerning the characteristics of the participants between the two groups, and to investigate effectiveness in relation to reduction in the incidence of aspiration pneumonia.

I focused on the detection of aspiration and pharyngeal post-swallow residue as a method of US examination for the prevention of aspiration pneumonia. In addition, some previous studies have shown that US examination was useful in measuring the movement of hyoid bone, and also the volume of suprahyoid muscles, which had important roles in the prevention of aspiration and pharyngeal residue [30-32, 68]. A combination of these assessment

methods will provide comprehensive swallowing care for the prevention of aspiration pneumonia, including modification of food and liquid types, changes in feeding methods, changes in posture, and the introduction of swallowing exercises to improve and maintain swallowing ability. Recent studies have suggested that relatively simple swallowing exercises such as a jaw-opening exercise, which just involves repetitive opening the jaw to its maximum and maintaining this position, had the potential to improve swallowing ability in elderly people with dysphagia [44]. Using bedside US examination for the assessments of swallowing ability as a screening method for the detection of abnormal swallowing, and as a follow-up examinations for the evaluation of swallowing care, is expected to prevent aspiration pneumonia. Among the multidisciplinary team approach including nurses, medical doctors, dentists, speech-language pathologists, physical therapists, dietitians, and care workers; nurses who have knowledge of the pathophysiology of swallowing in the practice of daily swallowing care will have a role in performing US examination during mealtimes. Nurses will be able to provide swallowing care, and to propose better swallowing care to other healthcare providers regarding the prevention of aspiration pneumonia. Evidence that recommendations for swallowing care guided by frequent US examination during mealtimes can prevent aspiration pneumonia will promote the use of this method among clinicians. When this is achieved, US examination will contribute to the comprehensive prevention of aspiration pneumonia and the promotion of a more active aging society.

In the future, this method will need to be applied by other clinicians in multicenter randomized-controlled studies. To achieve this, two skills will be mainly required: accurate evaluation of US images, and proficient attachment of a transducer to obtain clear images. To use this method in participants with differently shaped cervical areas, the accumulation of cases involving individuals with dysphagia will be required. In beginners, some image processing methods may assist in the detection of aspiration and pharyngeal post-swallow residue in complex US images. For the training concerning the attachment of a transducer, standardization of this method is needed. Future studies will be required to establish a training method for US examination during mealtimes, to evaluate the capability of this method among clinicians, and to investigate its effectiveness in preventing aspiration pneumonia using a large sample size. This study confirmed that aspiration and pharyngeal post-swallow residue during mealtime could be prevented. In addition, the development of an assessment and prevention method for silent aspiration during sleep will be required in future studies for the prevention of aspiration pneumonia.

In conclusion, swallowing care guided by frequent US examinations during mealtimes reduced the frequency of aspiration and residue during an 8-week period in individuals with severe dysphagia relative to standard swallowing care alone.

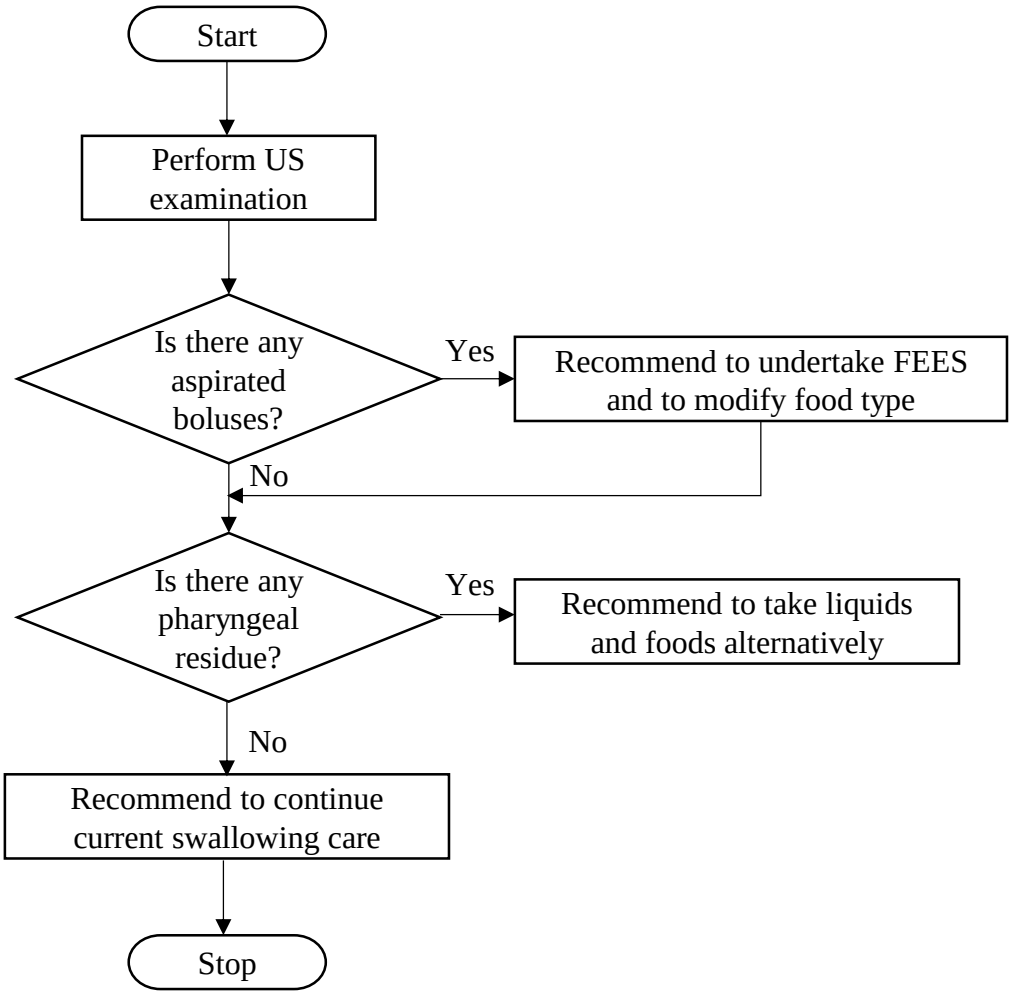


Figure 5. Algorithm used to apply the results of ultrasound examination to swallowing care.

FEES: fiberoptic endoscopic evaluation of swallowing; US: ultrasound.

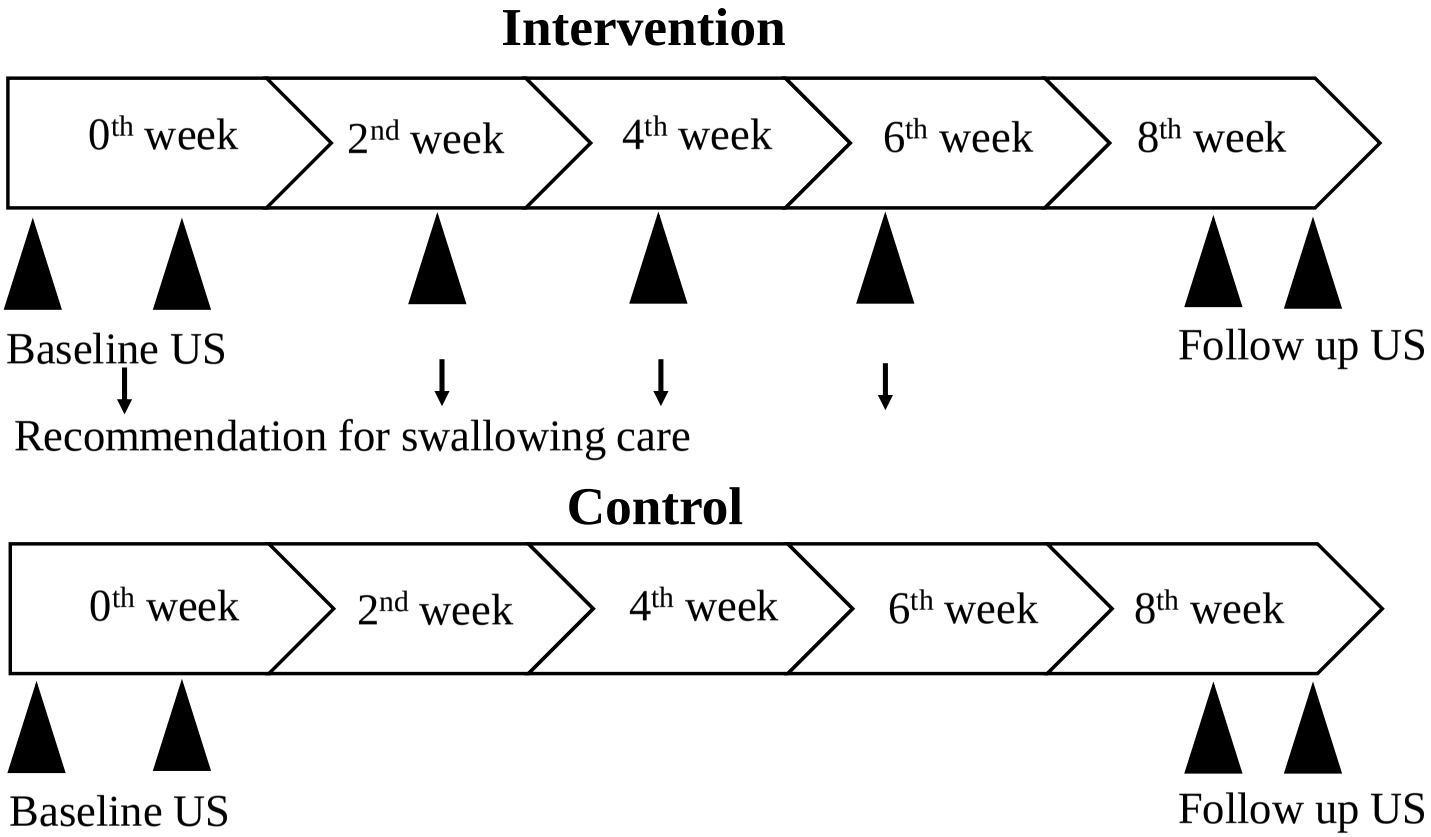


Figure 6. Diagram illustrating the examination flow in the intervention and control groups.

Arrow heads represents the US examinations which consisted of nine measurements.

US: ultrasound.

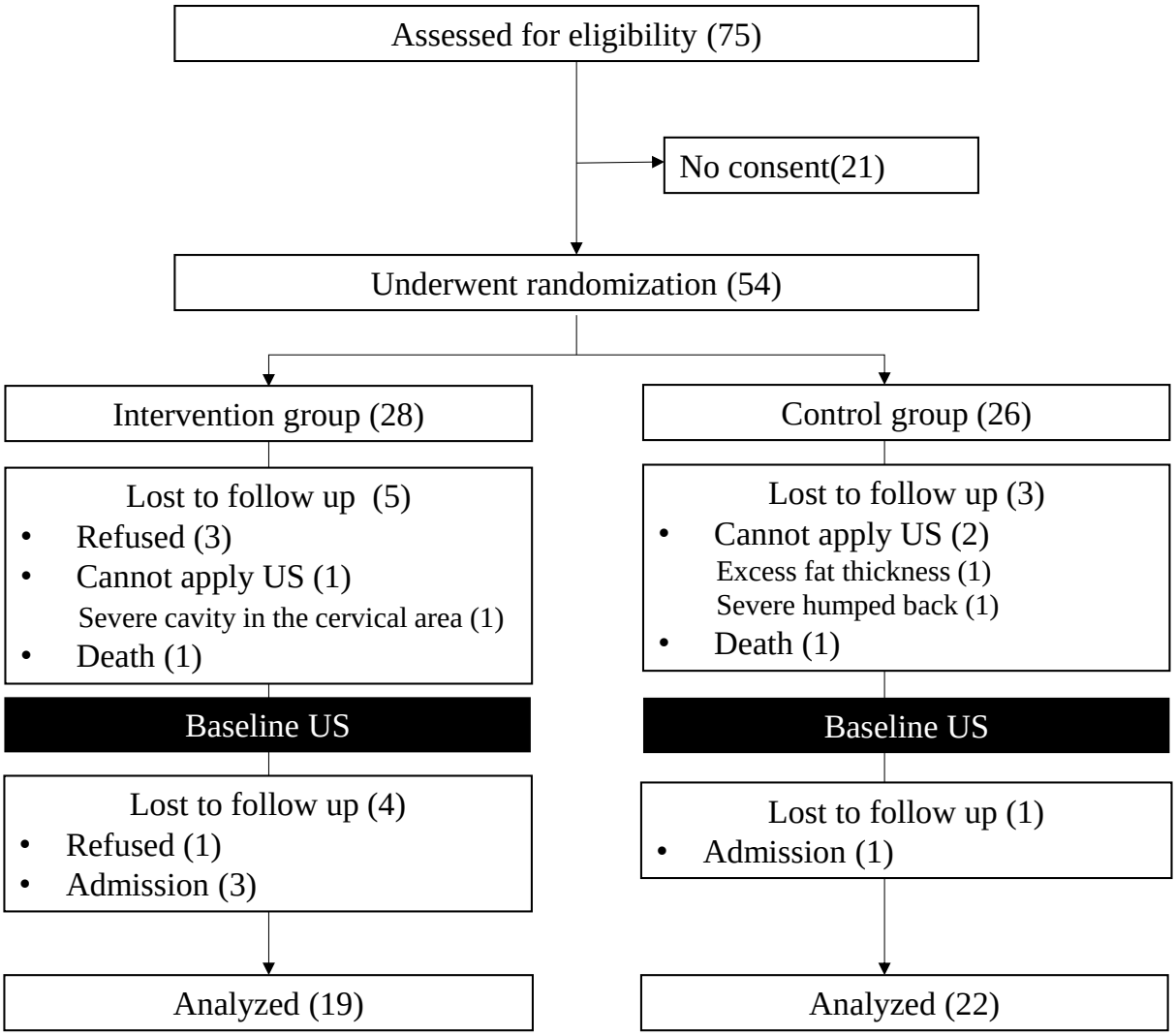


Figure 7. Flow diagram of the participants.

US: ultrasound.

Table 6. Baseline characteristics of the participants.

	Intervention group (n = 28)	Control group (n = 26)	P value
Age (years), median (Q1, Q3)	86 (81, 91)	85 (79, 91)	0.722†
Females, n (%)	24 (85.7)	23 (88.5)	1.000‡
Cerebrovascular disease, n (%)	8 (28.6)	12 (46.2)	0.181§
Aspiration pneumonia, n. (%)	6 (21.4)	2 (7.7)	0.253‡
Body mass index, median (Q1, Q3)	20.3 (18.4, 22.9)	19.5 (18.6, 21.3)	0.438†
Charlson Risk Index, median (Q1, Q3)	1 (1, 2)	2 (1, 3)	0.089†
Underwent FEES or VFSS, n (%)	6 (21.4)	4 (15.4)	0.730‡
Type of food			0.846‡
Regular, n (%)	5 (17.9)	5 (19.2)	
Chopped, n (%)	6 (21.4)	3 (11.5)	
Soft, n (%)	12 (42.9)	13 (50.0)	
Mousse, n (%)	4 (14.3)	4 (15.4)	
Other types, n (%)	1 (3.57)	1 (3.85)	
Required assistance for eating, n (%)	8 (28.6)	8 (30.8)	0.860§
Intensive-care group, n (%)	7 (25.0)	6 (23.1)	0.869§
Aspiration detected by US, n (%) (N = 46)*	2 (8.70)	3 (13.0)	1.000‡
Residue detected by US, n (%) (N = 46)*	3 (13.0)	7 (30.4)	0.284‡
Severity of dysphagia			
Severe, n (%)	3 (10.7)	1 (3.9)	0.046‡
Moderate, n (%)	1 (3.6)	8 (30.8)	
Normal, n (%)	19 (67.8)	14 (53.8)	
Unknown, n (%)	5 (17.9)	3 (11.5)	

FEES: fiberoptic endoscopic evaluation of swallowing; US: ultrasound;

VFSS: videofluoroscopic swallowing study; Q1: first quartile; Q3: third quartile.

*Eight participants who withdrew from the study were excluded from the analyses.

†Wilcoxon rank sum test; ‡Fisher's exact test; §Chi-square test.

Table 7. Distribution of the severity of dysphagia and follow-up results.

Severity	Intervention group (n = 28)			Control group (n = 26)		
	Baseline	Follow-up*		Baseline	Follow-up*	
Severe, n (%)	3 (10.7)	Reduced	2	1 (3.9)	Reduced	0
		Increased	0		Increased	0
Moderate, n (%)	1 (3.6)	Reduced	0	8 (30.8)	Reduced	3
		Increased	0		Increased	5
Normal, n (%)	19 (67.8)	Maintained	12	14 (53.8)	Maintained	12
		Increased	5		Increased	2
Unknown, n (%)	5 (17.9)	–	–	3 (11.5)	–	–

*Only participants who undertook the follow-up ultrasound examinations are shown in the table.

Table 8. Changes in the frequency of aspiration and residue in the intervention group.

US results	ID	Baseline	Follow-up	Dysphagia	Comparison	*Difference (%)
Aspiration	19AL	10/18	4/16	Severe	Reduced	31
Aspiration	10AH	0/18	4/18	Normal	Increased	–
Residue	19AL	14/18	2/16	Severe	Reduced	65
Residue	17AL	9/18	4/18	Severe	Reduced	28
Residue	12AL	0/8	6/13	Normal	Increased	–
Residue	22AL	0/13	3/18	Normal	Increased	–
Residue	35AL	0/16	2/18	Normal	Increased	–
Residue	40AL	0/16	3/16	Normal	Increased	–

One examination basically contains nine measurements. Baseline and follow-up examination were repeated twice over 2 days. Participants in whom aspiration or residue were detected more than twice in one examination were included in this table. Participants whose frequency of aspiration and residue were reduced at follow-up relative to baseline were labeled as “Reduced”, and the remaining participants were labeled as “Increased”.

*For the participants who were labeled as Reduced, the differences in the frequency at baseline and follow-up were calculated.

Table 9. Changes in the frequency of aspiration and residue in the control group.

US results	ID	Baseline	Follow-up	Dysphagia	Comparison	*Difference (%)
Aspiration	8BL	3/18	3/9	Moderate	Increased	–
Aspiration	7BH	4/18	3/13	Moderate	Increased	–
Aspiration	36BL	2/15	3/18	Moderate	Increased**	–
Aspiration	29BL	0/15	4/12	Normal	Increased	–
Residue	36BL	2/15	2/18	Moderate	Increased**	–
Residue	2BL	2/18	0/18	Moderate	Reduced	11
Residue	4BL	2/18	0/18	Moderate	Reduced	11
Residue	11BL	2/18	0/18	Moderate	Reduced	11
Residue	21BL	2/18	2/12	Moderate	Increased	–
Residue	39BL	2/10	6/18	Moderate	Increased	–
Residue	5BH	0/18	2/9	Normal	Increased	–

One examination basically consists of nine measurements. Baseline and follow-up examination were repeated twice over 2 days. Participants in whom aspiration or residue were detected more than twice in one examination were included in this table. Participants whose frequency of aspiration and residue were reduced at follow-up relative to baseline were labeled as “Reduced”, and the remaining participant as “Increased”.

*For the participants who were labeled as Reduced, the differences in the frequency at baseline and follow-up were calculated.

**For the participants whose evaluation of the comparison was inconsistent between aspiration and residue, only those participants who showed a reduction in both aspiration and residue were defined as Reduced and others were defined as Increased.

CONCLUSION

The objective was to prevent aspiration pneumonia by the introduction of US examination during mealtimes. A method for the detection of pharyngeal post-swallow residue involving US examination in addition, to a method for the detection of aspiration, was confirmed. Pharyngeal post-swallow residue was observed as a misty hyperechoic area above the vocal folds. The sensitivity and specificity regarding the detection of pharyngeal post-swallow residue was 67% and 75%, respectively. It was demonstrated in the feasibility study involving eight participants in a special elderly nursing home that a developed US examination was acceptable during mealtimes; US examination during mealtimes detected aspiration and pharyngeal post-swallow residue which were related to aspiration pneumonia. A randomized controlled trial involving 54 participants in the same facility found that frequent US examination during mealtimes, and recommendations for swallowing care, effectively reduced the frequency of aspiration and residue in individuals with severe dysphagia relative to standard care alone. Future studies are expected to promote and spread the use of this new method among many clinicians, and establish evidence for the prevention of aspiration pneumonia.

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Appendix 1. CONSORT Checklist.

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	45
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Not applicable
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	45–47
	2b	Specific objectives or hypotheses	46–47
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	47
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not applicable
Participants	4a	Eligibility criteria for participants	47
	4b	Settings and locations where the data were collected	47
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	50–51
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	50–52
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size	7a	How sample size was determined	52–53
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	48
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	48
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	48–49
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	48–49

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	49
	11b	If relevant, description of the similarity of interventions	Not applicable
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	53–54
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Not applicable
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	54
	13b	For each group, losses and exclusions after randomisation, together with reasons	54–55
Recruitment	14a	Dates defining the periods of recruitment and follow-up	54
	14b	Why the trial ended or was stopped	Not applicable
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	67
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	53
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	55–57
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	55
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Not applicable
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	55
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	58–61
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	60
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	57–58
Other information			
Registration	23	Registration number and name of trial registry	47
Protocol	24	Where the full trial protocol can be accessed, if available	47
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	72