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Submission date: 04-Apr-2023 06:59AM (UTC+0800)
Submission ID: 2055043219
File name: sopharyngeal_Carcinoma_Patients_with_Oropharyngeal_Dysphagia.pdf (425.75K)
Word count: 4754
Character count: 27202

Correlation of Pharyngeal Residue with Penetration-Aspiration in Post-Radiotherapy Nasopharyngeal Carcinoma Patients with Oropharyngeal Dysphagia

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Abstract

Background: Nasopharyngeal carcinoma (NPC) ranks first for head and neck malignancies, and radiotherapy is a recommended treatment. Most post-radiotherapy NPC patients experience oropharyngeal dysphagia that results in pharyngeal residue. Pharyngeal residue is thought to be a risk factor for aspiration-penetration.

Objective: Examining the correlation between pharyngeal residue and penetration-aspiration in post-radiotherapy NPC patients.

Method: Participants have been identified since 2018 to find out the total number of NPC patients. In the period January-October 2019, identification of NPC patients was performed according to participant criteria. Participants were examined for fiberoptic endoscopic evaluation of swallowing (FEES), pharyngeal residue using the Yale Pharyngeal Residue Severity Rating Scale (YPR-SRS), and penetration-aspiration using Penetration-Aspiration Scale (PAS). Statistical tests were used Spearman correlation test with $p<0.05$.

Results: The highest participant's pharyngeal residue appeared in vallecula when given soft bolus (96.55%), and in pyriform sinus when given thick liquid bolus (72.41%). Most participants with soft bolus had the highest negative penetration (72.59%) and positive penetration in thick liquid bolus (51.72%), while most had negative aspirations with the lowest value (89.66%). There is aspiration in 10.34% of patients when given a dilute liquid. There was a significant correlation between pharyngeal residue in vallecula and pyriform sinus with penetration-aspiration ($p<0.05$). There was a positive association with the use of soft bolus ($r=0.623$), thick liquid bolus ($r=0.631$), and dilute liquid bolus ($r=0.891$).

Conclusions: There is a significant association between pharyngeal residue and penetration-aspiration in post-radiotherapy NPC patients.

Keywords: *Nasopharyngeal carcinoma, radiotherapy, pharyngeal residue, penetration-aspiration*

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Introduction

Nasopharyngeal carcinoma (NPC) is a squamous cell carcinoma originating from nasopharyngeal epithelium. This carcinoma ranks first for head and neck malignancies[(1)]. Radiotherapy is a recommended treatment because of the radiosensitive nature of NPC. Giving radiotherapy in addition to killing cancer cells can also damage normal cells that causes various side

effects. Protection of surrounding organs is difficult to perform when using conventional radiotherapy. Organs such as parotid, tongue, pharyngeal mucosa and pharyngeal constrictor muscle are often sacrificed during radiotherapy, resulting in oropharyngeal dysphagia. Oropharyngeal dysphagia can cause reduced food intake, malnutrition, decreased activity, and even aspiration. Aspiration is the most serious complication of oropharyngeal dysphagia because it can lead to aspiration pneumonia to death. Management of oropharyngeal dysphagia in post-radiotherapy NPC patients is still not optimal, so parameters are needed to predict the incidence of aspiration[2-4].

Oropharyngeal dysphagia can result in pharyngeal residue, which is a risk factor for penetration-aspiration. Pharyngeal residue are secretions before swallowing and bolus residue after swallowing in pharynx which cannot be completely cleansed by swallowing[5,6]. The incidence of aspiration increases as a result of pharyngeal residue because larynx has experienced relaxation so that bolus can enter the airway[7]. Aspiration occurs when bolus has passed under vocal cords, whereas penetration is the presence of bolus material in larynx that does not pass through vocal cords[4, 8].

Post-radiotherapy NPC patients often experience oropharyngeal dysphagia with a prevalence reaching 75%. Management of oropharyngeal dysphagia is needed to eliminate aspiration which can cause aspiration pneumonia to death. As many as 65.9% of post-radiotherapy NPC patients have aspiration. One risk factor for penetration of aspiration is pharyngeal residue. Patients with pharyngeal residues have a thirty times greater risk for aspiration[5, 9, 10].

The most common procedures for evaluating oropharyngeal dysphagia in head and neck cancer patients are videofluoroscopy (VFS) and fiberoptic endoscopic evaluation of swallowing (FEES). Videofluoroscopy is considered a gold standard for examination of oropharyngeal dysphagia, but its use is limited because of high costs, cannot be removed, and the presence of radiation exposure. The FEES method is currently more widely used because it can be performed at the bedside and allows direct visualization of swallowing structures including nasopharynx, hypopharynx, larynx, and vocal cords[11].

Assessment for penetration-aspiration during ingestion process can use Penetration-Aspiration Scale (PAS). This method consists of eight scales that describe the depth of bolus penetration or aspiration into the airway, the sensation felt by patient to the presence of penetration or aspiration, and the effectiveness in removing bolus from the airway[7, 12]. Different parameters can be used to assess pharyngeal residue because there is no consensus on the scale of assessment of the value of pharyngeal residue. Recent research showed that The Yale Pharyngeal Residue Severity Rating Scale (YPR-SRS) has the highest reliability when compared to other parameters[5, 9].

The number of NPC patients in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, has increased annually in 2017 by 125 patients, in 2018 by 137 patients, and in 2019 (until October) by 101 patients. Thus far, there is no study examining correlation between pharyngeal residue and penetration-aspiration in post-radiotherapy NPC patients at hospital. Based on the description above, the researchers aimed to analyze the **association** between pharyngeal residue and penetration-aspiration in post-radiotherapy NPC patients.

Method and Materials

Participants: Participants in this study were NPC patients who had completed radiotherapy that met the inclusion and exclusion criteria. Inclusion criteria were NPC patients aged 18-74 years, had completed radiotherapy using three-dimensional conformal radiation therapy (3D-CRT) techniques for 35 times in accordance with NCCN guidelines[13], had dysphagia complaints, were willing to undergo FEES examination in maximum twelve months after radiotherapy, the Glasgow Coma Scale of compos mentis (456), and can sit. Exclusion criteria included patients having other diseases that can cause dysphagia (stroke, head trauma, brain base tumors, cervical vertebral trauma, meningitis, Guillain Barre syndrome, diabetes mellitus, and goitre), underwent radiotherapy for more than 35 times, used nasogastric tubes, used tracheostomy tubes, respiration rate more than 24 times per minute, and oxygen saturation <94%. Participants first received an explanation of the study details including the benefits, objectives, rights and obligations of the participant. In addition, participants who were willing to take part in the research must fill in the consent form.

Design: The study was conducted at the Oncology Poly of Dr. Soetomo General Academic Hospital,

Surabaya, Indonesia, from January-October 2019. This study used a cross-sectional design with consecutive sampling techniques. The number of participants was 29 NPC patients. Participants were assessed for characteristics, pharyngeal residue, and penetration-aspiration after receiving radiotherapy for 35 times. This study had passed ethical test (1031/KEPK/III/2019). NPC stadium referred to the classification of Tumors, Nodules, Metastases (TNM) developed by Union International Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC)[14, 15].

Fiberoptic Endoscopic Evaluation of Swallowing: Participants were examined for FEES by the Otorhinolaryngology Head and Neck Surgery Specialist (Broncoesophagologist consultant). FEES examination used endoscopy (Olympus Evis Exera II, Olympus Medical System, Tokyo, Japan). Patients were seated, and left and right nasal cavity were given decongestant Oxymetazoline HCl spray 0.05%. The endoscopy tip was inserted through nose to nasopharyngeal cavity (between soft palate and top of epiglottis) where the gel was applied first. Prepare three bolus of different consistency (soft, thick liquid, dilute liquid) each ± 5 ml. Participants were asked to swallow the bolus once to see whether there was vallecular residue and pyriform sinus after the white-out period. The white-out period is formed due to changes in tissue position after swallowing reflex. The order of bolus usage was soft bolus, thick liquid, and dilute liquid. Furthermore, the endoscopy was rapidly moved to the area of laryngeal vestibule to evaluate penetration and aspiration.

Pharyngeal Residue Assessment: Pharyngeal residue is secretion before and after ingestion of bolus residue in vallecula and pyriform sinus which cannot be completely cleansed by swallowing. Pharyngeal residual assessment was obtained through FEES examination using the YPR-SRS scale[5]. The scale of vallecular residue is divided into five, namely scale 1 (none) if there are no residuals found in vallecula, scale 2 (trace) if the residue only covers vallecular mucosa or fills 1%-5%, scale 3 (mild) if the residue fills vallecula up to a quarter full (5%-25%) with visible epiglottic ligaments, scale 4 (moderate) if the residue fills vallecula to half full (25%-50%) with invisible epiglottic ligaments, and scale 5 (severe) if the residue fills valecula more than 50% to the upper edge of epiglottis. Pyriform sinus residual rating scale is also divided into five, namely scale 1 (none) if there is no residual pyriform sinus, scale 2 (trace) if the residue only covers pyriform sinus mucosa or fills 1%-5%, scale 3 (mild) if the residue fills pyriform sinus up to a quarter full (5%-25%), scale 4 (moderate) if the residue fills pyriform sinus up to half full (25%-50%), and scale 5 (severe) if the residue fills pyriform sinus more than 50% to reach aryepiglottic folds.

Penetration-Aspiration Assessment: Penetration is the presence of bolus material in larynx which does not pass through vocal cords after swallowing phase. Aspiration is the presence of bolus material that has passed under vocal cords. Penetration-aspiration assessment used PAS, which the rating scale is divided into eight[12]. Scale 1 indicates no boluses enter larynx. Scale 2 shows that the bolus has entered larynx, remains above vocal cords, and can be removed from larynx. Scale 3 shows that the bolus has entered larynx, remains above vocal cords, but cannot be removed from larynx. Scale 4 is a condition when bolus has entered larynx, touches vocal cords, and can be removed from larynx. Scale 5 indicates that the bolus has entered larynx, touches vocal cords, but cannot be removed from larynx. Scale 6 shows that the bolus has entered larynx, passes through vocal cords and can be removed from larynx. Scale 7 is a condition when the bolus has entered larynx, passes through vocal cords, but cannot be removed from larynx despite attempts to remove it. Scale 8 shows that the bolus enters larynx, passes through vocal cords, and no attempt to remove it. Scale 1 shows the absence of penetration-aspiration. Scale 2-5 illustrates penetration, while scale 6-8 shows aspiration. Aspiration may not be identified in post-radiotherapy of head and neck cancer patients. Symptoms of aspiration in patients who have undergone radiotherapy are often unclear, and they do not feel anything due to sensory disturbance in the trachea area that is called silent aspiration.

Statistic Analysis: Data obtained in the study were displayed in tabular form, and were analyzed statistically. The association between pharyngeal residues with penetration-aspiration was analyzed using the Spearman correlation test. This research used significance level $p<0.05$. Statistical test analysis employed the IBM SPSS Statistics software version 21.0 (IBM Corp., Armonk, NY, USA).

Results

Characteristics of Participants: Most participants belonged to the age group of 46-55 years (37.93%), followed by age group of 36-45 years and 56-65 years (20.69% each). The average participant age was

48.41±13.20 years, with the youngest age at 18 years and the oldest age at 68 years. Most participants were male (72.41%). All participants did not undergo metastasis to other organs, and most participants had stage-IV NPC (55.17%). Most participants had a T4-type tumor classification (41.38%) and followed by a T3-type tumor (27.59%). T4 is a tumor that extends intracranially and/or involves cranial nerve, hypopharynx, infratemporal fossa, or masticator space, while T3 is a tumor that invades bone structure and/or paranasal sinuses. In addition, most participants had an N2-type nodule (44.83%), followed by an N3-type nodule as much as 27.59%. N2 is categorized as bilateral cervical lymph node, with the largest size ≤6 cm, above Supraclavicular fossa, while N3 is categorized as cervical lymph node >6 cm, and/or towards Supraclavicular fossa. Most participants suffered injuries due to radiotherapy in the range of 3-6 months as much as 51.72% (Table 1).

Participants complained of several problems related to dysphagia, including drooling or saliva coming out of the mouth as much as 2 participants (6.90%), food came out of the lips as much as 3 participants (10.34%), regurgitation or food and drink coming out of nose as much as 5 participants (17.24%), cough when eating or drinking as much as 7 participants (24.14%), choking while eating or drinking as much as 9 participants (31.03%), reduced saliva that leads to difficulty swallowing as many as 29 participants (100.00%), require water to help swallow as many as 28 participants (96.55%), avoiding foods with certain consistency as much as 18 participants (62.07%), require certain portion size as much as 7 participants (24.14%), longer mealtime length as much as 27 participants (93.10%), having the sensation of food getting stuck in the throat as many as 20 participants (68.96%), and changed voice as many as 16 participants (55.17%).

Pharyngeal Residue: Most participants had vallecular residue when given soft bolus (96.55%; 3.21±1.01), while 89.66% of participants had the residue when given thick liquid bolus (2.14±1.22). On the other hand, when given dilute liquid bolus, most participants experienced pharyngeal residue in vallecula as much as 68.97% (2.41±0.87). Most participants experienced pharyngeal residue in pyriform sinus when given soft bolus as much as 62.07% (2.41±1.18), thick liquid bolus as much as 72.41% (2.00±0.93), and dilute liquid bolus as much as 62.07% (2.03±1.08; Table 2).

Penetration-Aspiration: Most participants had no penetration-aspiration when given soft bolus as much as 72.59% negative penetration and all negative aspirations (2.07±1.25). When given thick liquid bolus, most participants (51.72%) had positive penetration and all negative aspiration (2.07±1.25). On the other hand, when given dilute liquid bolus, most participants had no penetration-aspiration as much as 55.17% of negative penetration and 89.66% of negative aspiration (2.52±1.78). When, we gave a dilute liquid bolus as much as 10.34% of the participants experienced aspiration (table 3).

Correlation of Pharyngeal Residue with Penetration-Aspiration in Post-Radiotherapy NPC Patients: Correlation between pharyngeal residue in vallecula with penetration-aspiration in the administration of soft bolus was p=0.025 with r=0.416, thick liquid bolus was p=0.003 with r=0.494, and dilute liquid bolus was p<0.001 with r=0.807. These results indicated a significant **association** between pharyngeal residue in vallecula and penetration-aspiration. Correlation between pharyngeal residues in pyriform sinus and penetration-aspiration in the administration of soft bolus was p<0.001 with r=0.623, thick liquid bolus was p<0.001 with r=0.631, and dilute liquid bolus was p<0.001 with r=0.891. These results showed a significant **association** between pharyngeal residue in pyriform sinus and penetration-aspiration (Table 3).

Table 1. Characteristics of Nasopharyngeal Carcinoma Patients with Oropharyngeal Dysphagia

Characteristics of Participants	n (%)
Age (Year)	
17 – 25	3 (10.34)
26 – 35	1 (3.45)
36 – 45	6 (20.69)
46 – 55	11 (37.93)
56 – 65	6 (20.69)
66 – 74	2 (6.90)

Characteristics of Participants	n (%)
Sex	
Male	21 (72.41)
Female	8 (27.59)
Tumor Classification	
T1	2 (6.90)
T2	7 (24.14)
T3	8 (27.59)
T4	12 (41.38)
Nodule Classification	
N0	2 (6.90)
N1	6 (20.69)
N2	13 (44.83)
N3	8 (27.59)
Metastasis Classification	
M0	29 (100.00)
M1	0 (0.00)
Stage	
Stage I	0 (0.00)
Stage II	3 (10.34)
Stage III	10 (34.48)
Stage IV	16 (55.17)
Time of Injury due to Radiotherapy (month)	
<3	9 (31.03)
3-6	15 (51.72)
>6	5 (17.24)

T = tumor, N = nodule, and M = metastasis based on Union International against Cancer (UICC) and American Joint Committee on Cancer (AJCC)

Table 2. Pharyngeal Residue Distribution

Pharyngeal Residue	Soft Bolus (%)		Thick Liquid Bolus (%)		Dilute Liquid Bolus (%)	
	+	-	+	-	+	-
Vallecula	28 (96.55)	1 (3.45)	26 (89.66)	3 (10.34)	20 (68.97)	9 (31.03)
Pyriform sinus	18 (62.07)	11 (37.93)	21 (72.41)	8 (27.59)	18 (62.07)	11 (37.93)

Table 3. Correlation of Pharyngeal Residue with Penetration-Aspiration in Post-Radiotherapy Nasopharyngeal Carcinoma Patients

Variables	Soft Bolus	Thick Liquid Bolus	Dilute Liquid Bolus
Penetration (%)			
(+)	8 (27.59)	15 (51.72)	13 (44.83)
(-)	21 (72.41)	14 (48.28)	16 (55.17)
Aspiration (%)			
(+)	0 (0.00)	0 (0.00)	3 (10.34)
(-)	29 (100.00)	29 (100.00)	26 (89.66)
Vallecula	0.025*	0.003*	0.000**
Pyriform sinus	0.000**	0.000**	0.000**

* Significant $p < 0.05$; ** Significant $p < 0.001$

Discussion

Oropharyngeal dysphagia in post-radiotherapy NPC patients is secondary due to nerve and soft tissue damage. This can occur in the short or long term with varying degrees of severity. Changes in swallowing structure can occur due to early and late effects of radiotherapy. Radiation causes axonal injury, demyelination, extensive fibrosis in and around nerves, and ischemia in blood vessels that provide vascularization to nerves. Not all structural changes in swallowing due to radiotherapy can be explained completely. Reduced retroflection from epiglottis and retraction of tongue base will cause pharyngeal residue in vallecula. Reduction of pharyngeal contraction and relaxation of upper esophageal sphincter results in pharyngeal residue in pyriform sinus. Pharyngeal residue is a risk factor for aspiration after the ingestion phase. Aspiration in post-radiotherapy head-neck cancer patients mainly occurs after swallowing phase, thus pharyngeal residue must be considered as primary symptoms of oropharyngeal dysphagia in this population. Pharyngeal residue can cause penetration-aspiration after swallowing phase because bolus enters airway when larynx has been relaxed [7, 16-19].

Pharyngeal residue is a risk factor for penetration-aspiration in post-radiotherapy head-neck cancer patients. A study found a significant **association** between pharyngeal residue and penetration-aspiration at each given bolus consistency ($p<0.05$) [10]. Increased pharyngeal residue in dysphagia patients is directly proportional to the incidence of penetration-aspiration. Penetration-aspiration increases along with the increase in pharyngeal residue in vallecula and pyriform sinus at each given bolus consistency and is statistically significant ($p<0.001$) [9]. The results of penetration-aspiration in post-radiotherapy head-neck cancer patients mainly occur after the swallowing phase compared to before or when swallowing ($p<0.05$) [7].

The location of pharyngeal residue in vallecula or pyriform sinus influences penetration-aspiration although there are still differences regarding the more dangerous location. Some studies mentioned residue in pyriform sinus are more dangerous than in vallecula, while other studies showed the opposite [7]. A study found a significant correlation between pharyngeal residue in pyriform sinus and aspiration in post-radiotherapy NPC patients ($p<0.001$) [20]. Aspiration is more often caused by pharyngeal residue in pyriform sinus compared to vallecula. The greater distance between vallecula to laryngeal anterior chamber than pyriform sinus to laryngeal anterior chamber might result in aspiration due to a large amount of residue in pyriform sinus. Residue in the lower pharyngeal area increase the risk of penetration-aspiration. Vallecular residue are more difficult to enter laryngeal vestibule because of the presence of epiglottis as a barrier, but epiglottic function in head and neck cancer patients can be damaged due to fibrosis, malformations, or tissue damage so that failure continues to prevent residues from entering larynx [7, 21].

This study found a significant correlation between pharyngeal residue in vallecula and pyriform sinus with penetration-aspiration, but did not distinguish the more dangerous areas between the two. The **association** between pharyngeal residue in pyriform sinus and penetration-aspiration showed a stronger correlation when compared with residue in vallecula at all given bolus consistencies. The type and consistency of bolus also play an important role in the occurrence of penetration-aspiration. Some studies mentioned that dilute bolus is easier to cause aspiration when compared with thick bolus, whereas other studies showed the opposite results [7, 9, 22, 23]. Some studies found a significant **association** between pharyngeal residue with penetration-aspiration, and the correlation was stronger when given dilute bolus [21, 24]. Pharyngeal pressure decreases significantly when given liquid compared to soft bolus. This might be due to liquid viscosity that allows gravity to take over the transfer of flow through pharynx. Liquids are more at risk of causing penetration-aspiration when compared to soft boluses in post-radiotherapy NPC patients who experience pharyngeal contraction disorders. Liquid boluses cannot provide enough stimulation to pharyngeal wall due to interference with nerve function that plays a role in swallowing [3, 25].

Some studies reported a stronger correlation between pharyngeal residue and penetration-aspiration when given soft bolus compared to liquid [9, 10]. This might be caused by differences in types of bolus given, which are solid, soft, and liquid. The last fluid bolus given can be overestimated due to residual residues from previous solid and soft boluses. Assessment of repeated swallowing management to clear pharyngeal residues can provide a different interpretation of penetration-aspiration. Fluid boluses can easily flow into the airways, but are also easier to cough out. Thick bolus is difficult to enter the airway, but it is not easy to be removed again after entering so that it can cause airway obstruction. Assessments made after repeated swallowing will cause

soft boluses to appear to be more likely to result in aspiration than liquid boluses [9, 26].

This research did not distinguish which type and consistency of boluses that are more dangerous for penetration-aspiration. A stronger correlation between pharyngeal residues and penetration-aspiration was obtained when given dilute liquid bolus compared to thicker bolus on vallecula or pyriform sinus. This study proved that there was a significant **association** between pharyngeal residue and aspiration-penetration in post-radiotherapy NPC patients, so that pharyngeal residue could be used to predict penetration-aspiration in post-radiotherapy NPC patients.

Conclusions

Most post-radiotherapy NPC patients have oropharyngeal dysphagia, which can lead to penetration-aspiration. FEES examination is performed to assess penetration-aspiration and pharyngeal residue, while YPR-SRS is used to pharyngeal residue scoring and PAS is used to penetration-aspiration scoring. There is a significant correlation between pharyngeal residue and penetration-aspiration in post-radiotherapy NPC patients. The correlation between pharyngeal residue and penetration-aspiration in the administration of dilute liquid bolus shows the strongest results. There is a strong **association** between pharyngeal residues in pyriform sinus and penetration-aspiration in the administration of liquid bolus.

Conflict of Interest: The authors declare they have no conflict of interest.

Funding: None

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Ethical Approval: All procedures performed in studies involving human participants were accordance with the 1964 Helsinki Declaration at the ethics committee in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (*1031/KEPK/III/2019*).

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