Predictive clinical factors for penetration aspiration in patients with nasopharyngeal carcinoma after radiotherapy

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Submission date: 04-Apr-2023 09:12AM (UTC+0800)
Submission ID: 2055139666
File name: s_for_penetration_aspiration_in_patients_with_nasopharyngeal.pdf (206.84K)
Word count: 4226
Character count: 23490

How to Cite:
Pratama, L. A. H., Romdhoni, A. C., & Herawati, S. (2022). Predictive clinical factors for penetration-aspiration in patients with nasopharyngeal carcinoma after radiotherapy. *International Journal of Health Sciences*, *6*(S8), 2185–2194. https://doi.org/10.53730/ijhs.v6nS8.12563

Predictive clinical factors for penetration-aspiration in patients with nasopharyngeal carcinoma after radiotherapy

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***Abstract*---**Penetration-aspiration is the most serious complication in patients with nasopharyngeal carcinoma (NPC) after radiotherapy. Radiotherapy has been shown to increase the patient's survival rate and life expectancy but it showed serious side effects such as oropharyngeal dysphagia. It's related morbidity and mortality such as penetration-aspiration could progress to aspiration pneumonia, sepsis, and death if not treated properly. Factors suspected to be the determinants of penetration-aspiration were the location of the pharyngeal residue, the stage of NPC, and the time after radiotherapy. This primary objective of this study was to determine the clinical factors of penetration-aspiration in patients with NPC after radiotherapy. In a cross sectional, observational analytic study, a total of 24 patients were obtained with consecutive sampling technique. Fiberoptic endoscopic evaluation of swallowing (FEES) examination was performed on patients with NPC after radiotherapy to assess pharyngeal residue and penetration-aspiration. The Yale Pharyngeal Residue Severity Rating Scale (YPR-SRS) and the Penetration-Aspiration Scale (PAS) was used to assess the presence of pharyngeal residue and penetration-aspiration, respectively. Statistical analysis used multiple logistic regression (p<0,05) and Wald statistics to find a

stronger relationship between variables. Multiple logistic regression showed a significant relationship between NPC stage and time after radiotherapy with penetration-aspiration on soft bolus administration (p<0,05). Wald statistic showed a stronger relationship between time after radiotherapy (328,686) and penetration-aspiration than the relationship between NPC stage and penetration of aspiration (298,118). NPC stage and time after radiotherapy are the predictive clinical factors of the incidence of penetration-aspiration in NPC patients after radiotherapy. The time after radiotherapy is the most dominant factors. Residual location (vallecula and piriform sinus) is not the predictive clinical factor of the incidence of penetration-aspiration in NPC patients after radiotherapy.

***Keywords*---**nasopharyngeal carcinoma, radiotherapy, pharyngeal residue, penetration-aspiration, life expectancy.

Introduction

Nasopharyngeal carcinoma (NPC) patients although treated with modern therapeutic modalities, still faced with the threat of recurrence or complications (Romdhoni et al., 2020). Penetration-aspiration is the most serious complication that can occur in NPC patients after radiotherapy. Radiotherapy has been shown to increase patient survival rates but it came with serious side effects such as oropharyngeal dysphagia, mucositis, neuropathy, and serostomia. Oropharyngeal dysphagia is one of the most common radiotherapy side effects and occurred in 76% of NPC patients undergoing radiotherapy (Li et al., 2019). Poor propulsion, weak pharyngeal strength, and/or impaired upper esophageal sphincter relaxation in oropharyngeal dysphagia patients result in pharyngeal residue causing penetration-aspiration and ultimately leads to aspiration pneumonia, sepsis, and death if not treated properly (Neubauer et al., 2015; Chen et al., 2019). As many as 65.9% NPC patients after radiotherapy experienced aspiration with 20-65% mortality rate (Li et al., 2019).

The predictive clinical factors of the incidence of penetration-aspiration in NPC patients after radiotherapy were not clearly known. The purpose of this study was to prove that vallecular residue, sinus priformis residue, NPC stage, and time after radiotherapy were the predictive clinical factors of the incidence of aspiration penetration in NPC patients after radiotherapy. The study could be used for early detection of oropharyngeal dysphagia in NPC patients undergoing radiotherapy so that appropriate therapy can be given to prevent complications that may occur.

Method

The research was conducted at ENT Oncology Unit Dr. Soetomo General Academic Hospital Surabaya from June 2021 to August 2021. The research was an observational analytic with a cross sectional design. Sampling with consecutive sampling technique until the sample size is met as many as 24 samples. FEES examination was performed on samples that met the inclusion and exclusion criteria to assess pharyngeal residue and aspiration-penetration by

an ENT Specialist (Bronchoesophagology Consultant). The Yale Pharyngeal Residue Severity Rating Scale (YPR-SRS) and the Penetration-Aspiration Scale (PAS) was used to assess the presence of pharyngeal residue and penetration-aspiration, respectively. The examination was conducted using three types of boluses such as soft bolus, thick liquid and dilute liquid, respectively.

The YPR-SRS scale classified the severity of vallecula and piriform sinus residues into 5 degrees (Table 1), while the PAS classified the incidence of penetration-aspiration into 8 scales. A scale of 1 indicates no penetration-aspiration. A scale of 2-5 indicates the occurrence of penetration while a scale of 6-8 describes the occurrence of aspiration (Table 2).

Table 1
The severity of vallecular and piriform sinus residues

I	*None*	0%	*No residue*
II	*Trace*	1-5%	*Trace coating of the mucosa*
III	*Mild*	5-25%	*Up wall to quarter full, epiglottic ligament visible (vallecula residue)*
IV	*Moderate*	25-50%	*Up wall to half full, epiglottic ligament covered (vallecula residue)*
V	*Severe*	>50%	*Filled to epiglottic rim (vallecula residue), Filled to aryepiglottic fold (piriform sinus residue)*

Table 2
Penetration Aspiration Scale (PAS)

Description	Score
Material does not enter the airway	1
Material enters the airway, remains above the vocal folds, and is ejected from the airway	2
Material enters the airway, remains above the vocal folds, and is not ejected from the airway	3
Material enters the airway, contacts the vocal folds, and is ejected from the airway	4
Material enters the airway, contacts the vocal folds, and is not ejected from the airway	5
Material enters the airway, passes below the vocal folds, and is ejected into the larynx or out of the airway	6
Material enters the airway, passes below the vocal folds, and is not ejected from the trachea despite effort	7
Material enters the airway, passes below the vocal folds, and no effort is made to eject	8

The data obtained was analyzed statistically using multiple logistic regression ($p<0.05$) and Wald statistic to analyze the most dominant factor as the cause of penetration-aspiration. This research was approved by the Health Research Ethics Committee of Dr. Soetomo General Academic Hospital Surabaya (0216/KEPK/VI/2021).

Results

The relationship between NPC stage, length of post-radiotherapy, vallecula residue and piriform sinus residue with aspiration-penetration is shown in Tables 3,4, and 5, respectively.

Table 3
The relationship between NPC stage and penetration-aspiration

	Soft bolus			Total
	PAS 1	PAS 2-5	PAS 6-8	
Early	5 (71.4%)	2 (28.6%)	0 (0.0%)	7(100%)
Advanced	11 (64.7%)	4 (23.5%)	2 (11.8%)	17(100%)
	Thick liquid			Total
	PAS 1	PAS 2-5	PAS 6-8	
Early	4 (57.1%)	2 (28.6%)	1 (14.3%)	7(100%)
Advanced	8 (47.0%)	7 (41.2%)	2 (11.8%)	17100 (%)
	Dilute liquid			Total
	PAS 1	PAS 2-5	PAS 6-8	
Early	5 (71.4%)	0 (0.0%)	2 (28.6%)	7(100%)
Advanced	14 (82.3%)	1 (5.9%)	2 (11.8%)	17(100%)

Table 4
The relationship between the time after radiotherapy with penetration-aspiration

	Soft bolus			Total
	PAS 1	PAS 2-5	PAS 6-8	
≤6 month	6 (60.0%)	0 0.0(%)	4 (40.0%)	10(100.0%)
>6 month	10 (71.4%)	2 (14.3%)	2 (14.3%)	14(100.0%)
	Thick liquid			Total
	PAS 1	PAS 2-5	PAS 6-8	
≤6 month	4 (40.0%)	5 (50.0%)	1 (10.0%)	10(100.0%)
>6 month	8 (57.1%)	4 (28.6%)	2 (14.3%)	14(100.0%)
	Dilute liquid			Total
	PAS 1	PAS 2-5	PAS 6-8	
≤6 month	8 (80.0%)	0 (0.0%)	2 (20.0%)	10(100.0%)
>6 month	11 (78.6%)	1 (7.1%)	2 (14.3%)	14(100.0%)

NPC stages based on UICC/AJCC are classified into stages I, II, III, and IV. Stage I and II referred as early stages, while stage III and IV are advanced stages. In this study, most of the patients were callsified in advance stage (17 patients) and the rest were classified in early stage (7 patients). Patients with advance stages were more likely to experience penetration (PAS 2-5) and aspiration (PAS 6-8) in soft bolus and thick fluid bolus (Table 3). The incidence of penetration (PAS 2-5) on dilute fluid bolus was found more in patients with advanced NPC, while the incidence of aspiration (PAS 6-8) was found in 2 patients with early and advanced NPC, respectively.

Most of the patients in this study came within >6 months after radiotherapy (14 patients) while the rest patients came ≤6 months after radiotherapy (10 patients). Patients with duration of post-radiotherapy >6 months were more likely to experience penetration (PAS 2-5) in soft bolus and thick fluid bolus (Table 4). While the incidence of aspiration (PAS 6-8) was found more in NPC patients with a duration of post-radiotherapy ≤6 month. The incidence of penetration (PAS 2-5) and aspiration (PAS 6-8) on thick fluid and dilute bolus does not show a significant difference in terms of numbers or statistically.

From table 5, it can be seen that the incidence of penetration (PAS 2-5) in soft and thick bolus administration was more found in NPC patients with residues in the vallecula than in the piriform sinus. The incidence of penetration (PAS 2-5) on dilute fluid bolus was found in 1 NPC patient, respectively, with residues in the vallecula and piriform sinus. While the incidence of aspiration (PAS 6-8) was found in equal numbers in the vallecula and piriform sinus in each given bolus.

Table 5
Relationship between residue location with penetration-aspiration

	Soft bolus			Total
	PAS 1	PAS 2-5	PAS 6-8	
Vallecula	16 (66.7%)	6 (25.0%)	2 (8.3%)	24(100.0%)
Piriform Sinus	9 (69.2%)	2 (15.4%)	2 (15.4%)	13(100.0%)
	Thick liquid			Total
	PAS 1	PAS 2-5	PAS 6-8	
Vallecula	12 (50.0%)	9 (37.5%)	3 (12.5%)	24(100.0%)
Piriform Sinus	8 (44.4%)	7 (38.9%)	3 16.7(%)	18(100.0%)
	Dilute liquid			Total
	PAS 1	PAS 2-5	PAS 6-8	
Vallecula	9 (90.0%)	1 (10.0%)	0 (0.0%)	10(100.0%)
Piriform Sinus	3 (75.0%)	1 (25.0%)	0 (0.0%)	4(100.0%)

From multiple logistic regression between NPC stage and time after radiotherapy with penetration-aspiration on soft bolus, the result was p=0.000 (table 6). These results showed a significant relationship between NPC stage and time after radiotherapy with penetration-aspiration on soft bolus administration ($p<0.05$), whereas thick and dilute fluid boluses did not show a significant relationship ($p>0.05$).

Table 6
Relationship between NPC stage, time after radiotherapy, vallecula residue and piriform sinus residue with penetration-aspiration

	Soft bolus		Thick liquid	Dilute liquid
	Significance (p)	Wald statistic	Significance (p)	Significance (p)

NPC stage with penetration-aspiration	0.000	296.118	0.756	0.357
Time after radiotherapy with penetration-aspiration	0.000	328.686	0.554	0.773
Vallecula residue with penetration-aspiration	0.999	-	0.998	0.713
Piriform sinus residue with penetration-aspiration	0.997	-	0.995	-

From multiple logistic regression to assess the relationship between vallecular residue and penetration-aspiration, the results indicate that there is no significant relationship between residue location and aspiration-penetration ($p>0.05$) on soft bolus, thick fluid, or dilute fluid.

The Wald statistic was performed to assess the strength of the relationship between variables that showed a significant relationship with the incidence of penetration-aspiration. Wald's statistic gives 296,118 results for the relationship between NPC stage and penetration-aspiration and 328,686 for the relationship between the time after radiotherapy with penetration-aspiration. This shows a stronger relationship between time after radiotherapy and aspiration-penetration compared to the relationship between NPC stage and aspiration penetration.

Discussion

Nasopharyngeal carcinoma (NPC) is a squamous cell carcinoma that appears in the nasopharynx (the area above the throat and behind the nose) (Romdhoni et al., 2020).1 It is a malignant tumor that is easily infiltrate local tissues, metastasis and tumor growth is rapid (Romdhoni et al., 2016). The general prognosis of nasopharyngeal carcinoma (NPC) is currently based on the assessment of clinical stadium by assessing primary tumor (T), cervical metastatic nodule (N) and widespread metastasis (M) (Nugroho et al., 2021).

Most of the patients in this study came at an advanced stages (table 2). The results of this study showed similarities to the study in Taiwan, in 82,9% post-radiotherapy NPC patients at advanced stage were evaluated for dysphagia (Chang et al., 2011). Other research showed similar results with as many as 88.9% of patients in this study presenting at an advanced stage. Patients often come at an advanced stage because the early symptoms of NPC are often not typical and tend to be ignored by patients so that patients come for treatment when symptoms are getting worse when the NPC stage is at an advanced stage, which in turn makes the results of therapy not optimal and the prognosis gets worse (Luk et al., 2013). The doctors also contribute to the delay because they tend to ignore or misdiagnose the unspecific symptoms of NPC (Romdhoni et al., 2020).

The results of this study showed that there was a significant relationship between NPC stage and penetration-aspiration on soft bolus administration (table 2). The higher the stage of NPC, the higher the risk of penetrating aspiration with soft bolus administration. Oropharyngeal dysphagia causes pharyngeal residue which

was the cause of penetration-aspiration in patients. The severity of oropharyngeal dysphagia correlates with the occurrence of penetrating aspiration. Dysphagia can occur before radiotherapy as a direct result of the location and size of the primary tumor (Greco et al., 2018). Dysphagia that occurs in head and neck cancer patients is often related to the underlying disease and the therapy administered Dewan, 2020).

In this study, there was no assessment of dysphagia complaints in patients before undergoing radiotherapy. Dysphagia before radiotherapy can occur in patients with advanced NPC, considering the possible influence of tumor size and spread that can affect nerves and swallowing function in general. Patients who cannot swallow adequately before therapy have a greater risk of chronic swallowing dysfunction after therapy (Chang et al., 2011). Superior, middle, and inferior pharyngeal constrictor muscles are more easily tolerate radiation doses with smaller tumor sizes than in the case of large tumors (Jiang et al., 2018). In contrast, two other study explained that neither tumor location nor tumor stage predicts the risk of dysphagia. It is most likely that the afferent nerves associated with the swallowing process have changes due to radiation, one of which is evidenced by the discovery of changes in taste in patients and impaired sensation of the larynx in some patients (Szczesniak et al., 2014; Kaae et al., 2020).

The results of this study showed a significant relationship between the time after radiotherapy with penetration-aspiration on soft bolus administration (table 3). The earlier the post-radiotherapy period (<6 months), the higher the risk of aspiration penetrating. The Wald statistic shows a stronger relationship between time after radiotherapy and aspiration-penetration compared to the relationship between NPC stage and aspiration penetration (table 5). The severity of pharyngeal residue as assessed by YPR-SRS was found to be higher in patients with a short duration of radiotherapy. In the majority of patients, tissue inflammation and dysphagia due to radiotherapy mainly occur during and immediately after radiotherapy (Kaae et al., 2020; Langmore & Kriscuinas, 2010). As many as 60% of patients mainly experienced dysphagia in the first 1 year after radiotherapy, then decreased by 36% after 5 years and tended to experience complaints again at 8 years after radiotherapy. Serostomia occurs in quite large numbers of patients (87%) in the first 1 year of monitoring and is the most important factor in the incidence of dysphagia in patients (Baudelet et al., 2018). The acute inflammatory response characterized by tissue erythema, mucositis, edema, serostomia, and painful swallowing sensation gradually improved in the first 6 months after radiotherapy. Some patients even experience rapid improvement and most of them appeared within 4-6 weeks after radiotherapy (Kaae et al., 2020).

Several other studies reported that no correlation was found between the prevalence or severity of dysphagia with time since the start of therapy. A patient may develop severe fibrosis after radiation even though initially only mild acute injury, or a patient with severe acute mucositis (grade 3 or 4) could eventually develop minimal side effects after 8-9 months post-irradiation (King et al., 2016). Multiple logistic regression in this study was conducted to analyze the relationship between vallecula residues and piriform sinus residues with penetration-aspiration with the result that there was no significant relationship

between residue location and penetration-aspiration on soft, thick, or dilute boluses (table 5).

The results of this study are in accordance with several literatures and studies that provide different results for the location of the most influential and harmful pharyngeal residues on the incidence of penetration-aspiration in patients. In general, the location of the pharyngeal residues in the vallecula or piriform sinus has an influence on the incidence of penetration-aspiration although there are still differences regarding the more dangerous location. Some studies say residues in the piriform sinus are more dangerous than those in the vallecula, while other studies show the opposite (Pisegna, 2017). There was a significant correlation between pharyngeal residues in the piriform sinus and aspiration in NPC patients after radiotherapy ($p<0.001$) (Ku et al., 2019). Aspiration is more often caused by pharyngeal residues in the piriform sinus than in the vallecula (Pisegna, 2017; Simon et al., 2019). A positive correlation between pharyngeal residue and penetration-aspiration was only found in the pharyngeal residue in the piriform sinus when dilute fluid was administered ($p<0.05$) (Ho, 2021). The greater distance between the vallecula to the laryngeal vestibule than the piriform sinus to the laryngeal vestibule may result in more aspiration occurring because of residues in the piriform sinus. Residues in the lower pharyngeal area increase the risk of aspiration-penetrating. Residues in the vallecula are harder to enter into the laryngeal vestibule due to the presence of the epiglottis as a barrier, but the function of the epiglottis in head and neck cancer patients can be damaged due to fibrosis, malformation, or tissue damage so that there is still a failure to prevent residues from entering the larynx (Pisegna, 2017; Simon et al., 2019).

The pharyngeal residue in the vallecula had a significant relationship with the occurrence of penetration-aspiration, while the residue in the piriform sinus showed no correlation. This may be due to repeated swallowing, which is a functional strategy for dealing with residues in the piriform sinus. The location of the piriform sinus in close proximity to the upper esophageal sphincter allows residues to be relieved by repeated swallowing, but this strategy is not effective at treating vallecular residues. Residues in the vallecula tend to be resistant to repeated swallowing (Molfenter & Steele, 2013).

Conclusion

NPC stage and post-radiotherapy duration are the predictive clinical factors of the incidence of aspiration penetration in NPC patients after radiotherapy on soft bolus administration. Post-radiotherapy duration is the most dominant factor. The more advanced the stage of NPC, the higher the risk of penetrating aspiration with soft bolus administration. The earlier the post-radiotherapy period (<6 months), the higher the risk of aspiration penetrating with soft bolus administration. Residual location (vallecula and piriform sinus) is not a predictive clinical factor of the incidence of aspiration penetration in NPC patients after radiotherapy.

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