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Original Article

Risk factors for recurrent pneumonia in post-irradiated patients with nasopharyngeal carcinoma

Jing-Jie Wang [a], Rong-San Jiang [a,b,c], Ting-Ting Yen [a,c], Kai-Li Liang [a,b,c,*]

[a] *Department of Otolaryngology, Taichung Veterans General Hospital, Taichung, Taiwan, ROC*
[b] *School of Medicine, Chung Shan Medical University, Taichung, Taiwan, ROC*
[c] *Faculty of Medicine, National Yang-Ming University, Taipei, Taiwan, ROC*

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Abstract

Background: Nasopharyngeal carcinoma (NPC) is a common cancer in eastern Asia. Chemoradiotherapy is the main treatment modality for NPC. Dysphagia and aspiration is not uncommon in post-irradiated NPC patients. The purpose of this study was to investigate the risk factors for recurrent pneumonia and the prognosis.

Methods: A retrospective chart review was conducted from January 2004 to December 2014. NPC patients who had been hospitalized for pneumonia in the study hospital were enrolled. The diagnosis of pneumonia was based on radiological evidence of chest inflammation and clinical symptoms. Patients' characteristics including demographic data, the hospital course, and the outcome of pneumonia were collected and analyzed.

Results: A total of 113 NPC patients were enrolled in this study. Among them, 96 NPC patients had pneumonia after radiotherapy: 43 had pneumonia twice, and 18 had multiple episodes of pneumonia. Forty-nine patients had tube feeding. The 30-day mortality rate was 51%. The mortality rate was significantly associated with metastatic nasopharyngeal carcinoma ($r = 0.328$, $p < 0.001$). Older age, smoking, body weight loss, and lower cranial nerve (vagus or hypoglossal nerve palsy) were significant predictors of multiple episodes of pneumonia ($r^2 = 0.687$, $p = 0.033$, 0.034, 0.036, and 0.027, respectively).

Conclusion: We concluded that old age, smoking, body weight loss, and lower cranial nerve palsies are predisposing factors for multiple episodes of pneumonia in post-irradiated NPC patients. Metastatic cancer status usually leads to a lethal outcome. Early interventions to manage dysphagia in high-risk patients are necessary.

Keywords: Aspiration pneumonias; Deglutition disorder; Enteral nutrition; Nasopharyngeal carcinoma; Risk factors

1. Introduction

Pneumonia is a leading cause of death due to infection globally. Pneumonia usually affects the elderly.[1,2] Furthermore, the presence of comorbidities including chronic respiratory and cardiovascular diseases, dementia, dysphagia, and chronic renal or liver diseases increase the risk of pneumonia.[2] Patients with head and neck cancers (HNCs) are prone to developing pneumonia. An important etiology for pneumonia in HNC patients is deglutition disorder. The anatomical changes of the upper aerodigestive tract resulting from tumor destruction or surgeries result in deglutition disorder. In addition, chemoradiotherapy is an important treatment modality for HNCs. Deglutition disorder is a major late treatment side effect after chemoradiotherapy for HNCs, and may lead to malnutrition and aspiration pneumonia.[3-6] Nasopharyngeal carcinoma (NPC) is a common

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* Corresponding author. Dr. Kai-Li Liang, Department of Otolaryngology, Taichung Veterans General Hospital, 1650, Section 4, Taiwan Boulevard, Taichung 407, Taiwan, ROC.

E-mail addresses: kellyliang1107@gmail.com, kelly1107@vghtc.gov.tw (K.-L. Liang).

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neoplasm in southern China, Hong Kong, and Taiwan.[7] The primary treatment modality for NPC is chemoradiotherapy. Our recent analysis using Taiwan's National Health Insurance Research Database found that the incidence of pneumonia in the post-irradiated NPC population in Taiwan was around 5.5%.[8] However, this database did not provide sufficiently detailed information to allow an exploration of risk factors for developing pneumonia. It had been reported that approximately 90% of deaths due to pneumonia occur in people aged over 65 years.[2] The outcome of pneumonia in middle-aged NPC patients had not been reported. In our experience, the prognosis of pneumonia in NPC patients is generally poor. The purpose of this retrospective study was to investigate the risk factors and outcomes of NPC patients who were hospitalized with pneumonia at a teaching hospital.

2. Methods

The Ethics Committee of Taichung Veterans General Hospital approved this study. A retrospective chart review was conducted from January 2004 to December 2014. NPC patients who had been hospitalized for pneumonia in the study hospital were enrolled. The diagnosis of pneumonia was based on radiological evidence of chest inflammation and clinical symptoms including fever, cough, or dyspnea. Patients under 20 years of age were excluded. Patients' characteristics including demographic data, hospital course, and outcome of pneumonia were collected by chart review and analyzed. NPC cancer staging was performed according to the 7th edition of the American Joint Committee on Cancer system.[9] If a patient died within 30 days of a pneumonia episode and a causal relationship was established, then pneumonia was recorded as the cause of death.

Continuous variables are presented with means (standard deviation). Spearman correlation coefficient was used to analyze the relationship between pairs of variables. Furthermore, multivariable logistic regression analysis was performed to assess the risk factors associated with multiple episodes of pneumonia. A two-sided $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS 17.0 (SPSS, Inc., Chicago, IL, USA).

3. Results

The numbers of patients received treatment or follow-up for NPC, hospitalized for pneumonia, or for both diseases in the study hospital are listed in Table 1. There were 6,651 NPC patients and 16,130 hospitalized pneumonia patients during the study period. Two hundred and sixteen NPC patients had been hospitalized for pneumonia. The estimated incidence of hospitalized for pneumonia in NPC patients was 3.2%. We performed a retrospective chart review enrolling 113 NPC patients who had been admitted to our department for pneumonia. We found that 96 NPC patients had pneumonia after radiotherapy. The other 17 patients did not receive radiotherapy or had pneumonia during or before the radiotherapy. The demographic data of the study subjects are shown in Table 2.

Table 1
Numbers of patients who received treatment for nasopharyngeal carcinoma, pneumonia, or both diseases during the study period.

Year	NPC[a]	Pneumonia[b]	Both[c]
2004	1,199	1,581	12
2005	1,175	1,511	20
2006	1,303	1,362	18
2007	1,271	1,371	21
2008	1,249	1,470	27
2009	1,353	1,571	17
2010	1,325	1,886	22
2011	1,433	1,845	22
2012	1,365	1,812	26
2013	1,278	1,743	30
2014	1,266	1,976	24
2004–2014	6,651	16,130	216

[a] Number of patients with diagnosis of nasopharyngeal carcinoma who received in-hospital or outpatient treatment.
[b] Number of hospitalized patients with diagnosis of pneumonia.
[c] Number of hospitalized patients with diagnosis of nasopharyngeal carcinoma and pneumonia.

Table 2
Characteristics of post-irradiated patients with nasopharyngeal carcinoma admitted for pneumonia in the study hospital.

Characteristics	N = 96	Percentage
Sex F/M (N)	19/77	19.8% vs. 80.2%
T stage[a]		
T1	12	12.5%
T2	23	24%
T3	18	18.8%
T4	27	28,1%
Unknown	16	16.7%
N stage[a]		
N0	10	10.4%
N1	12	12.5%
N2	39	40.6%
N3	18	16.7%
Unknown	18	16.7%
M stage[a]		
M0	64	66.7%
M1	19	19.8%
Unknown	13	13.5%
Comorbidity[b]	30	31.3%
Smoking[c]	49	51%
Lower cranial nerve palsy[d]	38	40.6%
Disease status at pneumonia diagnosis		
No evidence of cancer	32	33.3%
Metastatic disease	36	37.5%
Loco-regional disease	26	27.1%
Second cancer	2	2.1%
Radiotherapy (RT)		
CRT[e]	11	11.5%
IMRT[f]	66	68.8%
Unknown	19	19.8%
Received 2nd course RT	32	33.3%

[a] AJCC 7th edition, initial cancer stage.
[b] Comorbidity = pre-existing diabetes, respiratory or cardiovascular diseases, chronic renal or liver diseases, autoimmune disease.
[c] Current or ex-smokers.
[d] Vagus nerve or hypoglossal nerve palsies at the time of pneumonia.
[e] Conventional two-dimensional radiotherapy.
[f] Intensity modulated radiotherapy.

Among the post-irradiated NPC patients, 43 had pneumonia twice, and 18 of them had 3 or more pneumonia episodes. All patients received empirical medical treatment including antibiotics after admission. The medical treatment was then adjusted according to their sputum cultures and clinical responses. Seven patients were receiving tube feeding before developing pneumonia. Forty-two patients were maintained on tube feeding after development of pneumonia. Forty-seven patients did not need or refused tube feeding. Choking and aspiration were common in NPC patients, and silent aspiration was diagnosed in some patients (Fig. 1). The 30-day mortality rate of pneumonia of post-irradiated NPC patients was 51%. Among the 49 patients who died of pneumonia, 16 were smokers, 13 had comorbidities such as diabetes or other chronic diseases, 12 had hypoglossal or vagus nerve palsy, 10 had local recurrent tumor, and 26 had metastatic tumor (9 had lung metastases). The mortality rate was significantly associated with metastatic nasopharyngeal carcinoma ($r = 0.328$, $p < 0.001$).

The mean latency of developing pneumonia after radiotherapy in our patients was 54 months. In addition, the longer the patient survived following radiotherapy for NPC, the higher was the incidence of multiple episodes of pneumonia ($r = 0.238$, $p = 0.019$). Having pneumonia twice was

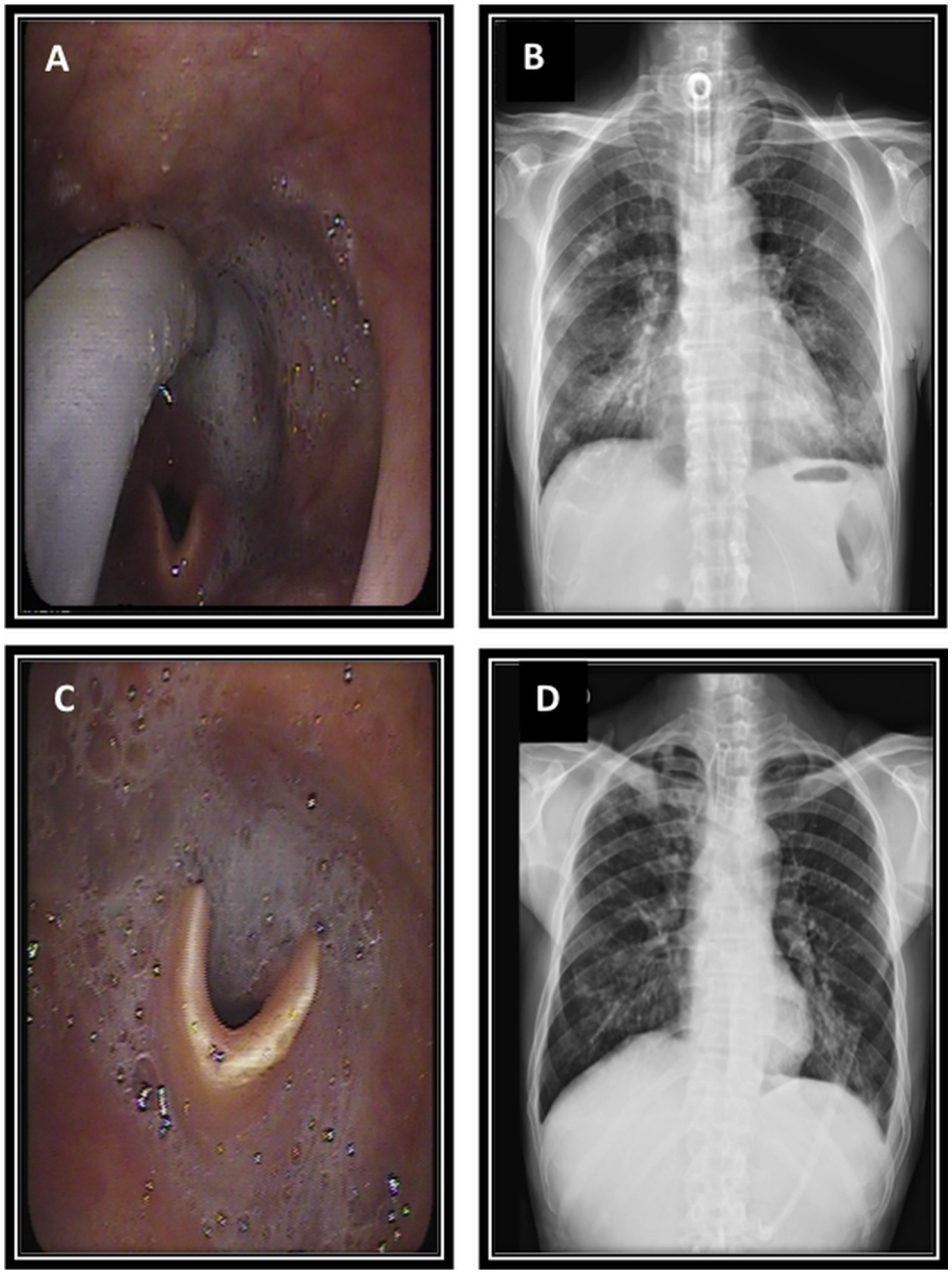

Fig. 1. Two male patients received radiotherapy for nasopharyngeal carcinoma for over 10 years. Both had progressive dysphagia after radiotherapy. Severe late sequelae including carotid blowout syndrome, vagus and hypoglossal cranial nerve palsies occurred. Laryngoscope examination demonstrated saliva pooling in the hypopharynx and silent aspiration to the larynx (A), (C). Both patients had repeated aspiration pneumonia (B), (D). They required tube feeding and tracheostomy.

significantly associated with increasing age ($r = 0.511$, $p = 0.001$) and smoking ($r = 0.253$, $p = 0.013$). Having multiple episodes of pneumonia was significantly associated with age 65 years or older ($r = 0.329$, $p = 0.001$), smoking ($r = 0.24$, $p = 0.019$), and lower cranial nerve palsies (vagus or hypoglossal nerve palsy, $r = 0.322$, $p = 0.001$) (Table 3). Multivariable logistic regression analysis was performed to assess the risk factors for multiple episodes of pneumonia in post-irradiated NPC patients. We found that age 65 years or older, smoking, body weight loss, and lower cranial nerve (vagus or hypoglossal nerve palsy) were significant predictors of multiple episodes of pneumonia ($r^2 = 0.687$, $p = 0.033$, 0.034, 0.036, and 0.027, respectively).

4. Discussion

A literature review conducted in Europe revealed that the incidence of pneumonia increased with certain lifestyle factors, age, and the presence of comorbidities.[2] There is solid evidence that smoking is associated with the risk of pneumonia, both for current and former smokers.[2, 10-12] In our results, we found half of our patients were current or former smokers, and smoking was associated with recurrent pneumonia. Elderly patients are more likely to have impaired swallow and cough function, and degenerative neurologic diseases.[1] Aspiration was the most common etiology for pneumonia in patients with neurological diseases and among the elderly patients.[10] Previous studies reported that HNC patients are at risk of dysphagia and aspiration pneumonia after chemoradiotherapy.[5, 13-15] Shune et al.[6] investigated the incidence of pneumonia in a series of HNC patients treated with radiotherapy: 32% of the 324 patients developed severe dysphagia and 18 patients developed aspiration pneumonia in the first year after radiotherapy. The etiologies of dysphagia in irradiated patients are multifactorial.[16, 17] The lack of saliva in irradiated patients contributes to poor oral hygiene, as well as impairment of food bolus formation and transportation to the pharynx.[18] In addition, radiotherapy-related neuromuscular incoordination and impairment of pharyngeal sensation result in prolonged pharyngeal transit time and aspiration. Bilateral neck irradiation damages the neck fat, fascia, and neuron axons, resulting in constriction of neck movement, pharyngeal expansion and sensation. Furthermore, vagus and hypoglossal cranial palsies, in addition to other radiation-induced toxicities could impair oral and pharyngeal swallowing.[19, 20] Chang et al.[21] evaluated 184 irradiated NPC patients and found that swallowing function continued to deteriorate over the years after radiotherapy. We found that the longer the patients survived after radiotherapy, the higher was the incidence of repeated pneumonia. This indicates that dysphagia exhibits progressive deterioration over time. Nearly 40% of our pneumonia patients had vagus or hypoglossal cranial palsies. Also, lower cranial nerve palsy was a strong predisposing factor for having three or more episodes of pneumonia.

Table 3
Correlations of recurrent (twice) or multiple episodes of pneumonia (at least 3 episodes) with patients' characteristics.

Variables	Pneumonia twice		Pneumonia ≥3 episodes	
	r value[a]	*p* value	*r* value	*p* value
Age	0.334	0.001*	0.329	0.001*
Sex	0.61	0.557	0.197	0.055
Smoking	0.253	0.013*	0.238	0.019*
Body weight loss (kg)	−0.195	0.133	−0.22	0.089
Lower cranial nerve palsy	0.095	0.359	0.267	0.009*

[a] Spearman's correlation coefficient, *$p < 0.05$.

Body weight loss was another important predisposing factor for multiple episodes of pneumonia in our patients. This suggests that dysphagia-related malnutrition is associated with the development of pneumonia. Early tube feeding for nutritional support and avoidance of choking is recommended for patients with dysphagia. Half of pneumonia patients enrolled in this study needed tube feeding: most of them accepted tube feeding following diagnosis of pneumonia. Only a few of our patients received tube feeding before developing pneumonia. However, some patients were reluctant to receive tube feeding. Reasons for refusal included the negative impact on body image and the lack of pleasure associated with eating.

Our results demonstrated that the outcome of pneumonia in post-irradiated NPC patients was very poor. Shindo et al.[22] reported the 30-day mortality rate of hospitalized pneumonia patients with pathogens sensitive to the initial antibiotics was 11%, and 17% for pneumonia patients with pathogens resistant to the initial antibiotics. In the study by Shindo, elderly patients and patients with neoplastic disease had worse outcomes.[22] The outcomes of our patients were much worse even though all patients received empirical antibiotics initially with subsequent adjustment of their treatment when the culture results were known. Intensity-modulated radiotherapy (IMRT) is the current standard of treatment for NPC.[23] IMRT can achieve excellent 5-year local control rates. However, late complications such as neurologic damage and dysphagia are common after T3 to T4 NPC.[24] Most of our enrolled patients received IMRT for NPC (68.6%). About half of them were T3 to T4 NPC (46.9%). Furthermore, one third of our patients had received a second course of radiotherapy. Re-radiation is significantly associated with severe radiation complications.[8] The high mortality rate in our NPC patients with pneumonia could result from their late radiation-related dysphagia. In addition, the mortality rate of pneumonia in our patients was significantly associated with metastatic cancer status. Metastatic diseases resulted in cancer cachexia and immunological deficit, making metastatic patients susceptible to pulmonary infection.[22,25]

There are a number of preventive strategies to decrease the risk of pneumonia, including oral hygiene, altered food viscosity, adjusted intake positioning, swallowing therapy, and tube feeding.[1] Silent aspiration is not uncommon in post-irradiated NPC patients. Regular endoscopic or videofluoroscopic evaluation is recommended in all post-irradiated NPC patients, though some do not suffer from dysphagia. Early preventive intervention or tube feeding could possibly reduce the morbidity and mortality rates.

There were several potential limitations in this study. First, this was a retrospective chart review. There were differences in the subjects' characteristics and treatment modalities. Second, only hospitalized patients were enrolled in this study. Some pneumonia patients with mild symptoms could receive treatment in the outpatient department. Further prospective controlled studies are necessary to obtain a better understanding of this difficult disease entity.

In conclusion, old age, smoking, body weight loss, and lower cranial nerve palsies are predisposing factors for multiple episodes of pneumonia in post-irradiated NPC patients. Metastatic cancer status leads to lethal outcome. Early intervention to manage dysphagia is essential for preventing pneumonia in high-risk patients.

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