Title：

Clinical features of patients with second primary lung cancer following head and neck cancer

Running Head：

Lung cancer after head and neck cancer

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Abstract

Background: Survivors of head and neck cancer (HNC) often develop second primary lung cancer (SPLC), due to a common risk factor, that is, smoking. Our multicenter experience has been reviewed to evaluate how the history of diagnosis of HNC affects the outcomes of patients undergoing pulmonary resection for SPLC.

Methods: A multicenter retrospective analysis of patients hospitalized between January 2012 and December 2018 has been performed. From a cohort of 4,521 patients undergoing therapeutic pulmonary resection for primary non-small cell lung cancer, 100 patients with previous history of HNC (HNC group) have been identified. They were compared with a control group consisting of 200 patients without HNC history from the same cohort pair-matched with operating facility, age, sex, and pathological stage of lung cancer.

Results: At the time of surgery for SPLC, the HNC group showed malnutrition with lower prognostic nutritional index (PNI) compared with the control group ($p < 0.001$). The HNC group were determined to have postoperative complications more frequently ($p = 0.02$). The 5-year overall survival rates in the HNC and control groups were 59.0% and 83.2%, respectively ($p < 0.001$). Statistically, HNC history, lower PNI, squamous cell lung cancer, and TNM stage were identified to be independently associated with poor survival.

Conclusions: Patients with SPLC following primary HNC often present with malnutrition and are predisposed to have postoperative complications and poor survival after pulmonary resection.

Introduction

Worldwide, head and neck cancer (HNC) represents approximately 6% of all cancers[1], and more than 60,000 cases are newly diagnosed annually[2]. Previous research showed that HNC survivors often develop second primary lung cancer (SPLC) due to a common risk factor, that is, smoking[3, 4], and the estimated risk accounted for more than 16% in 10 years[5]. Patients with first primary HNC developing SPLC were reported to show worse prognosis than those patients with HNC only[6]. Moreover, some reports have defined the HNC history as a risk factor of postoperative complications and poor prognosis in patients with SPLC [7, 8].

Lifestyle factors that are correlated with increased risk of developing HNC, such as smoking and alcohol abuse, may also contribute to development of malnutrition among HNC survivors [9]. Moreover, cancer itself can result to malnutrition in the condition of cachexia, and common treatment options for HNC, including surgery, radiotherapy, chemotherapy, or combinations of these three, are also likely to further contribute to poor nutritional status[10]. Malnutrition is frequently observed in cancer patients and is often associated with detrimental metabolic consequences including muscle wasting, leading to higher mortality and morbidity[11]. Thus, nutritional optimization of these patients has been identified to be of utmost significance in the management of HNC patients.

While factors contributing to the development of HNC and the characteristic background of HNC survivors may increase risk of postoperative complications and poor survival following resection for SPLC, these have yet to be explored in the existing literature. Thus, in this retrospective study, we aimed to characterize the clinical features of patients undergoing pulmonary resection for SPLC following primary HNC and to investigate how the history of HNC affects their perioperative outcomes and prognosis.

Patients and methods

Patient selection

A database of the patients undergoing pulmonary resection for primary lung cancer in 10 institutions of Okayama University Thoracic Surgery Study Group in Japan has been prospectively maintained. Using this database, a retrospective review of a total of 4,521 patients between January 2012 and December 2018 has been conducted. The subjects were all Asian. Among them, 101 patients have been identified as having HNC history before the initial diagnosis of SPLC. Patients with thyroid cancer were excluded due to different risk factors and 1 patient was excluded due to small cell lung cancer. Diagnosis of SPLC was comprehensively determined by the attending surgeon based on histological subtypes, early TNM stage of HNC, interval from HNC treatment, or imaging findings of lung tumor.

The study population was then divided into two groups: The HNC group consisted of 100 patients with HNC history, whereas the control group consisted of 200 patients without previous HNC history from the database. For the control group, two patients were randomly selected for every patient in HNC group. They were matched as 2/1 for the following variables: operating facility, age at the time of surgery, sex, and the TNM stage of lung cancer (Figure 1).

This study protocol (No. 2007-028) was approved by the Ethics Committee of Okayama University Hospital, and every joint research facility also got permission from each Ethics Commission. Written informed consent from each patient was waived, and all methods in this study were in compliance with the relevant guidelines and regulations.

Data collection

The variables related to previous HNC included the date of initial and last treatment, lesion site, histology, TNM stage, surgical procedure, associated treatments (endoscopic submucosal dissection [ESD], radiotherapy, chemotherapy), and recurrence. For lung cancer, the following variables were recorded: age at the time of surgery, sex, smoking status, body mass index (BMI), Charlson Comorbidity Index, recent nutrition index before the surgery (neutrophil-lymphocyte ratio [NLR], prognostic nutritional index [PNI], controlling nutritional status

[CONUT] score), respiratory function, surgical type of resection, operation time, histologic findings, postoperative course, and the presence of postoperative complications. The PNI value was calculated using the formula 10 × serum albumin level (g/dl) + 0.005 × lymphocyte count (n/μl) in the peripheral blood, while the CONUT score was calculated from serum albumin levels, total cholesterol levels, and total lymphocyte counts as previously reported[12]. Overall survival (OS) was defined as the time interval from the pulmonary resection until death or the last recorded follow-up. The median follow-up time of survivors in this study was 50.1 months (range: 0.5–109.8 months)

Statistical analyses

All statistical analyses were performed using EZR version 1.42 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria)[13]. GraphPad Prism 9.0 (GraphPad Software Inc.) was used for graphic display.

Quantitative variables were expressed as mean ± standard deviation or median values. A comparison of patient characteristics and univariate analysis of postoperative outcome have been studied using Fisher's exact test for quantitative variables and Student's t-test or Mann–Whitney U test for continuous variables. In multivariate analysis for the associations of postoperative complications with risk factors, variables except previous HNC history were used as continuous value to calculate odds ratios. OS was calculated using the Kaplan–Meier method, whereas differences between the groups were assessed using the log-rank test. The receiver operating characteristic curve for the 3-year mortality was obtained to calculate optimal cutoff values for quantitative variables to differentiate. The Cox multivariate proportional hazards model was used to examine the relationship between clinicopathologic variables and OS and to estimate 95% confidence intervals. For the variables entered into multivariate analysis, the number of factors that can be incorporated into the analysis was first

determined considering the number of total events, and then among candidates with significant differences in the univariate analysis, so as not to be confounded as much as possible. The proportional hazard assumption was assessed and confirmed to be satisfied for all factors.

Results

Patient characteristics and management of lung cancer

In total, 100 patients were eligible for the HNC group. Table 1 summarizes the detail of primary HNC. The most frequent site of HNC origin was the pharynx in 35 patients (35.0%). Squamous cell carcinoma was the most common histologic type. For HNC treatment, 49 patients (49.0%) underwent surgery, and more than half of the patients (57.0%) received radiotherapy alone or in combination with surgery or chemotherapy. The median interval between the last HNC treatment and pulmonary resection for SPLC was 41 months. In total, 4,420 patients without HNC history underwent pulmonary resection for lung cancer, and 200 patients were assigned to control group by matched-pair method. The characteristics of the study population are shown in Table 2. The pack-years of smoking exposure ($p < 0.001$) and Charlson score ($p < 0.001$) were significantly higher in the HNC group. Lower BMI ($p = 0.002$), lower PNI ($p < 0.001$), and higher CONUT score ($p < 0.001$) in the HNC groups indicate the malnutrition of patients with previous HNC. NLR tended to be higher in the HNC group than those in the control group ($p = 0.06$). Postoperative complications were noted to be significantly more common in the HNC group than control group ($p = 0.02$). The details of the complications are shown in Supplemental Table 1. Pulmonary fistula was the most frequent complication followed by pneumonia, supraventricular tachycardia, and chylothorax. In addition, HNC group showed significantly higher 90-day mortality than control group, indicating that these postoperative complications might lead to worsening short-term prognosis.

Furthermore, when focusing on the clinical factors of the HNC group and patients with history

of any other malignancies assigned to the control group, a similar tendency was observed; the HNC group showed further worse nutritional condition, including higher NLR ($p = 0.01$) and CONUT score ($p = 0.008$), and lower PNI ($p = 0.01$). They had postoperative complications more frequently than those with other malignancy history ($p = 0.007$) (Supplemental Table 2 and 3).

Risk factors for postoperative complications

In the overall population, 62 patients (20.7%) experienced at least one postoperative complication after the surgery for lung cancer. Multivariate analysis revealed the following factors to be independently associated with high risk of postoperative complications: Charlson index ($p = 0.04$), PNI ($p = 0.03$), and operation time ($p < 0.001$) (Table 3). In the HNC group, previous radiotherapy and neck dissection given as the treatment for primary HNC did not show significant relevance to complications after the surgery for SPLC (Supplemental Table 4).

Survival analyses

Kaplan–Meier survival estimates of total cases are shown in Figure 2. The median follow-up period of survivors after surgery for lung cancer of the HNC group and control group was 50.6 months (range: 4.6–109.8 months) and 50.1 months (range: 0.5–106.2 months), respectively. The survival estimates were significantly different ($p < 0.0001$). The 5-year survival of the HNC group was 59.0% (95% CI, 46.3–69.7%), while 83.2% (95% CI, 76.0–88.4%) for the control group. In multivariate analysis, the presence of HNC history showed a significant influence to poor prognosis ($p = 0.03$). Moreover, PNI ($p < 0.001$), squamous cell lung cancer ($p = 0.04$), and TNM stage ($p = 0.01$) also remained as independent predictive factors (Table 4). For further assessment of the impact of PNI on prognosis, we divided the patients in HNC group into those with higher PNI (≥48.0, n = 48) and with lower PNI (<48.0, n = 51). Then the patients with lower PNI showed significantly poorer prognosis (5-year OS: 75.3% vs 44.8%, $p = 0.004$) (Supplemental Figure 1).

In the HNC group, five patients (5.0%) died from HNC, and lung cancer was the second common cause of death in both groups (Supplemental Table 5). Figure 3 shows the cumulative mortality of lung cancer and other causes following surgery for lung cancer. While cumulative risk due to lung cancer did not differ between the two groups, other causes (other cancers or noncancer causes) led to death more frequently in the HNC group, with a 5-year cumulative mortality of 27.6% (95% CI, 12.4–40.2%) and 10.1% (95% CI, 5.0–15.0%) ($p = 0.006$) for the HNC and control groups, respectively. These results indicate that other death causes which can be ascribed to their characteristic background have a dampening effect on poor survival.

Subgroup analysis of patients with lung adenocarcinoma

Finally, to dispel the concerns that cases with metastatic lung tumor from HNC might be enrolled in this study, the HNC group and control group were compared only in cases of lung adenocarcinoma, because patients with lung adenocarcinoma in the HNC group can be considered as developing second primary with high possibility due to high proportion of squamous cell carcinoma in primary HNC. Even in this situation, similar results could be obtained; the HNC group showed malnutrition including lower BMI ($p = 0.03$), lower PNI ($p < 0.001$), and higher CONUT score ($p = 0.002$) and develop postoperative complications more frequently ($p = 0.03$) (Supplemental Table 6). The survival estimates were significantly different with the 5-year survival of 67.9% (95% CI, 52.4–79.4%) for the HNC group and 85.1% (95% CI, 76.5–90.7%) for the control group ($p = 0.002$) (Supplemental Figure 2). Multivariable analysis revealed PNI ($p = 0.002$) and TNM stage ($p = 0.02$) to be independent risk factors of poor survival (Supplemental Table 7 and 8).

Comment

Compared with the general population, HNC survivors with impaired respiratory function, impaired nutritional status, and higher preoperative comorbidity show an increased risk of death from any cause. About a quarter of all deaths in HNC survivors are due to second primary malignancies[14, 15]. Among them, lung cancer is the most common second primary malignancy reported to account for 53%, followed by esophageal cancer (10%)[16]. Cigarette smoking can bring about second primary malignancies, as it is a common risk factor for major malignancies. Recent studies have proposed that the prevalence of malnutrition in HNC patients is one of the highest in all malignancies, ranging from 20% to 74%[10, 17-19]. Malnutrition may occur before and during treatment for HNC as well as after therapy. While in the pre-therapy phase this is mainly due to the cancer itself, the common treatments including surgery, radiotherapy, and chemotherapy can result in further significant symptoms affecting food intake, including dysphagia, odynophagia, and anorexia[20]. In our retrospective case-control study, patients with HNC history had heavier smoking history and presented lower BMI and nutrition index than those in the control group, supporting the previous findings since PNI and CONUT score have been investigated in detail as prognostic factors for various types of cancer[21, 22]. Moreover, the HNC group showed a tendency of presenting higher NLR, which is also accepted as an important indicator of malnutrition and adverse prognosis among patients with various cancers [23, 24]. Previous reports have identified the poor nutritional condition, especially lower PNI, as a significant risk factor of both postoperative complications and adverse long-term survival in patients who underwent pulmonary resection for lung cancer[25-27], and similar results were also obtained in our study. Furthermore, interestingly, previous HNC history itself has been revealed to be an independent risk factor of poor survival.

Among long-term survivors of lung cancer, about half of deaths occur due to lung cancer [28, 29], whereas more than 70% of HNC survivors die from other causes including 23% of other malignancies and 44% of noncancer causes[16]. More frequent deaths from other causes except for HNC and lung cancer in the HNC group may result from any disease caused by malnutrition

or their distinctive background.

As per current findings, deciding how we should treat these SPLC patients following primary HNC with preoperative comorbidities and nutritional abnormality is important. Since our study showed that patients with lower PNI had a significantly poorer prognosis even focusing in HNC group, improving nutritional status may lead to their better prognosis. We recommend that nutritional optimization be a component of pre-operative patient care for patients diagnosed with SPLC. This is supported by preceding reports indicating that the nutritional support can reduce the risk of mortality and improve functional and quality-of-life outcomes in cancer patients[30, 31]. In order to better evaluate the role of malnutrition in the development of postoperative complications and poor prognosis, as well as to assess if this risk is modifiable, a prospective randomized intervention study would be necessary.

The main strength of our study is its multicenter case-control study design with groups matched for fundamental factors related to prognosis and comparative discussion focusing on nutritional status. However, this study has several limitations. First, this is a retrospective study which may contain potential bias with missing data. Second, when sampling the patients of control group, we adopted a matched-pair method using the minimum factors to reveal the characteristic background of patients in HNC group. This may lead to some bias in analyzing the association between each factor and short- and long-term outcomes. Finally, SPLC cannot be completely distinguished from metastatic tumor. Although no definitive biomarkers to distinguish them are available so far, this error can be assumed to be minimum with reference to a report showing that a considerable number of lung lesions clinically interpreted as metastases from primary HNC were suggested to be second primaries[32]. In order to eliminate this possibility, only cases of lung adenocarcinoma have been compared additionally. Similar results as regards patient characteristics and risk factors for survival can be seen as well; thus, it is thought that there is no blurring in our argument.

Conclusion

In conclusion, patients with SPLC following primary HNC often present with malnutrition and are more prone to develop postoperative complications than those patients without HNC history. Previous HNC and malnutrition can adversely affect prognosis.

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Conflict of interest

Authors have nothing to disclose as regards commercial support.

Abbreviations

HNC	head and neck cancer
SPLC	second primary lung cancer
PNI	prognostic nutritional index
ESD	endoscopic submucosal dissection
BMI	body mass index
NLR	neutrophil-lymphocyte ratio
CONUT	controlling nutritional status
OS	overall survival
%VC	vital capacity as percent of predicted
FEV1.0	forced expiratory volume in 1 second

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Table 1. Characteristics of HNC patients (n = 100)

Variable	
Subsite of HNC	
Pharynx	35 (35.0%)
Larynx	31 (31.0%)
Tongue	12 (12.0%)
Oral cavity	12 (12.0%)
Others	10 (10.0%)
Treatment for HNC	
Surgery	35 (35.0%)
Surgery + radiotherapy	14 (14.0%)
ESD	5 (5.0%)
Chemoradiotherapy	25 (25.0%)
Radiotherapy	18 (18.0%)
Chemotherapy	1 (1.0%)
Unknown	2 (2.0%)
Histological subtypes of HNC	
Squamous cell carcinoma	83 (83.0%)
Adenocarcinoma	1 (1.0%)
Others	4 (4.0%)
Unknown	12 (12.0%)
Interval between last HNC treatment and lung resection (months)	
Median (range)	41 (1-427)

Table 2. Comparison of clinical and pathological factors

	HNC group (n=100)	Control group (n=200)	p value
Age	70.8 ± 8.5	70.9 ± 7.7	.83
Male	91 (91.0%)	183 (91.5%)	>.99
BMI (kg/m2)	21.8 ± 3.2	22.9 ± 3.0	.002
Smoking status	90 (90.0%)	160 (80.0%)	.03
Cumulative smoking (pack-years)	52.5 (0-280)	39.0 (0-270)	<.001
Charlson comorbidity index	2.47 ± 1.42	1.73 ± 1.42	<.001
NLR*	2.99 ± 1.62	2.60 ± 1.48	.06
PNI*	47.9 ± 4.9	50.6 ± 5.2	<.001
CONUT score†	1.82 ± 1.08	1.19 ± 1.46	<.001
%VC‡	98.4 ± 17.1	99.9 ± 15.8	.35
FEV1.0 (ml)§	2310 ± 633	2411 ± 608	.22
%FEV1.0§	87.1 ± 20.2	89.1 ± 17.3	.40
Type of surgery			.42
Pneumonectomy	0 (0%)	1 (0.5%)	
Lobectomy	61 (61.0%)	123 (61.5%)	
Segmentectomy	20 (20.0%)	50 (25.0%)	
Wedge resection	19 (19.0%)	26 (13.0%)	
Histological subtypes of lung cancer			.03
Adenocarcinoma	60 (60.0%)	149 (74.5%)	
Squamous cell carcinoma	37 (37.0%)	46 (23.0%)	
Others	3 (3.0%)	5 (2.5%)	
pStage			.75
0	2 (2.0%)	6 (3.0%)	
I	84 (84.0%)	164 (82.0%)	
II	7 (7.0%)	14 (7.0%)	
III	6 (6.0%)	15 (7.5%)	
IV	1 (1.0%)	0 (0%)	
Operation time (hours)	3.4 (0.7-9.9)	3.5 (0.6-8.1)	.98
Postoperative day for discharge	9 (3-73)	8 (2-65)	.10
Postoperative complication	29 (29.0%)	33 (16.5%)	.02

NOTE: including missing data of

*4cases, †87cases, ‡7cases, and §6cases

Table 3. Univariate and multivariate analysis of risk factors for postoperative complications (n = 300)

	univariate			multivariate		
Variables	Postoperative event (n=62)	No postoperative event (n=238)	p value	OR	95% CI	p value
Previous HNC	29 (46.8%)	71 (29.8%)	.02	1.43	0.76-2.68	.27
Age	72.2 ± 6.0	70.5 ± 8.4	.14			
Male	61 (98.4%)	213 (89.5%)	.02			
BMI (kg/m2)	22.0 ± 3.4	22.7 ± 3.0	.13			
Smoking status	58 (93.5%)	192 (80.7%)	.001			
Cumulative smoking (pack-years)	48 (0-280)	43 (0-270)	.01	1.01	1.00-1.01	.19
Charlson comorbidity index	2.46 ± 1.60	1.85 ± 1.40	.003	1.26	1.02-1.57	.04
NLR	3.13 ± 2.07	2.62 ± 1.36	.16			
PNI	47.6 ± 6.0	50.3 ± 5.0	<.001	0.93	0.88-0.99	.03
CONUT score	1.88 ± 1.73	1.28 ± 1.22	.009			
%VC	94.6 ± 19.1	100.7 ± 15.2	.01			
FEV1.0 (ml)	2215 ± 561	2422 ± 625	.02			
Type of surgery			.02			
Pneumonectomy	0 (0%)	1 (0.4%)				
Lobectomy	46 (74.2%)	138 (58.0%)				
Segmentectomy	13 (21.0%)	57 (23.9%)				
Wedge resection	3 (4.8%)	42 (17.6%)				
Operation time (hours)	4.0 (1.0-9.9)	3.3 (0.6-8.1)	.001	1.56	1.22-2.17	<.001

Table 4. Univariate and multivariate analysis for overall survival (n = 300)

		univariate			multivariate	
Variables	n	5-year OS	95% CI	p value	OR (95% CI)	p value
Previous HNC				<.001	1.80 (1.07-3.02)	.03
Yes	100	59.0%	46.3-69.7			
No	200	83.2%	76.0-88.4			
Sex				.41		
Male	274	74.8%	68.1-80.3			
Female	26	76.7%	46.9-91.1			
Age (years)				.005	1.67 (0.83-3.36)	.15
< 67	85	84.0%	72.7-90.9			
≥ 67	215	70.9%	62.7-77.7			
BMI				<.001		
< 20.9	84	56.1%	43.0-67.3			
≥ 20.9	216	82.3%	75.0-87.6			
Charlson comorbidity index				.003		
0-1	105	86.9%	76.6-92.8			
≥ 2	195	68.6%	60.3-75.8			
Cumulative smoking (pack-years)				.001	1.60 (0.76-3.38)	.22
< 26.5	94	85.5%	73.7-92.3			
≥ 26.5	206	70.1%	62.0-76.8			
NLR				<.001		
< 3.8	242	81.3%	74.6-86.4			
≥ 3.8	54	45.7%	25.6-63.8			
PNI				<.001	0.20 (0.10-0.39)	<.001
< 49.5	135	57.6%	46.8-67.0			
≥ 49.5	161	89.6%	81.4-94.3			
CONUT score				.002		
0-1	128	81.9%	72.2-88.5			
≥ 2	85	60.2%	46.5-71.5			
%VC				<.001		
< 91.3	79	52.6%	38.9-64.6			
≥ 91.3	214	82.4%	74.9-87.8			
FEV1.0 (ml)				<.001		

< 2570	182	67.2%	57.8-74.9			
≥ 2570	112	85.7%	75.7-91.8			
Type of surgery				.07		
Pneumonectomy	1	NA	NA			
Lobectomy	184	80.9%	73.2-86.6			
Segmentectomy	70	66.0%	51.1-77.3			
Wedge resection	45	59.0%	34.3-77.0			
Histological subtypes				.01	1.71 (1.00-2.90)	.04
Adenocarcinoma	209	79.7%	72.3-85.4			
Squamous cell carcinoma	83	63.5%	49.4-74.7			
pStage				.002	1.50 (1.10-2.03)	.01
0	8	85.7%	33.4-97.9			
I	248	77.4%	70.1-83.2			
II	21	60.0%	35.7-77.6			
III	21	58.6%	33.6-77.0			
IV	1	NA	NA			
Postoperative complications				.004		
Yes	62	65.5%	50.4-77.0			
No	238	77.2%	69.8-83.0			

Figure legends

Figure 1. Study population

Figure 2. Kaplan-Meier survival estimates after pulmonary resection for lung cancer of the patients with or without previous HNC history. Solid lines describe the probability of survival and the dashed lines represent the 95% confidence interval.

Figure 3. Cumulative mortality rate of the two groups