Pharyngocutaneous fistula and delay in free oral feeding after pharyngolaryngectomy for hypopharyngeal cancer

Sayaka Suzuki, MD,[1,2]* Hideo Yasunaga, MD, PhD,[1] Hiroki Matsui, MPH,[1] Hiromasa Horiguchi, PhD,[3] Kiyohide Fushimi, MD, PhD,[4] Tatsuya Yamasoba, MD, PhD[2]

[1]Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo, Tokyo, Japan, [2]Department of Otolaryngology and Head and Neck Surgery, Faculty of Medicine, The University of Tokyo, Tokyo, Japan, [3]Department of Clinical Data Management and Research, Clinical Research Center, National Hospital Organization Headquarters, Tokyo, Japan, [4]Department of Health Policy and Informatics, Tokyo Medical and Dental University Graduate School of Medicine, Tokyo, Japan.

Accepted 5 March 2015
Published online 00 Month 2015 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/hed.24055

ABSTRACT: *Background.* Risk factors for pharyngocutaneous fistula and associated delay in free oral feeding after pharyngolaryngectomy for patients with hypopharyngeal cancer remain uncertain.

Methods. We used a Japanese national inpatient database to perform a retrospective cohort study between 2007 and 2013. We performed multivariable logistic regression analysis to identify patient characteristics associated with pharyngocutaneous fistula formation, and Cox regression analysis to evaluate factors affecting the interval from pharyngolaryngectomy to free oral feeding.

Results. Among 549 eligible patients, 33 had developed pharyngocutaneous fistula, 19 of whom required surgical closure. Preoperative radiotherapy significantly increased risk of pharyngocutaneous fistula (odds ratio [OR] = 3.17; 95% confidence interval [CI] = 1.10–9.12; $p = .033$). Pharyngocutaneous fistula significantly prolonged the interval to oral feeding (median days, 67 vs 20 in those with and without pharyngocutaneous fistula, respectively; hazard ratio [HR], = 0.26; 95% CI = 0.15–0.44; $p < .001$).

Conclusion. Preoperative radiotherapy was associated with increased occurrence of pharyngocutaneous fistula and subsequent delay in free oral feeding. © 2015 Wiley Periodicals, Inc. *Head Neck* **00:** 000–000, 2015

KEY WORDS: hypopharyngeal cancer, pharyngolaryngectomy, pharyngocutaneous fistula, free oral feeding

INTRODUCTION

Hypopharyngeal cancer accounts for approximately 20% of newly diagnosed head and neck cancer in Japan.[1] Although early-stage hypopharyngeal cancer is potentially curable, this disease is usually diagnosed at a locally advanced stage. Despite advances in organ preservation strategies involving chemotherapy and radiotherapy, pharyngolaryngectomy remains an important primary treatment option for stage III and IV resectable hypopharyngeal cancer.

One of the important determinants of quality of life after pharyngolaryngectomy is swallowing function. Pharyngocutaneous fistula formation, which although rarely fatal[2] is nonetheless the most annoying postsurgical complication,[3–5] inevitably delays initiation of free oral feeding. Patients with pharyngocutaneous fistula suffer not only from the presence of the fistula itself, but also from the psychological and traumatic effects of tube feeding.

Numerous studies have reported the risk of fistula formation after total laryngectomy[6,7] and the appropriate timing for recommencing oral feeding after total laryngectomy.[8] However, only a few studies have addressed the risk of pharyngocutaneous fistula formation after pharyngolaryngectomy.[9–11] Further, to our knowledge, there is a lack of data on the interval from pharyngolaryngectomy to free oral feeding in patients with hypopharyngeal cancer and little is known about factors affecting this interval.

The purposes of our retrospective observational study were twofold. First, we used a national inpatient database in Japan to investigate the factors that contribute to the development of pharyngocutaneous fistula after pharyngolaryngectomy. Second, we assessed the interval from pharyngolaryngectomy to the start of free oral feeding.

MATERIALS AND METHODS

Data source

Data from the Diagnosis Procedure Combination database, which is a national inpatient database in Japan that includes administrative claims data and discharge abstract data,[12] were analyzed for each patient. This database contains: (1) main diagnoses, comorbidities at admission, and complications after admission, with the corresponding International Statistical Classification of Diseases-10 codes; (2) surgical interventions, with the original Japanese codes; (3) age, sex, and patient characteristics (weight, height, Brinkman Index); (4) TNM classification

***Corresponding author:** S. Suzuki, Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 1130033, Japan. E-mail: sayasuzuki-tky@umin.ac.jp

recommended by the Union for International Cancer Control and cancer stage; (5) drugs and devices used; and (6) type of hospital (academic or nonacademic). The database also stores the dates of commencement and termination of each drug or device and the route of administration (eg, tube feeding through nasogastric tube or gastric stoma, parenteral nutrition), as well as the date of each procedure (pharyngolaryngectomy, tracheotomy, and videofluoroscopic assessment of swallowing).

The cancer stages recorded in the database were mainly based on preoperative findings. However, when the cancer stage based on intraoperative findings differed from that based on preoperative findings, physicians were required to record the intraoperative staging.

Data were collected for 6 months (July 1 to December 31) each year from 2007 to 2010; the duration per year of data collection was extended to 12 months in 2011. In 2012, 6.8 million patients were included, representing more than 50% of all inpatient admissions to acute care hospitals in Japan. The physicians in charge are required to record the information about diagnoses and therapy from the patients' medical charts to maximize accuracy of these data.

Patient selection and background characteristics

Data on patients with diagnoses of hypopharyngeal cancer (International Statistical Classification of Diseases-10 code C139, malignant neoplasm of hypopharynx) on admission who had undergone pharyngolaryngectomy between July 2007 and March 2013 (51 months in total) were extracted.

Patient characteristics assessed included age, sex, body mass index (BMI kg/m^2), smoking status (nonsmoker/current or ex-smoker), cancer stage, comorbidities, preoperative radiotherapy within 6 months before pharyngolaryngectomy, preoperative chemotherapy within 6 months before pharyngolaryngectomy, and tracheotomy (on the day before pharyngolaryngectomy, on the day after pharyngolaryngectomy, or not performed). Based on the Quan et al[13] protocol, each comorbidity on admission was assigned a weighted score to enable calculation of the Charlson Comorbidity Index (CCI).[14] BMI was classified according to the World Health Organization definitions of underweight (BMI <18.50 kg/m^2), normal weight (range, 18.50–24.99), overweight and obese (≥25.00).[15] Normal weight was subclassified as low normal (range, 18.50–22.99) and high normal (range, 23.00–24.99). Any malignancy was assigned a weighted score of 2, which means that all eligible patients had at least a CCI of 2. This score enabled categorization of patients as having any coexisting disease other than hypopharyngeal cancer (CCI ≥3) or not (CCI = 2). Data on radiotherapy and chemotherapy within the 6 months before pharyngolaryngectomy were extracted with the aim of discriminating between patients who had undergone preoperative irradiation and neoadjuvant chemotherapy from those who received chemotherapy and radiotherapy as organ-preserving treatments.

The study protocol was approved by the Institutional Review Board of The University of Tokyo. Because of the anonymous nature of the data, the requirement for informed consent was waived.

Assessment of outcomes

The primary outcomes were: (1) occurrence of pharyngocutaneous fistula formation, and (2) the interval (days) from pharyngolaryngectomy to commencing free oral feeding. The overall time assessed was the postoperative length of stay. Patients who were discharged before starting free oral feeding or who died during hospitalization were defined as censored cases.

Statistical analyses

Fisher's exact test was used to compare inhospital mortality between patients with and without pharyngocutaneous fistula. Univariable logistic regression analyses were performed to identify patient characteristics associated with pharyngocutaneous fistula formation. Variables with $p < .2$ according to univariable analysis were subjected to multivariable logistic regression analysis.

The Kaplan–Meier method and log-rank test were used to compare the interval (days) from pharyngolaryngectomy to the start of free oral feeding between patients with and without pharyngocutaneous fistula. In addition, the Kaplan–Meier method and log-rank test were performed to analyze associations between T, N, or overall cancer stage and the interval from pharyngolaryngectomy to the start of free oral feeding. The Cox proportional hazard regression was modeled to assess potential factors affecting the interval from pharyngolaryngectomy to the start of free oral feeding, including age, sex, BMI category, smoking status, cancer stage, CCI, type of hospital (academic or nonacademic), blood transfusion, pharyngocutaneous fistula formation, preoperative chemotherapy within 6 months before pharyngolaryngectomy, preoperative radiotherapy within 6 months before pharyngolaryngectomy, and tracheotomy. To investigate the multicollinearity between the independent variables, variance inflation factors were checked for each independent variable. A variance inflation factor >10 was considered to indicate multicollinearity.

All analyses were performed with the Statistical Package for Social Sciences version 20.0 (IBM SPSS, Armonk, NY). The p values < .05 were considered statistically significant.

RESULTS

We identified 549 patients with hypopharyngeal cancer who had undergone pharyngolaryngectomy during the study period. Table 1 shows relevant patient characteristics and the number of patients with each characteristic who developed pharyngocutaneous fistula. The mean age was 66.05 years (SD, 8.39 years) and most patients were men (86.7%). Overall, 156 patients (28.4%) did not have smoking habits. At the time of pharyngolaryngectomy, the disease of 295 patients (53.7%) was at stage IV. Only 23 patients had received both preoperative chemotherapy and radiotherapy. Fifty-eight patients (10.6%) had undergone tracheotomy before pharyngolaryngectomy.

Ten patients (1.8%) died during hospitalization: 2 of 33 patients (6.1%) with pharyngocutaneous fistula and 8 of 516 patients (1.6%) with nonpharyngocutaneous fistula died. According to Fisher's exact test, there was no significant difference in the incidence of hospital death

TABLE 1. Patient characteristics ($n = 549$) and pharyngocutaneous fistula formation.

Characteristics	No. of patients (%)	Pharyngocutaneous fistula, no. (%)
Age, y		
≤64	217 (39.5)	12 (5.5)
65–74	247 (45.0)	14 (5.7)
≥75	85 (15.5)	7 (8.2)
Sex, male (%)	476 (86.7)	31 (6.5)
BMI		
<18.5	124 (22.6)	8 (6.5)
18.5–22.9	216 (39.3)	10 (4.6)
23.0–24.9	53 (9.7)	3 (5.7)
≥25	38 (6.9)	3 (7.9)
Unknown	118 (21.5)	9 (7.6)
Smoking status		
Nonsmoker	156 (28.4)	8 (5.1)
Current or ex-smoker	250 (45.5)	17 (6.8)
Unknown	143 (26.0)	8 (5.6)
cT classification		
1	20 (3.6)	0
2	88 (16.0)	5 (5.7)
3	128 (23.3)	7 (5.5)
4	178 (32.4)	9 (5.1)
Unknown	135 (24.6)	12 (8.9)
cN classification		
0	146 (26.6)	9 (6.2)
1	49 (8.9)	1 (2.0)
2	220 (40.1)	11 (5.0)
3	2 (0.4)	0
Unknown	132 (24.0)	12 (9.1)
Cancer stage		
I	11 (2.0)	0
II	41 (7.5)	3 (7.3)
III	65 (11.8)	7 (10.8)
IVA	274 (49.9)	14 (5.1)
IVB	16 (2.9)	0
IVC	5 (0.9)	1 (20.0)
Unknown	137 (25.0)	11 (8.0)
Comorbidities		
CCI ≥3	378 (68.9)	19 (5.0)
Diabetes mellitus	150 (27.3)	9 (6.0)
Hepatic disorder	33 (6.0)	3 (9.1)
Renal failure	9 (1.6)	0
Hypertension	99 (18.0)	9 (9.1)
Cardiovascular disease	37 (6.7)	3 (8.1)
Cerebrovascular disease	15 (2.7)	1 (6.7)
Chronic obstructive lung disease	21 (3.8)	1 (4.8)
Anemia	23 (4.2)	1 (4.3)
Tracheotomy		
No	369 (67.2)	23 (6.2)
Before pharyngolaryngectomy	58 (10.6)	4 (6.9)
After pharyngolaryngectomy	122 (22.2)	6 (4.9)
Blood transfusion	249 (45.4)	12 (4.8)
Preoperative chemotherapy*	125 (22.7)	5 (4.0)
Preoperative radiotherapy*	32 (5.8)	6 (18.8)
Academic hospital	327 (59.6)	16 (4.9)

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index.
* Performed within the 6 months before pharyngolaryngectomy.

between patients with and without pharyngocutaneous fistula ($p = .117$). One patient, 82 years old, died of cardiopulmonary arrest on the first postoperative day; the remaining 9 patients all survived more than 30 days after pharyngolaryngectomy.

Pharyngocutaneous fistula formation occurred in 33 patients (6.0%), 19 (3.4%) of whom required surgical closure of their fistulas.

Table 2 shows the results of univariable logistic regression analysis of factors possibly affecting pharyngocutaneous fistula formation. Age ≥75 years and smoking habit (either current or former) seemed to be associated with pharyngocutaneous fistula formation. Compared with patients of low normal weight, both underweight and

TABLE 2. Univariable regression analysis of factors possibly affecting pharyngocutaneous fistula formation.

Variables	OR	95% CI	*p* value
Age, y			
≤64	Reference		.646
65–74	1.03	0.46–2.27	.949
≥75	1.53	0.58–4.04	.387
Sex, female	0.40	0.10–1.73	.222
BMI category			
<18.5	1.42	0.55–3.70	.472
18.5–22.9	Reference		.817
23.0–24.9	1.23	0.33–4.66	.754
>25	1.77	0.46–6.74	.405
Unknown	1.70	0.67–4.31	.263
Smoking status			
Nonsmoker	Reference		.766
Current or ex-smoker	1.35	0.57–3.21	.497
Unknown	1.10	0.40–3.00	.858
cT classification			
1, 2	Reference		.453
3	1.19	0.36–3.87	.770
4	1.10	0.36–3.36	.871
Unknown	2.01	0.69–5.89	.203
cN classification			
0	Reference		.291
1	0.32	0.04–2.57	.281
2, 3	0.79	0.32–1.97	.617
Unknown	1.52	0.62–3.74	.359
Cancer stage			
I, II	Reference		.712
III	1.05	0.22–4.91	.951
IV	0.86	0.24–3.07	.813
Unknown	1.39	0.37–5.18	.623
Comorbidities			
CCI ≥3 (vs CCI = 2)	0.59	0.29–1.21	.153
Diabetes mellitus	1.00	0.45–2.20	.995
Hepatic disorder	0.78	0.10–5.96	.807
Renal failure	0.00	0.00	.999
Hypertension	1.78	0.80–3.95	.159
Cardiovascular disease	1.27	0.29–5.60	.755
Cerebrovascular disease	1.12	0.14–8.79	.914
COPD	0.78	0.10–5.96	.807
Anemia	0.70	0.09–5.37	.733
Tracheotomy			
No	Reference		.832
Before pharyngolaryngectomy	1.11	0.37–3.35	.847
After pharyngolaryngectomy	0.78	0.31–1.96	.594
Blood transfusion	0.67	0.32–1.40	.287
Preoperative radiotherapy*	3.23	1.16–9.04	.025
Preoperative chemotherapy*	0.82	0.33–2.04	.669
Academic hospital	0.62	0.31–1.26	.184

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; CCI, Charlson Comorbidity Index; COPD, chronic obstructive lung disease.
* Performed within the 6 months before pharyngolaryngectomy.

TABLE 3. Logistic regression analysis of factors possibly affecting pharyngocutaneous fistula formation.

Variables	OR	95% CI	*p* value
Age, y			
≤64	Reference		
65–74	1.07	0.48–2.42	.867
≥75	1.54	0.58–4.12	.387
Sex, female	0.36	0.08–1.58	.176
Preoperative radiotherapy*	3.17	1.10–9.12	.033
CCI			
2	Reference		
≥3	0.57	0.27–1.18	.130
Academic hospital	0.73	0.35–1.44	.386

Abbreviations: OR, odds ratio; CI, confidence interval; CCI, Charlson Comorbidity Index.
* Performed within the 6 months before pharyngolaryngectomy.

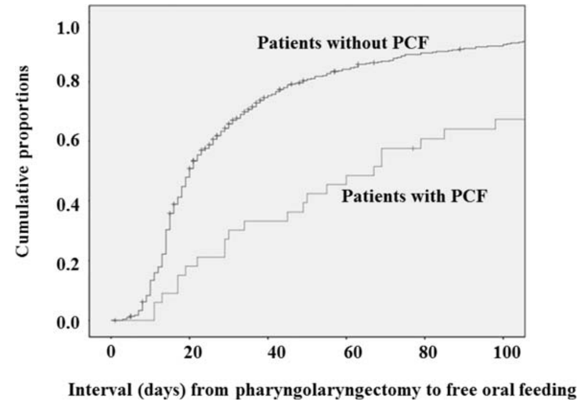

FIGURE 1. Interval to starting free oral feeding after pharyngolaryngectomy. PCF, pharyngocutaneous fistula.

overweight patients seemed to be associated with pharyngocutaneous fistula formation. Female sex, academic hospitals, and coexisting comorbidity on admission (CCI ≥3) seemed to be less likely to be associated with pharyngocutaneous fistula than male sex, nonacademic hospitals, and no comorbidity on admission, respectively. Tracheotomy on the day before pharyngolaryngectomy seemed to be associated with pharyngocutaneous fistula formation, but tracheotomy on the day after pharyngolaryngectomy was not. However, none of these associations was statistically significant.

Type of hospital, CCI, and preoperative radiotherapy had p values $< .2$ in the univariable analyses and were therefore further evaluated by multivariable logistic regression analysis.

Variance inflation factors for the independent variables assessed were all <2.0. Table 3 shows the results of multivariable logistic regression analysis. Patients who had received preoperative radiotherapy were 3 times more likely to have pharyngocutaneous fistula formation (odds ratio [OR] = 3.17; 95% confidence interval [CI] = 1.10–9.12; $p = .033$). No other factors were significantly associated with pharyngocutaneous fistula formation.

In all, 508 of 549 patients achieved free oral feeding during their hospitalization. Until the initiation of free oral feeding, nutritional support had been provided by enteral feeding through nasogastric tubes (430 patients), through gastric stomas (79 patients), and by parenteral nutrition (409 patients). These types of nutritional support were used in the following combinations: nasogastric tube only (131 patients); gastric stoma only (9 patients); parenteral nutrition only (79 patients); combination of nasogastric tube and parenteral nutrition (299 patients); and combination of gastric stoma and parenteral nutrition (31 patients).

The log-rank test showed a significant difference in the interval (days) from pharyngolaryngectomy to commencing free oral feeding between patients who did and did not develop pharyngocutaneous fistulas (median days, 67; 95% CI = 46–88 vs median days, 20; 95% CI = 18–22, respectively; $p < .001$; see Figure 1). According to the log-rank test, there were no significant associations between T, N, or overall cancer stage or the interval from pharyngolaryngectomy to commencement of free oral feeding. Overall cancer stage was selected as an independent variable for the subsequent Cox regression model.

Table 4 shows the results of Cox regression analysis of the interval (days) from pharyngolaryngectomy to initiating free oral feeding. Underweight, overweight/obese, CCI ≥3, and tracheotomy after pharyngolaryngectomy seemed to be associated with longer intervals to restarting

TABLE 4. Cox regression analysis of interval (days) from pharyngolaryngectomy to starting free oral feeding.

Variables	HR	95% CI	*p* value
Age, y			
≤64	Reference		
65–74	1.02	0.84–1.25	.824
≥75	1.10	0.84–1.44	.485
Sex, female	1.11	0.84–1.47	.460
BMI category			
<18.5	0.91	0.721.16	.448
18.5–22.9	Reference		
23.0–24.9	1.19	0.85–1.65	.316
>25	0.87	0.60–1.26	.471
Unknown	1.09	0.85–1.42	.494
Smoking status			
Nonsmoker	Reference		
Current or ex-smoker	1.01	0.80–1.28	.913
Unknown	1.13	0.88–1.45	.350
Cancer stage			
≤III	1.18	0.93–1.50	.179
Any IV	1.14	0.87–1.49	.359
CCI			
2	Reference		
≥3	0.82	0.67–1.00	.058
Blood transfusion	0.97	0.81–1.17	.746
Pharyngocutaneous fistula formation	0.40	0.27–0.58	< .001
Preoperative chemotherapy*	1.10	0.87–1.39	.416
Preoperative radiotherapy*	1.05	0.70–1.57	.815
Tracheotomy			
No	Reference		
Before pharyngolaryngectomy	0.99	0.80–1.23	.921
After pharyngolaryngectomy	0.87	0.64–1.18	.359
Academic hospital	1.02	0.85–1.23	.831

Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index; CCI, Charlson Comorbidity Index.
*Performed within the 6 months before pharyngolaryngectomy.

free oral feeding; however, these apparent differences were not significant. Starting free oral feeding was significantly delayed in patients with pharyngocutaneous fistula (hazard ratio [HR] = 0.26; 95% CI = 0.15–0.44; $p < .001$). No other factors were significantly associated with this interval.

DISCUSSION

Our study included 549 patients who had undergone pharyngolaryngectomy from 2007 to 2013. To our knowledge, this is the largest study that has focused on patients who underwent pharyngolaryngectomy in a nationwide clinical setting. This retrospective cohort study revealed that preoperative radiotherapy tripled the probability of developing pharyngocutaneous fistula and was the only significant risk factor for pharyngocutaneous fistula formation. The presence of pharyngocutaneous fistula tripled the interval from pharyngolaryngectomy to free oral feeding. No other factors were significantly associated with this interval.

The reported proportions of pharyngocutaneous fistula after total laryngectomy vary widely from 2.6% to 21.6%,[6,7,16,17] these variations being attributable to differences in sample sizes, study periods, and treatment strategies. Additional resection of pharyngeal mucosa significantly increases the incidence of pharyngocutaneous fistula formation after total laryngectomy.[17,18] However, relatively few studies have reported the incidence of postoperative pharyngocutaneous fistula after pharyngolaryngectomy: 5.0% (6 of 119),[19] 22% (12 of 55),[11] 30.6% (15 of 49),[20] and 52.5% (52 of 160).[4] In our study, we found a relatively low proportion (6%) of fistulas after pharyngolaryngectomy, surgical closure of pharyngocutaneous fistulas having been performed in 3.4% of the patients.

According to a published meta-analysis of 26 laryngectomy studies (excluding cases with flap reconstruction),[6] prior tracheotomy and postoperative hemoglobin concentration <12.5 g/dL were risk factors for pharyngocutaneous fistula formation. A recent analysis of 218 consecutive patients who underwent total laryngectomies found that preoperative hypoalbuminemia, diabetes mellitus, chronic pulmonary diseases, and hepatic disorder were independent predictors of pharyngocutaneous fistula.[7] Another retrospective analysis of 217 patients who underwent total laryngectomies found that previous chemoradiotherapy, malignancy of hypopharyngeal origin, preoperative hypoalbuminemia, more extensive pharyngeal resection, and flap reconstruction were predictors of pharyngocutaneous fistula.[2] However, we found no association between pharyngocutaneous fistula and prior tracheotomy, diabetes mellitus, chronic obstructive pulmonary diseases, or hepatic disorder. A negative impact of preoperative radiotherapy on pharyngocutaneous fistula formation is biologically plausible because of the associated delay in wound healing, which is believed to be caused by impaired fibroblast function, increased fibrosis, and poorer blood supply to the irradiated area.[21,22] Further, preoperative radiation within a few months before surgery reportedly causes more difficulties with wound healing than when administered more than 6 months before surgery.[23]

The impact of smoking and smoking cessation on wound healing after surgery for head and neck cancer remains controversial. A recent systematic review of various types of surgery found that postoperative wound healing and infection occurred at significantly higher rates in current smokers than in nonsmokers, and in ex-smokers than in never smokers.[24] However, there has been a lack of data on the association between smoking and pharyngocutaneous fistula after pharyngolaryngectomy. We found a relatively high proportion of pharyngocutaneous fistula in smokers; however, this was not statistically significant. This lack of statistical significance may be attributable to low statistical power because of the small number of pharyngocutaneous fistula events and the relatively high number of patients with missing data.

The effect of BMI on wound healing is still a matter of debate. A previous study of gastrointestinal cancer surgery in Japan reported an association between higher BMI and higher proportion of wound infection.[25] However, higher BMI is reportedly associated with a lower proportion of overall postoperative complications in free flap reconstruction of head and neck cancer surgery.[26] To our knowledge, no studies on the association between BMI and pharyngocutaneous fistula after pharyngolaryngectomy have been published. In the present study, underweight and overweight patients had relatively high proportions of pharyngocutaneous fistula; however, these differences were not significant.

A noteworthy fact was that, unlike in previous studies,[2,6] in our study, neither diabetes mellitus nor prior tracheotomy was associated with increased incidence of pharyngocutaneous fistula formation. Although the reason for this discrepancy is unclear, we speculate that differences between study groups in clinical settings, including surgical procedure and strictness of preoperative glycemic control, may have been contributory factors.

Whether preoperative adjuvant radiotherapy improves the oncologic prognosis for patients with hypopharyngeal cancer remains controversial.[27] A few randomized controlled studies in the 1970s and 1980s demonstrated that preoperative radiotherapy was inferior to postoperative radiotherapy in terms of survival rate and postoperative complications. Compared to adding chemotherapy to locoregional treatment, preoperative radiation therapy alone has been shown to have an unfavorable effect on overall survival.[28] In the present study, preoperative radiation therapy was the only factor significantly associated with occurrence of pharyngocutaneous fistula. Thus, it is difficult to justify routine administration of preoperative radiation therapy.

As for the association between pharyngocutaneous fistula and oral feeding, a recent study of 191 patients with head and neck cancer who had undergone microvascular reconstruction showed that defects of the hypopharynx and radiotherapy before surgery strongly predicted postoperative difficulty in swallowing, as assessed by whether patients were eventually able to take food orally or remained dependent on nasogastric tubes.[18] In addition, merely the presence of a pharyngocutaneous fistula is known to independently impair swallowing outcome.[11] We found that in patients who undergo a pharyngolaryngectomy, pharyngocutaneous fistulas resulted in delayed starting of postoperative oral feeding: these patients took more than 3-fold longer than patients without pharyngocutaneous fistulas to initiate free oral feeding. Thus, identifying high-risk patients would allow head and neck surgeons to consider further approaches to minimizing the potential for pharyngocutaneous fistula, such as transferring vascularized tissue to the area as a free or pedicled flap.

This study should be interpreted in the context of some limitations that were inherent to its design. First, it was a retrospective observational study and treatment (radiotherapy/chemotherapy/pharyngolaryngectomy) assignment was not random. Second, the database did not contain information on laboratory data, pathological findings, concurrent neck dissection, whether flap reconstruction was performed, or extent of resection (ie, partial or total pharyngolaryngectomy). Third, the recorded comorbidities are generally less accurate in administrative claims databases than in planned prospective studies.

In conclusion, in our study, radiotherapy within the 6 months before pharyngolaryngectomy was significantly associated with a higher proportion of pharyngocutaneous fistula occurrence, regardless of other patient characteristics. The presence of pharyngocutaneous fistula significantly delayed initiation of free oral feeding.

REFERENCES

1. Japan Society for Head and Neck Cancer, Cancer Registry Committee. Report of Head and Neck Cancer Registry of Japan. Clinical statistics of registered patients, 2011. *Japan J Head Neck Cancer* 2013;39(Suppl):52–73.
2. Timmermans AJ, Lansaat L, Theunissen EA, Hamming–Vrieze O, Hilgers FJ, van den Brekel MW. Predictive factors for pharyngocutaneous fistulization after total laryngectomy. *Ann Otol Rhinol Laryngol* 2014;123:153–161.
3. Soylu L, Kiroglu M, Aydogan B, et al. Pharyngocutaneous fistula following laryngectomy. *Head Neck* 1998;20:22–25.
4. Tsou YA, Hua CH, Lin MH, Tseng HC, Tsai MH, Shaha A. Comparison of pharyngocutaneous fistula between patients followed by primary laryngopharyngectomy and salvage laryngopharyngectomy for advanced hypopharyngeal cancer. *Head Neck* 2010;32:1494–1500.
5. Medina JE, Khafif A. Early oral feeding following total laryngectomy. *Laryngoscope* 2001;111:368–372.
6. Paydarfar JA, Birkmeyer NJ. Complications in head and neck surgery: a meta-analysis of postlaryngectomy pharyngocutaneous fistula. *Arch Otolaryngol Head Neck Surg* 2006;132:67–72.
7. Boscolo–Rizzo P, De Cillis G, Marchiori C, Carpenè S, Da Mosto MC. Multivariate analysis of risk factors for pharyngocutaneous fistula after total laryngectomy. *Eur Arch Otorhinolaryngol* 2008;265:929–936.
8. Aires FT, Dedivitis RA, Petrarolha SM, Bernardo WM, Cernea CR, Brandão LG. Early oral feeding following total laryngectomy: a systematic review. *Head Neck* 2014. [Epub ahead of print].
9. Chang DW, Hussussian C, Lewin JS, Youssef AA, Robb GL, Reece GP. Analysis of pharyngocutaneous fistula following free jejunal transfer for total laryngopharyngectomy. *Plast Reconstr Surg* 2002;109:1522–1527.
10. Yu P, Hanasono MM, Skoracki RJ, et al. Pharyngoesophageal reconstruction with the anterolateral thigh flap after total laryngopharyngectomy. *Cancer* 2010;116:1718–1724.
11. Gadepalli C, de Casso C, Silva S, Loughran S, Homer JJ. Functional results of pharyngo-laryngectomy and total laryngectomy: a comparison. *J Laryngol Otol* 2012;126:52–57.
12. Iwagami M, Yasunaga H, Doi K, et al. Postoperative polymyxin B hemoperfusion and mortality in patients with abdominal septic shock: a propensity-matched analysis. *Crit Care Med* 2014;42:1187–1193.
13. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;43:1130–1139.
14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–383.
15. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004;363:157–163.
16. Akyol MU, Ozdem C, Celikkanat S. Early oral feeding after total laryngectomy. *Ear Nose Throat J* 1995;74:28–30.
17. Saydam L, Kalcioglu T, Kizilay A. Early oral feeding following total laryngectomy. *Am J Otolaryngol* 2002;23:277–281.
18. Khariwala SS, Vivek PP, Lorenz RR, et al. Swallowing outcomes after microvascular head and neck reconstruction: a prospective review of 191 cases. *Laryngoscope* 2007;117:1359–1363.
19. Omura G, Ando M, Saito Y, Kobayashi K, Yamasoba T, Asakage T. Disease control and clinicopathological prognostic factors of total pharyngolaryngectomy for hypopharyngeal cancer: a single-center study. *Int J Clin Oncol* 2014. [Epub ahead of print].
20. Vandenbrouck C, Sancho H, Le Fur R, Richard JM, Cachin Y. Results of a randomized clinical trial of preoperative irradiation versus postoperative in treatment of tumors of the hypopharynx. *Cancer* 1977;39:1445–1449.
21. Ganly I, Patel S, Matsuo J, et al. Postoperative complications of salvage total laryngectomy. *Cancer* 2005;103:2073–2081.
22. Eustaquio M, Medina JE, Krempl GA, Hales N. Early oral feeding after salvage laryngectomy. *Head Neck* 2009;31:1341–1345.
23. Tibbs MK. Wound healing following radiation therapy: a review. *Radiother Oncol* 1997;42:99–106.
24. Sørensen LT. Wound healing and infection in surgery. The clinical impact of smoking and smoking cessation: a systematic review and meta-analysis. *Arch Surg* 2012;147:373–383.
25. Yasunaga H, Horiguchi H, Matsuda S, Fushimi K, Hashimoto H, Ayanian JZ. Body mass index and outcomes following gastrointestinal cancer surgery in Japan. *Br J Surg* 2013;100:1335–1343.
26. Patel RS, McCluskey SA, Goldstein DP, et al. Clinicopathologic and therapeutic risk factors for perioperative complications and prolonged hospital stay in free flap reconstruction of the head and neck. *Head Neck* 2010;32:1345–1353.
27. Strong MS, Vaughan CW, Kayne HL, et al. A randomized trial of preoperative radiotherapy in cancer of the oropharynx and hypopharynx. *Am J Surg* 1978;136:494–500.
28. Pignon JP, Bourhis J, Domenge C, Designé L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. *Lancet* 2000;355:949–955.