ORIGINAL ARTICLE

COMPARISON OF PHARYNGOCUTANEOUS FISTULA BETWEEN PATIENTS FOLLOWED BY PRIMARY LARYNGOPHARYNGECTOMY AND SALVAGE LARYNGOPHARYNGECTOMY FOR ADVANCED HYPOPHARYNGEAL CANCER

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Abstract: *Background.* We analyzed the incidence rate, possible etiology, and management of pharyngocutaneous fistula after laryngopharyngectomy between hypopharyngeal cancer patients who received surgery first and subsequently concurrent chemoradiation therapy (CCRT) and those who received CCRT first followed by surgical salvage.

Methods. This is a case cohort, retrospective study collected in a tertiary medical center from January 1996 to July 2007.

Results. From the total of 160 patients, 52 patients (32.5%) developed pharyngocutaneous fistula. There is a significant difference between the pharyngocutaneous fistula rate of those with initial CCRT and the initial surgery groups. By univariate analysis and multiple logistic regression, tests revealed that preoperative radiation and hypo-albuminemia are risk factors for pharyngocutaneous fistula. A prolonged hospital course was noted among patients in the fistula group, especially when they received surgical repair, had hypo-albuminemia (albumin, <2.5 g/dL), or received preoperative radiation therapy (pre-OPRT).

Conclusions. Preoperative radiation therapy and hypo-albuminemia increase the fistula rate significantly. A prolonged hospital course was noted among all fistula patients. © 2010 Wiley Periodicals, Inc. *Head Neck* **32:** 1494–1500, 2010

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Pharyngocutaneous fistula following pharyngolaryngectomy is a serious and intractable complication. This study is focused on pharyngocutaneous fistula after surgery between patients with preoperative radiation and nonradiated hypopharyngeal cancer.

The development of pharyngocutaneous fistula is the most common and troublesome complication in the early postoperative period following surgery. Pharyngocutaneous fistula is a major cause of morbidity and prolonged hospital stay.[1] If left untreated, it can lead to fatal

complications such as carotid artery rupture and sepsis.[2]

Factors implicated in fistula formation include preoperative radiotherapy, concurrent neck dissection, tumor stage, and type of closure of pharynx (primary or flap reconstruction).[3] This study was designed to evaluate the risk factors of pharyngocutaneous fistula after pharyngolaryngectomy, and to survey the differences between the hypopharyngeal cancer patients who received concurrent chemoradiation therapy (CCRT) as initial treatment versus surgery as initial treatment.

PATIENTS AND METHODS

This is a case cohort, retrospective study collected in a tertiary medical center from January 1996 to July 2007. A retrospective study was performed in 362 advanced hypopharyngeal cancer patients, from January 1997 to July 2006. There were 250 patients with hypopharyngeal cancer who initially received CCRT as organ preservation therapy with curative intent, but 48 patients had treatment failure after CCRT and finally received salvage surgery. The other 112 patients received the operation as initial treatment and 83% of them received adjuvant CCRT for the concern for high risk of recurrence ascribed to pathologic predictors, including perineural invasion, extracapsular spread, and close resection margins (within 5 mm). There were a total of 160 patients who received laryngopharyngectomy and were included in our study. Among 250 patients who received CCRT as initial treatment, 48 patients received salvage laryngopharyngectomy because of CCRT failure and were categorized as the CCRT initial group. The other 112 patients who received the operation as initial treatment and adjuvant CCRT were categorized as the operation initial group. Their ages ranged from 37 to 91 years (median, 57 years). In all, 112 patients had T3 lesions (70%), and 48 (30%) had T4 lesions.

In the CCRT initial group, 7 of the 48 patients underwent unilateral neck dissection, 4 patients underwent bilateral neck dissection, and 37 patients did not undergo neck dissection. In the operation initial group, 50 patients underwent unilateral neck dissection, 32 patients underwent bilateral neck dissection, and 30 patients did not undergo neck dissection. Reconstruction of the postlaryngopharyngec-

tomy defect was performed in accord with the treatment decisions of the surgeons, including primary closure and nonprimary closure (such as pectoralis major myocutaneous flap, anterior lateral thigh flap [ALT], gastric pull-up, free jejunal flap, deltopectoral flap). After the surgery, Zantac (H2 blocker) and routine antibiotics with cefazolin (1 g), administered intravenously every 8 hours, were given for at least 5 days. Esophagogram was performed 14 days after surgery. If there was no fistula seen on the esophagogram, oral feeding was permitted. In the CCRT initial group, the average total dosage of RT was 6480 cGy, and was followed by cisplatin-based chemotherapy. In the operation initial group, the average salvage radiation therapy was 5840 cGy and was followed by cisplatin-based chemotherapy. We surveyed the incidence of fistula rate, time of onset, and risk factors that might cause pharyngocutaneous fistula. The chi-square test and logistic regression were used to evaluate the correlation of factors that may cause a pharyngocutaneous fistula.

In patients who received primary closure for the surgical defect, a running Connell-type suture was used in a single vertical line to close the pharynx. A second layer of horizontal interrupted sutures approximate the 2 inferior constrictor muscles and their upper edge to the base of the tongue. Skin was closed with 2 layers involving the insertion of suction drains.

The other patients underwent nonprimary suture reconstruction surgery by pectoralis major myocutaneous flap performed by us, gastric pull-up by chest surgeons, and free jejunal flap and free ALT flap reconstruction by plastic surgeons.

In managing the fistula, we offered 2 treatment strategies. The first was conservative treatment, which gave fistula patients intensive wound dressing and debridement at bedside with no surgical rescue. The second was the surgical repair group that closed the fistula in the operating room under general anesthesia with primary closure or flap reconstruction.

We defined the patients with anemic condition by postoperative hemoglobin data under 10 mg/dL, and hypo-albuminemic condition under 2.5 mg/dL.

The medical conditions of all patients were recorded in accord with medical charts and were categorized, including ischemic heart disease with heart echo revealing at least 2-vessel coronary artery disease over 50% stenosis and under

Table 1. Demographic of patients with operated hypopharyngeal cancer by fistula.

Variable	No. (%) Fistula ($n = 52$)	No. (%) No fistula ($n = 108$)	p value
Age	57.0 ± 11.4	53.4 ± 10.8	<.0001
Sex (male/female)	45/7 (86.5/13.5)	97/11 (89.8/10.2)	.596
Alcohol (Yes)	21 (40.4)	51 (47.2)	.498
Betel nut (Yes)	41 (78.8)	66 (61.1)	.031
Smoking (Yes)	41 (78.8)	73 (67.6)	.191
Diabetes mellitus (Yes)	11 (21.2)	11 (10.2)	.085
Hypo-albumin (Yes)	26 (50.0)	7 (6.5)	<.0001
Ischemic heart disease (Yes)	13 (25.0)	11 (10.2)	.018
Liver cirrhosis (Yes)	11 (21.2)	10 (9.3)	.047
Anemia (Yes)	19 (36.5)	31 (28.7)	.364
Tumor volume (cc)	21.8 ± 8.3	21.6 ± 6.5	.927
T4 classification (Yes)	38 (73.1)	74 (68.5)	.586
Neck dissection (Yes)	30 (57.7)	63 (58.3)	1.000
Pre-OPRT (Yes)	28 (58.3)	20 (41.7)	<.0001
Primary closure (Yes)	34 (65.4)	70 (64.8)	1.000
Supraglottic involvement (Yes)	17 (32.7)	18 (16.7)	.026

Abbreviation: pre-OPRT, preoperative radiation therapy.

regular medical control, diabetes mellitus treated by insulin or oral hypoglycemic agents for >2 years, and liver cirrhosis noted with at least Grade A Child–Pugh Classification from medical records. A personal history including smoking, alcohol drinking, and betel quid chewing was recorded retrospectively in accord with the medical charts; the missing data were all supplied from phone interviews or personal interviews during regular follow-up of the patients. All the TNM staging was registered in accord with the American Joint Committee on Cancer (AJCC, 5th edition), and the patients were all regularly followed in accord with the head and neck treatment guidelines.

RESULTS

Pharyngocutaneous fistula was observed in 28 of the 48 patients (58.3%) in the CCRT initial group, and 24 of the 112 patients (21.4%) in the operation initial group.

Time Interval Radiation Therapy and Surgery. The timing of an operation after irradiation had influential effects on the occurrence of a fistula. Among the 48 CCRT initiated treated patients, there was a higher pharyngocutaneous fistula rate in patients who received salvage operation within 3 months after radiation therapy (26/35, 74.3%) compared with salvage operation done after finishing CCRT for 3 months (2/13, 15.4%;

$p = .009$). Patients had a lower rate of fistula formation if they received a salvage operation after finishing radiation 3 months.

Possible Risk Factors for Developing Pharyngocutaneous Fistula. There are many possible risk factors thought to exist for developing pharyngocutaneous fistula in surgical patients with hypopharyngeal cancer. Most of them are still controversial despite the many studies performed. In our studies, age, sex, T classification, tumor volume, postoperative anemic condition, reconstruction method, diabetes mellitus, neck dissection, smoking, drinking, and betel quid chewing were not significant factors for pharyngocutaneous fistula, but preoperative radiation and hypo-albuminemia, ischemic heart disease, liver cirrhosis, and tumor with supraglottic involvement were significant factors, as shown in Table 1.

Multivariate Analysis of Pharyngocutaneous Fistula. In the multivariate analysis of possible risk factors that contribute to the pharyngocutaneous fistula, we found hypo-albuminemia, anemia, neck dissection, and preoperative radiation therapy (pre-OPRT) were the risk factors of pharyngocutaneous fistula formation (see Table 2).

Stratified Analysis in the CCRT Initial Group. The relationship between pharyngocutaneous fistula formation and the investigated parameters in

Table 2. Estimation of fistula risk by multivariate analysis.

Variable	Coefficient, *r*	Standard error	Odds ratio	*p* value
Age >65 y	−.643	0.572	0.526	.262
Male sex	−.326	0.713	0.722	.647
Alcohol (Yes)	−.585	0.498	0.557	.240
Betel nut (Yes)	−.037	0.541	0.964	.945
Smoking (Yes)	.026	0.578	1.026	.964
Diabetes mellitus (Yes)	−.251	0.846	0.778	.767
Hypo-albumin (Yes)	2.762	0.595	15.836	<.0001
Ischemic heart disease (Yes)	.544	0.905	1.723	.548
Liver cirrhosis (Yes)	.028	0.704	1.029	.968
Anemia (Yes)	1.018	0.521	2.768	.051
Tumor volume ≥25 cc	.674	0.586	1.963	.250
T4 classification (Yes)	−.664	0.598	0.515	.267
Neck dissection (Yes)	1.435	0.679	4.198	.035
Pre-OPRT (Yes)	2.867	0.764	17.588	<.0001
Primary closure (Yes)	−.469	0.476	0.625	.324
Supraglottic involvement (Yes)	.851	0.610	2.341	.163

Abbreviation: pre-OPRT, preoperative radiation therapy.

the CCRT initial group are summarized in Table 3. With hypo-albuminemia, post-CCRT salvage neck dissection, comorbidities with diabetes mellitus or ischemic heart disease, or reconstruction of the pharynx with primary closure were found to have a statistically significant increased rate of pharyngocutaneous fistula formation.

Stratified Analysis in the Operation Initial Group. Hypo-albuminemia and anemia were the only risk factors that caused pharyngocutaneous fistula in the operation initial group in our survey, as shown in Table 4.

Repair Method for Pharyngocutaneous Fistula. In managing pharyngocutaneous fistulae in all 52 fistula patients, there were 24 patients (46.2%) who received conservative treatment and 28 patients (53.8%) who received surgical repair (16 received flap reconstruction, 12 received primary closures). Initial CCRT fistula patients did have a higher surgical repair rate (67.8% vs 32.2%; *p* = .029) compared with that of the initial surgery fistula patient group.

Prolonged Hospital Course. A longer hospital course was noted for the patients with fistula. The average stay in the hospital for patients without pharyngocutaneous fistula was 20.7 days, whereas the length of hospitalization for patients with a fistula was 37.6 days (*p* < .001).

There was also a longer hospital course for patients with pharyngocutaneous fistulas initially treated by CCRT (34.7 vs 23.3; *p* = .03)

and for those who underwent surgical rescue for their fistulae (46.8 vs 32.4; *p* < .001). Poor nutrient conditions in patients with pharyngocutaneous fistulas such as hypo-albuminemia also led to a longer hospital course in our survey (38.9 vs 24.6; *p* < .001).

DISCUSSION

The early signs of fistula include tender and erythematous neck, fever, and increased turbid discharge from drainage tubes. Keeping alert for these early signs could help us recognize the possible fistula as early as possible, and this will prevent patients from suffering from major infection and sepsis.[4]

The wide variability in the rate of fistulization was explained by variation in patient selection and surgical technique.[5] However, there were few studies discussing the hypopharyngeal patient comorbidities with diabetes mellitus, ischemic heart disease, and liver cirrhosis and the method of reconstruction of the pharyngeal defect. Therefore, we analyzed the patients with operated advanced hypopharyngeal cancer that had been treated initially with CCRT or surgery to find the possible risks that contribute to fistula formation as shown in Table 1. We found the hypo-albuminemia, anemia, neck dissection (or not), and preoperative radiation therapy were the significant factors in our multivariate analysis as shown in Table 2; hypo-albuminemia and preoperative radiation therapy were both highly significant in univariate and multivariate analysis in our study.

Table 3. Stratified analysis of risk factors that cause pharyngocutaneous fistula in CCRT initiated group.

Variable	No. (%)		
	Fistula (n = 28)	No fistula (n = 20)	p value
Sex			.385
Male	24 (55.8)	19 (44.2)	
Female	4 (80.0)	1 (20.0)	
Alcohol			.381
Yes	11 (50.0)	11 (50.0)	
No	17 (65.4)	9 (34.6)	
Betel nut			.683
Yes	23 (56.1)	18 (43.9)	
No	5 (71.4)	2 (28.6)	
Smoking			1.000
Yes	24 (58.5)	17 (41.5)	
No	4 (57.1)	3 (42.9)	
Diabetes mellitus			.032
Yes	7 (100.0)	0 (0.0)	
No	21 (51.2)	20 (48.8)	
Hypo-albumin			<.0001
Yes	15 (93.8)	1 (6.3)	
No	13 (40.6)	19 (59.4)	
Ischemic heart disease			.006
Yes	9 (100.0)	0 (0.0)	
No	19 (48.7)	20 (51.3)	
Liver cirrhosis			.716
Yes	6 (66.7)	3 (33.3)	
No	22 (56.4)	17 (43.6)	
Anemia			.528
Yes	7 (50.0)	7 (50.0)	
No	21 (61.8)	13 (38.2)	
Neck dissection			.001
Yes	11 (100.0)	0 (0.0)	
No	17 (45.9)	20 (54.1)	
T classification			.488
3	7 (70.0)	3 (30.0)	
4	21 (55.3)	17 (44.7)	
Primary closure			.017
Yes	22 (71.0)	9 (29.0)	
No	6 (35.3)	11 (64.7)	
Supraglottic involvement			.763
Yes	10 (62.5)	6 (37.5)	
No	18 (56.3)	14 (43.7)	

Abbreviation: CCRT, concurrent chemoradiation therapy.

In many other reports, patients at a more advanced stage had higher fistula rates,[6] but these findings do not fully match out results. Our study confirms that fistulae are more likely in patients who received chemoradiotherapy before surgery, and this appears to be a consensus in the literature.[6] When we stratified patients into operation initial and CCRT initial groups, we found a trend of higher pharyngocutaneous fistula formation in the CCRT initial group that received post-CCRT neck dissection, comorbidities with diabetes mellitus or ischemic

heart disease, or reconstruction of the pharynx with primary closure. In the operation initial group, the patients with hypo-albuminemia or anemia tended to develop pharyngocutaneous fistula. However, we found only hypo-albuminemia as the significant factor in both operative initial and CCRT initial group by multivariable analysis, as seen in Tables 3 and 4 ($p < .0001$, $p < .0001$). There were studies revealing the effect of preoperative irradiation in patients with head and neck cancers that show a 53.8% pharyngocutaneous fistula rate in patients treated with salvage surgery after a failed CCRT treatment.[7]

Table 4. Stratified analysis of risk factors that cause pharyngocutaneous fistula in operation initiated group.

Variable	No. (%)		
	Fistula (n = 24)	No fistula (n = 88)	p value
Sex			1.000
Male	21 (21.2)	78 (78.8)	
Female	3 (23.1)	10 (76.9)	
Alcohol			.819
Yes	10 (20.0)	40 (80.0)	
No	14 (22.6)	48 (77.4)	
Betel nut			.101
Yes	18 (27.3)	48 (72.7)	
No	6 (13.0)	40 (87.0)	
Smoking			.631
Yes	17 (23.3)	56 (76.7)	
No	7 (17.9)	32 (82.1)	
Diabetes mellitus			.735
Yes	4 (26.7)	11 (73.3)	
No	20 (20.6)	77 (79.4)	
Hypo-albumin			<.0001
Yes	11 (64.7)	6 (35.3)	
No	13 (13.7)	82 (86.3)	
Ischemic heart disease			.735
Yes	4 (26.7)	11 (73.3)	
No	20 (20.6)	77 (79.4)	
Liver cirrhosis			.128
Yes	5 (41.7)	7 (58.3)	
No	19 (19.0)	81 (81.0)	
Anemia			.048
Yes	12 (33.3)	24 (66.7)	
No	12 (15.8)	64 (84.2)	
Neck dissection			.605
Yes	19 (23.2)	63 (76.8)	
No	5 (16.7)	25 (83.3)	
T classification			.635
3	7 (18.4)	31 (81.6)	
4	17 (23.0)	57 (77.0)	
Primary closure			.224
Yes	13 (17.6)	61 (82.4)	
No	11 (28.9)	27 (71.1)	
Supraglottic involvement			.120
Yes	7 (36.8)	12 (63.2)	
No	17 (18.3)	76 (81.7)	

In our study, the CCRT initial patients showed higher fistula rates (58.3%) than those of the operation initial patients (21.4%; $p < .0001$), and preoperative RT clearly is a risk factor for pharyngocutaneous fistula formation in our findings. In addition, the hypo-albuminemia is also a significant risk in both CCRT initiated and operation initiated patients in our study.

It is well known that the principle of conservative treatment is proper salivary diversion, complete debridement, nutritional support, proper antibiotic use in accord with culture reports, and early drainage of fluid with debriding of necrotic tissue.[8] Surgical repair should be considered only after conservative treatment failure.[9] The methods of surgical repair include primary closures after fistulae debridement, pectoralis major myocutaneous flap reconstruction, local muscle flap reconstruction, gastric pull-up, free jejunal flap, and free-flap reconstruction.[10,11] In our survey, there were higher mortality rates in patients receiving surgical repair methods because of intractable fistula after surgical rescue. This was especially true in the radiated fistula group, in which there were 2 patients with radiated fistula who expired after surgical repair: 1 by gastric pull-up and the other by ALT reconstruction.

In our stratified study, the addition of neck dissection to total laryngectomy is also another contributing factor for fistula development in preoperative radiated patients. However, the neck dissection was not the risk factor in the operation initiated group. Pinar et al[12] reported a significantly higher incidence of pharyngocutaneous fistula when neck dissection was combined with total laryngectomy. Our results, however, revealed a higher rate of pharyngocutaneous fistula only for the CCRT initiated group of patients who had an accompanying neck dissection. In the literature, primary closure instead of nonprimary closure is reported as another risk factor for pharyngocutaneous fistula formation.[13] However, we found this trend only among the CCRT initiated patients. In the operation initiated patients, no different fistula rate was found by primary closure and nonprimary closure methods. The observed pharyngocutaneous fistula in 71% of patients with primary closure of the pharynx is compared with 29% in nonprimary closure in the CCRT initiated group, as shown in Table 3.

To our knowledge, the role of ALT flap in fistula formation in patients with advanced hypo-pharyngeal cancers has not been studied; this is the first time survey of the pharyngocutaneous fistula formation and ALT flap reconstruction in the CCRT initiated failure in patients with advanced hypopharyngeal cancer. We found that the incidence of pharyngocutaneous fistula formation in the CCRT initiated group by ALT reconstruction for pharyngeal reconstruction was low in our study. Fourteen ALT free-flap reconstructions were performed in the CCRT initiated failure patients; there were only 2 patients who developed a fistula and who were cured by conservative management. Therefore, ALT reconstruction for a laryngopharyngeal defect still might be recommended for patients with poor response after organ preservation therapy. Withrow et al[13] also gave a similar report, suggesting free flap as a sound reconstruction method. They used 16 radial forearm flaps and 1 rectus flap as planned reconstruction for salvage laryngectomy defects, compared with a primary closure method. Their conclusion also suggested vascularized tissue as a free flap is associated with a lower fistula rate and may improve outcomes.[13]

In our opinion, it is mandatory to treat advanced hypopharyngeal cancer with ALT free-flap reconstruction to minimize the pharyngocutaneous fistula rate and to achieve a wider margin for better disease control. However, concerning repair of the fistula, the free flap is not recommended for radiated fistula patients. This is because it is difficult to harvest feeding vessels in the infected, radiated, fistulated necrotic tissues instead of using the pectoralis major myocutaneous flap reconstruction method for fistula repair.[14] The hospital stay also increased among all patients with fistulae, especially in fistulated patients with hypo-albuminemia, in previously radiated patients, or in those who returned to surgery for repair of a persistent fistula. A prolonged hospital course was also related to return to the operating room within 30 days of the index operation and the occurrence of 2 or more operative complications.[15]

CONCLUSIONS

Although there are controversies over risk factors for fistula formation, we confirmed that preoperative CCRT and postoperative hypo-albuminemia are indeed risk factors for fistula formation in patients treated for advanced

hypopharyngeal cancer. In the CCRT initial group, neck dissection, diabetes mellitus, ischemic heart disease, and the primary closure method were shown to be additional risks for developing a pharyngocutaneous fistula. ALT free flap is still mandatory for reconstruction of the defect after laryngopharyngectomy in CCRT initial patients. Most fistulae could be treated conservatively in the operation initial group, but surgical repair is being considered more often for preoperative radiated fistula patients. Pectoralis major myocutaneous flap is the first priority to be considered to repair the radiated fistula compared with other free flaps. A longer hospital course was noted in patients with fistula formation after surgery, especially when they were radiated before surgery, involving a poor nutritional condition or returning for surgery to repair a persistent fistula.

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