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ORIGINAL RESEARCH–HEAD AND NECK SURGERY

Comparison of pharyngeal stenosis between hypopharyngeal patients undergoing primary versus salvage laryngopharyngectomy

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ABSTRACT

OBJECTIVE: To survey the risk factors of pharyngeal stenosis after laryngopharyngectomy in patients with advanced hypopharyngeal cancers.
STUDY DESIGN: Case series with chart review.
SETTING: Tertiary medical center.
SUBJECTS AND METHODS: Pharyngeal stenosis rates and risk factors were compared between two groups of laryngopharyngectomy patients: a group that underwent concurrent chemoradiation therapy followed by surgical salvage, and a surgery initiated group with adjuvant chemoradiation.
RESULTS: Of 160 patients, 25 developed pharyngeal stenosis, which was diagnosed by barium esophagography with a pooling of barium contrast above the neopharyngeal inlet. These patients required nasogastric tube feeding or gastrostomy feeding because an oral liquid diet could not meet their nutritional needs. Primary closure and old age were risk factors for pharyngeal stenosis. Pharyngeal stenosis did not affect survival in patients with advanced hypopharyngeal cancer who underwent laryngopharyngectomy.
CONCLUSION: Primary closure reconstruction is discouraged in patients over the age of 65 years.

Pharyngeal stenosis after pharyngolaryngectomy is difficult to treat, and the diagnosis of pharyngeal stenosis is not always evaluated in an objective manner.[1-4] In addition, pharyngolaryngeal reconstruction has several options available for the patients, and there is no uniform agreement among surgeons as to which of the most frequently used techniques offers the best results. In the present study, we focused on pharyngeal stenosis after laryngopharyngectomy in patients with advanced hypopharyngeal cancer. The development of pharyngeal stenosis is a troublesome complication in the late postoperative period after surgery[3] because the patients frequently have to suffer from malnutrition, dysphagia, long-term nasogastric tube (NGT) insertion, gastrostomy, and loss of quality of life. Until now, few studies have reported any risk factors or comparisons among the reconstruction methods. Also, the diagnosis of pharyngeal stenosis is not objective and there is no evaluation standard, leading to over- or underestimation. This is the first study of postoperative pharyngeal stenosis diagnosed by barium esophagography in advanced hypopharyngeal cancer patients who underwent primary or salvage laryngopharyngectomy.

Factors associated with the development of pharyngeal stenosis include concurrent chemoradiation therapy (CCRT), tumor stage, and the type of closure of the pharynx (primary closure or flap reconstruction).[5] In this study, we also aimed at determining which factors contribute to pharyngeal stenosis in advanced hypopharyngeal cancer treated surgically.

Materials and Methods

This case series by chart review study was conducted in a tertiary medical center from January 1996 to July 2007. All patients were followed up for 11 to 56 months (median, 26 months; upper quartile, 22 months; lower quartiles, 34 months). Data concerning the diagnosis, treatment, and clinical course of the disease were gathered from the clinical records of each patient by the authors in China Medical University Hospital.

The 160 advanced hypopharyngeal cancer (HPC) patients (stage III, IV by American Joint Committee on Cancer [AJCC] 5th edition) underwent laryngopharyngectomy with two different treatment strategies (surgery initiated group with adjuvant chemoradiation and CCRT initiated group followed by surgical salvaged because of persisted disease after CCRT for at least 6 weeks), and they were all retrospectively reviewed under Institutional Review Board approval of the China Medical University Hospital. Patients with advanced-stage HPC (T3 and T4) were advised to undergo surgery and postopera-

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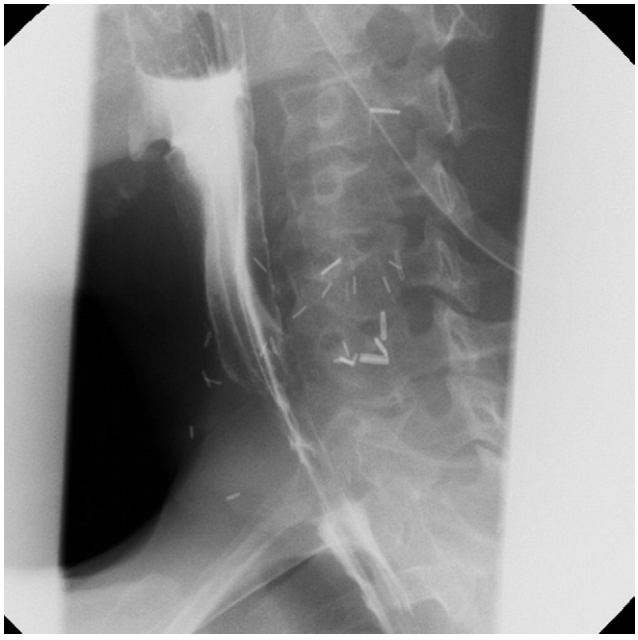

Figure 1 Lateral view of barium esophagography revealed pharyngeal stenosis with barium contrast medium pooling above the stenotic portion of the neopharynx.

tional chemoradiation therapy. Patients who declined surgery underwent CCRT. Those who did not have a complete response were offered surgical salvage.

After surgery, an H2 blocker (Zantac; GlaxoSmithKline, London, England) and antibiotics with cefazolin (1 g) were routinely given to the patients intravenously every eight hours for at least five days. An esophagogram was subsequently conducted on the fourteenth postoperative day and before oral feeding, which was permitted if no fistula was found.

The feeding of all patients was evaluated at six months after the treatment course. If a patient still required an NGT, barium esophagography was performed to check for pharyngeal stenosis. If barium contrast pooled above the neopharynx with barium stasis, pharyngeal stenosis was diagnosed (Figs 1 and 2).

Patients were defined as having anemia if their postoperative hemoglobin levels were below 10 mg/dL and as having hypoalbuminemia if their serum albumin levels were below 2.5 mg/dL. Postoperative pharyngocutaneous fistulas were recorded in the chart records, as was the dosage of radiation received by each patient.

Personal history, including smoking one pack or more daily for over five years (5 pack-years), alcohol consumption of one or more bottles of wine (> 20% concentration) per week for over two years, and betel nut chewing of over 10 nuts per day for over one year, were recorded in the patients' medical charts. Missing data were supplied by telephone interviews or personal interviews during regular follow-up. All TNM staging was identified by the surgeons on the basis of AJCC (5th edition). Patients were regularly followed up according to the treatment guidelines.

Univariate and multivariate analyses were performed with χ^2 test, Student t test, and logistic regression to systematically evaluate all the correlated factors that may predispose patients to pharyngeal stenosis. Data were deemed to be significant when the P value was less than 0.05. The SPSS 15th edition software (SPSS Inc., Chicago, IL) was used for statistical analysis.

Results

We evaluated 160 patients with advanced HPC who received laryngopharyngectomy. The ages of the patients ranged from 37 to 90 years (median, 57 years). Fifty-seven (35.62%) patients had T3 lesions, and 123 (64.38%) had T4 lesions. There were 25 (15.62%) who developed pharyngeal stenosis.

There were 104 patients who received primary closure for reconstruction of the neopharynx. The other 56 patients underwent flap reconstruction surgery instead of a primary closure, including 25 pedicled pectoralis major myocutaneous flaps (PMMCFs), 13 gastric pull up, four free jejunum flap reconstruction, and 14 free anterolateral thigh flap reconstruction. Only 3 patients developed pharyngeal stenosis (5.3%): two by pedicle flap (PMMCF) (8.0%) and one by free flap (free jejunum flap) (3.2%); no difference could be found between the treatments of pedicle flap (PMMCF) and free flap ($P = 0.43$).

There were three patients who developed pharyngeal stenosis in the setting of flap closure reconstruction (5.3%), and 22 patients developed pharyngeal stenosis by primary closure reconstruction (21.2%); there is higher significant stenosis occurrence rate in the primary closure group ($P = 0.01$). The surgical initiated group comprised 112 patients.

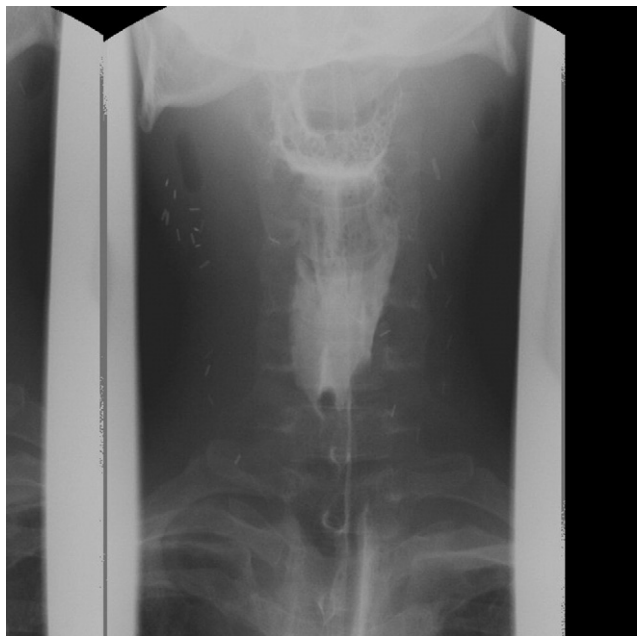

Figure 2 Anterior-posterior view of barium esophagography revealed pharyngeal stenosis with barium contrast medium pooling above the stenotic portion of the neopharynx.

Table 1
Comparison of the surgery initiated group versus CCRT failure group

Variables	Surgery initiated, n = 112 (%)	CCRT failure, n = 48 (%)	*P* value*
Age (mean ± SD), yrs	54.1 ± 10.4	56.4 ± 12.3	0.259
Sex (M/F)	99/13 (88.4/11.6)	43/5 (89.6/10.4)	1.000
Alcohol consumption (yes)	50 (44.6)	22 (45.8)	1.000
Betel nut chewing (yes)	66 (58.9)	41 (85.4)	0.001
Smoking (yes)	73 (65.2)	41 (85.4)	0.013
Hypoalbuminemia (yes)	17 (15.2)	16 (33.3)	0.018
Anemia (yes)	36 (32.1)	14 (29.2)	0.853
T4 stage (yes)	74 (66.1)	38 (79.2)	0.132
Neck dissection (yes)	82 (73.2)	11 (22.9)	<0.0001
Primary closure (yes)	74 (66.1)	30 (62.5)	0.719
Postoperative fistula (yes)	24 (21.4)	28 (58.3)	<0.0001
Postoperative stenosis (yes)	9 (8.0)	16 (33.3)	<0.0001

CCRT, concurrent chemoradiation therapy; *SD*, standard deviation.
*Student *t* test for continuous variable and χ^2 test for categorical variable.

The CCRT failure group (n =48) received chemoradiation plus surgical salvage. Postoperative radiation therapy (1.8-2.0 Gy/d, 5 days/week × 6-7 weeks) was administered to 72 patients, and no one died during the course of treatment. The average overall accumulated dosage was 5840 cGy (standard deviation [SD], ±4.2 Gy; range, 54-60). The chemotherapy agents were cisplatin 100 mg/m^2 for one day and 5-fluorouracil 1000 mg/m^2, which were used as adjuvant chemotherapy.

The CCRT failure group comprised 48 patients who had undergone radiation therapy with a curative intent (1.8-2.0 Gy/d, 5 days/week × 7-8 weeks). The average overall accumulated dosage was 6480 cGy (SD, ±6.3 Gy; range, 63.0-73.8). The chemotherapy agent was cisplatin 100 mg/m^2 given on the first day of the first, fourth, and seventh weeks in the concurrent strategy. All the patients underwent surgical salvage because of persisted disease for at least six weeks after finishing CCRT.

Student's t Test and χ^2 Test to Compare the Primary versus Salvage Group

The characteristics of the patients in the primary surgery and salvage surgery groups are summarized in Table 1. There were no differences in age, gender, T4 stage, and primary closure between the two groups (Table 1). The comparison between the primary surgery and salvage surgery groups demonstrates an increased rate of both postoperative fistula and stenosis in patients who failed CCRT (Table 1).

Possible Risk Factors for Pharyngeal Stenosis

By univariate and multivariate analyses, the age index > 65 years and primary closure reconstruction were two significant factors for postoperative pharyngeal stenosis (Tables 2 and 3). However, gender, smoking, drinking, betel nut chewing, anemia, hypoalbuminemia, T4 stage, neck dissec-

Table 2
Univariate analysis of risk factors for pharyngeal stenosis in postoperative hypopharyngeal cancer patients

Variables	Stenosis, n = 25 (%)	No stenosis, n = 135 (%)	*P* value
Age (mean ± SD), yrs	59.6 ± 11.4	53.9 ± 10.8	0.018
Age > 65 yrs	12 (48.0)	23 (17.0)	0.001
Sex (M/F)	20/5 (80.0/20.0)	122/13 (90.4/9.6)	0.163
Alcohol consumption (yes)	10 (40.0)	62 (45.9)	0.665
Betel nut chewing (yes)	22 (80.0)	85 (63.0)	0.019
Smoking (yes)	21 (84.0)	93 (68.9)	0.153
Hypoalbuminemia (yes)	10 (40.0)	23 (17.0)	0.015
Anemia (yes)	10 (50.0)	40 (29.6)	0.350
T4 stage (yes)	20 (80.0)	92 (68.1)	0.342
Neck dissection (yes)	12 (48.0)	81 (60.0)	0.278
Preoperative concurrent chemoradiation therapy (yes)	16 (64.0)	32 (23.7)	<0.0001
Primary closure (yes)	22 (88.0)	82 (60.7)	0.011
Postoperative fistula (yes)	16 (64.0)	36 (26.7)	<0.0001

SD, standard deviation.

Table 3
Multivariate analysis of risk factors for pharyngeal stenosis in postoperative hypopharyngeal cancer patients

Variables	Coefficient	SE	OR (95% CI)	*P* value
Age > 65 yrs	1.920	0.646	6.82 (1.92-24.17)	0.003
Male sex	−0.401	0.791	0.67 (0.14-3.16)	0.612
Alcohol consumption (yes)	0.312	0.591	1.37 (0.43-4.36)	0.598
Betel nut chewing (yes)	1.441	0.848	4.22 (0.80-22.28)	0.090
Smoking (yes)	0.000	0.721	1.00 (0.24-4.11)	1.000
Hypoalbuminemia (yes)	0.214	0.629	1.24 (0.36-4.25)	0.734
Anemia (yes)	0.817	0.623	2.26 (0.67-7.67)	0.190
T4 stage (yes)	1.246	0.727	3.48 (0.84-14.46)	0.087
Neck dissection (yes)	−0.263	0.688	0.77 (0.20-2.96)	0.703
Preoperative concurrent chemoradiation therapy (yes)	1.022	0.698	2.78 (0.71-10.90)	0.143
Primary closure (yes)	2.053	0.757	7.79 (1.77-34.32)	0.007
Postoperative fistula (yes)	1.070	0.639	2.92 (0.83-10.20)	0.094

SE, standard error; *OR*, odds ratio; *CI*, confidence interval.

tion, postoperative pharyngocutaneous fistula (PCF), and preoperative CCRT were not risk factors (Tables 2 and 3). In our study, failed CCRT as a risk factor for postoperative stenosis did not reach significance in multivariate analysis, whereas the age index > 65 years and primary closure remained statistically significant. There were nine patients who developed postoperative pharyngeal stenosis in the 112 patients who underwent surgery initiated with adjuvant chemoradiation therapy (8.0%); however, 16 patients developed pharyngeal stenosis in the 48 surgical salvaged patients following failed CCRT (33.3%) ($P < 0.001$).

Subgroup Analysis of Patients Who Underwent Primary Closure

In the subgroup analysis of patients who underwent primary closure reconstruction, the age index > 65 years and the index of developed postoperative pharyngocutaneous fistula were risk factors for pharyngeal stenosis (Table 4).

Management of Pharyngeal Stenosis

The management of pharyngeal stenosis was difficult in advanced hypopharyngeal patients who underwent total laryngopharyngectomy. Of the 25 patients with pharyngeal stenosis, only one received salvaged gastric pull-up after excision of the stenotic portion. The other 24 patients received only NGT feeding (n = 17) and gastrostomy (n = 7).

Among the 24 patients who used NGTs or gastrostomy tubes, six received esophageal bougination, whereas three developed pharyngeal rupture and fistulas complicated by deep neck infections. All of them failed to eat a soft-food diet.

Survival Differences

There were no difference in the survival rate analysis between postoperative advanced hypopharyngeal cancer patients who developed pharyngeal stenosis and those who did not (Fig 3).

Discussion

Long-term NGT feeding or liquid diet feeding is not rare among patients who undergo laryngopharyngectomy.[1] In this study, pharyngeal stenosis was defined as persistent NGT feeding with abnormal barium esophagography find-

Table 4
Subgroup analysis of risk factors for pharyngeal stenosis in postoperative hypopharyngeal cancer patients with neopharyngeal reconstruction by primary closure in a multivariate analysis (n = 104)

Variables	Coefficient	SE	OR (95% CI)	*P* value
Age > 65 yrs	1.678	0.665	5.36 (1.45-19.73)	0.012
Male sex	−0.588	0.825	0.56 (0.11-2.80)	0.476
Hypoalbuminemia (yes)	0.551	0.666	1.74 (0.47-6.41)	0.408
Anemia (yes)	0.794	0.679	2.21 (0.58-8.37)	0.243
T4 stage (yes)	0.754	0.738	2.13 (0.50-9.02)	0.306
Neck dissection (yes)	0.039	0.700	1.04 (0.26-4.10)	0.955
Preoperative concurrent chemoradiation therapy (yes)	0.820	0.737	2.27 (0.54-9.62)	0.265
Postoperative fistula (yes)	1.615	0.693	5.03 (1.29-19.57)	0.020

SE, standard error; *OR*, odds ratio; *CI*, confidence interval.

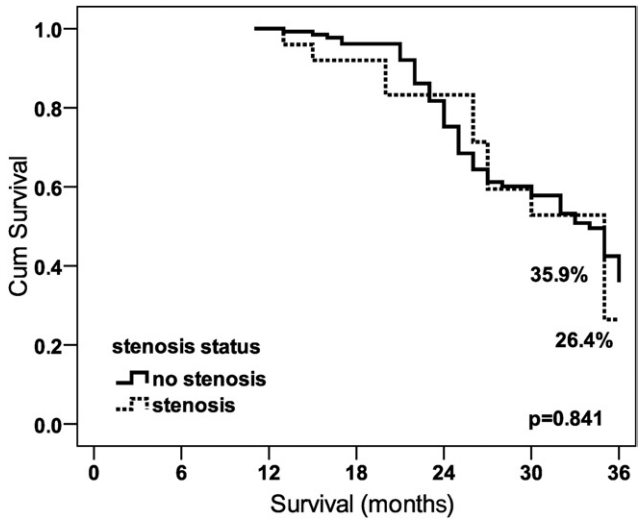

Figure 3 Survival rate of pharyngeal stenosis and nonpharyngeal stenosis in postoperative advanced hypopharyngeal cancer patients.

ings of barium pooling or stasis above the inlet of the nasopharyngeal tract (relative stenotic pharyngeal tract).

In our univariate analysis, we found that preoperative CCRT and primary closure were both risk factors for pharyngeal stenosis. In addition, the age index > 65 years, betel nut chewing, and hypoalbuminemia were also factors leading to pharyngeal stenosis; however, primary closure and the age index > 65 years remained risk factors in the multivariate analysis.

Elderly patients with head and neck cancers frequently develop swallowing problems. Therefore, old age is considered as a risk factor of pharyngeal stenosis in patients with hypopharyngeal cancers treated by CCRT.[6] There have also been reports that old age is a risk factor for pharyngeal stricture in hypopharyngeal cancer patients who received surgical treatment.[7] We also found the age index > 65 years was a risk factor for pharyngeal stenosis. Although some studies have found that elderly patients present with higher incidences of swallowing problems,[6] the age index > 65 years has not been found to be a risk factor for postoperative pharyngeal stenosis.[5]

Although the prevalence rate of postoperative pharyngeal stenosis is estimated to be 12 to 33 percent, the incidence was 15.62 percent in this study. Our estimation is objective and reasonable because the diagnosis of pharyngeal stenosis was made after a long-term observation period of six months, and all cases of pharyngeal stenosis were confirmed by barium esophagography.

Radiation therapy is a considerable risk factor that may cause a series of problems with swallowing.[6] The rate of pharyngeal stenosis was higher among hypopharyngeal cancer patients who received radiation therapy, even if they later received a pharyngolaryngectomy with free flap reconstruction.[8-10]

However, in our study, receiving failed CCRT was only a significant factor by univariate analysis but was not significant in the multivariate analysis (Tables 1 and 2). Patients receiving primary closures who were aged > 65 years were found to be at higher risk of pharyngeal stenosis. Therefore, the primary closure and the age index > 65 years were the two most critical factors related to stenosis.

Although failed CCRT is not a significant risk factor in multivariate analysis, it was found to be significant in developing higher postoperative fistula and stenosis rates in CCRT failure patients in univariate analysis (Tables 1 and 2). Therefore, we still recommend that surgeons consider using the flap closure for CCRT-failed patients in the future.

Overall, there is a higher rate of pharyngeal stenosis among advanced hypopharyngeal cancer patients with a primary closure than among those in the nonprimary closure group. The remaining posterior pharyngeal wall may not be sufficient for the reconstruction of the neopharynx in these patients. The section margin for a large tumor usually requires a 5-mm distance, such that the remaining posterior pharyngeal wall is not sufficient to reconstruct the neopharynx. In terms of the sufficient amount of residual mucosa for the primary closure of pharyngeal remnants after total laryngectomy, Hui et al[11] and others have suggested that a minimum of 1.5-cm relaxed and 2.5-cm stretched posterior pharyngeal wall mucosa is needed to restore swallowing in non-CCRT patients.[11,12]

In our opinion, primary suture is not recommended for older patients with advanced hypopharyngeal cancers. Instead, flap reconstruction is suggested to decrease the complications of pharyngeal stenosis.[4] When treating patients with advanced hypopharyngeal cancer, flap reconstruction can be considered to obtain a wider safety margin, minimize pharyngeal stenosis, and achieve better disease control.

There was no difference in the survival rates between the groups with and without pharyngeal stenosis. This may be due to small sample size and short periods of follow-up. Further investigations with larger samples or a longer follow-up period may provide more solid evidence to confirm our findings.

Conclusion

Flap reconstruction for neopharyngeal reconstruction, instead of primary closure reconstruction, is recommended for patients with advanced hypopharyngeal cancer to reduce the occurrence of pharyngeal stenosis. The age of the patient and the type of closure are the two most critical factors related to stenosis, and flap closure reconstruction is strongly recommended for patients > 65 years of age.

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Y-A.T, D-T.B., and M-H.T. contributed equally to this article.

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Disclosures

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