Table 3. Pathologic characteristics and overall survival of selected patients with metastasis to the upper mediastinal lymph nodes

Characteristic	No. of patients (%)	1-year survival (%)	3-year survival (%)	*P* value
Tumor status				
T1/2	3 (27)	100	100	0.517
T3	4 (36)	75	75	
T4	4 (36)	75	50	
Node status				
N0	0			
N1	11 (100)	91	71	
Metastatic status				
M0	0			
M1 lymph	11 (100)	91	71	
Differentiation				
Well	5 (45)	80	60	0.486
Moderate	6 (55)	80	80	
Lymphatic invasion				
Negative	7 (64)	86	69	0.828
Positive	4 (36)	75	75	
Vascular invasion				
Negative	1 (9)	100	100	0.544
Positive	10 (91)	90	68	
Larynx				
Preserved	4 (36)	100	100	0.196
Laryngectomy	7 (64)	86	57	
Residual tumor				
R0	9 (82)	89	64	0.359
R1	2 (18)	100	100	

Survival and Pattern of First Failure

With a median follow-up period of 39.5 months (range, 16–64 months), the median survival time was 33 months. The 1- and 3-year overall survival rates were 90 and 67%, respectively (Fig. 2). Tumors recurred in four patients (36%). The pattern of recurrence was more often distant metastasis (75%) than locoregional spread (0%).

Toxicity

All toxicities are listed in Table 4. The majority of treatment-related toxicities included myelosuppression. Leukopenia, neutropenia and mucositis of Grade 3 or greater occurred in 36, 18 and 9% of the patients, respectively. No patients died during treatment. During and after treatment, no ischemic change or necrosis due to the effects of radiation and concurrent chemotherapy was found in the reconstructed organs.

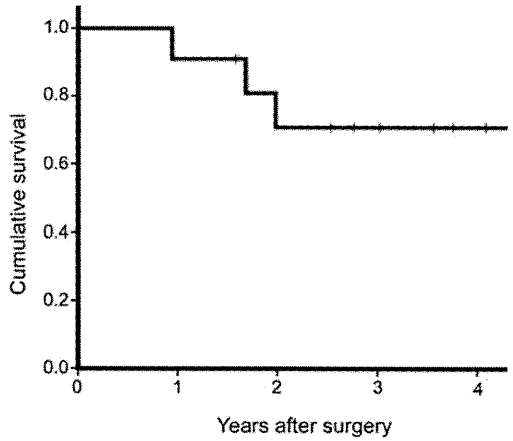

Figure 2. Overall survival curve.

Table 4. Hematologic and non-hematologic adverse events during post-operative radiation and concurrent chemotherapy

Events	G1, no. (%)	G2, no. (%)	G3, no. (%)	G4, no. (%)
Hematologic				
Leukopenia	0	6 (55)	4 (36)	0
Neutropenia	0	5 (45)	2 (18)	0
Anemia	0	2 (18)	0	0
Non-hematologic				
Nausea	7 (64)	0	0	0
Anorexia	7 (64)	1 (9)	0	0
Fatigue	6 (55)	0	0	0
Diarrhea	0	1 (9)	0	0
Esophagitis	1 (9)	0	0	0
Mucositis	2 (18)	0	1 (9)	0
Dysphagia	4 (36)	1 (9)	0	0
Radiation dermatitis	2 (18)	3 (27)	0	0
Renal (creatinine)	3 (27)	7 (64)	0	0

DISCUSSION

Carcinoma of the cervical esophagus extends easily and frequently upward to the hypopharynx or downward to the thoracic esophagus, and most tumors are located at the border of the hypopharynx or the thoracic esophagus. However, carcinoma of the cervical esophagus is a disease distinct from carcinoma of the hypopharynx or thoracic esophagus. Larynx-preserving esophagectomy for carcinoma of the cervical esophagus can be performed safely and can lead to the long-term survival of selected patients (2,3). In the present study, even if patients had metastasis to the upper mediastinal lymph nodes, larynx-preserving cervical esophagectomy could be performed (Table 3). The selection of reconstructive procedure depends on the resected length of the esophagus necessary to ensure adequate distal esophageal margins,

whether gastric pull-up adapts to total esophagectomy and whether free jejunal transfer accommodates the cervical esophagectomy with or without pharyngolaryngectomy.

Kakegawa et al. (4) have reported that the incidence of metastasis to the upper mediastinal lymph nodes (11.4%) is similar to that to the cervical paratracheal lymph nodes (14.3%) and deep cervical lymph nodes (14.3%). In the present study, the incidence of metastasis to the upper mediastinal lymph nodes was 38% (Table 1). The lymphatic drainage of the cervical esophagus is primarily to the paratracheal lymph nodes; therefore, carcinoma of the cervical esophagus spreads easily and frequently upward to the cervical lymph nodes or downward to the upper mediastinal lymph nodes or both. For this reason, we routinely perform dissection of the upper mediastinal lymph nodes as well as that of the bilateral cervical paratracheal and the deep cervical lymph nodes.

The reported 3- and 5-year survival rates for cervical esophageal carcinoma treated with surgical resection range from 18 to 35.4% and from 12 to 42%, respectively (2,5–8). The prognosis of patients with cervical esophageal cancer is worse than that of patients with hypopharyngeal cancer (7,8). Factors previously reported to influence the long-term survival of patients include both carcinoma of the cervical esophagus and carcinoma of the hypopharynx. Therefore, we reported prognostic factors affecting survival in our previous study, including carcinoma of the cervical esophagus (excluding hypopharyngeal cancer). In our previous study, prognostic factors affecting survival after surgical resection were sex, high T factor, lymph node involvement, palpable cervical lymph nodes, vocal cord paralysis, lymphatic invasion and extracapsular invasion (2). In particular, the 3-year survival rate in patients with metastasis to mediastinal lymph nodes (M1 lymph/Stage IV) was 0% (2). Therefore, we believe that carcinoma of the cervical esophagus requires multimodal treatment, such as post-operative radiotherapy with concurrent chemotherapy.

Cooper et al. (9) (Radiation Therapy Oncology Group 9501) and Bernier et al. (1) (European Organization for Research and Treatment of Cancer Trial 22931) have both reported that concurrent post-operative radiotherapy and chemotherapy with cisplatin for locally advanced cancers of the head and neck significantly improves the rates of local and regional control and of disease-free survival compared with post-operative radiotherapy alone. Bernier et al. have also demonstrated an improvement in the overall survival rate. Single-modality treatment after surgical resection cannot guarantee long-term survival; therefore, multimodal therapy, such as post-operative chemotherapy and radiotherapy, is essential for the treatment of cervical esophageal carcinoma. However, we are concerned about the adverse effects of post-operative chemoradiotherapy upon the reconstructed organs, especially free jejunal grafts, and the patient's general condition after the operation. Single- and multi-institutional randomized studies and retrospective studies have shown that the concurrent chemotherapy regimen modified by reducing the platinum dose, increasing its frequency and adding a complementary chemotherapeutic agent remains well tolerated and is more effective than radiotherapy alone (10–12).

On the basis of the results of our previous study and these studies of post-operative adjuvant or definitive radiotherapy with concurrent chemotherapy for locally advanced carcinoma of the head and neck, we performed a pilot study and retrospectively assessed the toxic effects and efficacy of post-operative radiotherapy with concurrent low-dose cisplatin chemotherapy in selected patients with metastasis to the upper mediastinal lymph nodes (M1 lymph/Stage IV), a factor indicating an extremely poor prognosis. Nine patients (82%) completed post-operative radiotherapy and two or more cycles of concurrent chemotherapy with cisplatin. The majority of treatment toxicities included myelosuppression. Leukopenia, neutropenia and mucositis of Grade 3 or greater occurred in 36, 18 and 9% of the patients, respectively. However, during the protocol treatment, no Grade 4 treatment-related toxicity occurred and no patients died. A low dose of cisplatin decreases the likelihood of adverse effects and death related to post-operative treatment with the combination of radiotherapy and concurrent chemotherapy with cisplatin (1). During and after treatment, no reconstructed organs underwent ischemic change or necrosis due to the effects of radiation and concurrent chemotherapy. The combination of post-operative radiation and concurrent chemotherapy with low-dose cisplatin is a well-tolerated treatment with mild-to-moderate adverse effects which causes no damage to reconstructed organs.

With a median follow-up period of 39.5 months (range, 16–64 months), the median survival time was 33 months. The 1- and 3-year overall survival rates were 90 and 67%, respectively (Fig. 2). Tumors recurred in four patients (36%). The pattern of recurrence was more often distant metastasis (75%) than locoregional spread (0%). In our previous study, the 3-year survival rate was 0% in patients with metastasis to mediastinal lymph nodes (M1 lymph/Stage IV), and the pattern of recurrence after operation was more often locoregional spread (82%) than distant metastasis. Triboulet et al. (7) have reported that post-operative radiotherapy for carcinoma of the hypopharynx and cervical esophagus improves survival and achieves a 3-year survival rate of 35%. However, large randomized, controlled studies have demonstrated that the combination of post-operative radiotherapy with concurrent chemotherapy is superior to post-operative radiation alone (1). The combination of post-operative radiation and concurrent chemotherapy with low-dose cisplatin improves the rates of locoregional control and overall survival in patients with locally advanced squamous cell carcinoma of the cervical esophagus. We advocate that the indications for the combination of post-operative radiation with concurrent chemotherapy be expanded to include patients with a high T factor and lymphatic invasion, as this treatment is well tolerated, is associated with mild-to-moderate adverse effects and improves survival rates.

CONCLUSION

The combination of post-operative radiation and concurrent chemotherapy with low-dose cisplatin is well tolerated, is associated with mild-to-moderate adverse effects and has the potential to improve the rates of locoregional control and overall survival in patients with locally advanced squamous cell carcinoma of the esophagus. Therefore, we advocate that the indications for this treatment be expanded to include patients with a high T factor and lymphatic invasion.

Conflict of interest statement

None declared.

References

1. Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefebvre JL, Greiner RH, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med* 2004;350:1945–52.
2. Daiko H, Hayashi R, Saikawa M, Sakuraba M, Yamazaki M, Miyazaki M, et al. Surgical management of carcinoma of the cervical esophagus. *J Clin Oncol* 2007;96:166–72.
3. Kadota H, Sakuraba M, Kimata Y, Hayashi R, Ebihara S, Kato H. Larynx-preserving esophagectomy and jejunal transfer for cervical esophageal carcinoma. *Laryngoscope* 2009;119:1274–80.
4. Kakegawa T, Yamana H, Ando N. Analysis of surgical treatment for carcinoma situated in the cervical esophagus. *Surgery* 1985;97: 150–7.
5. Jones AS, Roland NJ, Hamilton J, Rowley H, Nandapalan V. Malignant tumours of the cervical oesophagus. *Clin Otolaryngol Allied Sci* 1996;21:49–53.
6. Nishimaki T, Kanda T, Nakagawa S, Kosugi S, Tanabe T, Hatakeyama K. Outcomes and prognostic factors after surgical resection of hypopharyngeal and cervical esophageal carcinomas. *Int Surg* 2002;87:38–44.
7. Triboulet JP, Mariette C, Chevalier D, Amrouni H. Surgical management of carcinoma of the hypopharynx and cervical esophagus: analysis of 209 cases. *Arch Surg* 2001;136:1164–70.
8. Wang HW, Chu PY, Kuo KT, Yang CH, Chang SY, Hsu WH, et al. A reappraisal of surgical management for squamous cell carcinoma in the pharyngoesophageal junction. *J Clin Oncol* 2006;93:468–76.
9. Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med* 2004;350:1937–44.
10. Jeremic B, Milicic B, Dagovic A, Vaskovic Z, Tadic L. Radiation therapy with or without concurrent low-dose daily chemotherapy in locally advanced, nonmetastatic squamous cell carcinoma of the head and neck. *J Clin Oncol* 2004;22:3540–8.
11. Taylor SGt, Murthy AK, Vannetzel JM, Colin P, Dray M, Caldarelli DD, et al. Randomized comparison of neoadjuvant cisplatin and fluorouracil infusion followed by radiation versus concomitant treatment in advanced head and neck cancer. *J Clin Oncol* 1994;12:385–95.
12. Watkins JM, Zauls AJ, Wahlquist AH, Shirai K, Garrett-Mayer E, Gillespie MB, et al. Low-dose weekly platinum-based chemoradiation for advanced head and neck cancer. *Laryngoscope* 2010;120:236–42.

Japanese Journal of Clinical Oncology Advance Access published April 5, 2011

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2011
doi:10.1093/jjco/hyr046

Original Article

Analysis of Operative Mortality and Post-operative Lethal Complications after Head and Neck Reconstruction with Free Tissue Transfer

Kentaro Tanaka[1,*], Minoru Sakuraba[1], Shinpei Miyamoto[1], Ryuichi Hayashi[2], Mitsuru Ebihara[2], Masakazu Miyazaki[2], Takeshi Shinozaki[2], Hiroyuki Daiko[2] and Tomoyuki Yano[1]

[1]Division of Plastic and Reconstructive Surgery and [2]Division of Head and Neck Surgery, National Cancer Center Hospital East, Chiba, Japan

*For reprints and all correspondence: Kentaro Tanaka, Department of Plastic and Reconstructive Surgery, Graduate School of Medical Sciences, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyou-ku, Tokyo 113-8519, Japan. E-mail: kenta.plas@tmd.ac.jp

Received December 29, 2010; accepted March 8, 2011

Objective: Operative mortality is the most important index for assessing operative results, which has rarely been examined in reconstructive surgery. The aims of this study were to establish a representative index of operative mortality after head and neck reconstruction and to consider measures to improve operative results.

Methods: We reviewed cases of head and neck reconstruction by means of free tissue transfer performed from July 1992 through December 2005 at the National Cancer Center Hospital East, Chiba, Japan. The subjects were 1249 patients with a mean age of 62 years. Operative mortality was evaluated on the basis of the 30-day post-operative mortality rate and the in-hospital mortality rate. Statistical analysis was performed with the Cochran–Armitage test.

Results: The 30-day post-operative mortality rate was 0.88% (11 of 1249 patients), and the in-hospital mortality rate was 1.84% (23 of 1249 patients). The 30-day post-operative mortality was significantly correlated with age ($P = 0.002$), but the in-hospital mortality was not ($P = 0.148$). Among patients older than 80 years, the 30-day post-operative mortality rate was 8.57%. The most common cause of 30-day post-operative death was cerebral infarction. Of the 23 in-hospital deaths, 13 were due to cancer recurrence.

Conclusions: These results indicate that head and neck reconstruction with free flaps is reliable. However, the high 30-day post-operative mortality rate among patients 80 years or older should be considered when deciding whether to operate. To decrease the operative mortality rate, careful perioperative management is needed to prevent complications and shorten the hospital stay.

Key words: operative mortality – 30-day post-operative mortality – in-hospital mortality post-operative lethal complication – head and neck reconstruction with free tissue transfer

INTRODUCTION

Many indexes have been used to assess the effects of surgical treatment. Among these indexes, the most important one for assessing operative results is the operative mortality rate. On the basis of recent reports on surgical mortality from numerous institutions, the suitability of surgical procedures or measures to improve treatment results have been widely discussed (1–5). However, few comprehensive studies of outcome measures have been performed in the field of reconstructive surgery.

It would appear that the head and neck reconstructive procedure itself does not directly affect the operative mortality, but the reconstructive procedure with free tissue transfer usually requires about 4 to 6 hours moreover. It is common knowledge that the long operative duration is associated with post-operative complications (6). Furthermore, in cases that need reconstructive surgery, the primary cancer tends to spread widely and the extent of ablation is large compared with non-reconstructive cases. So, there is a possibility that the head and neck reconstructive procedure affects the operative mortality indirectly.

The aims of this study were to analyze patients who had died after head and neck reconstruction using free tissue transfer and to establish a representative index of operative mortality. In addition, we considered measures to improve operative results after head and neck reconstruction.

PATIENTS AND METHODS

We reviewed the charts of all patients who had undergone head and neck reconstruction from July 1992 through December 2005 at the National Cancer Center Hospital East, Chiba, Japan. The subjects of this study were 1249 patients (963 men and 286 women) with a mean age of 62 years (range, 19–91 years). After the ablation of head and neck cancers, all patients underwent reconstructive surgery with free tissue transfer. The primary diseases and reconstructive procedures of all 1249 patients are shown in Table 1. The post-operative courses of all patients were obtained from their charts, and patients who died post-operatively or were discharged from the hospital were identified and analyzed. Operative mortality was evaluated with the following two indexes. The first index was the 30-day post-operative mortality rate, which is the rate of all deaths, regardless of cause, occurring within 30 days after surgery in or out of the hospital. The second index was the in-hospital mortality rate, which is the rate of post-operative deaths in-hospital on and after the 31st post-operative day without discharge. Furthermore, these outcomes were analyzed according to the age group and compared statistically by means of the Cochran–Armitage test. Clinical factors that were suspected to contribute to operative mortality were evaluated.

RESULTS

Of the 1249 patients, 11 (8 men, 3 women) died within 30 days of surgery, for a 30-day post-operative mortality rate of 0.88%. There were 23 in-hospital death cases (22 men and 1 woman), for an in-hospital mortality rate of 1.84%. The subjects of this study were divided into four groups according to age. There were 527 patients aged 59 years or younger, 431 patients aged 60–69 years, 256 patients aged 70–79 years and 35 patients 80 years or older. The 30-day post-operative mortality rate and the in-hospital mortality rate of the four age groups each are shown in Table 2.

Table 1. Primary diseases and reconstructive procedures of all 1249 patients

	Number of patients
Site of cancer	
Hypopharynx	333 (27%)
Tongue	262 (21%)
Oropharynx	153 (12%)
Esophagus	101 (8%)
Lower gingival	98 (8%)
Buccal mucosa	87 (7%)
Oral floor	79 (6%)
Maxilla	65 (5%)
Larynx	30 (2%)
Other (parotid gland, thyroid gland etc.)	
Flap	
RAMC	471 (38%)
FJ	413 (33%)
ALT	214 (17%)
Fibula	68 (5%)
Radial forearm	40 (3%)
Iliac	17 (1%)
Scapular	12 (1%)
Latissimus dorsi	10 (1%)
Other (groin, omentum etc.)	

RAMC, rectus abdominis musculocutaneous; FJ, free jejunum transfer; ALT, anterolateral thigh.

Table 2. Thirty-day postoperative mortality, in-hospital mortality and age-specific mortality

Age (years)	Number of patients	30-day postoperative deaths (rate)	In-hospital deaths (rate)
≤59	527	2 (0.38%)	7 (1.33%)
60–69	431	3 (0.69%)	9 (2.09%)
70–79	256	3 (1.17%)	6 (2.34%)
≥80	35	3 (8.57%)	1 (2.86%)
Total	1249	11 (0.88%)	23 (1.84%)

Both the 30-day post-operative mortality rate and the in-hospital mortality rate tended to increase with age. However, the 30-day post-operative mortality rate was significantly correlated with age ($P = 0.002$), but the in-hospital mortality rate was not ($P = 0.148$) (Fig. 1). Therefore, the 30-day post-operative mortality rates of the four age groups were analyzed in greater detail. For the three groups of patients younger than 80 years, mortality rates became slightly, but not significantly, higher as the ages of the

groups increased; however, the mortality rate of patients 80 years and older was significantly greater than those of the other age groups ($P = 0.003$).

In the 11 cases of 30-day post-operative death, the primary diseases included hypopharyngeal cancers in 4 cases (37%), lower gingival cancers in 2 cases (18%) and, in 1 case each, tongue cancer (9%), oral floor cancer (9%), oropharyngeal cancer (9%), cervical esophageal cancer (9%) and fistula after esophageal reconstruction (9%). Free flaps transferred for reconstructive surgery included five free jejunal flaps (42%), three rectus abdominis musculocutaneous (RAMC) flaps (25%), two anterolateral thigh (ALT) flaps (17%), one scapular flap (8%) and one radial forearm flap (8%). A comparison of primary diseases and reconstructive procedures between all 1249 cases and the cases of 30-day post-operative death (Fig. 2) showed no significant differences. The causes of death were classified into two types: systemic complications and local complications. The causes of 30-day post-operative deaths were systemic complications in nine cases and local complications in two cases. The systemic complications included three cases of cerebral infarction and one case each of acute pancreatitis, methicillin-resistant *Staphylococcus aureus* pneumonia, perforation of a gastric ulcer, ischemic colitis and airway obstruction. The cause of death was unknown in one case. Details of the three post-operative deaths due to cerebral infarction are shown in Table 3. The primary diseases were oropharyngeal cancer, lower gingival cancer and hypopharyngeal cancer, and the reconstructive procedures were transfer of an RAMC flap in two patients and transfer of a free jejunal flap in one patient. The local complications were rupture of the carotid artery caused by anastomotic leakage and wound infection in two cases. Details of these cases are shown in Table 4.

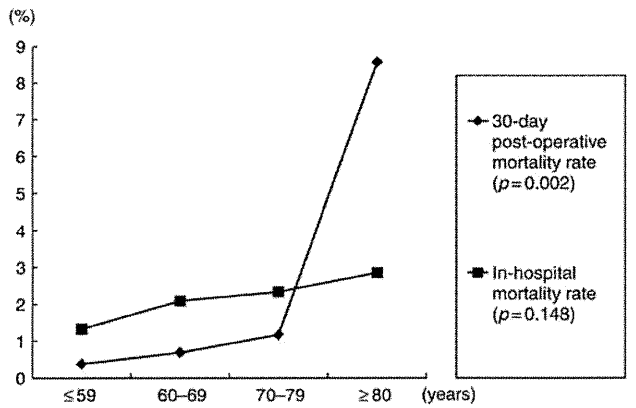

Figure 1. Changes in mortality rates with age.

In the 23 cases of in-hospital death, the primary diseases included hypopharyngeal cancers in 5 cases (22%), tongue cancers in 5 cases (22%), oropharyngeal cancers in 4 cases (17%), buccal mucosal cancers in 4 cases (17%), oral floor cancers in 2 cases (9%) and, in 1 case each, lower gingival cancer (4%), esophageal cancer (4%) and laryngeal cancer (4%). Free flaps used for reconstructive surgery were RAMC flaps in 12 cases (53%), free jejunal flaps in 7 cases (30%), ALT flaps in 2 cases (9%), a groin flap in 1 case (4%) and an omental flap in 1 case (4%). The comparison of primary diseases and reconstructive operation procedures between all

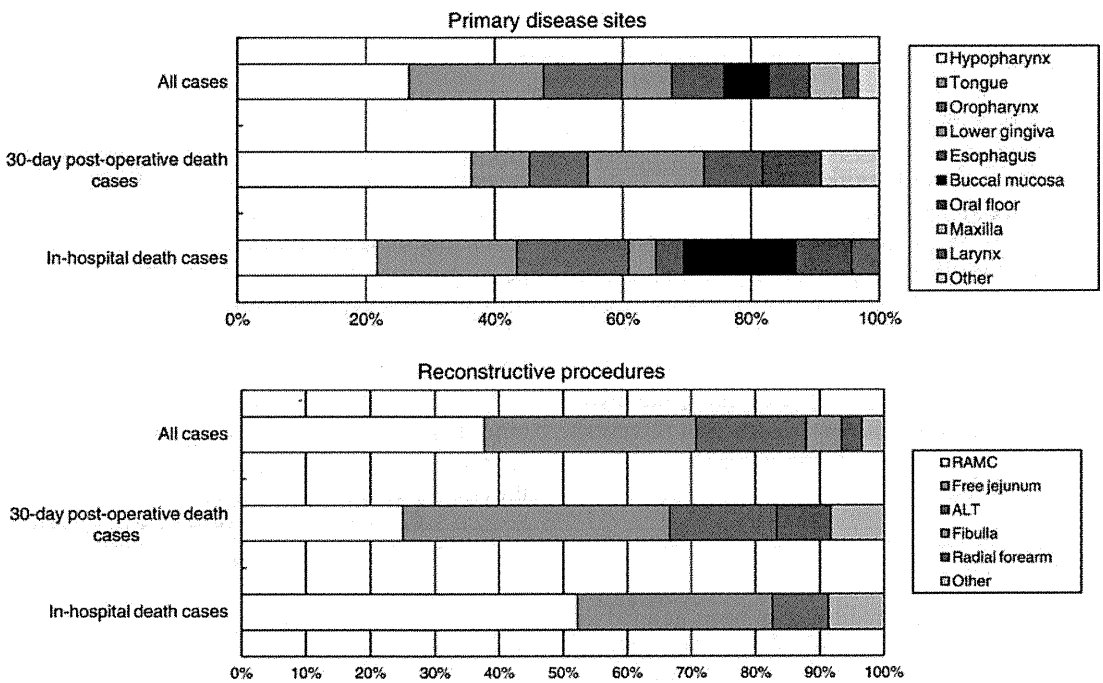

Figure 2. Comparison of primary disease sites and operative procedures between all cases and operative death cases.

Table 3. Details of three post-operative deaths due to cerebral infarction

Case	1	2	3
Age (years), sex	67, male	81, female	80, male
Primary disease	Oropharyngeal cancer	Lower gingival cancer	Hypopharyngeal cancer
Operative procedure	RAMC flap	RAMC flap	Free jejunum transfer
Previous disease	Chronic cardiac failure, atrial fibrillation, hypertension	Cerebral infarction, hypertension	Diabetes mellitus
Clinical course	POD 3: delirium	POD 5: symptom of cerebral infarction	POD 5: cardiac arrest resuscitation
	POD 10: escape from hospital	POD 16: cardiac arrest resuscitation	POD 7: diffuse cerebral infarction (CT scanning)
	POD 17: old cerebral infarction (MRI imaging)	POD 21: death	POD 8: death
	POD 18: hemorrhagic cerebral infarction, deglutition pneumonia, sepsis		
	POD 29: death		

POD, post-operative day.

Table 4. Details of two postoperative deaths caused by local complications

Case	1	2
Age (years), sex	57, male	68, female
Primary disease	Hypopharyngeal cancer	Fistula after esophageal reconstruction
Operative procedure	Free jejunum transfer	Free jejunum transfer, anterolateral thigh flap
Previous disease	Acute pancreatitis, radiation therapy	Esophageal cancer
Clinical course	POD 3: infection caused by suture leakage (oral side)	POD 2: reoperation (venous thrombosis), dyspnea
	POD 4: debridement, pharyngeal fistula formation (deltopectoral flap), bleeding after operation, ligation of carotid artery, consciousness disorder	POD 3: fever
	POD 5: death	POD 5: arterial bleeding, hypotension
		POD 6: suture leakage (anal side), septic shock
		POD 11: death

1249 cases and the in-hospital death cases is shown in Figure 2. There were also no characteristics in these items. The length of post-operative hospitalization in the 23 cases of in-hospital death ranged from 32 to 234 days (mean, 81 days). The causes of death in cases of in-hospital death tended to differ from those in cases of 30-day post-operative death. Thirteen of 23 in-hospital deaths were due to cancer recurrence. In the other 10 cases, the causes of death were pneumonia (2 cases), hepatic insufficiency (2 cases), infectious diseases resulting in septic shock (2 cases), acute myocardial infarction (1 case), respiratory obstruction (2 cases) and meningitis caused by cervical abscess (1 case).

DISCUSSION

Operative mortality has been traditionally been defined as any death, regardless of cause, occurring (i) within 30 days after surgery in or out of the hospital or (ii) more than 30 days after the operation during the same hospitalization. However, these traditional definitions have both advantages and disadvantages for evaluating operative results. Therefore, several institutions have attempted to re-define operative mortality so that it could be assessed more accurately depending on the type of operation (7). In the present study, post-operative death was evaluated using traditional definitions. However, we discriminated between the two definitions, because these mortality rates were expected to differ.

Studies of operative mortality have been performed in other fields of surgery, such as cardiac surgery, esophageal surgery, gastric cancer surgery and lung cancer surgery. Previously reported operative mortality rates have ranged from 0.5 to 4.0% (8–14). In the present study of patients who had undergone head and neck reconstruction with free tissue transfer, the overall 30-day mortality rate was 0.88%, and the in-hospital mortality rate was 1.84%. We believe that our results are comparable to those for other well-established operative procedures, such as gastrectomy, lobectomy, colorectomy and hepatic resection. This result

confirms our operative indications and the therapeutic validity of head and neck reconstructive surgery. These results also indicate that head and neck reconstruction using various types of free flaps is reliable.

The age-specific mortality rate tended to increase with age. However, statistical analysis showed that age was not related to the in-hospital mortality rate. Only the 30-day post-operative mortality rate was significantly related to age. In particular, in patients 80 years or older, the 30-day post-operative mortality was significantly higher than those in younger age groups. In patients younger than 59 years and in those aged 60–69 years, head and neck reconstructive surgery was considered extremely safe because the respective mortality rates of 0.38 or 0.69% were low enough to justify elective surgery. However, the operative mortality rate of 8.57% in patients 80 years or older is similar to that associated with coronary artery bypass grafting (15). Care must be taken when deciding operative indications for elderly patients. In particular, the greatest care must be taken when performing reconstructive surgery, especially in patients 80 years or older. However, despite the greater perioperative risk, the clinical benefit justifies surgery in octogenarians.

In the 11 cases of 30-day post-operative death, the primary diseases and the reconstructive procedures did not differ significantly from those of all cases. Therefore, neither of these factors was related to operative mortality. The most frequent cause of 30-day post-operative death was cerebral infarction, which occurred in three patients. The details of the clinical courses of these three patients are as follows. Symptoms appeared from 5 to 18 days after surgery, and these patients died from 8 to 29 days after surgery. These patients had specific characteristics as follows: age 80 years or older, history of cerebral infarction, hypertension, atrial fibrillation, cardiac failure and diabetes mellitus. In other words, careful perioperative management is needed in patients with such risk factors. Other systemic complications, such as acute pancreatitis, methicillin-resistant *S. aureus* pneumonia, perforation of a gastric ulcer, ischemic colitis, airway obstruction, developed in only one case each. In actuality, these complications cannot be predicted pre-operatively. On the other hand, rupture of the carotid artery could be prevented by preventing inflammation from extending to the carotid artery. Two cases of local complication involved rupture of the carotid artery. There were no specific characteristics in these cases, but these patients died in the early post-operative period. Therefore, the extension of inflammation to the surrounding tissue is possible in all cases. To prevent lethal complications, such as carotid artery infection, local complications must be diagnosed as early as possible. When signs of local complication are observed, early treatment, including wound opening, lavage, debridement, use of antibiotics and reoperation, should be performed.

In the 23 cases of in-hospital death, the primary diseases and reconstructive procedures also did not differ significantly from those in all cases. As was the case with the 30-day post-operative mortality rate, neither primary disease nor reconstructive procedure affected the in-hospital mortality rate. Patient age was also not significantly related to the in-hospital mortality rate. The most common cause of in-hospital death, accounting for more than half of cases, was recurrent cancer. These cancers recurred during the prolonged post-operative hospital stay, ranging from 32 to 234 days (mean, 81 days). The longer the patient stayed in the hospital because of post-operative complications, even if they were themselves not lethal, the more likely was the primary disease to recur. Clearly, post-operative complications, such as flap necrosis, wound infection and anastomotic leakage, can lengthen the post-operative hospital stay. Therefore, a conscious effort must be made to reduce post-operative complications and to shorten the post-operative hospital stay.

We have found that both systemic and local complications greatly affect operative mortality rates, including the 30-day post-operative mortality rate and the in-hospital mortality rate. To improve both immediate operative results and long-term operative results, it is important to reduce the rate and severity of post-operative complications. In other words, the improvement of surgical techniques, the evaluation of risk factors and the careful observation of clinical courses will play important roles in head and neck reconstruction.

CONCLUSION

In the present series of head and neck reconstruction using free tissue transfer, the 30-day post-operative mortality rate was 0.88%, and the in-hospital mortality rate was 1.84%. These results indicate that head and neck reconstruction with various types of free flaps is reliable. Patient age was significantly related with the 30-day post-operative mortality rate. In particular, the high 30-day post-operative mortality rate of 8.57% in patients 80 years and older should be considered when deciding whether to operate. Cerebral infarction was the most common cause of 30-day post-operative deaths. Avoiding local complications, such as carotid artery infection, is another important factor in decreasing the operative mortality rate. Regarding in-hospital deaths, more than half were due to tumor recurrence. Measures for decreasing the number of in-hospital deaths include reducing the number and severity of post-operative complications and shortening the hospital stay.

Conflict of interest statement

None declared.

References

1. Csikesz NG, Simons JP, Tseng JF, Shah SA. Surgical specialization and operative mortality in hepato-pancreatico-biliary (HPB) surgery. *J Gastrointest Surg* 2008;12:1534–9.

2. Kwan TL, Lai F, Lam CM, Yuen WC, Wai A, Siu YC, et al. Population-based information on emergency colorectal surgery and evaluation on effect of operative volume on mortality. *World J Surg* 2008;32:2077–82.
3. Meunier K, Mucci S, Quentin V, Azoulay R, Arnaud JP, Hamy A. Colorectal surgery in cirrhotic patients: assessment of operative morbidity and mortality. *Dis Colon Rectum* 2008;51:1225–31.
4. Modrall JG, Rosero EB, Smith ST, Arko FR, 3rd, Valentine RJ, Clagett GP, et al. Operative mortality for renal artery bypass in the United States: results from the National Inpatient Sample. *J Vasc Surg* 2008;48:317–22.
5. Christein JD, Kendrick ML, Que FG. What affects mortality after the operative management of hepatic abscess? *HPB (Oxford)* 2006; 8:175–8.
6. Yasunaga H, Yanaihara H, Fuji K, Horiguchi H, Hashimoto H, Matsuda S. Impact of hospital volume on postoperative complications and in-hospital mortality after renal surgery: data from the Japanese Diagnosis Procedure Combination Database. *Urology* 2010;76:548–52.
7. Jacobs JP, Mavroudis C, Jacobs ML, Maruszewski B, Tchervenkov CI, Lacour-Gayet FG, et al.; STS Congenital Database Taskforce; Joint EACTS-STS Congenital Database Committee. What is operative mortality? Defining death in a surgical registry database: a report of the STS Congenital Database Taskforce and the Joint EACTS-STS Congenital Database Committee. *Ann Thorac Surg* 2006;81:1937–41.
8. Asiyanbola B, Chang D, Gleisner AL, Nathan H, Choti MA, Schulick RD, et al. Operative mortality after hepatic resection: are literature-based rates broadly applicable? *J Gastrointest Surg* 2008;12:842–51.
9. Echahidi N, Pibarot P, Després JP, Daigle JM, Mohty D, Voisine P, et al. Metabolic syndrome increases operative mortality in patients undergoing coronary artery bypass grafting surgery. *J Am Coll Cardiol* 2007;50:843–51.
10. Lee ES, Park SI, Kim YH, Bae CH, Moon HW, Chun MS, et al. Comparison of operative mortality and complications between bronchoplastic lobectomy and pneumonectomy in lung cancer patients. *J Korean Med Sci* 2007;22:43–7.
11. Yonemura Y, Wu CC, Fukushima N, Honda I, Bandou E, Kawamura T, et al.; East Asia Surgical Oncology Group. Operative morbidity and mortality after D2 and D4 extended dissection for advanced gastric cancer: a prospective randomized trial conducted by Asian surgeons. *Hepatogastroenterology* 2006;53:389–94.
12. Ho V, Heslin MJ, Yun H, Howard L. Trends in hospital and surgeon volume and operative mortality for cancer surgery. *Ann Surg Oncol* 2006;13:851–8.
13. Engel AF, Oomen JL, Knol DL, Cuesta MA. Operative mortality after colorectal resection in the Netherlands. *Br J Surg* 2005;92:1526–32.
14. Park DJ, Lee HJ, Kim HH, Yang HK, Lee KU, Choe KJ. Predictors of operative morbidity and mortality in gastric cancer surgery. *Br J Surg* 2005;92:1099–102.
15. Schmidtler FW, Tischler I, Lieber M, Weingartner J, Angelis I, Wenke K, et al. Cardiac surgery for octogenarians—a suitable procedure? Twelve-year operative and post-hospital mortality in 641 patients over 80 years of age. *Thorac Cardiovasc Surg* 2008;56:14–9.

NARROW BAND IMAGING ENDOSCOPY FOR UNKNOWN PRIMARY TUMOR SITES OF THE NECK

Takeshi Shinozaki, MD, Ryuichi Hayashi, MD, Mitsuru Ebihara, MD, Masakazu Miyazaki, MD, Hiroyuki Daiko, MD, Masahisa Saikawa, MD, Satoshi Ebihara, MD

Department of Head and Neck Surgery, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa City, Japan.
E-mail: tashinoz@east.ncc.go.jp

Accepted 5 April 2011
Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/hed.21825

Abstract: *Background.* Examinations used to search for unknown primary tumors of squamous cell carcinomas of the neck include CT, MRI, laryngoscopy, gastrointestinal endoscopy, and positron-emission tomography (PET). Narrow band imaging (NBI) endoscopy in which an optical color-separation filter is used to narrow the bandwidth of spectral transmittance is also used.

Methods. Twenty-eight patients in whom primary squamous cell carcinomas could not be detected with conventional white light laryngoscopy underwent NBI endoscopy and PET.

Results. Primary lesions were detected with NBI endoscopy in 3 patients, but no primary lesions were detected with PET. However, PET was used to detect a lower gingival cancer and a palatine tonsillar cancer.

Conclusion. Both PET and NBI endoscopy is effective for detecting unknown primary tumors of squamous cell carcinomas of the neck. © 2011 Wiley Periodicals, Inc. *Head Neck* **00:** 000–000, 2011

Keywords: narrow band imaging; positron emission tomography; unknown primary tumor; sensitivity for detecting; less invasive examination

Patients with cancers of the head and neck sometimes present with metastases to the cervical lymph nodes. In many cases, a primary tumor cannot be identified with laryngoscopy, CT, or MRI. Two percent to 9% of metastases to lymph nodes in the head and neck are reportedly from an unknown primary tumor.[1–4]

Modalities used to search for unknown primary tumors of squamous cell carcinoma include CT, MRI, laryngoscopy, gastrointestinal endoscopy, and positron-emission tomography (PET). Some authors recommend that unilateral or bilateral tonsillectomy should be performed for patients with adequate lymphoid tonsillar tissue.[5] Some authors report that the combination of ^{18}fluorodeoxyglucose (FDG)-PET and CT is useful for detecting primary tumors.[6–8] However, there is no consensus about which examinations should be included in an optimal diagnostic evaluation.

In the esophagus, Lugol chromoendoscopy facilitates the detection of lesions at an early stage. However, Lugol staining cannot be used in the head and neck region because it causes severe mucosal irritation, which produces pain and discomfort and can result in aspiration into the airway.

In narrow band imaging (NBI) endoscopy, an optical color-separation filter is used to narrow the bandwidth of spectral transmittance. The filter is placed in the optical system of the illumination. The filter decreases illumination in all wavelengths except for 2 narrow wavelengths. The central wavelengths of the bands are 415 and 540 nm. The image is reproduced in the processor with the information from the illumination of the 2 bands (Figure 1). Narrow bandwidth filters increase the likelihood that malignant lesions will be visualized. Lesions with a well-developed microvasculature are particularly well visualized (Figure 2).

The time required for NBI endoscopy is only 15 to 30 minutes when lidocaine spray is used for local anesthesia, and patients stay at the hospital for only 2 hours. Furthermore, NBI endoscopy is less invasive than gastrointestinal endoscopy. Finally, NBI endoscopy for head and neck lesions is less costly than gastrointestinal endoscopy.

In the present study, we used NBI endoscopy to search for unknown primary tumors of squamous cell carcinomas causing metastatic mucosal lesions of the head and neck.

PATIENTS AND METHODS

The study consisted of 28 patients (22 men, 6 women; median age, 60 years; age range, 36–78 years) who visited our clinic from January 2003 through July 2009 and were found by means of needle aspiration cytologic examination to have squamous cell carcinoma with an unknown primary tumor that could not be detected with conventional white-light laryngoscopy. The N classification was N1 in 3 patients, N2a

Correspondence to: T. Shinozaki

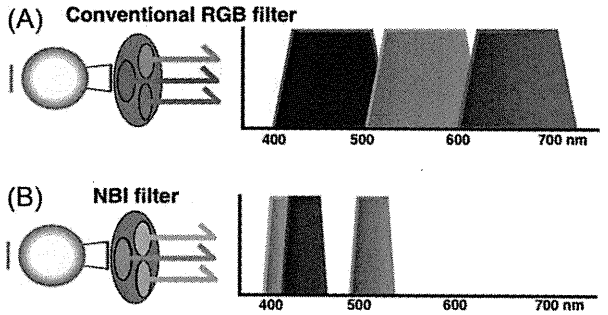

FIGURE 1. Conventional medical video endoscope system with the RGB sequential illumination method (CLV-Q260SL, Olympus Medical Systems, Tokyo, Japan) and the narrow band image (NBI) system. **(A)** The conventional system has a xenon lamp and rotation disk with 3 RGB optical filters. The rotary filter and monochromatic charge-coupled device (CCD) are synchronized, and 3 band images are generated sequentially. Color images can be synthesized by using 3 band images by the video processor. **(B)** The NBI is a novel system using narrow banding filters instead of conventional RGB broadband filters. The center wavelengths of 3 NBI filters using this study were 415, 445, and 500 nm, respectively. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

in 2 patients, N2b in 17 patients, and N3 in 6 patients. All patients underwent CT, whole-body FDG-PET, NBI endoscopy, and upper gastrointestinal endoscopy. All patients gave written informed consent.

Equipment. The equipment used for NBI endoscopy was a magnifying videoendoscope (Q240Z, Olympus Medical Systems, Tokyo, Japan) and a sequential RGB light source with NBI function (CLV-Q260SL, Olympus Medical Systems). The endoscope had a capability of 80 times optical magnification. The NBI system has been described in detail in previous studies. In this system, the central wavelengths of NBI were 415 and 540 nm, and each had a bandwidth of 30 nm.

RESULTS

Primary tumors were detected in 5 patients (Figure 3). The tumors in 3 patients were detected with NBI endoscopy. In 2 patients, superficial squamous carcinoma were detected in a palatine tonsil, and in the other patient, a thick squamous carcinoma was detected in the pyriform sinus and was identified as a primary lesion that had metastasized to a cervical lymph node. The lesions were thick but were of a color similar to that of normal mucosa, so they could not be visualized with white light (Figure 4). Neither of these primary lesions was detected with PET (Figure 5). However, PET was used to detect a lower gingival cancer and a palatine tonsillar cancer, which were identified as primary lesions metastasizing to the neck. Twenty-three patients were treated for

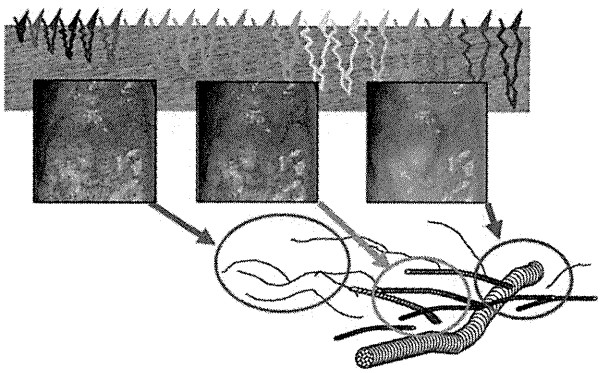

FIGURE 2. Narrow bandwidth filters increase the likelihood that malignant lesions will be visualized. Lesions with a well-developed microvasculature are particularly well visualized. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

unknown primary squamous cell carcinomas. In 1 of these 23 patients, a mesopharyngeal squamous cell carcinoma was detected 2 years after radiation therapy.

DISCUSSION

Classic workups for patients with unknown primary tumors of squamous cell carcinoma include thorough physical examinations of the head and neck and the upper aerodigestive tract, CT, and MRI followed by panendoscopy. Random biopsies of the head and neck region can be useful for detecting primary tumors in patients with squamous cell carcinoma, but the detection rate is only 10%. Ugumori et al[9] have reported that irregular microvascular patterns can be detected more easily with NBI laryngoscopy. Directed biopsy with NBI laryngoscopy may increase the detection rate.[9]

Several studies have evaluated the role of FDG-PET imaging in patients with unknown primary tumors of metastatic squamous cell carcinoma. Based on a literature review by Rusthoven et al,[6] FDG-PET

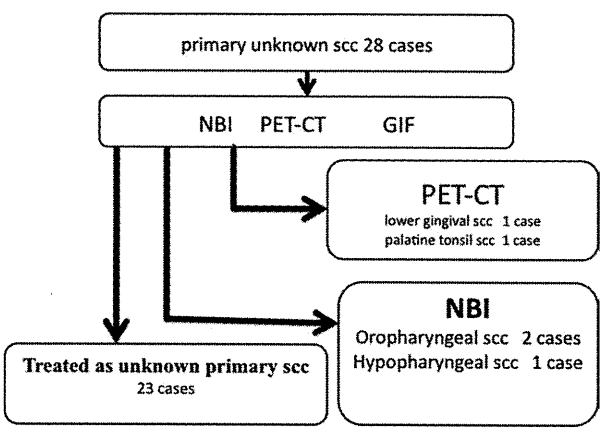

FIGURE 3. Schema of result.

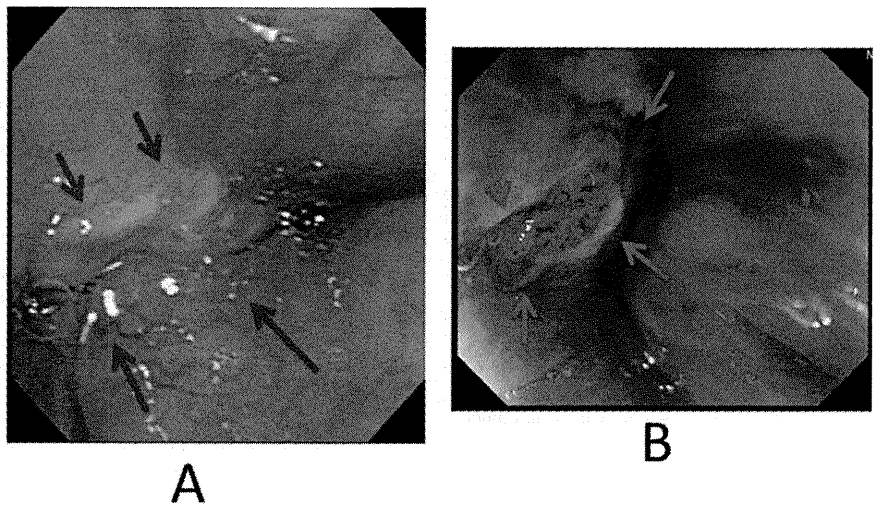

FIGURE 4. Endoscopic findings. **(A)** Conventional white-light image; **(B)** narrow band image (NBI). The cancerous lesion was difficult to visualize with conventional white-light imaging. In contrast, a well-demarcated brownish area in the hypopharynx was detected with NBI. Magnifying observation with NBI revealed an irregular microvascular pattern inside the lesion.

detects approximately 25% of primary tumors not detected with other modalities. In the present series, PET was used to detect tonsillar cancers and gingival cancers.

PET can yield both false-negative and false-positive results. Neither small primary tumors nor low-uptake tumors are detected with PET. Cianchetti et al[8] have suggested that PET is unlikely to improve the probability of detecting unknown primary tumors. On the other hand, when expertise in CT or MRI or both is less developed, PET studies may be useful. We also believe that the discovery of unknown primary tumors will become easier, even without PET, with further technical improvements in CT and MRI.

FIGURE 5. With ^{18}fluorodeoxyglucose (FDG)-positron-emission tomography (PET)/CT, only masses in the left upper part of the neck were detected (arrow). The primary lesion of the right hypopharynx was not detected with FDG-PET/CT.

A thorough workup for an unknown primary tumor of squamous cell carcinoma would include examinations of the parenchyma with CT, MRI, PET, and of tubular lumens with endoscopy. A highly skilled endoscopist can often detect cancerous lesions with white-light endoscopy alone, but NBI endoscopy provides greater sensitivity for detecting primary tumors and may decrease the likelihood that lesions will be overlooked.

With NBI endoscopy, cancers of the head and neck can be identified more readily than with conventional white-light endoscopy. Muto et al[10] have reported that NBI can be used to detect superficial cancers of the oropharynx and hypopharynx. Watanabe et al[11] have reported that NBI endoscopy provides high sensitivity and specificity for the diagnosis of superficial laryngeal cancers based on abnormalities of the intraepithelial microvasculature. Hayashi et al[12] have reported NBI endoscopy can be used to detect unknown primary cancers that have metastasized to cervical lymph nodes.

NBI endoscopy is a less invasive examination and is cost-effective. Furthermore, NBI endoscopy provides high sensitivity for detecting abnormal lesions.

Our study supports the usefulness of NBI endoscopy for detecting mucosal lesions. Our findings suggest that the likelihood of detecting unknown primary cancers increases when directed biopsies with NBI laryngoscopy and PET are added to classic workups.

CONCLUSIONS

Both PET and NBI endoscopy are useful for detecting unknown primary tumors of squamous cell carcinoma metastasizing to cervical lymph nodes.

REFERENCES

1. Coker DD, Casterline PF, Chambers RG, Jaques DA. Metastases to lymph nodes of the head and neck from an unknown primary site. Am J Surg 1977;134:517–522.
2. Gluckman JL, Robbins KT, Fried MP. Cervical metastatic squamous carcinoma of unknown or occult primary source. Head Neck 1990;12:440–443.
3. Nguyen C, Shenouda G, Black MJ, Vuong T, Donath D, Yassa M. Metastatic squamous cell carcinoma to cervical lymph nodes from unknown primary mucosal sites. Head Neck 1994;16:58–63.
4. Mendenhall WM, Million RR, Cassisi NJ. Squamous cell carcinoma of the head and neck treated with radiation therapy: the role of neck dissection for clinically positive neck nodes. Int J Radiat Oncol Biol Phys 1986;12:733–740.
5. Righi PD, Sofferman RA. Screening unilateral tonsillectomy in the unknown primary. Laryngoscope 1995;105(5 Pt 1):548–550.
6. Rusthoven KE, Koshy M, Paulino AC. The role of fluorodeoxyglucose positron emission tomography in cervical lymph node metastases from an unknown primary tumor. Cancer 2004;101: 2641–2649.
7. Roh JL, Kim JS, Lee JH, et al. Utility of combined (18)F-fluorodeoxyglucose-positron emission tomography and computed tomography in patients with cervical metastases from unknown primary tumors. Oral Oncol 2009;45:218–224.
8. Cianchetti M, Mancuso AA, Amdur RJ, et al. Diagnostic evaluation of squamous cell carcinoma metastatic to cervical lymph nodes from an unknown head and neck primary site. Laryngoscope 2009;119:2348–2354.
9. Ugumori T, Muto M, Hayashi R, Hayashi T, Kishimoto S. Prospective study of early detection of pharyngeal superficial carcinoma with the narrowband imaging laryngoscope. Head Neck 2009;31:189–194.
10. Muto M, Nakane M, Katada C, et al. Squamous cell carcinoma in situ at oropharyngeal and hypopharyngeal mucosal sites. Cancer 2004;101:1375–1381.
11. Watanabe A, Taniguchi M, Tsujie H, Hosokawa M, Fujita M, Sasaki S. The value of narrow band imaging endoscope for early head and neck cancers. Otolaryngol Head Neck Surg 2008;138: 446–451.
12. Hayashi T, Muto M, Hayashi R, et al. Usefulness of narrowband imaging for detecting the primary tumor site in patients with primary unknown cervical lymph node metastasis. Jpn J Clin Oncol 2010;40:537–541.

頭頸部外科　21 (2)：185～190，2011

副耳下腺に発生した粘表皮癌の1例

鈴木健介[1)]　篠崎　剛[1)]　林　隆一[1)]
海老原　充[1)]　宮崎眞和[1)]　大幸宏幸[1)]
斎川雅久[1)]　藤井誠志[2)]

要旨：副耳下腺は主耳下腺より独立して耳下腺前部および咬筋上部に位置する異所性の唾液腺である。副耳下腺の出現する割合は成人の約20～70%と報告されているが，そこから発生する腫瘍は比較的まれである。症例は66歳男性。5年前から左頬部腫瘤を自覚していたが，徐々に増大傾向にあるため近医を受診した。同院で切開生検が施行され，粘表皮癌の診断にて当科を紹介されて受診した。左頬部皮下に34×23mmの腫瘤を認め，画像所見などから副耳下腺由来の悪性腫瘍を疑い，手術を施行した。副耳下腺腫瘍における悪性腫瘍の割合は主耳下腺のそれより高く，頬部皮下に発生する腫瘍は，副耳下腺腫瘍の可能性を考慮する必要がある。
キーワード：副耳下腺，粘表皮癌，頬部腫瘤

Summary **Mucoepidermoid carcinoma arising in the accessory parotid gland: Case report:**
Kensuke Suzuki[1)], Takeshi Shinozaki[1)], Ryuichi Hayashi[1)], Mitsuru Ebihara[1)], Masakazu Miyazaki[1)], Hiroyuki Daiko[1)], Masahisa Saikawa[1)] and Satoshi Fujii[2)]. [1)] Division of Head and Neck Surgery, National Cancer Center Hospital East, [2)] Pathology Division, Research Center for Innovative Oncology, National Cancer Center Hospital East

We describe a 66-year-old man with mucoepidermoid carcinoma arising in the accessory parotid gland. A painless mass in the left cheek had been gradually growing for five years. The patient was referred to our hospital after an incisional biopsy at another hospital indicated a diagnosis of mucoepidermoid carcinoma. Both CT and MRI showed a solid, 18×14 mm tumor lying on the masseter muscle, but which did not affect the parotid gland. In light of the clinical background in addition to the radiological and histological findings, mucoepidermoid carcinoma of the accessory parotid gland was suspected. The tumor was surgically removed through a midcheek incision. The buccal branch of the facial nerve and Stensen's duct were involved in the tumor and were sacrificed. The tumor was composed of mucous and epidermoid cells leading to a pathological diagnosis was low-grade mucoepidermoid carcinoma. Slight paresis of the buccal branches resolved two months after surgery. The patient has remained free of recurrence during seven months of follow-up.

The accessory parotid gland is found in 20-70% of individuals and it comprises salivary tissue that is separated from the main parotid gland and lies on the masseter muscle. However, accessory parotid tumors are rare. The frequency of malignant accessory parotid gland tumors is higher than that of malignancies of the main parotid gland tumor, the reported frequency of which is 42-52%. Although the incidence of accessory parotid gland tumors is low, the possibility of such tumors should be considered in a differential diagnosis of a cheek mass.

Key words: accessory parotid gland, mucoepidermoid carcinoma, cheek mass

[Received Mar. 18, 2011, Accepted Jun. 25, 2011]

[1)] 国立がん研究センター東病院頭頸科
[2)] 国立がん研究センター東病院臨床開発センター臨床腫瘍病理部
[平成23年3月18日受付，平成23年6月25日受理]

はじめに

副耳下腺は主耳下腺より独立して耳下腺前部および咬筋上部に位置する異所性の唾液腺である[1-6]。副耳下腺の出現する頻度は成人の約20～70%と報告によりさまざまであるが[1,2,7,8]，そこから発生する腫瘍は比較的まれである[9,10]。今回われわれは副耳下腺に発生した粘表皮癌の1例を経験したので若干の文献的考察を加えて報告する。

症　例

患者：66歳男性。

主訴：左頬部の腫脹。

既往歴：高脂血症。

家族歴：特記すべきことなし。

現病歴：5年前から左頬部腫瘤を自覚していたが，徐々に増大傾向にあるため2010年4月に近医耳鼻咽喉科を受診した。同院で切開生検が施行され，粘表皮癌との診断にて，同年6月に当科を紹介されて受診した。

初診時現症：左頬部に22mmの切開生検後の瘢痕を認め，皮下に34×23mmの可動性良好な腫瘤が認められた（図1）。顔面神経麻痺は認められなかった。その他，鼻咽腔や喉頭に異常所見は認められず，頸部リンパ節も触知されなかった。

画像検査：頭頸部CTでは左咬筋外側に径18×14mm大の辺縁不整な結節病変が認められた（図2）。CT上は耳下腺浅葉が前方に伸びている所見はみられず独立した病変が考えられた。頭頸部領域に有意な腫大リンパ節は認められなかった。MRIでも同様の所見であったが，咬筋への浸潤を疑う所見が認められた。また患側耳下腺の萎縮が認められた（図3）。

経過：前医の生検結果や腫瘍の局在部位から，副耳下腺原発の悪性腫瘍を考え，2010年7月に手術を施行した。左頬部の瘢痕周囲を切開し，腫瘍直上からのアプローチを行った。腫瘍は咬筋上に存在しており，耳下腺との連続性は認めなかった。顔面神経頬筋枝およびステノン管は同定可能であったが，これらは腫瘍に巻き込まれており，温存不可能と考え合併切除した（図4）。深部では咬筋を一部腫瘍につけて切除した。ステノン管の切除範囲が大きく，MRIで耳下腺の萎縮を認めていたこともあり，ステノン管の再建は行わなかった。肉眼的には，15

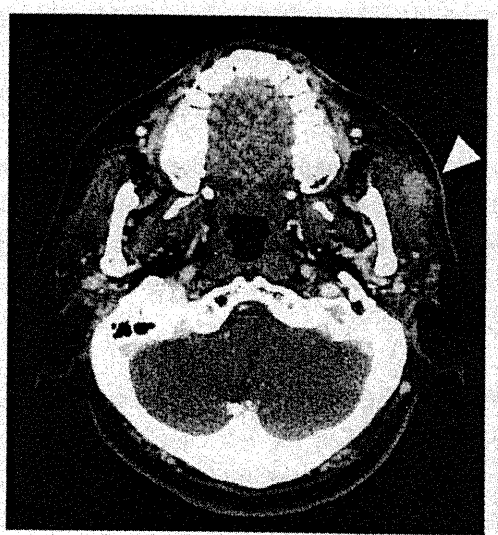

図2　CT所見
左咬筋外側に径18×14mm大の辺縁不整な結節病変を認めた（矢頭）。

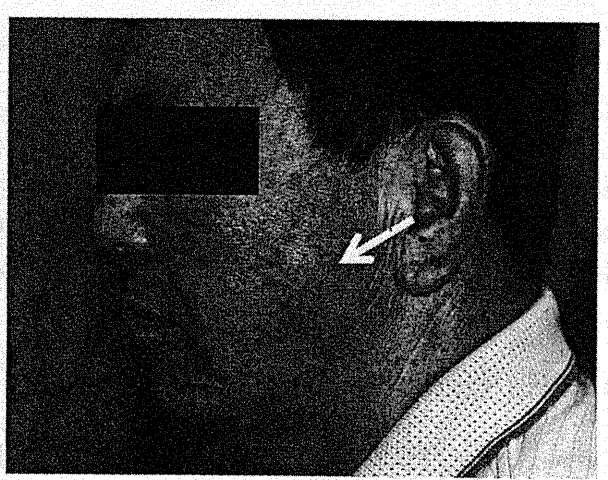

図1　初診時所見
左頬部皮下に34×23mmの可動性良好な腫瘤を認めた（矢印）。

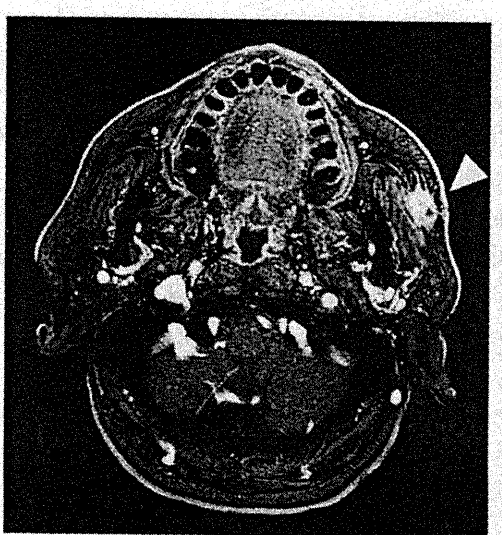

図3　MRI所見（T1強調水平断造影）
咬筋への浸潤を疑う所見を認めた（矢頭）。

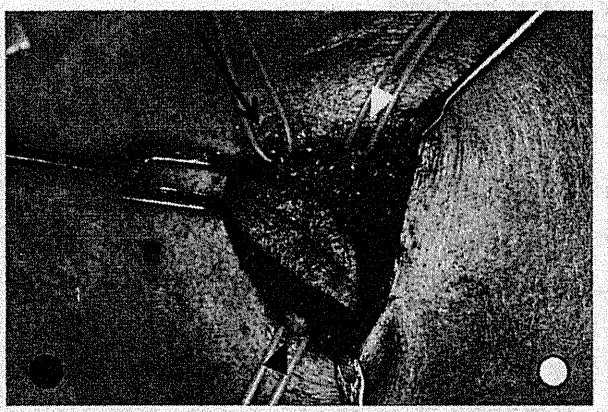

図 4　手術所見
顔面神経頬筋枝およびステノン管は腫瘍に巻き込まれていた（矢印：顔面神経頬筋枝，白矢頭：ステノン管口腔側，黒矢頭：ステノン管耳下腺側）。○：頭側。●：尾側。

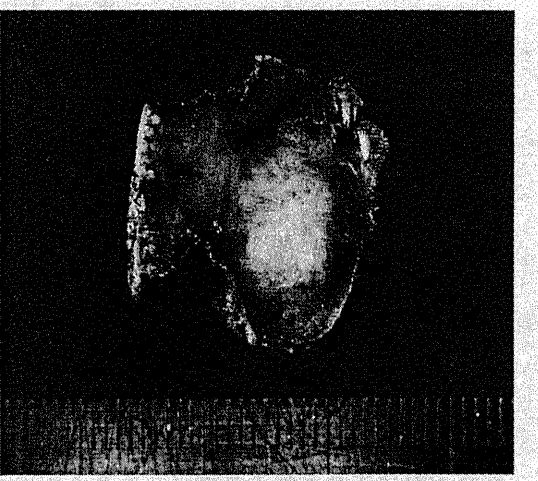

図 5　摘出標本
15×15mm 大の灰黄白色充実性腫瘍を認めた。

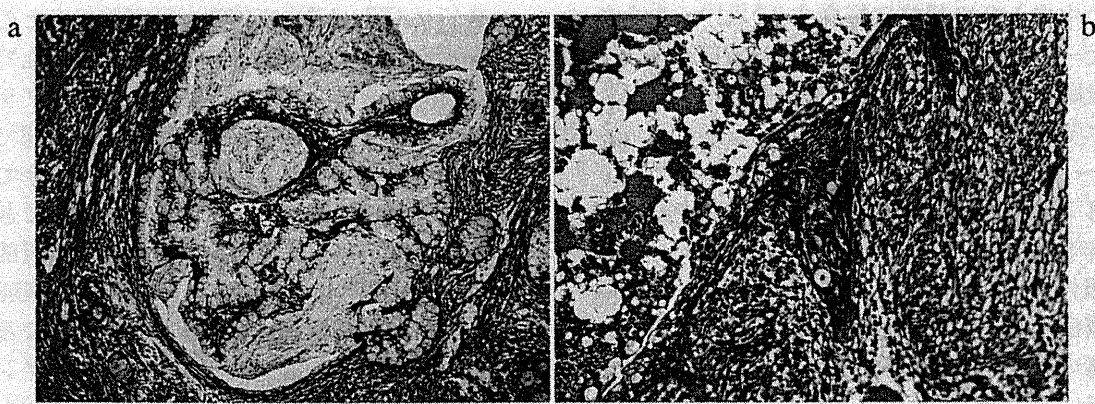

図 6　病理組織検査所見
a（HE 染色）：粘液細胞からなる腺管を認める。
b（HE 染色）：嚢胞の辺縁に扁平上皮細胞からなる充実性胞巣を認める。

×15mm 大の灰黄白色充実性腫瘍を認めた（図 5）。

病理組織学的所見：摘出した腫瘍の HE 染色標本では，粘液細胞からなる腺管構造を認め（図 6a），嚢胞の辺縁には扁平上皮細胞からなる充実性胞巣を認めた（図 6b）。中間細胞の存在や，角化像も散見された。腫瘍組織の周囲にはリンパ濾胞を伴う慢性炎症像をみる非腫瘍性唾液腺組織を認めた。以上の所見より，mucoepidermoid carcinoma と診断し，非腫瘍性組織の存在から，副耳下腺に発生した粘表皮癌として矛盾はないと考えられた。悪性度は Goode らの分類（表 1）[11] によると，嚢胞成分の割合が 20％未満で，その他の病理組織学的特徴を満たさないことから Score は 2 点，low grade と診断した。切除断端は陰性であった。病理組織学的には，ステノン管および顔面神経頬筋枝への明らかな腫瘍細胞の浸潤は認めなかった。

術後は耳下腺の腫脹や疼痛を認めず，術後 7 日目に退院となった。左頬筋枝領域に軽度の顔面神経麻痺を認めたが 2 か月で改善した。現在術後 7 か月で再発なく経過良好である。

表 1　粘表皮癌の悪性度分類 [15]

病理組織学的特徴	Point value
嚢胞成分の割合が 20％未満	2 点
神経浸潤	2 点
壊死	3 点
核分裂像（4 以上 /10HPF）	3 点
退形成	4 点
Grade	**Point score**
Low	0～4
Intermediate	5～6
High	7 以上

HPF：high-power fields

表 2　本邦における副耳下腺粘表皮癌症例

報告者	報告年	年齢	性	側	腫瘍径（mm）	切開法	追加治療	合併症
Yoshihara ら[17]	1999	9	女	右	約 20	S 字切開	なし	なし
篠ら[8]	2007	34	女	右	25	S 字切開	術後 RT66Gy	不明
榎本ら[18]	2008	52	男	右	25×15×12	腫瘍直上	なし	不明
自験例	2011	66	男	左	15×15	腫瘍直上	なし	頬筋枝麻痺（2か月で回復）

考　察

副耳下腺は主耳下腺より独立して耳下腺前部および咬筋上部に位置する異所性の唾液腺であり[1-6]，通常，ステノン管に注ぐ固有の副管（排泄管）を持つ。発生部位は鼻翼と上口唇の中間点と耳珠を結んだ線の中央 1/3 の部位に好発する[8,12,13]。大きさは米粒大～母指頭大で，組織学的には漿液腺優位で耳下腺組織に類似しているが，粘液腺の割合が耳下腺に比べ多い[12,14]。副耳下腺の出現する頻度は成人の約 20 ～ 70%と報告によりさまざまである[1,2,7,8]。

副耳下腺腫瘍の耳下腺腫瘍全体に占める割合は 1960 年代に 7.7%とする報告がなされたが[13]，その後の報告では 0.7 ～ 2.2%とされており，比較的まれな腫瘍と考えられる[9,10]。耳下腺腫瘍における悪性腫瘍の頻度が 25%であるのに対して，副耳下腺腫瘍では 42 ～ 52%とより高率に悪性腫瘍が発生する[2,9,10]。良性腫瘍としては多形腺腫が，悪性腫瘍では粘表皮癌が多い[2,10]。耳下腺腫瘍に比べると，副耳下腺腫瘍における粘表皮癌の占める割合は高いとされるが，これは副耳下腺に粘液腺が多いことが一因であると推察されている[14]。

粘表皮癌は唾液腺または気管粘膜腺に発生する腫瘍で，組織学的には粘液産生細胞，扁平上皮細胞（類上皮細胞），中間細胞から構成される。好発部位は大唾液腺が 53%で，その中でも耳下腺が圧倒的に多い（45%）。以下顎下腺（7%），舌下腺（1%）と続き，残りは小唾液腺に発生する。発症平均年齢は 40 ～ 50 歳で，男女比 2：3 で女性に多い[15]。病理組織学的に low grade，intermediate grade，high grade に分類され，5 年生存率はそれぞれ 95%，80 ～ 90%，25 ～ 30%と報告されている[16]。1991 年の WHO 分類で，mucoepidermoid tumor が mucoepidermoid carcinoma として分類されて以降，われわれが検索し得た限り，本邦での副耳下腺原発粘表皮癌は本症例を含めて 4 例の報告があった[8,17,18]（表 2）。腫瘍径はいずれも 15 ～ 25mm 大で，手術のアプローチ法としては S 字切開あるいは腫瘍直上の皮膚切開が選択されていた。1 例で腫瘍の残存が疑われたため術後照射が施行された[8]。大唾液腺原発の悪性腫瘍と同様に，high grade のものや進行した症例に対しては術後照射が適応になる[5]。

副耳下腺腫瘍の診断に関しては，まず解剖学的位置からその可能性を疑うことが大切である。画像検査では CT，MRI で腫瘍と耳下腺組織との間に連続性がないことが必要条件である。その上で唾液腺造影，シアロ CT，あるいは MR-シアログラフィーなどでステノン管に流入する排泄管が確認できれば確定診断は可能である。確認できない場合であっても副耳下腺由来の腫瘍であることを否定できない。穿刺吸引細胞診は唾液腺組織の確認や，質的診断に有用である[8,14]。最終的には臨床所見や病理組織学的所見も踏まえて確定診断を行うことになる。本症例においては，手術所見で腫瘍からステノン管に注ぐ固有の排泄管は確認できなかったが，腫瘍の解剖学的位置および病理組織所見より，副耳下腺原発と考えた。

頬部に発生する腫瘍として鑑別すべき疾患に，神経鞘腫，皮様嚢腫，脂肪腫などの良性腫瘍，リンパ節，咬筋原発の腫瘍，耳下腺腫瘍，ステノン管原発腫瘍，小唾液腺由来の腫瘍，迷入唾液腺由来の腫瘍などが挙げられる。病理組織学的所見から，腫瘍の組織亜型は鑑別できるが，後 4 者の発生由来組織については，下記の検討により同定できる。耳下腺腫瘍は腫瘍と耳下腺との連続性を認めなかったこと，ステノン管原発腫瘍は病理組織学的にステノン管への明らかな腫瘍細胞の浸潤を認めなかったことより否定された。また腫瘍の存在部位が咬筋の外側であったことから小唾液腺原発ではないと考えられた。迷入唾液腺は鰓裂の遺残が原因であり，その被覆上皮から発生するとされており，前頸部下方に局在することが多く，頬部への発生はきわめてまれである。また，多くは唾液腺皮膚瘻孔の形をとり[12]，否定的であると考えられた。

副耳下腺腫瘍の治療は手術が第一選択となる。手術に際しては，腫瘍へのアプローチ法と耳下腺，咬

筋，顔面神経およびステノン管の処置が問題となる。アプローチ法としては，腫瘍直上の皮膚切開，口内法，耳下腺手術に準じたS字切開が挙げられる[4,5]。腫瘍直上の皮膚切開の利点は皮切が短く，剥離範囲が少なくてすむことが挙げられるが，整容上の問題があり，悪性腫瘍であった場合の周囲組織の十分な切除に対しては不十分なことが多い[4]。また顔面神経の同定が時として困難で，術後の顔面神経麻痺も少なくない[10]。口内法は整容面で優れるため，咬筋前方に位置する小さな腫瘍に対しては適応となり得るが，視野が悪く，顔面神経麻痺などの副損傷の可能性が高い。また実際には副耳下腺腫瘍は咬筋表層にあることが多いため，口腔内からのアプローチは困難が伴い，ほとんど行われていない[14]。

耳下腺手術に準じたS字切開は皮切が長く比較的広範囲の剥離を必要とするが，これらのアプローチ法の中では視野が最も良好で，副損傷のリスクが低く，多くの報告でS字切開が推奨されている。Johnsonら[10]は腫瘍直上の皮膚切開により摘出術を施行した10例中4例に顔面神経麻痺を認めたのに対し，S字切開13例中麻痺は1例も生じなかったと報告している。顔面神経分枝の同定方法としては耳下腺前縁で同定する方法と，顔面神経本幹を確認し，そこから末梢に向かって分枝を剥離していく方法がある。前述の通り副耳下腺腫瘍は悪性腫瘍の頻度が高く，確実な切除のためには良好な術野を得ることが必要である。良性の小さな腫瘍に対しては，耳下腺前縁で分枝を同定する方法で十分対応可能であるが，大きい腫瘍，悪性腫瘍に対しては本幹からのアプローチも考慮すべきと考えられる。本症例においては前医で切開生検が施行されており，生検による播種の可能性を考えると皮膚も合併切除する必要があり，必然的に腫瘍直上からのアプローチとなった。

ステノン管の温存は，耳下腺の機能温存や術後の唾液瘻を防止するために重要である。しかし，本症例のように悪性腫瘍であり，ステノン管に浸潤が疑われる場合は合併切除すべきである。切除後ステノン管を再建するか否かについては，残存耳下腺組織量と管の切除範囲で決定する。すなわち耳下腺組織が十分残存し，管の切除範囲が小さい場合や，管の中枢側が十分残存していれば管の再建術を試みるべきである[4,7]。本症例のように管の切除範囲が比較的大きく再建術が困難なケースでは管を中枢側で結紮し，耳下腺の萎縮を待ち機能を廃絶せざるを得ない場合もある。本症例では経過が長く，耳下腺の萎縮もあり，術後耳下腺の腫脹や疼痛などは認めなかった。

自験例においては，低悪性度であり，切除断端は陰性であったため追加治療は行わなかった。今後も慎重に経過観察を行う予定である。

まとめ

副耳下腺に発生した粘表皮癌の1例を報告した。副耳下腺腫瘍の診断や手術法，粘表皮癌について文献的考察を加えた。耳下腺前方の頬部皮下に発生する腫瘍は，副耳下腺腫瘍の可能性を考慮する必要があると考える。

本稿の要旨は第21回日本頭頸部外科学会（2011年1月27日，宇都宮）にて報告した。

文　献

1) Frommer J: The human accessory parotid gland, its incidence, nature, and significance. Oral Surg 43：671-676, 1977.
2) Stenner M, Preuss SF, Httenbrink HB, et al: Accessory parotid gland lesions: case report and review of literature. Eur Arch Otorhinolaryngol 265：1135-1138, 2008.
3) Hamano T, Okami K, Sekine M, et al: A case of accessory parotid gland tumor. Tokai J Exp Clin Med 29：131-133, 2004.
4) 吉原俊雄：副耳下腺・ステノン管の手術．耳鼻臨床，99：80-81，2006.
5) Derrick T. Lin, George L. Coppit, Brian B. Burkey, et al: Tumors of the accessory lobe of the parotid gland: A 10-year experience. Laryngoscope 114：1652-1655, 2004.
6) Lewkowicz A, Levy Y, Zeltser R, et al: Accessory parotid gland masses. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 89：610-612, 2000.
7) 高橋光明，高原　幹，松井玲子，他：副耳下腺腫瘍に対する手術法．頭頸部外科，7：1-6，1997.
8) 篠　美紀，大氣誠道，大池信之，他：頬部に発生した粘表皮癌の1症例．耳喉頭頸，79：861-865，2007.
9) 倉田奈都子，野口佳裕，杉本太郎，他：副耳下腺から発生した多形腺腫例．耳鼻臨床，102：121-125，2009.
10) Johnson FE, Spiro RH: Tumors arising in accessory parotid tissue. Am J Surg 138：576-578, 1979.
11) Goode RK, Auclair PL, Ellis GL: Mucoepidermoid carcinoma of the major salivary glands: clinical and histocytologic analysis of 234 cases with evaluation of grading criteria. Cancer 82：1217-1224, 1998.
12) 草野太郎，利根川守，林　稔，他：副耳下腺に発生したPleomorphic Adenomaの1例．日形会誌，29：97-101，2009.
13) Perzik SL, White LL: Surgical management of preauricular tumors of the accessory parotid apparatus. Am J Surg 112：498-503, 1966.
14) 長谷川達央，内田真哉，松波達也：まれな頬部腫瘍の2例―副耳下腺腫瘍とステノン管原発腫瘍―．耳鼻臨床，97：245-249，2004.
15) Auclair PL, Goode RK, Gnepp DR, et al: Salivary

gland neoplasms: general considerations, Surgical pathology of the salivary glands (ed by Ellis GL, Auclair PL, Gnepp DR), 135-164, WB Saunders, Philadelphia, 1991.
16) Seifert G, Brocheriou C, Cardesa A, et al: WHO international histological classification of tumours. Tentative histological classification of salivary gland tumours. Pathol Res Pract 186 : 555-581, 1990.
17) Yoshihara T, Suzuki S, Nagao K: Mucoepidermoid carcinoma arising in the accessory parotid gland. Int. J. Pediatr. Otorhinolaryngol 48 : 47-52, 1999.
18) 榎本由貴乃，梅本尚可，池田涼子，他：頬部に生じた粘表皮癌（mucoepidermoid carcinoma）の1例. Skin Surgery, 17 : 87-89, 2008.

分担研究者　岩瀬哲

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Iwase S, Yamamoto D, Kuroda Y, Kawaguchi T, Kitamura K, Odagiri H, Teramoto S, Akazawa K, Nagumo Y.	Phase II trial of preoperative chemotherapy for breast cancer: Japan Breast Cancer Research Network (JBCRN)-02 trial.	Anticancer Res.	31(4)	1483-7	2011