treated at 80 mg/m^2 experiencing febrile neutropenia. All four patients whose creatinine clearance was decreased to <60 mL/min after the first cycle of chemotherapy developed febrile neutropenia lasting more than 4 days. Of these, two each were treated at S-1 dose levels of 60 and 80 mg/m^2.

The incidence of grade 3 or 4 mucositis and dysphagia increased with increasing dose and occurred in all patients treated at 80 mg/m^2, indicating that S-1 at 80 mg/m^2 was intolerable in this treatment. One patient who achieved a complete response after completion of CRT experienced pharyngeal stricture as an adverse event, declined surgical treatment and is still alive without any evidence of recurrence. Fifteen patients (71%) received nutritional support via a feeding tube, with a median feeding tube duration of 199 days and 1-year feeding tube dependence of 14%.

Pharmacokinetic analysis of S-1. Pharmacokinetic data on administration of S-1 as oral capsules (day -4) and suspensions via a feeding tube (day -2) were available for 16 patients (Table 4). Tmax values for tegafur, 5-FU, CDHP and Oxo were significantly lower with the suspension than oral capsules, while Cmax values for tegafur, CDHP and Oxo were significantly higher. However, the Cmax for 5-FU and AUC of all parameters did not significantly differ by administration route. Moreover, although no clear relationship was seen between any parameter and adverse events, a weak correlation was seen between the AUC of tegafur and the rate of neutropenia ($P = 0.106$).

Treatment outcomes. Of the 21 patients treated with CRT, 18 experienced a complete response. Two additional patients who had been diagnosed with residual neck lymph node metastasis underwent salvage neck dissection, and pathology revealed no residual tumor. With a median follow up of 49 months (range,

Table 2. Overall toxicity (n = 21)

Toxicity	No. patients (Grade)				% of patients	
	1	2	3	4	Grade 1–2	Grade 3–4
Hematological toxicity						
Leucopenia	8	4	3	5	57	38
Neutropenia	5	2	3	5	33	38
Febrile neutropenia	–	–	6	0	–	29
Anemia	10	6	3	2	76	24
Thrombocytopenia	10	2	2	1	57	14
Non-hematological toxicity						
Nausea	4	4	5	0	38	24
Vomiting	8	2	0	0	48	0
Anorexia	4	3	1	0	33	5
Fatigue	5	6	1	0	52	5
Mucositis	4	1	14	1	24	71
Dysphagia	3	1	15	0	19	71
Dermatitis	3	12	3	0	71	14
Diarrhea	1	2	2	0	14	10
Elevated bilirubin	2	1	0	0	14	0
Elevated AST	2	4	0	0	29	0
Elevated ALT	3	4	0	0	33	0
Elevated creatinine	2	1	0	0	14	0
Xerostomia	7	12	0	0	90	0
Salivary change	3	9	0	0	57	0

ALT, alanine transaminase; AST, aspartate transaminase.

Table 3. Grade 3 or 4 toxicity by S-1 dose level

	Grade 3 or 4 toxicity					
	S-1 dose level: 40 mg/m^2 per day (n = 3)		S-1 dose level: 60 mg/m^2 per day (n = 12)		S-1 dose level: 80 mg/m^2 per day (n = 6)	
	No. patients	%	No. patients	%	No. patients	%
Hematological toxicity						
Leucopenia	1	33	5	42	2	33
Neutropenia	1	33	4	33	3	50
Febrile neutropenia	0	0	3	25	3	50
Anemia	0	0	4	33	1	17
Thrombocytopenia	0	0	2	17	1	17
Non-hematological toxicity						
Anorexia	0	0	3	25	2	33
Mucositis	1	33	7	58	6	100
Dysphagia	1	33	8	67	6	100
Dermatitis	0	17	2	17	1	17
Diarrhea	0	1	2	17	0	0

Table 4. Phamacokinetics of S-1 by the administration route (n = 15)

	Administration route			
	Oral (n = 15)	Feeding tube (n = 15)	Ratio	P-value
Tegafur				
T_{max} (min)				
Median	126.0	65.0	0.50	0.0012
Range	30–483	28–246	0.13–1.03	
C_{max} (ng/mL)				
Median	1571.0	1841.1	1.11	0.0009
Range	729–2373	804–2658	0.95–1.49	
AUC (μg × min/mL)				
Median	1416.6	1421.8	0.99	0.64
Range	573.2–3888.1	408.1–4306.5	0.71–1.16	
5-FU				
T_{max} (min)				
Median	239.0	121	0.78	0.013
Range	60–483	59–246	0.26–2.00	
C_{max} (ng/mL)				
Median	120.1	107.4	1.00	0.56
Range	26.5–188.6	29.4–176.5	0.73–1.47	
AUC (μg × min/mL)				
Median	33.6	29.4	0.94	0.63
Range	12.5–54.2	16.8–48.7	0.64–1.34	
CDHP				
T_{max} (min)				
Median	120.0	62	0.50	0.0009
Range	60–483	30–246	0.12–1.03	
C_{max} (ng/mL)				
Median	183.8	205.2	1.22	0.04
Range	72.0–358.8	101.5–584.6	0.71–1.78	
AUC (μg × min/mL)				
Median	66.0	65.7	1.03	0.15
Range	28.6–83.3	37.9–115.0	0.83–1.42	
Oxo				
T_{max} (min)				
Median	120.0	118.0	0.51	0.0005
Range	90–243	58–122	0.26–1.01	
C_{max} (ng/mL)				
Median	26.2	35.0	1.51	0.041
Range	3.8–60.1	11.5–212.4	0.48–3.58	
AUC (μg × min/mL)				
Median	7.5	9.2	1.39	0.21
Range	1.9–18.7	3.1–57.9	0.68–4.71	

5-FU, 5-fluorouracil; CDHP, 5-chloro-2,4-dihydroxypyridine; Oxo, potassium oxonate.

doi: 10.1111/j.1349-7006.2010.01799.x

44–62 months), local recurrence only, distant metastasis and both local recurrence and distant metastasis were observed in four, four and one patient, respectively. A total of nine patients died, five from local recurrence, three from disease progression of distant metastases and one from progression of residual neck lymph node. Estimated rates of 3-year locoregional PFS, PFS and OS were 75%, 48% and 62% respectively.

Discussion

In this phase I study of S-1 in combination with CRT in patients with unresectable locally advanced SCCHN, MTD of S-1 was 80 mg/m^2 per day. S-1 at 60 mg/m^2 per day for 14 days with concurrent CRT was well tolerated, and provided promising activity in these patients. Administration of S-1 as a suspension via a feeding tube or by oral capsule can be considered therapeutically interchangeable.

S-1 contains CDHP, which inhibits DPD. As 50% of CDHP is excreted in the urine, renal dysfunction might directly affect the inhibitory effect on DPD and lead to increased 5-FU concentrations.[10] Although the current standard dosing regimen for cisplatin is a single intravenous infusion of 100 mg/m^2, this regimen has a higher incidence of renal toxicities than lower doses. We therefore selected divided doses of the CDDP to reduce renal toxicity.

The incidence and severity of both hematological and non-hematological toxicities increased in accordance with the increasing dose. At a dose level of S-1 80 mg/m^2, half experienced febrile neutropenia lasting more than 4 days and all developed grade 3 or 4 mucositis, indicating that the dose of S-1 80 mg/m^2 was intolerable. The MTD was therefore set at 80 mg/m^2 per day of S-1. Two patients treated with S-1 at 60 mg/m^2 experienced grade 3 diarrhea. One of these patients did not receive anti-diarrhea drugs until the development of grade 3 diarrhea and infection, which was regarded as a DLT. The second experienced grade 3 diarrhea following grade 3 febrile neutropenia. Because the administration of S-1 had finished 1 week previously, this diarrhea was not related to S-1 but to the neutropenia or antibiotic drugs, and was not regarded as a DLT. However, this patient experienced grade 3 febrile neutropenia for more than 4 days, which was regarded as a DLT. Three patients experienced grade 3 febrile neutropenia for more than 4 days at S-1 60 mg/m^2. In other words, four of 12 patients receiving S-1 at 60 mg/m^2 experienced a DLT. Another experienced febrile neutropenia lasting 2 weeks despite the use of granulocyte colony-stimulating factor and was subsequently diagnosed with myelodysplastic syndrome on bone marrow study, indicating that this patient was inappropriate for evaluation of the recommended dose of S-1 in combination with CRT.

In the present study, all four patients whose creatinine clearance was decreased to <60 mL/min after the first cycle of chemotherapy developed febrile neutropenia lasting more than 4 days, and two of these were treated at a dose level of S-1 60 mg/m^2. The higher incidence of febrile neutropenia in the present study is therefore likely related to decreased creatinine clearance. Grade 1 creatinine or creatinine clearance of more than 50 mL/min had to have occurred by the time of the next cycle, while dose modification according to creatinine clearance was not performed. Dose modification according to creatinine clearance could have reduced or prevented these toxicities. Based on these results, we are convinced of the need for dose modification according to creatinine clearance in the treatment with S-1. In this regard, recent studies of S-1 have indeed used dose modification according to creatinine clearance.[11,12]

Although a slightly higher incidence of DLT was observed at this level, suggesting that it was not suitable for consideration as the recommended dose (RD), these toxicities might have been reduced by dose modification according to creatinine clearance and appropriate anti-diarrhea medication. Furthermore, this dose level was well tolerated in the other eight patients, with acceptable toxicity. We therefore established S-1 at 60 mg/m^2 per day as the RD. The clinically appropriate dose of S-1 in combination with CRT can only be determined in phase II trials.

Previous studies demonstrated a significant correlation between 5-FU plasma concentration, in particular 5-FU AUC, and therapeutic activity and toxicity.[13–17] Moreover, two phase I studies of S-1 showed a significant correlation between diarrhea grade and 5-FU AUC,[17,18] one of which additionally demonstrated a significant correlation between diarrhea grade and 5-FU Cmax.[18]

In the present study, pharmacokinetic analysis revealed that the Tmax of all parameters, including tegafur, 5-FU, CDHP and Oxo, were significantly lower on administration as a suspension, whereas the Cmax of tegafur, CDHP and Oxo were significantly higher than with oral capsules, indicating that the absorption of S-1 is higher in suspension. However, the Cmax for 5-FU and AUC of all parameters did not significantly differ by the administration route, indicating that the two routes can be considered therapeutically interchangeable.

In the present study, 18 of 21 patients achieved a complete response, while an additional two patients who had been pathologically diagnosed revealed no residual tumor on salvage neck dissection, with 3 years OS of 61.9%. Considering the small number of patients, these findings indicate that this regimen may provide promising activity in patients with unresectable locally advanced SCCHN.

Severe mucositis in locally advanced SCCHN patients receiving CRT frequently leads to dysphasia and weight loss. These patients may require adequate nutritional support to avoid treatment interruption, which can adversely impact the treatment outcome. However, although the relative benefits of prophylactic versus therapeutic PEG feeding tube placement are controversial, we are convinced that prophylactic PEG feeding tube replacement is indispensable to the completion of these high-intensity treatments. Although all PEG feeding tube replacements in this study were performed by pull techniques, few severe complications and no tumor seeding were observed. Furthermore, despite the high incidence of toxicities, all but one patient completed the CRT, indicating the likely usefulness of a prophylactic PEG feeding tube.

Feeding tube placement prior to CRT due to pre-existing dysphagia and advanced T stage are associated with prolonged feeding tube dependence.[19] In the present study, 71% of patients received nutritional support via a feeding tube, with a median feeding tube duration of 199 days and a 1-year feeding tube dependence of 14%. Additionally, one patient who achieved a complete remission subsequently experienced pharyngeal stricture after the completion of CRT, indicating that all patients should receive evaluation by a speech-language pathologist throughout the course of CRT, swallowing exercises, even though a feeding tube is in place, and rapid rehabilitation.

Concern has been expressed over the considerable ethnic differences in the tolerated doses of S-1. These relate to the varying efficiency rates of conversion of tegafur to 5-FU by CYP2A6 of the CYP450 enzyme system, now identified as the principal enzyme responsible for this conversion process.[20–23] A phase I study of S-1 plus CDDP in Western patients with advanced gastric carcinoma showed that the S-1 dose tolerated by Western patients is lower than that by Japanese patients, but that the AUC of FU appears higher in white rather than Japanese patients in a comparable dose range of S-1.[24] This is mostly attributed to different polymorphisms in the *CYP2A6* gene among Asians and whites. The RD of the present study is likely to be unsuitable for Western patients, and further study

to determine the RD of this combination for these patients is required.

In conclusion, S-1 at 60 mg/m^2 per day for 14 days was well tolerated with concurrent CRT with CDDP. Furthermore, no difference was seen in the pharmacokinetics of S-1 between administration as a suspension and orally as a whole capsule, indicating that these can be considered therapeutically interchangeable. Although these data are preliminary, activity was highly promising, and this approach warrants further investigation. A multicenter phase II study of this approach by the Japan Clinical Oncology Group (JCOG) is ongoing.[11]

Acknowledgment

The authors would like to thank the patients and families who participated in this study, and their colleagues.

Disclosure Statement

The authors have no conflict of interest.

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doi: 10.1111/j.1349-7006.2010.01799.x

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2011;41(4)508–513
doi:10.1093/jjco/hyr012
Advance Access Publication 18 February 2011

A Pilot Study of Post-operative Radiotherapy with Concurrent Chemotherapy for High-risk Squamous Cell Carcinoma of the Cervical Esophagus

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Received November 28, 2010; accepted December 27, 2010

Objective: After complete resection of carcinomas of the head and neck, including carcinoma of the cervical esophagus, the pattern of first failure is more often locoregional than distant metastasis. We retrospectively evaluated the safety and efficacy of the combination of post-operative radiation and concurrent chemotherapy with low-dose cisplatin for high-risk squamous cell carcinoma of the cervical esophagus.
Methods: From 2005 through 2008, 34 patients with previously untreated squamous cell carcinoma of the cervical esophagus underwent cervical esophagectomy with or without laryngectomy. Of these 34 patients, 11 with disease-positive lymph nodes in the upper mediastinum (M1 lymph/Stage IV) confirmed by pathologic examination were enrolled. Patients received radiotherapy (66 Gy in 33 fractions) and concurrent low-dose cisplatin.
Results: Nine patients completed the planned radiotherapy and two or more courses of chemotherapy. Grade 3 toxicities during chemoradiotherapy were leukopenia (36% of patients), neutropenia (18%) and mucositis (9%). At a median follow-up time of 39.5 months, the overall 1- and 3-year survival rates were 91 and 71%, respectively.
Conclusions: The combination of post-operative radiation and concurrent chemotherapy with low-dose cisplatin is well tolerated and has the potential to improve the rates of locoregional control and overall survival in patients with high-risk advanced squamous cell carcinoma of the esophagus.

Key words: cervical esophageal squamous cell carcinoma – post-operative radiotherapy with concurrent chemotherapy – nodal M1 disease

INTRODUCTION

Locally advanced head and neck cancer is optimally treated with multimodal approach, involving resection followed by radiotherapy and concurrent chemotherapy (1). Carcinoma of the cervical esophagus has a poor prognosis, with reported 3- and 5-year survival rates ranging from 18 to 35.4% and from 12 to 33%, respectively (2). We have previously reported on the prognosis, patterns of first failure and significant clinicopathologic factors affecting survival in cases of squamous cell carcinoma of the cervical esophagus (2). In particular, the 3-year survival rate was 0% in patients with metastasis to mediastinal lymph nodes (M1 lymph/Stage IV). We have maintained that multimodal treatment, such as post-operative radiotherapy with concurrent chemotherapy, is essential for the treatment of cervical esophageal carcinoma (2). On the basis of the results of our previous study, we performed a pilot study and retrospectively assessed the toxic

effects and efficacy of the combination of post-operative radiotherapy and concurrent chemotherapy with low-dose cisplatin in selected patients who had squamous cell carcinoma of the cervical esophagus with metastasis to the upper mediastinal lymph nodes (M1 lymph/Stage IV), a factor indicating an extremely poor prognosis.

PATIENTS AND METHODS

Patients Population and Eligibility

From January 2005 through December 2008, 34 patients with previously untreated carcinoma of the cervical esophagus underwent surgical resection at the National Cancer Center Hospital East. The clinical and pathologic characteristics of the 34 patients are shown in Table 1. Pre-operative and post-operative staging was based on the 1997 International Union Against Cancer TNM classification. Cases with metastasis to the mediastinal lymph nodes were classified as M1-lymph disease.

All patients with metastasis to the upper mediastinal lymph nodes (M1 lymph/Stage IV) defined as complete removal of all macroscopic tumor masses were eligible for the study if they met all of the following criteria: histologically confirmed diagnosis of squamous cell carcinoma; age of 18 years or older and 75 years or younger; performance status of 0 or 1 according to the Eastern Cooperative Oncology Group scale; adequate bone marrow, hepatic and renal function; no previous chemotherapy or radiotherapy; and written informed consent provided before recruitment.

Pre-treatment Evaluation

Pre-treatment evaluations in all patients included physical examination, barium-swallow examination, endoscopy with biopsy, ultrasonography of the neck and computed tomography of the neck and chest.

Study Treatment

The protocol required that radiotherapy be performed as soon as satisfactory healing had occurred after surgery. The protocol also called for radiotherapy to start within 8 weeks after surgery.

The treatment consisted of two or three cycles of cisplatin at a dose of 20 mg/m^2 of body surface area on days 1–4, 22–25 and 43–46, repeated every 3 weeks, with concurrent radiotherapy to a total dose of 66 Gy in 33 fractions over 6 weeks.

Because gross tumors were already resected, gross tumor volume was not defined in the case of adjuvant radiotherapy. Clinical target volume (CTV) was defined as the total volume of the surgical bed of the primary tumor plus volumes and metastatic lymph nodes considered at risk of containing microscopic disease. The CTV was further categorized into two volumes: the CTV boost (CTVb), which included the surgical bed of the primary tumor and metastatic lymph nodes, and the CTV subclinical (CTVs), which included the CTVb plus regional lymph nodes (cervical, supraclavicular and superior mediastinum lymph node areas) (Fig. 1). The upper cervical lymph node area (level II) was excluded from the irradiation field if no lymph node metastasis was found in this area. From four to eight beams were applied from various angles to the CTVs to a total dose of up to 46 Gy. A booster dose of 20 Gy was given to the CTVb using multiple fields to shield the spinal cord for a total dose of 66 Gy.

Table 1. Clinical and pathologic characteristics of 34 patients undergoing surgery for squamous cell carcinoma of the cervical esophagus

Variable	No. of patients
Sex	
Female/male	8/26
Tumor location	
Ce/-Ph/-Ut	18/5/10
Ce-Ph-Ut	1
Clinical T status	
T1/2	5/2
T3/4	15/12
Clinical N status	
N0/1	16/18
Clinical M stage	
M0	25
M1 lymph	9
Clinical stage	
I/II/III/IV	4/8/12/10
Larynx	
Preserved	10
Laryngectomy	24
Pathologic T status	
T1/2	6/2
T3/4	17/9
Pathologic N status	
N0	13
N1	21
Pathologic M status	
M0	20
M1lymph/1 organ	13/1
Pathologic stage	
I/II/III/IV	2/10/8/14
Completeness of resection	
R0/1	30/3
R2	1

Ce, cervical esophagus; Ph, hypopharynx; Ut, upper third of thoracic esophagus.

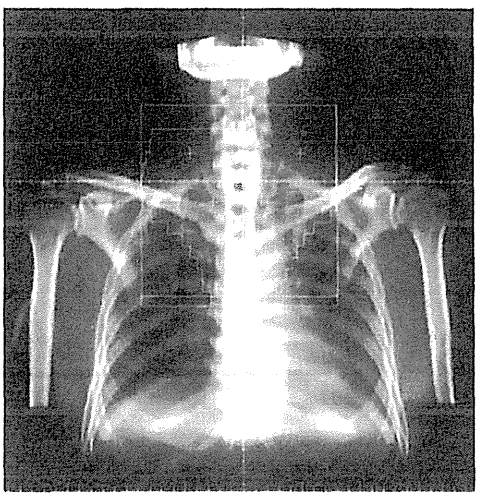

Figure 1. Planning film demonstrating a representative treatment field for post-operative radiation in a patient with metastases to the upper mediastinal lymph nodes.

Toxicity Assessment and Dose Modification

Toxicity assessments, including complete blood cell counts and serum chemistry profiles, were performed weekly during chemoradiotherapy and every 3 weeks during the protocol study. Toxicity assessments for all patients were performed with the National Cancer Institute Common Toxicity Criteria (version 3.0). The dose was reduced by 20% if any toxicity reached Grade 3.

Follow-up

All patients were regularly followed up with routine physical and laboratory examinations at our hospital. Computed tomography of the neck and chest was performed annually to detect possible recurrent disease. The median follow-up period for all patients was 39.5 months (range, 12–64 months).

Statistical Analysis

Survival time was measured from the date of surgery until death or the most recent follow-up examination. Length of survival was determined with the Kaplan–Meier method, and the log-rank test was used for comparisons. All analyses were performed with the SPSS statistical software package (version 17.0.2; SPSS, Inc., Chicago, IL, USA).

RESULTS

Patient Characteristics

Pathologic examination showed lymph node involvement in the upper mediastinum in 13 patients (Table 1). Eleven of 13 patients were enrolled to receive post-operative radiotherapy with concurrent chemotherapy, but 2 of the 13 patients refused post-operative adjuvant treatment. The baseline characteristics of patients enrolled in this protocol are shown in Table 2. The median age was 58 years (age range, 40–70 years), and eight patients were men and three were women. More than 70% of tumors were clinically T3 or T4. Seventy-three percent of tumors had metastasized to lymph nodes before operation. Pathologic characteristics of selected patients with metastases to the upper mediastinal lymph node are listed in Table 3. Seventy-two percent of tumors were T3 or T4, and all patients had regional lymph node involvement. Complete resection (R0) was achieved in 82% of the patients.

Compliance with Treatment

Nine patients (82%) completed post-operative radiotherapy with two or more of concurrent chemotherapy with cisplatin. One patient who had received 66 Gy of radiotherapy stopped chemotherapy after receiving one cycle. Another patient stopped radiotherapy after receiving a radiation dose of 54 Gy. Toxicity was assessed in all 11 patients.

Table 2. Clinical characteristics of selected patients with metastasis to the upper mediastinal lymph nodes

Characteristic	No. of patients (%)
Sex	
Female	3 (27)
Male	8 (73)
Age in years	
Median (range)	58 (40–70)
Tumor location	
Ce	7 (64)
Ce-Ut	3 (27)
Ce-Ph-Ut	1 (9)
Tumor status	
T1	1 (9)
T2	2 (18)
T3	2 (18)
T4	6 (55)
Node status	
N0	3 (27)
N1	8 (73)
Metastatic status	
M0	5 (45)
M1 lymph	6 (55)
Stage	
I	1 (9)
II	0
III	4 (36)
IV	6 (55)

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.

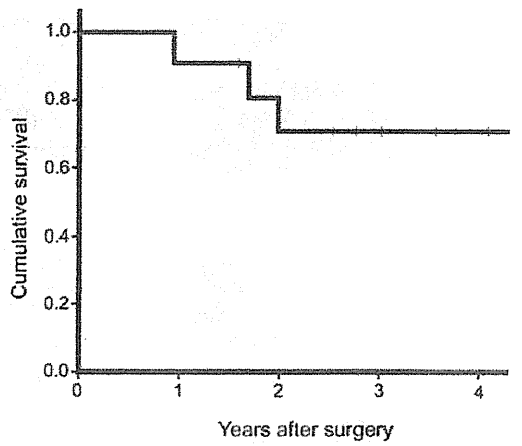

Figure 2. Overall survival curve.

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.

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ORIGINAL ARTICLE

Free Jejunal Patch Graft for Reconstruction After Partial Hypopharyngectomy With Laryngeal Preservation

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Objectives: To examine postoperative complications and swallowing function associated with free jejunal patch graft transfer after partial hypopharyngectomy with laryngeal preservation.

Design: Retrospective medical record review.

Setting: Academic research.

Patients: A consecutive series of 43 patients who underwent free jejunal patch graft transfer after partial hypopharyngectomy with laryngeal preservation composed the study sample. They represented the following 3 groups based on the type of hypopharyngeal defect: 13 patients with defects of the posterior wall (PW group), 28 patients with defects extending to the unilateral piriform sinus (PS-PW group), and 2 patients with defects extending to the bilateral piriform sinuses (PS-PS group).

Main Outcome Measures: Postoperative complications and oral intake ability were compared among the groups.

Results: Except for 1 patient, all the patients in the PW and PS-PS groups resumed oral intake within 2 weeks after surgery. Four patients in the PS-PW group had severe dysphagia, 2 of whom could not discontinue tube feeding.

Conclusions: Free jejunal patch graft transfer after partial hypopharyngectomy allows satisfactory swallowing function, with a low complication rate. Postoperative dysphagia was slightly more common in the PS-PW group than in the PW group.

Arch Otolaryngol Head Neck Surg. 2011;137(2):181-186

ALTHOUGH TOTAL PHARYNgolaryngectomy has long been the standard treatment for locally advanced hypopharyngeal cancer, partial hypopharyngectomy with laryngeal preservation has recently become possible, and its indications have steadily been expanding for selected patients.[1-6] Reconstruction after partial hypopharyngectomy with laryngeal preservation is a challenging problem because of the risk of postoperative aspiration. Free jejunal patch graft (FJPG) transfer is widely accepted as the method of first choice for reconstruction[6-8]; however, few investigations have examined postoperative complications and swallowing function. Furthermore, the relationship between postoperative functional results and defect type remains unclear. In the present retrospective study, we examined clinical results (including postoperative complications and swallowing function by defect type) of FJPG transfer after partial hypopharyngectomy with laryngeal preservation.

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METHODS

Forty-three patients with hypopharyngeal cancer underwent FJPG transfer immediately after partial hypopharyngectomy with laryngeal preservation at the National Cancer Center Hospital East, Kashiwa, Japan, from December 9, 1992, through June 20, 2008, and were included in the study. The patients were 37 men and 6 women who had a mean (SD) age of 62.3 (8.2) years. Thirty-nine patients had primary cancer and 4 had recurrent cancer after initial treatment. Among those with primary cancer, 7 patients were classified as having stage I; 24, as having stage II; 6, as having stage III; and 2, as having stage IV according to the *TNM Classification of Malignant Tumours*[9] (**Table 1**).

SURGICAL TECHNIQUES

A segment of jejunum approximately 15-cm long was harvested in the usual manner. After a small segment of jejunum to be exteriorized for postoperative monitoring had been prefabricated, the remaining segment of jejunum was trimmed on the oral and anal sides by referring to the longitudinal length of the resected

Table 1. TNM Classification Among 39 Patients[a]

	Stage				
Stage	N0	N1	N2	N3	Total
T1	4	1	1	1	7
T2	13	3	6	2	24
T3	2	2	2	0	6
T4	0	2	0	0	2
Total	**19**	**8**	**9**	**3**	**39**

[a]According to the *TNM Classification of Malignant Tumours*.[9] Four patients had recurrent cancer.

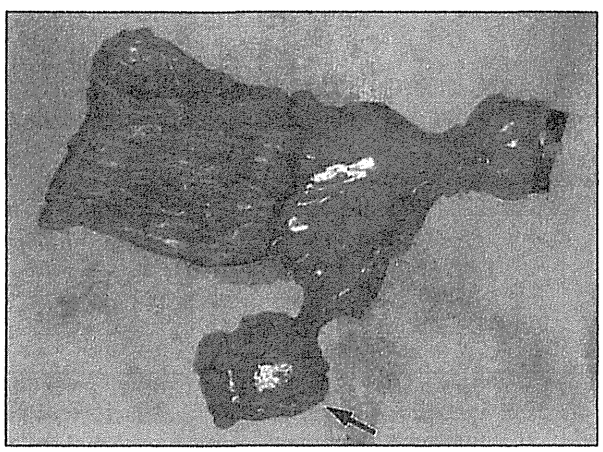

Figure 1. Jejunum graft after prefabrication. The arrow indicates the segment to be exteriorized for postoperative monitoring.

specimen (**Figure 1**). The jejunum was then opened along the antimesenteric border and transferred to the hypopharyngeal defect in an isoperistaltic fashion and fixed with 4-0 monofilament absorbable sutures. First, the jejunum was sutured to where a suture is the most difficult to place, which is usually the most caudal point on the side opposite the surgeon. Next, the jejunum was sutured in sequence to the posterior, caudal, and cranial margins with a single-layer inverting interrupted suture (**Figure 2**). Finally, the anterior margin was closed with a Gambee suture. The jejunum was set into the defect under in situ tension, and the redundant portion of the jejunum was appropriately trimmed. After mucosal closure was completed, a microvascular anastomosis was performed between the jejunal pedicle and the cervical vessels.

EVALUATION

The medical records of 43 patients were examined to analyze the following variables: patient history, defect type, postoperative recipient site complications, postoperative course, and oral intake ability. Postoperative recipient site complications analyzed were total necrosis of the FJPG, fistula formation, and surgical site infection.

Patients were classified into the following 3 groups based on the type of hypopharyngeal defect: patients with defects of the posterior wall (PW group), patients with defects extending to the unilateral piriform sinus (PS-PW group), and patients with defects extending to the bilateral piriform sinuses (PS-PS group) (**Figure 3**).

Barium swallow examinations were performed 7 to 10 days after surgery. If the examination revealed no leakage and no significant aspiration, the patient was allowed to start oral intake. If leakage or severe aspiration was present, the examination was repeated 7 days later. The number of days after surgery until the start of oral intake was noted. For patients who had undergone tracheostomy, the number of days until closure of the tracheal stoma was also recorded.

Postoperative swallowing function was indicated by the type of diet the patient could tolerate after recovery and before disease progression (100% oral diet, partial oral diet, or 100% tube

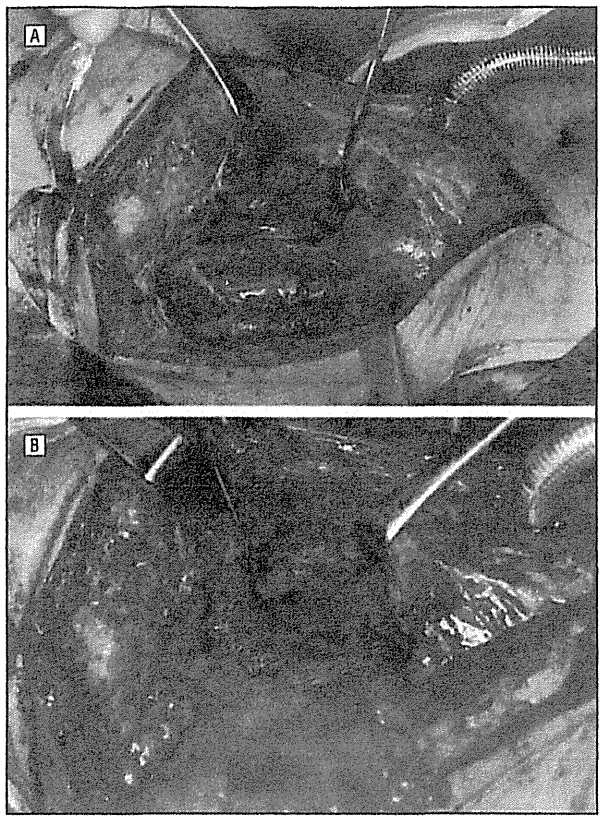

Figure 2. Defect after partial hypopharyngectomy with laryngeal preservation and right modified neck dissection (A). The posterior wall and the right piriform sinus were resected. Intraoperative view is after the jejunum had been sutured to the posterior margin of the defect (B).

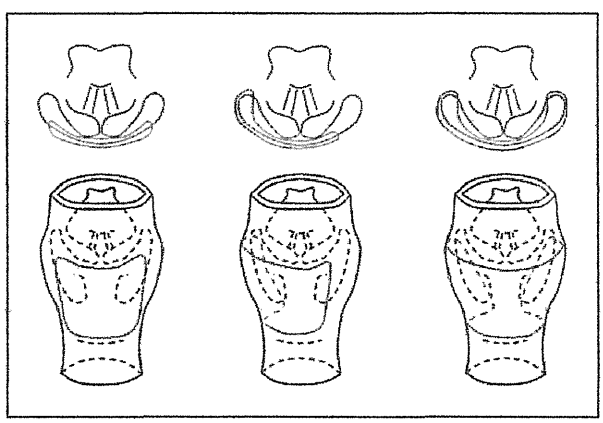

Figure 3. Classification of the hypopharyngeal defect. View from the cranial side (top row) and view from the posterior side (bottom row) are shown. The red line indicates the defect. The PW group (left column) shows defects of the posterior wall. The PS-PW group (center column) shows defects extending to the unilateral piriform sinus. The PS-PS group (right column) shows defects extending to the bilateral piriform sinuses.

Table 2. Characteristics by Defect Type Among 43 Patients

Characteristic	PW Group (n=13)	PS-PW Group (n=28)	PS-PS Group (n=2)	P Value[a]
Sex, No. of patients				
Male	10	25	2	.36
Female	3	3	0	
Age, mean, y	58.8	63.5	67.0	.09[b]
Follow-up period, mean, mo	28.6	26.8	80.5	.85[b]
History of RT or CRT, No. of patients (radiotherapy dose range, Gy)	1 (59)	7 (40-70)	0	.19

Abbreviations: CRT, chemoradiotherapy; PS-PS, defect extending to the bilateral piriform sinuses; PS-PW, defect extending to the unilateral piriform sinus; PW, defect of the posterior wall; RT, radiotherapy.
[a]Comparison between the PW and PS-PW groups using the Fisher exact test unless otherwise indicated.
[b]Using unpaired *t* test.

Table 3. Postoperative Recipient Site Complications by Defect Type Among 43 Patients

Complication	Patients, No. (%) PW Group (n=13)	PS-PW Group (n=28)	PS-PS Group (n=2)	P Value[a]
Overall complications	2 (15)	4 (14)	0	.63
Total necrosis of the FJPG	1 (8)	1 (4)	0	.54
Fistula formation	0	3 (11)	0	.31
Surgical site infection	1 (8)	2 (7)	0	.69

Abbreviations: FJPG, free jejunal patch graft; PS-PS, defects extending to the bilateral piriform sinuses; PS-PW, defects extending to the unilateral piriform sinus; PW, defects of the posterior wall.
[a]Comparison between the PW and PS-PW groups using the Fisher exact test.

feeding). Background and postoperative course were analyzed in patients who could not resume oral intake within 2 weeks after surgery.

STATISTICAL ANALYSIS

Statistical analysis was performed between the PW and PS-PW groups using a commercially available software program (Statcel, version 2; OMS Publishing, Saitama, Japan). The PS-PS group was excluded from statistical analysis because the sample size was too small. The Fisher exact, unpaired *t*, and Mann-Whitney tests were used. Differences with $P < .05$ were considered statistically significant.

RESULTS

Pathological diagnosis was squamous cell carcinoma in 40 patients and adenosarcoma, endocrine carcinoma, and spindle cell carcinoma in 1 patient each. The median follow-up period was 39.9 months, and 17 patients (40%), at the time of study completion, were alive without recurrent disease.

Patient data are summarized in **Table 2**. Hypopharyngeal defects were of the PW type in 13 patients, the PS-PW type in 28 patients, and the PS-PS type in 2 patients. In all the patients, the cartilaginous prominence of the arytenoepiglottic fold was preserved. No significant differences were noted in age ratio or sex ratio between the PW and PS-PW groups. One patient in the PW group (8%) and 7 patients in the PS-PW group (25%) had received radiotherapy to the neck. Two of these patients in the PS-PW group had received concomitant chemotherapy.

POSTOPERATIVE RECIPIENT SITE COMPLICATIONS

Complication rates are given in **Table 3**. There were no significant differences in the overall complication rate or the rates of total necrosis of the FJPG, fistula formation, or surgical site infection between the PW and PS-PW groups. Total necrosis of the FJPG occurred in 1 patient in the PW group (8%) and in 1 patient in the PS-PW group (4%). Pharyngocutaneous fistulas developed in 3 patients in the PS-PW group (11%) but healed with conservative treatment. No pharyngocutaneous fistulas developed in patients in the PW group. No complications developed in patients in the PS-PS group.

POSTOPERATIVE COURSE AND ORAL INTAKE ABILITY

Postoperative course and oral intake ability by defect type are summarized in **Table 4** and **Table 5**. Oral intake could be resumed within 2 weeks after surgery in all patients in the PW and PS-PS groups except for 1 patient with total necrosis of the FJPG. She underwent salvage surgery by external fistula formation using a deltopectoral flap. Multiple operations were required to close the external fistula, and she could not start an oral diet until 75 days after the first surgical procedure. In the PS-PW group, 5 patients could not resume oral intake within 2 weeks after surgery. Four of the patients experienced severe aspiration, and the fifth patient (with total necrosis of the FJPG who underwent successful salvage surgery

Table 4. Postoperative Course by Defect Type Among 43 Patients

Postoperative Event	Postoperative Day, Median (Range)			
	PW Group (n=13)	PS-PW Group (n=28)	PS-PS Group (n=2)	*P* Value[a]
Initiation of oral intake	11 (6-75)	11 (6-73)[b]	13 (11-14)	.92
Closure of tracheal stoma	13 (8-75)	13 (11-112)	21 (18-24)	.78

Abbreviations: PS-PS, defects extending to the bilateral piriform sinuses; PS-PW, defects extending to the unilateral piriform sinus; PW, defects of the posterior wall.
[a]Comparison between PW and PS-PW groups using the Mann-Whitney test.
[b]The patient who could not discontinue tube feeding was excluded.

Table 5. Oral Intake Ability by Defect Type Among 43 Patients

Method of Nutrition	Patients by Defect Type, No. (%)			
	PW Group (n=13)	PS-PW Group (n=28)	PS-PS Group (n=2)	*P* Value[a]
100% Oral diet	13 (100)	26 (93)	2 (100)	.32
Partial oral diet	0	1 (4)	0	
100% Tube feeding	0	1 (4)	0	

Abbreviations: PS-PS, defects extending to the bilateral piriform sinuses; PS-PW, defects extending to the unilateral piriform sinus; PW, defects of the posterior wall.
[a]Comparison between the PW and PS-PW groups using the Fisher exact test.

Table 6. Summary of 4 Patients in the PS-PW Group With Severe Dysphagia and Aspiration Pneumonia

Sex/Age, y	Comorbidity	Previous Treatment	Postoperative Day		Method of Nutrition
			Initiation of Oral Intake	Closure of Tracheal Stoma	
M/59	Personality disorder	None	42	12	100% Oral diet
M/60	Personality disorder after cerebral contusion	60-Gy RT	45	16	100% Oral diet
F/70	Upper esophageal stenosis, with 3 endoscopic balloon dilations	None	73	23	Partial oral diet
M/74	Esophageal cancer, with subtotal esophagectomy and reconstruction with retrosternal gastric pull-up	None	Impossible	112	100% Tube feeding

Abbreviations: PS-PW, defects extending to the unilateral piriform sinus; RT, radiotherapy.

by transfer of an anterolateral thigh flap) started an oral diet 17 days after the first surgical procedure. The number of days until the start of oral intake did not differ significantly between the PW and PS-PW groups.

Temporary tracheostomies were created at the time of surgery in 38 patients, and all were closed after surgery. The number of days until closure of the tracheal stoma did not differ significantly between the PW and PS-PW groups. However, in the PS-PS group, the time until closure was longer than in the other groups.

Overall, 41 of 43 patients (95%) were eventually able to tolerate an oral diet without the need for tube feeding. All the patients in the PW and PS-PS groups tolerated a 100% oral diet, whereas of 28 patients in the PS-PW group, 26 patients (93%) tolerated a 100% oral diet and 2 patients (7%) could not discontinue tube feeding. The rate of dependence on tube feeding did not differ significantly between the PW and PS-PW groups. Four patients underwent postoperative adjuvant radiotherapy because of a microscopically involved mucosal margin of resection or extranodal spread of disease. They were able to tolerate oral intake after radiotherapy.

The background and postoperative course of patients with severe dysphagia and aspiration pneumonia who could not start oral intake for more than 2 weeks after surgery are listed in Table 6. Two patients had personality disorders and were not adherent to our instructions about swallowing rehabilitation; they finally started oral intake 42 and 45 days after surgery. The other 2 patients had a history of esophageal disease and were 70 years or older. One of these patients had undergone endoscopic balloon dilation 3 times for idiopathic upper esophageal stenosis. The other patient had undergone subtotal esophagectomy for esophageal cancer and reconstruction with retrosternal gastric pull-up. Postoperative videofluorographic studies in these 2 patients showed

severe obstruction at the esophageal orifice and aspiration during laryngeal elevation. One of the patients resumed oral intake 73 days after surgery but remained partially dependent on tube feeding. The other patient could not resume oral intake and continued tube feeding.

COMMENT

This study demonstrated that satisfactory swallowing function with a low complication rate can be achieved with FJPG transfer for reconstruction of defects after partial hypopharyngectomy with laryngeal preservation. Neither the complication rate nor postoperative swallowing function was significantly affected by defect type; however, postoperative dysphagia was slightly more common in the PS-PW group than in the PW group.

Various methods have been used for reconstruction after partial hypopharyngectomy.[1-6,10-13] Recently, radial forearm free flap transfer and FJPG transfer have become the 2 most popular methods of reconstruction. Some surgeons prefer radial forearm free flap transfer because of its minimal invasiveness and good accessibility[1,3-5]; however, the substantial risk of fistula formation is a major disadvantage of the radial forearm free flap.[6,13] In addition, the absence of self-lubrication in the skin flap impairs swallowing function.[6] Several years ago, we routinely used radial forearm free flaps, as well as FJPGs, for reconstruction after partial hypopharyngectomy, but we have stopped using radial forearm free flaps because of their high complication rate. The use of FJPGs for head and neck reconstruction was first reported by Buckspan et al[10] in 1986. Nakatsuka et al[6] used the FJPG for reconstruction after partial hypopharyngectomy with laryngeal preservation and demonstrated its superiority to the radial forearm free flap. The advantages of FJPG are a low rate of fistula formation and favorable passage of food because of its self-lubricating surface. A major disadvantage is the need for laparotomy; however, it was previously shown that FJPGs can be safely harvested even in patients who are older or who have undergone abdominal surgery.[14] Another concern with the FJPG is aspiration of mucus secretions from the jejunum. Giovanoli et al[12] reported that the volume of jejunal secretions increases markedly in the early phase after free jejunal transfer. However, aspiration pneumonia, which can result from jejunal secretions, did not develop in any patient in the present series. When the supraglottic structure of the larynx has been preserved, aspiration of jejunal secretions does not seem to be a problem.

The results of the present study show that patients with PW defects are strong candidates for reconstruction by FJPG transfer. However, 4 patients in the PS-PW group experienced severe aspiration. A possible reason is that proximity of the defect to the larynx prolonged laryngeal edema and impaired hypopharyngeal clearance. However, swallowing dysfunction in our patients could not be directly attributed to the extent of the defects. Two patients had personality disorders, and the other patients had a history of esophageal disease. In addition, the 2 patients who could not discontinue tube feeding were 70 years or older. The other patients in the PS-PW group with neither personality disorders nor a history of esophageal disease resumed oral feeding within 2 weeks. In addition to advanced age, which is known to have an adverse effect on laryngeal preservation,[15,16] personality disorders and a history of esophageal disease are, we believe, limiting factors for laryngeal preservation.

The major consideration when reconstructing a PS-PW defect is whether to restore the anatomical shape of the piriform sinus or to reconstruct a narrow pharyngeal space with a taut jejunum. In the present series, we transferred the jejunum under in situ tension and obtained satisfactory results. In contrast, some authors have suggested that the transferred jejunum should be taut because pooling of food at the affected side becomes problematic when the jejunum is transferred under low tension.[7] However, postoperative videofluorographic studies of our patients with severe dysphagia showed pooling of the contrast medium on the healthy side but not on the affected side. We believe that tautness of the transferred jejunum is minimally important for this type of reconstruction and that transfer of the jejunum under tight tension is unnecessary. Of course, formation of a blind loop should be prevented; however, this rarely occurs unless the FJPG transferred is much larger than the resected specimen.

In this series, 2 patients in the PS-PS group were successfully treated and tolerated an oral diet without severe aspiration. However, we believe that patients with this type of defect are not good candidates for laryngeal preservation and that total pharyngolaryngectomy should be the standard treatment. The outcome of laryngeal preservation and FJPG transfer for such wide defects is unknown because our sample size was too small to address this issue.

The use of intensive organ preservation therapy is considered a standard option for hypopharyngeal cancer, with surgery reserved for salvage. However, we believe that radiotherapy or chemoradiotherapy should not be the first-line treatment for small hypopharyngeal cancer because of the high risk of second primary cancer of the aerodigestive tract in these patients. Hypopharyngeal cancer is generally treated with wider-field radiation therapy than is used for laryngeal cancer, which renders the treatment more difficult in case of second primary head and neck cancer. From the functional point of view, the results of this study compare favorably with those of organ preservation therapy.[17,18] Therefore, we choose operative treatment as a first choice for small hypopharyngeal cancer that can be resected with laryngeal preservation.

A limitation of FJPG transfer is that it is not indicated for defects extending to the supraglottic region. Reconstructing an arytenoepiglottic fold of appropriate height after partial pharyngolaryngectomy is important to prevent postoperative aspiration.[8] However, reconstructing the complex supraglottic structures with an FJPG is difficult because of its minimal plasticity. In addition, jejunal secretions can cause frequent aspiration if the internal wall of the larynx is reconstructed with a jejunal graft. Therefore, we use a radial forearm free flap instead of an FJPG for reconstruction after partial pharyngolaryngectomy.

Submitted for Publication: November 23, 2009; final revision received July 20, 2010; accepted August 25, 2010.
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Author Contributions: Drs Miyamoto, Sakuraba, Hayashi, Ebihara, Miyazaki, Daiko, Shinozaki, and Kimata had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Miyamoto, Sakuraba, Hayashi, and Kimata. *Acquisition of data:* Miyamoto, Sakuraba, Asano, Ebihara, Miyazaki, Daiko, and Shinozaki. *Analysis and interpretation of data:* Miyamoto and Sakuraba. *Drafting of the manuscript:* Miyamoto, Asano, Hayashi, Ebihara, Miyazaki, Daiko, and Shinozaki. *Critical revision of the manuscript for important intellectual content:* Sakuraba and Kimata. *Administrative, technical, and material support:* Miyamoto, Sakuraba, Asano, Ebihara, Miyazaki, Daiko, and Shinozaki. *Study supervision:* Sakuraba, Hayashi, and Kimata.
Financial Disclosure: None reported.

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J. Jpn. Bronchoesophagol. Soc.
Vol. 61 No. 2, 2010

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シンポジウム4　Salvage Surgery（食道癌，喉頭・下咽頭癌）

化学放射線治療後遺残，再発症例に対する救済手術

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キーワード：頭頸部癌，化学放射線治療，救済手術

I. はじめに

近年，頭頸部癌に対する化学放射線療法が広く行われるようになり，その有用性が報告される一方で，遺残・再発症例に対する外科治療が論じられるようになってきた。しかし，それら外科療法の安全性や適応に関しては一定の見解は得られていないのが現状であろう。

当院での化学放射線治療後の救済手術について検討する。

II. 対象と方法

2004年1月より2008年12月までに当院にて化学療法同時併用放射線治療を行った症例は30例であった。男性26例，女性4例，平均年齢は62歳（42～75歳），観察期間の中央値は19カ月であった。全例扁平上皮癌で，原発部位では下咽頭が21例と最も多く，中咽頭3例，頸部食道3例，喉頭1例，原発不明1例であった。切除標本の病理診断にて放射線潰瘍と診断された3例を除く27例を対象として検討した。頸部リンパ節に対する対応としては，化学放射線治療後明らかに遺残ないしは再発が確認された時点で手術を行うこととしており，いわゆるplanned neck dissectionは行っていない。

III. 結　果

救済手術で原発巣切除のみ行った症例は8例，原発切除と頸部郭清術を行った症例は9例，頸部郭清のみを行った症例は10例であった。郭清範囲では内頸静脈周囲の郭清（level II–IV）を行った症例が7例，残存ないしは再発部位の部分郭清（1ないし2 level）を行った症例が12例，原発巣の遺残・再発に対し救済手術を行ったが頸部は制御されていたために郭清術を行わなかった症例が8例であった。

2年頸部制御率は70%であった。内頸静脈周囲郭清群で71%，部分郭清ないしは郭清なし群で63%と有意な差は認めなかった。郭清のみを行った群と郭清と原発巣切除を行った群での頸部制御率はそれぞれ89%，57%であり，原発切除を行った群での頸部制御は不良であった。2年生存率は58%であった。化学放射線治療の効果と予後の検討では原発巣，頸部ともCRとなった症例では52%，いずれかがnon CRであった症例では60%であり，両者の間に有意な差は認めなかった。しかし，原発巣切除を要した群では43%，郭清のみの群では90%と原発巣切除を要した群で予後が不良であった。

IV. 考察と結論

化学放射線治療後の頸部郭清では，内頸静脈周囲郭清群と部分郭清ないしは郭清なし群で頸部制御率に有意な差は認めなかったことから，残存・再発部分の部分郭清も許容しうると考えられた。郭清範囲の縮小が可能であれば救済術後の死腔を減らすことにもつながり，術後合併症の予防にも寄与することになるが，原発巣制御の可否や化学放射線治療の治療内容などさらに適応を詳細に検討する必要がある。原発巣の制御の可否が頸部制御および生存に影響することが示唆された。頸部郭清のみの救済手術症例の予後は，原発巣の切除を要する症例と比べ良好であり，頸部リンパ節のみの残存・再発症例に対しては積極的に郭清術を考慮すべきと考えられた。

V. おわりに

当院での化学療法同時併用放射線治療後の救済手術について検討し報告した。

本稿は第61回日本気管食道科学会の抄録／会議録である。
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JOHNS
特集●耳鼻咽喉科疾患の診療に関するガイドライン―解釈と有効な使い方●

頭頸部癌診療ガイドライン

林　隆一*
Ryuichi HAYASHI

● Key Words ●ガイドライン，頭頸部癌，治療方針●

はじめに

ガイドラインは，①適切な治療の提示，②施設間格差の解消，③安全な治療の確立と治療成績の向上，④人的・経済的負担の軽減，⑤医療者と患者との相互理解，などに役立てる目的で体系的な方法に則って作成された文書とされる。あくまでも標準的な指針であり，すべての患者に画一的な診療を強制するものではない[1]。『頭頸部癌診療ガイドライン』（日本頭頸部癌学会編）は頭頸部癌診療に携わる医療者を対象としたものとして作成された。ここでは，『頭頸部癌診療ガイドライン』について，作成の経緯をはじめ遭遇した問題点，基本方針と構成，今後の課題について述べる。

I．ガイドライン作成の経緯

厚生労働省，日本癌治療学会から日本頭頸部癌学会への診療ガイドライン作成の業務委託があり，厚生労働省がん研究助成金“がん専門施設を活用したがん治療の標準化に関する共同研究”にかかわっていた班員がメンバーの中心となって，日本頭頸部癌学会に診療ガイドライン検討委員会が発足した。そして「頭頸部癌診療ガイドラインの作成」をテーマとして平成13年度から平成17年度にわたり班会議が運用された。

『頭頸部診療ガイドライン（案）』として平成18年には草稿はかたまっていたものの，ガイドラインの専門家による修正や一部の癌腫の取り扱い規約の改訂により校正に時間を要した。その後平成20年6月に日本頭頸部癌学会理事会に提出し承認を得，同年9月日本癌治療学会ガイドライン検討委員会に提出，平成21年3月金原出版より『頭頸部癌診療ガイドライン』として発刊された。

II．ガイドライン作成上の問題点

頭頸部癌は罹患数が少なく，原発部位も多いことからガイドラインの作成は困難な作業となった。頭頸部癌として1つのガイドラインでまとめることは，それぞれの癌腫の特性やそれに対する治療が多様であるため不可能である。そのため，口腔癌では舌癌についてのみ作成することとし，上顎洞癌，上・中・下咽頭癌，喉頭癌，甲状腺癌，唾液腺癌（耳下腺癌），原発不明頭部転移癌の8疾患を対象として作成することになった。

ガイドラインの作成はエビデンスに基づくことが理想的であるが，エビデンスレベルの高い報告は本邦には少なく，欧米の文献を採用することが必ずしもわが国の実際の臨床を反映しない状況にも遭遇した。また，頭頸部癌の治療は癌の根治と機能保持といういわば相反することを両立せねばならず，それは患者側の治療に対する要求の多様化につながっている。これらの背景やガイドラインが初回のものであることも考慮し，現状の治療をできるだけ取り入れることとした。そのため本ガイドラインでは推奨度の設定がなされていない。しかし，ガイドラインの作成においてはエビデンスと同様コンセンサスも重要な事項であり，この点については各作成委員の間で十分な論議をつくし，表現や記載方法に反映されたと考えている。

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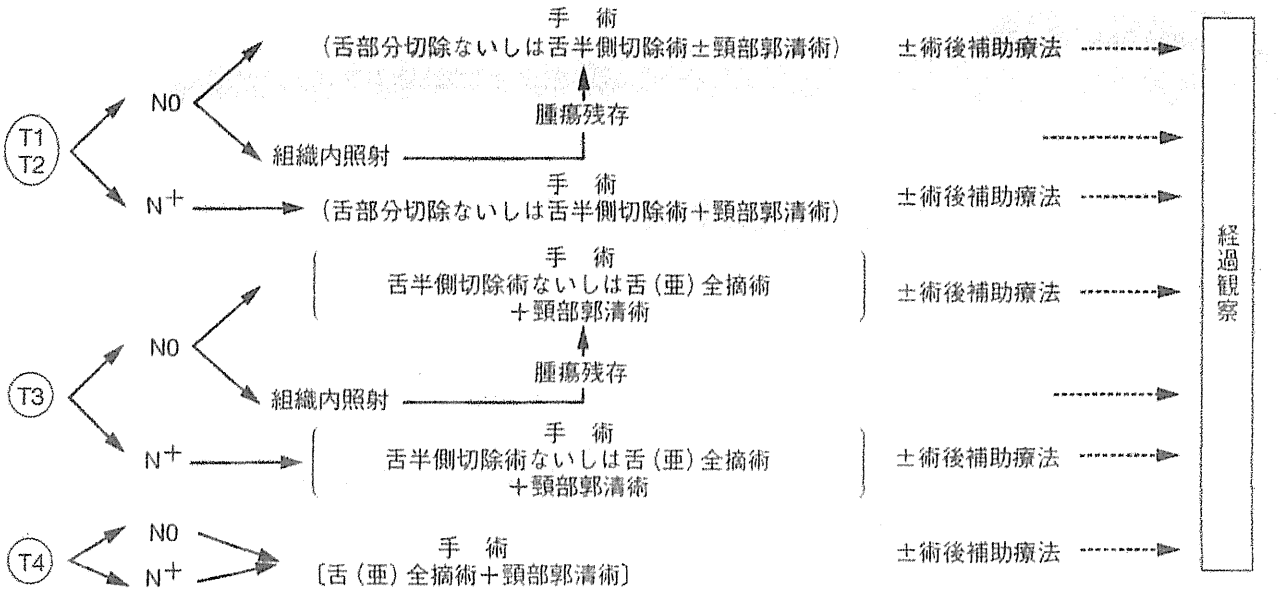

図 1　舌癌でのアルゴリズム（文献 2 より改編引用）

Ⅲ．ガイドラインの基本方針と構成

一般的に行われている診断・治療法の適応を示すことを原則とし，各診断・治療法の技術的な問題には立ち入るものではない。治療の項の基本的な構成は，まず TNM 分類を記載し，T 分類に従って治療のアルゴリズムを記載している。このアルゴリズムを作成するという形式は日本癌治療学会からの要請によるものである。治療法のアームが 2 本存在する場合は，上段のアームの治療が一般的に行われるか，推奨されるものとした。

続いて放射線治療，手術，化学療法の各治療法の適応について解説している（図 1）[2]。術前術後の補助療法や化学放射線治療については特定の原発部位によらないため治療に対する見解としてまとめた。

文献については MEDLINE，医学中央雑誌にて 2001 年から 2005 年のものを検索し必要に応じてハンドリサーチを追加，その結果英文 99 編，和文 47 編を採用した。エビデンスレベルは表に示す通り 3 段階の表記とした（表 1）。そして，頭頸部癌治療の現状を理解する一助として，頭頸部悪性腫瘍全国登録のデータを一部掲載している

表 1　エビデンスレベルの分類

レベルⅠ	システマティック・レビュー，メタアナリシス，ランダム化比較試験
レベルⅡ	非ランダム化比較試験，分析的疫学的研究（コホートや症例対象研究による），横断研究
レベルⅢ	記述研究（症例報告やケースシリーズ）による，患者データに基づかない専門委員会や専門家個人の意見

Ⅳ．今後の課題

『頭頸部癌診療ガイドライン』は 2009 年 3 月に刊行され 1 年が過ぎた。今後は有効性を評価し，次回の TNM 分類の変更にあわせて改訂作業を進めていかなければならない。ガイドラインは学生・研修医のテキストとしてまた，新たな臨床試験や研究テーマの発見のきっかけにもなるものである。頭頸部癌診療は日々進歩している。新しい診断・治療法をとりいれつつ，また本邦での臨床試験から得られたエビデンスを収集し，改訂を定期的に繰り返していくことが必要と考えられる。

おわりに

作成に関わった 1 人としてガイドラインの発刊に至る背景について述べた。まだまだ不備な点が多々あるが，本ガイドラインは初版であり今後は

多くの先生方の批判や指摘を受けながら，より充実した内容のガイドラインに改訂していくことが必要であろう

文　献

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MB ENT. 113：124-128，2010

◆特集・耳鼻咽喉科外来診療―私の工夫―

中・下咽頭におけるNBIの有用性

篠﨑　剛[*1]　林　隆一[*2]

Key words：NBI(narrow band imaging)システム，表在癌(superficial carcinoma)，原発不明癌(carcinoma of unknown primary tumor site)

Abstract　頭頸部領域の粘膜病変を観察する方法としてNBI(narrow band imaging)システムがある．短波長のみで構成される観察光によって，粘膜表層の血管を描出しやすくしたシステムである．正常重層扁平上皮粘膜はやや白みがかった緑色調に，表在癌などのために血管密度が高くなった発赤部位は褐色に観察される．通常光と比較して表在病変の描出に優れているため，原発巣の検出や病変範囲の確認に有用である．耳鼻咽喉科で用いられている咽喉頭ファイバーと同様に使用することが可能である．ファイバーにはいくつかの種類があり，目的とする観察部位や生検の有無，患者の条件によって使い分けている．

はじめに

食道領域ではヨード色素内視鏡がスクリーニング検査法として確立し，早期癌，特に内視鏡的切除術(EMR)の対象となる表在癌が増えている．

消化器内視鏡の進歩，高リスク患者(アルコール多飲，ヨード多発不染)に対するスクリーニングによって咽喉頭粘膜にも表在性の早期癌が発見されるようになってきている．頭頸部領域ではヨード色素内視鏡検査は刺激が強く，極度の苦痛や不快感を与えるため頭頸部領域のスクリーニング検査法として用いることは困難である．意識下で表在病変を観察する方法として観察光の波長を利用した内視鏡システムが有用である[1,2]．本稿では耳鼻咽喉科用として市販されており，表在病変の観察に有用であるNBI(narrow band imaging)システムについて述べる．

NBIとは

電子内視鏡では内視鏡先端のCCDから取り込まれた信号を演算し，画像を構成して検者へ表示している．NBIシステムとは観察光の長い波長側をカットして狭帯域の短波長のみで構成される観察光に変換するシステムのことである(図1)．長い波長がカットされることで観察光は深部に到達せず，観察部位の浅部のみを観察することになる．このため，表面の構造をより選択的に描出することが可能である．観察光の波長は粘膜表層に存在する毛細血管を明瞭に描出できるよう，血液中のヘモグロビンに吸収されやすい狭帯域化された2つの波長(390～445 nm/530～550 nm)の光を照射することにより，粘膜表層の毛細血管，粘膜微細模様の強調表示を行っている(図2)．内視鏡から出る観察光は青白い光であり，得られるモニター上の映像は415 nmの画像情報をRGB端子のグリーンとブルーに割り当て，540 nmの画像情報をレッドに割り当てている．正常重層扁平上皮粘膜は血管に乏しく，光学的な反射が強いためやや白みがかった緑色調に描出される．表在癌などのために血管密度が高くなった発赤部位は褐色

[*1] Shinozaki Takeshi．〒277-8577　千葉県柏市柏の葉6-5-1　国立がんセンター東病院頭頸科
[*2] Hayashi Ryuichi．同科，外来部長