Table 1 Baseline characteristics

Characteristic	No. of patients $N = 53$	%
Male	46	86.8
Female	7	13.2
Median age (range), years	65.0 (47–76)	
<65 years	24	45.3
≥65 years	29	54.7
Performance status		
0	28	52.8
1	25	47.2
Smoking history		
Smokers	5	9.4
Non-smokers	2	3.8
Previous smokers	46	86.8
Advanced/recurrent disease		
Recurrent	41	77.4
Advanced	12	22.6
Stage IVa	1	1.9
Stage IVb	10	18.9
Stage IIa*	1	1.9
Adenocarcinoma	1	1.9
Squamous cell carcinoma	52	98.1
Primary lesion location		
Cervical plus upper thoracic esophagus	3	5.7
Upper thoracic esophagus	8	15.1
Upper plus middle thoracic esophagus	2	3.8
Middle thoracic esophagus	29	54.7
Lower thoracic esophagus	8	15.1
Abdominal esophagus	3	5.7
Prior treatment**		
Neoadjuvant chemotherapy	7	13.5
Post-operative adjuvant chemotherapy	14	26.9
Chemoradiation therapy	30	57.7
Chemotherapy for residual or recurrent lesion	12	23.1
Surgery	24	46.2
Radiotherapy	34	65.4
Other therapy	3	5.8
Reasons for prior chemotherapy failure**		
Disease progression	25	48.1
Recurrence	5	9.6
Adverse events	1	1.9
Other***	26	50.0
Treatment-free interval**, ****		
≦6 months	39	75.0
>6 months	13	25.0

* Patient excluded from the efficacy analyses, because it was found that the target lesion was not a metastatic esophageal tumor

** Stage IIa patient (*) was excluded from the count

*** Completed planned course of therapy

**** Duration from last day of prior treatment therapy

neoadjuvant chemotherapy, and 14 (26.4%) had received adjuvant chemotherapy. Most of the prior chemotherapy regimens were a combination of a platinum agent and a fluoropyrimidine. The number of patients who failed prior therapy due to disease progression was 25/52 (48%), while 1/52 (1.9%) failed due to toxicity (Table 1).

The median number of cycles delivered was 2 (range 1–8), and the median number of administrations was 10 (range 1–42). In this study, all patients received paclitaxel at an initial dose of 100 mg/m^2—if a patient experienced a severe adverse event, dosage was reduced to 80 mg/m^2 and then to 60 mg/m^2. The median time to the first dose reduction was 84 days and the median dose intensity was 78.5 mg/m^2/week (range: 39.8–100 mg/m^2/week), which was >90% of expected dosing. The median total duration of treatment was 3 months (range: 0.2–14.0). After the initial dose of 100 mg/m^2, the dose was reduced to 80 mg/m^2 in 23 patients (43.4%) and reduced further to 60 mg/m^2 in 7 patients (13.2%).

Table 2 Response to therapy (RECIST criteria)

Response						Response rate (%)	95% CI
CR	PR	SD	PD	NE	Total		
4	19	14	8	7	52	44.2	(30.5, 58.7)

Characteristic	Response					Total	Response rate (%)
	CR	PR	SD	PD	NE		
PS							
0	2	13	7	1	4	27	55.6
1	2	6	7	7	3	25	32.0
Histology							
Adeno	0	1	0	0	0	1	100.0
SCC	4	18	14	8	7	51	43.1
Advanced/recurrent							
Recurrent	4	16	10	6	5	31	48.8
Stage IV	0	3	4	2	2	11	27.3
Prior treatment							
Chemoradiation							
−	1	8	6	5	2	22	40.9
+	3	11	8	3	5	30	46.7
Chemotherapy							
CDDP+ 5-FU (+ADM)	3	17	14	7	6	47	42.6
TFI							
≦6 months	2	13	10	8	6	39	38.5
>6 months	2	6	4	0	1	13	61.5

PS performance status (ECOG), *Adeno* adenocarcinoma, *SCC* squamous cell carcinoma, *CDDP* cisplatin, *5-FU* fluorouracil, *ADM* adriamycin, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable, *TFI* Treatment-free interval

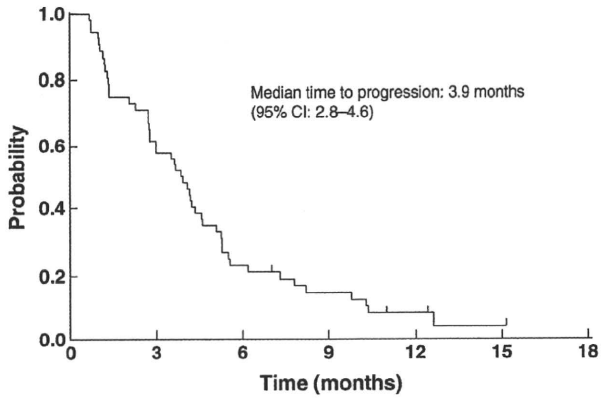


Fig. 1 Time to progression curve for patients with esophageal cancer treated with weekly paclitaxel and who had received prior platinum therapy. The median follow-up time of patients was 3.9 months, with a median time to progression of 3.9 months (95% CI: 2.8, 4.6 months)

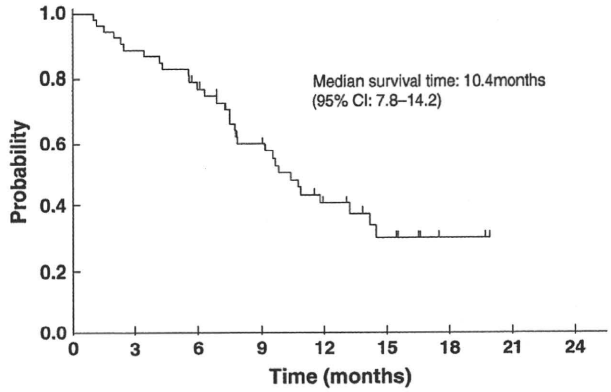


Fig. 2 Overall survival curve for patients with esophageal cancer treated with weekly paclitaxel and who had received prior platinum therapy. The median follow-up time of patients for overall survival was 9.1 months, with a median overall survival of 10.4 months (95% CI: 7.8, 14.2 months)

Response and survival

Response to therapy is shown in Table 2. Response rate is typically used as a primary endpoint in the phase II study of single agents in advanced esophageal cancer [21]; in this study, the overall response rate was 44.2% (23/52; 95% CI: 30.5, 58.7%) among patients evaluable for response. Among all treated patients, the response rate was 43.4% (23/53; 95% CI: 29.8, 57.7%), corroborating the result in the 52 response-evaluable patients. CR occurred in 4 patients and PR in 19. Responses were seen in 20 of 41 patients (48.8%) with recurrent disease and in 3 of 11 patients (27.3%) with advanced disease. Among the 29 patients without response, 14 showed stable disease (SD) on therapy, including 4 patients with advanced disease. Twenty-two of 51 (43.1%) patients with squamous cell carcinoma had responses. Median duration of overall response was 4.8 months (95% CI; 3.2, 7.1) for the 23 patients with CR or PR (95% CI: 3.2, 7.1 months). One patient had disease progression after 5.5 months in CR. Three patients were censored without disease progression, in which CR duration was ≥6.9 months. The median follow-up time for overall survival and time to progression was 9.1 months and 3.9 months, respectively. The median time to progression was 3.9 months (95% CI: 2.8, 4.6 months) (Fig. 1). Median overall survival was 10.4 months (95% CI: 7.8, 14.2 months) (Fig. 2).

Toxicity

Toxicity in the 53 assessable patients is shown in Table 3. Grade 3 or 4 non-hematologic toxicity was infrequent. The most common Grade 3 or 4 non-hematologic toxicities were anorexia (9.4%), fatigue (9.4%), constipation (7.5%),

Table 3 Toxicity, $n = 53$

	n (%)	
	All grades	≥Grade 3
Hematologic adverse events		
Leukopenia	43 (81.1)	24 (45.3)
Neutropenia	42 (79.2)	28 (52.8)
Anemia	4 (7.5)	2 (3.8)
Thrombocytopenia	6 (11.3)	1 (1.9)
Non-hematologic adverse events		
Nausea	23 (43.4)	1 (1.9)
Constipation	15 (28.3)	4 (7.5)
Diarrhea	15 (28.3)	1 (1.9)
Stomatitis	13 (24.5)	0 (0)
Vomiting	13 (24.5)	0 (0)
Anorexia	26 (49.1)	5 (9.4)
Fatigue	38 (71.7)	5 (9.4)
Pyrexia	18 (34)	0 (0)
Edema	9 (17.0)	1 (1.9)
Hypersensitivity	2 (3.8)	1 (1.9)
Myalgia	16 (30.2)	0 (0)
Arthralgia	15 (28.3)	0 (0)
Neuropathy: sensory	43 (81.1)	3 (5.7)
Neuropathy: motor	8 (15.1)	0 (0)
Pneumonia	6 (11.3)	4 (7.5)
Febrile neutropenia	2 (3.8)	2 (3.8)
Infection	2 (3.8)	1 (1.9)
Interstitial lung disease	3 (5.7)	2 (3.8)
Alopecia	44 (83.0)	0 (0)
Rash	15 (28.3)	1 (1.9)
Nail disorder	5 (9.4)	0 (0)

pneumonia (7.5%), and sensory neuropathy (5.7%). Sensory neuropathy of any grade was observed in 81.1% of patients. Other common non-hematologic toxicities of any grade were alopecia (83.0%), fatigue (71.7%), anorexia (49.1%), nausea (43.4%), pyrexia (34.0%), myalgia (30.2%), constipation (28.3%), diarrhea (28.3%), arthralgia (28.3%), rash (28.3%), stomatitis (24.5%), and vomiting (24.5%). One patient experienced a Grade 4 hypersensitivity reaction (anaphylactic shock) and recovered with appropriate measures and treatment discontinuation.

The most common forms of Grade 3 or 4 hematologic toxicities were neutropenia (52.8%) and leukopenia (45.3%). Grade 3 or 4 thrombocytopenia was rare, occurring in only 1 patient (1.9%). Neutropenia and leukopenia of any grade occurred in 81.1% and 79.2% of patients, respectively. Out of a total of 146 cycles delivered, leukopenia of any grade occurred in 81.5% (119) of cycles and neutropenia occurred in 80.8% (118) of cycles. Median nadirs of leukocyte count and neutrophil count were 2,000/μL (range: 800–2,980/μL) and 957/μL (range: 101–1,463/μL), respectively. In most cases, leukocyte and neutrophil counts returned to normal (decreases of Grade 1 or lower) and median time to recovery was 14 days for leukocytes and 8.5 days for neutrophils.

There were a total of 15 serious adverse events related to paclitaxel in 12 patients: pneumonia (4), interstitial lung disease (3), febrile neutropenia (2), ileus (1), hypersensitivity (1), herpes zoster (1), tuberculosis (1), anorexia (1), and respiratory failure (1). One patient had 4 serious laboratory adverse events related to paclitaxel: anemia, neutropenia, leukopenia, and thrombocytopenia. There were no treatment-related deaths.

Adverse events resulted in discontinuation of therapy in 18 (34.0%) patients, the most common events being myelosuppression ($n = 3$) and sensory neuropathy ($n = 3$). Dose reductions for toxicity occurred in 23 patients (43.4%). The most common reason for a dose reduction for toxicity was sensory neuropathy (10 [18.9%]). Adverse events leading to skipped or delayed dosing occurred in 126 courses (19.6%) and 21 courses (22.6%), respectively. The most common reason for skipped or delayed doses was neutropenia (28 [52.8%]).

Discussion

Results of this study demonstrate that weekly paclitaxel 100 mg/m^2 administered by 1-h infusion (median dose intensity 78.5 mg/m^2/week) shows substantial anti-tumor activity in patients with advanced or recurrent esophageal cancer. In this study, the overall response rate was 44.2% and included four complete responders. The median duration of response was 4.8 months (95% CI: 3.2, 7.1 months) in 23 responding patients, and their median treatment time of 5.9 months was therefore long.

Patients had either progressed on platinum-based therapy or they had discontinued treatment for reasons of toxicity. The rate of response observed in the current trial is considerably higher than the 13% response rate observed by Ilson et al. [21] in a previous study of weekly paclitaxel for a similar patient population (advanced or recurrent esophageal cancer). Moreover, the latter study enrolled patients with or without prior chemotherapy, and only 1 partial response (1/21, 5%) was observed among patients previously treated. The higher response rate observed in our study and the activity against esophageal cancer refractory to prior chemotherapy may be due to the higher dose of paclitaxel administered (100 mg/m^2/week versus 80 mg/m^2/week) in the current study. Most patients in the current study had squamous cell carcinoma, whereas two-third of the patients in Ilson study had adenocarcinoma.

There is currently no standard systemic therapy for advanced or recurrent esophageal cancer, and therefore response rates are of interest in a palliative setting. As expected, the response rate in the current study was higher among patients with recurrent (48.8%) than among those with advanced disease (27.3%). Although a small number of patients with metastatic disease were included in this study, the rate of response compares favorably to rates achieved with other single agents used in populations with advanced esophageal carcinoma, e.g., docetaxel and vinorelbine [25, 26].

In the current trial, partial response or stable disease was seen in 7/11 patients with metastatic disease. Among all patients who did not respond, 48.3% (14/29) showed stabilization of disease on therapy. Median overall survival for all patients was 10.4 months. Other studies have reported median survival times of between 7 and 13 months for patients with recurrent or advanced esophageal carcinoma treated with paclitaxel alone or in combination with chemotherapy [13, 15, 21, 27]. In this study, the response rates for recurrent/advanced patients with a TFI >6 months and with a TFI ≤6 months were 61.5% (8/13) and 38.5% (15/39), respectively. However, there was no significant relationship between TFI and response rate as has been seen in other studies [28].

Paclitaxel was fairly well tolerated in this study. The most common types of Grade 3–4 hematologic toxicity were neutropenia and leukopenia, which were relatively common. However, only 2 patients (3.8%) developed febrile neutropenia. While the majority of patients (81.1%) experienced sensory neuropathy of Grade 1 or higher, only 5.7% of patients experienced Grade 3–4 sensory neuropathy. Dose reductions for toxicity were required for 23 (43.4%) patients, most commonly for sensory neuropathy, leukopenia, and neutropenia. The median time from nadir

to recovery was 14 days for leukopenia and 8.5 days for neutropenia. There were no treatment-related deaths. All treatment-related serious adverse events were previously known adverse effects of paclitaxel.

In summary, our results show that paclitaxel administered weekly at a dose of 100 mg/m^2 has high activity and manageable toxicity in patients with advanced or recurrent esophageal cancer. While esophageal cancer is relatively sensitive to chemotherapy, relapse is common and responses are typically short-lived, underscoring the need for second-line chemotherapy. Our study suggests that paclitaxel at the dose administered is a promising option for patients who have been previously treated with platinum-based chemotherapy and warrants further investigation in a phase III study.

Acknowledgments The Paclitaxel Esophageal Cancer Study Group comprises the following institutions: National Cancer Center Hospital, Tokyo; National Cancer Center Hospital East, Chiba; Shizuoka Cancer Center, Shizuoka; Aichi Cancer Center Central Hospital, Aichi; Osaka Medical College, Osaka; Tochigi Cancer Center, Tochigi; Kinki University School of Medicine, Osaka; The Cancer Institute Hospital of JFCR, Tokyo; Kitasato University East Hospital, Kanagawa; Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka; Saitama Cancer Center, Saitama; and Graduate School of Medicine, Osaka University, Osaka, Japan. This study was supported by a grant from Bristol-Myers K.K.

References

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ (2007) Cancer statistics, 2007. CA Cancer J Clin 57:43–66
2. Parkin DM, Bray F, Ferlay J, Pisani P (2005) Global cancer statistics, 2002. CA Cancer J Clin 55:74–108
3. Blot WJ, McLaughlin JK (1999) The changing epidemiology of esophageal cancer. Semin Oncol 26:2–8
4. Devesa SS, Blot WJ, Fraumeni JF Jr (1998) Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. Cancer 83:2049–2053
5. Vizcaino AP, Moreno V, Lambert R, Parkin DM (2002) Time trends incidence of both major histologic types of esophageal carcinomas in selected countries, 1973–1995. Int J Cancer 99: 860–868
6. Akiyama H, Tsurumaru M, Udagawa H, Kajiyama Y (1994) Radical lymph node dissection for cancer of the thoracic esophagus. Ann Surg 220:364–372
7. Baba M, Aikou T, Yoshinaka H, Natsugoe S, Fukumoto T, Shimazu H, Akazawa K (1994) Long-term results of subtotal esophagectomy with three-field lymphadenectomy for carcinoma of the thoracic esophagus. Ann Surg 219:310–316
8. Fujita H, Kakegawa T, Yamana H, Shima I, Toh Y, Tomita Y, Fujii T, Yamasaki K, Higaki K, Noake T (1995) Mortality and morbidity rates, postoperative course, quality of life, and prognosis after extended radical lymphadenectomy for esophageal cancer. Comparison of three-field lymphadenectomy with two-field lymphadenectomy. Ann Surg 222:654–662
9. Mera K, Otsu A (2003) Practice of chemotherapy in esophageal cancer. Clin Gastroenterol 6:291–297
10. Iizuka T, Kakegawa T, Ide H, Ando N, Watanabe H, Tanaka O, Takagi I, Isono K, Ishida K, Arimori M (1992) Phase II evaluation of cisplatin and 5-fluorouracil in advanced squamous cell carcinoma of the esophagus: a Japanese Esophageal Oncology Group Trial. Jpn J Clin Oncol 22:172–176
11. Ajani JA, Ilson DH, Daugherty K, Pazdur R, Lynch PM, Kelsen DP (1994) Activity of taxol in patients with squamous cell carcinoma and adenocarcinoma of the esophagus. J Natl Cancer Inst 86:1086–1091
12. Gong Y, Ren L, Zhou L, Zhu J, Huang M, Zhou X, Wang J, Lu Y, Hou M, Wei Y (2009) Phase II evaluation of nedaplatin and paclitaxel in patients with metastatic esophageal carcinomas. Cancer Chemother Pharmacol 64:327–333
13. El Rayes BF, Shields A, Zalupski M, Heilbrun LK, Jain V, Terry D, Ferris A, Philip PA (2004) A phase II study of carboplatin and paclitaxel in esophageal cancer. Ann Oncol 15:960–965
14. Ilson DH, Ajani J, Bhalla K, Forastiere A, Huang Y, Patel P, Martin L, Donegan J, Pazdur R, Reed C, Kelsen DP (1998) Phase II trial of paclitaxel, fluorouracil, and cisplatin in patients with advanced carcinoma of the esophagus. J Clin Oncol 16:1826–1834
15. Lin CC, Hsu CH, Cheng JC, Wang HP, Lee JM, Yeh KH, Yang CH, Lin JT, Cheng AL, Lee YC (2007) Concurrent chemo radiotherapy with twice weekly paclitaxel and cisplatin followed by esophagectomy for locally advanced esophageal cancer. Ann Oncol 18:93–98
16. Abu-Rustum NR, Aghajanian C, Barakat RR, Fennelly D, Shapiro F, Spriggs D (1997) Salvage weekly paclitaxel in recurrent ovarian cancer. Semin Oncol 24:S15
17. Fennelly D, Aghajanian C, Shapiro F, O'Flaherty C, McKenzie M, O'Connor C, Tong W, Norton L, Spriggs D (1997) Phase I and pharmacologic study of paclitaxel administered weekly in patients with relapsed ovarian cancer. J Clin Oncol 15:187–192
18. Horiguchi J, Rai Y, Tamura K, Taki T, Hisamatsu K, Ito Y, Seriu T, Tajima T (2009) Phase II study of weekly paclitaxel for advanced or metastatic breast cancer in Japan. Anticancer Res 29:625–630
19. DeVore RF III, Jagasia M, Johnson DH (1997) Paclitaxel by either 1 h or 24 h infusion in combination with carboplatin in advanced non-small cell lung cancer: preliminary results comparing sequential phase II trials. Semin Oncol 24:S12
20. Maier-Lenz H, Hauns B, Haering B, Koetting J, Mross K, Unger C, Bauknecht T, du BA, Meerpohl HG, Hollaender N, Diergarten K (1997) Phase I study of paclitaxel administered as a 1 h infusion: toxicity and pharmacokinetics. Semin Oncol 24:S19
21. Ilson DH, Wadleigh RG, Leichman LP, Kelsen DP (2007) Paclitaxel given by a weekly 1 h infusion in advanced esophageal cancer. Ann Oncol 18:898–902
22. Nokihara H, Tamura T, Matsumoto Y (2002) Weekly paclitaxel in solid tumor, a phase I trial. Jpn J Lung Cancer 42. Abstract E-13
23. Seidman A, Hudis C, Albanell J, Tong W, Tepler I, Currie V, Moynahan M, Theodoulou M, Gollub M, Baselga J, Norton L (1998) Dose-dense therapy with weekly 1 h paclitaxel infusions in the treatment of metastatic breast cancer. J Clin Oncol 16:3353–3361
24. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG (2000) New guidelines to evaluate the response to treatment in solid tumors. European organization for research and treatment of cancer, national cancer institute of the United States, national cancer institute of Canada. J Natl Cancer Inst 92:205–216
25. Conroy T, Etienne PL, Adenis A, Wagener DJ, Paillot B, Francois E, Bedenne L, Jacob JH, Seitz JF, Bleiberg H, Van Pottelsberghe C, Van Glabbeke M, Delgado FM, Merle S, Wils J (1996) Phase II trial of vinorelbine in metastatic squamous cell esophageal carcinoma. European organization for research and treatment of cancer gastrointestinal treat cancer cooperative group. J Clin Oncol 14:164–170

26. Muro K, Hamaguchi T, Ohtsu A, Boku N, Chin K, Hyodo I, Fujita H, Takiyama W, Ohtsu T (2004) A phase II study of single-agent docetaxel in patients with metastatic esophageal cancer. Ann Oncol 15:955–959
27. Cho SH, Chung IJ, Song SY, Yang DH, Byun JR, Kim YK, Lee JJ, Na KJ, Kim HJ (2005) Bi-weekly chemotherapy of paclitaxel and cisplatin in patients with metastatic or recurrent esophageal cancer. J Korean Med Sci 20:618–623
28. Takashima A, Shiraro K, Hirashima Y, Takahari D, Okita N, Akatsuka S, Eguchi Nakajima T, Matsubara J, Yasui H, Asakawa T, Kato K, Hamguchi T, Muro K, Yamada Y, Shimada Y (2008) Chemosensitivity of patients with recurrent esophageal cancer receiving perioperative chemotherapy. Dis Esophagus 21:607–611

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

Hiroyuki Daiko[1,*], Ryuichi Hayashi[1], Minoru Sakuraba[1], Mitsuru Ebihara[1], Masakazu Miyazaki[1], Takeshi Shinozaki[1], Masahisa Saikawa[1], Sadatomo Zenda[2], Mitsuhiko Kawashima[2], Makoto Tahara[3], Toshihiko Doi[3] and Atsushi Ohtsu[3]

[1]Department of Surgery, National Cancer Center Hospital East, [2]Division of Radiation Oncology, National Cancer Center Hospital East and [3]Division of Digestive Endoscopy and Gastrointestinal Oncology, National Cancer Center Hospital East, Chiba, Japan

*For reprints and all correspondence: Hiroyuki Daiko, Department of Surgery, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan. E-mail: hdaikou@east.ncc.go.jp

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.

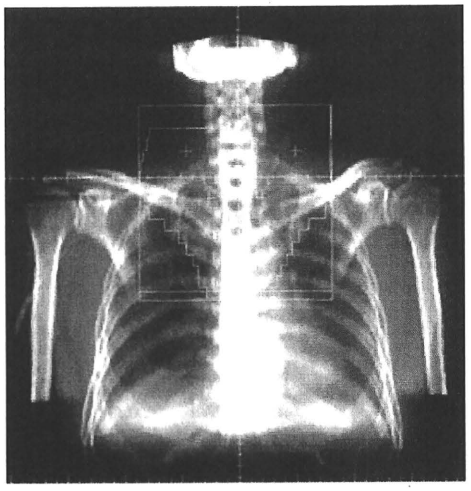


Figure 1. Planning film demonstrating a representative treatment field for post-operative radiation in a patient with metastases to the upper mediastinal lymph nodes.

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.

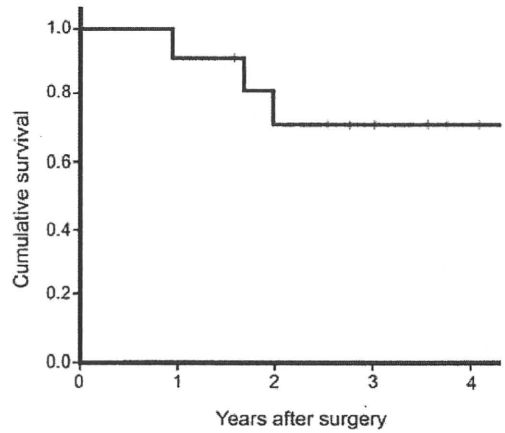


Figure 2. Overall survival curve.

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.

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.

Radiotherapy and Oncology 95 (2010) 240–244

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Esophageal cancer radiotherapy

Analysis of dose–volume histogram parameters for radiation pneumonitis after definitive concurrent chemoradiotherapy for esophageal cancer

Hirofumi Asakura [a,*], Takayuki Hashimoto [a], Sadamoto Zenda [a,d], Hideyuki Harada [a], Koichi Hirakawa [a,e], Masashi Mizumoto [a], Kazuhisa Furutani [a], Shuichi Hironaka [b], Hiroshi Fuji [c], Shigeyuki Murayama [c], Narikazu Boku [b], Tetsuo Nishimura [a]

[a] Division of Radiation Oncology; [b] Division of Gastrointestinal Oncology; and [c] Division of Proton Therapy, Shizuoka Cancer Center Hospital, Shizuoka, Japan; [d] Division of Radiation Oncology, National Cancer Center Hospital East, Chiba, Japan; [e] Department of Radiology, Faculty of Medicine, Saga University, Saga, Japan

ARTICLE INFO

Article history:
Received 3 February 2009
Received in revised form 7 February 2010
Accepted 8 February 2010
Available online 10 March 2010

Keywords:
Esophageal cancer
Chemoradiotherapy
Radiation pneumonitis
Dose–volume histogram

ABSTRACT

Purpose: To evaluate dose–volume histogram (DVH) parameters as predictors of radiation pneumonitis (RP) in esophageal cancer patients treated with definitive concurrent chemoradiotherapy.

Patients and methods: Thirty-seven esophageal cancer patients treated with radiotherapy with concomitant chemotherapy consisting of 5-fluorouracil and cisplatin were reviewed. Radiotherapy was delivered at 2 Gy per fraction to a total of 60 Gy. For most of the patients, two weeks of interruption was scheduled after 30 Gy. The percentage of lung volume receiving more than 5–50 Gy in increments of 5 Gy (V5–V50, respectively), and the mean lung dose (MLD) were analyzed.

Results: Ten (27%) patients developed RP of grade 2; 2 (5%), grade 3; 0 (0%), grade 4; and 1 (3%), grade 5. By univariate analysis, all DVH parameters (i.e., V5–V50 and MLD) were significantly associated with grade $\geqslant 2$ RP ($p < 0.01$). The incidences of grade $\geqslant 2$ RP were 13%, 33%, and 78% in patients with V20s of $\leqslant 24\%$, 25–36%, and $\geqslant 37\%$, respectively. The optimal V20 threshold to predict symptomatic RP was 30.5% according to the receiver operating characteristics curve analysis.

Conclusion: DVH parameters were predictors of symptomatic RP and should be considered in the evaluation of treatment planning for esophageal cancer.

 Radiotherapy and Oncology 95 (2010) 240–244

Radiation pneumonitis (RP) is one of the most dose-limiting toxicities for patients receiving thoracic radiotherapy for lung cancer. There have been many reports discussing the relationship between the incidence of pneumonitis and dose–volume histogram (DVH) parameters of the lung such as the percentage of irradiated volume exceeding 20 Gy (V20) of the lung in lung cancer patients [1–15].

On the one hand, concurrent chemoradiotherapy has become a standard treatment in the nonsurgical management of esophageal cancer [16,17], and RP is one of the major concerns in esophageal cancer patients treated with definitive chemoradiotherapy [18]. Although DVH parameters of the lung are expected to be predictors of RP in esophageal cancer patients treated with concurrent chemoradiotherapy, many different factors, such as the location of the disease, the type of chemotherapeutic agents used and the pretreatment condition of the lung, should be considered when utilizing the data obtained from studies with lung cancer patients for the treatment of esophageal cancer. A retrospective analysis [19] demonstrated that the DVH parameters of the lung were associated with postoperative pulmonary complications among esophageal cancer patients treated with concurrent chemoradiotherapy followed by surgery, but there are few reports on the relationship between DVH parameters and RP in patients of esophageal cancer treated with definitive concurrent chemoradiotherapy.

The purpose of this study is to evaluate DVH parameters as predictors of RP in esophageal cancer patients treated with definitive concurrent chemoradiotherapy.

Patients and methods

The medical and radiation records of all esophageal cancer patients treated with concurrent chemoradiotherapy at Shizuoka Cancer Center Hospital between September 2002 and December 2004 were retrospectively reviewed. Of 129 patients with squamous cell carcinoma, we identified a total of 37 patients who met the following inclusion criteria: (1) carcinoma of thoracic esophagus; (2) concomitant chemotherapy consisting of 5-fluorouracil and cisplatin; (3) follow-up time >1 year from start of radiotherapy; (4) 75 years of age or younger; (5) no previous

* Corresponding author. Address: Division of Radiation Oncology, Shizuoka Cancer Center Hospital, 1007 Shimonagakubo, Nagaizumi, Shizuoka 411-8777, Japan.
E-mail address: h.asakura@scchr.jp (H. Asakura).

0167-8140/$ - see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.radonc.2010.02.006

chemotherapy or radiotherapy; and (6) no previous thoracic surgery.

Thirty patients with shorter than 1 year follow-up were excluded from the analysis. Among these patients, 20 died of esophageal cancer, 2 died of intercurrent disease, 1 died of treatment-related complication (grade 5 RP), and 7 were lost to follow-up.

Radiotherapy was planned to be delivered at 2 Gy per fraction to a total of 60 Gy with a conventional beam arrangement, that is, anteroposterior (AP): posterior–anterior (PA) fields up to 40 Gy followed by off-cord oblique fields. The prescription dose was specified at the International Commission on Radiation Units and Measurements (ICRU) 50 reference point. Treatment was delivered using a linear accelerator with a megavoltage photon beam. Typically, concurrent chemoradiotherapy was performed as follows. The initial AP: PA fields included the primary tumor, the metastatic lymph nodes, and the elective nodal regions. Two weeks of interruption after a total dose of 30 Gy was scheduled, and elective nodal regions were treated to a dose of 40 Gy. The treatment planning was based on CT scans obtained during quiet respiration in the treatment position. Three-dimensional dose calculations were performed using *Pinnacle*^{3} *version7.6c* (ADAC, Milpitas, CA) with tissue density inhomogeneity correction. The planning grid was 4 mm in each dimension. The gross tumor volume was defined as the primary tumor and the metastatic lymph nodes. The clinical target volume for the primary tumor was defined as the gross tumor volume plus about 3 cm craniocaudally. The planning target volumes for the primary tumor and metastatic lymph nodes were determined with 1–2 cm margins. Concurrent chemotherapy consisted of two cycles of cisplatin 40 mg/m^2 on days 1 and 8 and continuous infusion of 5-fluorouracil 400 mg/m^2/day on days 1 to 5 and 8 to 12, repeated every 5 weeks. For most stage I patients, elective nodal irradiation was not performed, no interruption of radiotherapy was scheduled, and concurrent chemotherapy consisted of cisplatin 70 mg/m^2 on day 1 and continuous infusion of 5-fluorouracil 700 mg/m^2/day on days 1 to 4, repeated every 4 weeks. Majority of stage IIA–IVB patients received consolidation chemotherapy consisted of 5-fluorouracil and cisplatin after concurrent chemoradiotherapy.

The lungs were contoured as a single organ. The percentage of lung volume that received more than 5 Gy, 10 Gy, 15 Gy, 20 Gy, 25 Gy, 30 Gy, 35 Gy, 40 Gy, 45 Gy, and 50 Gy (V5–V50, respectively) and the mean lung dose (MLD) were analyzed.

RP was graded based on symptoms described in the medical records and changes in CT images by a consensus of two radiation oncologists according to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAEv3.0). Patients were categorized into a no-RP group (RP of grade 0–1) or an RP group (RP of grade 2–5).

We evaluated the association between some selected DVH parameters (i.e., V10, V20, and V30) and an incident of grade 2 or higher RP.

The relationships between clinical and DVH parameters and the incidence of RP were analyzed using Mann–Whitney's *U* test for quantitative variables and Fisher's exact test for categorical variables. The actuarial incidence of RP was calculated using the Kaplan–Meier method, and the differences between groups were compared using the log-rank test. Patients without grade 2 or higher RP were censored at the time of death or last follow-up. Spearman's rank correlation analysis was used to determine correlations between DVH parameters. Analysis for each DVH parameter using the receiver operating characteristics (ROC) curve was also done to select the most relevant threshold to predict symptomatic RP. Optimal threshold for each DVH parameter was defined as the point yielding the minimal value for $(1 - \text{senitivity})^2 + (1 - \text{specificity})^2$, which was the point on the ROC curve closest to the upper left-hand corner (0, 1) [20]. Data were considered statistically significant at values of $p < 0.05$.

Results

The patients' characteristics are shown in Table 1. There were 36 men and 1 woman with a median age of 64 years (range, 47–75 years). The median follow-up period from the start of radiotherapy was 32.2 months (range, 12.6–47.5 months). The median follow-up for the 24 surviving patients was 33.7 months (range, 19.8–47.5 months). All stage IVB patients in this study were categorized as stage IVB due to the existence of non-regional lymph node metastasis such as supraclavicular lymph node. No patient had visceral metastasis.

The regional lymph nodes were electively irradiated in 30 patients. Thirty-five patients completed the irradiation. Two patients broke irradiation at a total dose of 54 Gy and 56 Gy, due to fever and myelosuppression, respectively.

CT scanning after radiotherapy was performed according to the physician's preference. In most of the cases (35/37), CT scanning was performed within 1 month after the completion of radiotherapy, and was performed variably according to symptoms or the determination of remission status thereafter. The number of times that CT scanning was performed within 6 months after the completion of radiotherapy was 3.9 ± 1.1 (mean ± SD). RP grading is shown in Table 2. Twenty-four patients had grade 0–1 RP (no-RP group), and grade 2 or higher RP were observed in 13 patients (RP group). The median time to develop RP was 4.2 months (range, 3.0–8.3 months).

Table 1
Patient characteristics ($n = 37$).

	No. (%)
Age (year)	
Range	47–75
Median	64
Sex	
Male	36 (97)
Female	1 (3)
Performance status (ECOG)	
0–1	34 (92)
2	3 (8)
3	0 (0)
Stage	
I	6 (16)
IIA	4 (11)
IIB	3 (8)
III	12 (32)
IVA	2 (5)
IVB	10 (27)
Location of primary tumor	
Upper	3 (8)
Middle	25 (68)
Lower	9 (24)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Table 2
Incidence of RP.

Grade (CTCAEv3.0)	No. (%)
0–1	24 (65)
2	10 (27)
3	2 (5)
4	0 (0)
5	1 (3)

Abbreviations: RP, radiation pneumonitis; CTCAEv3.0, Common Terminology Criteria for Adverse Events version 3.0.

Table 3
Univariate analysis of clinical factors related to grade 2 or higher RP.

	RP	no-RP	*p* value
Age (year)			
<64	7	11	0.737
64≤	6	13	
Stage			
I/II	4	9	0.912
III	5	7	
IV	4	8	
Location of primary tumor			
Upper/middle	10	18	1.000
Lower	3	6	

Abbreviation: RP, radiation pneumonitis.

Table 4
Univariate analysis of DVH parameters related to grade 2 or higher RP.

	RP (Mean ± SD)	no-RP	*p* value
MLD (cGy)	1659 ± 389	1074 ± 442	<0.001
V5 (%)	58.2 ± 9.9	40.2 ± 15.5	<0.001
V10	45.4 ± 9.6	30.6 ± 12.4	0.001
V15	39.4 ± 9.7	26.1 ± 11.1	0.002
V20	34.8 ± 9.0	21.6 ± 10.1	<0.001
V25	27.5 ± 8.3	16.0 ± 8.2	<0.001
V30	24.2 ± 7.4	13.5 ± 7.1	<0.001
V35	21.2 ± 6.8	11.6 ± 6.3	<0.001
V40	16.2 ± 6.3	8.6 ± 5.0	<0.001
V45	9.0 ± 4.4	5.2 ± 3.0	0.008
V50	7.0 ± 3.8	3.8 ± 2.3	0.009

Abbreviations: DVH, dose–volume histogram; RP, radiation pneumonitis; SD, standard deviation; MLD, mean lung dose; V5–V50, percentage of lung volume receiving more than 5–50 Gy.

The incidence of RP was investigated as a function of some clinical factors, including age, clinical stage, and location of primary tumors. The results of the univariate analyses are shown in Table 3. None of the clinical factors was significantly associated with RP.

The median MLD of all 37 patients was 1395 cGy (range, 198–2262 cGy). The median V5, V10, V15, V20, V25, V30, V35, V40, V45, and V50 values of all 37 patients were 50% (range, 6–74%), 37% (range, 4–60%), 32% (range, 3–54%), 28% (range, 3–48%), 21% (range, 2–37%), 18% (range, 2–32%), 16% (range, 2–29%), 10% (range, 1–26%), 6% (range, 1–17%), and 4% (range, 1–14%), respectively.

In univariate analysis, all DVH parameters (i.e., V5–V50 and MLD) were found to be significantly associated with grade 2 or higher RP (Table 4).

Spearman's rank correlation coefficients between DVH parameters are shown in Table 5. Close correlations among all DVH parameters were found (range of Spearman r_s, 0.866–0.996; $p < 0.001$), and therefore we did not perform multivariate analysis.

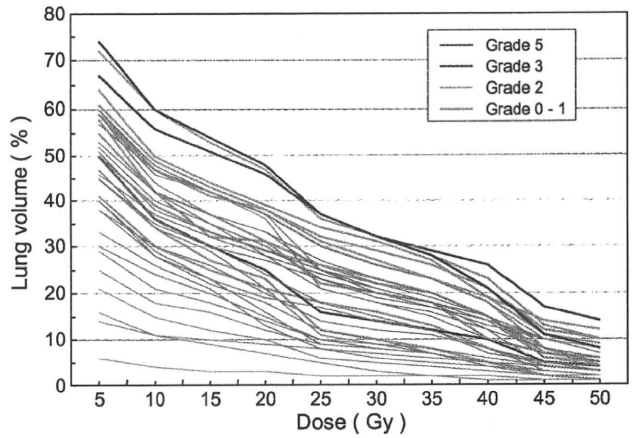


Fig. 1. DVH curves of all 37 patients. Grade 2 or higher RP occurred in 13%, 33%, and 78% of patients with V10 of 35% or less, 36–46%, and 47% or more, respectively. Grade 2 or higher RP occurred in 13%, 33%, and 78% of patients with V20 of 24% or less, 25–36%, and 37% or more, respectively. Grade 2 or higher RP occurred in 13%, 31%, and 88% of patients with V30 of 15% or less, 16–25%, and 26% or more, respectively.

DVH curves of all 37 patients, made by plotting for doses from 5 to 50 Gy in increments of 5 Gy, are shown in Fig.1.

A significant association between selected DVH parameters (i.e., V10, V20 and V30) and the incidence of grade 2 or higher RP was found after data were stratified according to patient subgroups (Table 6). The cumulative incidence curves for RP at grade 2 or higher stratified by V20 are shown in Fig. 2. The 1-year cumulative

Table 6
Observed rates of radiation pneumonitis as a function of DVH parameters.

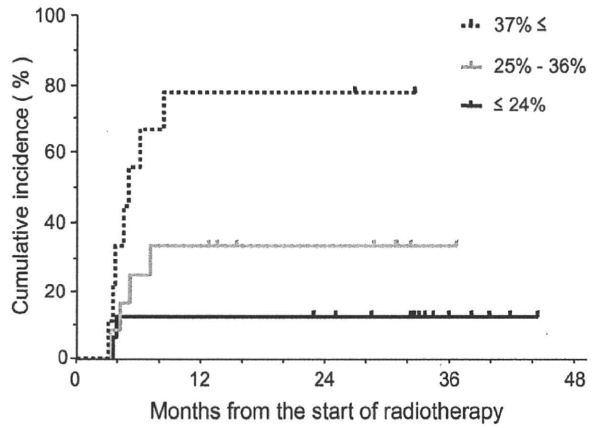
Parameters (%)		RP	no-RP	RP Rate (%)	*p* value
V10	≤35	2	14	13	0.006
	36–46	4	8	33	
	47≤	7	2	78	
V20	≤24	2	14	13	0.006
	25–36	4	8	33	
	37≤	7	2	78	
V30	≤15	2	14	13	0.001
	16–25	4	9	31	
	26≤	7	1	88	

Abbreviations: DVH, dose-volume histogram; RP, radiation pneumonitis; V10-V30, percentage of lung volume receiving more than 10–30 Gy.

Table 5
Spearman's rank correlation coefficients between DVH parameters.

	$p < 0.001$ in each case										
	MLD	V5	V10	V15	V20	V25	V30	V35	V40	V45	V50
MLD	–										
V5	0.983	–									
V10	0.988	0.991	–								
V15	0.980	0.983	0.994	–							
V20	0.994	0.984	0.993	0.989	–						
V25	0.971	0.935	0.947	0.934	0.963	–					
V30	0.967	0.934	0.946	0.931	0.960	0.996	–				
V35	0.969	0.940	0.948	0.935	0.962	0.994	0.995	–			
V40	0.966	0.928	0.939	0.928	0.956	0.985	0.982	0.984	–		
V45	0.931	0.910	0.909	0.909	0.916	0.913	0.909	0.914	0.939	–	
V50	0.898	0.877	0.872	0.866	0.873	0.883	0.879	0.889	0.915	0.983	–

Abbreviations: DVH, dose–volume histogram; MLD, mean lung dose; V5–V50, percentage of lung volume receiving more than 5–50 Gy.



No. of patients at risk

37% ≤	9	6	3	2	2	2	2	1	1	0	0	0
25% - 36%	12	11	8	8	5	5	5	5	2	1	0	0
≤ 24%	16	14	14	14	14	14	13	12	11	4	2	1

Fig. 2. Actuarial curve of grade 2 or higher RP stratified by V20. The actuarial incidences of RP at 1 year are 12.5%, 33.3%, and 77.8% in patients with V20 of 24% or less, 25–36%, and 37% or more, respectively ($p = 0.003$).

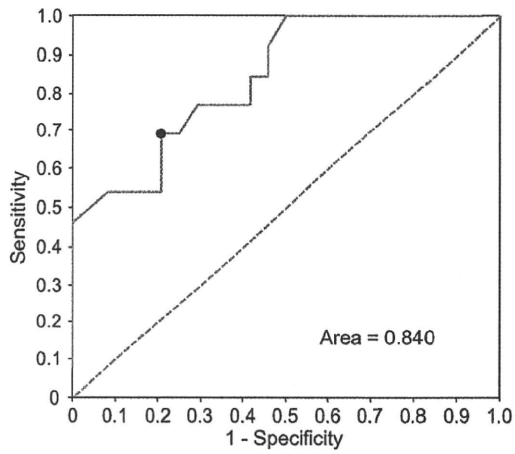


Fig. 3. ROC curve and the associated area for V20 as a predictor for grade 2 or higher RP. Optimal threshold value is 30.5% (plotted using black circle) and corresponds to sensitivity of 0.692 and specificity of 0.792.

incidences of grade 2 or higher RP were 12.5%, 33.3%, and 77.8% in patients with V20 values of 24% or less, 25–36%, and 37% or more, respectively ($p = 0.003$).

Results of the ROC curve analysis are shown in Table 7. Area under the ROC curve (AUC) for V10, V20, and V30 were 0.829, 0.840, and 0.854, respectively. Optimal threshold for V10, V20, and V30 were 38.5%, 30.5%, and 21.5%, respectively. The ROC curve and optimal threshold for V20 are shown in Fig. 3. The incidence of grade 2 or higher RP was 64.3% in patients with V20 values higher than determined threshold (30.5%) whereas it was 17.4% in patients with V20 values lower than the determined threshold.

Stage I patients treated on a modified chemoradiation schedule are included in this study. Therefore, we have confirmed the analysis of the residual caseload (stage IIA–IVB), which also resulted in the same findings. Focusing on the results for V20 corresponding to those in Table 4, we would draw the same conclusion that this DVH parameter was a significant predictor of grade 2 or higher RP ($p = 0.007$). Also, we could say the same thing regarding the results of the comparison of the cumulative incidence curves for RP at grade 2 or higher stratified by V20 ($p = 0.025$).

Table 7
ROC curve analysis for DVH parameters related to grade 2 or higher RP.

	AUC	95% Confidence interval for AUC	Optimal threshold	
			Value	Sensitivity/ specificity (%)
MLD	0.837	0.706–0.967	1431 cGy	76.9/70.8
V5	0.838	0.708–0.968	54.0%	69.2/79.2
V10	0.829	0.696–0.961	38.5%	76.9/70.8
V15	0.809	0.669–0.950	36.0%	61.5/79.2
V20	0.840	0.711–0.969	30.5%	69.2/79.2
V25	0.845	0.711–0.978	25.5%	69.2/91.7
V30	0.854	0.726–0.983	21.5%	69.2/87.5
V35	0.862	0.737–0.988	19.5%	69.2/91.7
V40	0.833	0.692–0.975	14.5%	69.2/83.3
V45	0.766	0.599–0.933	5.5%	76.9/62.5
V50	0.761	0.591–0.932	3.5%	84.6/58.3

Abbreviations: ROC, receiver operating characteristics; AUC, area under the ROC curve; MLD, mean lung dose; V5–V50, percentage of lung volume receiving more than 5–50 Gy.

Discussion

The present study showed the relationship between DVH parameters and the occurrence of symptomatic RP in esophageal cancer patients treated with definitive chemoradiotherapy. The incidence of grade 2 or higher RP in patients with a V20 of ⩾37% was high (78%) in the present study. In studies investigating the relationship between the incidence of RP and DVH parameters in lung cancer patients, many authors [2,4,9,12,13] have graded RP according to the National Cancer Institute-Common Toxicity Criteria version 2.0 (NCI-CTCv2.0), which defines grade 2 toxicity as showing radiographic changes and requiring steroids, and grade 3 toxicity as showing radiographic changes and requiring oxygen. In the present study, RP was graded according to CTCAEv3.0, in which grade 2 toxicity is defined as symptomatic, not interfering with ADL, and grade 3 as symptomatic, interfering with ADL or oxygen indicated. Some patients defined as grade 2 RP in CTCAEv3.0 might be defined as grade 1 RP in NCI-CTCv2.0, and some patients defined as grade 3 in CTCAEv3.0 might be defined as grade 2 in NCI-CTCv2.0. These differences should be considered when comparing the incidence and severity of RP between the present study and other publications.

In addition, from the standpoint of the evaluation of radiation-induced lung toxicity, it is sometimes difficult to distinguish clearly between pneumonitis and subsequent pulmonary fibrosis. Because it is possible that patients with symptoms of radiation pulmonary fibrosis may be included in the RP group, the term "radiation pneumopathy", which encompass radiation pneumonitis and pulmonary fibrosis, might be suitable for the subjects of this study.

The optimal V20 threshold to predict symptomatic RP was 30.5% according to the ROC curve analysis; however, grade 5 RP occurred in one patient with a V20 of 25%. This patient showed interstitial pneumonia on CT imaging prior to chemoradiotherapy. The comorbidity of the patient might influence the occurrence of severe lung toxicity regardless of the comparatively low V20.

Several DVH parameters such as V5, V10, V15, V20, V30, and MLD have been reported as predictors of the incidence of RP in lung cancer patients. However, if DVH parameters have correlations with each other, it would be difficult to select the most valuable parameter for predicting the incidence of RP. In the current study, all DVH parameters (i.e., V5–V50 and MLD) were found to be significantly associated with grade 2 or higher RP (Table 4). Thus, we can use not only V20 but also other DVH parameters such as V10 and V30 to predict the incidence of RP when we perform

radiotherapy treatment planning with conventional beam arrangements for esophageal cancer (Table 6). Because of the close correlations among all DVH parameters (Table 5), the single DVH parameter that is most important in predicting the occurrence of RP could not be determined.

Recently, Wang et al. [21] reported that the radiation dosimetric factors were not associated with the time to occurrence of grade $\geqslant 2$ RP in esophageal cancer patients treated with definitive chemoradiotherapy. Although the median V5 and V10 in their study (=59% and 43%, respectively) were higher than those of the current study, the median V20 in their study (=23%) was lower than that of the current study. The prescribed doses delivered to 95% of the planning target volume ranged from 45.0 to 50.4 Gy in their study. As the authors mentioned in their report, the radiation dose used in their study was relatively low, which might have influenced the difference in the results between their study and the current study.

The characteristics of patients analyzed in the current study differ from the characteristics of patients with esophageal malignancies in Western countries, and this difference should be taken into account to evaluate the results of this study. In Japan, more than 90% of primary esophageal malignancies are SCC, and esophageal adenocarcinoma is a rare disease [22]. Therefore we focused on SCC in the present study. In fact, only two patients were excluded from the analysis due to adenocarcinoma. This may explain the finding that 68% of the tumors in the present study were tumors of the mid-esophagus. The number of female esophageal cancer patients is also small in Japan, and only one patient analyzed in this study was female.

Due to the strict inclusion criteria of this study, the number of patients recruited in the present study was not very large. The study is unique, however, in that the patient characteristics are homogeneous (i.e., no patient received induction chemotherapy, all patients received concurrent chemotherapy consisting of 5-fluorouracil and cisplatin, and all patients received radiotherapy with conventional beam arrangements) compared with many of the studies involving lung cancer patients. On the other hand, the results of the current study may be applicable only for the limited number of patients who satisfy the inclusion criteria of this study. Because the shape of the DVH curves and the radiation dose received by the lung in each treatment fraction may differ between radiotherapy techniques using conventional beam arrangements (i.e., AP:PA fields followed by off-cord oblique fields) and three-dimensional conformal radiotherapy using multiple fields applied simultaneously during each treatment fraction, the implications of each DVH parameter may differ from one another, and the threshold value of the DVH parameters needed to predict symptomatic RP may vary in each radiotherapy technique, and thus further studies addressing this issue are needed.

Conclusion

Our findings suggest that DVH parameters are predictors of symptomatic RP after definitive concurrent chemoradiotherapy for esophageal cancer and should be considered in the evaluation of treatment planning.

Conflict of interest statement

The authors have no conflict of interest in connection with the paper.

Acknowledgments

The authors thank Haruo Yamashita (medical physicist, Division of Proton Therapy, Shizuoka Cancer Center) and Atsushi Kawaguchi (biostatistician, Biostatistics Center, Kurume University) for their support in this analysis.

References

[1] Graham MV, Purdy JA, Emami B, et al. Clinical dose–volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys 1999;45:323–9.
[2] Hernando ML, Marks LB, Bentel GC, et al. Radiation-induced pulmonary toxicity: a dose–volume histogram analysis in 201 patients with lung cancer. Int J Radiat Oncol Biol Phys 2001;51:650–9.
[3] Yorke ED, Jackson A, Rosenzweig KE, et al. Dose–volume factors contributing to the incidence of radiation pneumonitis in non-small-cell lung cancer patients treated with three-dimensional conformal radiation therapy. Int J Radiat Oncol Biol Phys 2002;54:329–39.
[4] Tsujino K, Hirota S, Endo M, et al. Predictive value of dose–volume histogram parameters for predicting radiation pneumonitis after concurrent chemoradiation for lung cancer. Int J Radiat Oncol Biol Phys 2003;55:110–5.
[5] Claude L, Perol D, Ginestet C, et al. A prospective study on radiation pneumonitis following conformal radiation therapy in non-small-cell lung cancer: clinical and dosimetric factors analysis. Radiother Oncol 2004;71:175–81.
[6] Kim TH, Cho KH, Pyo HR, et al. Dose–volumetric parameters for predicting severe radiation pneumonitis after three-dimensional conformal radiation therapy for lung cancer. Radiology 2005;235:208–15.
[7] Wang S, Liao ZX, Wei X, et al. Analysis of clinical and dosimetric factors associated with treatment related pneumonitis (TRP) in patients with non-small-cell lung cancer (NSCLC) treated with concurrent chemotherapy (CCT) and three-dimensional conformal radiotherapy (3D-CRT). Int J Radiat Oncol Biol Phys 2006;66:1399–407.
[8] Rancati T, Ceresoli GL, Gagliardi G, Schipani S, Cattaneo GM. Factors predicting radiation pneumonitis in lung cancer patients: a retrospective study. Radiother Oncol 2003;67:275–83.
[9] Fay M, Tan A, Fisher R, MacManus M, Wirth A, Ball D. Dose–volume histogram analysis as predictor of radiation pneumonitis in primary lung cancer patients treated with radiotherapy. Int J Radiat Oncol Biol Phys 2005;61:1355–63.
[10] Kwa SL, Lebesque JV, Theuws JC, et al. Radiation pneumonitis as a function of mean lung dose: an analysis of pooled data of 540 patients. Int J Radiat Oncol Biol Phys 1998;42:1–9.
[11] Fu XL, Huang H, Bentel G, et al. Predicting the risk of symptomatic radiation-induced lung injury using both the physical and biologic parameters V(30) and transforming growth factor beta. Int J Radiat Oncol Biol Phys 2001;50:899–908.
[12] Schallenkamp JM, Miller RC, Brinkmann DH, Foote T, Garces YI. Incidence of radiation pneumonitis after thoracic irradiation: dose–volume correlates. Int J Radiat Oncol Biol Phys 2007;67:410–6.
[13] Chang DT, Olivier KR, Morris CG, et al. The impact of heterogeneity correction on dosimetric parameters that predict for radiation pneumonitis. Int J Radiat Oncol Biol Phys 2006;65:125–31.
[14] Jin H, Tucker SL, Liu HH, et al. Dose–volume thresholds and smoking status for the risk of treatment-related pneumonitis in inoperable non-small cell lung cancer treated with definitive radiotherapy. Radiother Oncol 2009;91:427–32.
[15] Dehing-Oberije C, De Ruysscher D, van Baardwijk A, Yu S, Rao B, Lambin P. The importance of patient characteristics for the prediction of radiation-induced lung toxicity. Radiother Oncol 2009;91:421–6.
[16] Kleinberg L, Forastiere AA. Chemoradiation in the management of esophageal cancer. J Clin Oncol 2007;25:4110–7.
[17] Berger B, Belka C. Evidence-based radiation oncology: oesophagus. Radiother Oncol 2009;92:276–90.
[18] Ishikura S, Nihei K, Ohtsu A, et al. Long-term toxicity after definitive chemoradiotherapy for squamous cell carcinoma of the thoracic esophagus. J Clin Oncol 2003;21:2697–702.
[19] Wang SL, Liao Z, Vaporciyan AA, et al. Investigation of clinical and dosimetric factors associated with postoperative pulmonary complications in esophageal cancer patients treated with concurrent chemoradiotherapy followed by surgery. Int J Radiat Oncol Biol Phys 2006;64:692–9.
[20] Akobeng AK. Understanding diagnostic tests 3: receiver operating characteristic curves. Acta Paediatr 2007;96:644–7.
[21] Wang S, Liao Z, Wei X, et al. Association between systemic chemotherapy before chemoradiation and increased risk of treatment-related pneumonitis in esophageal cancer patients treated with definitive chemoradiotherapy. J Thorac Oncol 2008;3:277–82.
[22] Japan Esophageal Society. Comprehensive registry of esophageal cancer in Japan. Available at http://esophagus.jp/crec.html.

ORIGINAL ARTICLE

IMPORTANCE OF COMORBIDITY IN HYPOPHARYNGEAL CANCER

Akihiro Homma, MD, PhD, Tomohiro Sakashita, MD, Nobuhiko Oridate, MD, PhD, Fumiyuki Suzuki, MD, PhD, Seigo Suzuki, MD, PhD, Hiromitsu Hatakeyama, MD, PhD, Takatsugu Mizumachi, MD, PhD, Shigenari Taki, MD, Satoshi Fukuda, MD, PhD

Department of Otolaryngology-Head and Neck Surgery, Hokkaido University Graduate School of Medicine, Kita 15, Nishi 7, Kita-ku, Sapporo 060-8638, Japan. E-mail: ak-homma@med.hokudai.ac.jp

Accepted 20 March 2009
Published online 17 June 2009 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/hed.21158

Abstract: *Background.* Comorbidity has an impact on survival in laryngeal cancer in several reports. However, the importance of comorbidity in hypopharyngeal cancer (HPC) has not been reported.

Methods. A retrospective medical record review of 156 patients with HPC treated between 1995 and 2005 was performed. Comorbid illness was measured by the Adult Comorbidity Evaluation-27. A Cox proportional hazards model was used to determine the factors related to overall survival.

Results. Comorbidity was absent in 55 (35.2%) of the patients, mild in 39 (25%), moderate in 28 (17.9%), and severe in 34 (21.8%). There were statistically significant differences between the survival rates in accord with age, stage, subsite, and comorbidity (45.1% for none or mild vs 27.7% for moderate or severe; $p = .0073$). Age, stage, and comorbidity were identified as independent prognostic factors in the multivariate analysis.

Conclusion. Comorbidity, along with the clinical stage, should be considered in treatment planning for patients with HPC. © 2009 Wiley Periodicals, Inc. *Head Neck* **32:** 148–153, 2010

Correspondence to: A. Homma

Contract grant sponsor: Ministry of Education, Culture, Sports, Science and Technology, Japan.

This article was presented at the 7th International Conference on Head and Neck Cancer, July 19–23, 2008, San Francisco, California, USA.

Keywords: head and neck cancer; hypopharyngeal cancer; comorbidity; ACE-27; prognosis

The overall prognosis of patients with cancer of the hypopharynx remains poor. Hypopharyngeal cancers (HPCs) are usually of advanced primary stage with a high tendency for submucosal spread and enlarged ipsilateral or bilateral regional lymph node deposits. These features combine to make locoregional control of such cancers difficult. Although the ability to achieve locoregional control and/or preservation of organ function by surgery or radiotherapy with chemotherapy has improved, the survival rates remain essentially unchanged. This is attributed to the rising incidence of distant metastases and intercurrent diseases, as well as second primary malignancies.[1] In addition, many patients with HPC have comorbidities and/or impaired nutritional status. These factors should be taken into account, along with tumor-node-metastasis (TNM) clinical stage, when deciding on the optimal therapy.

Comorbidity has been shown to play a major role in the treatment, outcome, and prognosis of

a variety of malignancies.[2–4] The Adult Comorbidity Evaluation-27 index (ACE-27) is a validated instrument that has been widely used to assess head and neck cancer.[5] The ACE-27 is a modified version of the original Kaplan-Feinstein index,[6] which was developed initially for adult-onset diabetes mellitus, and includes items pertinent to cancer. The ACE-27 score has been shown to have an impact on survival in laryngeal cancer in several reports.[7–9] However, the importance of comorbidity in HPC has not yet been reported. The aims of this study were to identify, quantify, and analyze the impact of comorbidity burden, as assessed by the ACE-27, on patients with HPC at our institution.

MATERIALS AND METHODS

A retrospective medical record review of 156 patients with previously untreated squamous carcinomas of the hypopharynx who were treated at Hokkaido University Hospital, Japan, between 1995 and 2005 was performed. The age at diagnosis, sex, and performance status measured using The Eastern Cooperative Oncology Group performance status score before treatment[10] were included in this analysis.

Comorbidity factors were classified using the ACE-27, which includes 27 different cogent comorbid ailments.[11] In this system, comorbidity is classified into 3 categories in accord with severity: severe, moderate, and mild. An overall comorbidity score is determined in accord with the highest single scoring ailment, except when 2 or more moderate ailments are present; in this situation, the overall comorbidity score is designated severe.

At the time of initial diagnosis, the TNM staging in accord with the 2002 American Joint Committee on Cancer criteria was recorded and used in our analyses. The first course of therapy was recorded, as well as any therapeutic complications and recurrence.

Statistical Analysis. All patients were closely observed during the follow-up period, which ranged in length from 17 to 164 months (median, 79 months; mean, 87 months). Data were entered into the Statview software package database (Version 4.5; Abacus Concepts, Berkeley, CA). The follow-up period was defined as the time from the first antineoplastic therapy for HPC at the first visit to Hokkaido University Hospital until the date of last contact or death. The overall survival (OS) probability was calculated using the Kaplan-Meier method and was compared using the log-rank test. The level of statistical significance was $p < .05$. For the determination of factors related to OS, the Cox proportional hazards model was used. Contingency table analyses based on chi-square statistics were used to determine the statistical significance of associations between categorical variables. Statistical significance was defined as a 2-tailed $p < .05$. Statistical calculations were also performed using the Statview software package.

RESULTS

Table 1 shows the demographic, clinical, and treatment data for the study population. The group comprised 150 men (96.2%) and 6 women (3.8%), with a median age at diagnosis of 62 years (range, 43–86 years). The clinical stage was I in 6.4% of the patients ($n = 10$), II in

Table 1. Patients' demographic, clinical, and treatment details.

Variables	*N*	%
Age (range, 43–86; median, 62)		
<75 y	142	91.0
≥75 y	14	9.0
Sex		
Male	150	96.2
Female	6	3.8
Stage		
I	10	6.4
II	17	10.9
III	28	17.9
IV	101	64.7
Subsite		
Pyriform sinus	122	78.2
Posterior wall	20	12.8
Postcricoid	14	9.0
Comorbidity		
None	55	35.3
Mild	39	25.0
Moderate	28	17.9
Severe	34	21.8
Performance status		
0	52	33.3
1	59	37.8
2	39	25.0
3	6	3.8
4	0	0.0
Primary treatment		
Radiation	102	65.4
Surgery	52	33.3
Chemotherapy	1	0.6
Best supportive care	1	0.6

Table 2. TNM stage.

T/N	0	1	2a	2b	2c	3	Total (%)
1	10	5	2	2	0	1	20 (12.8%)
2	17	12	3	18 (1)*	7	1	58 (37.2%)
3	8	4	3 (1)*	23 (3)*	11	2	51 (32.7%)
4	4	4	0	10	5	4 (1)*	27 (17.3%)
Total (%)	39 (25.0%)	25 (16.0%)	8 (5.1%)	53 (34.0%)	23 (14.7%)	8 (5.1%)	156

**Value in parentheses reflects no. of patients by M1.*

10.9% ($n = 17$), III in 17.9% ($n = 28$), and IV in 64.7% ($n = 101$). The primary subsite was pyriform sinus in 122 (78.2%) of the patients, posterior wall in 20 (12.8%), and postcricoid in 14 (9%). The performance status was 0 in 33.3% of the patients ($n = 52$), 1 in 37.8% ($n = 59$), 2 in 25% ($n = 39$), and 3 in 3.8% ($n = 6$). As a primary treatment, radiation therapy with/without chemotherapy was performed in 102 (65.4%) of the patients, surgical resection was performed in 52 (33.3%), chemotherapy alone was performed in 1 (0.6%), and best supportive care was administered to 1 (0.6%).

Table 2 summarizes the TNM staging of the study population. In total, 6 patients had distant metastasis at the initial diagnosis.

Among the study group, 55 (35.3%) of the patients had no comorbidity, 39 (25%) had mild comorbidity, 28 (17.9%) had moderate comorbidity, and 34 (21.8%) had severe comorbidity (Table 1). No statistically significant association was found between comorbidity and age, sex, clinical stage, subsite, performance status, or primary treatment (Table 3).

Table 4 shows the distribution of the comorbidities by type and severity. Table 5 shows the distribution of the comorbidities among the various tumor stages. There were no associations between any diseases and particular TNM stages. The survival of this body cohort, based on the ailments exhibiting comorbidity, was analyzed. A significant difference in the survival rates was found among patients with stomach/intestine ailments in accord with severity (39.1% for none or mild severity, $n = 150$, vs 16.7% for moderate or severe severity, $n = 6$;

Table 3. Distribution of comorbidity in the cohort.

Variable	*N*	No. of patients (%)	No. of patients by severity			*p* value
			Mild	Moderate	Severe	
Age						
<75 y	142	92 (64.8)	37	25	30	.7686
≥75 y	14	9 (64.3)	2	3	4	
Sex						
Male	150	99 (66.0)	38	28	33	.3743
Female	6	2 (33.3)	1	0	1	
Stage						
I	10	7 (70.0)	2	0	5	.4179
II	17	12 (70.6)	5	2	5	
III	28	16 (57.1)	7	6	3	
IV	101	66 (65.3)	25	20	21	
Subsite						
Pyriform sinus	122	80 (65.6)	32	20	28	.4906
Posterior wall	20	14 (70.0)	3	6	5	
Postcricoid	14	7 (50.0)	4	2	1	
Performance status						
0	52	25 (48.1)	13	5	7	.087
1	59	41 (69.5)	18	8	15	
2	39	30 (76.9)	8	13	9	
3	6	5 (83.3)	0	2	3	
Primary treatment						
Radiation	102	70 (68.6)	25	20	25	.3692
Surgery	52	29 (55.8)	13	7	9	

Table 4. Distribution of comorbidities by type and severity.

System	Ailment	No. of patients (%)	No. of patients by severity		
			Mild	Moderate	Severe
Cardiovascular	Myocardial infarction	3 (1.9)	2	1	0
	Angina/coronary artery disease	6 (3.8)	5	1	0
	Congestive heart failure	0 (0)	0	0	0
	Arrhythmias	4 (2.6)	0	4	0
	Hypertension	35 (22.4)	34	1	0
	Venous disease	0 (0)	0	0	0
	Peripheral arterial disease	1 (0.6)	1	0	0
Respiratory		3 (1.9)	2	1	0
Gastrointestinal	Hepatic	9 (5.8)	6	3	0
	Stomach/intestine	8 (5.1)	2	6	0
	Pancreas	4 (2.6)	4	0	0
Renal	End-stage renal disease	0 (0)	0	0	0
Endocrine	Diabetes mellitus	13 (8.3)	8	3	2
Neurological	Stroke	6 (3.8)	3	3	0
	Dementia	0 (0)	0	0	0
	Paralysis	2 (1.3)	2	0	0
	Neuromuscular	1 (0.6)	1	0	0
Psychiatric		1 (0.6)	0	1	0
Rheumatologic		0 (0)	0	0	0
Immunological	AIDS	0 (0)	0	0	0
Malignancy	Solid tumor including melanoma	51 (32.7)	9	17	25
	Leukemia and myeloma	0 (0)	0	0	0
	Lymphoma	0 (0)	0	0	0
Substance abuse	Alcohol	9 (5.8)	1	8	0
	Illicit drugs	0 (0)	0	0	0
Body weight	Obesity	0 (0)	0	0	0

$p = .0045$). There were no significant differences in the survival rates in accord with the severity among patients with other ailments, although those with solid tumors showed a slight difference ($p = .0596$). The 5-year OS of all the patients was 38.2% (Table 6). There were statistically significant differences between the survival rates in accord with the age (40.7% for patients aged <75 years vs 14.3% for patients aged >75 years; $p = .0001$), stage (57.3% for stages I–III vs 27.7% for stage IV; $p < .0001$),

Table 5. Comorbidity distribution among various tumor stages.

System	No. of patients (%)	No. of patients by stages			
		I	II	III	IV
All	156	10	17	28	101
Cardiovascular	40 (25.6)	2	3	3	32
Respiratory	3 (1.9)	1	0	0	2
Gastrointestinal	21 (13.5)	3	1	4	13
Renal	0 (0)	0	0	0	0
Endocrine	13 (8.3)	1	0	3	9
Neurological	8 (5.1)	1	0	2	5
Psychiatric	1 (0.6)	0	0	0	1
Rheumatologic	0 (0)	0	0	0	0
Immunological	0 (0)	0	0	0	0
Malignancy	51 (32.7)	4	11	8	28
Substance abuse	9 (5.8)	0	1	2	6
Body weight	0 (0)	0	0	0	0

Table 6. Overall survival rates according to demographic, clinical, and treatment variables.

Variable	*N*	5-yr survival, %	*p* value
All	156	38.2	
Age			
<75 y	142	40.7	.0001
≥75 y	14	14.3	
Stage			
I–III	55	57.3	<.0001
IV	101	27.7	
Subsite			
Pyriform sinus	122	41.5	.0144
Postcricoid or posterior wall	34	26.5	
Comorbidity			
None–mild	94	45.1	.0073
Moderate–severe	62	27.7	
Performance status			
0–2	150	38.5	.4991
3	6	33.3	
Primary treatment			
Radiation	102	37.3	.2918
Surgery	52	41.3	