Table 7. Previous reports of palliative concurrent chemoradiotherapy for dysphagia in inoperable, advanced esophageal cancer

Literature	*n*	Pathology	Chemotherapy	Radiotherapy (Gy)	Treatment failure (%)	TRD rate (%)	Improvement rate of dysphagia (%)	Survival (months)
Coia (22)	49	SCC, Adeno	5-FU, MMC	50	NS	NS	91	8
Urba and Turrisi (23)	27	SCC, Adeno	5-FU, CBDCA	40	0	4	59	6
Hayter et al. (18)	22	SCC, Adeno	5-FU, MMC	30	NS	5	68	5
Harvey et al. (17)	106	SCC, Adeno, small cell, undifferentiated and others	5-FU, CDDP	35	5	6	78	7
Burmeister et al. (20)	24	SCC, Adeno	5-FU	30–35	17	NS	67	9
Cho (21)	27	SCC	S-1, CDDP	54	0	0	77.8	11.6
Present study	40	SCC	5-FU, CDDP	40	5	5	75	10.3

TRD, treatment-related death; SCC, squamous cell carcinoma; Adeno, adenocarcinoma; 5-FU, 5-fluorouracil; MMC, mitomycin C; NS, not stated; CBDCA, carboplatin; Small cell, small cell carcinoma; Undifferentiated, undifferentiated carcinoma; CDDP, cisplatin.

from 67 to 91% (Table 7). The effects of our palliative regimen are comparable to those reported in these studies.

Our treatment regimen was well tolerated. No patient failed to complete radiation, and only two patients (5%) received fewer than two complete courses of the planned chemotherapy. Death within 30 days of completion of radiation was observed in two patients (5%). The rates of treatment failure and treatment-related deaths in the previous studies are shown in Table 7. As for these two parameters, the toxicity profile of our regimen is equivalent to those of the previous studies.

There have been some studies evaluating chemotherapy for locally advanced or metastatic squamous cell esophageal cancer (10–14). Bleiberg et al. (12) reported that WHO Grade 3 and 4 toxicities were observed from combined chemotherapy of 5-FU and CDDP: leukocytes in 14% of the patients and platelets in 14%. Iizuka et al. (14) evaluated the combination of 5-FU and CDDP in advanced squamous cell carcinoma of the esophagus and reported WHO Grade 3 and 4 toxicities of hemoglobin, leukocytes and platelets in 13, 8 and 5% of the patients, respectively. In our study, CTCAE Grade 3 and 4 leukocytes, hemoglobin and platelets developed in 15, 23 and 0% of the patients, respectively. The higher rates of hematological toxicities in our study seem to arise because of the concurrent radiation. In the studies of definitive chemoradiotherapy with a radiation dose of 50–70 Gy (20,28–32), Grade 3 and 4 toxicities were observed at a rate of 9–33% hemoglobin, 24–78% leukocytes and 14–20% platelets. These figures are generally higher than in our study, probably due to the higher radiation dose. Non-hematological toxicities were not severe in our study. Although Grade 3 esophageal perforation and febrile neutropenia occurred in 5 and 3% of the patients, respectively, they were properly managed.

Regression of the primary lesion was observed in 90% of the patients and 12 (30%) achieved CR. This effect probably results in the effective improvement of dysphagia. In definitive chemoradiotherapy of esophageal cancer, the irradiation dose to the primary lesion is 50.4 or 60 Gy in Japan. The CR rates of the primary lesion following definitive chemoradiotherapy are 62% in T3 cases and 37% in T4 cases, respectively (33). The CR rate of the primary lesion in our study was lower than this, probably because of the lower radiation dose of 40 Gy. A higher dose could lead to better and longer dysphagia relief through tumor regression, but it is important to balance palliative outcome with the costs of treatment, namely toxicities of higher irradiance and the effort of hospital visits, especially in those patients who cannot expect a cure.

The prognosis of Stage IVB esophageal cancer is poor. The median survival time has been reported to be 5–11 months (7,11,17,18,22,23,29,34) in patients who receive any treatment (including chemotherapy, chemoradiotherapy or surgery). In our study, the median survival time was 10.3 months, which is relatively good compared with previous studies of palliative therapies including chemoradiotherapy (Table 7). The survival effect is an important therapeutic aim in incurable Stage IVB esophageal cancer. Our result suggests that the addition of 40 Gy of radiotherapy to palliative chemotherapy is not associated with a negative effect on survival. However, we have to accept that there could be a selection bias in our retrospective study. It should be noted that 24 out of 40 patients have only lymph node metastasis in our study, who are known to have better outcome than those with visceral metastasis.

As for the histological type of the tumor, both squamous cell carcinoma and adenocarcinoma were included in the western studies (17–20,23), whereas only squamous cell carcinoma was included in Asian studies, including ours (21). The incidence of adenocarcinoma of the esophagus has increased considerably in western countries over the past three decades (35), whereas squamous cell carcinoma remains the major histological type of esophageal cancer in Japan and most Asian countries. It has been reported that there has been no dramatic increase in adenocarcinoma in Japan (36). Our study included only patients with squamous

cell carcinoma, in order that we represent actual Japanese clinical practice.

In conclusion, our retrospective study suggests that our palliative regimen of chemoradiotherapy, 5-FU plus CDDP combined with concurrent 40 Gy irradiation, can provide effective palliation of dysphagia through tumor regression with a tolerable toxicity profile in incurable Stage IVB esophageal cancer. However, since there are inevitable biases that could not be ruled out in our retrospective study, further prospective studies are required to elucidate the most durable and swift palliation with lower toxicity and better survival.

Conflict of interest statement

None declared.

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Appendix

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Clinical Outcome of Small Cell Lung Cancer with Pericardial Effusion but without Distant Metastasis

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Background: Pericardial effusion is defined as M1a in the Union Internationale Contre le Cancer seventh tumor, node, metastasis edition for lung cancer. The clinical course of small cell lung cancer (SCLC) with pericardial effusion but without distant metastasis (M1a) has not been adequately investigated.

Methods: The medical records of patients with SCLC treated at the National Cancer Center Hospital East between July 1992 and December 2007 were reviewed. During this period, 766 patients were newly diagnosed as having SCLC. Thirty-three of the 416 patients with limited disease (LD) SCLC (8%) had pericardial effusion. Seventy-nine patients with LD-SCLC (19%) had ipsilateral pleural effusion or dissemination. Of these, 16 patients had both pericardial and ipsilateral pleural effusion. We divided the 96 M1a patients into two subgroups: group A ($n = 33$) included patients with pericardial effusion, and group B ($n = 63$) included patients with ipsilateral pleural effusion or disseminated pleural nodules but without pericardial effusion.

Results: The median survival time among the patients with LD-M1a was 13.4 months (95% confidence interval: 10.7–16.6 months), and the 1-, 2-, 3-, and 5-year survival rates were 56%, 18%, 9%, and 8%, respectively. The survival of the patients with LD-M1a was intermediate between those of the patients with LD-M0 and patients with extensive disease M1b ($p < 0.0001$). The overall survival period was not statistically different between groups A and B ($p = 0.5182$). Nineteen patients in group A received chemoradiotherapy, but only two patients survived for more than 2 years (2- and 5-year survival rate: 11% both). Twenty-six patients in group B received chemoradiotherapy, and four patients survived for more than 5 years (5-year survival rate: 18%).

Conclusions: Long-term survival was achieved among patients with SCLC with pericardial effusion but without distant metastasis who successfully underwent chemoradiotherapy, although 5-year survival rate in these patients was relatively lower than in patients with SCLC with ipsilateral pleural effusion but without pericardial effusion or distant metastasis.

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Disclosure: The authors declare no conflicts of interest.

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Key Words: Small cell lung cancer, Limited disease, Pericardial effusion.

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Lung cancer is the leading cause of cancer-related deaths worldwide. Small cell lung cancer (SCLC) accounts for approximately 15% of all forms of lung cancer. Compared with non-SCLC, SCLC grows rapidly, quickly disseminates to the regional lymph nodes and distant sites, and is sensitive to chemotherapy with a response rate of 70 to 80%. The Veterans Administration Lung Study Group proposed a clinical two-stage system for SCLC that distinguishes limited disease (LD) and extensive disease (ED). LD is defined as being limited to one hemithorax, including mediastinal, contralateral hilar, and ipsilateral supraclavicular lymph nodes, whereas ED represents tumor spread beyond these regions.[1] The current standard care for LD-SCLC is a combination of chemotherapy and thoracic radiotherapy (TRT). Conversely, ED-SCLC is treated with chemotherapy alone. The original definition of LD was a tumor volume that could be encompassed by a reasonable radiotherapy plan. According to the International Association for the Study of Lung Cancer (IASLC)'s consensus report, however, the classification of LD-SCLC includes bilateral hilar or supraclavicular nodal involvement and ipsilateral pleural effusion, regardless of whether the cytological findings are positive or negative.[2] Pericardial effusion has not been defined precisely.

In 2007, the IASLC proposed a new tumor, node, metastasis (TNM) classification for lung cancer,[3–6] and the Union Internationale Contre le Cancer (UICC) seventh TNM edition has been available since 2009. According to the UICC seventh TNM edition, malignant pleural or pericardial effusion and tumor with pleural nodules are defined as M1a, leading to stage IV. An analysis of 12,620 patients with SCLC in the IASLC database demonstrated that patients who have ipsilateral pleural effusion without extrathoracic metastases (M1a) have a survival that is intermediate between stages I and III without effusion and stage IV. Nevertheless, no information regarding the presence of pericardial effusion is available in the IASLC database.[7]

Our previous retrospective analysis also demonstrated that the survival of patients with LD-SCLC with ipsilateral pleural effusion was intermediate between those of patients with LD without ipsilateral pleural effusion and patients with

ED, and long-term survival was achieved by patients with LD-SCLC who successfully underwent definitive TRT after their ipsilateral pleural effusion had disappeared after induction chemotherapy.[8] In this retrospective study, we investigated the clinical course and overall survival among patients with LD-SCLC with pericardial effusion, compared with those among patients with ED-SCLC or LD-SCLC with or without ipsilateral pleural effusion.

PATIENTS AND METHODS

In this study, LD-SCLC was defined as disease limited to one hemithorax, including mediastinal, contralateral hilar, and supraclavicular lymph nodes, ipsilateral pleural effusion, and pericardial effusion; ED-SCLC was defined as tumor spread beyond these manifestations.

We retrospectively reviewed the medical records of patients with lung cancer treated at the National Cancer Center Hospital East between July 1992 and December 2007.

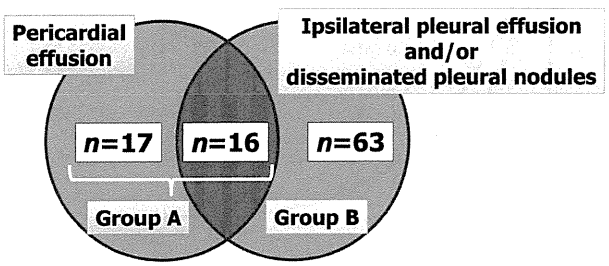

FIGURE 1. Patients with small cell lung cancer with M1a. Group A included patients with pericardial effusion, and group B included patients with ipsilateral pleural effusion or disseminated pleural nodules, but without pericardial effusion.

During this period, 766 patients were newly diagnosed as having SCLC. Four hundred sixteen patients were diagnosed as having LD-SCLC and 350 were diagnosed as having ED-SCLC using conventional staging procedures, including a medical history and physical examination, chest radiography, computed tomography (CT) scan of the chest, CT scan or ultrasound of the abdomen, bone scan, and CT scan or magnetic resonance imaging of the brain. Thirty-three of the 416 patients with LD-SCLC (8%, 95% confidence interval [CI]: 6–11%) had pericardial effusion and were included in this study. Seventy-nine of the 416 patients with LD-SCLC (19%, 95% CI: 15–23%) had ipsilateral pleural effusion or dissemination. Four patients had a disseminated mass without pleural effusion detected using CT scan. Sixteen patients with LD-SCLC had both pericardial and ipsilateral pleural effusion. Therefore, 63 patients with LD-SCLC had ipsilateral pleural effusion or dissemination without pericardial effusion. We divided the 96 M1a patients into two subgroups: group A included patients with pericardial effusion, and group B included patients without pericardial effusion. Group B patients had ipsilateral pleural effusion or disseminated pleural nodules (Figure 1).

The overall survival time was defined as the interval between the start of treatment and death or the final follow-up visit. The median overall survival time was estimated using the Kaplan-Meier analysis method.[9] Survival data were compared among the groups using a log-rank test. This study was approved by an institutional review board.

RESULTS

The patient characteristics are listed in Table 1. Eighty-three percent of the patients were male, and 81% had a performance status of 0 or 1. Fifty-four percent of the patients

TABLE 1. Patient Characteristics

	ED-SCLC (M1b)	LD-SCLC with Pericardial Effusion (M1a) (Group A)	LD-SCLC with Ipsilateral Pleural Effusion but without Pericardial Effusion (M1a) (Group B)	LD-SCLC (M0)
No. of patients	350	33	63	320
Sex				
Male	291	29	50	262
Female	59	4	13	58
Age (yr)				
Median	66	67	68	66
Range	28–85	37–82	46–83	22–87
Performance status				
0	22	0	4	108
1	224	25	47	190
2	63	6	9	15
3–4	41	2	3	7
Treatment delivered				
Chemotherapy	316	14	36	50
Chemoradiotherapy	25	19	26	224
Surgery + chemotherapy	0	0	0	33
Surgery alone	0	0	0	10
Best supportive care	9	0	1	3

LD, limited disease; SCLC, small cell lung cancer; ED, extensive disease.

TABLE 2. Timing of Thoracic Radiotherapy in Patients with M1a Small Cell Lung Cancer

Timing of Thoracic Radiotherapy	LD-SCLC with Pericardial Effusion (M1a) (Group A, n = 19)	LD-SCLC with Ipsilateral Pleural Effusion but without Pericardial Effusion (M1a) (Group B, n = 26)
Concurrently with the first course of chemotherapy	0	3
Concurrently with the second course of chemotherapy	0	4
Concurrently with the third course of chemotherapy	8	5
Concurrently with the fourth course of chemotherapy	4	0
Sequentially after chemotherapy	7	14

LD, limited disease; SCLC, small cell lung cancer.

received chemotherapy, and 38% received chemoradiotherapy. Six percent of the patients underwent surgical resection with or without adjuvant chemotherapy. Among the 96 patients with LD-M1a, all but one patient received chemotherapy (n = 50) or chemoradiotherapy (n = 45). Three patients underwent TRT (twice daily, 45 Gy in total) concurrently with the first course of chemotherapy. Four, 13, and four patients underwent TRT (once daily, 50 Gy in total) concurrently with the second, third, and fourth courses of chemotherapy, respectively. Twenty-one patients underwent TRT (once daily, 50 Gy in total) sequentially after chemotherapy. Among the group A patients, 12 patients underwent TRT concurrently with the third or fourth course of chemotherapy, and seven patients underwent TRT sequentially after chemotherapy. TRT was conducted if the pericardial effusion disappeared after induction chemotherapy. Among the group B patients, 12 patients underwent TRT concurrently with chemotherapy, and 14 patients underwent TRT sequentially (Table 2). Thirteen patients received prophylactic cranial irradiation of 25 Gy (seven patients in group A and six patients in group B).

Figure 2 shows the survival of all 766 patients with SCLC belonging to category M. The survival of patients with LD-M1a was intermediate between those of patients with LD-M0 and ED-M1b ($p < 0.0001$). Six hundred eighty-two patients have died. The median follow-up time was 65.8 months, ranging from 3.2 to 160.1 months. The median survival time among the patients with LD-M1a was 13.4 months (95% CI: 10.7–16.6 months), and the 1-, 2-, 3-, and 5-year survival rates were 56%, 18%, 9%, and 8%, respectively.

Survival analyses for the subgroup of patients with LD-M1a (n = 96) are shown in Figures 3, 4 and Table 3. Overall survival was not statistically different between groups A and B (p = 0.5182). All 14 patients who received chemotherapy in group A died within 3 years. One patient in

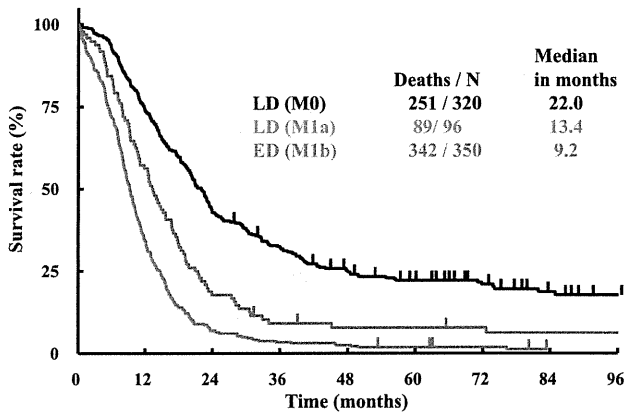

FIGURE 2. Overall survival among all 766 patients with M-category small cell lung cancer. LD, limited disease; ED, extensive disease.

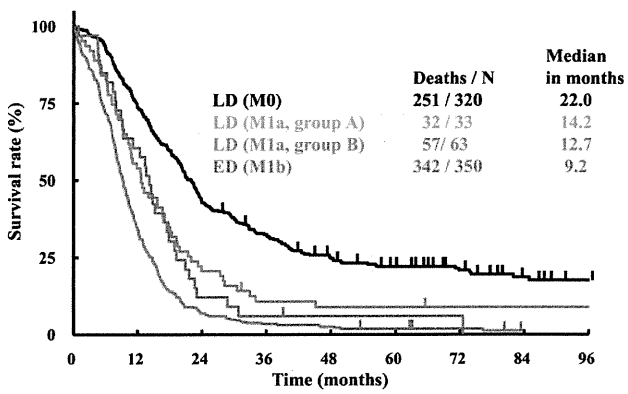

FIGURE 3. Overall survival among patients with M-category small cell lung cancer, subgroups A and B. LD, limited disease; ED, extensive disease.

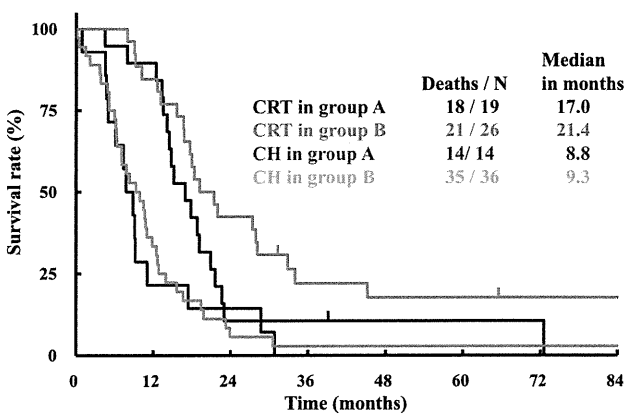

FIGURE 4. Overall survival among M1a patients with small cell lung cancer according to subgroups A, B, and initial treatment delivered. CRT, chemoradiotherapy; CH, chemotherapy.

group B who received chemotherapy as an initial treatment survived for more than 5 years, but this patient received chemoradiotherapy as a second-line treatment after a local

TABLE 3. Survival Data

Subgroup	No. of Patients	Median Survival Time (mo) (95% CI)	1-yr Survival Rate (%)	2-yr Survival Rate (%)	3-yr Survival Rate (%)	5-yr Survival Rate (%)
ED (M1b)	350	9.2 (8.5–10.0)	34	7	3	2
LD (M0)	320	22.0 (20.0–23.5)	74	43	33	22
LD with pericardial effusion (group A)	33	14.2 (9.1–17.5)	61	12	6	6
Receiving CRT	19	17.0 (13.6–21.0)	89	11	11	11
Receiving Chemotherapy	14	8.8 (4.7–11.1)	21	14	0	0
LD with ipsilateral pleural effusion but without pericardial effusion (group B)	63	12.7 (10.2–16.7)	54	21	11	9
Receiving CRT	26	21.4 (16.7–28.2)	85	42	22	18
Receiving chemotherapy	36	9.3 (6.3–11.8)	33	6	3	3

CI, confidence interval; ED, extensive disease; LD, limited disease; CRT, chemoradiotherapy.

TABLE 4. Six Patients with M1a Small Cell Lung Cancer who Survived for More Than 5 yr

Age (yr)	Sex	Group	Initial Treatment	Survival Time (mo)	State
64	M	A	Chemoradiotherapy	72.6	Dead
70	F	B	Chemoradiotherapy	146.5	Alive
53	M	B	Chemotherapy[a]	140.4	Alive
73	F	B	Chemoradiotherapy	138.0	Alive
72	M	B	Chemoradiotherapy	117.0	Alive
68	M	B	Chemoradiotherapy	65.5	Alive

[a] This patient received chemoradiotherapy as a second-line treatment after a local recurrence. Therefore, all six patients received chemoradiotherapy and achieved long-term survival for more than 5 yr.

M, male; F, female.

recurrence. Four of the 26 patients who received chemoradiotherapy in group B survived for more than 5 years (Table 4). Conversely, only 2 of the 19 patients who received chemoradiotherapy in group A survived for more than 2 years. One patient developed a local recurrence at 4 years and 10 months after the initiation of first-line chemoradiotherapy and died of lung cancer 14 months later. The remaining patient also developed a local recurrence at 2 years and 9 months after the initiation of first-line chemoradiotherapy and received second-line chemotherapy. This patient was still alive at the time of the data cutoff.

DISCUSSION

This retrospective analysis demonstrated that the survival of patients with SCLC and ipsilateral pleural or pericardial effusion (M1a) was intermediate between those of M0 and M1b patients. It is suitable that patients with ipsilateral pleural effusion or pericardial effusion belong to M1a category in the UICC seventh TNM edition. No statistically significant difference in the overall survival between M1a patients with pericardial effusion (group A) and those with ipsilateral pleural effusion but without pericardial effusion (group B) was observed. Among the patients who successfully underwent chemoradiotherapy, the patients in group B had 2-, 3-, and 5-year survival rates of 42%, 22%, and 18%, respectively, whereas the patients in group A had a 2-year survival rate of only 11%. Our previous retrospective analyses demonstrated that the median survival time of patients with cytologically positive and cytologically negative pleural effusion were 9.3 and 12.7 months, respectively. Furthermore, all 11 patients with cytologically positive pleural effusion died within 3 years.[8] Long-term survival for more than 5 years was achieved only by patients with cytologically negative pleural effusion. We speculate that an inflammatory process, such as atelectasis, causes ipsilateral pleural effusion in some patients. Conversely, most pericardial effusion is believed to be malignant. Therefore, long-term survival was seldom achieved by patients with pericardial effusion, even if they received chemoradiotherapy.

Recently, the applicability of the UICC seventh TNM edition for SCLC was investigated using the California Cancer Registry database. This database included 108 and 1518 M1a patients with pericardial effusion and pleural dissemination, respectively. No significant difference in overall survival was observed among patients with pleural or pericardial effusion (median survival time: 7 versus 7 months, 2-year survival rate: 16.7% versus 9.7%, respectively).[10] These data were comparable with our results. Nevertheless, no information regarding the treatment performed for the M1a patients was included in the previous article.

Our retrospective analysis has several limitations. First, the number of M1a patients with pericardial effusion was only 33, because only 8% of the patients with LD-SCLC exhibited pericardial effusion. Second, we did not conduct a cytological examination of the pericardial effusion. Pericardial puncture or drainage is usually performed in patients with cardiac tamponade. None of the patients in group A had cardiac tamponade; therefore, a pericardial puncture was technically difficult. Third, examination period was more than 15 years, from 1992 to 2007. Irinotecan, active for SCLC, has been commonly used from 2000 in Japan. Patients in this study were treated with a potential range of different chemotherapeutic agents during the period, which was not controlled.

Only 2 of 19 patients (11%) who received chemoradiotherapy in group A survived for more than 3 years. Con-

versely, all 14 patients who did not receive chemoradiotherapy in group A died within 3 years. TRT probably improves local control and achieves long-term survival in some patients. Definitive TRT is recommended in M1a patients with SCLC, if ipsilateral pleural or pericardial effusion has disappeared after induction chemotherapy.

In conclusion, the survival of patients with SCLC and ipsilateral pleural or pericardial effusion (M1a) is intermediate between those of M0 and M1b patients. No statistically significant difference in the overall survival of M1a patients with pericardial effusion and those with ipsilateral pleural effusion but without pericardial effusion was observed. Long-term survival was achieved among M1a patients with pericardial effusion who successfully underwent chemoradiotherapy, although 5-year survival rate in these patients was relatively lower than in M1a patients with ipsilateral pleural effusion but without pericardial effusion.

ACKNOWLEDGMENTS

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Long-term results of salvage photodynamic therapy for patients with local failure after chemoradiotherapy for esophageal squamous cell carcinoma

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Background and study aims: Local failure after chemoradiotherapy (CRT) remains a major problem for patients with esophageal squamous cell carcinoma (ESCC). The aim of this study was to clarify the long-term results of salvage photodynamic therapy (PDT) for local failure.

Patients and methods: Patients were treated with CRT, consisting of more than 50 Gy irradiation and concurrent chemotherapy. The indications for salvage PDT were as follows: 1) absence of lymph-node or distant metastasis after CRT; 2) failure lesion limited to T2; 3) refusal by patient to undergo salvage esophagectomy; 4) written informed consent. PDT was performed using an excimer dye laser at 48 and 72 hours after administration of Photofrin.

Results: A total of 37 consecutive patients underwent salvage PDT. The baseline stage before CRT was as follows: T1/T2/T3/T4 in 3/4/24/6 and N0/1 in 13/24 patients, respectively. Prior to PDT, 20 patients had a uT1 lesion, and 17 had a uT2 lesion; 24 patients had histologically proven local failure. A complete response was achieved in 22 patients (59.5%) following PDT. Esophageal fistulae, stenosis, and phototoxicity occurred in 4 (10.8%), 20 (54.1%), and 2 (5.4%) patients, respectively. Over a median follow-up period of 55 months, the 5-year progression-free (PFS) and overall survival rates of 37 patients following PDT were 20.7% and 36.1%, respectively. The 5-year PFS and overall survival of 24 patients with proven local failure were 17.6% and 34.6%, respectively.

Conclusion: Salvage PDT is a curative treatment option for patients with local failure after CRT for ESCC.

Introduction

Chemoradiotherapy (CRT) is a curative treatment option for esophageal squamous cell carcinoma (ESCC). However, local failure at the primary site after completion of CRT remains one of the major problems to be overcome for patients with ESCC. Salvage esophagectomy is now indicated for such patients, and it could be curative particularly for patients with T2 or earlier T-stage tumor or for patients without lymph node metastasis [1,2]. However, salvage esophagectomy is still associated with relatively higher morbidity and mortality compared with primary or planned esophagectomy [1–4]. Therefore, the development of curative and safety salvage treatment options for local failure is essential for improving the survival of patients treated with CRT.

We previously reported that patients who achieved complete response with CRT were very unlikely (< 1.0%) to experience a recurrence in locoregional lymph nodes [5]. This may lead to the hypothesis that, in patients who have only local failure after CRT, salvage local treatments such as endoscopic mucosal resection (EMR), and photodynamic therapy (PDT), could have curative potential. In fact, we first introduced EMR as a salvage treatment for local failure after CRT [6,7] and found that the long-term survival could be acceptable [7]. However, the indications for salvage EMR are limited to superficial lesions, and the procedure requires highly skilled endoscopists.

In contrast, PDT is indicated not only for superficial esophageal cancer as a curative treatment [8,9], but also as a palliative treatment for dysphagia due to stenosis of more advanced cancer [10]. Therefore, we consider that PDT could be a more powerful tool for salvage treatment after CRT. We previously reported acceptable short-term results of salvage PDT for local failure after definitive CRT for patients with ESCC [11]. Long-term results, however, have not been reported previously. The aim of the present study was to clarify the long-term survival of consecutive patients who have undergone salvage PDT for local failure after definitive CRT for ESCC.

Patients and methods

Patients

Between January 1998 and December 2004, 405 patients with ESCC were treated with CRT at the National Cancer Center Hospital East, Kashiwa, Japan. CRT consisted of more than 50 Gy external beam irradiation concurrent with two cycles of continuous infusion of 5-fluoruracil and cisplatin. In cases of renal insufficiency or cardiovascular disease, nedaplatin was used instead of cisplatin, because nedaplatin does not require hydration and has shown a low risk of renal toxicity [12].

The indications for salvage PDT were as follows: 1) absence of lymph node or distant metastases by computed tomography (CT) before PDT; 2) residual or recurrent tumor at primary site staging limited to within uT2 by endoscopic ultrasound (EUS); 3) EMR not indicated for reasons of concomitant deep ulceration or severe fibrosis due to radiation or lesion invading the deep submucosal layer; 4) refusal by patient to undergo surgery or physical complications that would have made surgery intolerable and; 5) provision of written informed consent. **Fig. 1** shows the flow of the patients through the study.

Of the 405 patients treated with definitive CRT, a complete response was achieved at the primary lesion in 234; the remaining 171 patients did not show a complete response. Of the 234 patients, 50 developed local recurrence at the primary site and eight patients were indicated for salvage PDT. Two patients with local recurrence were referred from another hospital to receive salvage PDT. Among the 171 patients with an incomplete response following CRT, 26 were indicated for salvage PDT, and one was referred from another hospital to receive salvage PDT. In total, therefore, 37 consecutive patients with local failure after definitive CRT were treated with salvage PDT and enrolled in the study. All information was collected from medical records and provided by the patients' physicians. This retrospective study was performed in accordance with the Declaration of Helsinki.

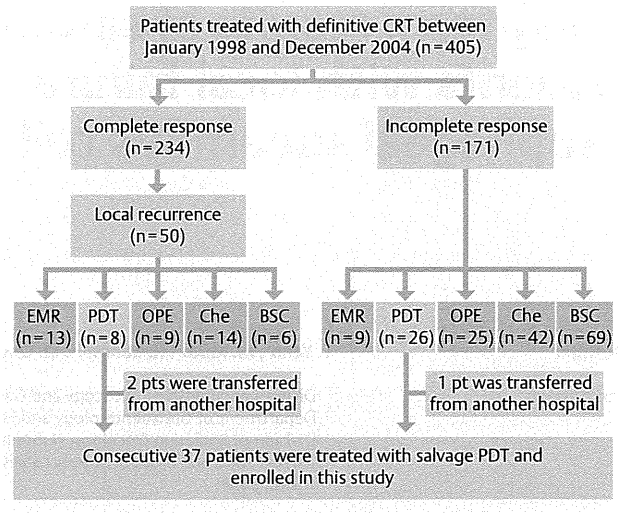

Fig. 1 Flow of patients through the study. CRT, chemoradiotherapy; EMR, endoscopic mucosal resection; PDT, photodynamic therapy; OPE, esophagectomy; Che, chemotherapy; BSC, best supportive care.

Staging

Clinical staging was determined by the TNM classification of the International Union Against Cancer [13]. Clinical T stage was evaluated by endoscopy, EUS, and CT, and clinical N and M stages were evaluated mainly by CT of the neck, chest, and abdomen. In this study, lymph node metastasis was clinically diagnosed if the lymph node was more than 10 mm in diameter on CT. All of the patients who were treated with definitive CRT at our institution are routinely evaluated by endoscopy and CT after completing CRT. Complete response at the primary site was defined as follows: i) disappearance of the tumor lesion and ulceration by endoscopic examination; ii) the absence of cancer cells in biopsy specimens [14]. The complete disappearance of metastatic lesions by CT was defined as complete response.

After confirmation of complete response, follow-up examination with endoscopy and CT was performed every 3 months for 2 years, and every 6 months thereafter. Biopsies of the primary site were routinely obtained at each follow-up endoscopic examination.

Local failures were classified into two groups: residual lesions and recurrent lesions. Residual lesions were defined as lesions that did not achieve complete response immediately after CRT. Recurrent lesions were defined as lesions that relapsed after achieving complete response. If the primary site showed obvious growth or if cancer cells were detected in a biopsy specimen, the lesion was diagnosed as a recurrence. Submucosal tumors or slightly protruding lesions at the primary site were suspected of representing a recurrence and were re-evaluated with EUS.

Before PDT, all patients were evaluated and staged using EUS (EU-M2000; Olympus Co. Ltd., Tokyo, Japan). Lesions were carefully examined with a high-frequency (20 Hz) ultrasound probe. When a hetero-echoic solid component in a submucosal or deeper layer was detected, a diagnosis of local failure lesion was made. The depth of the residual lesions by EUS was divided into either uT1 or uT2. Stage uT1 described lesions whose invasion was limited to the submucosal layer, and uT2 described those invading the muscularis propria layer.

Photodynamic therapy

PDT commenced with intravenous administration of 2 mg/kg of Photofrin (Pfizer Japan Inc.) followed by dye laser irradiation. A 630-nm wavelength laser beam was emitted by an excimer dye laser (EDL-1, Hamamatsu Photonics, Hamamatsu, Japan). The laser treatment was performed in two sessions at 48 and 72 hours after injection of Photofrin. The excimer dye laser was delivered via a microlens-type straight-tip fiber without any light diffuser introduced into the operative channel of the fiberscope (GIF-Q20; Olympus Co., Ltd.) and positioned in the esophagus. The total light density was 75 J/cm^2 with 4 mJ/pulse maximum pulse energy and 40 Hz pulse frequency, and no adaptation of delivered energy to radiotherapy time.

All patients were instructed to avoid direct exposure to sunlight for 1 month after the injection of Photofrin in order to protect them from skin photosensitization. To confirm the ulceration and development of tissue necrosis after PDT, patients were examined endoscopically 1 week after laser irradiation. To evaluate the response and luminal toxicity of PDT, endoscopic examination with biopsy was repeated at least every month until the response was confirmed. CT was used to evaluate the distant organ or lymph node metastasis every 3 months for the first 2 years, and every 6 months thereafter. The response to PDT was classified into two groups: 1) complete response, if there was no macroscopic or microscopic evidence of cancer; 2) incomplete response, if a tumor was seen at endoscopy and confirmed histologically to contain cancer cells. Recurrence after achieving com-

plete response by PDT was defined when cancer cells were histologically confirmed at the primary site, if the lymph node was larger than 10 mm, or if distant metastasis was present.

Statistics

The progression-free survival (PFS) was measured from the date of initial PDT to the first date of histologically confirmed residual lesion at the primary site or recurrence or disease progression at any site or death. The overall survival was measured from the date of initial PDT to the date of death for any reason or last follow-up visit. Survival time was calculated by the Kaplan–Meier method. Survival was compared between variables using log-rank tests. A P value of < 0.05 was considered significant. All statistics were performed by using the Dr SPSS II statistical software package (SPSS Japan Inc., Tokyo, Japan)

Results

Patient characteristics

The baseline characteristics of patients before CRT are summarized in **Table 1**.

The patients consisted of 35 men and two women, with a median age of 64 years (range 50–75 years). No patients had distant organ metastasis, and all lesions were histologically proven to be ESCC before CRT. Lesion characteristics before PDT are summarized in **Table 2**.

Histological confirmation could not be obtained in 13 patients; however, we strongly suspected local failure because the apparent elevation or ulcer formation occurred at the primary site.

Table 1 Baseline patient and lesion characteristics before chemoradiotherapy.

Characteristics	No. of patients (n = 37)
Sex	
Male	35
Female	2
Age, median (range), years	64 (50 –75)
Tumor location	
Upper	6
Middle	24
Lower	7
T-stage	
T1	3
T2	4
T3	24
T4	6
N-stage	
N0	13
N1	24
TNM-stage	
I	2
II	11
III	22
IV	2

Table 2 Lesion characteristics before photodynamic therapy.

Characteristics	No. of patients (n = 37)
Tumor status after chemoradiotherapy	
Recurrent	10
Residual	27
Tumor stage evaluated with EUS	
uT1	20
uT2	17
Ulceration	
Present	17
Absent	20
Circumference of the lesion	
< ¼	4
¼ – < ½	20
½ – < ¾	12
> ¾	1
Histologically proven cancer cells	
Positive	24
Negative	13

EUS, endoscopic ultrasound.

Response to salvage PDT

The interval between the last day of radiotherapy and initiation of PDT was 4 months (range 1–85 months) in the entire group of patients, 16 months (range 7–86 months) in 10 patients with local recurrence after achieving a complete response with CRT, and 2.5 months (range 1–17 month) in 27 patients with a residual lesion after CRT. The median total light dose for PDT was 675J (range 300–1000J), and the median hospital stay was 11 days (range 6–33 days). Complete response was attained in 22 of 37 patients with PDT, resulting in a complete response rate of 59.5% for salvage PDT (95% confidence interval [CI] 42.1–75.3). The complete response rate of the 20 patients with uT1 local failure was 75.0% (15/20; 95% CI 50.9–91.3), and that of the 17 patients with uT2 was 41.2% (7/17; 95%CI 18.4–67.1). The median time to confirm a complete response was 102.5 days (range 35–199 days).

Major complications of salvage PDT

Four patients (4/37, 10.8%) developed esophageal fistulae after salvage PDT. Their clinical T stages before CRT were T3 in three patients and T4 in one. All of them had local residual lesions just after CRT, and their T stages before PDT were uT2 in one patient and uT1 in three patients. All of them were treated with ≥ 600 J PDT irradiation. In one patient, the fistula closed with conservative treatment, and complete response was achieved without any metastasis. Another patient developed mediastinitis due to esophago-mediastinal fistula. Despite this patient being treated conservatively, by total parenteral nutrition and intravenous administration of antibiotics, she died with bleeding from the primary site at 63 days after PDT. An esophageal-aortic fistula was confirmed at autopsy. The remaining two patients died with cancer progression. Thus, treatment-related death with PDT was 2.7% (1/37).

Other complications occurred in 20 patients (20/37, 54.1%) who developed esophageal stenosis requiring balloon dilation. Among them, a complete response could not be achieved in 12 patients following PDT; it is therefore possible that their stenoses might have been caused by progressive refractory tumor as well as by lumen toxicity caused by PDT. Cutaneous phototoxicity requiring medication was experienced in two patients (2/37, 5.4%).

Clinical course after salvage PDT

The median follow-up period of all patients following salvage PDT was 55 months (range 18–75 months). The clinical flow chart of the 22 patients who achieved complete response with salvage PDT is presented in **Fig. 2**.

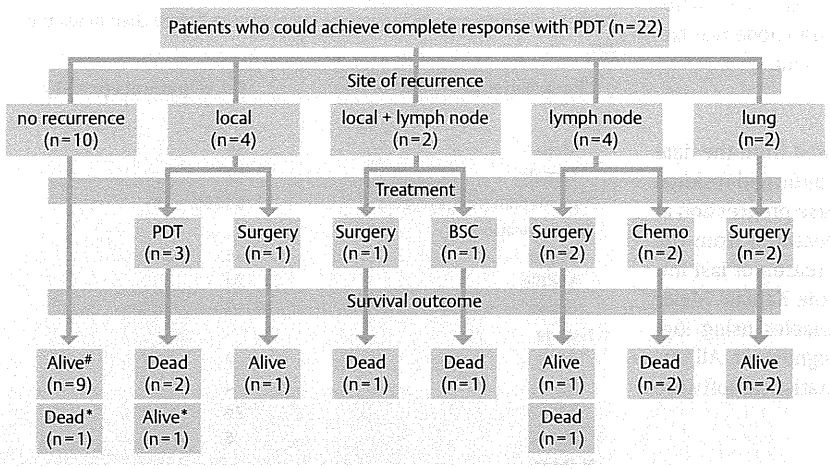

Fig. 2 The clinical flow chart of 22 patients in whom a complete response was achieved with salvage PDT. CR, complete response; PDT, photodynamic therapy; BSC, best supportive care; Chemo, chemotherapy; Dead*, dead from another disease; Alive#, alive with disease.

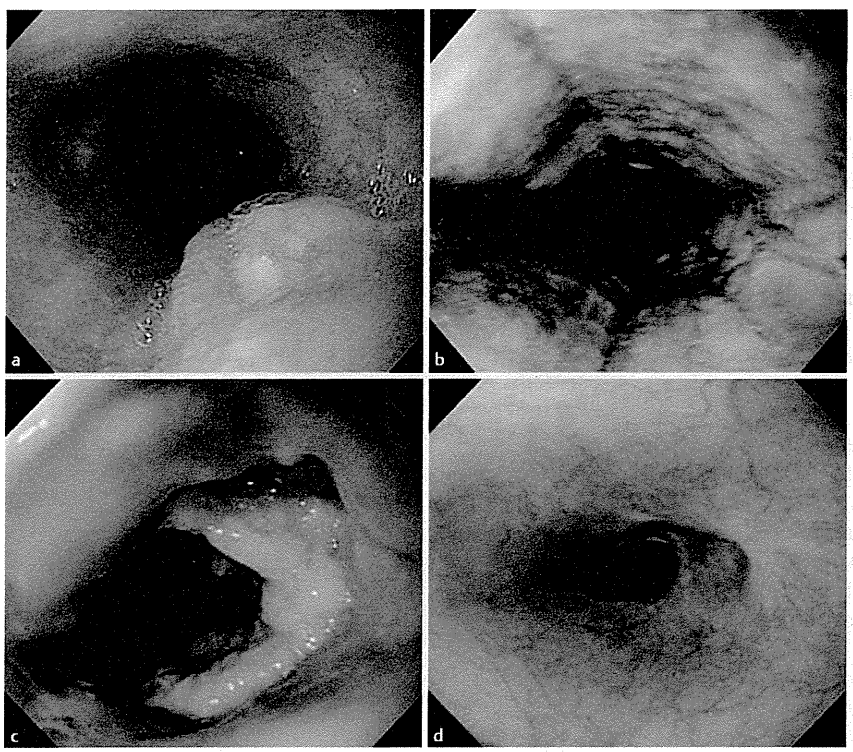

Fig. 3 A patient in whom complete response was achieved with salvage photodynamic therapy (PDT). **a** Local recurrence was detected after chemoradiotherapy and evaluated as uT1 with endoscopic ultrasound. **b** At 3 days after salvage PDT, circumferential ischemic change was observed. **c** At 1 month after salvage PDT, deep ulceration with dense necrotic tissue was observed at the primary site. **d** At 3 years after salvage PDT, treatment was evaluated as a complete response without any recurrence.

Ten patients did not develop any recurrence. Nine of them are still alive, and the tenth died of pneumonia without any esophageal cancer recurrence approximately 4 years after PDT. The details of these 10 patients are as follows: the baseline clinical stages before CRT were T1 (n = 1), T2 (n = 4), T3 (n = 3), and T4 (n = 2); N0 (n = 5) and N1 (n = 5); and stage I (n = 1), stage II (n = 4), stage III (n = 3), and stage IV (n = 2). Lesion characteristics before PDT were uT1 (n = 7) and uT2 (n = 3); six had histologically proven local failure before PDT and the other four had histologically unproven lesions before PDT. Moreover, the baseline tumor stage of five patients, except for the patient who died of pneumonia, with histologically proven local failure who survived without any recurrence before CRT was T1 (n = 1), T2 (n = 4), and all failure lesions were uT1 before PDT.

A representative case of a patient in whom complete response was achieved without any recurrence after salvage PDT is shown in **Fig. 3**.

Local recurrence at the primary site was detected in four patients, one of whom was cured with salvage esophagectomy and is still alive without recurrence. The remaining three patients were treated with a second PDT, but none of them achieved complete response. In two patients, local recurrence and simultaneous lymph node metastasis were detected. One of these was treated with esophagectomy and the other was followed with the best supportive care; however, both died of disease progression. Lymph node metastasis without local recurrence was detected in four patients, of whom two underwent surgery and the other two were treated with systemic chemotherapy. One of the patients who received curative resection for metastatic lymph node is still alive without recurrence; however, the remaining three patients died of cancer progression. Solitary lung metastasis was detected in two patients; both underwent surgery and are still alive without recurrence.

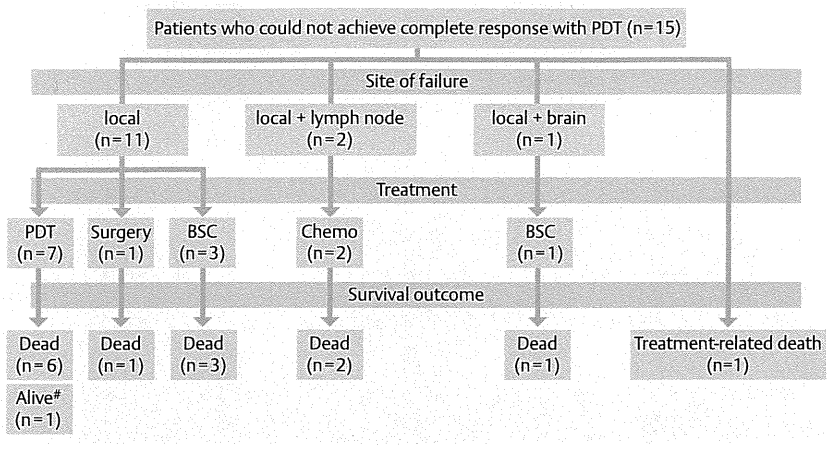

Fig. 4 Clinical flow chart of 15 patients in whom salvage photodynamic therapy did not achieve a complete response. CR, complete response; PDT, photodynamic therapy; BSC, best supportive care; Chemo, chemotherapy; Alive#, alive with disease.

A flow chart for the 15 patients in whom PDT could not achieve a complete response is shown in ◎ **Fig. 4**.

One patient died of bleeding after PDT as described above, 13 died of cancer progression, and one remains alive with the disease. The clinical courses of 13 patients without histologically proven carcinoma before PDT are as follows: nine patients achieved complete response after PDT, in three patients histologically proven residual tumors were detected after PDT, and the remaining patient died with aortic rupture, as described above. Of the nine patients showing complete response for PDT, four of them are still alive without any recurrence, three patients have developed histologically proven local recurrence after achieving complete response, one patient developed lymph node metastases without local recurrence, and one patient developed a solitary lung metastasis without local recurrence.

Survival

The PFS rates at 3 and 5 years from the initiation of salvage PDT were 31.9% (95%CI 16.7–47.1) and 20.7% (95%CI 6.4–30.5), respectively. The overall survival rates at 3 and 5 years from the initiation of salvage PDT were 47.4% (95%CI 30.9–63.8) and 36.1% (95%CI 19.2–53.0), respectively (◎ **Fig. 5**).

In addition, PFS and overall survival of 24 patients at 5 years with histologically proven local failure were 17.6% (95%CI 1.1–34.0) and 34.6% (95%CI 14.5–54.7), respectively. Furthermore, comparisons of PFS according to various clinical variables before CRT and before PDT are presented in ◎ **Fig. 6**.

Patients with clinical T1 or T2 had significantly higher 5-year PFS rates than those with T3 or T4 (T1/2 vs. T3/4 = 71.4% [95%CI 38.0–104.9] vs. 9.1% [95%CI −2.4 to 20.7]; $P = 0.005$), whereas there was no significant difference between patients with N0 and N1 (N0 vs. N1 = 27.7% [95%CI 2.1–53.3] vs. 16.2% [95%CI −1.2 to 33.6]; $P = 0.33$). On the other hand, the 5-year PFS of patients with uT1 before PDT was significantly higher than those with uT2 (uT1 vs. uT2 = 30.0% [95%CI 7.9–52.1] vs. 8.8% [95%CI −0.4 to 24.0]; $P = 0.02$). Patients with recurrence after complete response had a better 5-year PFS rate than patients with residual tumor (recurrent vs. residual = 40.0% [95%CI 9.6–70.4] vs. 13% [95%CI −2.2 to 28.1]; $P = 0.07$), although the difference was not statistically significant. There was no significant difference in progression-free survival between patients with and those without histologically proven cancer cells before PDT (negative vs. positive = 30.8% [95%CI 5.7–55.9] vs. 17.6% [95%CI 1.1–34.0]; $P = 0.61$).

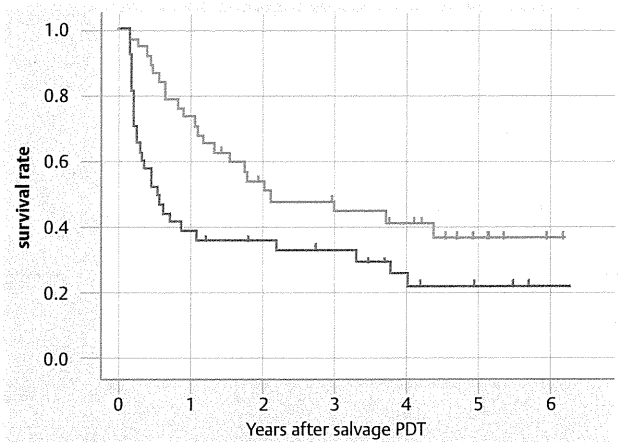

Fig. 5 Overall survival (blue line) and progression-free survival (red dotted line) of all 37 patients from the initiation of salvage photodynamic therapy (PDT).

Discussion

In the present study, salvage PDT for local failure after CRT for ESCC showed a high complete response rate. Moreover, the long-term survival was acceptable, because the prognosis of patients with local failure after CRT is usually quite dismal [14,15]. EMR is a salvage treatment option for local failure after CRT if the failure lesion is superficial. Indeed, we have reported the long-term results for salvage EMR, and the 5-year survival was 49.1% [7]. The difference in 5-year survival between salvage PDT and salvage EMR may depend on both their baseline clinical stage before CRT and clinical stage before salvage treatment. In salvage EMR, more than half of the patients had baseline clinical T1 lesions before CRT, and all of their local failure lesions were within the submucosal layer before EMR [7]. On the other hand, more than 80% (30/37) of patients had baseline clinical T3/4 lesions before CRT, and approximately half (17/37) of failure lesions were uT2 before PDT in the present study. Moreover, salvage EMR is technically quite difficult if the failure lesion has a severe fibrosis after CRT or if there is massive invasion of the submucosal layer. Therefore, PDT might be recommended as a salvage treatment for failure lesions evaluated as uT1 or when EMR is not indicated due to the abovementioned reasons.

The 5-year survival rate after salvage surgery is reported to be approximately 30% [1,2,4]. Most of the patients who achieved

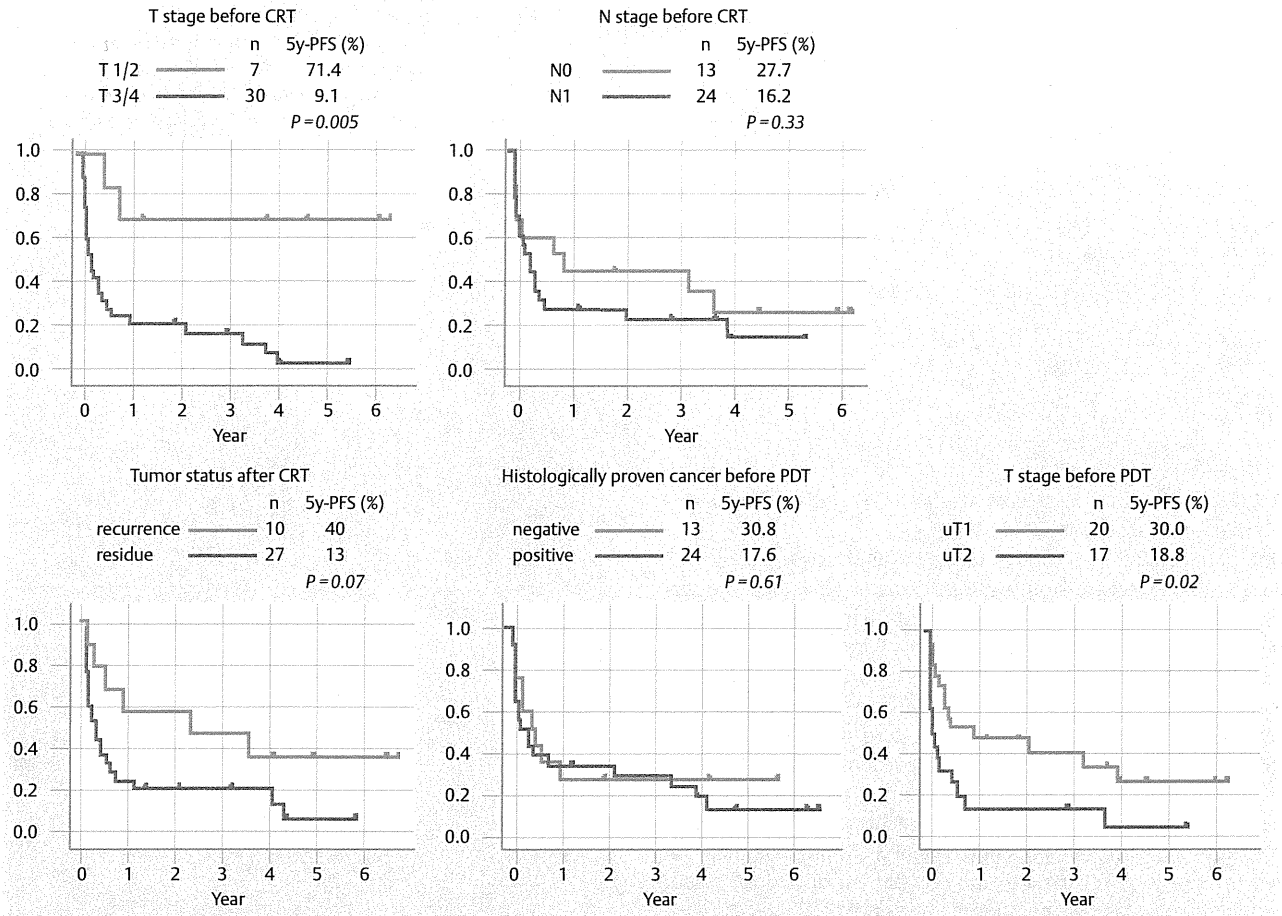

Fig. 6 Comparisons of progression-free survival curves according to various clinical variables before chemoradiotherapy and before photodynamic therapy.

long-term survival after salvage surgery showed T1 or T2 local failures without lymph node metastasis [1,2,4]. Swisher et al. reported that 5-year survival of patients with pathological T1 or T2N0 was 60% in salvage surgery; however no patient with pathological T3, or T4, or N1 survived longer than 7 months [1]. These data suggest that it is difficult to salvage patients with local failure more advanced than T3 and/or lymph node metastasis, even when they are treated with salvage surgery. However, these data cannot be simply compared with the results of salvage PDT, because these reports included patients with deeper local failure or locoregional lymph node metastasis.

The problem with the salvage surgery was a high incidence of complications (15%–39%) and a high treatment-related mortality rate (8%–22%) [1–4,16]. While, we have experienced one case (2.7%) of treatment-related death with salvage PDT in this study, the incidence rate was lower than for salvage surgery and no severe adverse events were associated with PDT. Thus, salvage PDT was a less-invasive treatment option compared with salvage surgery for patients with local failure after CRT. PDT is a treatment option, if local failure after CRT is limited to the muscularis propria layer, especially the submucosal layer without lymph node metastasis, and in patients in whom surgery would be intolerable because of physical complications. Therefore, PDT has a niche role between EMR and surgery in the salvage setting after CRT.

In the present study, 13/37 (35.1%) patients did not have a histologically proven tumor before PDT. We could not deny the possibility that the remarkable 5-year overall survival rate might be influenced by the patients with salvage surgery and by the patients without histologically proven tumor. Actually, of nine patients who are still alive without any recurrence, four patients had histologically unproven local failure before PDT. However, the 13 patients without histologically proven tumor were carefully evaluated by endoscopic examination and EUS and were found to have progressive development of ulceration of the space occupied by the lesion after achieving complete response for CRT. For the purpose of clarifying this disputable situation, we are now evaluating, in a prospective study, the efficacy and safety of salvage PDT only for histologically confirmed local failure after CRT for ESCC.

In the current study, 6 of 37 (16.2%) patients developed lymph node metastasis after PDT. Only one patient without local failure after PDT was cured by lymph node dissection. PDT has no curative potential if there is a high risk of lymph node metastasis. In salvage surgery, more than 30% of the patients developed locoregional or distant metastasis [1,16,17]. This means that the risk of lymph node metastasis is also high even for salvage surgery. Therefore, we have to investigate a more curative strategy for patients with high risk of recurrence even after salvage treatment.

The effect of second-line chemotherapy for patients with refractory or recurrent esophageal cancer after CRT is extremely limited. From the literature, the overall response rate of second-line systemic chemotherapy for previously treated esophageal cancer patients including local failure are low (0–16%), and complete

response is quite difficult to expect (0–6%) [18–21]. Therefore, second-line systemic chemotherapy for failure after CRT is only a palliative treatment. In fact, most of the patients with unresectable failure or distant metastasis were treated with second-line chemotherapy in the current study (**Fig. 1**). However, among the patients with local failure after CRT, some patients developed only local recurrence and these recurrent or residual lesions could be candidates for salvage PDT and expected to be cured.

As for major complications after salvage PDT, we experienced four cases (10.8%) of esophageal fistulae. Of these, one patient (2.7%) died due to an esophageal-aortic fistula. Esophageal perforation can develop even in patients receiving primary intent PDT for naïve esophageal cancer, as previously reported [8]. However, we cannot deny the possibility that radiation-induced esophageal damage was potentiated by PDT and that the structural damage occurs by transmural necrosis. Lecleire et al. reported a retrospective comparative study of primary intent PDT and salvage PDT after CRT [22]. They found two out of 15 cases (13.3%) of perforation in a salvage setting, whereas no cases (0/25) suffered perforation after primary intent PDT. In the present study, all four patients who developed fistulae had an initial T3 or T4 lesion and had a residual lesion just after CRT, and their total light dose was more than 600 J. Salvage PDT should be carefully performed, particularly in patients in the initial advanced stage and with residual local failure just after CRT. Furthermore, the total laser irradiation dose may correlate with esophageal fistulae.

Patients with baseline T1 or T2 before CRT, and uT1 before PDT tend to achieve long-term survival after PDT. In seven patients with baseline T1 or 2, six patients were evaluated uT1 before PDT. In addition, we could not deny the possibility that patients with more advanced local failure were included in the baseline T3/4 before CRT group, because EUS evaluation is more difficult just after CRT due to radiation esophagitis, especially in advanced cases. From the results of the present study, the treatment efficacy and long-term survival were quite different based on the T stage either before CRT or PDT, and earlier T-stage lesions tended to be cured with PDT, even in the salvage situation. In fact, the baseline tumor stage of five patients with histologically proven local failure who are still alive without any recurrence before CRT was T1 in 1, and T2 in 4, and all their failure lesions were uT1 before PDT. However, caution should be shown when interpreting these survival rates across different variables due to the small sample size.

In conclusion, salvage PDT could be a curative treatment option for patients with local failure after CRT for ESCC when their failure lesions are suspected at stage T2 or earlier without lymph node or distant metastasis.

Competing interests: None

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Physics Contribution

A New Brain Positron Emission Tomography Scanner with Semiconductor Detectors for Target Volume Delineation and Radiotherapy Treatment Planning in Patients with Nasopharyngeal Carcinoma

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Summary

Two treatment planning methods for nasopharyngeal carcinoma were compared: conventional whole-body BGO scintillator positron emission tomography and a new brain PET system using semiconductor detectors. The average absolute volume of GTV contoured with the use of the new brain PET system was significantly smaller than that of conventional whole-body BGO PET. The new brain PET system using semiconductor detectors can provide more accurate tumor delineation

Purpose: We compared two treatment planning methods for stereotactic boost for treating nasopharyngeal carcinoma (NPC): the use of conventional whole-body bismuth germanate (BGO) scintillator positron emission tomography ($PET_{CONV}WB$) versus the new brain (BR) PET system using semiconductor detectors ($PET_{NEW}BR$).

Methods and Materials: Twelve patients with NPC were enrolled in this study. [^{18}F]Fluorodeoxyglucose-PET images were acquired using both the $PET_{NEW}BR$ and the $PET_{CONV}WB$ system on the same day. Computed tomography (CT) and two PET data sets were transferred to a treatment planning system, and the $PET_{CONV}WB$ and $PET_{NEW}BR$ images were coregistered with the same set of CT images. Window width and level values for all PET images were fixed at 3000 and 300, respectively. The gross tumor volume (GTV) was visually delineated on PET images by using either $PET_{CONV}WB$ (GTV_{CONV}) images or $PET_{NEW}BR$ (GTV_{NEW}) images. Assuming a stereotactic radiotherapy boost of 7 ports, the prescribed dose delivered to 95% of the planning target volume (PTV) was set to 2000 cGy in 4 fractions.

Results: The average absolute volume (±standard deviation [SD]) of GTV_{NEW} was 15.7 ml (±9.9) ml, and that of GTV_{CONV} was 34.0 (±20.5) ml. The average GTV_{NEW} was significantly smaller than that of GTV_{CONV} ($p = 0.0006$). There was no statistically significant difference between the maximum dose ($p = 0.0585$) and the mean dose ($p = 0.2748$) of PTV. The radiotherapy treatment plan based on the new gross tumor volume ($PLAN_{NEW}$) significantly reduced maximum doses to the cerebrum and cerebellum ($p = 0.0418$) and to brain stem ($p = 0.0041$).

Conclusion: Results of the present study suggest that the new brain PET system using semiconductor detectors can provide more accurate tumor delineation than the conventional whole-body

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than the conventional system and offers functional and molecular radiotherapy treatment planning.

BGO PET system and may be an important tool for functional and molecular radiotherapy treatment planning. © 2011 Elsevier Inc.

Keywords: Nasopharyngeal carcinoma, Positron emission tomography, Radiotherapy planning, Semiconductor, Target volume delineation

Introduction

Since the advent of computed tomography (CT), sophisticated techniques in radiation treatment such as three-dimensional conformal radiotherapy, stereotactic radiotherapy, and intensity-modulated radiotherapy (IMRT) have been developed in order to focus and escalate the radiation dose to the tumor while sparing normal tissues. In these techniques, it is important to precisely determine the tumor volume. With their high anatomic resolution, CT and magnetic resonance images (MRI) have been used primarily for target volume delineation in radiotherapy treatment planning. However, when delineating the target volume, it is sometimes difficult to distinguish between tumor and nontumor tissues by using anatomical imaging alone. In the past 10 years, positron emission tomography (PET) labeled with [^{18}F]fluorodeoxyglucose (FDG), which is able to visualize molecular information for the tumor, has been widely used in oncology for diagnosis and staging of various cancers. This functional imaging has been adopted in radiotherapy, and several studies have examined the clinical impact of PET on radiotherapy planning (1–3). However, as PET does not provide an intrinsically accurate examination, with a spatial resolution of approximately 4 to 7 mm (4–6), it is difficult to determine tumor boundaries on conventional whole-body bismuth germanate (BGO) scintillator PET images. In 2007, a new brain PET scanner with semiconductor detectors, the first in the world, was developed with Hitachi, Ltd., and was installed at our institute (7). This brain PET system is equipped with small semiconductor detectors and a depth of interaction system with sufficient sensitivity to obtain higher spatial resolution (2.3 mm at 1 cm [National Electrical Manufacturers Association (NEMA) NU 2-2001]). Semiconductor detectors also have an advantage in energy resolution. Our new semiconductor PET detectors had an energy resolution of 4.1% full-width half maximum, which is superior to the energy resolution obtained with previously available scintillation detectors (*e.g.*, 10%–20%) (8, 9). The limited energy window set permits collection of accurate signal counts with lower noise counts. The scatter fraction of the new brain PET system was 23% (NEMA NU 2-1994), which was lower than those of other scintillation-based whole-body BGO PET scanners such as Exact HR+ (32.1%; NEMA NU 2-1994; Asahi-Siemens, Tokyo, Japan) (10, 11). In our previous study, the contrast obtained with the semiconductor brain PET scanner was 27% higher than that obtained with the conventional whole-body BGO scanner for both a cold spot phantom with 6-mm-diameter cold sphenoid defects and a dual-cylinder phantom with an adjusted concentration of 1:2 surrounded with water (7). In patients with nasopharyngeal carcinoma (NPC), the new brain PET system identified intratumoral inhomogeneity in more detail than the conventional whole-body BGO PET system, and the tumor edge was sharper on images obtained with the new brain PET system than on those obtained with the conventional whole-body BGO PET system (7). Therefore, the new brain PET system has the potential to provide high contrast and detailed images with sharper tumor edges in radiation treatment planning for NPC.

The purpose of this study was to evaluate effects of the new brain PET system for radiotherapy treatment planning for patients with NPC compared with those of a conventional whole-body BGO PET, Exact HR+.

Methods and Materials

Patients

Subjects in this study were 12 NPC patients who had been newly diagnosed between July 2007 and April 2009. The median age was 61 years old (range, 30–76 years old). Patient characteristics are shown in Table 1. Written informed consent was obtained from all patients.

Image acquisition and target volume delineation

Before undergoing the PET study, all patients fasted for at least 6 h. Serum glucose levels were checked in all patients before we administered [^{18}F]FDG. The dose of [^{18}F]FDG for each patient was 370 MBq. [^{18}F]FDG-PET images were acquired with the patients in a diagnostic, nontreatment position, with the new brain PET system using semiconductor detectors ($PET_{NEW}BR$) and with a conventional whole-body BGO PET system ($PET_{CONV}WB$) on the same day. $PET_{CONV}WB$ system studies were performed using Exact HR+ machine. Two time-course protocols were adopted and randomly selected. In Protocol 1, $PET_{CONV}WB$ images were acquired first, and in Protocol 2, $PET_{NEW}BR$ images were acquired first. Among the 12 patients, there were 7 patients in Protocol 1 and 5 patients in Protocol 2. The difference in the distribution was that the time-course protocols were used for all patients who received $PET_{NEW}BR$ scans, not just patients with NPC but also those with brain tumors, epilepsy, and other conditions.

CT was performed with a slice thickness of 2 to 5 mm. CT and two PET data sets were transferred to the Pinnacle^3 treatment planning system (version 8.0; Philips Medical Systems, Fitchburg, WI) for image registration, target volume delineation, and volume analysis. $PET_{CONV}WB$ and $PET_{NEW}BR$ images were coregistered with the same set of CT images. $PET_{NEW}BR$ images on the Pinnacle^3 treatment planning system were not displayed using the standardized uptake value scales for window level/width; instead, we used raw value scales (Bq/ml), and window width and level values in all PET images were fixed at 3000 and 300, respectively. Gross tumor volume (GTV) was visually delineated on PET images alone by an experienced nuclear medicine physician and a radiation oncologist in consensus. When the GTV contour was drawn, CT images were not used. Because the new brain PET scanner with semiconductor detectors is dedicated to brain imaging, the bottom level of $PET_{CONV}WB$ images used in this study was adjusted to almost the same as that of $PET_{NEW}BR$ images; the GTV was limited to the primary tumors and/or

Table 1 Patient characteristics

Patient	Sex	Age	T stage	N stage
1	M	30	T3	N2
2	M	61	T3	N3b
3	F	35	T4	N1
4	M	53	T2b	N1
5	F	55	T3	N2
6	M	61	T2a	N2
7	F	67	T2a	N1
8	M	76	T2b	N2
9	M	60	T1	N2
10	M	53	T1	N1
11	F	71	T3	N0
12	M	61	T2b	N2

retropharyngeal lymph nodes in this study. GTV_{CONV} was determined using PET_{CONV}WB images, while GTV_{NEW} was determined using PET_{NEW}BR images. There was an interval of approximately 1 week between the delineation of GTV_{NEW} and GTV_{CONV}. After the two types of GTV were delineated, the cerebrum and cerebellum and the brain stem were contoured on CT images.

Radiotherapy treatment planning simulation

The clinical target volume (CTV) was defined three-dimensionally as the GTV with a 2-mm margin, while the planning target volume (PTV) was defined as the CTV plus a 3-mm margin. Assuming a stereotactic radiotherapy boost of 7 ports, the prescribed dose delivered to 95% of PTV was set to 2000 cGy in 4 fractions. A radiotherapy treatment plan was prepared for GTV_{NEW} and GTV_{CONV}. Dose-volume histograms (DVHs) were calculated for the PTV, cerebrum, cerebellum, and brain stem in both plans.

Statistical analysis

Absolute volumes of GTV and DVH parameters were compared. Differences were evaluated using the paired *t*-test. A p value of <0.05 was considered statistically significant.

Results

Absolute volumes of GTV_{NEW} and GTV_{CONV} are shown in Table 2. The average (±standard deviation [SD]) absolute volume of GTV_{NEW} was 15.7 (±9.9; range, 4.9–31.6) ml, and that of GTV_{CONV} was 34.0 ml (±20.5; range, 10.6–75.9) ml. The average absolute volume of GTV_{NEW} was significantly smaller than that of GTV_{CONV} ($p = 0.0006$). Regardless of the order in which the two [^{18}F]FDG examinations were conducted, volumes of GTV_{NEW} were always smaller than GTV_{CONV} for all 12 patients.

Maximum and mean doses of PTV_{NEW} and PTV_{CONV} are shown in Table 3. There were no statistically significant differences between the maximum dose ($p = 0.0585$) or the mean dose ($p = 0.2748$). The maximum doses for cerebrum cerebellum (CC) and for brain stem (BS) in the radiotherapy treatment plan based on GTV_{NEW} ($PLAN_{NEW}$) and those in the plan based on GTV_{CONV} ($PLAN_{CONV}$) are shown in Table 4. In the $PLAN_{NEW}$, the average (±SD) maximum dose to CC was 2,001(±347; range, 1,278–2,430) cGy and that to the BS was 1,475 (±612; range, 586–2,243) cGy. In $PLAN_{CONV}$, the average maximum dose to CC was 2,233(±209; range, 1,627–2,442) cGy and that to the BS was 1,816 (±455; range, 664–2197) cGy.

Compared with $PLAN_{CONV}$, the $PLAN_{NEW}$ significantly reducedmaximum doses to CC ($p = 0.0418$) and BS ($p = 0.0041$). An example of $PLAN_{NEW}$ and $PLAN_{CONV}$ is shown in Figs. 1 and 2.

Discussion

Although PET offers better identification of tumor localization than the anatomical imaging modalities because of its higher contrast resolution, tumor boundaries are blurred on the conventional BGO PET system because of its relatively low spatial resolution due to its larger detectors and worse annihilation noncollinearity blurring because of the larger detector ring of whole-body BGO PET. Daisne *et al.* (12) reported thatPET-derived volumes are more accurate than CT or MRI-derived volumes for squamous cell carcinoma of the head and neck; however, they are still larger than those delineated from the surgical specimens (12).

We did not use CT images when delineating the GTV in order to evaluate the impact of the difference between the two PET scanners on radiotherapy treatment planning. The present study has shown that the absolute GTV volumes on the PET_{NEW}BR system are significantly smaller than those on the PET_{CONV}WB system and that the smaller size of the GTV on PET_{NEW}BR is not likely due to the time of examination. There are several potential reasons why the GTV is smaller for the new brain PET system using semiconductor detectors. One main reason is the difference between the spatial resolution levels of the two PET systems. Higher spatial resolution yielded shaper edge of the tumor, without doubt (7). Additional possible reasons were lower scatter fraction and higher contrast of the PET_{NEW}BR system (8–11). Further study is needed to determine how much geometry of the

Table 2 Absolute volume of GTV

Patient	GTV_{NEW} (ml)	GTV_{CONV} (ml)	Time course protocol
1	27.9	63.0	1
2	31.6	44.9	1
3	23.4	26.4	1
4	9.8	20.6	1
5	27.8	75.9	1
6	20.8	52.6	1
7	8.9	22.3	1
8	6.7	17.8	2
9	4.9	16.5	2
10	5.3	10.6	2
11	9.1	25.2	2
12	12.6	31.7	2
Average ± SD	15.7 ± 9.9	34.0 ± 20.5	
p value	0.0006		

Abbreviation: SD = standard deviation.

Table 3 Maximum and mean doses to PTV

	Maximum dose to PTV (cGy)		Mean dose to PTV (cGy)	
Patient	$PLAN_{NEW}$	$PLAN_{CONV}$	$PLAN_{NEW}$	$PLAN_{CONV}$
1	2,376	2,422	2,150	2,179
2	2,285	2,329	2,139	2,157
3	2,261	2,310	2,121	2,148
4	2,398	2,462	2,182	2,190
5	2,275	2,254	2,130	2,116
6	2,286	2,312	2,125	2,140
7	2,432	2,442	2,218	2,215
8	2,265	2,227	2,133	2,118
9	2,208	2,216	2,112	2,118
10	2,337	2,335	2,165	2,158
11	2,329	2,326	2,184	2,171
12	2,248	2,301	2,136	2,147
Average ± SD	2,308 ± 67	2328 ± 79	2,150 ± 32	2155 ± 31
p values	0.0585		0.2748	

Abbreviations: $PLAN_{CONV}$ = radiotherapy treatment plan based on GTV_{CONV}; $PLAN_{NEW}$ = radiotherapy treatment plan based on GTV_{NEW}; PTV = planning target volume; SD = standard deviation.

detectors, energy resolution of the semiconductor detector, reconstruction algorithm, and other mechanical factors were quantitatively influential on the size of GTV.

In the simulation of radiotherapy treatment planning, this target volume reduction resulted in a decrease in the radiation dose to organs at risk such as CC and the BS. Although we did not compare pathologic specimens to the target volumes on PET images, and it is unclear whether the $PET_{NEW}BR$-based GTV accurately reflected the true tumor volume, we consider the reduction of absolute GTV volumes to be due primarily to the tumor edge on the $PET_{NEW}BR$ image being more clearly defined. However, this reduction of GTV volumes might be smaller if CT images were used with both PET images for the delineation of GTV.

We adopted a method of visually interpreting the delineation of GTV. This method is commonly used (13–17) but is influenced by the display windowing and is dependent on operators. Therefore, several objective methods for contouring PET images have been developed, including isocontouring based on a fixed threshold of a standardized uptake value (1, 17–20), a fixed threshold of 40% to 50% of the maximum activity (3, 17, 20–22), and a threshold adapted to the signal-to-background ratios (2, 12, 17). However, the appropriate standardized technique for the segmentation of PET images is still under investigation in the head and neck regions (4–6, 23–26). It is probable that the lack of a standardized method for segmentation is due in part to the intrinsically low quality of PET images. As such, $PET_{NEW}BR$ images could lead to a new standardized segmentation method, and we consider it necessary to evaluate the interobserver variability of the target delineation and to compare objective segmentation methods for the $PET_{NEW}BR$ images.

Another limitation is that we did not compare our new brain PET results with those from a state-of-the-art brain PET system

Table 4 Maximum doses to cerebrum and cerebellum and brain stem

	Cerebrum and cerebellum (cGy)		Brain stem (cGy)	
Patient no.	$PLAN_{NEW}$	$PLAN_{CONV}$	$PLAN_{NEW}$	$PLAN_{CONV}$
1	2,182	2,340	1,895	2,176
2	2,224	2,333	2,137	2,191
3	2,260	2,310	2,186	2,189
4	1,278	2,377	1,223	1,879
5	2,227	2,246	2,072	2,197
6	1,737	1,627	1,327	2,011
7	2,430	2,442	1,371	1,603
8	1,878	2,196	1,068	1,613
9	1,860	2,164	980	1,532
10	2,056	2,163	586	664
11	2,329	2,326	2,243	2,173
12	1,555	2,274	606	1,564
Average ± SD	2,001 ± 347	2,233 ± 209	1,475 ± 612	1,816 ± 455
p value	0.0418		0.0041	

Abbreviations: $PLAN_{CONV}$ = radiography treatment plan based on GTV_{CONV}; $PLAN_{NEW}$ = radiotherapy treatment plan based on GTV_{NEW}; SD = standard deviation.

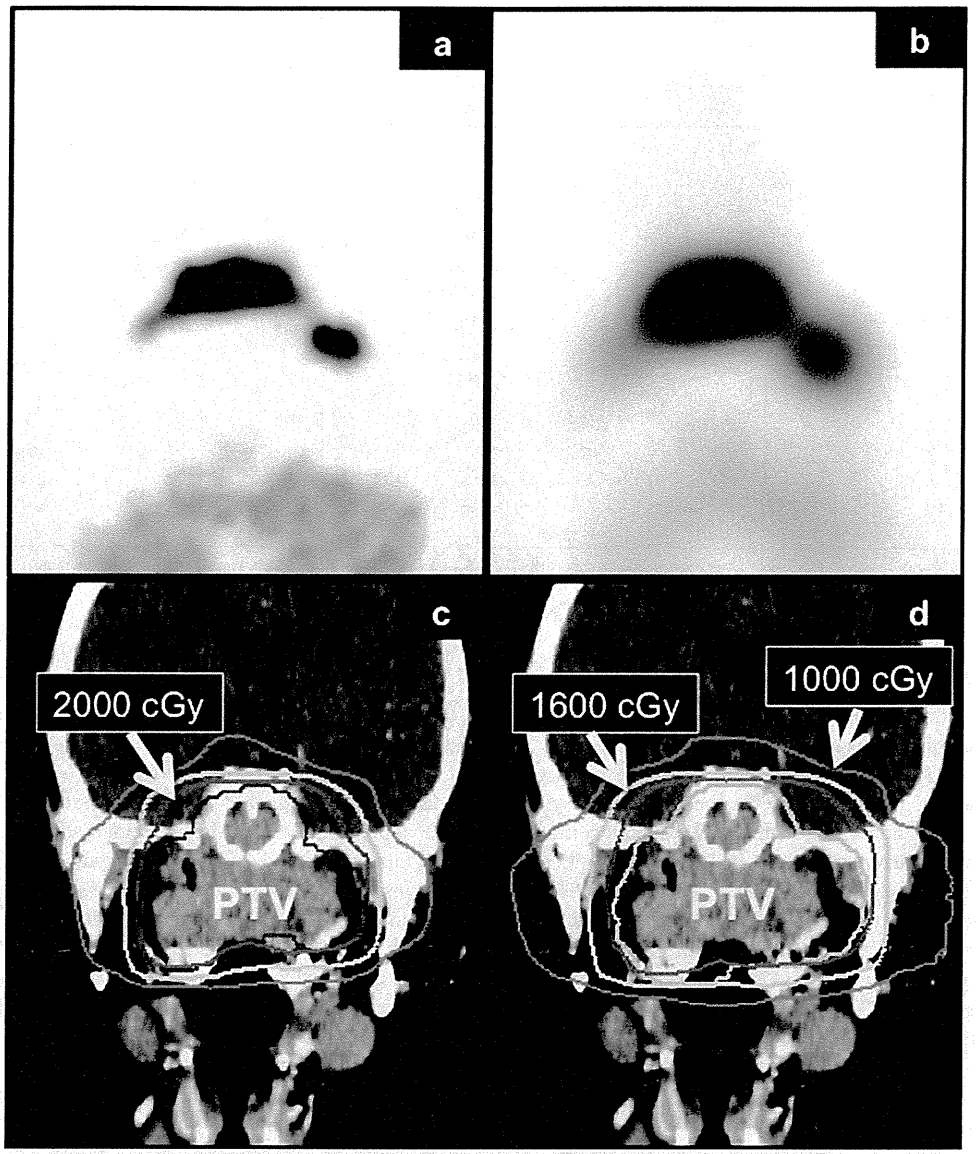

Fig. 1. (a) Brain semiconductor PET image and (b) whole-body BGO scintillator PET image from patient no. 5, with a T3N2M0 NPC are shown. On the brain semiconductor PET image, the boundary of tumor uptake is more clearly identified. (c) Radiotherapy treatment plan based on GTV_{NEW} ($PLAN_{NEW}$) and (d) radiotherapy treatment plan based on GTV_{CONV} ($PLAN_{CONV}$) from the same patient are shown. Blue, aqua, and orange lines show 2,000, 1,600, and 1,000 cGy isodose lines, respectively. The red line indicates PTV_{NEW}, while the green line indicates PTV_{CONV}.

such as Siemens HRRT, but just compared them with output from a relatively old, whole-body camera, the Siemens HR+ system with a standard ordered subset expectation maximization (OSEM) reconstruction method. We would like to stress the advantages of the new brain PET camera with higher resolution and less scatter noise which may better facilitate delineation of tumor for radiation therapy than the conventional whole-body BGO PET camera. However, the HR+ system provides relatively high-resolution PET images with the current reconstruction algorithm. We are now planning to develop a next prototype PET camera with wide aperture and high sensitivity. We consider it necessary to compare a state-of-the-art lutetium oxyorthosilicate (LSO) PET scanner with our new PET in the future.

We previously reported that the $PET_{NEW}BR$ scanner has the potential to provide better identification of intratumoral inhomogeneity (7). It is likely that IMRT can accurately deliver a higher dose to the lesion with higher intratumoral uptake on the new brain PET system using semiconductor detectors. In addition to [^{18}F]FDG labeling, there are various tracers related to tumor cell hypoxia, proliferation, or metabolism (4, 26). If the $PET_{NEW}BR$ imaging system and these tracers are incorporated into IMRT planning, functional and molecular target radiotherapy will become practicable.

Conclusions

Our results suggest that compared to the conventional whole-body BGO PET system, the new brain PET system using semiconductor detectors can provide better identification of tumor boundaries and more accurate tumor delineation; as such, it may