antigen 19–9 (CA19-9) level; and sequence of treatments. Contrast-enhanced CT was performed before starting every two cycles of primary chemotherapy, before and at the end of CRT, and every 2 months after CRT. Objective tumor response was evaluated radiologically according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [18]. CA19-9 was continuously measured once per month. Toxicities were prospectively recorded at each patient's visit using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The highest grades of toxicity observed during CRT and after CRT were recorded.

Statistical analysis

Overall survival from the start of primary chemotherapy and salvage CRT was estimated using the Kaplan-Meier method. Times to progression at the primary tumor site or distant sites were also calculated. Progression was defined as confirmation of progressive disease on CT images using the RECIST criteria. For univariate and multivariate analysis, all of the variables were dichotomized according to clinical relevance based on the previous literature. Univariate analyses were performed using the log-rank test. A Cox's proportional hazards model was developed to identify significant factors influencing survival after CRT. Possible confounded variables were excluded from multivariate analysis. All of the tests of hypotheses were conducted at an alpha level of 0.05 with a 95% confidence interval (CI). All of the statistical analyses were performed using SPSS Statistics version 17.0 (SAS Institute, Tokyo, Japan).

Results

Patient characteristics

Thirty patients with LAPC received primary chemotherapy and salvage CRT. The patient characteristics are summarized in [Table 1]. For first-line chemotherapy, all of the patients received GEM-based chemotherapy. GEM-based chemotherapy included GEM alone in 24 patients (80%) and GEM-based combination chemotherapy in six patients (20%).

Sequel of first-line chemotherapy

The median number of cycles of GEM in 24 patients who received GEM monotherapy was six (range, 1–41). Best tumor response assessed radiologically and best CA19-9 response to first-line chemotherapy are summarized in Table 2. A partial response (PR) was achieved in nine patients, with a response rate of 30%. Among 24 patients whose baseline serum CA19-9 level was >100 U/ml, the median CA19-9 level decreased from 1151 U/ml at baseline to 159 U/ml at minimum during first-line chemotherapy. In these patients, the CA19-9 level decreased by ≥ 50% in 21 patients (88%); the median

Table 2 Best response to primary chemotherapy

Tumor response	No. of patients	% patients
Radiological response		
Partial response	9	30
Stable disease	19	63
Progressive disease	2	7
CA19-9 response (base line CA19-9 > 100 U/ml)		
≥ 50% decrease	21	88
< 50% decrease	1	4
Increase	2	8

time to reach the minimum CA19-9 level was 4.0 (range, 1.8-13.0) months. After failure of first-line GEM-based chemotherapy, seven patients (23%) proceeded to second-line chemotherapy with S-1 alone. The median duration of continuing second-line chemotherapy was 3.0 months.

Eventually, 26 patients (87%) discontinued primary chemotherapy because of local tumor progression, whereas four patients (13%) discontinued chemotherapy because of interstitial pneumonitis caused by GEM. The reasons for discontinuation of the primary chemotherapy are summarized in Table 3.

Sequence of salvage CRT

Thirty patients started salvage CRT after the failure of the primary chemotherapy. The median time between the start of the primary chemotherapy and the start of CRT was 7.9 (range, 3.0-37.3) months. All of the patients completed the course of radiotherapy without major interruption. The median duration of CRT was 42 (range, 38–45) days. Administration of the combined chemotherapeutic agents involved protracted infusion of 5-FU in 14 patients (47%) and oral S-1 in 16 patients (53%). Toxicities during and after CRT are listed in Table 4. Hematological toxicity was relatively mild and there was no grade 4 toxicity. The most frequent grade 3 hematological toxicity was leucopenia. Grades 3 and 4

Table 3 The reasons for discontinued primary chemotherapy

Reason	No. of patients	% patients
Presence of any types of primary disease progression (n = 26)		
Enlargement of tumor	14	47
Elevation of tumor marker	7	23
Carcinomatous pain	5	17
Obstructive jaundice	5	17
Duodenal hemorrhage	2	7
Absence of disease progression (n = 4)		
Interstitial pneumonia	4	13

Table 4 Toxicity during and after salvage chemoradiotherapy

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Toxicity of any grade (%)	Toxicity of grade 3–4 (%)
Hematological toxicity							
Leukopenia	6	11	11	3	0	81	10
Neutropenia	12	13	5	1	0	61	3
Anemia	4	14	10	3	0	87	10
Thrombocytopenia	12	16	3	0	0	61	0
AST/ALT	20	9	2	0	0	35	0
Non-hematological toxicity							
Fatigue	7	17	5	2	0	77	6
Anorexia	4	18	3	5	1	87	19
Nausea	9	15	5	2	0	71	6
Vomiting	24	6	0	1	0	23	3
Diarrhea	21	8	2	0	0	32	0
Abdominal pain	20	9	2	0	0	35	0
Stomatitis	29	2	0	0	0	6	0
Skin rash	29	2	0	0	0	6	0
Infection	29	0	1	1	0	6	3
Gastrointestinal ulcer	27	0	2	1	1	13	6

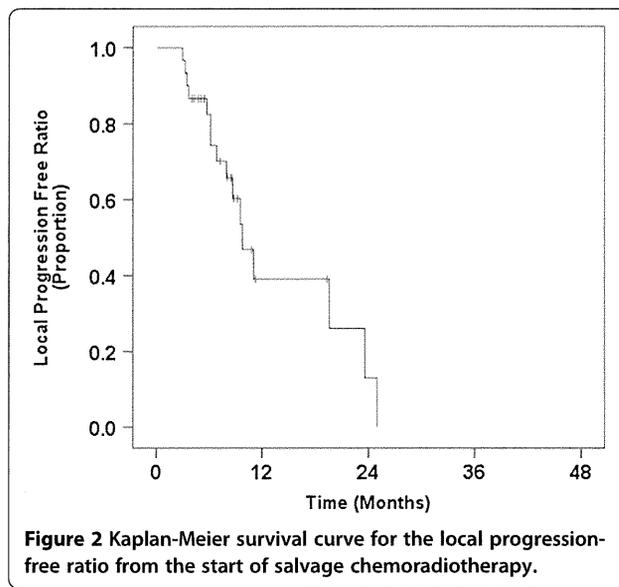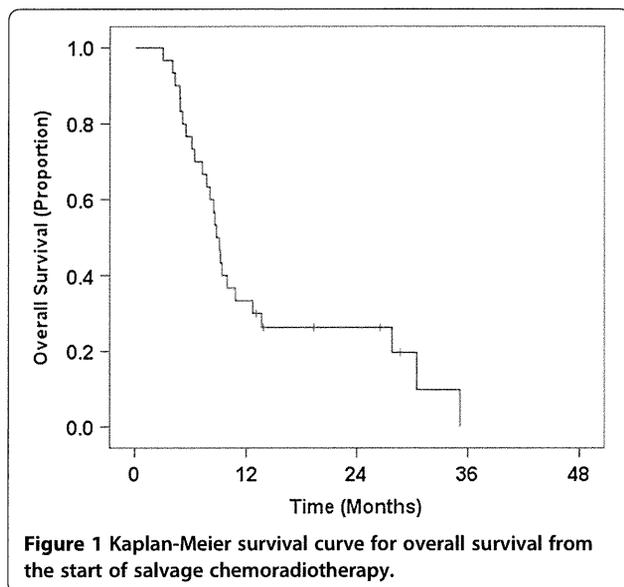*AST* aspartate transaminase, *ALT* alanine transaminase.

non-hematological toxicity included anorexia (19%), nausea (6%), fatigue (6%), gastrointestinal ulcer (6%), vomiting (3%) and bile duct infection (3%). After CRT, three patients developed a gastrointestinal ulcer; of these, two (grade 2) recovered after conservative treatment, and one (grade 3) required endoscopic hemostasis. Another patient developed a duodenal fistula involving the primary tumor at 2 months after completion of CRT (grade 4). This fistula was possibly caused by the necrosis of the huge primary tumor that penetrated the duodenal wall. Although the hemorrhage was transient, this patient needed to undertake long-term fasting and intravenous hyperalimentation, but later died of severe bile duct hemorrhage because of primary tumor progression.

Four patients were diagnosed as having distant metastasis immediately after the completion of salvage CRT. Because of poor general health and/or the lack of an efficacious chemotherapeutic regimen, these patients did not undergo further evaluation. The response of the primary tumor was evaluated radiologically at 2 months after the completion of CRT in 26 patients. Tumor response to CRT included a PR in one patient (3%), stable disease (SD) in 22 patients (73%) and progressive disease (PD) in three patients (10%). Among the 24 patients whose initial CA19-9 level was >100 U/ml, the median CA19-9 level decreased from 769 U/ml to 479 U/ml at minimum after CRT. The CA19-9 level decreased more than 50% in 14 patients (58%) after CRT. Relief of pain was achieved in 16 out of 19 patients (84%) who had experienced carcinomatous pain before CRT. After the

completion of salvage CRT, 20 patients (67%) started maintenance chemotherapy. Maintenance chemotherapy mainly consisted of the S-1 based regimen. The median duration of continued maintenance chemotherapy was 4 months.

Overall outcomes

The median overall survival time (MST) of the entire patient population from the start of salvage CRT was 8.8 (95% CI, 7.8-9.8) months. The 6 month, 1-year and 2-year survival rates from the start of salvage CRT were 76.7%, 33.3% and 26.3%, respectively (Figure 1). At the time of analysis, four patients were still alive, while 26 patients had died of disease progression. No patients underwent radical resection of their pancreatic cancer after CRT. The median progression-free survival (PFS) time from the start of salvage CRT was 4.9 (95% CI, 3.4-6.3) months. The 6 month, 1-year and 2-year PFS rates were 40.0%, 15.2% and 5.7%, respectively. Sites of disease progression after CRT were documented in all 28 patients with progression; they are summarized in Table 5. The sites of first failure after CRT included distant metastases in 17 patients (61%) and locoregional progression in 10 patients (36%); one patient (3%) had both sites of first failure after CRT. Although prophylactic nodal irradiation was not undertaken, isolated nodal recurrence as a first site of recurrence was observed in only one patient. The median local progression-free time from the start of CRT was 9.8 (95% CI, 7.2-12.3) months (Figure 2). The 6 month, 1-year and 2-year local

Figure 1 Kaplan-Meier survival curve for overall survival from the start of salvage chemoradiotherapy.

Figure 2 Kaplan-Meier survival curve for the local progression-free ratio from the start of salvage chemoradiotherapy.

progression-free rates were 82.5%, 39.1% and 13.0%, respectively. The median distant metastasis-free time from the start of CRT was 6.2 (95% CI: 2.6-9.8) months.

In two patients, the primary tumors showed no response to primary chemotherapy and they had PD (Table 2). The primary tumors of these two patients remained stable at the completion of CRT. One patient was not evaluated further because lung metastases emerged at the completion of CRT. She received best supportive care owing to her poor general condition. The primary tumor in the other patient remained stable for 9.6 months, then progressed locally. Both patients died of primary disease at 4.0 and 13.7 months after the start of CRT.

Considered overall, the MST from the start of primary chemotherapy was 17.8 (95% CI, 12.3-23.3) months. The
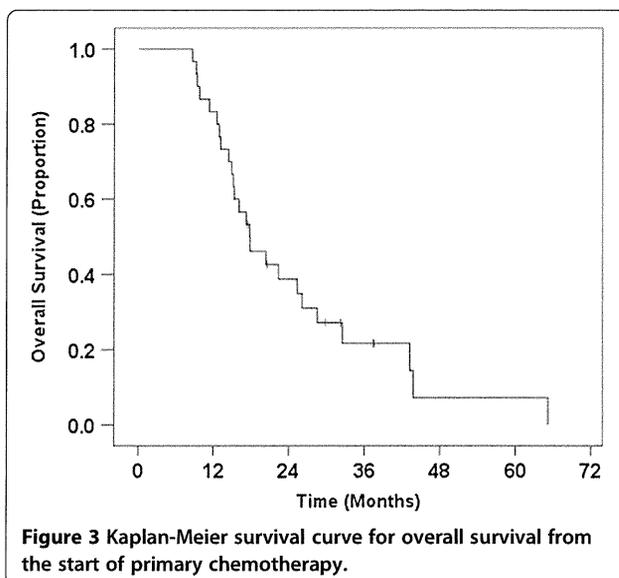
1-, 2-, 3- and 4-year survival rates from the commencement of first-line chemotherapy were 83.3%, 38.8%, 21.7% and 7.2%, respectively (Figure 3).

Univariate and multivariate analysis of pre-CRT factors influencing survival after CRT

Univariate analysis was performed on 11 different variables to evaluate their potential value in terms of survival after salvage CRT (Table 6). Significant prognostic factors for improved survival included KPS ($\geq$ 80; p = 0.022); number of regimens of primary chemotherapy (single; p = 0.006); pre-CRT tumor diameter $\leq$ 4 cm (p = 0.04); and pre-CRT serum CA19-9 level ($\leq$ 1000 U/ml; p = 0.002). The absence of local progression before

Table 5 Sites of first disease progression after salvage chemoradiotherapy

Disease site	No. of patients	% patients
None	2	7
Distant metastases	17	57
Liver	12	
Peritoneum	2	
Liver and peritoneum	1	
Lung	1	
Liver and lung	1	
Locoregional progression	10	33
Local progression	9	
Regional lymph node	1	
Local progression and distant metastases	1	3
Local and peritoneum	1	

Figure 3 Kaplan-Meier survival curve for overall survival from the start of primary chemotherapy.

Table 6 Results of univariate analysis of survival after salvage chemoradiotherapy

Factors	No. of patients	Median survival time (months)	6-month survival (%)	1-year survival (%)	2-year survival (%)	p-value
All patients	30	8.8	77	33	26	
Age						
< 65	14	8.1	79	29	14	
≥ 65	16	9.2	75	38	38	0.2
Gender						
Male	16	8.1	75	31	25	
Female	14	9.2	79	36	29	0.6
Karnofsky performance status						
≥ 80	28	9.1	79	36	28	
< 80	2	4.8	50	0	0	0.03
Primary tumor location						
Head	15	9.4	93	40	33	
Body / tail	15	8.5	60	27	18	0.5
Number of regimens of primary chemotherapy						
1	25	9.4	80	40	32	
2	5	6.1	60	0	0	0.006
Best response to primary chemotherapy						
PR	9	9.2	89	33	33	
SD or PD	21	8.5	71	33	24	0.6
Pre-chemoradiotherapy tumor diameter (cm)						
≤ 4	12	10.8	83	50	50	
> 4	18	8.5	72	22	0	0.04
Pre-chemoradiotherapy serum CA19-9 level (U/ml)						
≤ 1,000	29	10.8	90	47	42	
> 1,000	11	6.4	54	9	0	0.002
Local progression before starting chemoradiotherapy						
Absent	4	NA	80	60	60	
Present	26	8.8	76	28	19	0.15
Time from the start of primary chemotherapy to chemoradiotherapy						
≤ 6 months	12	8.5	75	33	25	
> 6 months	18	8.8	78	33	28	0.9
Combined chemoradiotherapy agents						
5-FU	14	7.2	64	21	14	
S-1	16	9.9	88	44	37	0.09

PR partial response, *SD* stable disease, *PD* progressive disease, *NA* not available.

salvage CRT (p = 0.15) and concomitant use of S-1 during salvage CRT (p = 0.09) were not significant prognostic factors. The time from the start of primary chemotherapy to salvage CRT was not associated with survival (p = 0.73). Using multivariate analysis, a lower pre-CRT serum CA-19-9 level (≤ 1000 U/ml; p = 0.009) and a single regimen of primary chemotherapy (p = 0.004) were found to be independent prognostic factors for survival after salvage CRT (Table 7).

Discussion

In the present study, the MST of the entire patient population from the start of salvage CRT was 8.8 months. The median time to local progression from the commencement of salvage CRT was 8.9 months. Before starting CRT, all of the patients experienced failure of the primary chemotherapy. However, the MST of 8.8 months for this cohort is comparable to the historical MST achieved after primary CRT combined with 5-FU

Table 7 Results of multivariate analysis of survival after salvage chemoradiotherapy

Variables	Factors	Hazard rate (95% CI)	*p*-value
Pre-chemoradiotherapy serum CA19-9 level (U/ml)	≤ 1000 versus > 1000	1 4.38 (1.45-13.22)	0.009
Number of regimens of primary chemotherapy	1 versus 2	1 6.28 (1.78-22.18)	0.004
Local progression before chemoradiotherapy	absent versus present	1 1.58 (0.34-7.18)	0.6
Pre-chemoradiotherapy tumor diameter (cm)	≤ 4.0 versus > 4.0	1 1.11 (0.35-3.46)	0.9

[2,14,19]; the median time to local progression was also similar [13]. In addition, the frequency of grade 3–4 non-hematological toxicity observed in the current study was also similar to that reported in previous studies. These findings show that CRT combined with S-1 or 5-FU had moderate anti-tumor activity and an acceptable toxicity profile in patients with LAPC, even after failure of GEM-based primary chemotherapy.

In the literature, the representative MST of patients with LAPC who were included in prospective clinical trials was reported to be 8.4-11.4 months for 5-FU-based CRT [2,3,14,19], 9.2-15.0 months for GEM monotherapy [15,20] and 10.3-11.1 months for GEM-based CRT [20,21]. Generally, only a few patients with LAPC survive for 3 years or more. The MST from salvage CRT in our cohort seems to be inferior to those reported in recent studies involving primary therapy for LAPC. However, if we consider primary chemotherapy and salvage CRT as a combined treatment strategy, the MST of 17.8 months from the start of primary chemotherapy is a promising result. Additionally, long-term survivors from the start of primary chemotherapy in our cohort seem to be distinct, with 22% achieving a 3-year overall survival. In our cohort, only patients who underwent primary chemotherapy and progressed locally without distant metastases were selected to receive salvage CRT. Because of the strong selection bias, we should not compare this outcome to that of prospective clinical trials in the literature. However, the existence of long-term survivors in our cohort suggests that salvage CRT should have some benefit in selected patients with LAPC, even after failure of the primary chemotherapy. The strategy of using chemotherapy alone as a primary treatment for LAPC, followed-by CRT for salvage intent, should be further investigated in prospective clinical trials.

Combined with radiotherapy, S-1 has been demonstrated to exert a synergistic effect against 5-FU-

resistant cancer xenografts [22]. We previously conducted a phase I trial to determine the maximum tolerated dose of S-1 with concurrent radiotherapy for LAPC [4]. This dose was 80 mg/m^2/day, which is the same as the full dose of S-1 when administered alone. The toxicity of CRT combined with S-1 for LAPC was generally mild and manageable with conservative treatment. Several phase II clinical trials of CRT combined with S-1 for LAPC achieved MSTs in the range 14.3-16.2 months [7,8]. These MSTs compare favorably with the historical MSTs reported for CRT combined with 5-FU of 8.4-11.4 months [2,14]. In the current study, either S-1 or 5-FU was combined with radiotherapy. Univariate analysis of survival after subsequent CRT showed a non-significant trend towards better results when CRT was combined with S-1 (Table 6). The occurrence of grade 3–4 non-hematological toxicity during and after CRT was less frequent among the patients who had received CRT combined with S-1, as compared with 5-FU (6% versus 43%). Because of the retrospective nature of this study, a difference in baseline characteristics may inhibit a fair comparison between the two agents. Although a direct comparison between S-1 and 5-FU has not yet been undertaken in a prospective clinical trial, CRT combined with S-1 is an attractive alternative to 5-FU-based CRT.

The value of S-1 in pancreatic cancer is not limited to its sensitizing effect during CRT. Single agent S-1 has excellent activity regarding chemo-naïve metastatic pancreatic cancer, with a response rate of 37.5% and a MST of 9.2 months [23]. S-1 is the first agent that has not proved inferior to GEM as a single agent for the treatment of advanced pancreatic cancer in a phase III randomized-controlled trial [16]. S-1 also retains its activity in relation to advanced pancreatic cancer even after the failure of GEM, with a response rate of 21% [24]. Accordingly, in the current study, the activity of salvage CRT with S-1 should be related to the excellent systematic effect of the agent on subclinical distant metastasis, as well as its local sensitizing effect.

Recently, induction chemotherapy has become a major component in the treatment strategy for LAPC. Two well-designed retrospective studies have shown that induction chemotherapy followed by CRT yielded a survival benefit over primary CRT or continued chemotherapy alone for LAPC [12,25]. More recently, several phase II prospective clinical trials have been conducted to evaluate the value of induction chemotherapy followed by CRT, which resulted in MSTs in the range 12.6-19.2 months [26-28]. The optimum duration of induction chemotherapy for LAPC continues to be a matter of debate. Recent prospective clinical trials that included induction chemotherapy for LAPC had chosen to evaluate the effects of 2–6 months of induction therapy [26-28]. In the current study, the median duration

of primary chemotherapy was 7 months, which is longer than those used in these prospective trials. Because patients with rapidly progressing occult-metastatic disease were excluded from the present study, the tumors in our cohort might have deviated to relatively chemo-responsive tumors. Therefore, the duration of primary chemotherapy was not associated with survival after CRT in the current study. We could not draw any conclusion with regard to the optimum duration of induction chemotherapy from this retrospective cohort study.

In agreement with the current study, previous studies have shown that a highly-elevated CA 19–9 level is a poor prognostic factor for patients who had received CRT for LAPC [29,30]. A highly elevated serum CA19-9 level in patients prior to CRT suggests chemo-resistance of the tumor, as well as the existence of progressive occult metastasis. These patients might gain little benefit from the addition of salvage CRT.

Multivariate analysis revealed that the use of two regimens of primary chemotherapy was an unfavorable factor for survival after CRT. The MST of the patients who received two regimens of primary chemotherapy was 6.1 months from the start of salvage CRT, and no patient survived for 12 months or longer thereafter (Table 6). In all of the patients (n = 5) who underwent two regimens of primary chemotherapy before CRT, S-1 was used as a second-line chemotherapy. Of these patients, three received salvage CRT combined with 5-FU, and two received salvage CRT combined with S-1. Because both 5-FU and S-1 are fluorinated pyrimidine agents, failure of the tumor to respond to treatment with S-1 should cause resistance to salvage CRT combined with either 5-FU or S-1. If there are any signs of failure to respond to the primary chemotherapy, without distant metastasis, salvage CRT could be a treatment of choice as a second-line therapy.

Because of the retrospective nature of the current study, there were a number of limitations that affected the interpretation of our findings. The number of patients was very limited and the patient population was not homogeneous because of different clinical backgrounds, and they received CRT with salvage intent. Also, the patients were collected for over a period of 7 years, non-consecutively. The clinical response to primary chemotherapy was generally better than previously reported, possibly because of the exclusion of patients with chemo-resistant occult distant metastasis. Only patients who underwent primary chemotherapy and progressed locally without distant metastases were selected and included in the current analysis.

Whether or not the addition of chemotherapy prior to CRT will contribute to prolonging the survival of patients with LAPC has not been elucidated with sufficient statistical power in a prospective clinical trial. We

are now investigating the value of induction chemotherapy with GEM versus no induction chemotherapy for LAPC in a multi-institutional randomized phase II study involving S-1 and concurrent radiotherapy (JCOG1106, UMIN000006811). A future phase III study will be conducted to compare GEM monotherapy and S-1 based CRT with or without induction GEM, depending on the results of the JCOG1106 study. Another phase III study, the GERCOR LAP 07 phase III trial (www.clinicaltrials.gov, identifier code NCT00634725) is also ongoing. This study was designed to elucidate the benefit of induction chemotherapy followed by CRT combined with capecitabine, with or without erlotinib during induction chemotherapy and a CRT phase. In future, results from these prospective clinical trials will become available to further define the role of chemotherapy followed by CRT for LAPC.

Conclusions
CRT combined with S-1 or 5-FU had moderate anti-tumor activity in patients with LAPC even after failure of GEM-based primary chemotherapy. If there are any signs of failure to primary chemotherapy without distant metastasis, salvage CRT could be a treatment of choice as a second-line therapy. Patients with a relatively low serum CA19-9 level after primary chemotherapy may obtain additional survival benefit from salvage CRT. The strategy of using chemotherapy alone as a primary treatment for LAPC, followed-by CRT with salvage intent should be further investigated in prospective clinical trials.

Authors' contributions
HM, YI and JI participated in the design of the study, performed the statistical analysis, interpretation of data, and drafted the manuscript. HM, YI, NM, MM and MS carried out the chemoradiotherapy and analyzed tumor response. CM, HU, TO and SK carried out the chemotherapy and analyzed tumor response. All of the listed authors contributed to the writing of the manuscript. All authors read and approved the final manuscript.

Author details
[1]Division of Radiation Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. [2]Divisions of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan.

References
1. Shinchi H, Takao S, Noma H, Matsuo Y, Mataki Y, Mori S, Aikou T: Length and quality of survival after external-beam radiotherapy with concurrent continuous 5-fluorouracil infusion for locally unresectable pancreatic cancer. Int J Radiat Oncol Biol Phys 2002, 53:146–150.
2. Moertel CG, Frytak S, Hahn RG, O'Connell MJ, Reitemeier RJ, Rubin J, Schutt AJ, Weiland LH, Childs DS, Holbrook MA, Lavin PT, Livstone E, Spiro H, Knowlton A, Kalser M, Barkin J, Lessner H, Mann-Kaplan R, Ramming K, Douglas HO Jr, Thomas P, Nave H, Bateman J, Lokich J, Brooks J, Chaffey J,

Corson JM, Zamcheck N, Novak JW: **Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: The Gastrointestinal Tumor Study Group.** *Cancer* 1981, **48**:1705–1710.

3. Gastrointestinal Tumor Study Group: **Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone.** *J Natl Cancer Inst* 1988, **80**:751–755.

4. Ikeda M, Okusaka T, Ito Y, Ueno H, Morizane C, Furuse J, Ishii H, Kawashima M, Kagami Y, Ikeda H: **A phase I trial of S-1 with concurrent radiotherapy for locally advanced pancreatic cancer.** *Br J Cancer* 2007, **96**:1650–1655.

5. Shirasaka T, Shimamato Y, Ohshimo H, Yamaguchi M, Kato T, Yonekura K, Fukushima M: **Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators.** *Anticancer Drugs* 1996, **7**:548–557.

6. Kim HM, Bang S, Park JY, Seong J, Song SY, Chung JB, Park SW: **Phase II trial of S-1 and concurrent radiotherapy in patients with locally advanced pancreatic cancer.** *Cancer Chemother Pharmacol* 2009, **63**:535–541.

7. Sudo K, Yamaguchi T, Ishihara T, Nakamura K, Hara T, Denda T, Tawada K, Imagumbai T, Araki H, Sakai M, Hatano K, Kawakami H, Uno T, Ito H, Yokosuka O: **Phase II study of oral S-1 and concurrent radiotherapy in patients with unresectable locally advanced pancreatic cancer.** *Int J Radiat Oncol Biol Phys* 2011, **80**:119–125.

8. Ikeda M, Ioka T, Ito Y, Yonemoto N, Nagase M, Yamao K, Miyakawa H, Ishii H, Furuse J, Sato K, Sato T, Okusaka T: **A multicenter phase II trial of S-1 with concurrent radiation therapy for locally advanced pancreatic cancer.** *Int J Radiat Oncol Biol Phys* 2013, **85**:163–169.

9. Manak E, Merkel S, Klein P, Papadopoulos T, Bautz WA, Baum U: **Resectability of pancreatic adenocarcinoma: assessment using multidetector-row computed tomography with multiplanar reformations.** *Abdom Imag* 2009, **34**:75–80.

10. Furuse J, Kinoshita T, Kawashima M, Ishii H, Nagase M, Konishi M, Nakagohri T, Inoue K, Ogino T, Ikeda H, Maru Y, Yoshino M: **Intraoperative and conformal external-beam radiation therapy with protracted 5-fluorouracil infusion in patients with locally advanced pancreatic carcinoma.** *Cancer* 2003, **97**:1346–1352.

11. Morak MJ, Hermans JJ, Smeenk HG, Renders WM, Nuyttens JJ, Kazemier G, van Eijck CH: **Staging for locally advanced pancreatic cancer.** *Eur J Surg Oncol* 2009, **35**:963–968.

12. Krishnan S, Rana V, Janjan NA, Varadhachary GR, Abbruzzese JL, Das P, Delclos ME, Gould MS, Evans DB, Wolff RA, Crane CH: **Induction chemotherapy selects patients with locally advanced, unresectable pancreatic cancer for optimal benefit from consolidative chemoradiation therapy.** *Cancer* 2007, **110**:47–55.

13. Huguet F, Girard N, Guerche CS-E, Hennequin C, Mornex F, Azria D: **Chemoradiotherapy in the management of locally advanced pancreatic carcinoma: a qualitative systematic review.** *J Clin Oncol* 2009, **27**:2269–2277.

14. Ishii H, Okada S, Tokuuye K, Nose H, Okusaka T, Yoshimori M, Nagahama H, Sumi M, Kagami Y, Ikeda H: **Protracted 5-fluorouracil infusion with concurrent radiotherapy as a treatment for locally advanced pancreatic carcinoma.** *Cancer* 1997, **79**:1516–1520.

15. Ishii H, Furuse J, Boku N, Okusaka T, Ikeda M, Ohkawa S, Fukutomi A, Hamamoto Y, Nakamura K, Fukuda H, JCOG Gastrointestinal Oncology Study Group: **Phase II study of gemcitabine chemotherapy alone for locally advanced pancreatic carcinoma: JCOG0506.** *Jpn J Clin Oncol* 2010, **40**:573–579.

16. Ioka T, Ikeda M, Ohkawa S, Yanagimoto H, Fukutomi A, Sugimori K, Baba H, Yamao K, Shimamura T, Chen J, Mizumoto K, Furuse J, Funakoshi A, Hatori T, Yamaguchi T, Egawa S, Sato A, Ohashi Y, Cheng A, Okusaka T: **Randomized phase III study of gemcitabine plus S-1 (GS) versus S-1 versus gemcitabine (GEM) in unresectable advanced pancreatic cancer (PC) in Japan and Taiwan: GEST study.** *J Clin Oncol* 2011, **29**:257s.

17. Nio K, Ueno H, Okusaka T, Morizane C, Hagihara A, Kondo S, Mayahara H, Ito Y: **Chemoradiotherapy versus gemcitabine-based chemotherapy in patients with unresectable, locally advanced pancreatic cancer.** *J Clin Oncol* 2010, **28**(Suppl):e14504.

18. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J: **New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).** *Eur J Cancer* 2009, **45**:228–247.

19. Cohen SJ, Dobelbower R Jr, Lipsitz S, Catalano PJ, Sischy B, Smith TJ, Haller DG, Haller DG, Eastern Cooperative Oncology Group: **A randomized phase III study of radiotherapy alone or with 5-fluorouracil and mitomycin-C in patients with locally advanced adenocarcinoma of the pancreas: eastern cooperative oncology group study E8282.** *Int J Radiat Oncol Biol Phys* 2005, **62**:1345–1350.

20. Loehrer PJ, Feng Y, Cardenes H, Wagner L, Brell JM, Cella D, Flynn P, Ramanathan RK, Crane CH, Alberts SR, Benson AB 3rd: **Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an eastern cooperative oncology group trial.** *J Clin Oncol* 2011, **29**:4105–4111.

21. Cardenes HR, Moore AM, Johnson CS, Yu M, Helft P, Chiorean EG, Vinson J, Howard TJ, Stephens AW, Tai DF, Loehrer PJ Sr: **A phase II study of gemcitabine in combination with radiation therapy in patients with localized, unresectable, pancreatic cancer: a Hoosier oncology group study.** *Am J Clin Oncol* 2011, **34**:460–465.

22. Nakata E, Fukushima M, Takai Y, Nemoto K, Ogawa Y, Nomiya T, Nakamura Y, Milas L, Yamada S: **S-1, an oral fluoropyrimidine, enhances radiation response of DLD-1/FU human colon cancer xenografts resistant to 5-FU.** *Oncol Rep* 2006, **16**:465–471.

23. Okusaka T, Funakoshi A, Furuse J, Boku N, Yamao K, Ohkawa S, Saito H: **A late phase II study of S-1 for metastatic pancreatic cancer.** *Cancer Chemother Pharmacol* 2008, **61**:615–621.

24. Morizane C, Okusaka T, Furuse J, Ishii H, Ueno H, Ikeda M, Nakachi K, Najima M, Ogura T, Suzuki E: **A phase II study of S-1 in gemcitabine-refractory metastatic pancreatic cancer.** *Cancer Chemother Pharmacol* 2009, **63**:313–319.

25. Huguet F, André T, Hammel P, Artru P, Balosso J, Selle F, Deniaud-Alexandre E, Ruszniewski P, Touboul E, Labianca R, de Gramont A, Louvet C: **Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies.** *J Clin Oncol* 2007, **25**:326–331.

26. Moureau-Zabotto L, Phélip JM, Afchain P, Mineur L, André T, Vendrely V, Lledo G, Dupuis O, Huguet F, Touboul E, Balosso J, Louvet C: **Concomitant administration of weekly oxaliplatin, fluorouracil continuous infusion, and radiotherapy after 2 months of gemcitabine and oxaliplatin induction in patients with locally advanced pancreatic cancer: a groupe coordinateur multidisciplinaire en O.** *J Clin Oncol* 2008, **26**:1080–1085.

27. Nakachi K, Furuse J, Kinoshita T, Kawashima M, Ishii H, Ikeda M, Mitsunaga S, Shimizu S: **A phase II study of induction chemotherapy with gemcitabine plus S-1 followed by chemoradiotherapy for locally advanced pancreatic cancer.** *Cancer Chemother Pharmacol* 2010, **66**:527–534.

28. Crane CH, Varadhachary GR, Yordy JS, Staerkel GA, Javle MM, Safran H, Haque W, Hobbs BD, Krishnan S, Fleming JB, Das P, Lee JE, Abbruzzese JL, Wolff RA: **Phase II trial of cetuximab, gemcitabine, and oxaliplatin followed by chemoradiation with cetuximab for locally advanced (T4) pancreatic adenocarcinoma: correlation of Smad4 (Dpc4) immunostaining with pattern of disease progression.** *J Clin Oncol* 2011, **29**:3037–3043.

29. Okusaka T, Okada S, Sato T, Wakasugi H, Saisho H, Furuse J, Ishikawa O, Matsuno S, Yokoyama S: **Tumor markers in evaluating the response to radiotherapy in unresectable pancreatic cancer.** *Hepatogastroenterology* 1998, **45**:867–872.

30. Koom WS, Seong J, Kim YB, Pyun HO, Song SY: **CA 19–9 as a predictor for response and survival in advanced pancreatic cancer patients treated with chemoradiotherapy.** *Int J Radiat Oncol Biol Phys* 2009, **73**:1148–1154.

Phrenic Nerve Injury after Radiofrequency Ablation of Lung Tumors: Retrospective Evaluation of the Incidence and Risk Factors

Yusuke Matsui, MD, Takao Hiraki, MD, Hideo Gobara, MD, Mayu Uka, MD, Yoshihisa Masaoka, MD, Akihiro Tada, MD, Shinichi Toyooka, MD, Toshiharu Mitsuhashi, MD, Hidefumi Mimura, MD, and Susumu Kanazawa, MD

ABSTRACT

Purpose: To retrospectively investigate the incidence of and risk factors for phrenic nerve injury after radiofrequency (RF) ablation of lung tumors.

Materials and Methods: The study included 814 RF ablation procedures of lung tumors. To evaluate the development of phrenic nerve injury, chest radiographs obtained before and after the procedure were examined. Phrenic nerve injury was assumed to have developed if the diaphragmatic level was elevated after the procedure. To identify risk factors for phrenic nerve injury, multiple variables were compared between cases of phrenic nerve injury and randomly selected controls by using univariate analyses. Multivariate analysis was then performed to identify independent risk factors.

Results: Evaluation of phrenic nerve injury from chest radiographs was possible after 786 procedures. Evidence of phrenic nerve injury developed after 10 cases (1.3%). Univariate analysis revealed that larger tumor size ($\geq$ 20 mm; $P = .014$), proximity of the phrenic nerve to the tumor ($<$ 10 mm; $P < .001$), the use of larger electrodes (array diameter or noninsulated tip length $\geq$ 3 cm; $P = .001$), and higher maximum power applied during ablation ($\geq$ 100 W; $P < .001$) were significantly associated with the development of phrenic nerve injury. Multivariate analysis demonstrated that the proximity of the phrenic nerve to the tumor ($<$ 10 mm; $P < .001$) was a significant independent risk factor.

Conclusions: The incidence of phrenic nerve injury after RF ablation was 1.3%. The proximity of the phrenic nerve to the tumor was an independent risk factor for phrenic nerve injury.

ABBREVIATIONS

FEV1.0 = forced expiratory volume at 1 second, OR = odds ratio, RF = radiofrequency, VC = vital capacity

Radiofrequency (RF) ablation has received considerable attention as a therapy for lung tumors. Although an international survey (1) reported a low mortality rate (0.4%), RF ablation of lung tumors results in various complications, including injuries in peripheral nerves such as the brachial and phrenic nerves (2,3). Because phrenic nerves provide motor innerva-

tion to the diaphragm, injury to these nerves may induce diaphragmatic paralysis and impair pulmonary function. Since patients who undergo RF ablation are often nonsurgical candidates because of preexisting impaired pulmonary function, phrenic nerve injury represents an important risk during treatment. However, this complication is poorly understood because of the paucity of reported cases. Therefore, the purpose of this study was to retrospectively evaluate the incidence of and risk factors for phrenic nerve injury after RF ablation of lung tumors.

MATERIALS AND METHODS

Study Population
Institutional review board approval was obtained to perform percutaneous RF ablation of lung tumors under computed tomography (CT) fluoroscopic guidance and to report the outcomes of RF ablation. In addition, informed consent

was also obtained from the patients before the procedure was begun. Between June 2001 and December 2011, 892 RF ablation procedures were performed for lung tumors at a single institution. Among those, chest radiographs before or after 78 procedures were not available; therefore, those procedures were excluded from the study. Data were obtained for the remaining 814 procedures.

RF Ablation Techniques

The RF ablation procedure was performed in an inpatient setting. A chest radiograph was obtained on admission. For the procedure, intramuscular hydroxyzine (25 mg) and intravenous fentanyl (0.1–0.3 mg) were used for conscious sedation. Intraprocedural pain was also treated with local anesthesia (n = 496) or a combination of local and epidural anesthesia (n = 316). Two procedures were performed under general anesthesia. Local anesthesia was induced by the administration of 1% lidocaine (5–10 mL). For epidural anesthesia, continuous infusion of 0.2% ropivacaine and 2 μg/mL fentanyl at 2–6 mL/h was used.

RF ablation was always performed percutaneously by using CT fluoroscopy guidance (Asteion or Aquilion 16; Toshiba, Tokyo, Japan). We used two types of electrodes: a multitined expandable electrode (LeVeen; Boston Scientific, Natick, Massachusetts) or a single internally cooled electrode (Cool-tip; Covidien, Mansfield, Massachusetts). The array diameters of the multitined expandable electrodes or the noninsulated tip lengths of internally cooled electrodes were selected on the basis of the tumor size; ablation of larger tumors requires the use of a larger electrode (ie, an electrode with a larger array diameter or a longer noninsulated tip).

The electrode was introduced into the tumor and connected to an RF generator (RF 2000 or RF 3000 [Boston Scientific] or CC-1 [Covidien]). When the Boston Scientific device was used, RF energy was applied until there was a rapid increase in impedance or automatic shutoff at 15 minutes. This application was repeated once at each site. When the Covidien device was used, an impedance control algorithm was selected, and the RF energy was applied for 10–12 minutes while infusing iced saline solution into the cooling lumen of the electrode. The ablation algorithm depended on the array diameter or the noninsulated tip length, ie, the use of larger electrodes required the use of higher RF power (4). We attempted to achieve ablation with a margin of at least 5 mm. Multiple overlapping ablations were performed to secure an adequate ablation margin if necessary. Chest radiographs were obtained 3 h after RF ablation and on the following day to evaluate complications.

Evaluation of Phrenic Nerve Injury

To evaluate the development of phrenic nerve injury, chest radiographs obtained before the procedure (ie, on admission) and after the procedure (ie, 3 h after the procedure and on the following day) were retrospectively reviewed, with the level of the diaphragm noted. Phrenic nerve injury was assumed to have developed if the diaphragm on the treated side was substantially elevated after the procedure. Substantial elevation was defined as elevation with a height greater than the width of an intercostal space. Even without phrenic nerve injury, the level of the diaphragm may be different at each examination, mainly because of the degree of inspiration. Therefore, elevation of the diaphragm on the treated side was evaluated by comparing it to the level of the diaphragm on the untreated side.

Identification of Risk Factors for Phrenic Nerve Injury

To identify risk factors for phrenic nerve injury, we analyzed multiple characteristics of the patients, tumors, and ablations. The patient characteristics included age and sex. The tumor characteristics included size and distance from the phrenic nerve (< 10 mm or ≥ 10 mm). When the phrenic nerve could not be identified on CT images, the anticipated location of the phrenic nerve was estimated on the basis of a standard imaging atlas (5). The distance from the phrenic nerve to the nearest tumor edge was measured on the CT images that were obtained before RF ablation. The ablation characteristics included electrode type (multitined expandable electrode or single internally cooled electrode), array diameter or noninsulated tip length of the electrode, maximum power applied during ablation, and RF application time. These variables were compared between cases of phrenic nerve injury and selected control cases. For control selection, we recruited eight randomly sampled controls per case by using a random number table; the number of controls selected was based on the fact that statistical power does not increase beyond this number of control cases.

Statistical Analysis

In cases of phrenic nerve injury in which pulmonary function data were available for before and after RF ablation, the post-procedural vital capacity (VC) and forced expiratory volume at 1 s (FEV1.0) were compared with the preprocedural VC and FEV1.0, respectively, by using the paired Student t test. Univariate analyses to determine the risk factors for phrenic nerve injury were performed by using the two-sided Student t test for numerical values and Fisher exact test for categoric values. Then, multivariate logistic regression analysis was performed to determine the independent risk factor. A P value of less than .05 was considered statistically significant. Odds ratios (ORs) were calculated for significant categorical variables. The analyses were performed by using SPSS software (version 16.0; SPSS, Chicago, Illinois).

RESULTS

The elevation of the diaphragm on the treated side could not be evaluated after 28 RF ablation procedures because of the

Table 1. Characteristics of the 10 Cases of Phrenic Nerve Injury after Radiofrequency Ablation of Lung Tumors

Pt. No.	Age (y)	Sex	Tumor Size (mm)	Tumor–Phrenic Nerve Distance (mm)	Electrode Type/Size*	Maximum Power (W)	Application Time (min)	Procedural Pain Site	Timing of DE†	Pre-/Postablation Measurement (L)	
										VC	FEV1.0
1	46	F	19	<10	LeVeen (2)	80	50	Nowhere	3 h	NA	NA
2	58	F	24	≥10	Cool-tip (3)	100	21	Shoulder	1 d	NA	NA
3	61	M	32	<10	Cool-tip (3)	135	27	Shoulder	3 h	NA	NA
4	73	M	30	<10	LeVeen (3)	150	69	Shoulder	3 h	NA	NA
5	77	F	30	≥10	LeVeen (4)	190	49	Shoulder, teeth	1 d	1.95/1.60	1.76/1.36
6	71	M	15	<10	LeVeen (3)	110	32	Shoulder	1 d	3.65/2.57	2.75/1.93
7	73	F	24	<10	Cool-tip (3)	120	18	Shoulder	3 h	2.07/1.54	1.90/1.54
8	66	M	26	<10	Cool-tip (3)	120	11	Shoulder	3 h	3.83/3.09	2.82/2.17
9	60	F	22	<10	Cool-tip (3)	110	30	Shoulder	3 h	1.62/1.60	1.18/1.13
10	55	F	14	<10	Cool-tip (3)	110	36	Mandible	3 h	2.99/2.52	2.28/1.92

Note.—Tumors were metastatic in nature in all patients. DE = diaphragmatic elevation, FEV1.0 = forced expiratory volume at 1 s, NA = data not available, VC = vital capacity.
* Array diameter or noninsulated tip length (cm).
† Onset of injury measured after ablation procedure.
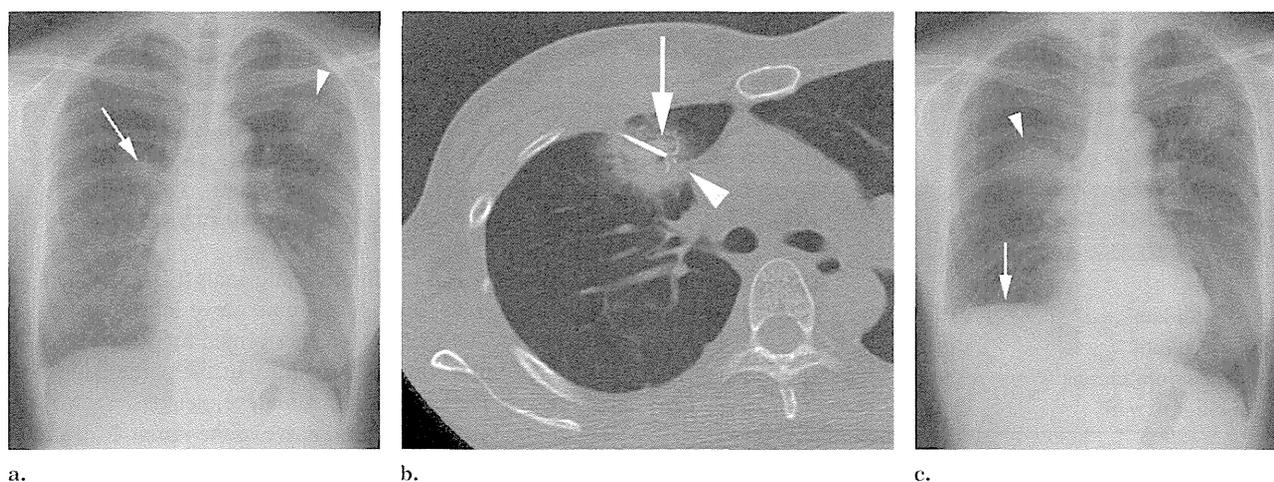
Figure 1. Phrenic nerve injury after RF ablation of a metastatic lung tumor from rectal cancer in a 46-year-old woman (case 1; Table 1). (a) On a preprocedural chest radiograph, the arrow denotes the target tumor and the arrowhead denotes a previously ablated tumor. (b) CT image obtained during RF ablation shows a multitined expandable electrode with array diameters of 2 cm inserted into the tumor (arrow). Arrowhead indicates the anticipated location of the phrenic nerve. Note that the ablation zone surrounds the tumor. (c) Chest radiograph obtained 3 h after RF ablation. The diaphragm on the treated side (arrow) is substantially elevated in comparison with that on the preprocedural chest radiograph (a). The arrowhead denotes the ablation zone.

presence of massive pleural effusion or pneumothorax after the procedure (n = 16), absence of the contralateral lung because of a history of pneumonectomy (n = 8), or RF ablation procedures in both lungs (n = 4). Phrenic nerve injury developed after 10 of the remaining 786 procedures (1.3%). The characteristics of the 10 cases are shown in Table 1. Images from a case of phrenic nerve injury are shown in Figure 1. Elevation of the diaphragm was demonstrated on a chest radiograph 3 hours after the procedure in seven cases; in the other three, it was not demonstrated 3 h after the procedures, but on the following day. The procedure was accompanied by patient-reported pain in

nine of the 10 cases. Pain was perceived in the shoulder in seven cases, the shoulder and teeth in one case, and the mandible in one case.

Pre- and postprocedural pulmonary function data were available in six of the 10 cases of phrenic nerve injury. In these six cases, the mean VC decreased significantly (P = .02) by a mean (±SD) of 18.2% ± 8.9 (range, 1.2%–29.6%) after RF ablation (2.69 L before ablation, 2.15 L after). Similarly, the mean value of FEV1.0 decreased significantly (P = .01) from 2.12 L before RF ablation to 1.68 L after RF ablation; therefore, FEV1.0 decreased by a mean of 19.1% ± 7.9 (range, 4.2%–29.8%) after RF ablation. In

Table 2. Results of Univariate Analyses to Determine Risk Factors for Phrenic Nerve Injury

Characteristic	Case (n = 10)	Control (n = 80)	P Value	Odds Ratio
Age (y)	64.0 ± 9.7	61.3 ± 10.8	.449	—
Sex (M/F)	4/6	55/25	.087	—
Tumor size (mm)	23.6 ± 6.2	18.7 ± 13.7	.272	
Tumor size group				—
<20 mm	3	57	Ref	1.00
≥20 mm	7	23	.014	5.78
Tumor distance from phrenic nerve				
<10 mm	8	3	<.001	102.7
≥10 mm	2	77	Ref	1.00
RF electrode type				
LeVeen	4	57	.07	—
Cool-tip	6	23	—	—
Array diameter/noninsulated tip length				
≤2 cm	1	53	Ref	1.00
≥3 cm	9	27	.001	17.7
Maximum power (W)	123 ± 30	67 ± 43	<.001	—
Maximum power group				
<100 W	1	64	Ref	1.00
≥100 W	9	16	<.001	36.0
RF application time (min)	34 ± 17	28 ± 26	.478	—

Note.—Values presented as means ± SD where applicable. Ref = reference value for calculation of odds ratio, RF = radiofrequency.

Table 3. Results of Multivariate Analysis to Determine Independent Risk Factor for Phrenic Nerve Injury

| Variable	P Value	Odds Ratio (95% CI)
Size ≥ 20 mm	.307	3.01 (0.36–24.8)
Distance from phrenic nerve <10 mm	<.001	66.8 (8.84–504.2)

(≥ 100 W; $P < .001$; OR, 36.0-fold higher for power < 100 W).

The results of the multivariate analysis to elucidate an independent risk factor for phrenic nerve injury are shown in Table 3. The analysis was performed by using variables including tumor size and proximity of the phrenic nerve to the tumors. The only identified independent risk factor was the proximity of the phrenic nerve to the tumor (< 10 mm; $P < .001$, OR, 66.8-fold higher for distances ≥ 10 mm).

two cases, shortness of breath was observed after the procedure. Although oxygen administration was required for 3 and 6 days after the procedures in these patients, respectively, the symptom resolved within 1 week. In the other eight cases, the patient was asymptomatic. A radiographically elevated diaphragm persisted during a mean follow-up period of 19.2 months (range, 1–53 mo) in all cases.

The results of the univariate analyses of potential risk factors for phrenic nerve injury are shown in Table 2. The following factors were significantly associated with the development of phrenic nerve injury after RF ablation: larger tumor size (≥ 20 mm in diameter; $P = .014$; OR, 5.78-fold higher for tumors < 20 mm in diameter), proximity of the phrenic nerve to the tumor (< 10 mm; $P < .001$; OR, 102.7-fold higher for distances ≥ 10 mm), larger electrode size (array diameter or noninsulated tip lengths ≥ 3 cm; $P = .001$; OR, 17.7-fold higher for distances ≤ 2 cm), and higher maximum power applied during ablation

DISCUSSION

Peripheral nerves are sensitive to heat, and therefore, they may be injured by the application of RF ablation in nearby areas. In rats, temperatures of 43°C–45°C damage the sciatic nerve (6,7). In cats, reversible blockade of the sciatic nerve by RF ablation application occurs at 40°C (8). Phrenic nerve injury has been noted as a complication of cardiac ablation. Bunch et al (9) revealed the effect of RF ablation at the pulmonary vein orifice on the phrenic nerves in dogs. Transient phrenic nerve injury occurred at a temperature of 47°C ± 3 after 38 seconds ± 32, and permanent injury occurred after additional energy was delivered at a temperature of 51°C ± 6 after 92 seconds ± 83.

To our knowledge, only two cases of phrenic nerve injury have been reported as complications of RF ablation of lung tumors (3). However, we speculate that a certain number of cases may be missed because most patients with

高
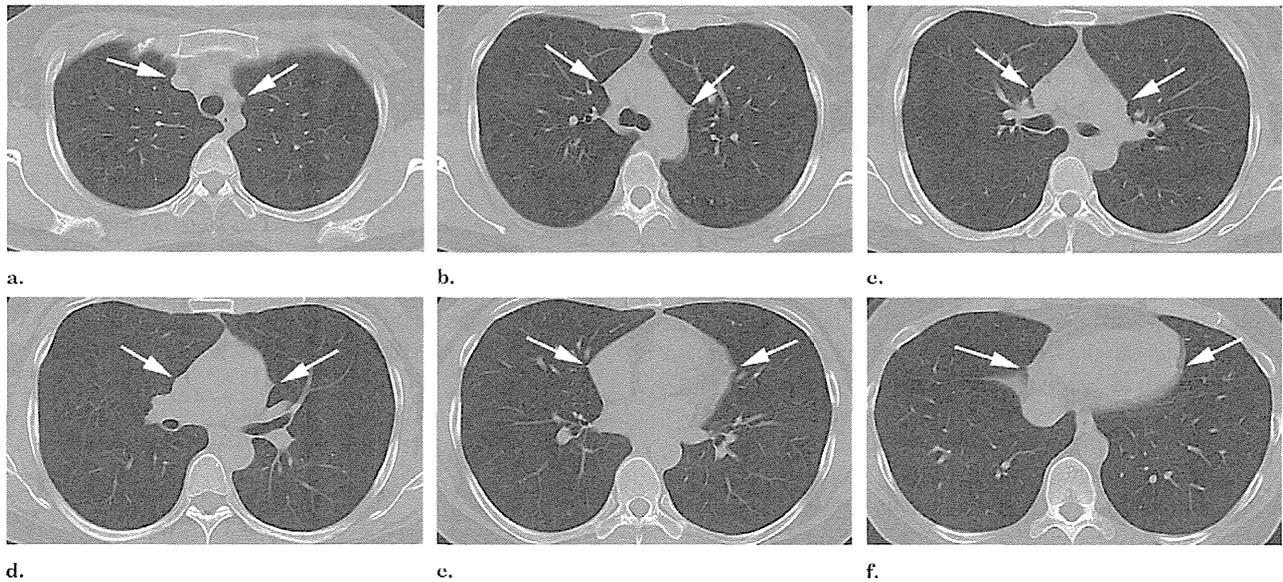
Figure 2. Chest CT images from a 41-year-old woman. Arrows denote the location of the phrenic nerves on each slice. **(a, b)** The right phrenic nerve lies lateral to the right brachiocephalic vein and the superior vena cava. The left phrenic nerve runs along the lateral aspect of the transverse arch of the aorta. **(c, d)** The two nerves subsequently pass anterior to their respective pulmonary hila. **(e, f)** The two nerves traverse inferiorly in a broad vertical plane along the margin of the heart between the fibrous pericardium and the mediastinal pleura.

phrenic nerve injury are asymptomatic, as revealed in the present study. Ablation operators should consider the anatomy of the phrenic nerve to minimize the risk of this complication. The anatomy of the phrenic nerve on CT images is shown in Figure 2. The phrenic nerves lie along the lateral mediastinum and run from the thoracic inlet to the diaphragm. They run through the upper chest, medial to the mediastinal pleura and the apex of the right or left lung. The right phrenic nerve lies lateral to the right brachiocephalic vein and the superior vena cava. The left phrenic nerve runs along the lateral aspect of the transverse arch of the aorta. The two nerves subsequently pass anterior to their respective pulmonary hila and traverse inferiorly in a broad vertical plane along the margin of the heart between the fibrous pericardium and the mediastinal pleura (5).

A previous study (10) showed impaired pulmonary function following unilateral diaphragmatic paralysis caused by iatrogenic complications, tumors, trauma, infection, and unknown causes. The present study also showed significant decreases in pulmonary function in cases of phrenic nerve injury after RF ablation; phrenic nerve injury reduced the values of VC and FEV1.0 by approximately 20%. The decrease in pulmonary function after RF ablation was quite a bit higher than that in a previous study (11) on influence of RF ablation of lung tumors on pulmonary function (mean proportions of VC and FEV1.0 after RF ablation of 93% and 95% at 1 mo and 95% and 95% at 3 mo, respectively).

Multivariate analysis was performed by using values of tumor size and proximity of the phrenic nerve to the tumor. Although the maximum power and electrode size were found to be significantly associated with phrenic nerve injury by univariate analysis, those variables were not evaluated in the multivariate analysis. We selected the electrode size according to the tumor size, and we varied the RF power according to the electrode size. Therefore, electrode size and maximum power were substantially correlated with tumor size. To avoid multilinearity, those two variables were excluded from the multivariate analysis. The multivariate analysis demonstrated that only the proximity of the phrenic nerve to the tumor was a significant independent risk factor.

We demonstrated that nine of the 10 cases of phrenic nerve injury (90%) were accompanied by procedural pain in the shoulder, teeth, or mandible. Such pain is likely referred from phrenic nerve stimulation. In addition to their function of providing motor innervation to the diaphragm, phrenic nerves transmit sensory information from the central intrathoracic and peritoneal surfaces of the diaphragm, radiating painful sensations from these areas to the neck and shoulder. Left shoulder pain caused by splenic rupture, or Kehr sign, is a typical example of referred pain from the phrenic nerve (12). Referred pain of the teeth and mandible may be explained by interconnections between the nuclei of the phrenic nerve and the trigeminal nerve, which carries sensations from these areas (13). Our results indicate that referred pain during RF ablation procedures may be predictive of the development of phrenic nerve injury after the procedure.

The creation of an artificial pneumothorax may offer a prophylactic treatment for phrenic nerve injury. Thornton et al (3) reported a single case in which phrenic nerve injury was avoided by creating an artificial pneumothorax between the tumor and the phrenic nerve. Similarly, creation of an artificial pneumothorax may protect the mediastinum and chest wall (14). In addition, an artificial pneumothorax is useful in minimizing pain during ablation by separating

ablated tumors from the chest wall and parietal pleura (15). However, this technique would not be feasible in the presence of pleural adhesions (14). Conversely, the use of thoracoscopic guidance instead of the traditional percutaneous approach would enable direct visualization and guarantee separation of the tumor from the mediastinal structures.

There are several limitations to the present study. This is a retrospectively designed study. The development of phrenic nerve injury was not evaluated by using a nerve conduction study. Although we reviewed postprocedural chest radiographs that were obtained 3 hours after RF ablation and on the following day, we did not review subsequent chest radiographs because they were not routinely obtained thereafter at determined time points. Therefore, delayed development of phrenic nerve injury was not evaluated in this study. Pulmonary function data were missing in four of the 10 cases of phrenic nerve injury. The phrenic nerve is not usually clearly visible on CT images, so, in the majority of cases, it was necessary to predict the location of the phrenic nerve based on standard anatomy; consequently, the estimated distance between a tumor and the phrenic nerve may be inaccurate.

In conclusion, the incidence of phrenic nerve injury after RF ablation of lung tumors was 1.3%. Phrenic nerve injury caused a significant decrease in pulmonary function. The proximity of the phrenic nerve to the tumor was an independent risk factor for phrenic nerve injury.

REFERENCES

1. Steinke K, Sewell PE, Dupuy D, et al. Pulmonary radiofrequency ablation—an international study survey. Anticancer Res 2004; 24:339–343.

2. Hiraki T, Gobara H, Mimura H, et al. Brachial nerve injury caused by percutaneous radiofrequency ablation of apical lung cancer: a report of four cases. J Vasc Interv Radiol 2010; 21:1129–1133.

3. Thornton RH, Solomon SB, Dupuy DE, Bains MS. Phrenic nerve injury resulting from percutaneous ablation of lung malignancy. AJR Am J Roentgenol 2008; 191: 565–568.

4. Hiraki T, Gobara H, Mimura H, et al. Radiofrequency ablation of lung cancer at Okayama University Hospital: a review of 10 years of experience. Acta Med Okayama 2011; 65:287–297.

5. Aquino SL, Duncan GR, Hayman LA. Nerves of the thorax: atlas of normal and pathologic findings. Radiographics 2001; 21:1275–1281.

6. Wondergem J, Haveman J, Rusman V, Sminia P, Van Dijk JD. Effects of local hyperthermia on the motor function of the rat sciatic nerve. Int J Radiat Biol Relat Stud Phys Chem Med 1988; 53:429–438.

7. De Vrind HH, Wondergem J, Haveman J. Hyperthermia-induced damage to rat sciatic nerve assessed in vivo with functional methods and with electrophysiology. J Neurosci Methods 1992; 45:165–174.

8. Brodkey JS, Miyazaki Y, Ervin FR, Mark VH. Reversible heat lesions with radiofrequency current. A method of stereotactic localization. J Neurosurg 1964; 21:49–53.

9. Bunch TJ, Bruce GK, Mahapatra S, et al. Mechanisms of phrenic nerve injury during radiofrequency ablation at the pulmonary vein orifice. J Cardiovasc Electrophysiol 2005; 16:1318–1325.

10. Elefteriades J, Singh M, Tang P, et al. Unilateral diaphragm paralysis: etiology, impact, and natural history. J Cardiovasc Surg (Torino) 2008; 49:289–295.

11. Tada A, Hiraki T, Iguchi T, et al. Influence of radiofrequency ablation of lung cancer on pulmonary function. Cardiovasc Intervent Radiol 2012, doi: 10.1007/s00270-011-0221. [Epub ahead of print July 2, 2011.]

12. Lowenfels AB. Kehr's sign—a neglected aid in rupture of the spleen. N Engl J Med 1966; 274:1019.

13. Blows WT. Diaphragmatic cramp as a possible cause of noncardiac chest pain and referred mandibular pain. J Neurosci Nurs 1999; 31:187–190.

14. Solomon SB, Thornton RH, Dupuy DE, Downey RJ. Protection of the mediastinum and chest wall with an artificial pneumothorax during lung ablations. J Vasc Interv Radiol 2008; 19:610–615.

15. Hiraki T, Gobara H, Shibamoto K, et al. Technique for creation of artificial pneumothorax for pain relief during radiofrequency ablation of peripheral lung tumors: report of seven cases. J Vasc Interv Radiol 2011; 22:503–506.

Impact of concurrent chemotherapy on definitive radiotherapy for women with FIGO IIIb cervical cancer

Yuuki KURODA[1,*], Naoya MURAKAMI[1], Madoka MOROTA[1], Shuhei SEKII[1], Kana TAKAHASHI[1], Koji INABA[1], Hiroshi MAYAHARA[1], Yoshinori ITO[1], Ryo-ichi YOSHIMURA[1], Minako SUMI[1], Yoshikazu KAGAMI[1], Noriyuki KATSUMATA[2], Takahiro KASAMATSU[3] and Jun ITAMI[1]

[1]Department of Radiation Oncology, National Cancer Center Hospital, Tokyo, Japan
[2]Department of Medical Oncology, National Cancer Center Hospital, Tokyo, Japan
[3]Department of Gynecologic Oncology, National Cancer Center Hospital, Tokyo, Japan
*Corresponding author. Department of Radiation Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji Chuo-ku, Tokyo, Japan, 104-0045; Tel: 81-(3)3542-2511; Fax: 81-(3)3545-3567; Email: yuuki.kuroda.96@gmail.com

The purpose of this retrospective study is to investigate the impact of concurrent chemotherapy on definitive radiotherapy for the International Federation of Gynecology and Obstetrics (FIGO) IIIb cervical cancer. Between 2000 and 2009, 131 women with FIGO IIIb cervical cancer were treated by definitive radiotherapy (i.e. whole pelvic external beam radiotherapy for 40–60 Gy in 20–30 fractions with or without center shielding and concomitant high-dose rate intracavitary brachytherapy with 192-iridium remote after loading system for 6 Gy to point A of the Manchester method). The concurrent chemotherapy regimen was cisplatin (40 mg/m^2/week). After a median follow-up period of 44.0 months (range 4.2–114.9 months) and 62.1 months for live patients, the five-year overall survival (OS), loco-regional control (LRC) and distant metastasis-free survival (DMFS) rates were 52.4, 80.1 and 59.9%, respectively. Univariate and multivariate analyses revealed that lack of concurrent chemotherapy was the most significant factor leading to poor prognosis for OS (HR = 2.53; 95% CI 1.44–4.47; P = 0.001) and DMFS (HR = 2.53; 95% CI 1.39–4.61; P = 0.002), but not for LRC (HR = 1.57; 95% CI 0.64–3.88; P = 0.322). The cumulative incidence rates of late rectal complications after definitive radiotherapy were not significantly different with or without concurrent chemotherapy (any grade at five years 23.9 vs 21.7%; P = 0.669). In conclusion, concurrent chemotherapy is valuable in definitive radiotherapy for Japanese women with FIGO IIIb cervical cancer.

Keywords: cervical cancer; IIIb; chemotherapy; radiotherapy; HDR

INTRODUCTION

External beam radiotherapy (EBRT) combined with intracavitary brachytherapy (ICBT) is the standard treatment for women with cervical cancer [1–3]. A combination of EBRT plus high-dose rate (HDR) ICBT for Japanese women with cervical cancer has provided acceptable outcomes and late complication rates despite the lower dose prescription in Japan than in the US [4–9]. In 2000s concurrent chemoradiotherapy (CCRT) became standard after the National Cancer Institute (NCI) announcement recommending concurrent chemotherapy in 1999 [10], however, the benefits of concurrent chemotherapy on definitive radiotherapy might not be applicable to concomitant EBRT plus HDR-ICBT and are not clear yet in Japan and other Asian countries [9]. We therefore performed a retrospective analysis in a mono-institutional group with newly diagnosed International Federation of Gynecology and Obstetrics (FIGO) IIIb cervical cancer treated by definitive radiotherapy, the purpose of this study being to investigate the impact of concurrent chemotherapy on definitive radiotherapy for Japanese women.

MATERIALS AND METHODS

Patients

We reviewed our database looking for women with newly diagnosed FIGO IIIb uterine cervical cancers with a

maximum diameter over 4 cm treated with definitive radio-therapy at the National Cancer Center Hospital between 2000 and 2009. Patients who received palliative EBRT alone, postoperative radiotherapy, interstitial brachytherapy or an experimental regimen of concurrent chemotherapy were excluded. A total of 131 women treated with EBRT plus HDR-ICBT were admitted to this retrospective analysis. All patients underwent pelvic examination, cystoscope, urog-raphy, computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US) and blood tests. Maximum tumor diameters were measured based on the MRI findings and/or US. FIGO staging was allocated for tumor boards of gynecological, medical and radiation oncologists. The patho-logical diagnosis was carried out with a central pathology review at our pathological division.

Treatment

Treatment selection was determined by the gynecological cancer board, our treatment policy for FIGO IIIb cervical cancer is CCRT to aim for loco-regional control (LRC) even if distant metastasis is not ruled out. Neoadjuvant chemotherapy was prohibited. The concurrent chemother-apy regimen was cisplatin (40 mg/m^2/week). Supportive treatments such as blood transfusions were encouraged during radiotherapy.

Radiotherapy

The radiotherapy field selected was the whole pelvis but exceptions were as follows: para-aortic node (PAN) area ir-radiation was acceptable in cases with suspicions of PAN metastasis, bilateral inguinal node area irradiation was ac-ceptable in cases with vaginal involvement of more than two-thirds of total vaginal length. Radiotherapy doses of 40–60 Gy in 20–30 fractions were carried out with a 4-field box or the anterior–posterior technique. Center shield radiotherapy (CS) was performed for a shorter overall treatment time (OTT) reducing organ at risk (OAR) exposure depending on tumor shrinkage. CS was carried out 3–4 days/week, and HDR-ICBT 1–2 days/week, but both therapies were not carried out on the same day. All patients underwent EBRT with 10-, 15- and 20-MV X-rays from linear accelerators (Clinac IX, Varian, Palo Alto, CA, USA). Two-dimensional conventional radiotherapy (2DCRT) was employed between 2000 and 2005, and three-dimensional conformal radiotherapy (3DCRT) was used between 2005 and 2010. All patients underwent HDR-ICBT with 192-iridium remote after loading system (RALS, Microselectron). The point A dose prescription for 6 Gy using the Manchester method was performed with the ICBT planning system (Plato®, Nucletron). Image-guided optimization was not applicable even in the case of CT-based ICBT planning. A tandem-cylinder was used only in cases with vaginal involvement of more than

one-third of total vaginal length or of an extraordinarily narrow vagina.

Follow-up

All patients were evaluated weekly for toxicity during radiotherapy through physical examinations and blood tests. CT and/or MRI scans and cytology were performed 1–3 months after radiotherapy for initial response, physical examination and blood tests were performed regularly every 1–6 months. Disease progression was defined by the response evaluation criteria in solid tumours (RECIST) version 1.1, new clinical symptoms or observable pelvic deficits.

Statistical analysis

Patient and treatment characteristics were compared using the Mann-Whitney U test and Pearson's chi-square test. OS was estimated from the beginning of radiotherapy to the date of death considered as an event, and censored at the time of last follow-up. LRC rate was estimated from the be-ginning of radiotherapy to the date of LRC failure includ-ing both central and lateral pelvic relapse considered as an event, and censored at the time of death or last follow-up. DMFS rate was estimated from the beginning of radiother-apy to the date of distant metastasis considered as an event, and censored at the time of death or last follow-up. The cu-mulative incidence rate of late rectal complication was esti-mated from the beginning of radiotherapy to the date of any grade rectal hemorrhage according to common termin-ology criteria for adverse events (CTCAE) version 4.0. [11] OS, LRC and DMFS, and the cumulative incidence rates of late rectal complication were calculated using the Kaplan–Meier method [12].

As a measure of radiotherapeutic intensity to point A, we used the equivalent dose in 2-Gy fractions (EQD$_2$) calcu-lated from total irradiated dose (D) and each dose (d) with α/β for 10 Gy and potential doubling time (Tpot) defined as five days' subtraction from EQD$_2$ with correction for tumor proliferation associated with OTT (EQD$_2$T) as shown in the following formula:

$$EQD_2 = D\left(\frac{d + \alpha/\beta}{2 + \alpha/\beta}\right)$$

$$EQD_2T = EQD_2 - \frac{\log_{e^2}}{\alpha}\frac{T - T}{T_{pot}}\bigg/\left(1 + \frac{2}{\alpha/\beta}\right)$$

T_K is the kick-off time of accelerated repopulation and was defined as 21 days, and 0.3 for α [13]. These parameters are not well estimated for cervical cancer so we used those for head and neck squamous cell carcinoma (SCC) and extrapolated them. The survival curves were compared using the log-rank test and Cox's proportional hazards model. In order to carry out univariate and/or multivariate

analysis comparing OS, LRC and DMFS rates, patients were categorized as follows: age (<60 vs ≥60), tumor bulk (<55 vs ≥55 mm), OTT (<6 vs ≥6 weeks), hemoglobin (Hb) before (<11.9 vs ≥11.9 mg/dl) and concurrent chemotherapy. We added univariate and multivariate analysis to assess the impact of concurrent chemotherapy on OS, LRC and DMFS after stratified analysis for age and tumor bulk. All statistical analyses were performed using PASW statistics (Version 18.0, SPSS Japan Inc., an IBM company, Chicago, IL, USA). A *P* value of <0.05 was considered significant.

RESULTS

Patient and treatment characteristics are shown in Table 1. There were differences in age and Hb level after treatment between the radiotherapy alone and CCRT groups. After a median follow-up period of 44.0 months (range 4.2–114.9 months) collectively and 62.1 months for live patients, five-year OS, LRC and DMFS rates were 52.4, 80.1 and 59.9%, respectively. Univariate and multivariate analyses revealed that default of concurrent chemotherapy was the most significant factor leading to poor prognosis for OS (HR = 2.53; 95% CI 1.44–4.47; *P* = 0.001) and DMFS (HR = 2.53; 95% CI 1.39–4.61; *P* = 0.002), but not for LRC (HR = 1.57; 95% CI 0.64–3.88; *P* = 0.322). (Table 2). The cumulative incidence rates of late rectal complications after definitive radiotherapy were not significantly different with or without concurrent chemotherapy (any grade at five years 23.9 vs 21.7%; *P* = 0.669) (Fig. 1). After stratifying 131 patients for age and tumor bulk, subgroup analysis with or without concurrent chemotherapy revealed that non-elderly women (HR = 2.78; 95% CI 1.25–6.18; *P* = 0.012) with even bulky length (HR = 2.53; 95% CI 1.26–5.07; *P* = 0.009) clearly benefit from concurrent chemotherapy (Table 3).

DISCUSSION

Various predictors such as treatment duration and anemia had been reported in the last decade before CCRT [14–18]. Concomitant EBRT with HDR-ICBT, which requires shorter treatment duration, was originally the mainstream treatment for women with cervical cancer in Japan [5]. Treatment durations of gross tumor irradiation had a median of 42 days, and were mostly 6 weeks, which is much shorter than the 8 weeks recommended by the American brachytherapy society (ABS) [14]. Concurrent chemotherapy has the potential hazard of treatment interruption associated with acute toxicities, however OTT was not significantly different between radiotherapy alone and CCRT (42 (30–69) vs 42 (36–62) days; *P* = 0.217). In this situation, OTT is no longer a prognostic factor [17]. Similarly, a low Hb value before radiotherapy has no

impact on survival, and is no longer a prognostic factor if anemia has been actively corrected using blood transfusion during radiotherapy [18].

Randomized trials have shown survival benefits of CCRT for cervical cancer [19–23]. Incorporating concurrent chemotherapy contributed to improvement in both LRC and DMFS [19–23]. This impact is less in stages III–IV than in stages I–II [20–23]. Our study also supported this impact on OS and DMFS even in cases of FIGO IIIb, but not on LRC (Table 2). The cumulative incidence rates of late rectal complications after definitive radiotherapy were not significantly different with or without chemotherapy (any grade at five years 23.9 vs 21.7%; *P* = 0.669) and reached a plateau (Fig. 1), though limited by the short follow-up period for late radiation-induced complications of other organs such as bladder or small intestine [7].

There were important limitations on this retrospective analysis: the advantage of concurrent chemotherapy might merely indicate that the reasons for not undergoing concurrent chemotherapy were associated with poor prognosis. Forty-two women with FIGO IIIb cervical cancer did not undergo concurrent chemotherapy in our study because of advanced age (77 (72–85) years) for 17 patients (40.4%), and the other half (53 (36–70)) had the following reasons for not undergoing concurrent chemotherapy:PAN irradiation for eight patients (19.0%), renal failure for three patients (7.2%), lack of patient's consent for five patients (11.9%), chronic hepatitis for two patients (4.8%), active pyometra, uncontrolled anemia, synchronous double cancer, hypertrophic cardiomyopathy, low white blood cell counts and sequential chemotherapy for one patient each (2.4%). These reasons not to perform concurrent chemotherapy seem to be clinically ordinary and acceptable, but could indicate a potential selection bias that modified the impact of concurrent chemotherapy. Our study revealed that concurrent chemotherapy is the most significant predictor of definitive radiotherapy, thus we conclude that concurrent chemotherapy combined with definitive radiotherapy for FIGO IIIb cervical cancer is advantageous for survival improvement.

Development of the optimal chemotherapy regimen and schedule to increase chemotherapeutic intensity as a cytotoxic agent but not a radiosensitizer seems to be warranted because our results indicated concurrent chemotherapy has impacts on DMFS but not on LRC. It is not reasonable for Japanese women with cervical cancer to undergo increased intensity of dose-dense concurrent chemotherapy due to a lack of relevant feasibility [24]. There is no evidence that platinum-doublet is superior to platinum-alone as concurrent chemotherapy for cervical cancer [22–23]. Therefore, devising the best form of concurrent chemotherapy is considered to be a limitation. The efficacy of adjuvant chemotherapy after definitive CCRT is unclear but worth testing as it is a feasible method [25].

**Table 1.** Patient and treatment characteristics for RT alone and CCRT

		RT alone (*n* = 42)	CCRT (*n* = 89)	*P*
Age	Median (range)	66 (36–85)	55 (29–73)	0.000
Tumor bulk	mm	55 (45–87)	55 (40–95)	0.302
Pathology	SCC	37 (88.1%)	82 (92.1%)	0.454
	non-SCC	5 (11.9%)	7 (7.9%)	
Hb before RT	mg/dl	11.9 (6.4–14.2)	11.9 (7.1–14.5)	0.653
Hb after RT	mg/dl	11.3 (7.6–14.4)	10.3 (6.9–12.3)	0.002
OTT	days	42 (30–69)	42 (36–62)	0.217
EQD_2	Gy	56.4 (44.0–74.0)	54.0 (52.2–74.0)	0.128
EQD_2T	Gy	50.0 (40.9–66.2)	48.2 (39.2–61.2)	0.177
wCDDP courses	1	0	5 (5.6%)	0.000
	2	0	6 (6.8%)	
	3	0	12 (13.5%)	
	4	0	23 (25.8%)	
	5	0	30 (33.7%)	
	6	0	13 (14.6%)	
Reason for RT alone	Advanced age	17 (40.4%)	0	0.000
	PAN irradiation	8 (19.0%)	0	
	No consent	5 (11.9%)	0	
	Renal function	3 (7.2%)	0	
	Hepatitis	2 (4.8%)	0	
	Others	7 (16.7%)	0	
Follow-up	months	30.7 (4.2–100.3)	48.8 (7.3–114.9)	0.001

RT = radiotherapy, CCRT = concurrent chemoradiotherapy, FIGO = International Federation of Gynecology and Obstetrics, SCC = squamous cell carcinoma, Hb = hemoglobin, OTT = overall treatment time, EQD_2 = the equivalent dose in 2-Gy fractions, EQD_2T = EQD_2 with correction for tumor proliferation associated with OTT, wCDDP = weekly cisplatin, ns = not significant.

Table 2. Univariate and multivariate analyses on OS, LRC and DMFS

Variants		*n*	OS Five years	OS uni	OS multi	LRC Five years	LRC uni	LRC multi	DMFS Five years	DMFS uni	DMFS multi
Age	<60	72	51.4	0.631	0.121	73.3	0.129	0.076	56.0	0.173	0.033
	≥60	59	53.7			89.2			64.8		
Tumor bulk	<55 mm	54	59.8	0.358	0.486	79.5	0.768	0.856	74.4	0.010	0.027
	≥55 mm	77	47.6			80.6			50.2		
OTT	<6 weeks	75	53.1	0.789	0.639	78.5	0.532	0.258	63.5	0.626	0.918
	≥6 weeks	56	50.8			82.6			56.0		
Hb before RT	<11.9 mg/dl	62	53.1	0.627	0.934	74.5	0.380	0.599	59.3	0.527	0.988
	≥11.9 mg/dl	69	52.2			84.8			60.6		
Concurrent chemotherapy	Yes	89	60.4	0.002	0.001	82.6	0.583	0.322	66.6	0.005	0.002
	No	42	33.5			68.3			44.7		

OS = overall survival, LRC = loco-regional control, DFMS = distant metastasis free survival, uni = univariate analysis, multi = multivariate analysis, OTT = overall treatment time, Hb = hemoglobin, ns = not significant.
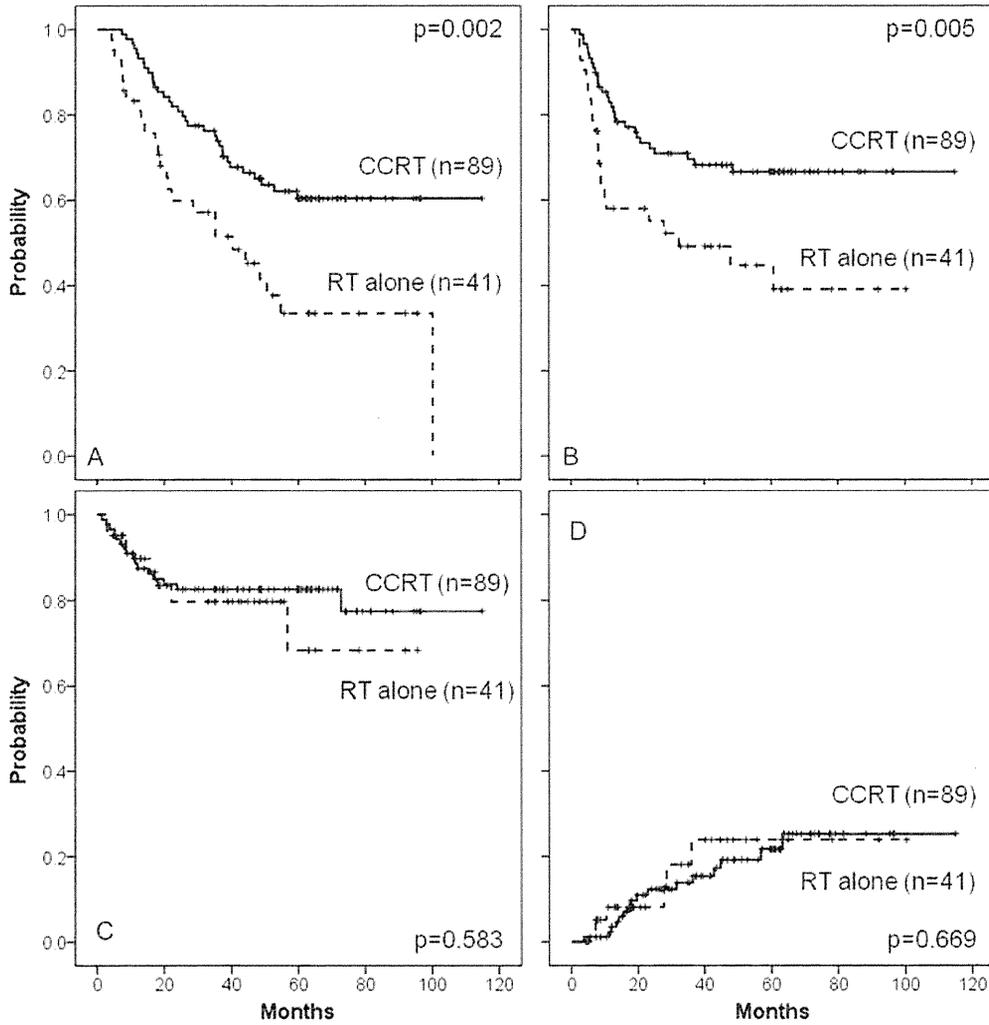
Fig. 1. OS (**A**), DMFS (**B**), LRC (**C**) and the cumulative incidence rates of late rectal complication (**D**) of women with FIGO IIIb cervical cancer after definitive radiotherapy with or without concurrent chemotherapy. Solid line for CCRT, dashed line for RT alone. OS = overall survival, DMFS = distant metastasis free survival, LRC = loco-regional control, CCRT = concurrent chemoradiotherapy, RT = radiotherapy.

Table 3. Impact of concurrent chemotherapy on OS, LRC and DMFS in the stratified analysis

		OS			LRC			DMFS		
		Log-rank	Cox's		Log-rank	Cox's		Log-rank	Cox's	
Variates		*P*	HR (95%CI)	*P*	*P*	HR (95%CI)	*P*	*P*	HR (95%CI)	*P*
Age	<60	0.005	2.78 (1.25–6.18)	0.012	0.145	2.31 (0.76–6.96)	0.136	0.001	2.83 (1.32–6.05)	0.007
	≥60	0.023	2.55 (1.10–5.89)	0.028	0.942	1.05 (0.23–4.85)	0.942	0.079	2.29 (0.88–5.94)	0.087
Tumor bulk	<55 mm	0.118	2.36 (0.85–6.52)	0.096	0.108	5.87 (1.27–27.0)	0.023	0.043	3.46 (1.01–11.9)	0.049
	≥55 mm	0.018	2.53 (1.26–5.07)	0.009	0.587	0.75 (0.22–2.49)	0.645	0.085	2.23 (1.12–4.44)	0.021

OS = overall survival, DMFS = distant metastasis free survival, ns = not significant.

In conclusion, though limited to a mono-institutional retrospective analysis, this study revealed that concurrent chemotherapy is valuable in definitive radiotherapy for Japanese women with FIGO IIIb cervical cancer. A randomized controlled trial is needed to establish the optimal chemotherapy combined with definitive radiotherapy for women with advanced cervical cancer.

ACKNOWLEDGEMENTS

REFERENCES

1. Thoms WW, Jr, Eifel PJ, Smith TL et al. Bulky endocervical carcinoma: a 23-year experience. Int J Radiat Oncol Biol Phys 1992;23:491–9.
2. Perez CA, Grigsby PW, Nene SM et al. Effect of tumor size on the prognosis of carcinoma of the uterine cervix treated with irradiation alone. Cancer 1992;69:2796–806.
3. Landoni F, Maneo A, Colombo A et al. Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer Lancet 1997;350:535–40.
4. Eifel PJ, Moughan J, Erickson B et al. Patterns of radiotherapy practice for patients with carcinoma of the uterine cervix: a patterns of care study. Int J Radiat Oncol Biol Phys 2004;60:1144–53.
5. Toita T, Kodaira T, Shinoda A et al. Patterns of radiotherapy practice for patients with cervical cancer (1999–2001): patterns of care study in Japan. Int J Radiat Oncol Biol Phys 2008;70:788–94.
6. Toita T, Kato S, Niibe Y et al. Prospective multi-institutional study of definitive radiotherapy with high-dose-rate intracavitary brachytherapy in patients with nonbulky (<4-cm) stage i and ii uterine cervical cancer (JAROG0401/JROSG04-2). Int J Radiat Oncol Biol Phys 2012;82:49–56.
7. Nakano T, Kato S, Ohno T et al. Long-term results of high-dose rate intracavitary brachytherapy for squamous cell carcinoma of the uterine cervix. Cancer 2005;103:92–101.
8. Toita T, Moromizato H, Ogawa K et al. Concurrent chemoradiotherapy using high-dose-rate intracavitary brachytherapy for uterine cervical cancer. Gynecol Oncol 2005;96:665–70.
9. Nagase S, Inoue Y, Umesaki N et al. Evidence-based guidelines for treatment of cervical cancer in Japan: Japan Society of Gynecologic Oncology (JSGO) 2007 edition. Int J Clin Oncol 2010;15:117–24.
10. NCI Issues Clinical Announcement on Cervical Cancer: Chemotherapy Plus Radiation Improves Survival. http://www.nih.gov/news/pr/feb99/nci-22.htm (11 April 2012, date last accessed).
11. National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, 2010. http://evs.nci. nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf (10 April 2012, date last accessed).
12. Kaplan EL, Meier P Nonparametric estimation from incomplete observations J Am StatAssoc 1958;53:457–81.
13. Hall EJ, Giaccia AJ. Radiobiology for the Radiologist: Time, Dose, and Fractionation in Radiotherapy, 6th edn. Philadelphia: Lippincott Williams & Wilkins, 2006, 378–97.
14. Nag S, Erickson B, Thomadsen B et al. The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the cervix. Int J Radiat Oncol Biol Phys 2000;48:201–11.
15. Lanciano RM, Martz K, Coia LR et al. Tumor and treatment factors improving outcome in stage III-B cervix cancer. Int J Radiat Oncol Biol Phys 1991;20:95–100.
16. Toita T, Kakinohana Y, Ogawa K et al. Combination external beam radiotherapy and high-dose-rate intracavitary brachytherapy for uterine cervical cancer: analysis of dose and fractionation schedule. Int J Radiat Oncol Biol Phys 2003;56:1344–53.
17. Chatani M, Matayoshi Y, Masaki N et al. High-dose rate intracavitary irradiation for carcinoma of the uterine cervix. The adverse effect of treatment prolongation. Strahlenther Onkol 1997;173:379–84.
18. Grogan M, Thomas GM, Melamed I et al. The importance of hemoglobin levels during radiotherapy for carcinoma of the cervix. Cancer 1999;86:1528–36.
19. Rose PG, Bundy BN, Watkins EB et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 1999;340:1144–53.
20. Morris M, Eifel PJ, Lu J et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med 1999;340:1137–43.
21. Eifel PJ, Winter K, Morris M et al. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of radiation therapy oncology group trial (RTOG) 90-01. J Clin Oncol 2004;22:872–80.
22. Green JA, Kirwan JM, Tierney JF et al. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. Lancet 2001;358:781–6.
23. Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. J Clin Oncol 2008;26:5802–12.
24. Watanabe Y, Nakai H, Shimaoka M et al. Feasibility of concurrent cisplatin use during primary and adjuvant chemoradiation therapy: a phase I study in Japanese patients with cancer of the uterine cervix. Int J Clin Oncol 2006;11:309–13.
25. Dueñas-González A, Zarbá JJ, Patel F et al. Phase III, open-label, randomized study comparing concurrent gemcitabine plus cisplatin and radiation followed by adjuvant gemcitabine and cisplatin versus concurrent cisplatin and radiation in patients with stage IIB to IVA carcinoma of the cervix. J Clin Oncol 2011;29:1678–85.

INTRODUCTION TO REVIEW ARTICLES

Current status of interventional oncology

Susumu Kanazawa

One of the recent advances in the field of cancer treatment is the appearance of interventional oncology. Interventional oncology now seems to be the fourth pillar of cancer care following surgical, radiation, and medical oncology. Modern advances in imaging and image guidance for the detection of cancer have led to the minimally invasive image-guided treatment of cancer, which is called interventional oncology. Interventional oncology can cause less morbidity than open surgery, and less toxicity than chemotherapy and radiation.

Interventional oncology itself is a new concept–combining interventional radiology with oncology. Interventional radiology is a medical sub-specialty of radiology which utilizes minimally invasive image-guided procedures to diagnose and treat diseases in nearly every organ system. The concept behind interventional radiology is to diagnose and treat patients using the least invasive techniques currently available in order to minimize risk to the patient and improve health outcomes.

The origins of interventional radiology are in the angiographic Seldinger techniques developed by cardiovascular radiologists in the late 1950s and early 1960s. Using these angiographic techniques, one can gain access to many organ systems by percutaneous puncture. The performance the radiologic procedures employed in interventional radiology has been facilitated by the development of high-resolution fluoroscopy, ultrasound, computed tomography (CT), and magnetic resonance imaging. Moreover, interventional radiology has benefited from growing developments in materials science, information technology, and biotechnology. Interventional radiology can be used to treat various diseases, including vascular, biliary, urological, neurological, and gastrointestinal diseases. Interventional radiology uses various techniques such as vascular embolization, vascular dilatation and recanalization, stent placement, vascular infusion, drainage tube placement, needle biopsy, foreign body retrieval, and thermal ablation.

Cancers in various organs can be now treated by using these interventional techniques, and the number of cancer patients treated by interventional techniques is rapidly increasing worldwide. For example, many patients with hepatocellular carcinoma have transcatheter arterial chemoembolization and/or radiofrequency ablation now. If the tumor size is not so large, renal cell carcinoma can be completely cured by image-guided radiofrequency or cryoablation. In the present decade, patients with stage 1 lung cancer have been cured by CT-guided radiofrequency ablation or by the use of microwave energy. Thus, the field of interventional radiology in cancer treatment has been enlarged. As a result, the concept of interventional oncology has emerged, which means that an independent category has appeared in interventional radiology.

In interventional oncology, physicians need to be skilled not only in the use of interventional techniques and in the diagnostic interpretation of images but to also have knowledge of oncology and patient care. To improve the level of evidence of the efficacy of interventional therapy in cancer, well-designed prospective clinical studies should be performed. The development of materials and devices for interventional oncology continues to contribute to improvements in the prognosis of cancer patients. Interventional therapy combined with chemotherapy and/or radiotherapy may be one of the new strategies for cancer treatment.

S. Kanazawa (✉)
Department of Radiology, Okayama University Medical School,
2-5-1 Shikatacho, Okayama 700-8558, Japan
e-mail: susumu@cc.okayama-u.ac.jp

🙛 Springer