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Salvage chemoradiotherapy after primary chemotherapy for locally advanced pancreatic cancer: a single-institution retrospective analysis

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Abstract

Background: There is no consensus on the indication for salvage chemoradiotherapy (CRT) after failure of primary chemotherapy for locally advanced pancreatic cancer (LAPC). Here we report on the retrospective analysis of patients who received salvage CRT after primary chemotherapy for LAPC. The primary objective of this study was to evaluate the efficacy and safety of salvage CRT after primary chemotherapy for LAPC.

Methods: Thirty patients who underwent salvage CRT, after the failure of primary chemotherapy for LAPC, were retrospectively enrolled from 2004 to 2011 at the authors' institution. All the patients had histologically confirmed pancreatic adenocarcinoma.

Results: Primary chemotherapy was continued until progression or emergence of unacceptable toxicity. Eventually, 26 patients (87%) discontinued primary chemotherapy because of local tumor progression, whereas four patients (13%) discontinued chemotherapy because of interstitial pneumonitis caused by gemcitabine. After a median period of 7.9 months from starting chemotherapy, 30 patients underwent salvage CRT combined with either S-1 or 5-FU. Toxicities were generally mild and self-limiting. Median survival time (MST) from the start of salvage CRT was 8.8 months. The 6 month, 1-year and 2-year survival rates from the start of CRT were 77%, 33% and 26%, respectively. Multivariate analysis revealed that 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 independent prognostic factors for survival after salvage CRT. The MST for the entire patient population from the start of primary chemotherapy was 17.8 months, with 2- and 3-year overall survival rates of 39% and 22%, respectively.

Conclusions: CRT had moderate anti-tumor activity and an acceptable toxicity profile in patients with LAPC, even after failure of gemcitabine-based primary chemotherapy. If there are any signs of failure of primary chemotherapy without distant metastasis, salvage CRT could be a treatment of choice as a second-line therapy. Patients with relatively low serum CA19-9 levels after primary chemotherapy may achieve higher survival rates after 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.

Trial registration: 2011–136

Keywords: Pancreatic cancer, Locally advanced pancreatic cancer, Induction chemotherapy, Salvage therapy, Chemoradiotherapy, Prognostic factor

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Background

The prognosis of pancreatic cancer remains dismal. The 5-year overall survival of patients with pancreatic cancer is < 5%. In Japan, about 27,000 patients are estimated to have pancreatic cancer, and almost the same numbers of deaths annually are attributable to this cancer. Although surgical resection offers the opportunity for cure, less than 20% of patients are diagnosed with pancreatic cancer at an early resectable stage. At initial diagnosis, ≥ 80% of patients with pancreatic cancer have locally advanced or metastatic disease.

Locally advanced pancreatic cancer (LAPC) is defined as surgically unresectable disease without detectable metastases. Historically, concurrent chemoradiotherapy (CRT) with 5-fluorouracil (5-FU) has been the standard treatment since it offers survival benefit when compared with best supportive care [1], radiotherapy alone [2] and chemotherapy with 5-FU alone [3]. Recently, 5-FU has been replaced by oral fluorouracil analogues such as S-1 in East Asia [4] and capecitabine in Western countries. When taken orally these drugs are much more convenient to administer than 5-FU, which usually requires protracted venous infusion. S-1 is an oral agent that contains tegafur, gimeracil and oteracil in a molar ratio of 1:0.4:1 [5]. S-1 is reported to be at least equivalent to or even more active than 5-FU when combined with radiotherapy for LAPC [6-8].

The standard method used for the detection of metastases from pancreatic cancer is computed tomography (CT). Several investigators have reported that intraoperative staging can reveal occult peritoneal dissemination in 6–37% of the patients with CT-diagnosed LAPC [9-11]. Analysis of patterns of failure after definitive CRT for LAPC has shown that more than half of the patient will have distant metastasis at the first time of failure [12]. Because radiotherapy involving the primary site offers little benefit to patients with occult distant metastasis, increasingly more oncologists believe that chemotherapy would be a preferable initial therapeutic approach for patients with LAPC [13]. During initial chemotherapy, rapidly progressive chemotherapy-resistant distant metastases will present within a few months. After 3–6 months of induction chemotherapy, LAPC that remained local would be an indication for consolidative or salvage CRT. However, there is no consensus on the indications for additional CRT following primary chemotherapy for LAPC, as well as the optimal time period for the administration of primary chemotherapy. Here we report on the results of a retrospective analysis of this strategy, including primary chemotherapy and salvage CRT, for patients with LAPC. The primary objective of our study was to evaluate the efficacy and safety associated with salvage CRT following primary chemotherapy for LAPC. The secondary objective was to elucidate the prognostic factors that affect survival after CRT.

Methods

Patients

Between October 2004 and August 2011, 98 patients who were diagnosed as having LAPC underwent CRT at the author's institution. Sixty-seven patients were excluded from the study because they had received definitive CRT as the first therapeutic modality. One patient was excluded because he had undergone consolidative CRT after primary chemotherapy. The remaining 30 patients underwent salvage CRT after the failure of primary management with chemotherapy alone. All of the patients had histologically confirmed pancreatic adenocarcinoma. They were subjected to intensive analysis. The clinical data from these patients were entered into the database in September 2012. Our institutional review board (Institutional Ethical Review Board of the National Cancer Center) approved this study.

Treatment strategy

At the first diagnosis, multidetector row CT involving the chest and abdomen were performed for the assessment of the local extension of the primary tumor, and for excluding distant metastases. CT based criteria regarding tumor unresectability included encasement or occlusion of the celiac trunk, common hepatic artery, superior mesenteric artery or aorta. All of the patients with obstructive jaundice underwent biliary drainage prior to treatment.

Until December 2007, primary management with CRT combined with 5-FU was the principal treatment of choice for patients with LAPC [14]. Since 2006, several prospective phase II clinical trials involving patients with LAPC were conducted at the authors' institution [4,8,15,16]. CRT combined with S-1 has been regarded as an optional treatment of choice in Japan [7,8]. A multi-institutional phase II trial with gemcitabine (GEM) alone for LAPC yielded promising results with a low toxicity profile [15]. Additionally, our retrospective study revealed that there was no difference in the survival rates of the patients who received CRT or GEM-based chemotherapy alone as a primary therapy for LAPC [17]. Although direct comparison between primary CRT and primary chemotherapy alone has not yet been made in a prospective clinical trial, GEM monotherapy has been regarded as the first treatment of choice in clinical practice since January 2008.

Currently, all of the patients with LAPC are informed of two first-line treatments of choice, namely GEM monotherapy and CRT combined with S-1. If a patient with LAPC has an indication suitable for participation in a clinical trial, the patient will be given additional information about that trial. The patients themselves selected

one of these treatments. The current study included patients who initially entered prospective clinical trials involving primary chemotherapy and who subsequently received CRT as a salvage treatment.

Eligibility criteria for salvage CRT

Indications for salvage CRT following chemotherapy included the following: no distant metastasis; no prior radiotherapy of the upper abdomen; Karnofsky performance status (KPS) ≥ 70; adequate hematologic function (leucocyte count ≥ 3,500/μL and platelet count ≥ 100,000/μL); and hepatic function (bilirubin ≤ 2.0 mg/dL, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤ 150 U/L) and renal function (serum creatinine < 1.5 mg/ml). The exclusion criteria were the presence of: an active gastroduodenal ulcer; watery diarrhea; ascites; active infection; or mental disorder. Written informed consent was obtained from each patient before starting each treatment.

First-line chemotherapy

Primary chemotherapy was continued until disease progression, the emergence of unacceptable toxicity or a patient's refusal of treatment. First-line chemotherapy mostly consisted of GEM alone [Table 1]. GEM was administered intravenously at a dose of 1,000 mg/m^2 over 30 min on days 1, 8 and 15, and was repeated every 4 weeks as one course. Patients with grade 3–4 hematological toxicities underwent dose reduction to 800 mg/m^2 or skipped at least one administration of GEM. Prophylactic granulocyte-colony stimulating factor support was not used.

Chemoradiotherapy

A planning CT was required to determine target volumes on the three-dimensional treatment planning system. A total dose of 50.4 Gy was delivered in 28 fractions using a linear accelerator of energy ≥ 10 MV. The clinical target volume (CTV) included the gross primary tumor and metastatic lymph nodes only. Elective nodal irradiation was not applied in this cohort. The planning target volume (PTV) was defined as the CTV plus 1 cm in all directions and a 1.5-2.0 cm margin in the craniocaudal direction to account for respiratory organ motion. The dose was prescribed to the center of the PTV. Typically, a 4 or 5 field technique was used to minimize high-dose radiation exposure in the surrounding organs.

Radiotherapy was delivered concomitantly with either 5-FU or S-1. Protracted 5-FU infusion was mainly administered until July 2008, and oral S-1 was given thereafter. Concomitant 5-FU was administered as a protracted venous infusion at a dose of 200 mg/m^2/day from days 1–5 each week during the course of radiotherapy [14]. S-1 was administered orally twice daily after breakfast and dinner on weekdays (Monday through Friday) during irradiation. The standard dose of S-1 with concurrent radiotherapy for LAPC was 80 mg/m^2/day [4]. Maintenance chemotherapy with S-1 was indicated for patients without obvious clinical progression during CRT, with sufficient performance status and organ function.

Table 1 Patient characteristics (n = 30)

Characteristic	No. of patients	% patients
Age (years)		
Median (range)	65 (42–81)	
Gender		
Male	16	53
Female	14	47
Karnofsky performance status		
90-100	22	73
70-80	8	27
0-60	0	0
Tumor location		
Head	15	50
Body and Tail	15	50
Nodal status		
Negative	18	60
Positive	12	40
Baseline tumor diameter (cm)		
Median (range)	4.5 (2.1-7.8)	
Baseline serum CA19-9 level (U/ml)		
Median (range)	872 (0–35490)	
≥ 1,000	14	47
100-1,000	11	37
< 100	5	17
Pre-CRT tumor diameter (cm)		
Median (Range)	4.1 (1.9-8.4)	
Pre-CRT serum CA19-9 Level (U/ml)		
Median	631 (0–50440)	
≥ 1,000	11	37
100-1,000	12	40
< 100	7	23
Regimens of primary chemotherapy		
Gemcitabine alone	24	80
Gemcitabine + α	6	20

CRT chemoradiotherapy.

Response and toxicity assessment

All of the medical charts of the eligible patients were reviewed. Information on potential prognostic factors was collected and included: age; gender; performance status; tumor diameter; change in serum carbohydrate

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 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.

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

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

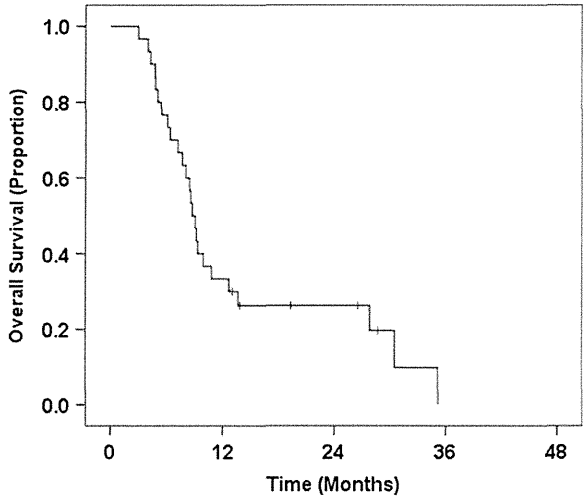

Figure 1 Kaplan-Meier survival curve for overall survival from the start of salvage chemoradiotherapy.

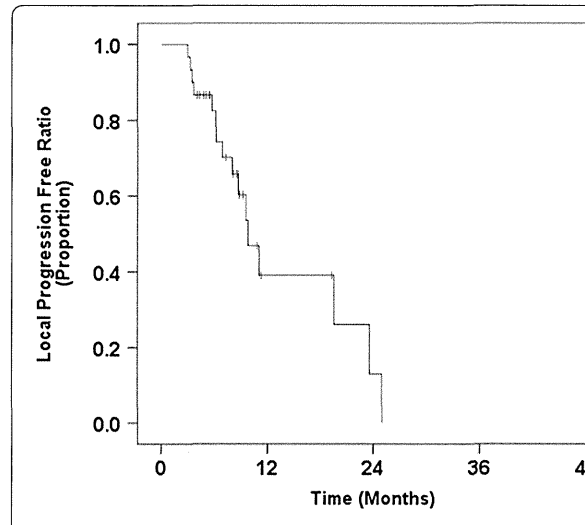

Figure 2 Kaplan-Meier survival curve for the local progression-free ratio from the start of salvage chemoradiotherapy.

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).

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	

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 (≥ 80; p = 0.022); number of regimens of primary chemotherapy (single; p = 0.006); pre-CRT tumor diameter ≤ 4 cm (p = 0.04); and pre-CRT serum CA19-9 level (≤ 1000 U/ml; p = 0.002). The absence of local progression before

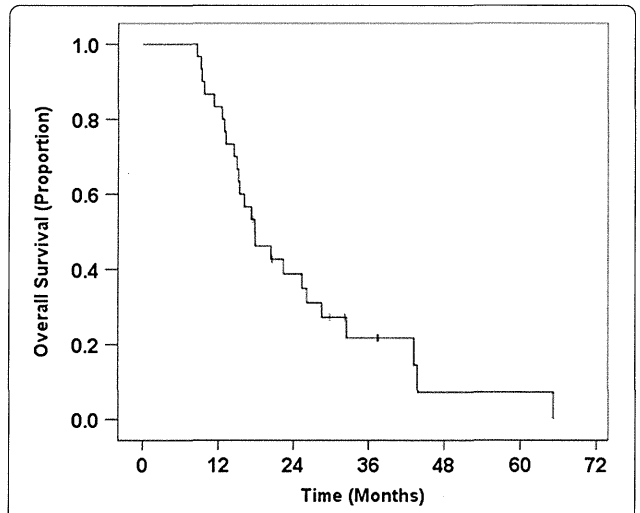

Figure 3 Kaplan-Meier survival curve for overall survival from the start of primary chemotherapy.

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 antitumor 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.

Competing interests

The authors declare that they have no competing interests.

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.

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Regular Paper

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

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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 radiotherapy 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, urography, 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 pathological 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 chemotherapy 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 irradiation was acceptable in cases with suspicions of PAN metastasis, bilateral inguinal node area irradiation was acceptable 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 beginning of radiotherapy to the date of LRC failure including 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 radiotherapy to the date of distant metastasis considered as an event, and censored at the time of death or last follow-up. The cumulative incidence rate of late rectal complication was estimated from the beginning of radiotherapy to the date of any grade rectal hemorrhage according to common terminology 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) calculated 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_2T) as shown in the following formula:

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

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

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

			OS			LRC			DMFS		
Variants		***n***	**Five years**	**uni**	**multi**	**Five years**	**uni**	**multi**	**Five years**	**uni**	**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.

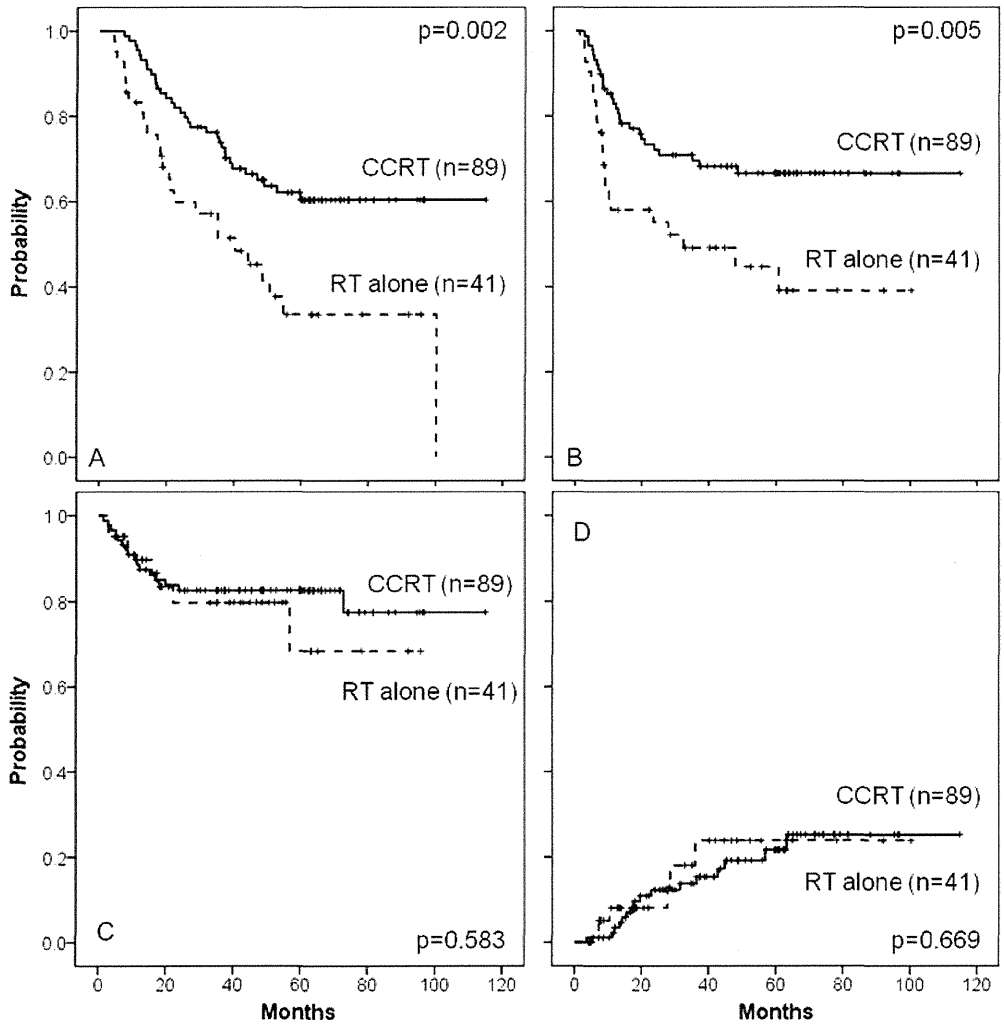

Fig. 1. OS (**A**), DMFS (**B**), LRC (**C**) and the cumulative incidence rates of late rectal complication (**D**) of women with FIGO IIIb cervical cancer after definitive radiotherapy with or without concurrent chemotherapy. Solid line for CCRT, dashed line for RT alone. OS = overall survival, DMFS = 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

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CLINICAL STUDY

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

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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 innervation 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.

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None of the authors have identified a conflict of interest.

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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).

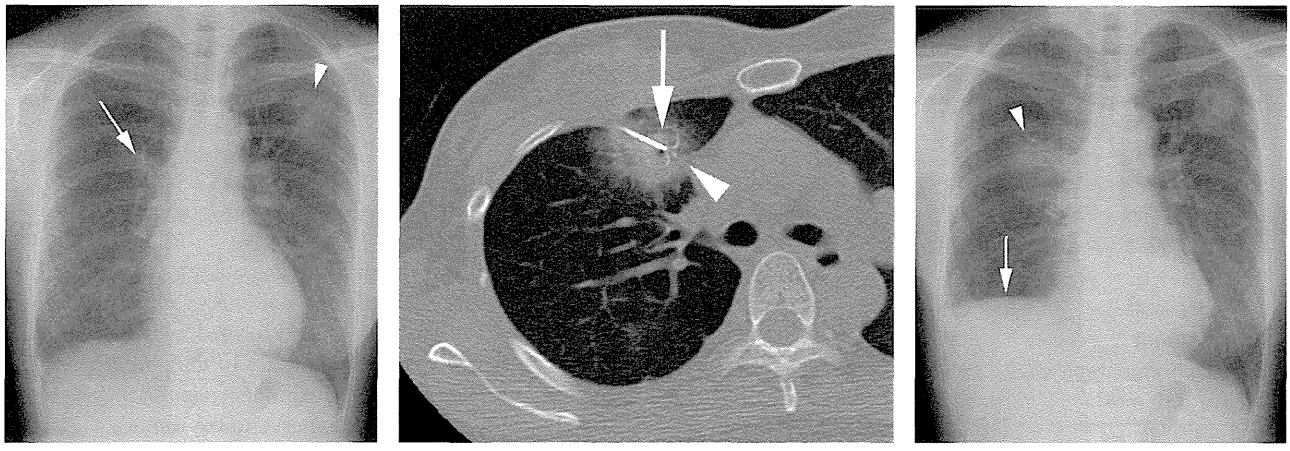
RESULTS

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.



a. b. c.

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)

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 (≥ 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).

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