TABLE 2. The Status and the Treatment of Recurrent Diseases in the Patients Who Did Not Receive Radiotherapy

Variables		N = 17
Disease-free interval after surgery, days		482 (97–1297)
Number of stations	Single/multiple	1/16
Site of LN recurrence	N1 level	0
	N2 level	6
	N3 level	11
Symptoms at recurrence	Present/absent	9/8
Maximum diameter of involved LN	20 or smaller/21 or larger	7/10
Treatment for recurrence	Chemotherapy	10
	EGFR-TKI therapy	2
	Supportive care	5
Reason why radiotherapy was not chosen	Extensive lymph node recurrence	6
	Lung fibrosis/COPD	7
	Others	4

EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; COPD, chronic obstructive pulmonary disease; LN, lymph node.

proportional hazard regression model. p values less than 0.05 were considered to be statistically significant. The statistical analyses were carried out using the JMP 8 software package (SAS Institute, Cary, NC).

RESULTS

Response to Treatment

Response to treatment was evaluated in all patients but one who died of another cause 4 months after the radiation treatment. Thirty-two of 49 patients (65%) had CR, 12 (24%) had partial response, and five (10%) had progressive disease. A univariate analysis showed that there were no variables associated with the response when patients' response to treatment was divided into with CR and the others. An example of a CR is shown in Figure 2. Relief of the associated symptoms was achieved after radiotherapy in 12 of 13 symptomatic patients. There were 16 patients with elevated CEA values before radiotherapy. Among them, the CEA values responded to radiotherapy in 13 patients (81%), and nine patients (56%) exhibited normal CEA values after radiotherapy.

Progression-Free Survival, Patterns of Failure, and Local Control after Radiotherapy

The median follow-up period after radiation therapy among the survivors was 41 months (range, 19–98 months). Two patients were lost to follow-up at 50 and 73 months after radiotherapy. The remaining survivors received the follow-up per the protocol and the recommendation until this study was closed. Disease progression after radiation therapy was observed in 36 patients (72%). Progression-free survival after radiotherapy is shown in Figure 3*A*. The 1-, 3-, and 5-year progression-free survival rates were 49.1%, 28.2%, and 22.2%, respectively. The median progression-free interval was

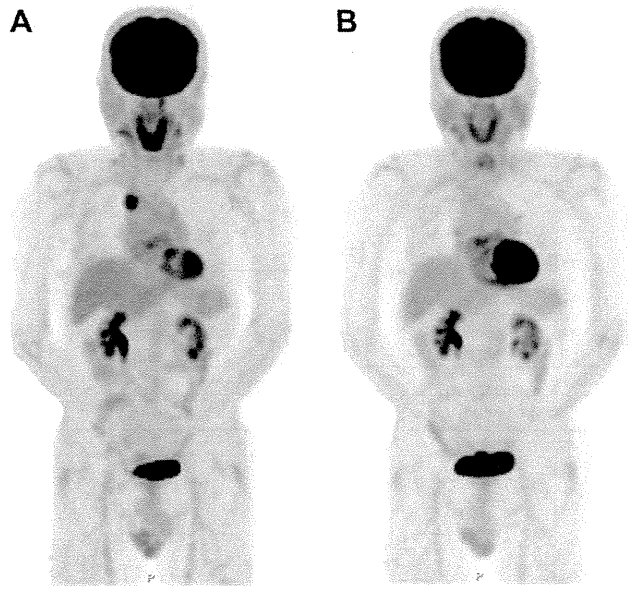

FIGURE 2. An example of complete response to radiotherapy for postoperative lymph node recurrence. PET scans of the whole body were obtained at baseline (*A*) and after 6 months of radiotherapy (*B*). PET, positron emission tomography.

12.0 months after radiotherapy. Ten (23%) of 43 patients who were followed up for more than 3 years showed no additional recurrence after radiotherapy. The initial sites of the disease progression are summarized in Table 3. In-field recurrence was observed in 18 patients (36%) during their entire follow-up period. The probability of local control is shown by the Kaplan–Meier method in Figure 3*B*. The 3- and the 5-year local control rates were 65.9% and 61.1%, respectively. The incidence of initial recurrence in thoracic lymph nodes and the in-field recurrence rate were not associated with the radiotherapeutic approach.

Overall Survival and Prognostic Factors after Radiotherapy

Twenty-seven patients (54%) died of lung cancer and two patients (4%) died of other causes within a 5-year follow-up period. The overall survival probability is shown in Figure 3*C*. The 1-, 3-, and 5-year overall survival rates were 84.0%, 52.7%, and 36.1%, respectively. The median overall survival was 37.3 months after radiotherapy. A univariate analysis was used to evaluate the prognostic impact of 16 clinicopathological factors listed in Table 1. The absence of symptoms and a single involved lymph node station at recurrence were significant favorable prognostic factors but others were not. A multivariate analysis showed that the absence of symptoms and single involved lymph node station were significant independent factors associated with the overall survival (Table 4). The median overall survival was 45.4 months for nonsymptomatic patients and 48.9 months for patients with a single involved lymph node station. There were 23 patients (46%) patients who were both nonsymptomatic and with single involved

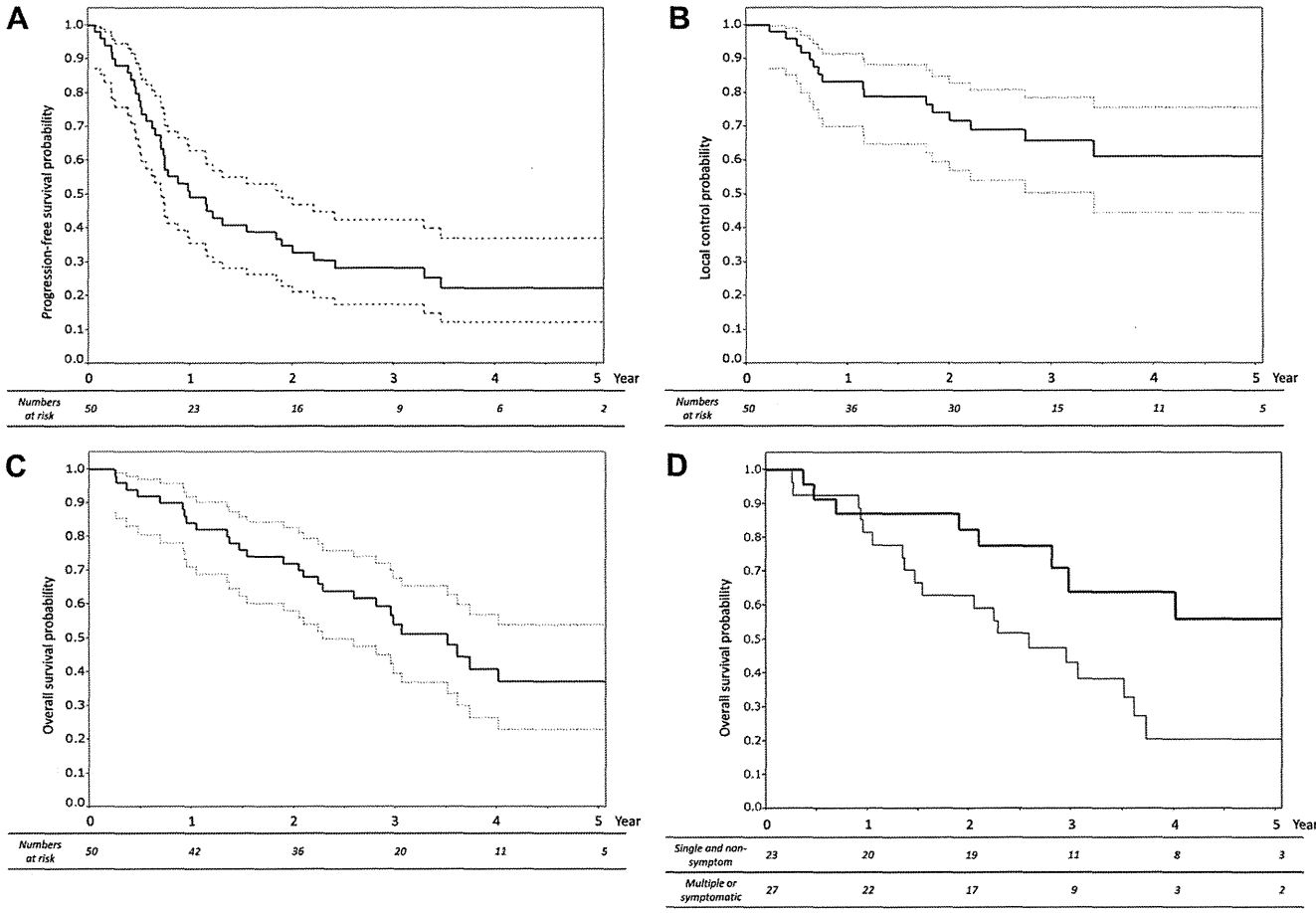

FIGURE 3. Plots of the progression-free survival (*A*), local control (*B*), and overall survival (*C*) probabilities with 95% confidence intervals (dash lines) among patients who received radiotherapy for thoracic lymph node recurrence after surgery. Plots of the overall survival (*D*) probabilities in the patients who were both nonsymptomatic and with single involved lymph nodes station ($n = 23$, bold line) and the patients who were symptomatic or with multiple involved lymph nodes stations ($n = 27$, faint line).

lymph nodes station. The overall survival probability of those patients and the remaining patients are shown in Figure 3*D*. The initial sites of the disease progression were not associated with these factors. The use of concurrent chemotherapy did not affect the overall or progression-free survival. There were five patients who had single-station lymph node recurrence in the supraclavicular area. Two of these patients survived more than 3 years after radiotherapy without any other disease recurrences.

Treatment Compliance and Toxicity

The planned total radiotherapy dose was delivered to 49 patients (98%) of 50 patients. One patient (2%) developed grade 2 pneumonitis and esophagitis at 56 Gy/60 Gy and refused further therapy. The remaining patients showed acute toxicity of grade 2 in six patients (12%) (esophagitis, pneumonitis, malaise, and arthralgia), acute toxicity of grade 3 in one patient (2%; dyspnea), and late toxicity of grade 3 in one patients (2%; pneumonitis). Grade 3 toxicities were observed in patients receiving regional nodal radiotherapy.

Overall Survival of the Patients Who Did Not Receive Radiotherapy

The overall probability of survival of the patients who did not receive radiotherapy is shown in Figure 4. The median survival was 443 days, and the 1-year and the 3-year survival probabilities were 58.8% and 5.9%, respectively.

DISCUSSION

Many of the patients who undergo radical resection for NSCLC develop recurrence with a dismal prognosis. The use of chemotherapy is generally recognized as a standard option to provide objective responses and small improvement in survival for patients with recurrent disease just as performed for initial stage IV patients.

Postoperative lymph node recurrence is common but it mostly occurs along with distant metastases.[4] Systemic therapy would be indicated for patients with recurrences in both lymph nodes and a distant organ. However, the disease is considered to be localized if thoracic lymph nodes are involved but no other metastasis is observed after systematic workup,

TABLE 3. Initial Site of Disease Progression after Radiotherapy

Site	Number of Patients
Pulmonary metastasis or pleural dissemination	11
Extrathoracic distant metastasis	7
Lymph nodes out of the radiation field	9
Lymph nodes within the radiation field	9
Alive without the disease	14

TABLE 4. Multivariate Analysis of Overall Survival after Radiotherapy

Variable	Reference	HR	95% CI	*p*
Symptom	Absent	3.86	1.72–8.57	0.0014
Number of stations	Single	2.70	1.21–6.12	0.0152

Cox proportional hazard model.
HR, hazard ratio; CI, confidence interval.

and these patients may have a chance to be cured. A report of the anatomic location of NSCLC recurrences in 378 patients showed that there were 30 mediastinal lymph node recurrences (7.9%).[6] Curative intent radiotherapy can be indicated for this specific state of the disease. The database of this institution yielded 50 patients who underwent thoracic radiotherapy in this setting, and the short- and the long-term outcomes of this treatment were analyzed. The treatment was completed in most of the patients and no serious complications were recorded. The median overall survival was 37 months and the 5-year survival rate was 36.1%. Ten (20%) of 50 patients were alive longer than 3 years without any additional recurrence after the radiotherapy. These results suggest that a subset of patients with postoperative lymph node recurrence may be cured or enjoy a long-lasting progression-free survival by thoracic radiotherapy.

To date there have been few reports that summarize the treatments for recurrent disease in the literature.[1–3,7] Previous reports show that the median postrecurrent survival ranges from 8.1 to 18.7 months. Limiting the results to the patients who underwent radiotherapy for lymph node recurrence or other locoregional recurrence shows a median survival after recurrence of 14 to 15 months.[5,8–10]

The CEA values were used for monitoring the treatment effects in this study. The normal CEA values were required for the CR definition after radiotherapy, although the use of CEA in NSCLC remains controversial. Several reports have indicated that elevated serum CEA levels are associated with an unfavorable prognosis and occult lymph node metastasis in NSCLC patients.[11,12] Indeed, we observed several patients whose lymph nodes shrank to normal size by radiotherapy but their CEA levels were still elevated comparing with the normal limit. By using the size criteria only, we might overestimate the CR rate.

The outcomes in the current study were favorable as a treatment for recurrent disease. The CR rate was as high as 65%. The median survival and the 5-year survival rate in the present series were considerably longer than those of previous reports.[5,8–10] This is partially because of significant improvements in conformal radiotherapy within the past one or two decades, which have enabled the use of intensive radiotherapy to treat recurrent disease with less radiation toxicity. Another reason may exist in the differences in patient backgrounds. More patients with associated symptoms were included and the size of the recurrent tumor was larger in the previous studies. In contrast, the disease was nonsymptomatic, the involved lymph nodes were localized in only one station, and the size of the target tumor was smaller than 30 mm in many of the patients in this study.

The prognostic impact of variables was evaluated by univariate and multivariate analyses to select the patients who may benefit most from this treatment. The analysis revealed

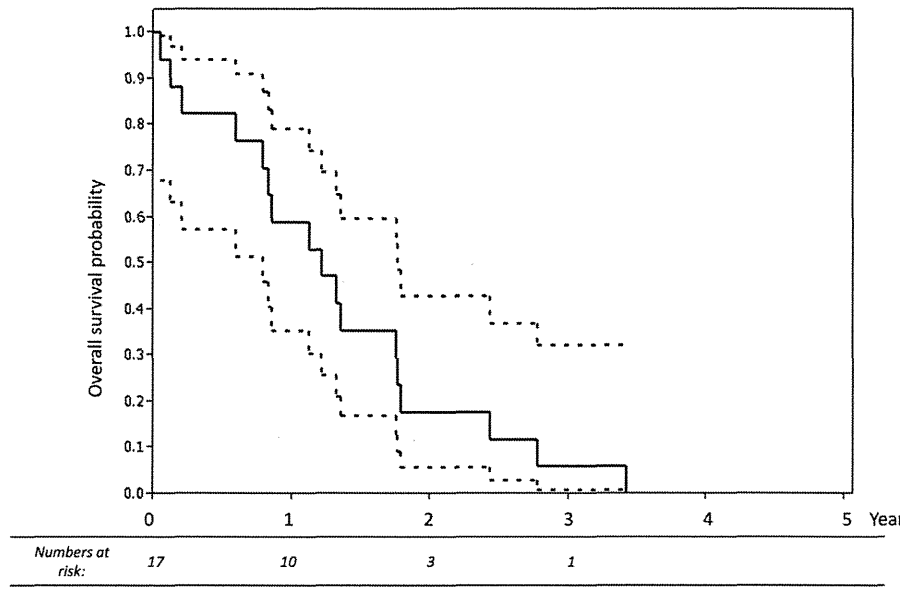

FIGURE 4. Plots of the overall survival probabilities with 95% confidence intervals (dash lines) among patients who did not receive radiotherapy ($n = 17$).

that absence of symptoms at the time of recurrence and a single involved lymph node station were favorable prognostic indicators after recurrence. Interestingly, both prognostic factors in this study were associated with early presentation of recurrence. The surveillance program in this institution, which includes chest CT one or two times a year is relatively intensive in comparison with the guideline-recommended programs.[13] PET scan was also useful, because PET distinguished thoracic lymph node recurrence from nonspecific postoperative change. The intensive surveillance using chest CT and PET may play an important role in the early diagnosis of lymph node recurrence. The results of the present study and the comparisons with previous studies suggest that early detection of recurrence after surgery may contribute to achieving good disease control after radiation and, as a result, longer survival.

A favorable local control rate within the irradiated field was obtained by thoracic radiotherapy without any severe adverse events. The radiation dose prescribed in this study was considered to be adequate. Radiotherapeutic approaches in this study were classified into regional nodal irradiation and involved-field irradiation. Regional nodal radiation therapy covers a larger field and, as a result, may allow more irradiation to adjacent organs such as lung and esophagus, in comparison with involved-field radiation, which targets only metastatic nodes. Local recurrence-free survival or patterns of failure after radiotherapy were not associated with the choice of the radiation approach. On the basis of this result, restricting the target volume to the involved nodal regions might be an option as a radiation approach for thoracic lymph node recurrence. These phenomena were similarly observed in the comparison between elective nodal irradiation and involved-field irradiation for locally advanced unresectable NSCLC.[14,15]

Systemic chemotherapy is a mainstay of treatment for recurrent NSCLC. Only a small number of patients received concurrent chemotherapy in this study. Considering that concurrent chemoradiotherapy is a standard treatment for the patients with inoperable stage III NSCLC, this approach can be another option for regional lymph node recurrence after surgery. When selecting the treatment strategy for patients with thoracic lymph node metastases, it should be noted that there were essential differences between stage III NSCLC and postoperative recurrences. First, the primary tumor had been resected in postoperative patients. Second, the nodal disease was observed after at least a few months of disease-free status. In addition, the sizes of involved lymph nodes were relatively small and their distribution was limited to a couple of stations in most of the recurrent patients. Therefore, thoracic lymph node recurrences were considered to be local disease, and curative intent radiation therapy was the treatment of choice. In contrast, the involved lymph nodes in inoperable stage III patients are usually bulky and extended to multiple nodal stations. Consequently, the prognostic advantage was not observed in the patients who received concurrent chemotherapy. However, because distant metastasis or pleural dissemination was the initial site of the disease progression in 18 patients (36%), the use of chemotherapy may thus have additional effects on controlling the subclinical systemic disease.

The strength of this study is that as a single-institutional study it provided complete information on the clinical course after surgery including recurrence, failure after radiotherapy, final outcomes, well-controlled planning, and quality of radiotherapy.

There are limitations that need to be acknowledged. This study may include the patients whose involved lymph nodes were relatively limited in terms of their number and their location. Because this retrospective analysis was inherently affected by a selection bias associated with the use of radiotherapy, a straightforward comparison between the patients who received radiotherapy and the patients who did not receive radiotherapy was not allowed. Therefore, the real possible benefits of radiotherapy for thoracic lymph node recurrence over chemotherapy alone remain uncertain. Another limitation, as in other studies of nonsurgical therapies, is the lack of a pathological diagnosis. Lymph node sampling under mediastinoscopy or thoracotomy is usually impossible or is a high-risk procedure because systematic mediastinal lymph node dissection is generally performed during the initial surgery. Accurate targeting of an involved lymph node by endobronchial ultrasound-guided transbronchial needle aspiration requires technical skills and experience because the anatomy in the mediastinum was affected by surgery. FDG-PET was used to make a diagnosis in 31 of 40 patients without pathological evidence; however, it was not available in the remaining nine patients. Even though FDG-PET shows good diagnostic performance in detecting recurrence in postoperative NSCLC patients with a fairly high sensitivity (97%) and specificity (96%) as seen in our previous report,[16] we could not eliminate the possibility of false-positive diagnoses in our study. In addition, the sample size of this study was relatively small because this type of recurrence is uncommon. Despite these essential shortcomings, the data demonstrated the favorable results of radiotherapy for patients whose characteristics were described in this study.

In conclusion, radiation therapy for thoracic lymph node recurrence after complete resection is safe and provides acceptable disease control. This treatment provides better outcomes if the disease is asymptomatic and has a single-station involvement. Early detection of thoracic lymph node recurrence may therefore improve the effectiveness of this treatment strategy.

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RESEARCH ARTICLE

Cytoreductive surgery and post-operative heated pleural chemotherapy for the management of pleural surface malignancy

Ken Kodama[1], Masahiko Higashiyama[2], Jiro Okami[2], Toshiteru Tokunaga[2], Ayako Fujiwara[2], Fumio Imamura[3], & Tomio Nakayama[4]

[1]*Department of Thoracic Surgery, Yao Municipal Hospital, Yao City, Osaka,* [2]*Department of Thoracic Surgery, Osaka Medical Centre for Cancer and Cardiovascular Diseases,* [3]*Department of Thoracic Oncology, Osaka Medical Centre for Cancer and Cardiovascular Diseases, and* [4]*Department of Cancer Control and Statistics, Osaka Medical Centre for Cancer and Cardiovascular Diseases, Osaka, Japan*

Abstract

Purpose: We retrospectively analysed the long-term outcomes of cytoreductive surgery and post-operative heated pleural chemotherapy (HPC) for thoracic malignancies with pleural spread. *Materials and methods*: Between 1987 and 2010, 160 patients were enrolled. There were 101 patients with non-small cell lung cancer (NSCLC), 25 with malignant pleural mesothelioma (MPM), 12 with thymoma, and 22 with tumours metastatic to the lung and pleura. Immediately after intra-thoracic administration of cisplatin or carboplatin, hyperthermia was performed by using an 8.00 MHz radiofrequency capacitive heating device for 1 to 4 courses in each patient. *Results*: There was no systemic toxicity or treatment-related mortality. Five-year overall survival rates were 37.4% in NSCLC, 15.9% in MPM, 91.7% in thymoma, and 25.8% in metastatic lung tumour. Five-year local relapse-free survival (RFS) rates were 55.2% in NSCLC, 24.4% in MPM, 64.8% in thymoma, and 27.2% in tumours metastatic to the lung and pleura. When 101 NSCLCs were categorised into pleural lavage cytology positive (grade 1: $n=37$), limited extent of carcinomatous pleuritis (grade 2: $n=21$), and extensive carcinomatous pleuritis (grade 3: $n=43$), 5-year overall survival rates were 62.5%, 49.2%, and 13.6%, respectively. The local RFS was significantly better in group 1/2 than in group 3. *Conclusions*: Although our study has some of the usual weaknesses of a single institution retrospective study, cytoreductive surgery and HPC are feasible and safe. It is suggested that HPC may have a potential role for local control as adjuvant treatment for cytoreductive surgery in patients with minor pleural spread.

Keywords

Cytoreductive surgery, heated pleural chemotherapy (HPC), pleural surface malignancy

History

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Introduction

Pleural dissemination and malignant effusion are common manifestations of disease progression in lung cancer, malignant pleural mesothelioma (MPM), invasive thymoma, and tumours metastatic to the lung and pleura. The majority of these are regarded as having no surgical indication. Many multimodality treatment programmes combining cytoreductive surgery, radiotherapy, chemotherapy, and many experimental treatments such as photodynamic therapy, immunotherapy, and gene therapy have been applied for selected patients among them; however, there has been no standard treatment for pleural surface malignancy.

It is difficult to detect pleural surface malignancy in the early phase, even using modern radiological imaging techniques. Recently, several investigators reported that the early phase of pleural surface malignancy can be detected by pleural lavage cytology at the time of thoracotomy in patients with lung cancer [1].

Hyperthermic intracavitary chemotherapy has been applied after cytoreductive surgery to enhance locoregional control for pleural [2] or peritoneal malignancies [3]. Intracavitary drug administration offers a theoretical advantage: the tumour is exposed directly to higher drug concentrations, whereas a lower incidence of toxic side effects may be expected compared with systemic chemotherapy. Several types of interaction of the heart with chemotherapeutic agents have been found [4,5].

Previously, we reported the results of a pilot study regarding heated pleural chemotherapy (HPC), designated 'post-operative intra-thoracic chemo-thermotherapy' (PICT) for carcinomatous pleuritis due to non-small cell lung cancer (NSCLC) with the objective of improving local cure [6]. In the present work we extended the retrospective study to select the subgroup that achieved an advantage from post-operative HPC among the patients with pleural surface malignancy due to not only NSCLC but also MPM, thymoma, or tumours metastatic to the lung and pleura from other organs.

Correspondence: Ken Kodama, MD, Department of Thoracic Surgery, Yao Municipal Hospital, 1-3-1 Ryuge-cho, Yao City, Osaka 581-0069, Japan. Tel: +81-72-922-0881. Fax: +81-72-924-4820. E-mail: cfaem800@jtw.zaq.ne.jp

Materials and methods

Patients

Between November 1983 and August 2010, we performed post-operative HPC following cytoreductive surgery for 184 patients with pleural surface malignancy. Of these, 14 early patients who underwent HPC from 1983 to 1987 using equipment different from Thermotron-RF8 (Yamamoto Vinitor, Osaka, Japan) were excluded. In addition, five patients whose operation resulted in exploratory thoracotomy, three with insufficient heating lower than 400 W of radio-frequency (RF) power, one without peri-pleural temperature measurement, and one with an insufficient clinical record were also excluded. Consequently, 160 patients treated between 1987 and 2010 were enrolled in this study. Their average age at the time of cytoreductive surgery was 56 ± 12.9 (range: 16–81) years; 92 were male and 68 were female.

There were 101 patients with NSCLC, 25 with MPM, 12 with thymoma, and 22 with tumours metastatic to the lung and pleura from other organs. Of 2,923 NSCLC patients who underwent surgery, 152 were found to have pleural surface malignancy at the time of thoracotomy. Of these, 64 patients underwent HPC following cytoreductive surgery from August 1987. In addition, 37 patients with cytologically proven cluster cancer cells on pleural lavage cytology also underwent heated pleural chemotherapy. HPC was employed for 25 of 26 MPM patients from July 1990, and 12 of 78 thymoma patients from October 1989. This modality was employed for 17 of 31 patients with pleural dissemination discovered at thoracotomy and five patients with positive cytological findings on pleural lavage cytology among 729 patients who underwent metastasectomy for tumours metastatic to the lung from March 1988.

Twenty-five patients with MPM were histologically subdivided into nine patients with epithelial type and 16 with non-epithelial type. When patients with MPM was classified according to IMIG-TNM staging [7], one patient had stage Ia, two patients stage Ib, two stage II, 13 stage III, and seven stage IV. Of 12 thymoma patients, four patients with de novo Masaoka stage IVa [8] and one with mucoepidermoid carcinoma underwent thymo-thymectomy followed by HPC. Six other patients underwent cytoreductive surgery followed by HPC for thymoma with pleural relapse. An addition, one patient had ectopic thymoma on the pleura and underwent HPC after removal of the thymoma to prevent pleural recurrence. However, there were no patients complicated with myasthenia gravis. Of the 22 patients with tumours metastatic to the lung and pleura, 13 patients had soft tissue sarcoma, four osteosarcoma, four other organ cancer, and one melanoma.

Patients for whom post-operative HPC was planned provided written informed consent after fully talking over the risks and benefits with their surgeons. Since 1996, chemotherapy combined with hyperthermia has been accepted by the Japanese government such that the public medical insurance has covered 70% of the medical fee. The institutional review board of Osaka Medical Centre approved this study (approval no. 1207095022), and waived the individual consent requirement to use clinical and pathological data from the institutional database because of the retrospective nature of this study.

Cytoreductive surgery

Procedures employed for cytoreductive surgery were extra-pleural pneumonectomy (EPP) in 27 patients, pneumonectomy in four, lobectomy in 77, sub-lobar resection in 48, and pleurectomy in four. We defined EPP or pneumonectomy as major resection, and lobectomy, sub-lobar resection, or pleurectomy as minor resection.

Post-operative heated pleural chemotherapy

Cisplatin (50–100 mg/chest cavity) or carboplatin (450 mg/chest cavity) adjusted to a volume of 200 mL with saline was administered into the chest cavity through a narrow chest drainage tube(s) retained at the time of the surgery beside the regular chest drainage tube. Teflon-coated probe of copper-constantan micro-thermocouple (IT-18, Physitemp Instrument, Clifton, NJ) with a sterilised sheath was also inserted into the chest cavity through the same tube and the orifice of the tube was sealed using gentamicin ointment to block air inflow into the chest cavity. Immediately after injection, hyperthermia was performed for 1 h using an 8.00 MHz radiofrequency (RF) capacitive heating device (Thermotron RF-8, Yamamoto Vinita, Osaka). Heated pleural chemotherapy (HPC) was started between 7 and 14 post-surgical days and performed for one to four courses in each patient (Figure 1).

The RF generator (Thermotron RF8) has a self-excited oscillation circuit at 8 MHz and 1,500 W maximum output power. The RF was applied through a pair of electrodes placed on opposite sides (anterior versus posterior) of the chest, and power was distributed locally through interaction of electric fields produced between the parallel-opposed electrodes. We employed a pair of electrodes with a large diameter of 25 cm in order to cover the whole hemithorax. The surface of the metal plate of the electrode was covered with a flexible water pad which was filled with 0.4% saline solution nearly electrically equivalent to muscle. In order to avoid excessive heating of the skin and subcutaneous fat, the overlay bolus connected to the water-cooled apparatus was sandwiched between the skin and the electrode pads. This device was developed in Japan [9] and the distribution of its specific absorption rate (SAR) was investigated by Paliwal and co-workers [10]. Basically, we employed the heating method described by Lee and co-workers [11]. The Thermotron RF8 was approved as a medical device for thermotherapy of cancer by the Ministry of Health and Welfare Japan on 15 December 1984. The same 8-MHz

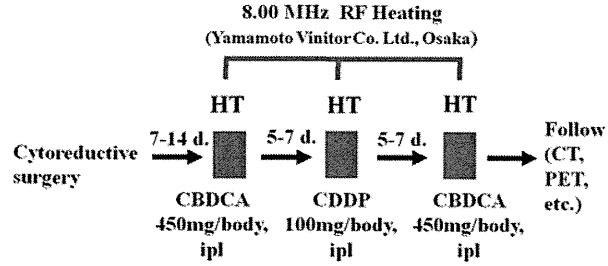

Figure 1. Heated pleural chemotherapy (HPC) protocol.

RF-capacitive heating device is currently in use for deep regional hyperthermia for the whole thoracic region in other institutes [12,13]. After completion of the therapy, cisplatin or carboplatin was removed from the chest cavity, if possible.

Statistical analysis

In the analysis of baseline characteristics of four groups with different diseases, analysis of variance (ANOVA) was used for parametric comparisons, proportions were compared by chi-square test, and frequency analysis was performed with Fisher's exact test. Pearson's correlation coefficient (r) was used to study the relationship between RF power (W) and maximal peri-pleural temperature (°C) achieved during heating.

Survival analyses for all-cause death and local relapse-free survival (RFS) were performed by means of the Kaplan-Meier approach. For both events, the days of the start of observation and the termination event were defined as the dates of surgery and event occurrence, respectively. Cases that had no termination event were considered as censored cases at the final observation date. Local relapse was defined as the appearance of a new lesion on chest computerised tomography (CT) and/or positron emission CT (PET) scan or exacerbation of the symptom within the treated hemithorax (pleura, hilum, and/or ipsilateral mediastinum). Vital status as of 21 March 2012 was confirmed through the Osaka Medical Centre cancer registry database.

NSCLC patients were categorised into three subgroups regarding grade of pleural dissemination (D-factor) or pleural effusion (E-factor) in accordance with the sixth edition of *General Rules for Clinical and Pathological Records for Lung Cancer* [14]. We categorised the patients in whom malignant cell clusters were detected only at the lavage cytology (D0E0) of the chest cavity as grade 1. Limited extent of carcinomatous pleuritis (D1E0 or D0E1) was categorised as grade 2, and extensive carcinomatous pleuritis (D1E1, D2E0-2, or D0-2E2) as grade 3. The survival rates were also compared among these three groups with different categories of pleural malignancy. The log-rank test was used for the comparison.

Statistical analyses were performed using IBM SPSS Statistics (version 19.0) software and Software R (version 2.12.0). Differences were considered significant when $p < 0.05$.

Results

Table I shows baseline characteristics of the four groups classified according to the original diseases. There was a

Table I. Baseline characteristics of the patients.

Characteristic	Disease				*p*-value
	NSCLC ($n = 101$)	MPM ($n = 25$)	Thymoma ($n = 12$)	Metastatic[a] ($n = 22$)	
Age, mean (SD), years	58 (11.5)	58 (9.2)	50 (14.5)	48 (17.4)	0.001[b]
Sex					
Female	57	17	5	13	0.488[c]
Male	44	8	7	9	
Surgical approach					
EPP	9	16	2	0	<0.0001[c]
Pneumonectomy	4	0	0	0	
Lobectomy	72	2	0	3	
Sub-lobar resection	16	6	3	19	
Pleurectomy	0	1	7	0	
Category of resection					
Major resection	13	16	2	0	<0.0001[c]
Minor resection	88	9	10	22	
N-status					
N0, N1	76	18	11	22	0.015[d]
N2	25	7	1	0	
D, E-status					
D0E0, D1E0, D0E1	58	1	7	14	<0.0001[d]
D1E1, D2E0-2, D0-2E2	43	24	5	8	
Max. RF power					
Average (SD), W	684 (149.7)	713 (82.2)	656 (97.0)	639 (130.0)	0.262[b]
Max. temperature					
Average (SD), °C	41.9 (1.67)	42.2 (1.96)	40.6 (1.56)	41.1 (1.65)	0.007[b]
Overall death					
Alive	32	4	10	4	<0.0001[d]
Death	69	21	2	18	
Local recurrence					
No recurrence	62	13	7	14	0.855[c]
Recurrence	39	12	5	8	
Follow-up					
Median, months	37	17	68	21	

NSCLC, non-small cell lung cancer; MPM, malignant pleural mesothelioma; EPP, extrapleural pneumonectomy.
[a]Tumours metastatic to the lung.
[b]Analysis of variance (ANOVA).
[c]Chi-square test.
[d]Fisher's exact test.

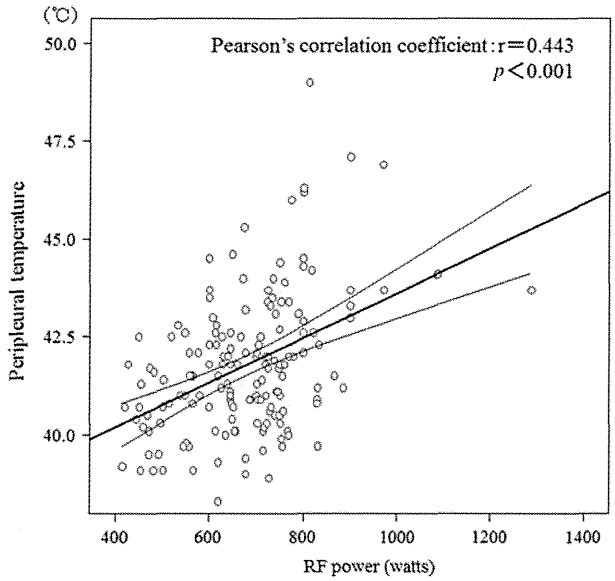

Figure 2. Correlation analysis between RF power and peri-pleural temperature in 160 patients with PICT.

significant difference in age among the groups ($p=0.001$). Surgical approaches employed as cytoreductive surgery were significantly different among the four groups ($p<0.0001$). When these approaches were categorised into major and minor resections, major resection such as EPP was frequently employed in the MPM group compared with the other groups. In the NSCLC group and the MPM group, 25 of 101 patients (25%) and seven of 25 patients (28%) had mediastinal lymph node metastasis (N2), respectively, while this occurred in only one of 12 thymoma patients (8%) and no patients with tumours metastatic to the lung and pleura ($p=0.015$). There was also a significant difference in D, E status when categorised into two groups, D0E0, D1E0, and D0E1 versus D1E1, D2E0-2, and D0-2E2 ($p<0.0001$). Averages of maximal temperature reached in each patient were significantly different ($p=0.007$) among the four groups, and the temperature was highest in the MPM group. A statistically significant positive correlation was observed between peri-pleural temperature and RF power. Pearson's correlation coefficient (r) and the corresponding p value for the correlation were 0.443 and 0.0001, respectively (Figure 2).

Post-operative HPC was performed for an average of 1.8 courses (range: 1–4 courses) for each patient. We generally administered a single course of HPC for patients with positive lavage cytology (D0E0). Another common reason for administering a single course of heated pleural chemotherapy was pleural adhesion of the residual lung to parietal pleura in minor resection; therefore, 2–4 courses were administered to patients with major resection such as pneumonectomy or EPP. There was neither surgery-related nor HPC-related mortality. The median follow-up periods after surgery were 37 months in NSCLC, 17 months in MPM, 68 months in thymoma, and 21 months in the metastatic lung tumour group. Overall survival rates for 3, 5 and 10 years were 59.7%, 37.4% and 13.9% in NSCLC, 21.3%, 15.9% and 8.0% in MPM, 91.7%, 91.7% and 73.3% in thymoma, and 36.1%, 25.8% and 10.3% in tumours metastatic to the lung and pleura, respectively. The median survival times (MST) of NSCLC, MPM, and tumours metastatic to the lung and pleura were 40 months, 19 months and 24 months, respectively. The MST in thymoma was not reached. The survival in thymoma was significantly better than those of the other three diseases ($p=0.0034$, 0.0011 and 0.0002).

Local RFS rates for 3, 5 and 10 years were 61.5%, 55.2% and 47.8% in NSCLC, 45.7%, 24.4% and 24.4% (at 7 years) in MPM, 74.1%, 64.8% and 54.0% in thymoma, and 54.4%, 27.2% and 27.2% (at 9 years) in tumours metastatic to the lung and pleura, respectively.

A total of 101 NSCLCs were categorised into pleural lavage cytology positive as grade 1 (D0E0: $n=37$), limited extent of carcinomatous pleuritis as grade 2 (D1E0 or D0E1: $n=21$), and extensive carcinomatous pleuritis as grade 3 (D1E1, D2E0-2 or D0-2E2: $n=43$) according to their intraoperative findings. As a result, 3-, 5-, and 10-year overall survival rates were 78.0%, 62.5% and 30.6% in grade 1, 70.2%, 49.2% and 20.5% in grade 2, and 40.5%, 13.6% and 0% in grade 3, respectively (Figure 3A). There were significant differences in survival between grade 1 and grade 3 ($p<0.0001$) and between grade 2 and grade 3 ($p=0.0029$). However, there was no significant difference between grade 1 and grade 2 ($p=0.2190$). When grade 1 and grade 2 were grouped together ($n=58$), the 3-, 5- and 10-year overall survival rates were 74.9%, 57.2% and 26.7%, respectively, showing a clear significant difference ($p<0.0001$) to grade 3 (Figure 3B). On the other hand, 3-, 5- and 10-year local RFS rates were 73.5%, 73.5% and 57.2% in grade 1, they were all the same rate of 57.9% in grade 2, and 50.5%, 26.0% and 26.0% (at 9 years) in grade 3, respectively (Figure 3C). A significant difference in local RFS curves was found between grades 1 and 3 ($p=0.041$). When grade 1 and grade 2 were grouped together ($n=58$), the 3-, 5- and 10-year local RFS rates were 68%, 68% and 58.3%, respectively, with a significant difference ($p=0.02$) to grade 3 (Figure 3D).

When the 101 patients with NSCLC were classified into minor and major resection groups according to the type of resection, 3-, 5- and 10-year survival rates were 62.9%, 39.9% and 12.9% in minor resection and 38.5%, 23.1% and 23.1% in major resection, respectively. The overall survival in minor resection had a trend towards a better outcome than major resection, although this difference was not statistically significant ($p=0.1150$) (Figure 4A). In contrast, 3-, 5- and 10-year local RFS rates were 58.9%, 52.5% and 44.4% in minor resection, respectively, and were all the same at 83.9% in major resection. The local RFS in major resection had a trend towards a better outcome than minor resection, although this difference was also not statistically significant ($p=0.1838$) (Figure 4C).

Similarly, MPM patients with major resection combined with HPC had better local RFS of 53.1% and 35.4% at 3 and 5 years than those with minor resection combined with HPC of 33.9% and 0% at 3 and 4 years ($p=0.0053$) (Figure 4D). However, there was no significant difference in overall survival between the two groups (25% and 16.7% versus 13.3% and 13.3% at 3 and 5 years) (Figure 4B).

There was no systemic toxicity or treatment-related mortality. Adverse events related to HPC for 164 patients are presented in Table II. No patients exhibited grade 2 or

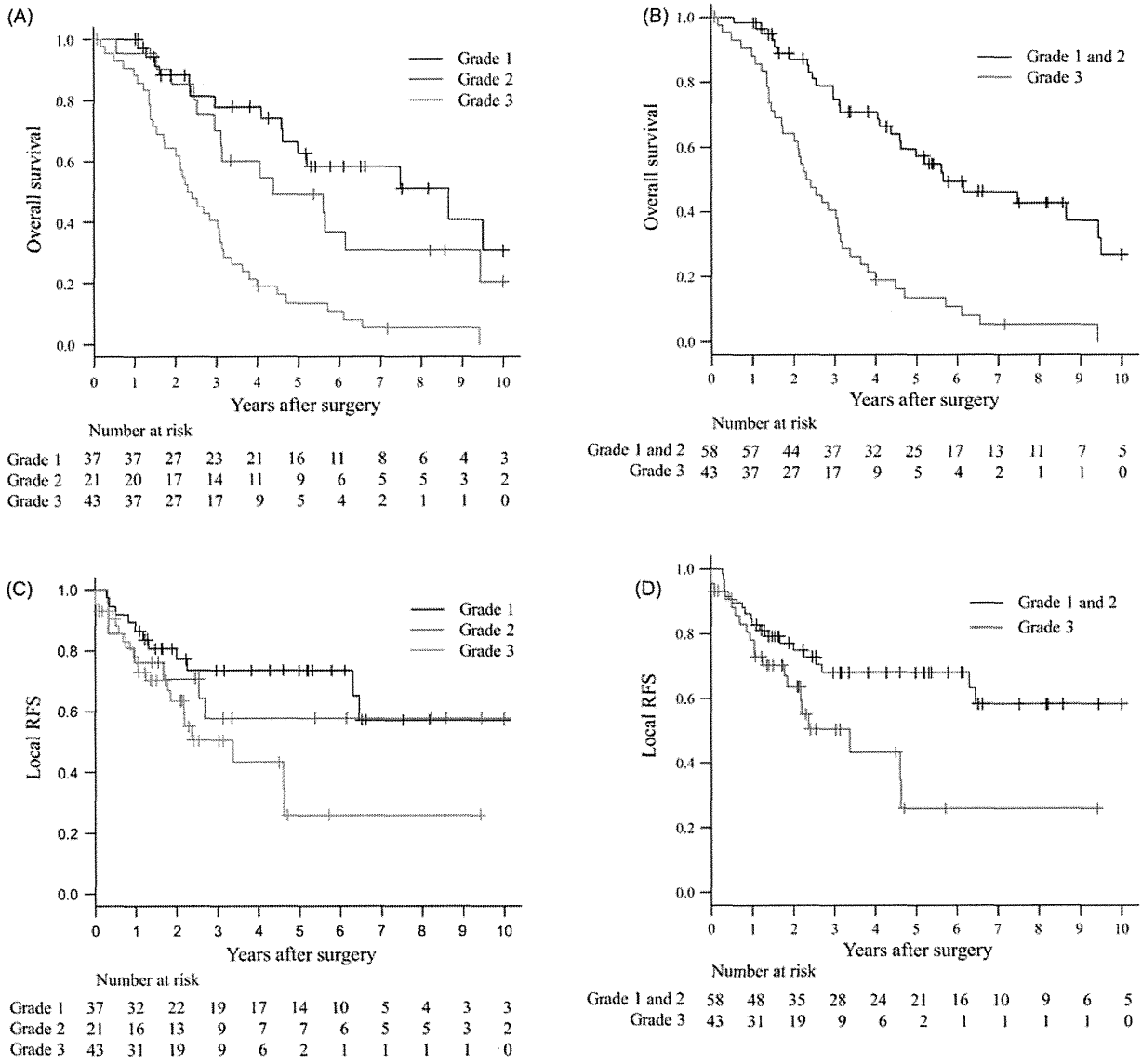

Figure 3. Overall survival curves (A and B) and local PFS curves (C and D) for 101 NSCLC patients according to the grade of pleural malignancy.

higher toxicity. The most common grade 1 toxicity was pain (53%) of the skin beneath the RF electrode on the anterior chest wall. As rare toxicities, two female patients (1.2%) exhibited induration in the breast, two patients (1.2%) a small spot of skin burn with bulla, one (0.6%) complained of anxiety, and one (0.6%) of vomiting. Of these 164 patients, four patients whose RF power did not exceed 400 W due to uncontrollable pain were excluded from the analysis.

Discussion

We started post-operative HPC in 1983 and experienced a case showing a dramatic response to it in 1988. In brief, a patient with multiple lung metastases and malignant pleurisy on both sides due to Ewing's sarcoma was treated on the right side with intra-thoracic injection of 50 mg of cisplatin and local heating using Thermotron RF8 for 60 minutes, along with concomitant systemic administration of 50 mg of cisplatin. Three courses of HPC were administered. Although the patient died 3 months later due to advanced metastases in the left lung and malignant pleurisy on the left side, metastases in the right lung parenchyma were stable on radiographs, and autopsy results showed no malignant lesions in the right thoracic cavity. Since no effective response had been obtained clinically and histologically before starting the HPC, despite frequent systemic administration of anti-cancer drugs, we concluded that heat acted synergistically with cisplatin on drug-resistant cells in this patient [15,16]. The same result of *in vitro* chemo-thermosensitivity test in human Ewing's sarcoma cell lines was reported by Debes and co-workers [17]. They disclosed the synergistic enhancement of cisplatin cytotoxicity by heat application, which might predict chemo- and thermosensitivity. Our co-worker, Ohguchi [18], also demonstrated by using a computer simulation of RF capacitive-type hyperthermia that heat transport from the body by air convection leads to reasonable temperature profiles in the body surface area, such as the pleural vicinity. On the basis of these lines of evidence, since 1988 we have extended HPC to pleural malignancy due to not only NSCLC but also MPM, thymoma and tumours

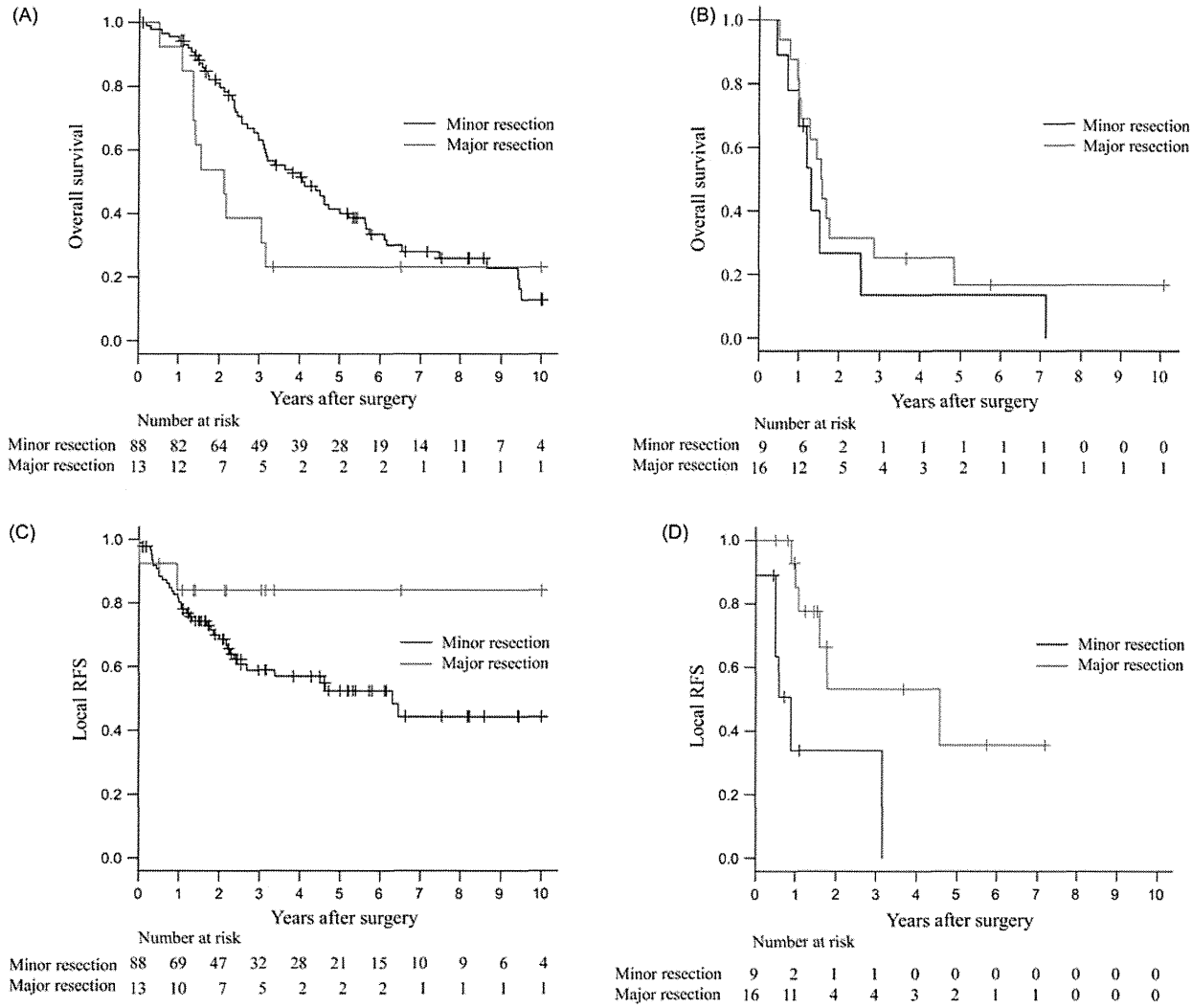

Figure 4. Overall and local RFS curves of 101 NSCLC (A and C) patients and 25 MPM (B and D) patients according to the type of resection.

Table II. Adverse events related to postoperative heated pleural chemotherapy (HPC) (NCI-CTC version 2.0).

	Common toxicity criteria		
Adverse event	0	1	≥2
Focal skin pain beneath the electrode	77	87 (53.0%)	0
Grade II burn beneath the electrode	162	2 (1.2%)	0
Formation of induration in the subcutaneous fat	162	2 (1.2%)	0
Anxiety during heating	163	1 (0.6%)	0
Vomiting	163	1 (0.6%)	0

Of 164 patients, two patients with focal skin pain and one with both pain and induration were excluded from the analysis because we had to control the RF power lower than 400 W to remove the pain.

metastatic to the lung and pleura. However, after we clarified the poor survival and local control of HPC in NSCLC patients with N2 disease and/or macroscopically residual disease in 1993 [6], the indication of post-operative HPC was basically towards patients with N0–1 diseases, regardless of the type of original malignancy. Platinum compounds are the most common drugs showing temperature-dependent supra-additive effects on not only cancer but also refractory sarcoma [19]. We reported that the free platinum concentration was kept at more than 10 μg/mL for 2 h immediately after a bolus injection of cisplatin (50–100 mg) in the pleural cavity [20].

We searched for articles indicating the outcome of the treatment for patients with pleural surface malignancy due to thymoma [21–28], MPM [12,29–34], or NSCLC [1,35–37] (Table III). According to our literature survey there were no reports concerning cytoreductive surgery for pleural surface malignancy discovered at the time of thoracotomy for tumours metastatic to the lung.

Because of the indolent nature of thymoma, the overall survival in thymoma was significantly better than those of other malignant diseases. At present there is no standard approach to advanced thymoma apart from an operation.

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Table III. Summary of studies concerning outcomes for the management of pleural surface malignancy arising from three different diseases.

Study	Study design (identified period)	Median follow-up (months)	No. of patients	Treatment modalities	Survival (%) at 1 year	3 years	5 years	10 years	MST (months)	MRFS (months)	Other information as specified
Disseminated thymoma											
Refaely et al.*[a] 2001 [21]	Single institution retrospective, stage IVa (1995–2000)	34	14	Resection + thermo-chemo		90	70				
Kondo et al. 2003 [22]	115 institutes retrospective, stage IVa (1990–1994)	NR	67	Not defined			70.6	45			Resectability rate of stage IV = 42%
Wright 2006 [23]	Single institution retrospective, stage IVa (1987–2003)	NR	5	Chemo + PP + RT			75	50	86		WHO B3 thymoma
Haung et al. 2007 [24]	Single institution retrospective, stage IVa (1996–2006)	32.2	18	Chemo + resection + hemi-thoracic RT		91	78	65			
Ishikawa et al. 2009 [25]	Single institution retrospective, stage IVa. IVb (1988–2006)	NR	11	Chemo + EPP + RT			81	70			
Lucchiet al. 2009 [26]	Single institution retrospective, stage II–III (1980–2006)	NR	20	Resection			43.1	25.8			From pleural recurrence resection
Siesling et al. 2012 [27]	RACECARE project, all stage (1978–2002)	NR	403	Not defined	85		65.6				
Yellin et al.*[a] 2013 [28]	Single institution retrospective (since 1995)	62	DNT 17 TPR 14 TC 4	Resection + HPCP			81 67 0	73 56 0			5-, 10-y PFS: 61%, 43% 5-, 10-y PFS: 48%, 18%
Kodama et al. 2013	Single institution retrospective (1989–2010)	68	12	Resection + HPC		91	91	73			DNT 4 TPR 6 Others 2
Malignant pleural mesothelioma											
Monneuse et al. 2003 [29]	Single institution retrospective, T1-4 (1990–2000)	89	17	Pleurectomy + chemo + hyperthermia	69	42	8		18		
Xia et al. 2006 [12]	Single institution retrospective, T1-3 (1995–2005)	NR	11	RT + chemo + hyperthermia	63	26	26		27		No surgery
Richards et al.*[b] 2006 [30]	Single institution prospective, epithelial type (1999–2002)	NR	24	Pleurectomy + chemo + hyperthermia	80	39					MST of 20 patients with epithelial tumour + high-dose cisplatin: 26 M
Rice et al. 2007 [31]	Single institution retrospective, stage I–IV (1995–2005)	NR	63	EPP + IMRT	21				14		In field recurrence: 5%
Tilleman et al. 2009 [32]	Single institution prospective, BWH stage I–III (2004–2006)	NR	121	EPP + chemo + hyperthermia					12.8		Ipsilateral recurrence: 17.4%. High % of patients with stage III
Tokunaga et al.*[c] 2011 [33]	Single institution retrospective, stage III–IV (1995–2008)	19	11	EPP + PICT	63.6				19	17	
Sugarbaker et al.*[b] 2013 [34]	Single institution retrospective, epithelial, stage I–IV (2001–2009)	NR	72	EPP or P/D + HIOC					35.3	27.1	13% had biphasic histological findings on the final pathological analysis
Kodama et al.*[c] 2013	Single institution retrospective, all stage (1990–2010)	17	25	EPP or P/D + HPC		21	16	8	18	21	20 cases had stage III or IV. 9 cases had epithelial type.
NSCLC with pleural surface malignancy											
Sawabata et al. 2002 [35]	Single institution retrospective, c-stage I–III (1980–1994)	NR	40	Resection			9		13		Malignant minor pleural effusion detected on thoracotomy 13 cases had local relapse
Muraoka et al. 2006 [36]	Single institution retrospective	NR	25	Resection + intrapleural cisplatin		52.6	11.3		47		Positive pleural lavage cytology or malignant effusion
Seto et al. 2006 [37]	Multi-institutional phase II trial, stage IIIB–IV (1998–2002)	34	80	Intrapleural hypotonic cisplatin ± any other treatments	39				7.9		1-year effusion progression free survival rate: 31.8%

(*continued*)

Table III. Continued

Study	Study design (identified period)	Median follow-up (months)	No. of patients	Treatment modalities	Survival (%) at				MST (months)	MRFS (months)	Other information as specified
					1 year	3 years	5 years	10 years			
Lim et al. 2010 [1]	Meta-analysis, p-stage I–IV (submission before 2008)	39	511	Not defined	80		31				Pleural lavage cytology positive
Kodama et al. 2013	Single institution retrospective, c-stage I–III (1987–2010)	37	101	Resection + HPC		60	37	14	44	78	37 cases had positive finding (cluster cells) on pleural lavage cytology

MST: median survival time; MRFS: median relapse-free survival; NR: not reported; PP: parietal pleurectomy; RT: radiation therapy; EPP: extrapleural pneumonectomy; DNT: de novo stage IVa thymoma; TPR: thymoma with pleural relapse; TC, thymic carcinoma; HPCP, heated pleural chemoperfusion; HPC, heated pleural chemotherapy; BWH, Brigham and Women's Hospital; IMRT, intensity-modulated radiation therapy; PICT, post-operative intra-thoracic chemo-thermotherapy; P/D, pleurectomy/decortication; HIOC, hyperthermic intraoperative cisplatin chemotherapy; NSCLC, non-small cell lung cancer.
*Same institutions.

Refaely and co-workers [21] reported that operation and perfusion thermochemotherapy are feasible and safe in patients with stage IVa thymoma with 3-year and 5-year actuarial survival rates of 70% and 55% (median follow-up: 34 months). According to a recent report by Ishikawa and co-workers [25], multimodality therapy combined with induction chemotherapy, surgery, and post-operative radiation therapy for stage IVa thymoma offers a good outcome, especially in patients with EPP. In their analysis, overall survival was 81% at 5 years and 70% at 10 years after cytoreductive surgery. Recently, Yellin and co-workers [28] reported that the 5-, 10- and 15-year overall survival rates for de novo stage IVa thymoma (DNT) and thymoma with pleural relapse (TPR) were 80.8%, 72.7% and 58.2% (DNT) and 66.7%, 55.6% and 27.8% (TPR) with a median follow-up of 62 months after resection and heated pleural chemoperfusion. They also suggested that completeness of resection and the perfusion temperature may play a role in local control. In our study 5- and 10-year overall survival rates were 91.7% and 73.3% for thymoma with pleural surface malignancy. The 10-year overall survival of 73% is among the best ever reported.

The goal of an operation in treating MPM is to remove all gross disease, achieving a macroscopically complete resection. Other modalities have been used to treat the residual microscopic disease that is always present. Monneuse and co-workers [29] reported the long-term results of intra-thoracic chemohyperthermia (ITCH) combined with pleurectomy/decortication (P/D) as cytoreductive surgery. They concluded that their procedure may offer unexpected long-term survival in a selected group of patients with T1 and T2 MPM or fibrosarcoma. According to the results of a phase II study of EPP followed by intracavitary intraoperative hyperthermic cisplatin for MPM reported by Tilleman and co-workers [32], recurrence of MPM was 51%, with ipsilateral recurrence in 17.4% of patients. Hospital mortality was 4.3%. About half of their patients had grade 3 or 4 morbidity, including atrial fibrillation in 23.9%. The median survival was 12.8 months. They concluded that hyperthermic intraoperative intracavitary cisplatin perfusion following EPP might enhance local control in the chest. It is noteworthy that they simultaneously carried out intracavitary cisplatin lavage of both ipsilateral chest cavity and abdominal cavities, which has high potential for inducing recurrence. We employed HPC to treat the residual microscopic disease in 25 MPM patients. Their 3-, 5-, and 10-year overall survival rates were 21.3%, 15.9% and 8%, respectively. The 3-, 5-, and 7-year local PFS rates were 45.7%, 24.4%, and 24.7%, respectively. When we restricted the analysis to patients with EPP (1995–2008), the median overall survival was 19 months, and the local recurrence rate was 36.4% [33]. When major resection is performed, the pleural surface may be exposed homogeneously to a high temperature and a high concentration of free platinum. The benefits of post-operative HPC are to reduce the amount of drugs such as cisplatin or carboplatin [12] and the ability to perform it repeatedly compared with intraoperative perfusion thermochemotherapy [21,28,29,32,34]. In contrast, HPC in combination with minor resection may lead to heterogeneous exposure of heat and drug on the pleural surface compared with intraoperative perfusion chemotherapy.

Recently, Ueda and co-workers [38] reported excellent outcomes of low dose chemotherapy and regional 8 MHz RF hyperthermia for multiple lung metastases of bladder cancer. Of note, in their presented case, all metastases showing complete response were close to the pleura, where there is an advantage of being well heated by RF. In this group of our study, the 3- and 5-year PFS rates were 54.4% and 27.2%, respectively. Most of the patients included in this group had pleural malignancy due to metastatic sarcoma. Recently, the effectiveness of neo-adjuvant chemotherapy combined with regional hyperthermia for the primary lesion of high risk soft tissue sarcoma was demonstrated in a randomised phase III trial (NCT 00003052) [39].

In our pilot study [2,6], we reported that the survival of NSCLC patients with pleural dissemination and concomitant p-N2 was significantly poor compared with that of patients with dissemination and concomitant p-N0-1. In the present study we extended the indication for HPC to patients with proven cancer cells as clusters at pleural lavage cytology (D0E0). However, we never performed HPC for patients with cancer cell positivity but without cluster formation at the cytology because of the low incidence of pleural recurrence [40]. Consequently, our survival analysis demonstrated that there were significant differences in both overall survival and RFS between patients with grade 1–2 and grade 3. Recently, the relationship between tissue platinum concentration and survival was assessed by Kim and co-workers [41]. Their study demonstrated a relationship between tissue platinum concentration and response in NSCLC, and suggested that reduced platinum accumulation might be an important mechanism of platinum resistance in a clinical setting. Our result suggested that a relatively small amount of malignant tumour present at the pleural surface (grade 1–2) is exposed to an extremely high concentration of platinum and its uptake into the cancer cells is reinforced by heating. However, it might have limited platinum diffusion into the centre of solid lesions categorised as grade 3.

There was no ≥grade 2 morbidity. However, about half of patients (53%) had a complaint of skin pain under an electrode placed on the anterior chest wall during heating. As we performed HPC without premedication and anaesthesia, we were able immediately to block the RF wave focally at the site of pain with a vinyl sheet. Consequently, we were able to prevent skin burn of ≥grade 2.

In conclusion, HPC was shown to be feasible and safe, even when combined with major resection such as extra-pleural pneumonectomy. It is suggested that HPC may offer excellent local control for patients with free tumour cells in the chest cavity and micrometastases on the pleural surface. Although these findings are of interest, they should be replicated in independent prospective studies to validate the importance of HPC.

Declaration of interest

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A possible abscopal effect of post-irradiation immunotherapy in two patients with metastatic lung tumors

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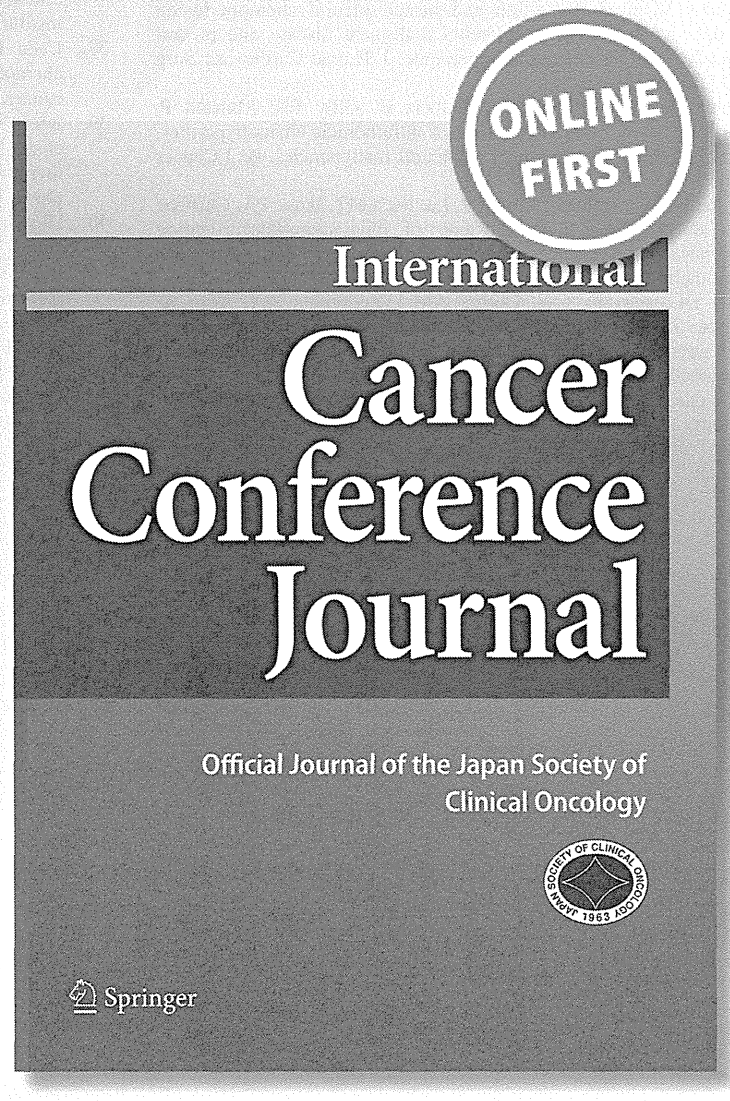

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CASE REPORT

A possible abscopal effect of post-irradiation immunotherapy in two patients with metastatic lung tumors

Ken Kodama · Masahiko Higashiyama · Jiro Okami · Toshiteru Tokunaga · Norimitsu Inoue · Takashi Akazawa · Tsukasa Seya

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Abstract As well as its local effects, radiotherapy leads to the delayed regression of distant non-irradiated lesions. These abscopal effects are most likely mediated by the innate immune system. Patient 1, a 74-year-old male, had concomitant left supraclavicular lymph node metastases and multiple lung metastases 2 years after complete resection of pathological stage IIA (T1bN1M0) lung adenocarcinoma. He received radiation therapy (RT) of 58 Gy for the supraclavicular lymph node metastases and then innate immunotherapy using the cell wall skeleton of *Mycobacterium bovis* bacillus Calmette–Guérin (BCG-CWS). Three months after the RT and 2 months after the immunotherapy, all lung metastases disappeared on computed tomography scans. Patient 2, a 40-year-old female, underwent stereotactic body RT (SBRT) for metastasis from a deep-seated urothelial carcinoma in the right upper lobe of the lung. Twenty-one months after the SBRT, we started administration of BCG-CWS to two new lesions that had appeared in the left lung. As a result, after 3 months, the lesions completely disappeared. Complete response was maintained for more than 1 year in both patients. We believe that an optimal combination of RT and immunotherapy will elicit abscopal effects that can be employed to attain a systematically achievable, rather than anecdotal, therapeutic goal.

Keywords Abscopal effect · Radiation therapy · Innate immunotherapy · Metastatic lung tumor

K. Kodama (✉)
Department of Thoracic Surgery, Yao Municipal Hospital, 1-3-1 Ryuge-cho, Yao, Osaka 581-0069, Japan
e-mail: cfaem800@jtw.zaq.ne.jp

M. Higashiyama · J. Okami · T. Tokunaga
Department of Thoracic Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan

N. Inoue · T. Akazawa
Molecular Genetics of Research Institute, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan

T. Seya
Department of Microbiology and Immunology, Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido, Japan

Introduction

The word "abscopal" is derived from the Latin words *ab*, meaning "position away from," and *scopos*, which means "a target for shooting at." Mole was the first to use this term in 1953 [1] to describe systemic effects that were observed at non-irradiated sites in an animal after treatment with localized radiotherapy (RT). Case reports describing abscopal effects observed after RT have been published for a variety of malignancies, including urothelial carcinoma, lymphoma, esophageal adenocarcinoma, hepatocellular carcinoma (HCC), uterine cervical carcinoma, thymic carcinoma, chronic lymphocytic leukemia, and melanoma [2–12]. Abscopal effects are usually associated with radiotherapy, but they are also sometimes seen after other treatments, such as surgery or even hyperthermia.

We experienced two cases with possible abscopal effects in which local RT followed by innate immunotherapy using the cell wall skeleton of *Mycobacterium bovis* bacillus Calmette–Guérin (BCG-CWS) [13] were associated with the regression of metastatic lung cancers at a distance from the irradiated site.

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Case presentations

Patient 1

A male patient received a diagnosis of lung adenocarcinoma in January 1997 at 74 years of age. His clinical course is shown in Fig. 1. He underwent right upper lobectomy with hilar and mediastinal lymph node dissection. Pathologic examination revealed T1bN0M0, stage IIA adenocarcinoma. He remained disease-free until November 1998, when a 20-mm-diameter lymph node was palpable in the left supraclavicular region and a chest computed tomographic (CT) scan revealed swelling of the lymph nodes and new multiple pulmonary nodules less than 10 mm in diameter. Metastatic adenocarcinoma was proven by percutaneous needle aspiration cytology of the lymph node.

For this elderly patient, who refused systemic chemotherapy, RT was initiated to the supraclavicular lymph node metastases, with 48 Gy supplied in 24 fractions plus a 10 Gy boost to the nodular lesion from 5 January to 17 February 1999.

After fully discussing the risks and benefits with his physicians and obtaining informed consent, the patient enrolled in a clinical phase II study on innate immunotherapy using BCG-CWS at Osaka Medical Center for Cancer and Cardiovascular Diseases [14]. The institutional review board of the Osaka Medical Center for Cancer and Cardiovascular Diseases approved this study in 1994. From 29 March 1999, he received intradermal inoculation of BCG-CWS at a dose of 200 μg every week, for a total of 4 doses, as part of induction therapy. The immunotherapy was then continued at a dose of 100 μg every 4 weeks as maintenance therapy until January 2001. The serum interferon-gamma (IFN-γ) values measured three times at 1-month intervals were 25.5, 70.4, and 1770 pg/ml (normal range <7.8 pg/ml), respectively.

Up to April 1999, the lymph node metastases were palpable and then decreased in size, finally becoming impalpable at the end of May 1999, after 4 doses of BCG-CWS. In August 1999, a CT scan showed the complete response of not only the irradiated lymph node metastases but also multiple pulmonary metastases.

He remained disease-free until June 2003. In May 2004, a CT scan showed a new lesion of size 50 × 20 mm in the left upper lobe of the lung. Cytological findings following bronchoscopy revealed adenocarcinoma. No definitive diagnosis as to whether it was a second primary or metastatic lesion was made. We started the oral administration of gefitinib at 250 mg/day. As a result, a good response was achieved, and this was maintained from August 2004 to the beginning of 2006. In July 2006, the tumor showed enlargement and was hypermetabolic on positron-emission tomography (PET), with a standard uptake value of 4.4. For

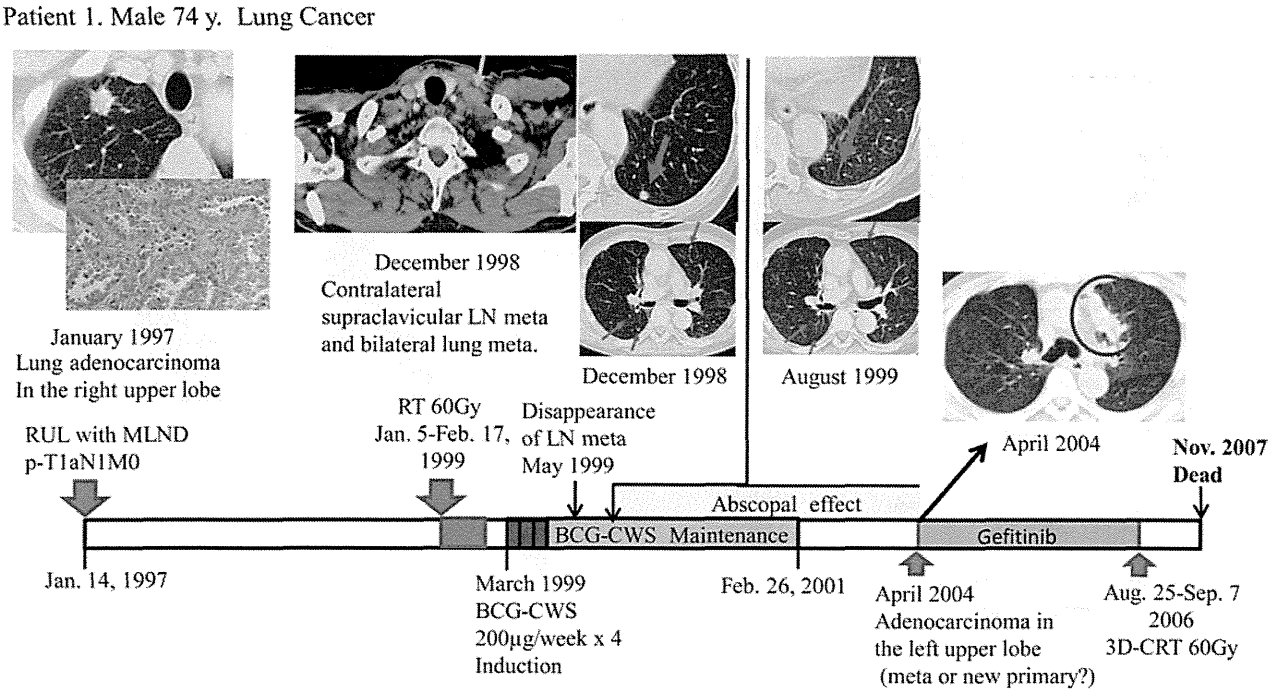

Fig. 1 Clinical course of patient 1. Axial CT images are shown, which are linked to a timeline showing therapy and disease status. *RUL* right upper lobectomy, *MLND* mediastinal lymph node dissection, *LN* lymph node, *RT* radiotherapy, *BCG-CWS* cell wall skeleton of *Mycobacterium bovis* bacillus Calmette–Guérin, *3D-CRT* 3-dimensional conformal radiotherapy

this tumor, we performed 3D conformal RT with 60 Gy in 10 fractions in August 2006. Although gamma-knife and whole-brain irradiation were employed for multiple brain metastases, he died due to disease progression in November 2007.

Patient 2

A female patient received a diagnosis of urothelial carcinoma in 1987 at 40 years of age, and initially underwent transurethral resection (TUR) with BCG intravesical therapy. Her clinical course is shown in Fig. 2. She developed lung metastasis and was treated with 2 cycles of chemotherapy consisting of methotrexate, epirubicin, and cisplatin (MEC). Then she underwent basal segmentectomy of the left lung in August 1997, followed by radical cystectomy with an ileal conduit for local recurrence 1 month after the segmentectomy. She remained disease-free until August 2007, when a CT scan showed a new 5-mm pulmonary nodule with a central cavity in the S3 of the right upper lobe of the lung. During observations made up to March 2008, the lesion increased in size to 10 mm in diameter. Therefore, we performed wide wedge resection (WWR) and confirmed the diagnosis of lung metastasis from the urothelial carcinoma. Thereafter, a deep-seated tumor appeared in the same lobe in April 2009. To avoid right upper lobectomy, stereotactic body radiation therapy (SBRT) with 48 Gy in 4 fractions was administered in June 2009 when she was 62 years old. In February 2011, two new lesions with central cavities were detected in the left upper and lower lobes, concomitant with post-irradiation scarring in the right upper lobe.

Because there was no other malignancy except for the left lung metastases, surgery was recommended as a possible treatment after fully discussing the risks and benefits with her surgeon, urologist, and radiologist. However, she refused surgical treatment. Accordingly, informed consent concerning BCG-CWS immunotherapy was obtained. The immunotherapy was started in March 2011 in the same manner as for patient 1. After 10 doses had been administered (November 2011), the two metastases with cavities had completely regressed on CT imaging. The patient has continued on a maintenance dose of BCG-CWS, and she has been disease-free without adverse effects to date (April 2013). Her serum IFN-γ value was <7.8 and 86.6 pg/ml at 1 and 2 months after the start of immunotherapy.

Discussion

The abscopal effect is a rare phenomenon, and the mechanism for it has not been clearly defined. Camphausen et al.

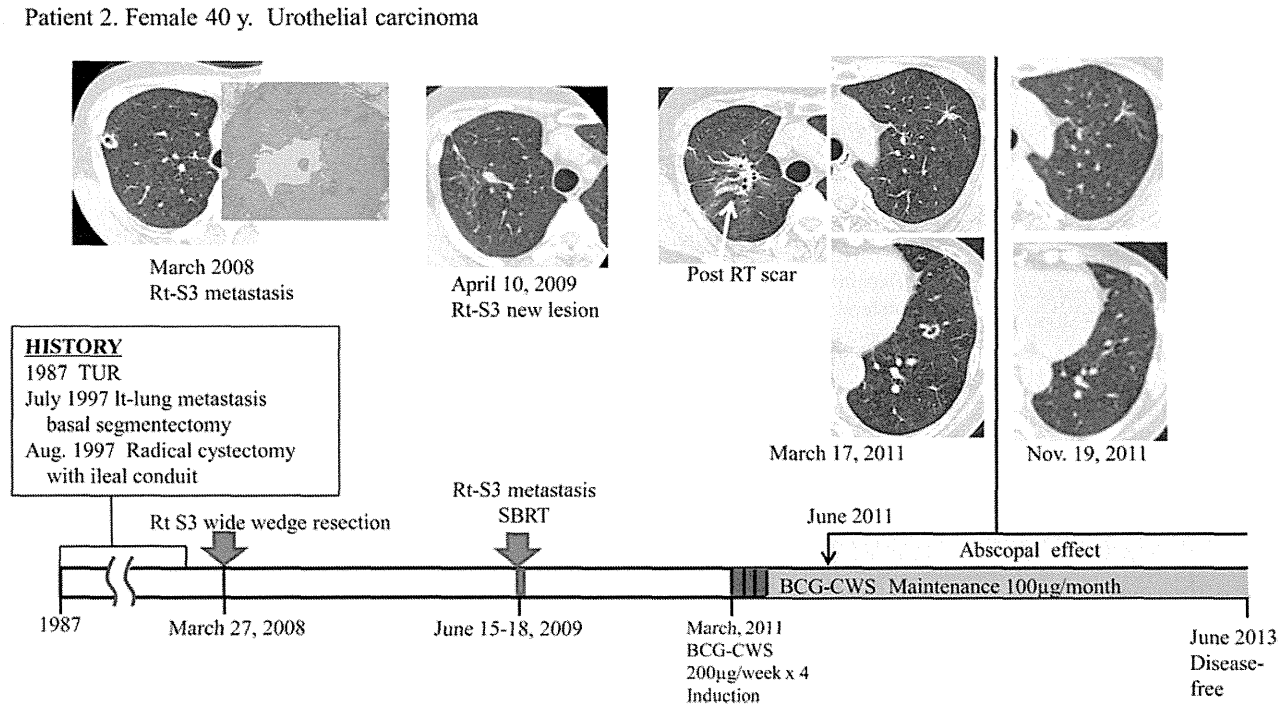

Fig. 2 Clinical course of patient 2. Axial CT images are shown, which are linked to a timeline showing therapy and disease status. The lesions showing an abscopal effect were in the left lung and had central cavities; these lesions presented the same characteristics as the resected and histologically proven metastasis on CT scan. *SBRT* stereotactic body radiation therapy