A New Strategy for Metachronous Primary Lung Cancer: Stereotactic Body Radiation Therapy with Concurrent Chemotherapy

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Abstract. *Background/Aim: Patients with malignant lung cancer often develop a solitary pulmonary nodule after treatment of the initial cancer. In those cases, it is difficult to distinguish primary lung cancer (PLC) from lung metastasis. Therefore, both local therapy for a single lung lesions and systemic therapy for micrometastases are needed. This retrospective study aimed to evaluate the safety and tolerability of concurrent stereotactic body radiation therapy (SBRT) and chemotherapy in patients with metachronous PLC. Patients and Methods: We reviewed the records of 10 patients with metachronous PLC treated with SBRT and concurrent chemotherapy with curative intent from 2007 to 2013. The delivered radiation dose was 48 Gy in four fractions. Results: All patients received SBRT with concurrent chemotherapy on schedule. Complete response rate was 90%. Safety profile of this treatment was compatible with that of traditional chemoradiotherapy. Conclusion: Our study showed good feasibility and safety for SBRT with concurrent chemoradiotherapy.*

Patients with malignant cancer often develop a solitary pulmonary nodule (SPN) following treatment of the initial cancer (1, 2). Several studies have reported that the risk of developing metachronous primary lung cancer (PLC) after surgical resection of prior early-stage lung cancer was estimated to be 1-2% per patient per year (3, 4). However, the diagnosis of metachronous PLC with the same histology as the initial cancer may be difficult because of the possibility of metastatic or recurrent disease (4). Regarding the treatment of early-stage metachronous PLC patients, whose metastatic disease is most likely determined by histology, physicians are always confronted with a difficult choice: patients require curative local treatment for early-stage metachronous PLC; however, for metastatic disease, local treatment is insufficient and patients require systemic therapy. No consensus exists concerning the optimal treatment strategy for early-stage metachronous PLC patients.

Surgical resection has been shown to be effective in early-stage metachronous PLC patients and should be considered as first-line therapy (5, 6). However, metachronous PLC patients have often significant comorbidities that preclude surgical resection or they refuse surgical treatment (3). Patients with metachronous PLC who have severe comorbidities or refuse surgery are good candidates for stereotactic body radiation therapy (SBRT) (7, 8). SBRT remains a mainstay treatment option for patients who refuse surgery or who are determined to be medically-inoperable (9). SBRT with concurrent chemotherapy, which may be not only a curative treatment for local lesions but also systemic therapy for potential metastases, is reasonable in patients with inoperable, early-stage metachronous PLC. Insufficient evidence exists regarding the efficacy and safety of SBRT with concurrent chemotherapy in lung cancer. Therefore, we administered concurrent SBRT with concurrent chemotherapy practically in inoperable early-stage metachronous PLC patients and evaluated this new treatment strategy retrospectively. To the best of our knowledge, this is the first study of SBRT with concurrent chemotherapy used for metachronous PLC.

Patients and Methods

Patients. This retrospective study was performed at the Institute of Biomedical Research and Innovation (Kobe, Japan). The data from 10 consecutive patients who were treated with SBRT and concurrent

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Table I. *Patients' characteristics*.

	Age	Gender	PS	Smoking history	Histology (1st primary cancer)	Histology (2nd primary cancer)	Stage (1st primary cancer)	Stage, T status (2nd primary cancer)	Treatment (1rst primary cancer)
No.1	67	F	0	Absence	Well diff Ad	Well diff Ad	1A	1A, (T1b)	Op
No.2	64	F	0	Absence	Papillary thyroid carcinoma	Ad (Lepidic pattern) TTF1(+),Thyroglobulin (-),SP-A(-)	1	1B, (T2a)	Op
No.3	66	M	0	Absence	Ad(Papillary pattern)	Ad (Papillary pattern)	1B	1B, (T2a)	Op
No.4	63	F	0	Absence	Ad(Papillary pattern)	Ad (Papillary pattern)	1A	1A, (T1a)	Op
No.5	58	M	0	Presence	Ad(Solid pattern)	Unknown	3A	1A, (T1a)	Op + adjuvant Chemo
No.6	61	M	0	Presence	Well diff Ad	Unknown	3B	1A, (T1a)	Cont Chemo RT
No.7	69	M	0	Presence	Poor diff Ad, TTF1(+),	Poor diff Ad, TTF1(+)	3A	1A, (T1b)	Cont Chemo RT + Op
No.8	79	M	0	Presence	Well diff Ad	Unknown	1B	1A, (T1a)	Op
No.9	59	F	0	Presence	Oesophageal squamous cell carcinoma	Unknown	2	1A, (T1a)	Cont Chemo RT + Op
No.10	72	M	0	Presence	Mesopharyngeal squamous cell carcinoma	Unknown	4A	1A, (T1a)	Cont Chemo RT+ Op

F, Female; M, male; PS, performance status; Ad, adenocarcinoma; Well diff, well-differentiated; poor diff, Poorly-differentiated; TTF1, thyroid nuclear factor 1; NK2 homeobox 1; SP-A, surfactant protein-A; Op, operation; Chemo, chemotherapy; Cont Chemo RT, concurrent chemoradiotherapy.

chemotherapy for metachronous PLC between October 2007 and July 2014 were evaluated retrospectively (Table I). All of the patients refused surgery or were determined to be medically inoperable (2 patients refused surgery and 8 were medically inoperable). We designated `metachronous' when the second solitary tumour was found some time after the first primary cancer. The diagnosis of metachronous PLC was confirmed by a multidisciplinary council consisting of radiologists, radiation oncologists and medical oncologists before the initiation of the treatment. All of the patients developed a solitary pulmonary lesion after definitive treatment of the initial cancer. Five patients received pathological diagnoses of adenocarcinoma and were diagnosed with the same histology as that of the initial cance (Table I). The other five patients were diagnosed with non-small-cell lung carcinoma (NSCLC) according to the clinical course and evaluation using fluorodeoxyglucose positron emission tomography (FDG-PET) and computed tomography (CT) because the tumours were too small in size to perform biopsy. Tumour staging was performed using CT or magnetic resonance imaging (MRI) of the head, CT of the chest and abdomen, as well as bone scintigraphy or FDG-PET/CT. These patients were restaged according to the seventh edition of the Tumour Node Metastasis (TNM) classification of the lung (10). An Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1 was necessary for inclusion in the current study (11). The present study was approved by the Institutional Review Board of our hospital.

Radiation therapy. Hypofractionated high-dose SBRT was performed to all patients with static non-coplanar 7-8 beams using 4-MV or 6-MV photons (12). The prescribed dose was 12 Gy per fraction at the isocenter and the total dose was 48 Gy with four fractions. In the radiation treatment planning, clinical target volume (CTV) was delineated to include the lung tumour and the surrounding spiculation. Internal target volume (ITV) was made by combined with CTVs on inhale CT and exhale CT and/or 4 dimensional CT (4D-CT) in order to account for the tumour respiratory motion. A 5-mm setup margin was added to the ITV to define PTV and a 5-mm portal margin was applied to ensure the PTV dose. In terms of organ at risk, the volume irradiated with 20 Gy or more (V20) was maintained less than 25% of the total lung. The doses to other critical organs were lower than our institutional dose constraints because all tumours were located peripherally and far from the critical organs.

Chemotherapy. Figure 1 shows the treatment schedule. The concurrent and consolidation chemotherapy regimen was platinum doublets with one of cisplatin (CDDP), carboplatin (CBDCA) and nedaplatin (CDGP) plus one of docetaxel (DOC), vinorelbine (VNR) and paclitaxel (PAC). Table II shows the treatment regimens and dosages. During radiotherapy, platinum doublets were administered concomitantly on the first day. The consolidation phase chemotherapy, initiated 3 to 4 weeks after concurrent chemoradiotherapy, was administered in three cycles. A maximum of one dose-level reduction was permitted per patient in the consolidation phase if the physician decided that a patient could not tolerate chemotherapy at the same dosage.

Treatment and toxicity evaluation. Treatment efficacy was assessed in all patients and toxicity was assessed in all of the treated patients. Patients were assessed for responses using CT within 8 weeks of completing the treatment and by FDG-PET/CT within 1 year. After the

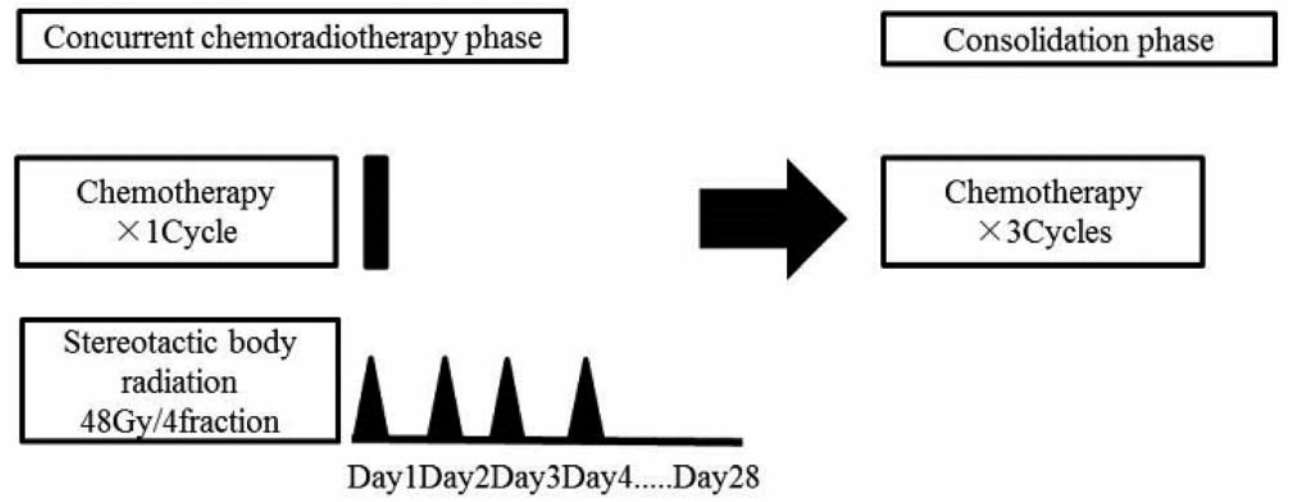

Figure 1. *Treatment schedule. Concurrent chemoradiotherapy phase: chemotherapy was administered concomitantly on the first day of the week. Irradiation was administered during a 1-week period. Consolidation phase: chemotherapy was administered on day 1 of each 3-week cycle.*

Table II. *Administered chemotherapy.*

	Concurrent chemotherapy regimen	Cycle	Consolidation chemotherapy regimen	Cycle	Dose reduction/ Regimen change
No.1	CDDP(60mg/m^2)+DOC(60mg/m^2)	1	CDDP(60mg/m^2)+DOC(60mg/m^2)	3	None
No.2	CDDP(60mg/m^2)+DOC(60mg/m^2)	1	CDDP(60mg/m^2)+DOC(60mg/m^2)	3	None
No.3	CDDP(60mg/m^2)+DOC(60mg/m^2)	1	CBDCA(AUC5)+PAC(175mg/m^2)	2	CDDP, DOC→CBDCA, PAC (Consolidation chemotherapy)
No.4	CDDP(60mg/m^2)+VNR(20mg/m^2)	1	CDDP(60mg/m^2)+VNR(20mg/m^2)	3	None
No.5	CDDP(70mg/m^2)+VNR(25mg/m^2)	1	CDDP(60mg/m^2)+VNR(20mg/m^2)	3	Dose reduction of CDDP and VNR
No.6	CBDCA(AUC5)+PAC(175mg/m^2)	1	CBDCA(AUC5)+PAC(60mg/m^2 day1-3)	3	None
No.7	CBDCA(AUC5)+PAC(175mg/m^2)	1	CBDCA(AUC5)+PAC(60mg/m^2 day1-3)	3	None
No.8	CBDCA(AUC4)+DOC(50mg/m^2)	1	CBDCA(AUC4)+DOC(50mg/m^2)	3	None
No.9	CDGP(100mg/m^2)+DOC(60mg/m^2)	1	CDGP(80mg/m^2)+DOC(50mg/m^2)	3	Dose reduction of CDGP and DOC
No.10	CDDP(60mg/m^2)+VNR(20mg/m^2)	1	CDDP(60mg/m^2)+VNR(20mg/m^2)	3	None

CDDP, Cisplatin; CBDCA, carboplatin; CDGP, nedaplatin; DOC, docetaxel; PAC, paclitaxel; VNR, vinorelbine.

treatment, chest radiography was performed every month, while thoracic CT was performed every 6 months. Patients underwent follow-up every month for 1 year and at least every 3 months thereafter.

Treatment response evaluation was made according to the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.09 (13), based only on the longest diameter of all the lesions as follows: Complete response (CR), disappearance of all the lesions; partial response (PR), ≥30% reduction of the sum of the longest diameters of all the lesions, referring to the sum of baseline longest diameters; progressive disease (PD), ≥20% increase in the sum of the longest diameters of the target lesions, referring to the smallest sum of the longest diameters recorded since the initiation of the treatment or the appearance of one or more new lesions; stable disease (SD), neither sufficient lesion shrinkage to qualify for PR nor sufficient lesion growth to qualify for PD, referring to the smallest sum of the longest diameters since the initiation of the treatment. Toxicity was evaluated in accordance with the National Cancer Institute Common Toxicity Criteria (NCI-CTC) 4.0.3 (14).

Statistical analysis. The 1- or 2-year progression-free survival (PFS) rate was defined as the number of subjects who had not progressed or died by 1 or 2 years from the date of their first dose, respectively, divided by the number of subjects in the cohort. The 1- or 2-year survival rate was defined as the number of subjects who had not died by 1 or 2 years from the date of their first dose, respectively, divided by the number of subjects in the cohort. Living patients were evaluated on the date of the last follow-up. We estimated the respective contribution of local progression and distant progression to tumour progression and the rate of chemotherapy implementation. The median follow-up duration was calculated using the reverse Kaplan–Meier method. JMP version 9.0.0 (SAS, Cary, NC, USA) was used for the statistical analyses.

Table III. *Adverse events experienced with each treatment.*

Adverse event	Toxicity grade		
	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Leukopenia	0	40	30
Neutropenia	0	20	50
Anaemia	10	10	0
Thrombocytopenia	10	0	0
Febrile neutropenia	0	30	0
Pneumonitis	30	0	0
Gastritis	0	10	0
Anorexia	20	20	0
Hypocalcemia	10	0	0
Vomiting	0	20	0
Nausea	10	0	0
Rash	10	0	0

Results

Patients' characteristics. Between October 2007 and December 2013, 10 patients were treated using SBRT with concurrent chemotherapy, including platinum doublets. The median follow-up for censored cases was 37.3 months (interquartile range (IQR)=24.6–58.2). The median interval time after initial therapy was 20.9 months (IQR=12.7–29.3). Characteristics of the patients are provided in Table I. The median age was 65 years; eight patients (80%) were stage IA and two (20%) were stage IB.

Administered treatment. Compliance to the protocol was acceptable. Table II shows the status of chemotherapy implementation. During the concurrent phase, all patients received concurrent chemotherapy. In the consolidation phase, nine (90%) patients received the three scheduled courses of therapy. One patient switched from CDDP to CBDCA due to gastritis, while the dosage of the regimen was decreased in two patients in the consolidation phase. All patients completed SBRT using 48 Gy of treatment.

Efficacy. Nine (90%) patients achieved a CR and one (10%) patient a PR. The objective response rate was 100%. Local recurrence was not observed in any patient. The 1-year PFS rate was 100% (10/10 cases) and the 2-year PFS rate was 87.5% (7/8 cases): two patients did not complete the full 2-year follow-up period. Only one patient had intrapulmonary metastasis after 23 months of treatment. The 2-year survival rate was 100% (8/8 cases) and all patients had survived by the end of the follow-up.

Toxicity. Table III shows the toxicity results. Grade 3/4 leucopoenia occurred in seven patients (70%), grade 3/4 neutropenia in seven (70%), grade 3 febrile neutropenia in two (20%) and grade 3 anaemia in one (10%). Grade 3 anorexia occurred in two patients (20%), grade 3 nausea in two (20%) and grade 3 gastritis due to chemotherapy in one (10%). No treatment-related deaths occurred.

Discussion

No consensus exists regarding the optimal treatment strategy for patients who are clinically-indistinguishable between metachronous PLC and lung metastasis. In the present study, the CR rate was excellent compared to previous studies (SBRT only). In addition, the present study demonstrated a higher 2-year survival rate than did previous studies (SBRT only) (7, 8). Our results, thus, suggest that SBRT with concurrent chemotherapy is an active local treatment with curative intent for the real metachronous PLC having the potential to prevent progressing micrometastases throughout the body and that SBRT with concurrent chemotherapy is one of the optimal treatments in patients who are clinically-indistinguishable between metachronous PLC and lung metastasis. A few reports have demonstrated the use of concurrent chemoradiotherapy with SBRT. Ulhoa-Cintra *et al*. showed the efficacy and feasibility of SBRT with concurrent chemotherapy (15). They reported that 50% of NSCLC patients experienced infield local control at 6 months and 1 year, 16% had distant progression at 6 months and 33% had distant progression at 1 year; the median survival was 20 months. However, these results were not assessed in a prospective clinical trial. In the present study, we combined SBRT with platinum doublets: CDDP (or CBDCA, CDGP) + DTX, CBDCA + PAC and CDDP + VNR. Thus, our study showed the expected response and feasibility. Seventy percent of patients developed grade 3/4 neutropenia, 20% febrile neutropenia and 10% anaemia. These results were compatible with those of previous studies evaluating traditional concurrent chemoradiotherapy (16, 17). No deaths were observed with treatment.

The present study had its limitations: it was retrospective in nature and comprised of small cohorts. Some cases could not undergo histological analysis because lesions were too small to obtain adequate samples. Additionally, chemoradiotherapy regimens were not uniform. The sample size in the present study was not large; therefore, it was difficult to reach a definitive conclusion. Further prospective clinical trials are warranted to evaluate the actual efficacy and safety of SBRT plus concurrent chemotherapy in early-stage metachronous PLC patients.

In conclusion, the present study showed good feasibility and safety of SBRT with concurrent chemotherapy in early-stage metachronous PLC patients. This new strategy is useful and needs to be assessed in a larger, prospective cohort study.

Conflicts of Interest

No conflicts of interest exist.

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