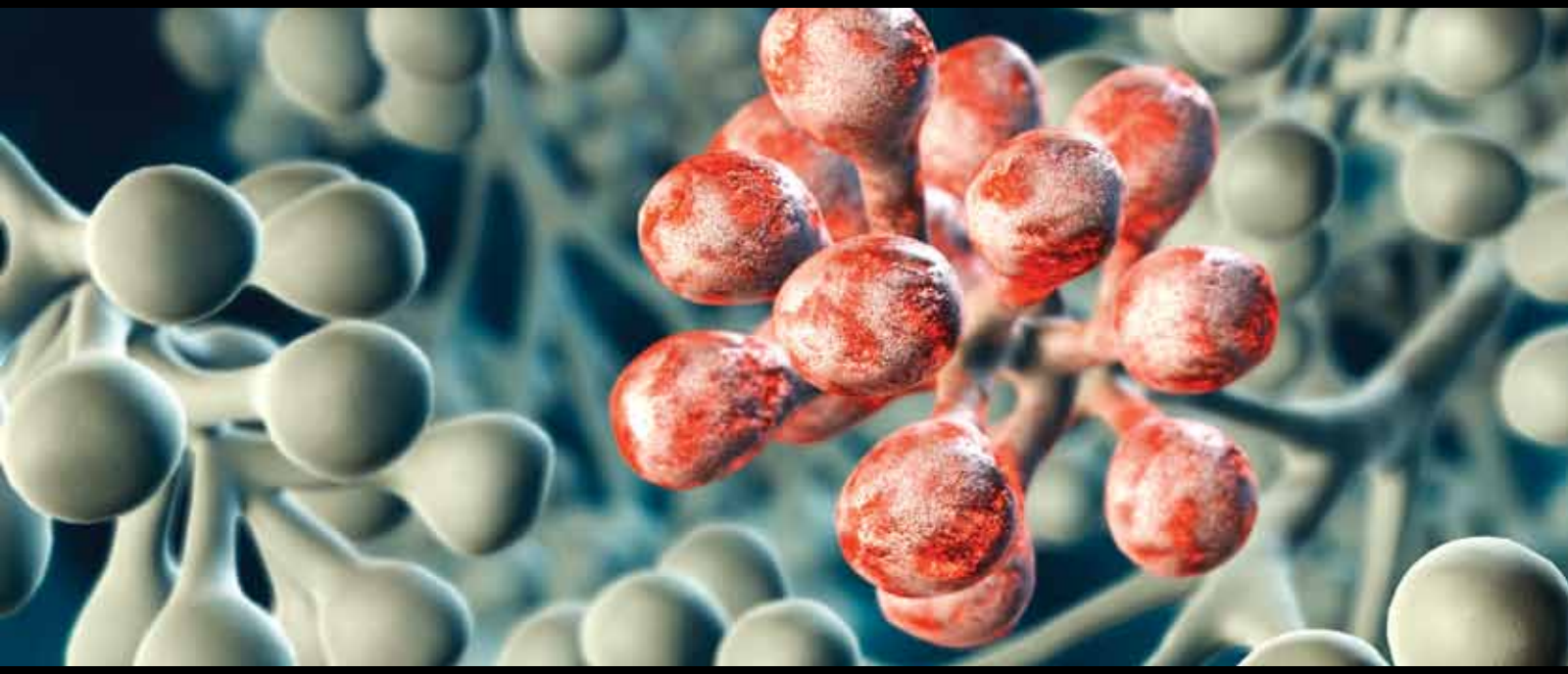
Oligometastases/Oligo-Recurrence of Lung Cancer

Guest Editors: Yuzuru Niibe, Joe Y. Chang, Hiroshi Onishi, Joseph Salama, Takao Hiraki, and Hideomi Yamashita



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Pulmonary Medicine

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Editorial Board

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Editorial

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Metastasis or recurrence of cancer has been considered as representing a near terminal life stage. As a result, for a long time, cancer patients with metastasis or recurrence have been classified as one group and treated using only systemic therapy. However, recent advances in cancer therapy have dramatically improved both local and systemic therapies. The concept of oligometastases was proposed by Hellman and Wechselbaum in 1995 [1] and revised by Niibe et al. in 2006 as oligo-recurrence [2]. These notions represent the first classification of metastasis or recurrence to identify subgroups for achieving long-term survival or even cure.

Oligometastases are defined as 1–5 distant metastases that can be treated by local therapy to achieve long-term survival or cure. The most important prognostic factor for oligometastases is the status of the primary lesion [3, 4]. Niibe et al. proposed the concept of oligo-recurrence to overcome this problem. Oligo-recurrence is thus defined as 1–5 distant metachronous metastases that can be treated by local therapy, under conditions of a controlled primary lesion. More favorable subgroups of oligometastases have subsequently been classified. Niibe et al. proposed the classification and naming of sync-oligometastases and oligo-recurrences [3]. Sync-oligometastasis indicates a state of oligometastases with active but controllable primary lesions. This classification appears reasonable.

Based on a review of the literature, we propose a more detailed classification of metastases and recurrence. Table 1 shows the Niibe-Onishi-Chang classification, which includes not only oligometastases, but also polymetastases. Oligometastases and oligo-recurrences usually offer a better prognosis than polymetastases. However, oligometastases and oligo-recurrence are cancer- and organ-specific. The appearance status of oligometastases or oligo-recurrence is thus sometimes equivalent to polymetastases such as in pancreatic cancer, sarcoma, or malignant melanoma, although the last one is related to the abscopal effect, a key cure-related phenomenon for oligometastases and oligo-recurrences [5–7]. Among oligometastases and oligo-recurrences, patients with 1-2 metastases and recurrences reportedly show better prognosis than those with 3–5 metastases and recurrences [8]. In oligo-recurrence of NSCLC in only the brain or adrenal gland, patients achieve favorable survival [4, 9]. Lung or liver metastases of colon or rectal cancer are also be associated with favorable survival [10, 11]. Patients with oligo-recurrence of renal cell carcinoma also achieve long-term survival [12]. In sync-oligometastases of NSCLC affecting only the brain or adrenal gland, patients reportedly achieve relatively favorable survival [9, 13]. In sync-oligometastases of colon and rectal cancer, renal cell cancer also reportedly shows relatively favorable survival [10–12]. In oligo-recurrence of breast cancer, patients are reported to achieve relatively favorable survival [14, 15]. Niibe et al. reported that all seven of breast cancer patients with bone-only oligo-recurrence were still alive at the last followup (median

Table 1: Niibe-Onishi-Chang classification.

Favorable	Intermediate		Unfavorable
	Relatively favorable	Relatively unfavorable	
Oligorecurrence Site no. 1-2 NSCLC (brain and adrenal gland) Colon and rectum cancer (lung and liver) Renal cell cancer	*oligo-recurrence* site no. 1-2 breast cancer (bone, lung, and liver) SCLC (brain) site no. 3–5 NSCLC (brain and adrenal gland) colon and rectum cancer (lung and liver) renal cell cancer	*oligo-recurrence* site no. 3–5 breast cancer (bone, lung, and liver) SCLC (brain)	*Oligometastases* and *oligo-recurrence* pancreatic cancer (any site) melanoma (any site) sarcoma (any site)
	sync-oligometastases site no. 1-2 NSCLC (brain and adrenal gland) colon and rectum cancer (lung and liver) renal cell cancer	*sync-oligometastases* site no. 3–5 NSCLC (brain and adrenal gland) colon and rectum cancer (lung and liver) breast cancer (bone, lung, and liver)	*polymetastases*

followup, 40 months). In sync-oligometastases of SCLC, several cases have been reported to survive more than 5 years [16, 17]. Patients with metastatic pancreatic cancer, sarcoma, or melanoma reportedly display unfavorable outcomes [18–20].

This new classification, the Niibe-Onishi-Chang classification, should be revised in the future due to the rapid improvements being achieved in local and systemic therapies for cancer. This classification is tentative, but is very important given the fact that even a decade ago, many oncologists considered patients with metastasis and recurrence in only a single group.

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Clinical Study

Carbon Ion Radiotherapy for Oligo-Recurrence in the Lung

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The clinical results after carbon ion radiotherapy for the metastatic lung tumors believed to be in the state of oligo-recurrence were evaluated. One hundred and sixteen lesions in 91 patients with lung cancer metastasis were treated with carbon ion radiotherapy at our institute from April 1997 to February 2011. Regarding the prescribed dose, total dose ranged between 40 gray equivalents (GyE) and 80 GyE, and fraction size ranged from 1 to 16 fractions. After a median followup period of 2.3 years (range, 0.3–13.1 years), the statistical overall survival rate and local control rate were 71.2% and 91.9% at 2 years after treatment, respectively. Treatment-related side effects were not a clinical problem. When classified by the primary organ, there were 49 cases of lung cancer, 20 cases of colorectal cancer, and 22 cases of others. The overall survival rate and local control rate for lung metastasis cases from lung cancer at 2 years after treatment were 81.5% and 92.4%, respectively, and 65.0% and 92.0% regarding lung metastasis from colorectal cancer. Carbon ion beam therapy for the metastatic lung tumors is a safe therapy, and the therapeutic effect is comparable to the outcome obtained from reported surgical resections.

1. Introduction

Radiotherapy is the principal treatment option for patients with early stage lung cancer and contraindications to receive surgery. The outcome from using conventional therapeutic techniques has been a 40–70% 5-year local control rate, but a local control rate equivalent to surgery is being reported due to recent advancements in irradiation techniques [1–4]. These irradiation techniques include SBRT, proton beam therapy, and carbon ion radiotherapy (CIRT).

Clinical trials for various types of tumors were initiated at the National Institute of Radiological Sciences (NIRS) from June 1994 using carbon ion beams, and dose fractionation suitable for individual diseases and irradiation techniques, such as a respiratory-gated radiotherapy and so forth, were developed. As a result, the healing of refractory cancers such as sarcoma of the bone and soft tissue, for which surgery is difficult, postoperative local recurrence of rectal cancer, and so forth, were achieved, and it was found that safe treatment is possible in a further shorter period regarding cancers of the prostate gland, the head and neck, lungs, and liver [1].

Treatment for nonsmall cell lung cancer was initiated in November 1994. Regarding peripheral stage I lung cancer, the fractionation number was gradually reduced from 9 times [5] to 4 times [6] while confirming the safety and efficacy. Currently, a clinical study is being carried out in which irradiation is completed in a day.

We herein report on our outcome from treating metastatic lung tumor believed to be in the state of oligo-recurrence [7], using carbon ion beams in which a good local control rate may be hoped for.

2. Materials and Methods

2.1. Patients. From April 1997 to February 2011, 116 lesions in 91 patients were treated with CIRT in our institute. The average age was 64.8 years old (range, 10–86 years) with a male/female ratio of 57/34. All patients were diagnosed by CT, PET, bone scintigraphy, and brain MRI before therapy. The histology and metastasis diagnosis of the tumors were determined based on the clinical course.

The conditions for applying the treatment to patients were as follows: the primary lesion is treated with no apparent local recurrence in the primary organ at the time of lung metastasis treatment, that is, the tumor is oligo-recurrence, there are no

Table 1: Patient characteristics.

Primary organ	Patient (n)	M/F	Age mean range	Tumor (n)	Size (mm) median range	Prescribed dose
Total	91	57/34	64.8 10–86	116	18 3–100	52.8 GyE/4 fr (n = 54) 60.0 GyE/4 fr (n = 23) Others (n = 39)
Lung cancer	49	35/14	69.8 39–86	58	18 3–75	52.8 GyE/4 fr (n = 34) 60.0 GyE/4 fr (n = 2) Others (n = 22)
Colorectal cancer	20	10/10	64.3 41–86	30	15 5–60	52.8 GyE/4 fr (n = 6) 60.0 GyE/4 fr (n = 17) Others (n = 7)
Other cancer	22	12/10	49.1 10–84	28	19 7–100	52.8 GyE/4 fr (n = 14) 60.0 GyE/4 fr (n = 4) Others (n = 10)

active lesions in organs other than the lungs, and there is one lesion in the lungs as a primary rule.

It is difficult to diagnose exactly the lung tumor as metastasis from primary lung cancer. In case, the lung tumor cannot be diagnosed as secondry primary lung cancer, we determined it as metastatic lung tumor.

Regarding the number of lesions per patient treated with carbon ion therapy, 4 lesions were treated in 2 cases, 2 lesions were treated in 19 cases, and only one lesion was irradiated in 70 patients.

The prescribed dose ranged from 40 GyE to 80 GyE, and this was divided into several fractions. The fractionation regimen of 52.8 GyE in 4 fractions was the most commonly used for the treatment of the 116 lesions, which was used on 54 tumors. This was followed by 23 lesions of 60.0 GyE in 4 fractions. In many cases, 52.8 GyE in 4 fractions was used for lung metastasis from lung cancer while 60.0 GyE in 4 fractions was used for colorectal cancer.

When classified by the primary organ, there were 49 cases of lung cancer, 20 cases of colorectal cancer, and 22 cases of other cancers. The breakdown of organs classified as other cancers included various types such as bone and soft tissue tumors, cervical cancer, thymic cancer, esophageal cancer, pharyngeal cancer, ovarian cancer, pancreatic cancer, hepatic cancer, and breast cancer, with the number of cases according to these organs being 4 cases or less.

Regarding the major axis length of the lung tumor, a small tumor was considered to be 3 mm while a large tumor was 100 mm, with a median of 18 mm. The median length of the tumor according to the primary organ was 18 mm, 15 mm, and 19 mm, respectively, regarding lung metastasis from lung cancer, lung metastasis from colorectal cancer, and other types of lung metastasis.

The patient characteristics are provided in Table 1.

Past history comprising several elements such as age, pulmonary function, cardiac function, and so forth, as investigated regarding all patients, who were either diagnosed by a surgeon as being medically unsuitable for surgery due to coexisting diseases or the patients themselves did not wish to undergo surgery.

This study was approved by the institutional review board of NIRS and was conducted in accordance with the ethical standards provided by the Declaration of Helsinki. Informed consent was obtained from all patients prior to treatment.

2.2. Treatment. Treatment was carried out within a week after treatment planning was created. In targeting, a visible legion on the CT image in the soft tissue condition was defined as the gross tumor volume (GTV). The clinical target volume (CTV) was determined by setting the margin more than 10 mm outside the GTV. To allow for the movement of the target during gated respiration, the internal margin was set by 5 mm outside the CTV. The planning target volume (PTV) was defined as CTV + internal margin. The total dose applied ranged from 40 GyE to 80 GyE to the isocenter, and 95% or more was irradiated to the PTV. Irradiation was carried out by dividing the total dosage into 1 to 16 fractions. Set-up corrections were carried out so that PTV would be less than 2 mm three dimensionally at every treatment.

2.3. Followup. Most patients underwent clinical examinations for followup, and CT scan of the thorax was carried out at our institute. Patients in which followup testing could not be carried out until completion underwent periodic CT scanning at another institute. The clinical outcomes of all patients have been confirmed.

The first followup examinations were performed 4 weeks after CIRT and in the following every 3 to 4 months. It is difficult to distinguish the change in normal tissues from radiation and tumor regrowth. We defined transitorily enlarged densities observed following approximately 3 months as locally controlled tumor. Meanwhile, local recurrence was determined from the enlarging tendency of tumors, as well as the outcome of CT image, PET scan, tumor marker, and biopsy.

3. Results

The statistical 2-year overall survival rate of 91 patients was 71.2% with a median observation period of 2.3 years (range,

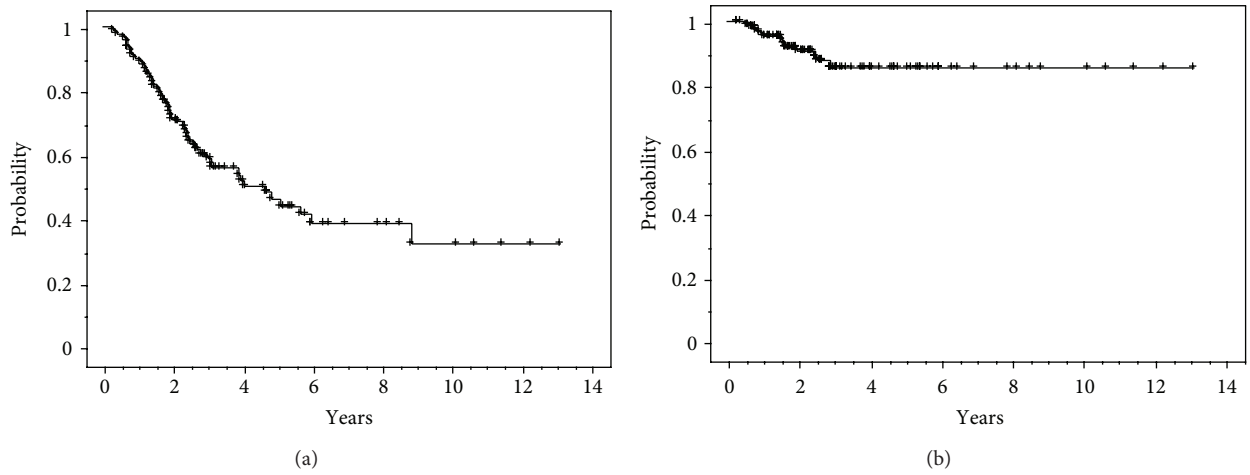

Figure 1: (a) Overall survival rate ($n = 91$). (b) Local control rate for lung metastases ($n = 116$).

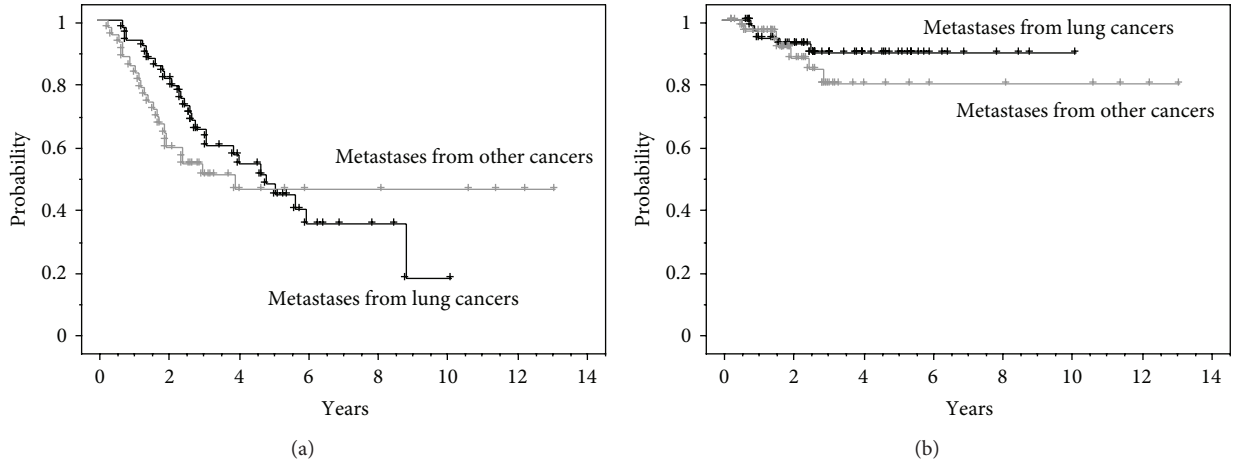

Figure 2: (a) Overall survival for lung metastases from lung cancer ($n = 49$) versus other cancer ($n = 42$). (b) Local control for lung metastases from lung cancers ($n = 58$) versus other cancers ($n = 58$).

0.3–13.1 years, Figure 1(a)). The local control rate of the 116 treated lesions was 91.9% at 2 years after therapy (Figure 1(b)).

The toxicities to the skin and lung caused by CIRT were assessed according to the NCI-CTC (early) and RTOG/EORTC (late). Early skin reactions were assessed for 116 lesions and late skin reactions for 114 lesions. Of the early reaction lesions, 116 were grade 1. Of the late reaction lesions, 114 were grade 1. Lung reactions were clinically assessed in the 116 lesions of 91 patients. Only five patients had grade 2 in early reaction; no adverse events greater than grade 2 were detected among early and late reactions.

Twelve of 91 patients (12 of 116 lesions) had recurrences. In fifty-five of 91 patients, new lesions appeared in other sites, for example, lung, bone, and brain. In following this treatment, 47 patients died. Regarding the cause of death, 5 of 26 patients (19.2%) of all deceased lung cancer died due to causes other than the primary disease such as pneumonia and so on; however, in metastasis from other cancers such as colorectal cancer, the cause of death in all cases was cancer death due to the primary disease.

The 2-year overall survival rate of lung metastasis cases from lung cancer was 81.5%, and the overall survival rate of lung metastasis from other than lung cancer was 59.3% (Figure 2(a)). The local control rate were 92.4% and 91.3%, respectively, (Figure 2(b)). Furthermore, the 2-year overall survival rate and local control rate of 30 lesions in 20 cases of lung metastasis from colorectal cancer was 65.0% and 92.0%.

The survival rate of 70 cases with one lesion irradiated with carbon ion beams and 21 cases in which there were several irradiated regions was compared. The 2-year cause specific survival rate was 72.4% and 75.4%, with no significant difference ($P = 0.3977$).

The effect of the tumor size on local control was investigated. When the local control rate of 116 tumors was compared regarding the length of the tumor, the local control rate was significantly superior regarding those shorter than 2 cm compared to those exceeding 2 cm (Figure 3). When lung metastasis from lung cancer was compared in the same manner, the local control rate was 100% regarding tumors that are 2 cm or smaller in length.

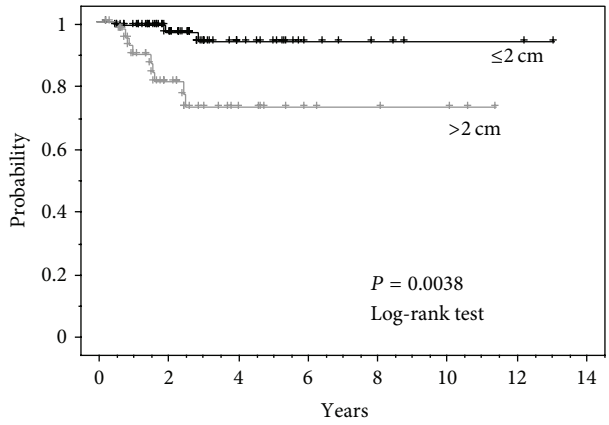

Figure 3: Local control for tumor diameter ≤2 cm ($n = 72$) versus >2 cm ($n = 44$) 3 y. Local control rate ≤2 cm: 93.4%, >2 cm: 72.7%.

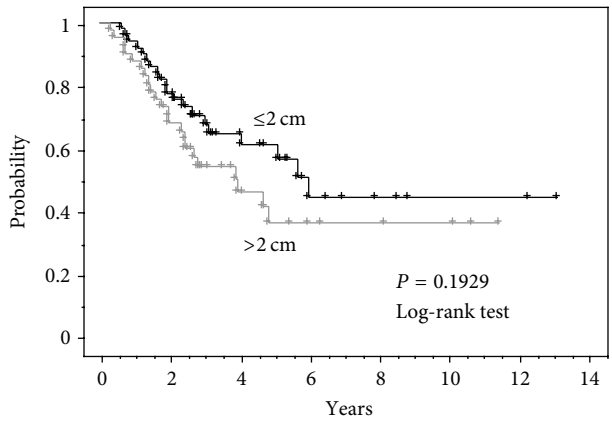

Figure 4: Cause specific survival for tumor diameter ≤2 cm ($n = 50$) versus >2 cm ($n = 41$) 3 y. Cause specific survival rate ≤2 cm: 70.6%, >2 cm: 54.3%.

Furthermore, the tumor size and the prognosis were investigated. The cause specific survival rate was compared regarding 50 cases in which the maximum diameter of the treated tumor was 2 cm or smaller and 41 cases in which it exceeded 2 cm. The 2-year cause specific survival rate was 77.5% regarding the group with a tumor diameter of 2 cm or smaller, and a good tendency was observed although there was no significant difference compared to those exceeding 2 cm, at 67.8% ($P = 0.1929$) (Figure 4).

Although there was no significant difference in comparing the cause specific survival rate of 10 cases in which local control was not obtained and other cases in which local control was obtained, there was no survivor of 5 years or longer regarding cases in which local control was not obtained.

The relationship between the time taken until commencing CIRT after treatment of the primary tumor and the prognosis was investigated in the cases of metastasis from lung cancer. The time taken until treatment of the primary lesion to treatment of the lung metastasis was classified into within 1 year, from 1 year to 2 years, from 2 years to 3 years, from 3 years to 5 years, and over 5 years, and the respective cause specific survival rates were compared. There was no difference in groups that took within 1 to 5 years until treatment, though the 3-year cause specific survival rate was from 60.6% to 72.7%. While in group of over 5 years, all 7 patients are still alive (median followup period: 3.5 years) except for one case of death due to another disease.

4. Discussion

We treated metastatic lung tumors believed to be "oligo-recurrence" using carbon ion beams in which a high local control rate may be expected.

A diagnosis of metastasis was determined from the clinical course. There were many cases in which pathologic tissues were not sampled due to reasons such as the following: biopsy was difficult because the tumor was small, a malignant tumor was clearly suspected upon imaging and clinical course, diagnosis was obtained from resected lung tumors in the past by surgery. We believe that diagnosis with a malignant tumor was justifiable but discrimination with the primary lung cancer may be indicated as problematic, especially regarding cases diagnosed with lung metastasis from lung cancer. As mentioned below, this cannot be ruled out, although the possibility is low.

Regarding adverse reactions, there were no patients with grade 3 or more regarding both early-reaction NCI-CTC and late-reaction RTOG/EORTC. It is believed that the advantages of adopting respiratory-gated radiotherapy and irradiation from 4 directions are exhibited by the low frequency of normal tissue damage [8].

Considering the poor systematic medical condition of the patients, that is, the fact that many patients who are medically unsuitable for surgery are being treated and this is having a major effect on the outcome of overall survival, it was believed that the treatment outcome was generally good. The overall survival rate was favorably comparable to the outcome of CIRT for stage I lung cancer [5, 6], and we believe that this suggests that our criteria for selecting these cases was appropriate.

One lesion was determined as the subject as a general rule, but there were cases in which multiple lesions were treated as a result of clinical course. No difference was observed between the patients who treated single lesion and multiple lesions in comparison of survival. It cannot be determined that cases in which one location alone was irradiated ultimately had only one metastasis, and perhaps cases in which multiple lesions were treated were advantageous in that treatment was successfully completed.

The local control rate is discussed. It is believed that the local control rate is generally permissible. In this outcome, the local control rate for the tumors that are 2 cm or less was particularly superior. In contrast, the local control for the tumors exceeding 2 cm was by no means satisfactory compared to the outcome of the CIRT for primary lung cancer when considering that most tumors are 3 cm or smaller.

There are reports mentioning that tumor size is a prognostic factor [9]. In this study, we evaluated the overall survival concerning tumor size, not volume. Although

the analysis outcome is omitted, smaller tumors have a tendency for better prognosis. One opinion is that the tumor doubling time affects the prognosis [10], thus suggesting that perhaps the same phenomenon is observed.

It is under discussion regarding whether or not the local treatment of metastatic lung tumors is effective for prolonging the prognosis. For the metastatic lesion, surgery or radiation therapy is carried out on some patients for potential effect, but the criteria for selecting cases in which an effect may be expected is not clear [11]. We determined the eligibility criteria as being the condition that is frequently used in carrying out surgical resection, that is, the primary lesion is controlled, there are no lesions in places other than the lungs, and there is only one lesion at the time of treatment as a rule. Whether or not our result is superior compared to chemotherapy and the best supportive care remains to be elucidated, but it was evaluated as being satisfactory compared to surgical resection cases due to metastasis [12] and the outcome of CIRT for stage I nonsmall cell lung cancer. In our outcome as well, there were no long-term survival cases of 5 years or more regarding cases in which local control was not achieved, although there was no significant difference, and it is believed that the prognosis is poor. However, in order to make an accurate evaluation, further analysis is necessary, including the effect of other treatments, such as chemotherapy, and the local control period.

There are reports mentioning that the period from treatment of the primary tumor is related to the prognosis after the treatment of lung metastasis [13]. The correlation between cause specific survival and the period from primary lesion treatment to metastasis treatment was investigated with lung metastasis cases from lung cancer in our cases as the subject; however, there was no clear difference. Moreover, 7 of 49 cases underwent the treatment of lung metastasis at 5 years or more after the primary lesion treatment; however, patients in all cases are still alive except for 1 case that died from another disease, so this group had good prognosis. Naturally, it cannot be denied that some primary lung cancers are mixed in from a diagnosis of metastasis.

From the results of this study, it was shown that high local control may be obtained by CIRT with suppressing adverse reactions and that an effect comparable to surgical resection may be obtained regarding metastatic lesions of a certain size. It is believed that an opportunity for treatment may be provided for oligo-recurrence cases in which resection could not be carried out in the past due to reasons such as declined pulmonary function. Furthermore, arguments that adaption may be expanded to cases that were not adaptable to treatment for multiple metastases in the past may be expected because CIRT is a low invasive remedy; however, it is believed that this must be carefully decided upon for evaluating whether or not a long-term prognosis is achieved.

In this report, the presence of metastatic lesions other than the lung or the treatment outcome thereof was not investigated. Regarding this, the treatment course of, for example, affiliated lymph node metastasis and brain metastasis in the case of lung cancer, and local lymph node metastasis, liver metastasis, in the case of colorectal cancer, must be analyzed and investigated in detail depending on the primary organ.

5. Conclusions

We herein reported on the outcome of CIRT for metastatic lung tumors diagnosed as being oligo-recurrent. Lung cancer occupied the majority regarding the breakdown of cases, with lung metastasis of colorectal cancer occupying half of the remaining cases. Lesions other than these were metastases of multiple types of cancer.

This is a safe and effective local treatment for lung metastasis patients without adaptation to surgery. Particularly regarding small tumors, the same tumor control as surgical treatment may be expected.

Considering the fact that many patients without medical adaptation to surgery are being treated, it is believed that the treatment outcome is good. And this indicates that our criteria for selecting oligo-recurrent cases were appropriate.

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Review Article

Stereotactic Body Radiotherapy for Metachronous Multisite Oligo-Recurrence: A Long-Surviving Case with Sequential Oligo-Recurrence in Four Different Organs Treated Using Locally Radical Radiotherapy and a Review of the Literature

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Stereotactic body radiotherapy (SBRT) for oligometastases represents a recent trend in radiation oncology. While abundant data are available regarding the use of SBRT for the treatment of lung or liver oligometastases from various retrospective series and prospective trials, relatively little information has been accumulated for the treatment of oligometastases at sites other than the lungs and liver, particularly for sequential oligometastases in multiple organs. Oligometastases with primary lesions controlled is called "oligo-recurrence." We describe herein the case of a lung cancer patient who developed repeated oligo-recurrence at multiple sites that were each controlled by radical radiotherapy and achieved long-term survival and discuss the merits of locally aggressive radiotherapy for this type of disease condition with reviewing the literature. Although further investigation should be undertaken to clarify the benefits, objectives, and methods of SBRT for the treatment of oligometastases, we believe utilization of SBRT may be worthwhile for patients with remote metastases who hope for treatment to acquire better local control and possible longer survival.

1. Introduction

Interest has been increasing in the use of local therapy for metastases in recent years, likely due to improvements in systemic therapy [1–5]. In a selected population of oligometastatic patients, surgical metastasectomy may prolong survival and data in the literature support this observation. Survival benefits were being reported for complete resection of metastatic lung tumors even in the 1990s. The International Registry of Lung Metastases (IRLM) reported that 5-year overall survival for patients with complete resection of metastatic lung tumors was 36%, compared with 13% for patients without, suggesting complete removal or ablation of metastatic lesions as an important predictor of long-term survival [2].

Although surgical metastasectomy remains the most common of the local therapies, representing the first-line standard, nonsurgical alternatives such as thermal ablation and stereotactic body radiotherapy (SBRT) have become increasingly popular as options for patients who are not surgical candidates or who decline surgery. This is because these options are generally less invasive than surgery and have demonstrated considerable promise in eradicating macroscopic tumor. The main aim of SBRT is to acquire better local control of the tumor by providing a higher dose of irradiation to a specified area during a short period. SBRT was initially developed in Sweden and Japan [6, 7]. SBRT has been available for more than 10 years and is gaining clinical interest as a means of achieving local radical treatment of tumors in various organs, particularly for patients with stage

I non-small-cell lung cancer (NSCLC) [8–13], not only in medically inoperable patients, but also in operable patients [14].

SBRT for oligometastases represents a recent trend in radiation oncology [15–17]. Concerning the survival benefit of locally aggressive radiotherapy for oligometastases the largest experience has been accumulated for patients with brain metastases treated by stereotactic radiosurgery. In 2005, the American Society for Therapeutic Radiology and Oncology (ASTRO) systematically reviewed the evidence for the use of stereotactic radiosurgery in adult patients with brain metastases, and concluded that radiosurgery boost with whole-brain radiotherapy improved survival in patients with a single brain metastasis [18]. Niibe et al. also indicated that patients with oligometastases and no extrathoracic lesions could receive survival benefits from SBRT [19].

Milano et al. analyzed a subset of 121 patients treated with curative-intent SBRT for a limited number of extracranial metastases [16]. The results of their study showed that patients fared well with respect to survival and disease control with aggressive SBRT, even after local failure and/or the development of new metastases. While abundant data are available regarding the use of SBRT for the treatment of lung or liver oligometastases from various retrospective series [20, 21] and prospective trials [16, 22, 23], relatively little information has been accumulated for the treatment of oligometastases at sites other than the lungs and liver, particularly for sequential oligometastases in multiple organs.

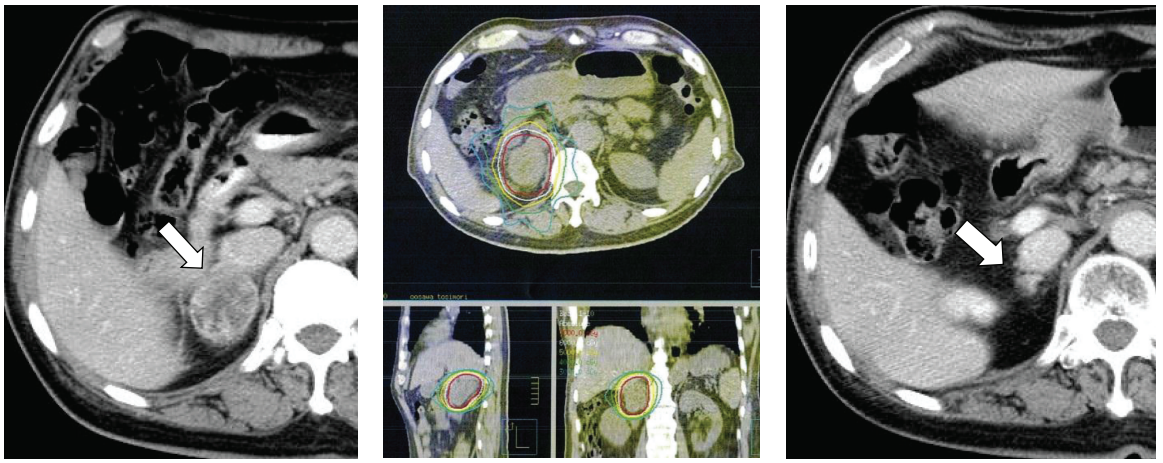
Oligometastases with primary lesions controlled is called "oligo-recurrence", that was first noted by Niibe et al. [24, 25]. We describe herein the case of a lung cancer patient who developed repeated oligo-recurrence at multiple sites that were each controlled by radical radiotherapy and achieved long-term survival, and discuss the merits of locally aggressive radiotherapy for this type of disease condition.

2. Clinical Case

Although SBRT in the strict definition generally includes large fraction size (generally not less than 5 Gy) and a short treatment-duration (generally within 3 weeks), we call the radiotherapy for the adrenal or abdominal lymph node metastases, that was done in a stereotactic manner but with 3 Gy in every fractions during over 3 weeks, "SBRT" in this case report.

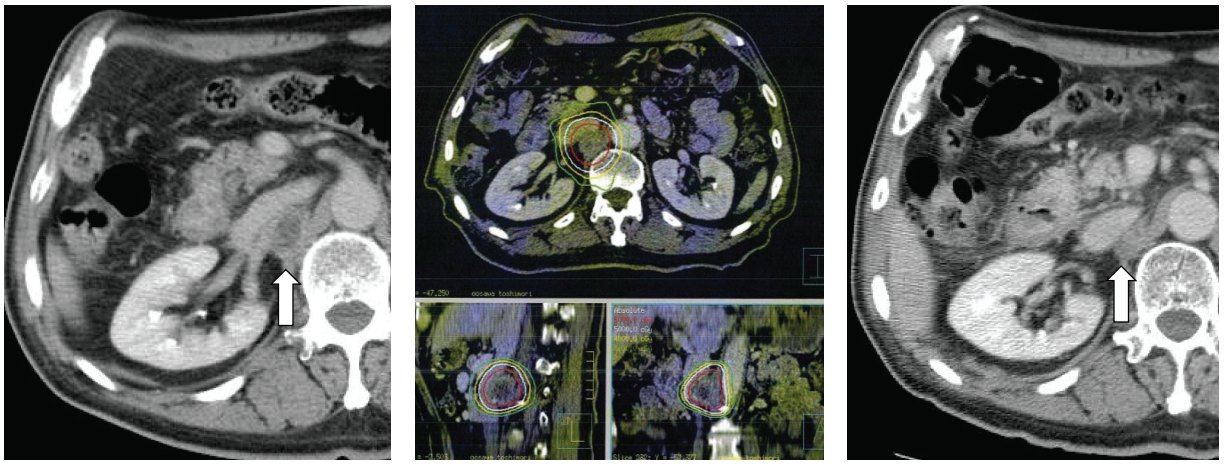
In October 2006, a 68-year-old Japanese man presented with T2N2M0 adenosquamous carcinoma in the right upper lobe of the lung. The patient underwent complete tumor resection with right upper lobectomy and mediastinal lymph nodes dissection. He had received adjuvant chemotherapy (four cycles of carboplatin; area under the curve (AUC) = 5 (1000 mg/body) on day 1 of a 21-day cycle) with weekly paclitaxel (1000 mg/m^2).

A right adrenal mass was found on routine computed tomography (CT) in March 2007 and was diagnosed as a solitary right adrenal metastasis by ^{18}F-fluoro-2 deoxy-D-glucose (FDG)-positron emission tomography (PET). Although the patient had taken tegafur-uracil (UFT) at 4.0 g/day for three months, the metastasis continued to enlarge (40 mm in diameter by June 2007; Figure 1(a)). The patient was therefore referred to our clinic for SBRT. Although other regimens of chemotherapy were considered, the patient wished to undergo SBRT as local intensive therapy. He showed a very positive and cheerful demeanor. During the SBRT planning sessions, the patient was trained in voluntary breath-holding during the inspiration phase using a respiratory indicator [26] to minimize the adrenal respiratory motions during irradiation [27]. Planning target volume (PTV) was determined as the gross tumor volume (GTV) of the right adrenal mass plus the personal internal margin, with an additional margin of 2 mm to compensate for intrasession reproducibility and to provide a safety margin. Precise reproducibility of tumor position in this patient under voluntary breath-holding was measured on repeated CT. Tumor position was adjusted to the planned position before every session using the CT on rails taken in the vicinity of the tumor. Ten different noncoplanar static beams were used for irradiation. The radiation port was made with dynamic sliding multileaves adjusted with 3 mm margins around the border of the PTV. Dose constraints of normal tissue were defined for the intestine and spinal cord. For the intestine, volumes with dose >52.5 Gy and >43.2 Gy in 10 fractions (biologically effective dose (BED) = 144.4 Gy and 105.0 Gy, resp., $\alpha/\beta = 3$ Gy) were restricted within 10 mL and 100 mL, respectively. For the spinal cord, maximum dose was restricted to <36 Gy in 10 fractions (BED = 79.2 Gy, $\alpha/\beta = 3$ Gy). These criteria represent a modification of the dose constraints provided in the protocol of the Japanese Clinical Oncology Group (JCOG)-0403 study, a prospective study of SBRT for stage I NSCLC. A total dose to the isocenter of 75 Gy in 25 fractions over 36 days was delivered using a 10-MV X-ray from June to July 2007. Isodose lines on CT are shown in Figure 1(b). The reason for the middle fraction size (3 Gy) was to avoid serious toxicity affecting the duodenum, because the second portion was included in the high-dose area. Administration of UFT was stopped before the start of the SBRT. After completion of SBRT, daily oral administration of tegafur-gimeracil-oteracil potassium (TS-1) was initiated at 80 mg/body. The patient complained of mild epigastralgia in December 2007, and grade 1 duodenitis was observed under fiberscopy. Symptoms improved with administration of oral antacids. In February 2008, the right adrenal tumor had decreased in size sufficiently to meet the criteria for partial response (PR; Figure 1(c)), but right para-aortic lymph node swelling (diameter, 30 mm; Figure 2(a)) was found on CT. This lesion was considered to represent a new metastasis of lung cancer. At this point of time, we informed the patient that he had systemic multiple metastases and that complete cure might be difficult. However, he was elected to undergo further local treatment and a second course of SBRT was therefore performed for this new lesion. The method of the SBRT was similar to that for the right adrenal metastasis. A total dose to the isocenter of 60 Gy shown in Figure 2(b) in 20 fractions over 28 days was delivered. A small overlap of treated volumes was produced between the first and second courses of SBRT, affecting the second portion of the duodenum, but dose constraints were not exceeded. No toxicities in relation to the second



(a) (b) (c)

Figure 1: (a) CT of right adrenal metastasis (arrow) before SBRT. (b) Dose distribution made with 10 noncoplanar beams for SBRT. Isodose lines show total doses (in 25 fraction) of 70 Gy, 60 Gy, 50 Gy, and 40 Gy, in 10 fractions, respectively, from the innermost area. The 30-Gy isodose line overlapped at the second portion of the duodenum with the 40-Gy isodose line of the SBRT for right adrenal metastasis, resulting in grade 2 duodenitis 1 month after SBRT. (c) CT at 6 months after SBRT, showing partial response of the lesion (arrow).



(a) (b) (c)

Figure 2: (a) CT of right para-aortic lymph node metastasis (arrow) before SBRT. (b) Dose distribution made with 10 noncoplanar beams for SBRT. Isodose lines show total doses (in 20 fractions) of 60 Gy, 50 Gy, 40 Gy, and 30 Gy, respectively, from the innermost area. (c) CT at 4 months after SBRT, showing partial response of the lesion (arrow).

course of SBRT were identified. Administration of TS-1 was stopped before the start of second SBRT and resumed after completion. In July 2008, the patient complained of acute hoarseness, and CT showed a new lymph node swelling in the left supraclavicular fossa (diameter, 25 mm; Figure 3(a)) and a left upper lung nodule (diameter, 20 mm; Figure 4(a)), although the right para-aortic lymph node lesion had decreased in size to represent PR (Figure 2(c)). Aspiration cytology was performed from the left supraclavicular fossa, revealing adenosquamous carcinoma cells. We considered that the condition of the patient at this time represented a more difficult stage and that the potential merits of local treatment were likely to be reduced. However, the patient again insisted on local radical treatment and we were persuaded by his eagerness. We first tried to control the left supraclavicular lesion. A total dose to the isocenter of 52.2 Gy in 29 fractions (shown in Figure 3(b); 1.8 Gy/fraction, twice a day, accelerated hyperfractionation) over 22 days was delivered to only the swollen left supraclavicular lymph node using conventional radiotherapy techniques. The reason why we did not use SBRT for the lesion was to avoid an adverse effect on the brachial plexus. Administration of TS-1 was continued during and after the sessions until February 2009. Hoarseness improved and FDG-PET-CT studies 1 month after this third course of radiotherapy showed marked reductions in size of the left supraclavicular lesion (Figure 3(c)) with no accumulation of FDG and no other abnormal accumulations. SBRT for left upper lobe metastases was then

performed in September 2008. SBRT for the left upper lung lesion was performed using a similar method to the previous right adrenal and para-aortic lesions, but the prescribed dose was 48 Gy in four fractions over 4 days to cover 95% of the PTV (Figure 4(b)). The tumor decreased in size to PR (Figure 4(c)) and has not progressed since. No other metastases have been identified since the completion of these four sessions of radiotherapy, including 3 courses of SBRT. Although fracture of the left rib within the PTV of the SBRT for the left lung metastases and idiopathic right pneumothorax occurred in March 2011 and August 2011, respectively, the patient has remained very well without cancer recurrence and has enjoyed hobby (dancing) cheerfully as recently as June 2012.

3. Discussion

Recent evidence suggests the presence of an oligometastatic state, where metastases are limited in both number and site. Weichselbaum and Hellman first proposed this concept of oligometastases as a state of "restricted tumor metastatic capacity" in 1995 [28], ushering in a paradigm shift in the strategy of cancer treatment.

Oligometastases has been hypothesized to represent a state of distant metastases in which local therapies, such as resection or radiation, may offer cure in some patients [29–31]. Locally curative treatment of oligometastases is regarded as an important resource for improving survival in a clinically significant subset of cancer patients [32, 33]. Local control of oligometastatic lesions may also slow or prevent further metastatic progression [34].

The maximum number of lesions that can be present to meet the definition of oligometastases has not been officially defined, but the number and organs affected by tumors is generally defined as ≤ 5 lesions in ≤ 2 organs. Salama et al. undertook a prospective study of SBRT for patients with metastases in 1–5 sites and reported 2-year progression-free and overall survival rates of 22.0% and 56.7%, respectively [22]. They concluded that patients with 1–5 metastases can be safely treated at multiple body sites and may benefit from SBRT. Aggressive treatment of such oligometastatic lesions can often be considered curative, because this treatment has been seen to prolong disease-free survival.

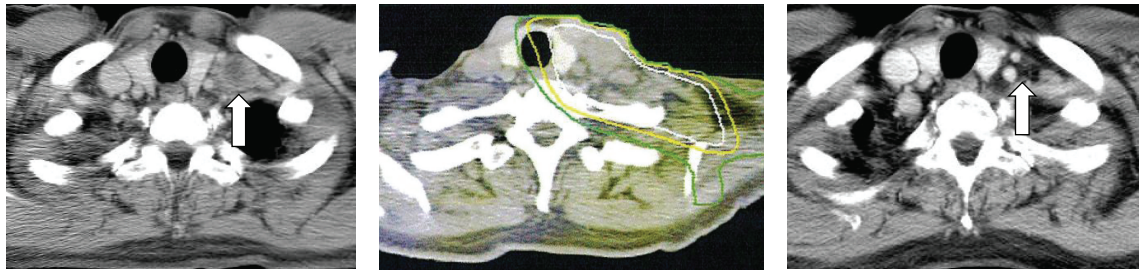
Several institutions have been actively using hypofractionated SBRT as a less-invasive locally curative treatment for oligometastases [32, 35, 36]. SBRT is mostly practiced for primary stage I NSCLC in Japan, followed by metastatic lung cancer, then metastatic liver cancer [37].

We will now provide an overview and discussion of SBRT for oligometastases in relation to the present case with adrenal, lymph node, and lung metastases.

Concerning SBRT for lung metastases, main reported outcomes are summarized in Table 1. The number of lung metastases of the enrolled patients distributed from 1 to 3 in most of the reports. Multiple retrospective [1, 5, 15, 20, 38, 39] and prospective [40–46] studies have shown promising local control (LC) with SBRT, with some investigations reporting LC rates of approximately 90%. Most studies have observed very low rates of serious toxicities. Norihisa et al. [38] reported that 43 metastatic lung tumors in 34 patients achieved a 2-year local control rate of 90% and a 2-year overall survival rate of 84.3% as a result of SBRT at 48–60 Gy in 4-5 fractions to the isocenter. Le et al. recently reported the results of a phase II trial using SBRT to a dose of 50 Gy in 10 fractions in the treatment of oligometastatic disease [41]. Lung metastases were treated in 41% and thoracic lymph nodes in 20% of patients. The 2-year local control rate for all treated lesions was 67%. Similarly, investigators from Heidelberg treated 61 patients with 71 lung metastases using single-fraction SBRT to an isocenter dose of 12–30 Gy and reported an actuarial local control rate of 74% at 2 years [43]. Hoyer et al. completed a phase II trial of SBRT to a dose of 45 Gy in 3 fractions for treatment of colorectal metastases, primarily involving the lung and liver. The actuarial 2-year local control rate in that series was 86% [44]. Rusthoven et al. reported a phase I/II prospective study of SBRT for metastatic lung tumors. Thirty-eight patients with 63 lesions treated with SBRT achieved a 2-year local control rate of 96%, but a 2-year overall survival of only 39% [46]. One of the important reasons behind this poor prognosis with SBRT though the good local control similar to rates reported using 60–66 Gy in 3 fractions for primary NSCLC [47] might be that the prospective study included patients with extrapulmonary lesions. McCammon et al. also reported excellent local control rates with a nominal dose of ≥ 54 Gy and suggested a dose-control relationship within the range of SBRT doses applied [48]. These results suggest that the higher, more intense dose of SBRT used in the current series likely contributed to the higher rate of local control rate observed, although patient selection bias is always a potential confounder in comparisons across studies.

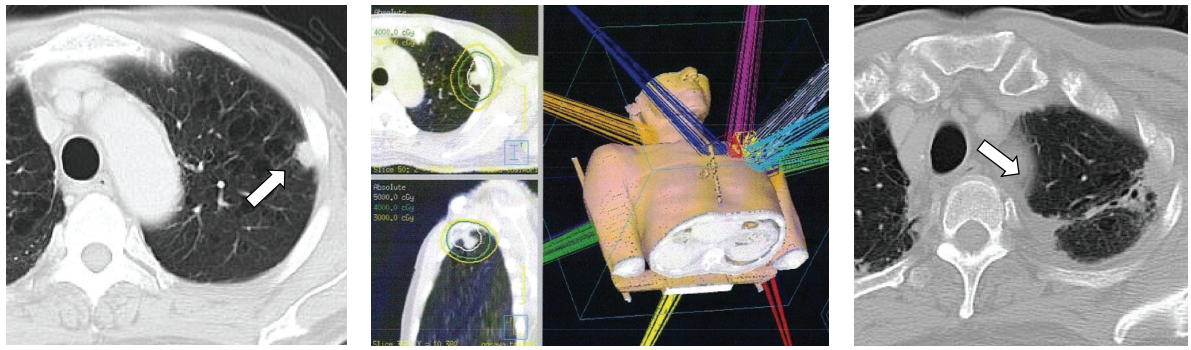
In contrast to SBRT for most lung or liver metastases, careful attention must be paid to the dose and fractions for areas of intestine surrounding the tumor such as the present case. In the presented case, although we referred to the dose constraints provided in the protocol of the JCOG-0403 study and fortunately the patient had not suffer severe bowel toxicity, the dose constraint for intestines may be rather high from a viewpoint of conventional radiotherapy because the intestine is a serial organ, volume effect would not be large, and the maximum dose or near maximum dose would be the major concern. The author have experienced a serious gastric ulcer event occurring after SBRT (60 Gy in 10 fractions) delivered with concomitant vinorelbine in a patient with left adrenal metastasis of lung cancer [49]. The true dose constraint for intestines in the hypofractionated radiotherapy should be more investigated hereafter. Recently, the benefits of dose concentration by Cyberknife to avoid normal tissues receiving high doses have been reported in SBRT for tumors located close to the bowel or esophagus [50–54].

Concerning adrenal metastases, they are increasingly being detected incidentally during followup or at the time of initial presentation with continuing progress in imaging techniques. A relevant meta-analysis reported improved survival after adrenalectomy in patients affected by adrenal metastases from lung cancer, achieving durable long-term



(a) (b) (c)

Figure 3: (a) CT of left supraclavicular lymph node metastases (arrow) before SBRT. (b) Dose distribution made with 4 coplanar beams for conventional radiotherapy. Isodose lines shows total doses (in 29 fracions) of 50 Gy, 40 Gy, and 30 Gy, respectively, from innermost area. (c) CT at 1 months after the RT, showing complete response of the lesion (arrow).



(a) (b) (c)

Figure 4: (a) CT of the left lung metastasis (arrow) before SBRT. (b) Dose distribution made with 10 noncoplanar beams for SBRT. The isodose lines shows total doses (in 4 fractions) of 50 Gy, 40 Gy, and 30 Gy, respectively, from innermost area. (c) CT at 2 years after SBRT, showing partial response of the lesion (arrow) with focal radiation fibrosis.

survival in approximately 25% of cases [55]. Although SBRT is commonly accepted as a safe and fairly effective treatment for controlling small cancer lesions, SBRT for the adrenal gland has been described in only a few studies summarized in Table 2 [56–59]. Chawla et al. [56] and Casamassima et al. [57] showed that adrenal SBRT may be considered a radical therapy not influenced by parameters such as primary tumor, synchronous or metachronous status, uni- or bilateral lesions, oligometastatic disease, or target volume. Oshiro et al. suggested that radiotherapy may contribute to the survival of patients with adrenal metastasis from lung cancer [58]. Milano et al. analyzed a subset of 121 patients treated with curative-intent SBRT for limited metastases and emphasized the advantages of SBRT versus surgery for the treatment of adrenal metastases, such as low incidence of side effects, good tolerability, and the noninvasive nature of treatment, allowing application in elderly or medically inoperable patients [60]. Although surgery resulted in appreciably better survival, this might, in part, have resulted from patient selection, such as patients with less bulky adrenal metastases and/or without additional metastases to other organs. The poor outcomes of patients with adrenal metastases treated using curative-intent SBRT compared with outcomes for patients without adrenal metastases [43] suggest that perhaps metastases to the adrenal glands are associated with a greater risk of occult metastatic disease, and such patients are thus less likely to benefit from curative-intent therapy.

Concerning SBRT for oligometastases to lymph nodes, conventional fractionated nonstereotactic radiotherapy is generally believed to attain poorer results, because doses are limited by normal tissue tolerance. Although several articles have dealt with conventional radiotherapy for isolated para-aortic lymph node recurrences from cervical cancer, most have reported only survival rates [25, 61–63]. Progressive disease after conventional radiotherapy in the para-aortic lymph node-treated area was reported to be 33, 50% in two studies [64, 65]. Whereas most patients with metastases to abdominal nodes are unfit for surgery, SBRT is known to lead to high local control rates up to 90% [32], which may in turn allow increased survival and better quality of life. SBRT for metastases to abdominal lymph nodes has rarely been reported, with only a few articles reporting on this as a specific topic [50–52] summarized in Table 3 and with most only including a few cases in a mixed series [45, 53, 54, 66, 67]. One of the reasons why SBRT or any form of high-dose radiation is not used for this population is the size of radiation field which is generally large and usually located closely to intestine or other critical organs. The better survival of patients who could receive SBRT for abdominal lymph node shown in Table 3 could attribute

Table 1: Studies of stereotactic body radiotherapy for pulmonary oligometastases.

Authors	Study design	Number of patients	Number of metastases in each patient	Primary organ	Dose/fractionation	Followup (months)	Outcomes	Toxicity
Okunieff et al. [20]	Retrospective	42	1 to 5	NA	50 Gy/5 fr (isocenter)	4–61 (median 15)	Crude LC: 94% MS: 23.4 months	Grade 3 (pleural effusion): 1
Kavanagh et al. [36]	Retrospective	34	1 or 2	Lung 15, Colorectal: 9 Others 10	48–60 Gy/4-5 fr (isocenter)	10–80 (median, 27)	2-year LC: 90% 2-year OS: 84.3%	Grade 3 pneumonitis: 3
Nagata et al. [37]	Retrospective	84	1 to 3	Lung 32, Colorectal 11, Kidney 7, others 34	26–48 Gy/1–8 fr (covering PTV)	14–80 (median, 17)	3-year LC: 82% 3-year OS: 16%	NA
Norihisa et al. [38]	Prospective	41	1 or 2	Lung 5, Breast 4, Kidney 4, Others 14	26–37.5 Gy/1–3 fr	2–37 (median, 9)	2-year LC: 80% 2-year OS: 33%	No grade 3, 4
Ernst-Stecken et al. [42]	Prospective	61	1 or 2	Lung 31, Colorectal 8, Others 22	12–30 Gy/fr (isocenter)	2–82 (median, 14)	2-year LC: 74% 2-year OS: 65%	Grade 3 pneumonitis: 3%
Hof et al. [44]	Prospective	38	1 to 3	Colorectal 9, Sarcoma 7, Kidney 7, others 15	48–60 Gy/3 fr (covering PTV)	6–48 (median, 16)	2-year LC: 96% MS: 19 months	Grade 3 pneumonitis: 4 Grade 3 chest wall: 2

Abbreviations: NA: not available; LC: local control rate; OS: overall survival rate; LPFS: locally progression-free survival rate.

Table 2: Reports of stereotactic body radiotherapy for adrenal oligometastases.

Authors	Study design	Number of patients	Primary organ	Dose/fractionation	Followup (months)	Outcomes	Toxicity
Nuyttens et al. [54]	Retrospective	30	Lung 20, others 10	16–50 Gy/4–10 fr (isocenter)	1–35	1-year LC: 44% 1-year OS: 55%	No grade > or =2
Tanvetyanon et al. [55]	Retrospective	48	Lung 24, Colorectal 12, others 12	36 Gy/3 fr (covering PTV)	3–63 (median, 17)	2-year LC: 90%	Adrenal deficiency: 1
Chawla et al. [56]	Retrospective	7	Lung 19	30–60 Gy/1–27 fr	NA	2-year OS: 33%	NA
Casamassima et al. [57]	Retrospective	19	Lung 4, others 3	16–27 Gy/1–3 fr (covering PTV)	1–60 (median, 38)	1-year LC: 63% MS: 8 months	NA

Abbreviations: LC: local control rate; OS: overall survival rate; NA: not available; MS: median survival time.

only to the selection bias that the area and volume of the lymph node metastases might be small. Although no definitive reports have described radical radiotherapy for left supraclavicular ("Virchow") lymph node oligometastases, because it is generally considered that it means a high signal of systemic metastases difficult to survive for the patient. Accordingly, the long survival of the present case in spite of the left supraclavicular lymph node metastases appears to offer important suggestions.

3.1. Oligo- but Multisite Metastases: What Is the Rationale for SBRT? Concerning the relationship between prognosis and primary organ or metastatic site, Milano et al. reported the results of a prospective study with curative-intent SBRT in 121 patients with ≤5 oligometastatic lesions from various primary organs [43]. In the results of that study, patients with primary breast cancer achieved significantly greater local control, progression-free survival, and overall survival rates than those with lung, pancreatic, biliary, or hepatic cancer. They also reported that patients who had adrenal metastases displayed significantly worse prognosis, and patients with lesions confined solely to bone exhibited better survival rates than patients who had other metastatic lesions [23]. Concerning the number of metastases, prognosis is generally regarded as poorer with increasing numbers. However, Milano et al. reported neither the numbers of organs involved nor the numbers of oligometastatic lesions which were significantly associated with measured outcomes, though greater net gross tumor volume (GTV), defined as the sum of GTVs from all treated tumors, was significantly correlated with worse local control [43]. Conversely, Salama et al. reported that the 2-year overall survival rate was better for patients with 1–3 metastases (60.3%) than for patients with 4-5 metastases (21.9%) in a prospective study of SBRT for patients with 1–5 metastatic cancer sites [22].

We do not necessarily recommend aggressive local treatments for patients with repeated oligo-recurrence in multiple organs including adrenal and left supraclavicular lymph node metastases, as in the present case. Actually, poor prognosis was foreseen in the present case because the patient showed four multiple metastases one after another at different sites with short intervals of <1 year. Some investigators have found a disease-free interval of ≥6–12 months as a prognostic factor for improved survival in patients with oligo-recurrent disease [55, 68, 69]. Milano et al. reported an analysis of 32 patients with repeated oligometastases who underwent ≥2 courses of SBRT with curative intent in 121 prospective patients with ≤5 lesions treated using SBRT [60]. In their results, the interval between first and second course of SBRT for new oligometastases was 1–71 months (median, 8 months). The 2-year overall survival and progression-free survival rates for these 32 patients were 65% and 54%, respectively, and patients experienced a trend toward improved overall survival (median, 32 versus 21 months, $P = 0.13$) compared with the other 89 patients who underwent only one SBRT course. The authors concluded that the results have shown that patients fare well with respect to survival and disease control with repeated aggressive SBRT for limited metastases, even after local failure and/or the development of new metastases.

Improvement of systemic chemotherapies, including molecular-targeted therapies, may allow micrometastases to be almost completely absent clinically. Punglia et al. reported that if systemic therapy improves, the role of local therapy would also improve and proposed a figure for this correlation [70]. Rather than eliminating the need for local therapies, improvements in systemic therapies appear to be increasing the prudent utilization of modern local therapies in patients presenting with more advanced cancer [71]. To be sure, in the present case, sequential but systemic oligometastases were fully controlled using radical radiotherapy combined with systemic chemotherapy.

The present patient has been alive and well now without disease. This patient history is beyond our expectation, in a good sense. We attributed the surprising survival from systemic disease in this case to the metastases occurring separately without primary site recurrence (oligo-recurrence state), and cancer cells that were sensitive to not only radiotherapy, but also chemotherapy. Good radio- and chemosensitivities were assumed through the response of the left supraclavicular lymph node metastasis to conventional radiotherapy. We also believe the positive and tolerant attitude of the patient might have contributed to the good prognosis in this case.

As the merit of SBRT should be achieved without severe acute or late toxicity, the lower fraction dose in the less

Table 3: Reports of stereotactic body radiotherapy for isolated abdominal lymph node metastases.

Authors	Study design	Number of patients	Primary organ	Dose/fractionation	Followup (months)	Outcomes	Toxicity
McCammon et al. [48]	Retrospective	30	Uterine cervix: 28 Uterine corpus: 2	30–45 Gy/3 fr (covering PTV) (+EBRT 27–45 Gy)	2–65 (median; 16)	4-year OS: 50.1% 4-year LC: 67.4	No severe complication on intestine
Onishi et al. [49]	Retrospective	7	Stomach: 7	45–51 Gy/3 fr (covering PTV)	19–33 (median: 26)	CR: 5/7, PR: 2/7 3-year OS, PFS: 43%, 29%	No severe complication
Choi et al. [50]	Retrospective	7	Colorectal: 7	36–51 Gy/3 fr (covering PTV)	15–70 (median; 26)	1-, 3-year OS: 100%, 71.4% MS: 37 months,	Grade 4 intestine: 1

Abbreviations: LC: local control rate; MS: median survival time; OS: overall survival rate; CR: complete remission; PR: partial remission; PFS: progression free survival.

hypofractionated schedule, such as in the present case, should be considered for targets near the intestine. In addition, advanced technologies such as volumetric intensity-modulated arc therapy, as well as CT image guidance, will prove highly useful for the purpose of keeping toxicity to a minimum without compromising target dose.

Whether the addition of SBRT can contribute to improved prognosis in patients with repeated metastases remains controversial. The only randomized trials showing improved overall survival with stereotactic irradiation have been in the setting of brain metastases [72]. Ongoing studies are testing the role of SBRT with concurrent systemic therapy in the initial management of patients with limited metastatic NSCLC (NCT00887315) [73].

4. Conclusion

A case of a patient with repeated postoperative oligo-recurrence of lung adenosquamous carcinoma to multiple organs who survived long-term following treatment with local radiotherapy and systemic chemotherapy was presented. He developed and was salvaged from multiple metastases one after another at different sites, comprising the adrenal, para-aortic and left supraclavicular lymph nodes, and lung.

Findings in the literature suggest the presence of an oligometastatic state, and local aggressive therapy for oligometastases may improve outcomes, including survival. SBRT has emerged as one option for local therapy against oligometastases in various body sites, most commonly in the lungs and liver. Retrospective studies and clinical trials have demonstrated promising results with the use of SBRT for oligometastases.

However, most reports describing the merits of localized therapies have been based on the results of effects on oligometastases within a single organ. In addition, most studies have relatively included only short follow-up intervals. Longer followup is necessary to better define the role of SBRT in the management of patients with oligometastases. Although further investigation should be undertaken to clarify the benefits, objectives, and methods of SBRT for the treatment of oligometastases, we believe utilization of SBRT would be worthwhile for patients with remote metastases who hope for treatment to acquire better local control and possible longer survival. Even if the disease condition is a little beyond the general definition of oligometastases, as in the present case, SBRT may be beneficial, at least certainly in giving patients courage.

Conflict of Interests

The authors have no conflict of interests of any kind to declare.

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Review Article

Lung Radiofrequency Ablation: Potential as a Therapy to Oligometastasis and Oligo-Recurrence

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The early results (e.g., patient survival) of RFA for the treatment of patients with NSCLC and pulmonary metastasis from various primary lesions including colorectal cancer, lung cancer, hepatocellular carcinoma, renal cell carcinoma, and sarcoma appear encouraging and suggest the potential to offer long-term survival for the patients with oligo-recurrence or oligometastasis of lung cancer. The usefulness of RFA for oligo-recurrence or oligometastasis of lung cancer should be clarified by prospective studies in the future.

1. Introduction

Primary lung cancer is the most common malignancy and the leading cause of death from cancer worldwide. In addition, the lungs are the second most frequent site of metastasis from extrathoracic cancers and the only site of metastasis in 20% of such cases. Surgical resection is the first-line treatment for nonsmall-cell lung cancers (NSCLC) and offers the best treatment opportunity. Surgery is also accepted as a treatment option for carefully selected patients with metastatic lung cancer. However, surgical resection is not suitable for many patients mainly because of the advanced stage of cancer, compromised lung function, and/or comorbidities. Although chemotherapy, radiation therapy, or a combination of these serves as alternative treatments for such patients, complete remission of the disease is rarely achieved. Therefore, research that focused on alternative therapies for lung cancer has been extensive in the past decades; such therapies include stereotactic radiation therapy, cryoablation, laser ablation, and radiofrequency (RFA).

RFA causes focal coagulation necrosis of tissue by delivery of energy in the form of an alternating electrical current with a frequency of 460 to 500 kHz in the range of radio waves. The location of the ablative effect is determined by the precise placement of the radiofrequency electrode, usually using imaging guidance. The radiofrequency electrical current is concentrated near the noninsulated tip of the electrode, and the circuit is completed by returning either to electrical grounding pads usually located on the patient's thighs. The alternating electrical current causes ionic dipolar molecules in surrounding tissue and fluids to agitate, resulting in frictional heating that is greatest adjacent to the noninsulated portion of the electrode. The heat energy is then distributed radially to surrounding tissues. When radiofrequency current is applied in a slow, controlled fashion, the tissue heating is local, typically ellipsoid in shape, and predictable in distribution.

At first, RFA was noted as a therapy for hepatocellular carcinoma. The favorable outcomes of the RFA in the liver have encouraged the application of this technique to cancer in other organs. In 2000, Dupuy et al. [1] firstly reported clinical application of this technique in the lung. Since then, RFA has been gaining popularity rapidly as a treatment of lung cancer. RFA of lung cancer is usually performed under CT-guidance and the techniques are quite simple and similar to those used for CT-guided lung biopsy. Herein, we review clinical outcomes of RFA of lung cancer and discuss the potential to be used as a therapy to oligometastasis and oligo-recurrence.

2. Rationale for RFA of Oligometastasis and Oligo-Recurrence

Oligometastasis and oligo-recurrence, proposed by Niibe and Hayakawa [2], are the condition of one or a few metastatic or recurrent lesions without and with controlled primary tumor, respectively. Although significance of local therapy of metastatic lesions for survival benefit may be controversial, the International Registry of Lung Metastases (IRLM) [3] reported that 5-year overall survival for patients with complete resection of metastatic lung tumors was 36%, compared with 13% for patients without it. Further, for the patient for whom lung metastases were completely resected, survival depended on tumor number; that is, smaller number of metastases indicated better survival. Such data may suggest the rationale for applying local therapy including RFA for oligometastasis and oligo-recurrence. The registry also reported that the patients with disease-free intervals of 36 months or more had better prognosis. Thus, the patients with slow growing tumors are more appropriate candidates for RFA.

3. RFA of Primary Lung Cancer

There have been several studies on RFA in the management of primary lung cancers. In 2007, Simon et al. [4] reviewed 75 cases of previously untreated stage I NSCLC, resulting in overall survival of 78%, 57%, and 27% at 1, 2, and 5 years, respectively. Those results seemed to compare favorably with previous studies using external beam radiotherapy in similar stage tumors. Survival was significantly associated with tumor size, with approximately 50% of 5-year survival for the patients with tumors <3 cm. Further encouraging results were reported in a prospective multicenter study by Lencioni and coworkers [5]. Their study included 33 patients with NSCLC treated with RFA; of those, 13 patients had medically inoperable stage I NSCLC. The overall survival in patients with NSCLC was 70% and 48% at 1 and 2 years, respectively, with cancer-specific survival of 92% and 73% at 1 and 2 years. Subgroup analysis revealed 2-year overall survival of 75% and 2-year cancer-specific survival of 92% in patients with inoperable stage I NSCLC. Hiraki et al. [6] reported the outcomes of 27 patients with stage I NSCLC who were treated with RFA. During median follow-up period of 22 months, the mean survival time was 42 months. The overall survival and cancer-specific survival rates were 90% and 100% at 1 year, 84% and 93% at 2 years, and 74% and 83% at 3 years, respectively. Most recently, Hiraki et al. [7] have updated their data using 50 patients with stage I NSCLC. During median follow-up period of 37 months, a median survival time was 67 months, the overall, cancer-specific and disease-free survivals were 94%, 100%, and 82% at 1 year, 86%, 93%, and 64% at 2 years, and 74%, 80%, and 53% at 3 years, respectively. Despite favorable survival data, local progression was observed in 16 (31%) of the 52 tumors. Lanuti et al. [8] reported that during a median follow-up of 17 months, median survival time was 30 months for 31 patients; survaial rate was 85% at 1 year, 78% at 2 years, and 47% at 3 years; local progression rate was 32%. Pennathur et al. [9] reported that during a mean follow-up of 29 months, survival rate for 19 patients was 95% at 1 year, and 68% at 2 years; local progression rate was 42%.

With regard to oligo-recurrence of NSCLC, Kodama et al. [10] carried out an interesting study. Their study included 44 patients who underwent lung RFA for recurrent NSCLC after surgery. Forty-three patients had no extrapulmonary metastasis; one patient had liver and splenic metastasis, which was also treated with RFA. Single or multiple intrapulmonary recurrences were ablated. During mean follow-up period of 29 months, the overall survival rates were 98% at 1 year, 73% at 2 years, and 56% at 3 years. The recurrence-free survival rates were 77% at 1 year and 41% at 3 years. Tumor size and sex were independent significant predictors in the multivariate analysis. This study indicated that RFA may offer a chance of long-term survival for the patients with oligo-recurrence of primary lung cancer.

4. RFA of Metastatic Lung Cancer

4.1. Metastasis from Colorectal Cancer. The cancer that most frequently metastasizes to the lung is colorectal cancer. Approximately 10% of the patients who undergo curative resection for colorectal cancer develop lung metastases [11]. Standard treatment options include surgical resection and chemotherapy. Many surgeons believe that surgical resection is the best treatment that offers the potential for long-term survival in selected patients. Several large studies on pulmonary metastasectomy have demonstrated similar survival after surgery, with approximately 40% of the 5-year survival rate. Further, systematic review of 1684 patients by Pfannschmidt et al. [12] showed 48% of 5-year survival. However, patients with pulmonary metastases are often nonsurgical candidates because of other coexistent metastases, poor cardiopulmonary function, or refusal to undergo surgery. A recent chemotherapy regimen using fluorouracil and leucovorin with irinotecan or oxaliplatin has been shown to prolong survival, but the long-term results are still less than satisfactory, with a median survival of 14.8–21.5 months for the patients with metastatic colorectal cancer [13].

The prospective multicenter study by Lencioni et al. [5] showed that overall survival rate was 89% at 1 year and 66% at 2 years in patients with colorectal metastases; cancer-specific survival was 91% at 1 year and 68% at 2 years. Hiraki et al. [14] also assessed survival rates for 27 patients with pulmonary metastases from colorectal cancer. During the median follow-up period of 20.1 months after RFA, the overall survival rates were 96% at 1 year, 54% at 2 years, and 48% at 3 years. The most significant prognostic factor was the presence of extrapulmonary metastasis at the time of RFA. While patients with extrapulmonary metastasis never survived for 2 years, survival rates for patients without extrapulmonary metastasis were favorable, indicating 100% at 1 year, 76% at 2 years, and 68% at 3 years. These results showed the potential of long-term survival of the patients with oligo-recurrence from colorectal cancer with RFA. Yamakado et al. [15] reported the outcomes of a retrospective multicenter study on RFA for pulmonary metastases from colorectal cancer. The estimated 3-year survival rate was

46% for all patients. Extrapulmonary metastasis, tumor size, and the carcinoembryonic antigen level were significant prognostic factors in the univariate analysis. The first two factors were significantly independent prognostic factors in the multivariate analysis. Thirty-six patients with small lung metastases (< or =3 cm) and no extrapulmonary metastases had a 3-year survival rate of 78%. Yamakado et al. [16] also reported single center experiences of RFA for pulmonary metastases from colorectal cancer. For 78 patients, the 1-, 3-, and 5-year survival rates were 84%, 56%, and 35%, respectively, during a mean follow-up period of 25 months. The median survival time was 38.0 months. Univariate analysis revealed maximum tumor diameter of 3 cm or less, single-lung metastasis, lack of extrapulmonary metastasis, and normal carcinoembryonic antigen (CEA) level as better prognostic factors. The latter two were significant independent prognostic factors. The 1-, 3-, and 5-year survival rates were 97.7% (95% CI, 93.3–100%), 82.5% (95% CI, 68.2–96.8%), and 57.0% (95% CI, 34.7–79.2%) in 54 patients with no extrapulmonary metastases and 96.9% (95% CI, 90.8–100%), 86.1% (95% CI, 71.1–100%), and 62.5% (95% CI, 36.3–88.6%) in 33 patients with negative CEA levels. More recently, Chua et al. [17] reported promising long-term outcome obtained by a prospective trial of 108 patients with pulmonary metastases from colorectal cancer. The median survival reached 60 months, which appeared equivalent to data obtained by metastasectomy.

4.2. Metastasis from Hepatocellular Carcinoma. Hiraki et al. [18] performed a retrospective multicenter study on RFA for pulmonary metastases from hepatocellular carcinoma HCC. This study included 32 patients who had no intrahepatic recurrence or had treatable intrahepatic recurrence, who had no other metastases, and for whom RFA was performed with curative intent (i.e., not palliatively). The overall survival rates were 87% at 1 year and 57% at 2 and 3 years during a median follow-up period of 20.5 months. Median and mean survival times were 37.7 months and 43.2 months, respectively. Significantly better survival rates were obtained for patients with an absence of viable intrahepatic recurrence, Child-Pugh grade A, absence of liver cirrhosis, absence of hepatic C virus infection, and α-fetoprotein level of 10 ng/mL or lower at the time of RFA. These results seem to suggest that pulmonary metastasis from HCC is suitable candidates for RFA, if primary cancer is well controlled (i.e., oligo-recurrence).

4.3. Metastasis from Renal Cell Carcinoma. In cases of pulmonary metastases from renal cell carcinoma, patient survival was evaluated using data from 2 institutions [19]. This study included 39 nonsurgical candidates who were divided into 2 groups: a curative ablation group, which was formed by 15 patients with 6 or fewer lung metastases measuring ≤6 cm that were confined to the lung and who had all lung tumors ablated, and the palliative ablation group, which included 24 patients with extrapulmonary lesions, 7 or more lung tumors, or large tumors of >6 cm, and who had mass reduction. The overall survival rates in the curative and palliative ablation groups were 100% and 90% at 1 year, 100% and 52% at 3 years, and 100% and 52% at 5 years, respectively. The maximum lung tumor diameter was a significant prognostic factor.

4.4. Metastasis from Sarcoma. Palussière et al. [20] reported the outcomes of RFA for pulmonary metastases from various kinds of sarcoma. This study included 29 patients with a maximum of 5 lung metastases and without extrapulmonary metastasis (i.e., oligo-recurrence). During median follow-up period of 50 months, the 1- and 3-year survival rates were 92.2% and 65.2%, respectively. Median disease-free survival was 7 months. This study suggests that RFA may offer a chance for long-term survival for patients with oligo-recurrence from sarcoma, although the disease may recur in a relatively short-term followup.

Nakamura et al. [21] reported on RFA for 20 patients with pulmonary metastases from musculoskeletal sarcomas. During the mean follow-up period of 18 months (range, 7 months to 54 months), 9 of 20 patients died of lung tumor progression. The 1- and 3-year survival rates from RF ablation were 58% and 29% with a median survival time of 12.9 months in all patients. Survival rate for 14 patients with controlled primary tumor (33% at year) was not significantly different from that for 6 patients without controlled primary tumor (52% at 1 year). Survival rate for 10 patients with ≤5 lung metastases (38% at year) was not significantly different from that for 10 patients with >5 lung metastases (88% at 1 year). Thus, survival did not seem to depend on whether oligo-recurrence or not in the population that they studied.

5. Advantages and Limitations of RFA

Major limitation of RFA may be limited local efficacy. RFA induces various complications. Food and Drug Administration in the United States made a public announcement regarding deaths following RFA of lung tumors in 2007. Rare but serious complications may occur including bronchopleural fistula [22], pulmonary artery pseudoaneurysm [23], systemic air embolism [24], injury of the brachial nerve and the phrenic nerve [25, 26], pneumonia [27], and needle-tract seeding of cancer [28]. A case of fatal acute deterioration of interstitial pneumonia after RFA has been also reported [29]. Survey is required to recognize an incidence of acute deterioration after RFA in the patients with interstitial pneumonia and thereby to determine a role of RFA in such patients.

Notable advantages of RFA include limited influence on pulmonary function. According to a report by Ambrogi et al. [30], the mean forced vital capacity (VC) was 2.63 and 2.80 L at 1 and 3 months, respectively, compared with 2.91 L before RFA; the mean forced expiratory volume in 1 s (FEV(1)) was 1.71 and 1.86 L at 1 and 3 months, respectively, compared with 1.97 L before RFA. The multicenter prospective study by Lencioni et al. [5] also showed mean forced VC and FEV1 of 2.6 and 1.7 L, respectively, at 1 month, compared with 2.9 and 1.9 L, respectively, before RFA in 22 patients with non-small cell lung cancer. Tada et al. [31] reported that the mean VC and FEV(1) before RFA and 1 and 3 months after RFA were 3.04 and 2.24 L, 2.79 and 2.11 L, and 2.85 and 2.13 L,

respectively. De Baère et al. [32] reported that pulmonary function did not decrease after RFA; the mean VC and FEV1 were 2.9 and 2.2 L, respectively, after RFA, compared with 2.9 and 2.2 L, respectively, before RFA.

The freedom to perform the procedure regardless of any previous therapy is another important advantage. Adhesion after pulmonary surgery or radiation-induced pneumonitis is not an obstacle for performing the procedure. Thus, the procedure may be used as a salvage treatment for oligo-recurrence after surgery and radiation therapy. At the same time, RFA procedure is not an obstacle for performing concurrent or adjuvant chemotherapy or adjuvant radiation therapy. According to the Norton-Simon hypothesis [33], the effectiveness of chemotherapy agents is proportional to the growth rate of the tumor and the fastest tumor growth rates occur when tumors are not bulky. Therefore, if RFA can downsize the primary tumor, the remaining tumor cells may become more sensitive to chemotherapy. The combination with such therapeutic modalities is expected to increase the efficacy of RFA not only through an additive effect but also due to synergistic effects [34]. The availability to repeat procedures whenever required is also an important advantage. Although RFA results in relatively high rate of local failure, local failure may be salvaged by repetition of the procedure [35].

6. Conclusions

In conclusion, the early results of RFA for the treatment of patients with NSCLC and pulmonary metastasis from various primary cancers appear encouraging and suggest the potential to offer long-term survival for the patients with oligo-recurrence or oligometastasis of lung cancer. The usefulness of RFA for oligo-recurrence or oligometastasis of lung cancer should be clarified by prospective studies in the future.

Abbreviation

RFA: Radiofrequency ablation.

Conflict of Interests

The authors have no conflict of interests.

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Review Article

A Call for the Aggressive Treatment of Oligometastatic and Oligo-Recurrent Non-Small Cell Lung Cancer

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Metastatic non-small cell lung cancer (NSCLC) carries a dismal prognosis. Clinical evidence suggests the existence of an intermediate, or oligometastatic, state when metastases are limited in number and/or location. In addition, following initial curative therapy, many patients present with limited metastatic disease, or oligo-recurrence. Metastasis-directed, anti-cancer therapies may benefit these patients. A growing evidence-base supports the use of hypofractionated, image-guided radiotherapy (HIGRT) for a variety of malignant conditions including inoperable stage I NSCLC and many metastatic sites. When surgical resection is not possible, HIGRT offers an effective alternative for local treatment of limited metastatic disease. Early studies have produced promising results when HIGRT was delivered to all known sites of disease in patients with oligometastatic/oligo-recurrent NSCLC. In a population of patients formerly considered rapidly terminal, these studies report five year overall survival rates of 13–22%. HIGRT for metastatic NSCLC warrants further study. We call for large, intergroup, and even international randomized trials incorporating HIGRT and other metastasis-directed therapies into the treatment of patients with oligometastatic/oligo-recurrent NSCLC.

1. Introduction

Lung cancer is the most lethal malignant tumor. Affecting over one million people each year, it results in approximately 951,000 deaths [1]. Eighty-five percent of lung cancer patients have non-small cell lung cancer (NSCLC), and about 40% of those will present with distant metastatic disease [2]. The current standard therapy for most metastatic NSCLC patients is doublet chemotherapy. Contemporary regimens, such as cisplatin and docetaxel, demonstrate superior outcomes compared to regimens of the last decade [3, 4]. Even with the most effective cytotoxic agents only 30% of patients respond to therapy and the median survival from diagnosis is approximately 1 year [5–7]. Worse still, the response to second line therapy is poor (7–11%) with a median survival of 8 months at best [8, 9]. Herein, we call for the systematic study of new approaches and integration of all available therapeutic modalities in the management of this humbling disease.

2. Oligometastases and Oligo-Recurrence

It has been proposed that the natural history of metastatic spread may proceed stepwise, and there exists an oligometastatic state when metastases are limited in number and/or location and therefore amenable to loco-regional therapy [10]. In other cases, when subclinical disease is eradicated by systemic therapy, the clinically apparent metastases may be considered "residual" oligometastases, which may serve as a nidus for further dissemination [11]. Furthermore, following initial curative therapy, a large number of patients will recur, and many will have recurrences limited in number and destination organ, that is, oligo-recurrence [12]. The key distinction between oligo-recurrence and oligometastasis

is that the primary tumor is controlled in the former and a small institutional series suggests more favorable prognosis [13]. Metastasis-directed anti-cancer therapies may benefit patients with *de novo* oligometastases, *induced* oligometastases, or oligo-recurrence.

A fact not often appreciated is that the oligometastatic/oligo-recurrent phenotype is common. Widespread use of more sensitive staging studies, such as PET/CT, has led to a growing incidence of stage IV NSCLC [14]. In addition, patients receiving systemic therapy for stage IV NSCLC often progress only in sites of known metastases. An analysis of metastatic NSCLC patients treated in a phase II protocol with oxaliplatin and paclitaxel at the University of Chicago, found that 50% (19/38) of patients had stable or progressive disease *only in sites that were initially involved with tumor without developing new metastatic lesions* [15]. This number grew to 65% (11/17) in the subset with 4 or fewer metastases. Similarly, an analysis of patients with limited metastatic NSCLC from the University of Colorado demonstrated that the patterns of progression are primarily within known sites of disease [16].

Tailored systemic therapy and targeted agents may further improve the control of subclinical disease and induce an oligometastatic state. Non-squamous NSCLC responds favorably to pemetrexed-based systemic regimens [17, 18]. The addition of a targeted antiangiogenic agent, bevacizumab, to carboplatin and paclitaxel [19] has resulted in improved survival. Patients with epidermal growth factor receptor (EGFR) mutations have superior progressive free survival when treated with EGFR inhibitors [20]. Similarly, identification of the EML4-ALK mutation results in superior survival when crizotinib, a small molecule ALK inhibitor, is included in the systemic therapy regimen [21]. Whole genome sequencing of NSCLC is underway [22] and may lead to identification of novel subtypes and personalized therapies.

Selected patients with limited metastatic disease have achieved cure and prolonged palliation with local and regional treatment. For example, resection of brain [33], lung [34], liver [35], and adrenal [36] metastases have resulted in long term cure of patients with metastatic NSCLC. In addition, aggressive treatment of intracranial metastases with stereotactic radiosurgery (SRS) has resulted in high long term disease control rates [37]. These long term survivors are clinical proof of the oligometastatic/oligo-recurrent state. Moreover, with improving systemic therapies, the control of oligometastases will play a larger role in determining patient outcome. Even if cure rates remain low, local treatment could prevent or ameliorate morbidity related to local tumor proliferation.

3. Hypofractionated, Image-Guided Radiotherapy (HIGRT)

For patients who are not candidates for surgical excision of metastatic disease, radiotherapy (RT) is an effective alternative local therapy. Fractionated RT has long played a role in the palliation of metastatic NSCLC. Technological improvements over the past decade have led to modern RT delivery systems capable of unprecedented precision and accuracy. Stereotactic, high-dose, single fraction brain irradiation, or stereotactic radiosurgery (SRS), was once considered the vanguard of RT. Today, improvements in tumor target delineation, RT dosimetry, respiratory motion management, and tumor targeting have led to the proliferation of brain SRS and stereotactic body radiotherapy (SBRT). SBRT, or stereotactic ablative radiotherapy (SABR), is perhaps more aptly described as hypofractionated, image-guided radiotherapy (HIGRT) now that stereotactic frames are rarely used.

An exploding body of literature supports the use of HIGRT for a variety of malignant conditions. Brain SRS is associated with excellent local control without significant toxicity. In fact, 80–95% of tumors less than 2 cm were permanently controlled by single doses of 18–20 Gy regardless of tumor type [38]. The local control for lung lesions is similarly excellent. Phase I and II American studies have demonstrated greater than 90% primary tumor control following HIGRT for medically inoperable NSCLC [39]. Japanese studies have also showed overall local control of 89.6% with an NCI-CTC grade 3–5 complication rate of only 2.1% [40]. Evidence-based guidelines now recommend definitive lung HIGRT for medically inoperable stage I NSCLC [41]. Promising results are also emerging to support the use of definitive HIGRT for prostate cancer [42, 43], and inoperable pancreatic cancer [44]. Lung [45, 46], liver [47, 48], and spinal [49–53] metastases have been effectively treated with HIGRT, including classically radioresistant histologies such as melanoma [54] and renal cell carcinoma [55]. What is striking in all these studies is that a high probability of durable treated metastasis control is possible with the use of high conformal, precisely targeted, (usually) substantially hypofractionated treatment courses regardless of metastatic site or histology. Equally encouraging has been the relative limited toxicity reported with these treatments.

Biologically, it is not clear why hypofractionated radiotherapy results in high tumor control rates. Hypofractionated radiotherapy has radiobiological advantages over standard fractionated RT including a greater potential cell kill and reduction in the deleterious effect of tumor proliferation during RT. Large radiation doses are thought to not only enhance tumor cell kill, but also engage sphingomyelin-based endothelial mechanisms of tumor control [56, 57]. Additionally, recent reports have identified immune-mediated mechanisms that may play a key role in controlling tumors following hypofractionated RT [58, 59]. The use of ablative radiotherapy in concert with immunomodulatory therapies have demonstrated an abscopal effect, that is, a response in nonirradiated metastases [60, 61]. This abscopal effect may become particularly relevant in the treatment of oligometastatic disease where the potentiation of an immune response could be particularly efficacious.

4. Metastasis-Directed HIGRT

Data are now beginning to emerge that the aggressive treatment of both the primary tumor and metastases with RT as an integral component can result in improved outcomes.

Median survival following conventional radiotherapy for brain metastases is 3–6 months and 1-year survival of 8% in a large retrospective series [62]. Even those with only 1-2 brain metastases have a 2-year survival of only 6% [63]. A number of studies have focused on the subgroup of patients with limited intracranial metastases from NSCLC (Table 1). In these studies, aggressive treatment of metachronous brain metastases in NSCLC patients, that is oligo-recurrence, without extracranial disease produced 5-year survival of 13.2% [23]. Additionally, in those with synchronous solitary brain metastases, aggressive treatment of intracranial metastases with radiosurgery as well aggressive treatment of intrathoracic disease resulted in 21% 5-year survival [24]. A recent review on this topic concludes that aggressive brain and thoracic treatment should be offered to these patients [64].

Reports, primarily from single institutions, have demonstrated favorable outcomes when patients with limited extracranial metastatic NSCLC received aggressive therapy to all known cancer sites (Table 1) [13, 26–29]. An analysis from the University of Rochester reported median survivals of patients with limited metastatic NSCLC treated with HIGRT to be similar to that of stage III NSCLC patients and exhibiting 5-year survival of 14% [26]. Twenty-five patients from the University of Chicago with a median of two extracranial metastases underwent HIGRT and had median survival similar to that seen in stage III patients at 23-month and 18-month overall survival of 53% [28]. Interestingly, those treated with prior systemic therapy, those progressing through chemotherapy immediately prior to HIGRT, and nonadenocarcinoma histology were associated with worse outcomes.

Looking at all these data, one message stands clear; all known cancer sites must be treated to benefit patients with limited metastatic NSCLC. An analysis of the M.D. Anderson Cancer Center Registry, presented at ASCO 2008 (abstr no. 19020), supports aggressive treatment of primary tumors and regional nodes in patients with metastatic NSCLC. This study found that patients with solitary brain metastases from NSCLC who received curative-intent thoracic locoregional treatment with either surgery or concomitant chemoradiotherapy median survival improved from 7 to 30 months ($P = 0.00186$), compared to those who did not. Additionally, this survival advantage was not statistically significant in patients with untreated extracranial metastases. Furthermore, patients with solitary brain metastases treated with surgical resection [13]or radiosurgery [24]significantly benefited from treatment to the primary tumor in addition to aggressive treatment of metastatic disease. This highlights the need to treat all known metastatic deposits whenever possible.

5. Metastasis-Directed HIGRT: Prospective Trials

Based on the promising data, it is clear that further study is needed to carefully integrate these novel RT techniques with standard systemic therapy platforms for patients with metastatic NSCLC. Attempts have been made to prospectively study HIGRT (Table 2). Each study has asked different questions so it is worth reviewing each in some detail.

The NCCTG initiated a randomized phase III study to test the hypothesis that RT to all known sites of disease following 4–6 cycles of systemic therapy in NSCLC patients with one to three metastatic sites would result in improved overall survival [30]. Following the completion of non-standardized systemic therapy, patients were randomized to observation or RT to all known sites of disease. The RT schema was 60 Gy in 2 Gy fractions or 45 Gy in 3 Gy fractions. The study was closed due to poor accrual. This was likely due to randomization following all chemotherapy, a time when patients and physicians are looking forward to an end of treatment. Additionally, the protracted courses of radiation over a six-week time span with historically limited control rates may have contributed.

The University of Chicago initiated a randomized phase II study in patients with 1–5 NSCLC metastases, testing the hypothesis that HIGRT to all known sites of metastatic disease during the third and fourth cycles of systemic therapy would improve progression-free and overall survival [31]. Based on prior institutional studies, cisplatin and docetaxel were used as the chemotherapy backbone and RT was given in 5 Gy fractions to a total dose of 50 Gy. Additionally, conventionally fractionated radiotherapy (60 Gy in 2 Gy fractions) was allowed when combined with systemic therapy for stage III-type intra-thoracic disease. Different from the NCCTG study, this study randomized patients prior to any therapy. This study too, had difficulty accruing, and closed prior to meeting the accrual goal.

Currently, a single arm phase II study at Wake Forest University is ongoing to test the hypothesis that HIGRT to all known extracranial metastasis following the completion of appropriate systemic therapy can improve outcomes of limited metastatic NSCLC [32]. All patients (with either de novo or recurrent metastases) receive 3 to 6 cycles of systemic therapy at the discretion of the treating medical oncologist and must have stable disease or a partial response. Similar to the University of Chicago study, fractionated therapy can be used to treat stage 3 type intra-thoracic disease. Different from the NCCTG study, hypofractionated image-guided radiotherapy is used which allows for the delivery of metastasis-directed therapy quickly. This study continues to accrue at several centers in North Carolina, USA. Currently, approximately 15 out of a planned 54 patients have been enrolled over the past 18 months.

6. Metastasis-Directed HIGRT: A Call to Action

Despite difficulties with accrual in this patient population, there is still a need for randomized studies. The slow accrual of these studies is attributable to shortfalls in study design, and an unfamiliarity among practitioners about the encouraging data is already available for this common problem. Although limited metastatic disease is relatively common, there is considerable heterogeneity with regard to location and number of metastases. Therefore, more flexible radiotherapy dosing schedules are needed. Likewise, flexibility in

Table 1: Selected series for the comprehensive treatment of metastatic NSCLC.

Study	*N*	Metastatic sites	Treatments	1-year PFS	5-year OS
University of Maryland [23]	72	Brain (metachronous)	SRS		13.2%
University of Maryland [24]	42	Brain (synchronous)	SRS, TS, RT, CRT, HIGRT		21%
Hopital Louis Pradel Hospices Civils de Lyon, Lyonnce [25]	51	Brain (synchronous)	BS, TS, RT, CRT		42% (BS + others) versus 5% (BS only)*
University of Rochester [26]	38	Multisite, 1–8 metastases	HIGRT		14%
Rush University Medical Center [27]	23	Multi-site, 1-2 metastases	TS, RT, HIGRT		22%
University of Chicago [28]	25	Multi-site, 1–5 metastases	HIGRT (3–10 fx)	28%	53% (18 mo)
Maastricht University Medical Center [29]	39	Brain, bone, adrenal	TS, SRS, RT, HIGRT		24%*

*2 yr estimates; SRS: stereotactic radiosurgery; BS: brain surgery; TS: thoracic Surgery; RT: radiotherapy; CRT: chemoradiotherapy; HIGRT: hypofractionated image-guided radiotherapy.

Table 2: Prospective study characteristics for comprehensive treatment of limited metastatic NSCLC with hypofractionated RT.

Study group	Inclusion	Systemic therapy	Radiotherapy	Outcome
NCCTG [30]	1–3 metastatic sites	Nonstandardized	60 Gy (2 Gy fx) 45 Gy (3 Gy fx)	Closed due to poor accrual
University of Chicago [31]	1–5 metastatic sites	Cisplatin docetaxel	50 Gy (5 Gy fx) 60 Gy (2 Gy fx) if Combined with CT	Closed due to poor accrual
Wake Forest University [32]	Limited metastatic NSCLC	Non-standardized	HIGRT or conventional RT	Open to accrual

the systemic therapy is also needed as tailored and targeted regimens gain favor. The currently open Wake Forest trial takes advantage of both of these issues by allowing selection of systemic therapy at the discretion of the treating medical oncologist and selection of the radiotherapy dose based on what the treating radiation oncologist perceives to be achievable. The most commonly used doses on the Wake Forest trial thus far have been 50 Gy in 5 fractions or 50 Gy in 10 fractions prescribed to the PTV margin.

Perhaps most importantly, study design should reflect thoughtful consideration of the ethical issues surrounding aggressive therapy for metastatic NSCLC. Specifically, studies that prioritize patient and physician equipoise are most likely to meet accrual goals. An ideal trial would register patients during the first two cycles of chemotherapy, but only randomize following restaging showing no evidence of progression. This would allow selection of patients with truly oligometastatic disease where chemotherapy would likely have impacted micrometastatic disease. Patients would then be randomized to (1) HIGRT followed by further systemic therapy or (2) systemic therapy with conventional RT reserved for standard palliative indications. Biologic correlative studies analyzing blood and tissue would be essential.

Furthermore, emerging data may improve patient selection beyond simple number and location of metastases. Favorable clinical factors such as better performance status [13], limited nodal involvement [65], no prior systemic therapy [28], lack of progression on systemic therapy [28], lack of extracranial metastases [66], metachronous (versus synchronous) brain metastases [67], and 1–3 metastases [28] have been identified. Histologic features such as nonsquamous NSCLC [28, 65] and targetable molecular mutations may also guide patient selection. Serum markers such as low carcinoembryonic antigen level [65] or upregulated Inf-gamma [68] appear to be associated with improved outcomes. An analysis of patients with limited metastases of any histology found that expression of microRNA 200c predicted for true oligometastatic disease with no progression or progression limited in number and destination organs [69].

Beyond improved tools to select patients who may derive survival benefits from this therapy, there are other reasons when HIGRT to all known metastatic sites may be beneficial. As noted above, HIGRT is associated with limited toxicity and favorable progression free-survival. For patients unable to tolerate systemic cytotoxic therapy, HIGRT may act as another "line" of therapy. This is an important consideration given the extremely limited activity of second and third line systemic therapies. Alternatively, early evidence suggests HIGRT may sensitize patients to systemic therapy due to the immunomodulatory abscopal effect (as noted above). If confirmed in NSCLC, such an effect could enhance the role of HIGRT for patients with limited or not-so limited metastatic NSCLC.

Additionally, ideal clinical trials may ultimately need to be developed that test the concept of aggressive local therapy with minimal toxicity in general rather than simply a radiotherapy approach to this disease. This should include combinations of surgery, thermal ablation, HIGRT, radio or chemoembolization, and radiotherapy tailored to each individual patient. Additionally, should patients progress with new sites of disease, metastasis-directed therapies with nonoverlapping toxicity profiles should be considered. This will be particularly useful for patients who have exhausted radiotherapy options due to issues of cumulative dose. In this way patients can be rendered free of macroscopically visible disease and the use of chemotherapy can be appropriately relegated to the goal of the eradication of microscopic disease.

7. Conclusion

From the data above it is clear that in appropriately selected patients, aggressive treatment of extracranial metastases and primary tumors can lead to meaningful improvements in overall and progression-free survival. Studies need to be conducted to explore the impact of these therapies. Clearly this will take a coordinated effort. It is unlikely that single cooperative groups will be able to independently accrue and complete these studies. It will take not only an intergroup effort, but also an international effort to complete these studies. The time to conduct these studies is now.

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Clinical Study

Stereotactic Body Radiotherapy for Metastatic Lung Cancer as Oligo-Recurrence: An Analysis of 42 Cases

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Purpose. To investigate the outcome and toxicity of stereotactic body radiotherapy (SBRT) in patients with oligo-recurrence cancer in the lung (ORCL). *Methods and Materials*. A retrospective review of 42 patients with ORCL who underwent SBRT in our two hospitals was conducted. We evaluated the outcome and adverse effects after SBRT for ORCL. *Results*. All patients finished their SBRT course without interruptions of toxicity reasons. The median follow-up period was 20 months (range, 1–90 months). The 2-year local control rate and overall survival were 87% (95% CI, 75–99%) and 65% (95% CI, 48–82%). As for prognostic factor, the OS of patients with a short disease-free interval (DFI) < 31.9 months, between the initial therapy and SBRT for ORCL, was significantly worse than the OS of long DFI $\geqq 31.9$ months ($P < 0.05$). The most commonly observed late effect was radiation pneumonitis. One patient had grade 4 gastrointestinal toxicity (perforation of gastric tube). No other $\geqq$ grade 3 acute and late adverse events occurred. There were no treatment-related deaths during this study. *Conclusions*. In patients with ORCL, radical treatment with SBRT is safe and provides a chance for long-term survival by offering favorable local control.

1. Introduction

Lung is one of the common sites of metastasis after definitive therapy for a primary cancer. So far, recurrent or metastatic lung cancers have been considered to uniformly carry a poor prognosis because multiple metastases tend to be difficult to treat intensively. Chemotherapy has been broadly applied as a standard management at these conditions. On the other hand, the innovation of methods of early detection of recurrence, such as positron-emission tomography (PET), allows the detection of limited site recurrent, called oligo-recurrence. Oligo-recurrence, proposed by Niibe et al. in 2006 [1–4], was the condition of one or a few metastatic or recurrent lesions occurred with controlled primary lesion. For case with oligo-recurrence cancer in the lung (ORCL), the controversy exists regarding the optimal approach of these metastatic sites. Despite surgical approach is considered as an alternative for a single metastasis, there are many patients with ORCL who were not amenable for metastasectomy. For them, less invasive techniques such as SBRT have been used to treat ORCL. In cases considered to have a favorable prognosis, radical treatment with SBRT seems to be beneficial for prolonging the survival time. However, the role of radiotherapy and the prognostic factors for oligo-recurrence have not yet been clearly elucidated [5]. In this study, we evaluated the efficacy and toxicity of SBRT for patients with oligo-recurrence cancer treated from 2001 through 2011 in two hospitals.

2. Materials and Methods

2.1. Patient Eligibility and Pretreatment Evaluation. A retrospective review of all patients with ORCL treated with SBRT after prior therapy at University of Tokyo Hospital and Kitasato University Hospital from April 2001 to July 2011 was conducted. Patients with ORCL who were not suitable for surgery due to medical or functional reasons were included in this analysis. Pretreatment evaluation included a complete medical history, physical examination, computed tomography (CT), pulmonary function tests, and laboratory tests. In

addition, 36 of 42 patients (86%) were evaluated with ^{18}F fluorodeoxyglucose (FDG)-PET before treatment. Inclusion criteria of this study were as follows: (a) primary cancer was completely treated; (b) the number of lung metastases were up to three; (c) there was no other distant metastasis or other distant metastasis was scheduled to be treated with curative intent after SBRT. As long as these evaluations fulfilled the inclusion criteria, there was no restriction regarding tumor size, location, or general pulmonary function. Radiotherapy was the exclusive treatment modality in all patients.

2.2. Radiotherapy. SBRT was given with 6 MV X-ray of a linear accelerator. In curative intention, hypofractionated SBRT was delivered to a median dose of 48 Gy (range, 20–56 Gy) with a median daily dose of 12 Gy (range, 8–30 Gy). Dose and fractionation schedules were chosen depending on location and institution. In University of Tokyo Hospital, SBRT was performed using the Synergy linear accelerator (ELEKTA), which fully integrates IGRT by means of kV-CT scanning. In Kitasato University Hospital, real-time tumor-tracking radiotherapy was used for SBRT. The gross tumor volume (GTV) or internal target volume (ITV) included the visible gross tumor mass on CT were delineated on a three-dimensional radiation treatment planning system (3D RTPS) using the lung window. The planning target volume (PTV) was created by adding five mm margin to the ITVs in all directions.

2.3. Follow-Up. After completion of therapy, patients were scheduled for regular follow-up visits 3 monthly during the first year, 6 monthly thereafter. Those who did not appear for a routine follow-up were contacted by phone. Follow-up evaluations included a history and physical examination and CT scans of the thorax. Additional imaging investigations such as FDG-PET were only required if there was clinical suspicion of recurrence. In this study, we define local recurrence as an increase in opacity size on CT imaging, along with either increased maximum standardized uptake values (SUVmax) $\geqq$ 5 on FDG-PET, or biopsy proof of disease [6]. Toxicity was evaluated and scored according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0, with toxicity occurring within 3 months after the initiation of RT classified as acute toxicity. Late toxicity was graded using the RTOG/EORTC criteria.

2.4. Statistical Analysis. The baseline follow-up date was the first day of radiotherapy, and the last follow-up date was the last Hospital visit or phone day. Overall survival (OS) was calculated from the start of the SBRT to the date of death, censoring the last follow-up date. Local control rate (LCR) was calculated from the start of the SBRT to the first local recurrence date, censoring death or last follow-up date.

To discuss risk factors for OS and LCR, the patients of ORCL were classified into two groups: early recurrence group and late recurrence group. The former group consisted of 21 patients whose disease-free interval (DFI), meaning interval between the start date of initial therapy and the start date of SBRT for ORCL, was shorter than 31.9 months (median DFI time). In addition, we compared OS and LCR following SBRT for ORCL from colorectal cancer (CRC) and other origins. OS and LCR curves were plotted using the Kaplan-Meier method. Log-rank testing was used to compare OS and LCR between the subsets of patients analyzed. All analyses were performed using SPSS software version 12.0 (SPSS Inc., Chicago, IL).

3. Results

From April 2001 to July 2011, we identified 42 patients with ORCL who were treated with SBRT. The median age was 69 years (range, 25–84 years). There were 30 men and 12 women. The median maximum diameter of metastatic tumor was 19 mm (range, 9–40 mm). Patient characteristics are shown in Table 1. One patient underwent chemotherapy for ORCL before SBRT and the other 41 patients did not undergo neoadjuvant, concurrent, or adjuvant chemotherapy for ORCL. Sites of primary disease included lung (n = 16), colon and rectum (n = 7), head and neck (6), esophagus (n = 4), uterus (n = 4), kidney (n = 2), and others (renal pelvis, breast, sarcoma; n = 3). Of these, 32 patients had lung metastasis alone, 8 patients had another lung metastasis treated with SBRT after initial SBRT, and 2 patients had a distant metastasis in addition to lung lesion (retroperitoneal node and adrenal gland). These distant metastases in both patients were also treated with SBRT after completing SBRT for lung lesion. At the time to analysis, they were alive without evidence of any recurrence.

All patients finished their SBRT course without interruptions of toxicity reasons. Acute toxicities were mild and tolerable except for one case. Grade 4 acute adverse event were observed in only 1 patient (2%), which displayed the perforation of the pulled-up gastric tube. This patient was a 59-year-old man, with esophageal cancer after total esophagectomy with esohageal replacement by means of a gastric tube, had undergone SBRT, consisting of 50 Gy in four fractions in 4 days. The D2 cc, the minimum dose in the most irradiated 2 cc of the gastric tube, was 48.66 Gy. He was a heavy smoker and had an alcohol problem. Two months later, he developed perforation of the gastric tube.

No other grade $\geq$ 3 acute side effects occurred. Twenty-one patients (50%) and 5 patients (12%) experienced grade 1 and 2 adverse event after irradiation of metastases, respectively. Of the 42 patients, 21 patients (50%) and 3 patients (7%) displayed grade 1 pneumonitis (asymptomatic, radiographic findings only) and grade 2 pneumonitis (symptomatic, not interfering with activities of daily living), respectively. No grade $\geq$ 3 late adverse events occurred until now. The median duration of follow-up was 20 months (range, 1–90 months) for all patients and 24 months (range, 6–90 months) for those alive. The 1- and 2-year local control rates were 91% (95% CI, 82–100%) and 87% (95% CI, 75–99%), respectively (Figure 1). At the time of last follow-up, 16 patients had died. The causes of death were recurrence (n = 9), other diseases (n = 7). The overall 1- and 2-year survival rates were 81% (95% CI, 69–94%) and 65% (95% CI, 48–82%), respectively (Figure 1), with a median survival time

Table 1: Patients characteristics ($n = 42$).

Variable	Distribution	No. of patients	%
Sex	Male	30	71
	Female	12	29
Age	Median	69 years	
	Range	25–84 years	
Karnofsky Performance status	Median	90	
	Range	50–90	
Number of metastases	1	32	76
	2	10	24
	$\geqq 3$	0	0
Maximum diameter (mm)	Median	19 mm	
	Range	9–40 mm	
Primary site	Lung	16	38
	Colon and rectum	7	17
	Head and neck	6	14
	Esophagus	4	10
	Uterus	4	10
	Kidney	2	5
	Other	3	5
Follow-up (months)	Median	20 months	
	Range	1–90 months	

of 40 months. Seventeen of 42 patients showed a long-term survival of longer than 2 years.

In present study, seven patients with ORCL originated from CRC and 35 patients originated from other origins were treated by SBRT. The 1- and 2-year LCR in ORCL from CRC and in ORCL from other origins were 83% and 67%, 89% and 89%, respectively (Figure 2). The overall 1- and 2-year survival rates in ORCL from CRC and in ORCL from other origins were 85% and 85%, 82% and 63%, respectively (Figure 3). These results showed no significant difference in LCR ($P = 0.31$) and OS ($P = 0.26$).

We also analyzed the LCR and OS differences stratified by DFI divided into < 31.9 or $\geqq 31.9$ months. As shown in Figure 4, the result indicated a negative correlation between DFI and LCR ($P = 0.29$). On the other hand, early recurrence group (short DFI) had significantly bad prognosis ($P < 0.05$; Figure 5).

4. Discussion

Although this is a retrospective study with a limited sample size, our results are also comparable to other studies in ORCL [7–9]. Norihisa et al. [10] also previously showed the results of SBRT for 43 metastatic lung cancers. In their series, the survival rates and local control rate at 2 years were reported to be 84.3% and 90%, respectively. Ricardi et al. [11] also reported a study of SBRT for oligometastatic lung tumors. Sixty-one patients treated with SBRT achieved 89% in local control and 66.5% in survival at 2 years.

Several studies have now shown that the local control after SBRT for lung metastases from CRC is worse than that from other origins. Takeda et al. [12] reported the difficulty of local control for ORCL from CRC. Norihisaet al. [10] proposed dose escalation in SBRT for CRC patients in order to achieve better local control. In the current study, there was no significant difference between CRC and other origins in LCR ($P = 0.31$) and OS ($P = 0.26$), respectively.

Furthermore, we also analyzed the OS and LCR differences stratified by DFI divided into < 31.9 or $\geqq 31.9$ months. As shown in Figure 5, short DFI was the prognostic factor ($P < 0.05$). Thus, even as oligo-recurrence, early metastasis may be bad prognostic factor.

It seems from these results that SBRT is an effective and safe treatment for patients with lung metastases as oligo-recurrence. In SBRT for lung metastases, limited toxicity rates are reported by several authors [12]. In our series, there was no patient with serious late toxicities except for one patient with perforation of gastric tube. Although it is likely that the perforation may be caused mainly by radiation to gastric tube, smoking and bad nutrition might have been partly related to this perforation. Several reports advocated that deterioration in smoking and bad nutritional status during radiotherapy could be associated with poorer short-term treatment outcomes and severe side effect [13, 14].

Several limitations of this study warrant mention. First, it was a retrospective review with a limited number of patients and limited follow-up. Second, we treated ORCL from various primary cancers by using different treatment

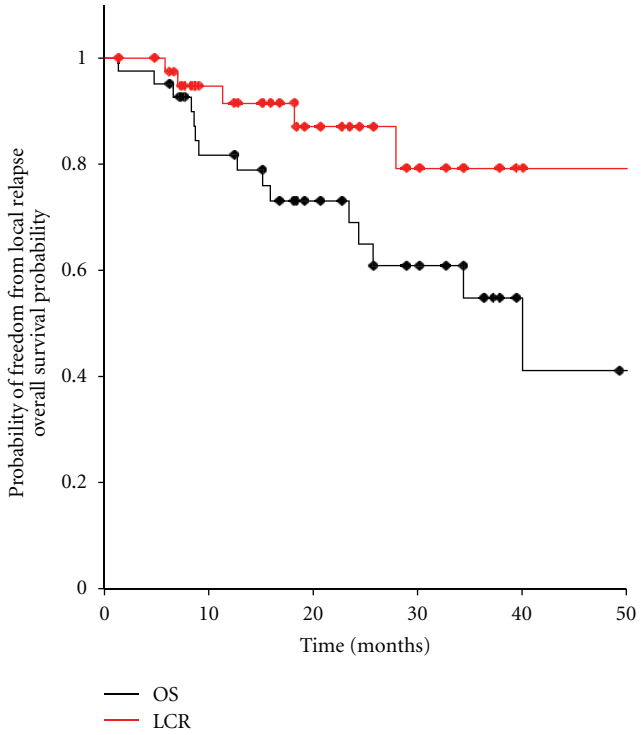

Figure 1: Overall survival and local control of 42 patients with oligo-recurrence cancer in the lung.

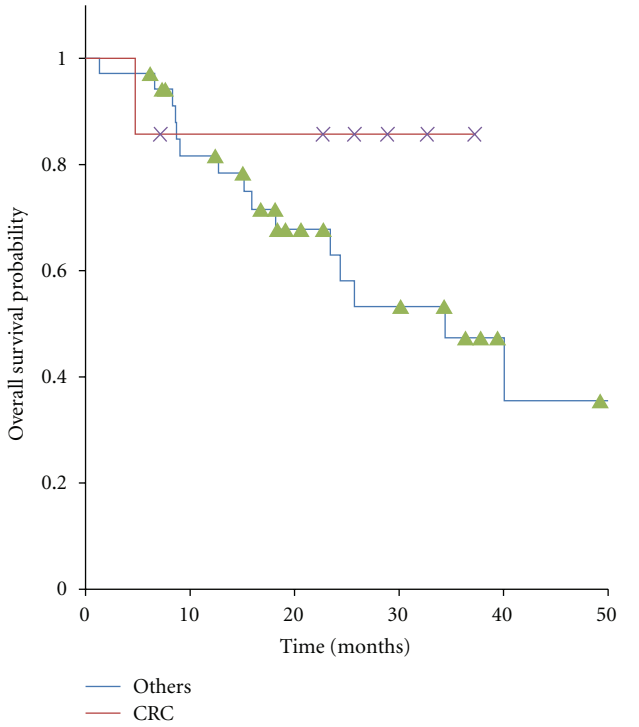

Figure 3: Kaplan-Meier curves for overall survival in 42 patients with oligo-recurrence cancer in the lung, cancers from colorectal cancer and ones from other origins.

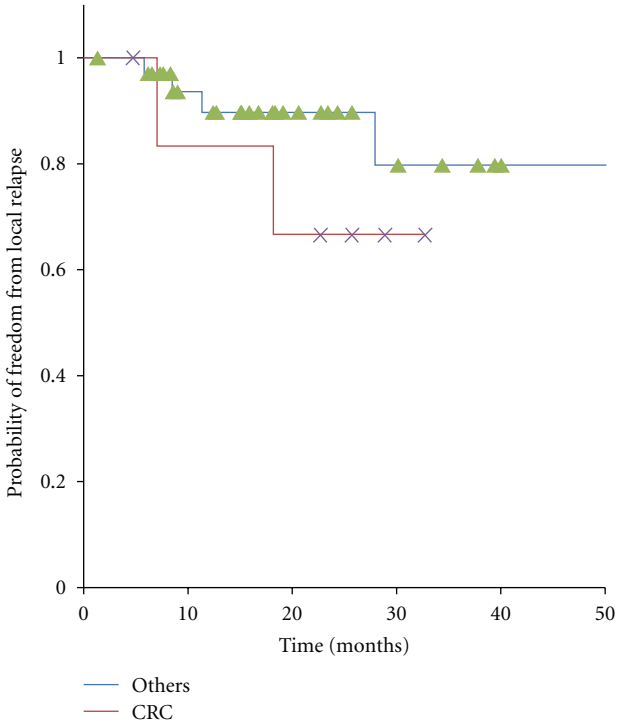

Figure 2: Kaplan-Meier curves for local control in 42 patients with oligo-recurrence cancer in the lung, cancers from colorectal cancer and ones from other origins.

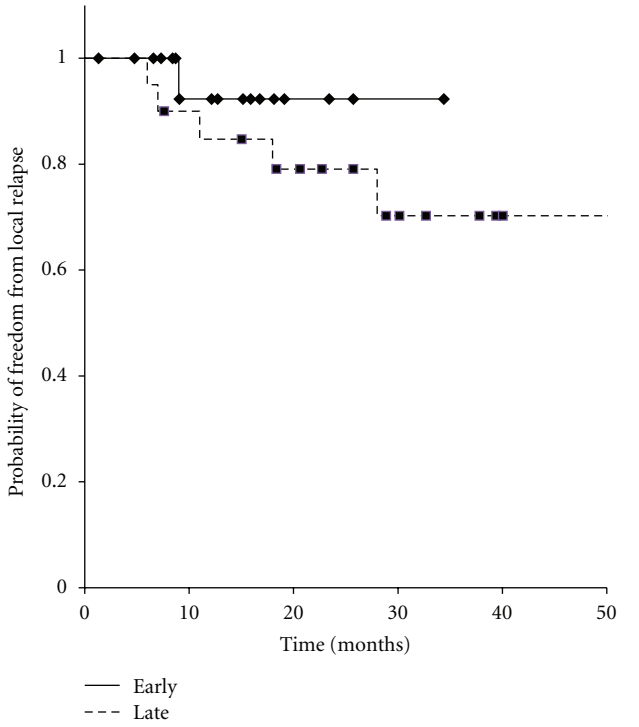

Figure 4: Kaplan-Meier curves for local control in 42 patients with oligo-recurrence cancer in the lung, early recurrence group versus late recurrence group.

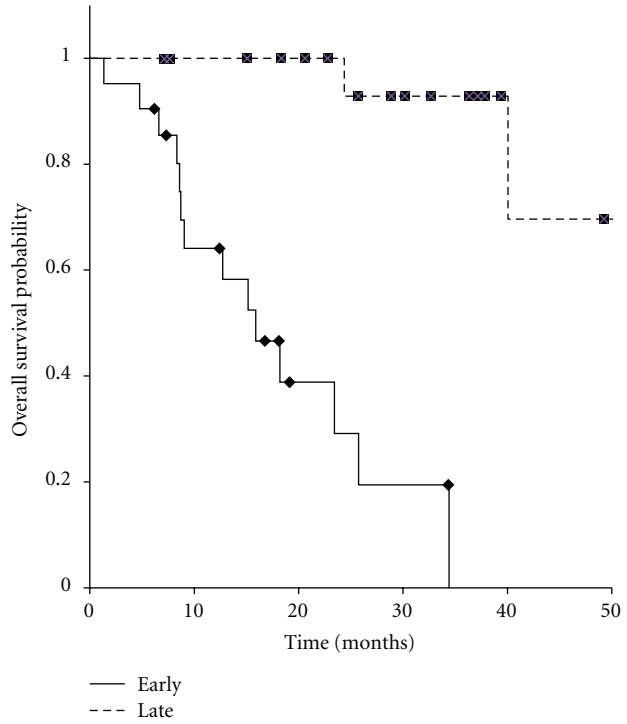

Figure 5: Kaplan-Meier curves for overall survival in 42 patients with oligo-recurrence cancer in the lung, early recurrence group versus late recurrence group.

protocol. There was a wide range of doses prescribed, and a variety of fractionation schema.

5. Conclusions

In patients with ORCL, radical treatment with SBRT offers good local control and provides a real chance for long-term survival. In addition, even in ORCL, SBRT is a safe and efficacious modality and appears to be well tolerated.

Conflict of Interests

The authors declare that they have no conflict of intrersts.

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Clinical Study

Radiotherapy for Oligometastases and Oligo-Recurrence of Bone in Prostate Cancer

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Purpose. To retrospectively evaluate the clinical significance of radiotherapy for oligometastases of bone in prostate cancer (PCa). *Methods and Materials*. Between 2003 and 2008, 35 PCa patients with oligometastases of bone were treated with radiotherapy. *Results*. The median radiotherapy dose was 40 Gy. The 3-year overall survival rates for all patients, for patients that received a radiotherapy dose of ≥40 Gy ($n = 21$) and for those that received <40 Gy ($n = 14$), were 77.2%, 90.5%, and 50.0%, respectively. Fourteen out of 16 patients (87.5%) who had pain were improved 1 month after radiotherapy. The median duration of pain relief was 12 months. Pathological fracture and spinal cord compression (SCC) were not seen at the treated sites but developed at nonirradiated sites in three patients (8.6%) and in one patient (2.8%), respectively. Although the high-dose group (≥40 Gy) achieved better survival than the low-dose group (<40 Gy), it was not independent prognostic factor in multivariable analysis. *Conclusions*. Radiotherapy of bone oligometastases in PCa was effective for long-term pain relief. Pathological fracture and SCC were not seen at the treated sites. A larger clinical trial is warranted to study the actual benefit following radiotherapy for oligometastases of bone in PCa.

1. Introduction

Patients with bone metastases from prostate cancer frequently experience skeletal morbidities as a result of their disease. Skeletal-related events (SREs), such as pathological fractures and spinal cord compression, are major causes of morbidity in patients with prostate cancer and may lead to other comorbidities including pain [1, 2].

Soloway et al. [3] reported an analysis of survival in prostate cancer patients with bone metastases using a semiquantitative grading system based upon the extent of disease (EOD) on the bone scintigram. They concluded that the EOD on the scintigram correlated with survival. This study also demonstrated that the 2-year survival rate in prostate cancer patients with EOD I, defined as having fewer than six bone metastases on bone scan, was 94%. Thus the clinical course of prostate cancer patients with a small number of bone metastases is relatively long. Successful management of bone metastases during these periods is essential for reducing the skeletal complications and for maximizing patients' quality of life. Therefore, we must carefully manage metastatic bone disease from an early stage in prostate cancer.

The aim of radiotherapy for metastatic bone disease is not only relief of bone pain but also healing and prevention of pathological fractures, with anticipated effects including improved mobility, function, and quality of life [4, 5]. In addition to these effects, the notion of oligometastases and oligo-recurrence has recently been proposed [6–9], with the suggestion that local therapy to a small number of gross metastatic sites and recurrences may result in prolonged

survival or even cure [6–10]. The most favorable prognostic factor of oligometastases is the state of primary lesion, which means that oligometastatic patients with controlled primary lesions achieve significant better survival than those with active primary lesions [11, 12]. The notion of oligo-recurrence overcomes this problem. Oligo-recurrence is the state that cancer patients with one to several metastases or recurrences have controlled primary lesions. Niibe and Hayakawa proposed this notion as oligo-recurrence [9].

The objective of this retrospective study was to evaluate the effect of radiotherapy on bone oligometastases and oligo-recurrence in patients with prostate cancer. We were also interested in the disease behavior in patients with bone oligometastases and oligo-recurrence.

2. Methods and Materials

Between January 2003 and December 2008, 136 Japanese men diagnosed with prostate cancer with bone metastases received radiotherapy directed at the metastatic bone lesions at Kitasato University Hospital, Japan. Their medical records were evaluated retrospectively. Thirty-five of the patients had bone metastases of EOD I, referred to as oligometastases or oligo-recurrence of bone in this study. EOD I has been defined by Soloway et al. [3] as the presence of fewer than six bone metastases on bone scan, with each site being less than 50% the size of a vertebral body. Indications for radiation to metastatic bone sites in patients with EOD I prostate cancer were bone pain or spinal cord compression, pathological fracture, or prevention of SREs.

We analyzed the overall survival and the effect of radiotherapy on pain relief and the incidence of SREs, including pathological fracture and spinal cord compression. Short-term pain relief was determined by comparing symptoms prior to radiotherapy to that 1 month after its completion. Pain relief response was classified as follows by taking the best point from the start of treatment: "response," when pain decreased or the daily dosage of the analgesic was decreased; "no change," when pain was unchanged and the dosage of the analgesic did not change; and "progressive disease," when pain increased or the dosage of the analgesic was increased.

For long-term pain relief, the time to progression was defined as the interval between the initial date of radiotherapy and the date when increased pain or increased dosage of the analgesic was first documented after the best pain relief response at treated sites.

Local treatment for prostate cancer might affect overall survival we divide patients into oligo-recurrence group which has treated enough locally such as prostatectomy and oligometastases group which has not been treated with local therapy for the prostate.

Overall survival was calculated as the time interval from the last day of radiotherapy for bone metastases to the time of death. Progression-free survival for bone pain was defined as the proportion of patients surviving with decreased pain from the onset of pain relief to pain relapse at a treated site. Patients were followed for a median of 36 months (range, 1–70 months) after radiotherapy.

Radiotherapy was performed using one port postero-anterior field for the middle thoracic spine/upper lumbar spine and two ports anteroposterior parallel opposed fields for the other spine, legs, and pelvic bone. The energy of radiotherapy was 6 or 10 MV X-rays.

The survival rate was calculated using the Kaplan-Meier method. Differences in patient characteristics between the two groups were compared by chi-square test or Fisher exact test, as appropriate. Multivariable analysis was performed by employing the Cox proportional hazards regression model to examine the interaction between total radiotherapy dose ($\geq$40 Gy versus <40 Gy) and other clinical variables and to estimate the independent prognostic effect of radiotherapy on survival by adjusting for confounding factors. Within the present study population, there were 11 deaths, which allow a maximum of two variables to be included in a multivariable regression model. Therefore all potential confounding factors of radiotherapy dose were reduced to one single composite characteristic by applying a propensity score [13]. The conventional P value < 0.05 was used to determine the level of statistical significance. Analyses were performed with Stata version 11 for Windows (Stata, Chicago, IL, USA).

3. Results

Table 1 shows the baseline characteristics of the study population according to the total radiotherapy dose. In prior treatment to the primary site, radical prostatectomy was performed in 10 patients, and radiotherapy including conformal external beam radiotherapy (3DCRT) alone and high dose rate brachytherapy (HDR) in combination with 3DCRT (HDR/3DCRT) was performed in eight patients. These eighteen patients were to be in the state of oligo-recurrence. Other seventeen patients are called as oligometastases group in this study. All 35 patients received hormonal therapy. Nine patients received Zoledronic acid. There were significant differences in baseline serum prostate-specific antigen, Eastern Cooperative Oncology Group performance status (ECOG PS) and oligostatus between total radiotherapy doses of $\geq$40 Gy and <40 Gy (Table 1).

Treatment characteristics are given in Table 2. The median local radiotherapy dose was 40 Gy (range, 30–50 Gy) in 10–25 fractions. The median biologically effective dose (BED) was 67 Gy_3 (range, 50–92 Gy_3) if α/β of 3 was applied. The reasons for radiotherapy were pain relief in 16 patients (45.7%), prevention of SREs in 17 patients (48.6%), and spinal cord compression in 2 patients (5.7%).

Figure 1 shows the overall survival curves after radiotherapy for metastatic bone disease. The 3-year overall survival rate for all patients was 77.2%. The overall survival rate of radiotherapy doses of >40 Gy and of <40 Gy was 90.5% and 50.0%, respectively ($P = 0.0116$). There is no significant difference between Oligo-recurrence group and Oligometastases group (Figure 2). A Cox proportional hazards model was applied to estimate the effect of radiotherapy dose on overall survival. The crude hazard ratio (HR) of high-dose group ($\geq$40 Gy) compared with low-dose group (<40 Gy) was 0.231 (95% CI, 0.067–0.798; $P = 0.021$), which indicated that high-dose group decreased the hazard of

Table 1: Patient characteristics (35 patients).

Variables	<40 Gy ($n = 14$)	≥40 Gy ($n = 21$)	Total ($n = 35$)	P value*
Age	72 (66–85)	70 (55–93)	71.5 (55–93)†	0.206
Baseline PSA (ng/mL)	72.0 (0.3–964)†	11.0 (0.1–142)†	34.0 (0.1–964)†	0.047
ECOG PS				
0–1	8	21	29 (82.9%)	0.002
≥2	6	0	6 (17.1%)	
No. of bone metastases	3 (1–5)†	2 (1–5)†	2 (1–5)†	0.218
CRPC	5 (35.7%)	2 (9.5%)	7 (20%)	0.090
Pain				
Yes	9 (64.3%)	7 (33.3%)	16 (45.7%)	0.094
Spinal cord compression				
Yes	2 (14.3%)	0	2 (5.7%)	0.153
Pathologic fracture				
Yes	4 (28.6%)	1 (4.8%)	4 (14.3%)	0.134
Oligostatus				
oligo-recurrence group	2 (14.3%)	16 (76.2%)	18 (51.4%)	0.000

Abbreviations. PSA: prostate-specific antigen; ECOG PS: Eastern Cooperative Oncology Group performance status; CRPC: castration-resistant prostate cancer.
†Median (range).
*Significance of difference between groups determined by chi-square test or Fisher exact test, as appropriate. $P < 0.05$ considered significant.

Table 2: Treatment characteristics.

Variables	Total $n = 35$
Total radiation dose (Gy)	40 (30–50)†
Biological effective dose (Gy_3)	67 (50–92)†
Reasons for radiotherapy	
Pain	16 (45.7%)
Spinal cord compression	2 (5.7%)
Prevention for SREs	17 (48.6%)
Treatment site	
Spine	15 (42.9%)
Femur	17 (48.6%)
Pelvis/hip	3 (8.6%)
Sternum	1 (2.8%)
Ribs	2 (5.7%)
Overall treatment time (days)	28 (12–43)†

Abbreviations. SREs: skeletal-related events.
†Median (range).

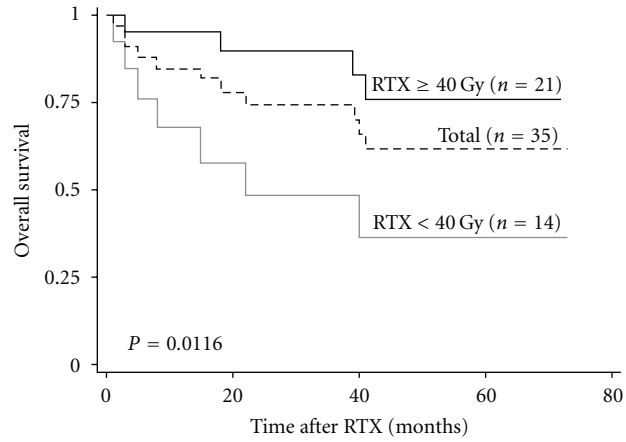

Figure 1: The overall survival curves for all patients ($n = 35$) and those that received a total radiotherapy dose of ≥40 Gy ($n = 21$) or <40 Gy ($n = 14$). RTX, radiotherapy.

death by four times that of low-dose group (Table 4). Then we performed multivariable analysis using propensity score to adjust the effect of receiving high-dose radiotherapy (≥40 Gy) given by other confounding variables including age, baseline PSA, ECOG PS, castration-resistant prostate cancer (CRPC), oligostatus into a single estimator. The results revealed that the HR of radiotherapy dose (≥40 Gy versus <40 Gy) changed to 0.630 (95% CI, 0.098–4.285; $P = 0.637$), which suggests that high-dose radiotherapy was not an independent risk factor for overall survival (Table 4).

The treatment outcomes are shown in Table 3. At 1 month after radiotherapy, 14 out of 16 patients (87.5%) with pain gained relief. Five of these patients (31.3%), however, experienced pain relapse in the treated sites. Figure 3 shows the progression-free survival for bone pain. One-year progression-free survival was 64.8%, and the median duration of pain relief was 12 months (range, 5–68 months). Two patients had a relapse of bone pain within 1 year after radiotherapy in ≥40 Gy and <40 Gy, respectively. With regard to SREs, spinal cord compression and pathological fracture were not seen at treated sites after radiotherapy. On the other hand, there were three patients (8.6%) with pathological fracture and one patient (2.8%) with spinal cord compression in nontreated sites after radiotherapy.

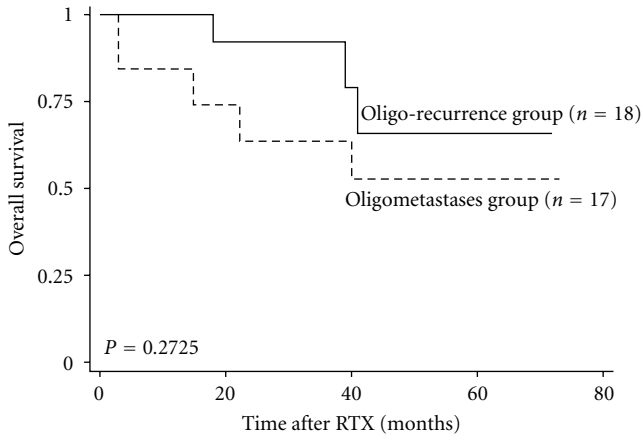

Figure 2: The overall survival curves for oligo-recurrence group ($n = 18$) and oligometastases group ($n = 17$). RTX, radiotherapy.

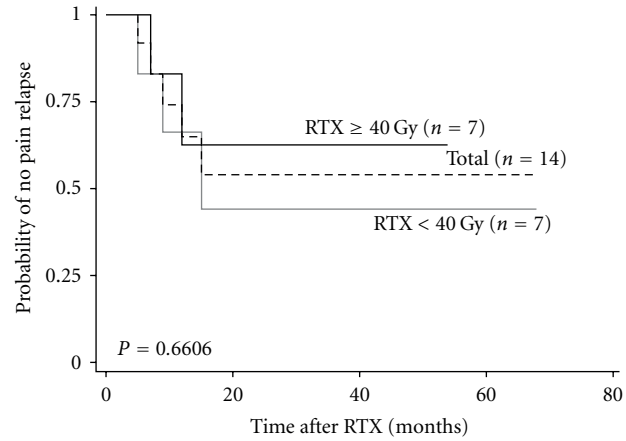

Figure 3: The progression-free survival curves for patients with bone pain who had pain relief response at 1 month after radiotherapy ($n = 14$) and with received total radiotherapy dose of ≥40 Gy ($n = 7$) and <40 Gy ($n = 7$). RTX, radiotherapy.

Table 3: Treatment outcomes.

Variables		No. of patients (%)
Pain relief ($n = 16$)	Short-term response	14 (87.5)
	No change	2 (12.5)
	Progressive disease	0
	Long-term progression	5 (31.3)
	Time to progression (months)	9 (5–15)†
Incidence of SREs after radiotherapy ($n = 35$)	Pathologic fracture	
	Treatment site	0
	Nontreatment site	3 (8.6)
	Spinal cord compression	
	Treatment site	0
	Nontreatment site	1 (2.8)

Abbreviations. SREs: skeletal-related events.
†Median (range).

4. Discussion

Prostate cancer is the most frequently diagnosed cancer and is second only to lung cancer as the leading cause of cancer-related deaths among in the USA. In Japan, it is estimated that the incidence and mortality cases for prostate cancer will increase 3-fold by 2020 compared with 2000. Previous studies showed that independent prognostic variables for survival among patients with prostate cancer were patient age, time to androgen-independent disease, the extent of metastatic disease, and number of metastases on bone scan [14]. Several studies have focused on quantifying or stratifying risk according to the extent of bone involvement and the number of metastatic sites of prostate cancer [3, 15–17]. They have shown that the number of metastatic lesions is a powerful prognostic indicator of the outcome in metastatic disease. Among these studies, Soloway et al. [3] reported that a scale based on a count of the number of metastatic bone lesions on bone scan was predictive when ≤5 (EOD I) or >20 (EOD IV) lesions were present. On the basis of this result, we grouped our prostate cancer patients with bone metastases likewise and applied radiotherapy to metastatic bone disease in EOD I cases (i.e., oligometastases and oligo-recurrence of bone in prostate cancer) regardless of the presence of the bone pain. Results of this study revealed that the 3-year overall survival rate after radiotherapy to oligometastases or oligo-recurrence of bone was 77.2% in prostate cancer. To our knowledge, no previous study has examined overall survival in this patient population. Although the widely accepted treatment for patients with metastatic prostate cancer is hormonal therapy, we should manage oligometastases, oligo-recurrence, and polymetastases separately because of their difference in prognosis. Hellman and Weichselbaum [7] reported that local therapy such as radiotherapy and surgery for one or several distant metastatic sites could be efficacious for survival in patients with oligometastases. Niibe et al. [8] and Niibe and Hayakawa [9] also proposed oligo-recurrence, a more strictly defined type of oligometastases, in which one or several metastatic or recurrent lesions occur with the controlled primary lesions. They suggest that the local treatment of the metastatic or recurrent lesions could improve prognosis. Many studies have been performed along these lines [6–10]. Niibe et al. [8] also indicated that high-dose radiotherapy for bone metastases could contribute to patient survival in breast cancer. In the current study, because patient baseline characteristics were different between groups receiving a total radiation dose of ≥40 Gy or <40 Gy and there is few events on survival in each group, usual multivariable analysis could not be performed without propensity score. Therefore, radiotherapy for oligometastases and oligo-recurrence of bone in patients with prostate cancer is worth prospective testing as an approach to improving survival.

The Radiation Therapy Oncology Group (RTOG) has previously studied various treatment fraction regimens for palliation of bone metastases. The RTOG 9714 study, a recent phase III trial centered on prostate cancer and breast cancer

Table 4: Univariable and multivariable analysis for the effect of radiotherapy on survival.

Factors	Univariable analysis			Multivariable analysis		
	HR	95% CI	*P* value*	HR	95% CI	*P* value*
RTX (≥40 Gy versus <40 Gy)	0.231	0.067–0.798	0.021	0.630	0.098–4.285	0.637
Propensity score†	n/d	n/d	n/d	0.300	0.024–3.763	0.351

Abbreviations. HR: hazard ratio; n/d: not done.
*Analyses were performed using Cox proportional hazard regression.
†Multivariable model indicates adjusted effect of RTX by applying propensity score which is a conditional probability of receiving RTX (≥40 Gy) given by other factors including age, baseline PSA, performance status, castration-resistant prostate cancer, and oligostatus.

with osseous metastases, revealed 8 Gy per single fraction was equal to 30 Gy in 10 fractions for the pain relief of osseous metastases at 3 months after irradiation [18]. However, this study evaluation point for pain relief is very early, at 3 months after radiotherapy. This is not appropriate appreciation for oligometastases and oligo-recurrence because of long-term survival. Niibe et al. reported high-dose radiation contributed to long-term pain relief in breast cancer [8]. Milano et al. also reported high-dose stereotactic body radiotherapy for bone oligometastases, oligo-recurrence was efficacious [19]. Moreover, other investigation in the same population demonstrated that the retreatment rate was significantly higher in the 8 Gy arm (18%) than in the 30 Gy arm (9%) [20].

In Japan, longer courses of radiotherapy with higher total doses of radiation remain the most commonly used, typically with a regimen of 30–40 Gy given in 10–20 treatment sessions. While conventional radiotherapy was used in this study, the results reveal a median duration of pain relief of 12 months, with approximately half of the patients experiencing relapsed bone pain. The bone pain trial which include 34% of prostate cancer patients in patient population showed 40% of pain relapse at 12 months [18]. Although those patient characteristics are different from our study, we considered our result in duration of pain relief is comparable with that study. However, these results indicate that conventional radiotherapy alone for pain relief may be inadequate for oligometastases and oligo-recurrence of bone in prostate cancer. Consequently, for the management of bone pain in patients with prostate cancer, we should consider altering the radiation dose or fraction using high-dose SBRT combining it with treatments such as systemic chemotherapy, zoledronic acid, and painkiller. Punglia et al. [21] reported that as improving systemic therapy, local therapy got survival benefit dramatically. Niibe and Hayakawa [9] also reported the significance of systemic therapy for oligometastases and oligo-recurrence treated by local therapy.

For patients without bone pain in this study, the main purpose of radiotherapy was prevention of SREs, including pathological fracture and spinal cord compression. The current study demonstrated that the complications were not seen in treated sites; however, three patients experienced pathological fracture and one patient had spinal cord compression in a nontreated site after radiotherapy. These results indicate that radiotherapy for metastatic bone disease may potentially decrease the incidence of SREs in treated sites. Both pathological fractures and spinal cord compression with neurologic deficit negatively affect quality of life [22]. Moreover neurologic recovery is unlikely if spinal compression is not relieved within 24–48 hours [23]. Therefore, efforts have recently been made to predict sites of fracture and to prevent the occurrence of a fracture by prophylactic therapy, which includes radiotherapy [24–26].

Our study has several limitations. Because it is retrospective, patient populations differ between total radiation dose received (≥40 Gy and <40 Gy). There was also no control group, that is, one that did not receive radiotherapy. Therefore, in the future, a large prospective study is required to investigate the actual benefits, including overall survival associated with radiotherapy for oligometastases and oligo-recurrence of bone in prostate cancer.

Conflict of Interests

The authors declare that they have no conflict of Interests.

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Review Article

Novel Insights of Oligometastases and Oligo-Recurrence and Review of the Literature

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Oligometastases and oligo-recurrence are among the most important notions of metastatic and recurrent cancer. The concept of oligometastases is related to the notion that cancer patients with 1–5 metastatic or recurrent lesions that could be treated by local therapy achieve long-term survival or cure, while the concept of oligo-recurrence is related to the notion that cancer patients with 1–5 metastatic or recurrent lesions that could be treated by local therapy have controlled primary lesions. Achievement of long-term survival or cure in patients with oligometastases and oligo-recurrence is cancer and organ specific. These facts rely on the seed and soil theory and multiple steps of cancer progression. Oligo-recurrence is considered to have a better prognosis than oligometastases. In patients with oligometastases and oligo-recurrence, the oligometastases and oligo-recurrence are sometimes cured with only local therapy, which is an example of the abscopal effect, previously described in relation to cure of lesions outside of the field of radiation therapy without systemic therapy. Oligometastases and oligo-recurrence can now be cured by less invasive local treatment methods combined with systemic therapy. The mechanisms of oligometastases and oligo-recurrence, as well as novel insights into these important concepts, are presented in this paper.

1. Introduction

Oligometastases and oligo-recurrence are among the most important notions of metastatic and recurrent cancer [1, 2]. These notions are now widely accepted by oncologists, and many reports of oligometastases and oligo-recurrence have been published. The concept of oligometastases is related to the notion that cancer patients with 1–5 metastatic or recurrent lesions that could be treated by local therapy achieve long-term survival or cure. However, the status of the primary lesion of these cancer patients has no restrictions, though patients with active primary lesions have a worse prognosis than patients with controlled primary lesions. Niibe et al. showed that the most important prognostic factor of oligometastases was the status of the primary lesion [3]. On the other hand, the concept of oligo-recurrence is related to the notion that cancer patients with 1–5 metastatic or recurrent lesions that could be treated by local therapy have controlled primary lesions [2]. Then, the biggest prognostic factor for oligometastases is overcome in oligo-recurrence. This is a very important point in oligo-recurrence. This notion has been proposed by Niibe et al. [2]. Another important point in oligo-recurrence is that the oligometastases are metachronous. Synchronous oligometastases have an active primary lesion. However, metachronous oligometastases almost always have a controlled primary lesion except for concomitant primary and distant recurrence (sites: 1–5).

Furthermore, achievement of long-term survival or cure in patients with oligometastases and oligo-recurrence is cancer- and organ-specific. These facts rely on the seed and soil theory and multiple steps of cancer progression [4, 5]. The seed and soil theory remains an accepted notion in modern biology and oncology [6–8]. The cancer cells' interactions with host organs are very complicated and

specific at the level of gene mutation, gene expression, molecular expression, MET-EMT cross-talk, and so on [6–10]. The multiple steps of cancer progression indicate that cancer cells in the primary lesion are not monoclonal and have a different metastatic potential [5]. Recently, cancer stem cells have been reported to play an important role in cancer progression and metastasis [11, 12].

In this paper, mechanisms of oligometastases and oligo-recurrence are discussed through a review of the literature and our experience, and novel insights into these mechanisms are presented.

2. Mechanisms of Oligometastases

In this paper, oligometastases are defined as the state in which patients have 1–5 metastatic or recurrent lesions with active primary lesions. This definition prevents confusing oligometastases with oligo-recurrence. Another way of considering this status is sync-oligometastases, in which cancer patients have 1–5 synchronous metastases with active primary lesions, excluding metachronous metastases.

Metastasis has been recently reported to arise from cancer stem cells [11, 12]. Primary tumor sites consist of various metastasis-potential cancer cells. Of these, cancer stem cells have metastasis potential, which is produced by cancer gene mutations. This means that sync-oligometastases cancer patients already have gene mutations in primary cancerous lesions [5, 11, 12]. Moreover, tumor-host cross-talk in gene mutations, gene expression, molecular expression, and MET-EMT interactions lead to organ-specific metastases [5, 6, 9, 10]. In nonsmall cell lung cancer (NSCLC), oligometastases often arise in patients who have brain-only or adrenal-only metastases [3, 13, 14]. In small cell lung cancer (SCLC), oligometastases often arise in patients who have brain-only metastases [15]. In uterine cervical cancer, oligometastases often arise in patients who have para-aortic lymph node-only metastases [16], while in colorectal cancer, oligometastases often manifest as liver-only metastases [17, 18]. These sync-oligometastases could be cured by local therapy combined with systemic therapy. In this situation, local therapy should treat both metastatic lesions and primary lesions to pursue cure or long-term survival.

Recently, Lussier et al. indicated that oligometastases enhanced by MicroRNA-200c lead to polymetastases after local radiation therapy [19]. This is a new finding related to cancer multistep progression. If MicroRNA-200c has not been enhanced in oligometastases, polymetastases do not occur. However, this has limitations, in that oligometastases occur in an organ-specific manner. This is explained by the above-mentioned modern seed and soil theory.

3. Mechanisms of Oligo-Recurrence

Oligo-recurrence is the state in which cancer patients have metachronous metastases after curative therapy for primary lesions. At recurrence, the cancer patients have no relapse of the primary lesions. This is very important with respect to local therapy. With local therapy it is relatively easy to treat 1–5 metastases and recurrences in one organ. However, primary lesion treatment is usually difficult with local therapy and includes radiation therapy, surgery, and radiofrequency ablative therapy, because primary lesion recurrence often involves regional lymph node metastases or invasion to adjacent organs. Furthermore, oligo-recurrence is the state of metachronous oligometastases. This is why we consider oligo-recurrence to have a better prognosis than sync-oligometastases.

Oligo-recurrence is also cancer and organ specific. The seed and soil theory is adapted in oligo-recurrence. In NSCLC, oligo-recurrence often arises with brain-only recurrences [3]. In uterine cervical cancer, oligo-recurrence often involves para-aortic lymph node-only recurrences [20–22]. In colorectal cancer, oligo-recurrence often involves liver- and lung-only recurrences [17, 23].

At the time of treatment for the primary lesion, oligo-recurrent cancer patients might have one to several micrometastases. These micrometastases remain dormant for a period. These then grow and can be detected by computed tomography, magnetic resonance imaging, positron emission tomography, and increasing tumor marker levels. This state is oligo-recurrence, with one to several gross recurrences. Interleukin has been reported to play a key role in the growth of micrometastases [24]; it is the switch that results in progression of micrometastases.

4. Relationship between the Abscopal Effect and Oligometastases and Oligo-Recurrence

The abscopal effect is defined as tumor outside of the irradiation field disappearing without systemic therapy when the radiation therapy target tumor is irradiated. This is a rare phenomenon. We have reported the abscopal effect in uterine cervical cancer [25] and hepatocellular carcinoma [26]. Other reports have documented the abscopal effect in malignant melanoma [27], malignant lymphoma [28], and others.

In patients with oligometastases and oligo-recurrence, radiation oncologists, oncologic surgeons, and interventional oncologists have sometimes found that oligometastases and oligo-recurrence have been cured with only local therapy. These patients are considered to have micrometastases. However, gross metastases and recurrent lesions treated by radiation therapy, surgery, and radiofrequency ablative therapy lead to cure. This phenomenon is considered to be the abscopal effect. The abscopal effect is reported to occur with surgery, as well radiation therapy [29]. The abscopal effect could diminish micrometastases (Figure 1), so that oligometastases and oligo-recurrence treated only by local therapy may sometimes be cured.

5. Relationship between Systemic Therapy and Oligometastases and Oligo-Recurrence

Punglia et al. reported that the survival benefit of local therapy increased as systemic therapy improved [30]. Niibe et al. reported that the survival benefit of local therapy increased

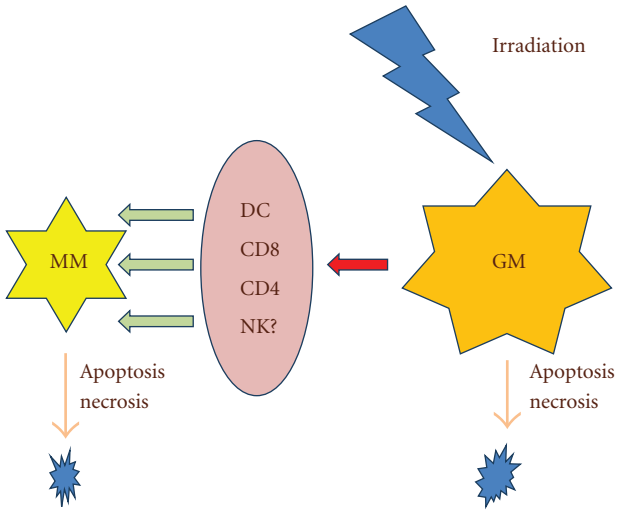

Figure 1: Relationship between the abscopal effect and disappearance of micrometastases. Abbreviations: GM: gross metastasis, DC: dendritic cell, NK: natural killer cell, MM: micrometastases.

dramatically as systemic therapy improved, indicating their original figure designating the sigmoid-curve relationship between increasing survival benefit of local therapy and improving systemic therapy [2]. This figure is very important because it revises the previous figure to a sigmoid-curve. Recently, systemic therapy has been improving, and the importance of local therapy, especially in cases with minimal invasiveness, is increasing dramatically. Stereotactic body radiation therapy (SBRT), intensity modulated radiation therapy (IMRT), proton therapy, heavy ion therapy, radiofrequency ablative therapy (RFA), video-assisted partial surgery, and robotic surgery are less invasive than therapies of a decade ago. These methods now apply to sync-oligometastases and oligo-recurrence combined with systemic therapy, including molecular-targeted therapy. With these, patients can benefit from improved outcomes with less invasive and treatments that are more likely to be successful for sync-oligometastases and oligo-recurrence.

6. Clinical Outcomes

6.1. Oligometastases and Oligo-Recurrence in the Lungs. Oligometastases and oligo-recurrence in the lungs treated by surgery were reported to achieve good outcomes in the 1990s, in a large population study [31] (Table 1). The International Registry of Lung Metastases (IRLM) reported a 5-year overall survival rate of 36% among 5206 patients with lung metastases treated by surgery. This report suggested that origin of the germ cell tumor was favorable survival. In 2009, oligometastases of colorectal cancer in the lungs treated by surgery were also found to achieve favorable survival [32]. Three hundred and seventy-eight patients underwent pulmonary resection for colorectal cancer metastases with curative intent, and a 3-year overall survival rate of 78% was achieved. This indicated that oligometastases of colorectal cancer are favorable candidates for curative-intent therapy.

Since the 2000s, stereotactic body radiation therapy has rapidly spread as medical physics improved. Stereotactic body radiation therapy has been revealed to be equivalent to surgery in tumor ablation [33]. In oligometastases of the lungs, Okunieff et al. reported a local control rate of 94% (median follow-up: 18.7 months) and a 2-year progression-free survival rate of 16% in patients treated with stereotactic body radiation therapy using mainly 50 Gy/5 fr [34]. Among them, cancer of breast or lung origin had better prognosis than those of other origins. Norihisa et al. reported a local control rate of 90% and an overall survival rate of 84.3% in patients after a 2-year followup using primarily 48–60 Gy/4-5 fr [35], and suggested that no differences existed between different tumor origins. One prospective study also reported that the local control rate was 96% and overall survival rate was 39% in patients after a 2-year followup [36]. In oligo-recurrence of the lungs, Takahashi et al. reported a local control rate of 87% and an overall survival rate of 65% in patients after a 2-year followup using 20–56 Gy/1–7 fr, and suggested that those of colorectal cancer origin had a better prognosis than others [37]. Inoue et al. reported an overall survival rate of 54% in patients after a 5-year followup using 40–48 Gy/4 fr, and suggested that disease-free interval (DFI) $\geq$36 was a significantly favorable prognostic factor [38].

6.2. Oligometastases and Oligo-Recurrence in the Liver. The most frequent liver metastases occur in colorectal cancer. However, colorectal cancer patients with liver metastases resected by surgery achieve favorable survival. The 5-year overall survival rate is about 40%–50% [39, 40] (Table 2). Furthermore, Adam et al. reported that initially unresectable colorectal liver metastasis could be cured by surgery after downsizing chemotherapy [41]. The cure rate was reported to be as high as 19%. Bismuth also reported that initially unresectable colorectal liver metastases could achieve a 5-year overall survival rate of 40% [42].

SBRT is also applied to liver metastases, as lung metastases can be curable by SBRT. van der Pool et al. reported that the 2-year local control and 2-year survival rates in colorectal cancer patients with liver metastases (i.e., mostly colorectal cancer) were 74% and 83%, respectively, after treatment with SBRT using mainly 37.5 Gy/3 fr [43]. Romero et al. conducted a prospective trial to treat liver metastases with SBRT using mainly 37.5 Gy/3 fr [44], and reported that the 2-year local control and 2-year overall survival rates were 86% and 62%, respectively. Rusthoven et al. conducted a prospective trial on liver metastases treated with SBRT using 36–60 Gy/3 fr [45], and found that the 2-year local control and survival rates were 92% and 30%, respectively, which indicated that favorable prognostic factors were the origins of colorectal cancer, breast cancer, and renal cell cancer.

7. Conclusions

The mechanisms of oligometastases and oligo-recurrence were reviewed, and novel insights are presented. Sync-oligometastases and oligo-recurrence can now be cured by less invasive local treatment methods combined with systemic therapy.

Table 1: Outcomes of oligometastases and oligo-recurrence in the lung.

Author	Year	Study design	Treatment method	Local control (%)	Overall survival (%)
IRLM [31]	1997	retrospective	surgery	—	36 (5 years)
Onaitis et al. [32]	2009	retrospective	surgery	—	78 (3 years)
Okunieff et al. [34]	2006	retrospective	SBRT	94 (median followup: 18.7 mo.)	16 (PFS)
Norihisa et al. [35]	2008	retrospective	SBRT	90 (2 years)	84.3 (2 years)
Rusthoven et al. [36]	2009	prospective	SBRT	96 (2 years)	39 (2 years)
Takahashi et al. [37]	2012	retrospective	SRS, SBRT	87 (2 years)	65 (2 years)
Inoue et al. [38]	2012	retrospective	SBRT	—	54 (5 years)

Abbreviations: SBRT: stereotactic body radiation therapy; SRS: stereotactic radiosurgery; mo.: months.

Table 2: Outcomes of oligometastases and oligo-recurrence in the liver.

Author	Year	Study design	Treatment method	Local control (%)	Overall survival (%)
Choti et al. [39]	2002	retrospective	surgery	—	40 (5 years)
Pawlik et al. [40]	2005	retrospective	surgery	—	58 (5 years)
Adam et al. [41]	2009	retrospective	chemotherapy → surgery	—	33 (5 years)
Bismuth et al. [42]	1996	retrospective	chemotherapy → surgery	—	40 (5 years)
van der Pool et al. [43]	2010	retrospective	SBRT	74 (2 years)	83 (5 years)
Romero et al. [44]	2006	prospective	SBRT	86 (2 years)	62 (5 years)
Rusthoven et al. [45]	2009	prospective	SBRT	92 (2 years)	30 (5 years)

Abbreviations: SBRT: stereotactic body radiation therapy.

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Review Article

Oligometastatic Disease at Presentation or Recurrence for Nonsmall Cell Lung Cancer

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Oligometastatic Non-Small Cell Lung Cancer (NSCLC) presents a unique opportunity for potential curative therapy. Improved cancer staging using PET/CT, MRI, and future cellular and molecular staging with circulating tumor cells and/or molecular markers will identify more patients with truly oligometastasis disease that will benefit from definitive local treatment. Recent development of noninvasive local ablative therapy such as stereotactic radiotherapy makes it possible to eradicate multiple local diseases with minimal side effect. Novel systemic therapy may also control systemic spread and therefore make it possible to improve survival by eliminating local diseases. More research, particularly prospective studies, is ideally randomized studies are needed to validate the concept of oligometastasis.

1. Introduction

Oligometastatic (OM) disease refers to a limited metastatic burden [1]. The precise definition of this entity has varied among studies, but the clinical significance is that this subgroup of patients may represent a population in which definitive treatment is feasible. As a result, numerous studies have been performed over the past several decades attempting to identify patients with OM malignancies that have indolent disease, the optimal treatment strategies in this setting, and prognostic factors for long-term survival with aggressive local therapy. In this paper, we discuss the current data on the pathophysiology of OM non-small cell lung cancer (NSCLC), compare the prognosis of OM at diagnosis (synchronous OM disease) and at recurrence (metachronous OM disease), and provide a literature review of studies assessing the role of aggressive therapy in this context. Our goal is to provide the reader with an understanding of the spectrum of OM NSCLC and to provide information that will assist the practicing oncologist in selecting patients for combined systemic and local treatments versus palliative approaches alone.

2. Proposed Pathophysiologic Mechanisms of Oligometastatic Disease

Several investigators have attempted to elucidate the biologic mechanism of OM disease. These studies have previously been summarized well in two reviews by Hellman and Weichselbaum [2, 3]. In these reviews, the authors describe the multiple steps of metastasis, as influenced by factors such as the microenvironment and tumor diversity and as outlined specifically by Gupta and Massagué [4]. These steps are as follows (1) aggressive phenotype, (2) prerequisites such as invasiveness, (3) a favorable microenvironment due to factors such as angiogenesis and inflammation, (4) intravasation, (5) increased life in transit due to improved vascular adhesion and platelet association, (6) a favorable distant environment, (7) homing in on the metastatic target, (8) extravasation by motility and vascular remodeling, (9) survival in the distant site, and (10) cancerization of the stroma and colonization in the distant site.

Given these steps in the development of metastatic disease, it follows that in an individual patient (microenvironment) and tumor, the capacity and timeframe to achieve

individual steps may vary by histology, organ system, or concurrent intervention. For example, lung cancer is predisposed to metastasize to the brain, lungs, adrenal glands, bone, and liver, while a metastasis to a structure such as the bladder, pancreas, or colon is rare. This predisposition is dependent on both the genomic nature of cancer, the seed, and the microenvironment (capacity for vascular adhesion, level of hypoxia), the soil, at that site.

In an illustrative example, Yachida et al. performed a multi-institutional study in which rapid autopsies were obtained of seven patients with terminal pancreatic cancer. All patients had metastatic deposits in at least two metastatic sites. The authors then compared the mutation status of the lesions in the metastatic sites with that of the index lesion. It was found that there were two types of mutations: "founder" mutations which were present in all samples from a given patient and "progressor" mutations present in one or more of the metastases but not in the index lesion. From this information, the authors were able to construct evolutionary maps of each patient's malignancy. Furthermore, the authors found that metastases at a given location had similar mutation signatures, and that the subclones could be placed in an "ordered hierarchy establishing an evolutionary path for tumour progression" [5]. Thus, extrapolating from pancreatic cancer, it appears as if the primary tumor is a mixture of geographically distinct subclones, and one could then infer that the presence of specific subclones dictates the extent, location, and timing of metastases. These findings set a basis for OM as a distinct entity of metastatic disease, with individualized treatment paradigms.

3. Synchronous versus Metachronous Oligometastatic Disease

Synchronous and metachronous OM represent two subsets of this disease. Particularly in the case of intrathoracic metastases, a dilemma for the treating physician is determining if a presenting patient has true metastases versus the development of multiple primary tumors. Several criteria have been described for distinguishing multiple primary tumors lung cancer (MPLC) versus metastatic disease. The most widely cited of these are those outlined by Martini and Melamed [13] and recently summarized in a review by Pfannschmidt and Dienemann [14]. Typically, synchronous multiple primary lung cancer (SMPLC) was defined as those physically distinct and separate tumors were diagnosed within 6 months and histology was different, or when the tumors had similar histology and located in different lobes or lungs, in the absence of lymphatic metastases in the common drainage basins and extrathoracic metastases at the time of diagnosis. Metachronous multiple primary lung cancer (MMPLC) was defined as those tumors were diagnosed beyond 6 months and fulfilled the above criteria. For MPLC, aggressive local treatment such as stereotactic ablative radiotherapy was reported to achieve median survival of 46.5 months and overall survival of 67% at 3 years and 22.3% at 5 years [15]. The prognosis of OM is poorer than MPLC in lung cancer. In synchronous tumors, the following criteria indicate metastatic disease: (1) same segment, (2) no carcinoma in situ, or (3) carcinoma in lymph node drainage sites common to both lesions. For metachronous tumors, metastatic disease is defined by: (1) interval less than 2 years and in the same lobe, or (2) interval less than 2 years and lymph node drainage sites involved common to both lesions. Niibe et al. recently proposed that a concept dividing OM into two categories: one with controlled primary and another with uncontrolled primary [16]. In general, OM with controlled primary site, so-called oligorecurrence, has better prognosis than OM with uncontrolled primary [17]. This classification helps us to identify patients whose primary tumor has been controled by local therapy such as surgery or radiotherapy but develop OM that could benefit significantly with local therapy to the limited sites of OM. Selective patients in this group may be potentially curable with systemic therapy plus local ablative therapy or surgical resection.

Of course, outside of the thorax, these criteria are not applicable. In most patients with a prior diagnosis of locoregionally confined NSCLC in which the primary tumor is treated and who subsequently develop a metastatic deposit of the same histology with no evidence of a separate primary tumor, it can be presumed that the disease is a metachronous metastatic recurrence. It has been shown that patients presenting with synchronous OM have poorer survival outcomes than those with metachronous OM, though as noted above, the optimal cutoff for distinguishing synchronous versus metachrounous OM has varied. For instance, Tanvetyanon performed a comprehensive review of patients that received adrenalectomy for OM NSCLC, 10 publications contributing 114 patients. Forty-two percent of patients had synchronous metastasis, defined as a disease-free interval (DFI) of $\leq$6 months. The authors found that overall survival (OS) was 12 months in those patients with synchronous metastasis, versus 31 months with metachronous OM [18]. In another study from Japan, investigators found that a DFI of at least 1 year was a prognostic factor for improved survival in patients with OM disease in the bone, lungs, and brain [19]. And in a study by Inoue et al. examining the role of stereotactic radiation to the brain and/or body in OM lesions, the authors found that the 5-year OS rate was 40% for patients with a DFI of $\geq$12 months and 10% for a DFI less than this period [20].

4. Prognostic Factors for Survival in Oligometastatic NSCLC

4.1. Number of Sites. The number of sites that has been classified as OM disease has varied, as authors have defined patients with this entity as any burden from 1 to 5 sites of disease. Several studies have demonstrated, however, that patients who have a larger number of sites have poorer survival outcomes. In the general metastatic setting, investigators from the University of Chicago have shown that baseline whole body metabolic tumor burden, as indicated by F-18 fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) scan, was associated with a poorer prognosis [24]. In the setting of OM disease treated with local therapy, Salama et al. reported their findings of stereotactic

Table 1: Selected studies of local treatment in oligometastatic NSCLC with brain metastases.

Study	Year	*N*	Criteria	Treatment	Findings
Hu et al. [6]	2006	84	Solitary brain metastasis	SRS or surgery	Stage I intrathoracic patients had better OS outcomes than stage III
Bonnette et al. [7]	2001	108	Brain metastasis (98 with solitary)	Surgery	Adenocarcinoma, T stage, complete resection with better outcomes
Rodrigues et al. [8]	2011	66	≤6 intracranial lesions	Image-guided SIB RT	Presence of systemic disease, lower performance status correlated with decreased OS
Iwasaki et al. [9]	2004	41	Solitary brain metastasis	Resection of primary site and brain metastasis	Risk score criteria for improved OS: adenocarcinoma, node-negative, normal CEA level
Mussi et al. [10]	1996	52	Solitary brain metastasis	Resection of primary site and brain metastasis	No status, lobectomy associated with decreased OS. 5-year OS in patients with synchronous/metachronous lesions 6.6/19%, respectively
Machiarini et al. [11]	1991	37	Solitary brain metastasis. Synchronous (<1 month) and metachronous included.	Resection of primary site and brain metastasis	Most frequent site of first recurrence was ipsilateral thorax ($n = 14$) and brain ($n = 6$). The receipt of adjuvant chemotherapy was strongest predictor of disease-free interval
Wronski et al. [12]	1995	231	Single (87%) or multiple (13%) metastatic intracranial lesions	Resection	Female gender, complete location, infratentorial location, no systemic metastases, age < 60 years associated with improved OS

ablative body radiation (SABR) in patients with 1–5 sites of metastatic disease and a life expectancy of at least 3 months. The primary sites included lung, head and neck, breast, colon/rectum, and kidney. The authors found that patients with 1-2 lesions had significantly better survival outcomes than those with 3–5 metastatic lesions [25]. These results have been recently updated by the same institution examining only patients with NSCLC, and the authors found that greater than two sites of disease were associated with worse progression-free survival (PFS) [26]. A study by Rodrigues et al. assessing RT in the setting of oligometastatic brain metastasis found that the cumulative brain metastases volume was of borderline significance when examining intracranial control [8]. In general, it is reasonable to presume that, particularly in the setting of the pathophysiology of metastatic disease described above, the lower the number of OM sites, the better the clinical outcome. In addition to the number of OM sites, the organ involved may also have the impact in clinical outcome. In general, the involvement of liver or bone may carry worse prognosis compared with adrenal or brain although the published data is limited.

4.2. Thoracic Disease Burden (T and N Stage). Several studies have shown that patients with earlier T and N stages have better improved survival outcomes in OM disease. For instance, investigators from MD Anderson Cancer Center examined 84 patients with newly diagnosed NSCLC and a solitary brain metastasis. The authors found that with aggressive treatment to the primary site, patients with stage I disease had survival outcomes that were comparable to those without brain metastases, but survival outcomes were much lower in those patients with stage III disease and a solitary brain metastasis versus those with stage III disease alone [6]. In another analysis of 103 patients with metastatic brain metastases, including 98 with a single brain metastasis, Bonnette et al. found that patients with both lower T and N stage had improved survival rates, leading the authors to conclude that aggressive treatment to the primary site should be favored in those patients without mediastinal lymph node involvement [7]. And in a study assessing the role of metastastectomy in patients with stage IV NSCLC undergoing metastastectomy for extracranial and extra-adrenal metastases, Salah et al. found that patients with stage III intrathoracic disease had 5-year survival rate of 0% versus 77% and 63% in those patients with stage II and I disease, respectively [27].

4.3. Histology. Similar to other stages of NSCLC, adenocarcinoma has been found to portend for a more favorable prognosis in OM disease. The study by Bonnette et al. described above found that patients with adenocarcinoma had improved survival outcomes compared to other histologic subtypes [7]. Iwasaki et al. attempted to elucidate prognostic criteria for patients with NSCLC and brain metastases in patients that underwent resection of either the lung or brain lesion. The authors found that an adenocarcinoma histology was estimated as a risk factor in their final model, along with node negative status and a normal carcinoembryonic antigen (CEA) level [9].

5. Data for Aggressive Local Therapy in Oligometastatic NSCLC by Site of Disease

5.1. Brain. Table 1 demonstrates selected studies of patients treated with local therapy in the setting of OM NSCLC [9–13]. Several points can be made from examining this table. First, the definition of oligometastatic varies among studies, from a solitary metastasis to up to 6 metastases. As a definition of 5 or less is consistent with most analyses in the literature, we would advocate these criteria in future analyses.

Table 2: Selected studies of local treatment in oligometastatic NSCLC with mixed metastatic sites.

Study	Year	N	Criteria	Treatment	Findings
Hanagiri et al. [21] (retrospective)	2011	36	Up to 5 metastastic sites, stage IV disease	Surgery or radiation	5-year OS with distant metastasis 30.1%, pleural dissemination 25.1%
Guerra et al. [22] (retrospective)	2012	78	Up to 5 synchronous metastatic sites, Definitive chemoRT (44 also underwent treatment to OM sites)	Surgery or radiation to OM sites	High radiation dose, performance status, lower intrathoracic tumor volume correlated with improved OS
Downey et al. [23] (prospective)	2002	23	Solitary synchronous lesions	MVP × 3, then surgery on all sites, then VP × 2	MVP poorly tolerated, 2/23 patients disease free at 5 years

Second, several of the prognostic factors above were shown to be correlated with survival outcomes, such as nodal status, histology, and synchronous versus metachronous disease. Finally, an aggressive approach to both the primary and the oligometastatic site was feasible and successful in selecting patients, and thus we would recommend considering a combined approach of systemic therapy with either resection or stereotactic radiosurgery (SRS) in patients with a solitary brain metastasis [17]. Patients with advanced nodal disease could be considered for such an approach, pending response to systemic treatment.

5.2. Adrenal Gland. There have been several small studies pertaining to aggressive treatment of the adrenal gland in the setting of OM NSCLC. As mentioned above, these studies have been pooled and analyzed by Tanvetyanon et al., who included 10 publications and 114 patients. The authors had the following findings: 42% of patients had synchronous metastases (DFI $\leq$ 6 months), with the remainder having metachronous lesions. Median DFIs were 0 and 12 months in these two groups, respectively. Second, serious complications from adrenalectomy in this setting were rare. Third, the 1- and 2-year OS rates were 80% and 52% for metachronous lesions and 45% and 30% for synchronous OM disease, while the 5-year survival rates were approximately 25% for each disease state [18]. A comprehensive review of prognostic factors in the setting of isolated adrenal metastases has not ever been performed to our knowledge, likely due to the small size of available studies. However, 5-year survival rates range from approximately 5 to >50% [18, 28–31], and we believe that similar prognostic factors can be extrapolated as has been observed in OM to the brain and mixed sites.

5.3. Studies Examining Aggressive Treatment to the Primary Site and Mixed Oligometastatic Sites. Several studies have examined the impact of treating the primary site and all OM sites of disease regardless of location, as depicted in Table 2. Hanagiri et al. retrospectively investigated the outcomes of 36 patients who underwent surgical resection to the primary site for stage IV NSCLC between 1995 and 2008 for up to 5 sites of metastatic disease. The metastatic sites ranged from brain, adrenal gland, axillary lymph nodes, liver, and contralateral pulmonary metastases. The overall 5-year survival rate in this group of patients was 26.8%, with improved OS rates (though not statistically analyzed) in patients with negative lymph nodes at the time of treatment (28.3 versus 20.4%) [21]. And Guerra et al. recently analyzed the role of aggressive chemoradiation to the primary site in the thorax with or without treatment to the distant lesions in a variety of OM sites. The authors found that more aggressive thoracic radiation, as manifested by increased radiation dose, was associated with improved OS outcomes [22].

One of the only prospective trials assessing the role of aggressive local therapy in the setting of OM disease was a phase II study performed at Memorial Sloan-Kettering Cancer Center. In this study, 23 patients with a synchronous solitary metastasis underwent three cycles of chemotherapy with mitomycin, vinblastine, and cisplatin (MVP) followed by resection of all disease sites and then two more cycles of VP therapy. The authors found that 12 patients completed induction chemotherapy, and 8 of these patients underwent R0 (microscopically negative margin) resections. Five patients had R0 resections without completing induction MVP. The median survival was 11 months, and 2 patients survived for 5 years without disease (<10%). The authors concluded that OS did not appear to be superior with this treatment strategy [23].

6. Treatment of Oligometastatic NSCLC: Where Are We Now?

Much has changed since the aforementioned prospective trial demonstrating no clear efficacy to an aggressive local approach after induction chemotherapy. First, over the past decade, radiation techniques have advanced greatly with the advent modalities such as intensity-modulated radiation therapy and stereotactic radiation. As a result, combined techniques of surgical resection and radiation can be used to more effectively treat residual sites of disease and minimize toxicity, both of which can be individualized based on the size and location of the disease, as well as a patient's anatomical characteristics. Second, targeted therapy has advanced systemic options, and patients can therefore be better selected for optimal treatment based on molecular characteristics. For example, randomized phase III trials have shown that patients with known epidermal growth factor receptor (EGFR) mutations experience prolonged survival outcomes compared with standard chemotherapy alone [32, 33]. Erlotinib is now Food and Drug Administration (FDA)

approved for the treatment of first-line NSCLC patients bearing EGFR mutations. Similar advances are being made with anaplastic lymphoma kinase (ALK) inhibitors, which are effective in patients that have rearrangements of the ALK gene [34]. Finally, maintenance chemotherapy has been shown to provide survival benefits in patients with metastatic NSCLC, either in the continuation maintenance or switch maintenance setting. In terms of continuation maintenance, Eastern Cooperative Oncology Group (ECOG) 4599 demonstrated a benefit for bevacizumab [35] and the Paramount Phase III study showed an improvement in PFS for pemetrexed [36]. Similarly, in the switch maintenance setting, the SATURN study demonstrated an improvement in OS with erlotinib [37], while a similar improvement in survival was shown with pemetrexed in the JMEN study [38].

These advances create opportunities for the treatment of oligometastatic NSCLC. Utilizing the information gained from multiple retrospective studies, this question would ideally be answered with a prospective trial in which patients are randomized to novel systemic therapy followed by aggressive local therapy utilizing both surgery and modern radiation techniques. Maintenance therapy should also remain an option in this patient population when appropriate, and patients could be stratified or included/excluded based on the prognostic factors gleaned from the analyses above. Given the emerging biologic and clinical evidence that oligometastatic NSCLC is a separate disease entity when compared to widespread metastatic disease, ideally patients could receive selective aggressive local therapy based on their specific disease characteristics, similar to other oncologic scenarios in which personalized medicine is the ultimate goal. A phase II clinical study to address this issue is ongoing in MD Anderson Cancer Center.

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Clinical Study

Clinical Outcomes of Stereotactic Body Radiotherapy for Patients with Lung Tumors in the State of Oligo-Recurrence

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We retrospectively evaluated the clinical outcomes of patients with oligometastatic lung tumors who underwent stereotactic body radiotherapy (SBRT). Twenty-two patients with one or two oligometastatic lung tumors were treated with SBRT at our institution between 1999 and 2009. With a median follow-up period of 25 months from the date of SBRT to the detection of oligometastatic lung tumors, the patients' 3- and 5-year overall survival (OS) and progression-free survival (PFS) rates were 72% and 54%, respectively. The median disease-free interval (DFI) between the treatment of the primary site and SBRT to oligometastatic lung tumors was 41 months. The OS of patients with a DFI $\geq$ 36 months was significantly longer than that of the patients with a DFI $<$ 36 months by the log-rank test ($P = 0.02$). For patients with a DFI $\geq$ 36 months, the 3- and 5-year OS rates were both 88%, compared to 50% for the patients with a DFI $<$ 36 months. The primary tumor of all patients was locally controlled when SBRT to oligometastatic lung tumors was performed, and thus they were in the state of "oligo-recurrence." Patients with oligometastatic lung lesions treated by SBRT had good prognoses. This was especially true of the patients with a long DFI and in the state of "oligo-recurrence."

1. Introduction

Most patients who have had any recurrent or metastatic sites of cancer are considered to be in their last stage of life. However, new notions of oligometastases and oligo-recurrence have been proposed [1–9]. Oligometastases is the state in which the patient shows distant recurrence in only a limited number of regions. The clinical state of oligometastatic dise-ase was proposed in 1995 by Hellman and Weichselbaum [1], who hypothesized that local control of oligometastases may yield improved systemic control and prolonged survival. Niibe et al. also discussed the state of oligo-recurrence [2–4]; they defined it as oligometastases with a controlled primary cancer site.

Stereotactic body radiotherapy (SBRT) with a high local dose has been applied to extracranial diseases such as peripheral stage I nonsmall cell lung cancer (NSCLC), and it has been reported to provide excellent local control and survival compatible with surgery [10, 11]. SBRT has also been used in Japan for patients with fewer than three lung metastases $\leq$5 cm in diameter. In the present study, we retrospectively analyzed our experience with SBRT for patients with oligometastatic lung tumors.

2. Methods and Materials

2.1. Patient Characteristics. A database of patients who received SBRT for metastatic lung tumors at our institution was used for the patient selection. There were 22 patients who had one or two oligometastatic lung tumors at the time of SBRT and had been treated with SBRT between 1999 and 2009. The diagnosis of the oligometastatic lung tumors was based on whole-body computed tomography (CT). Fluorodeoxy-glucose (FDG)-positron emission tomography (PET) was performed as needed. The primary tumor of all patients was locally controlled when SBRT to the oligometastatic lung tumors was performed. The treatment methods for the primary sites were surgery in 13 patients and definitive radiotherapy in nine. Definitive radiotherapy consisted of conventional radiotherapy in one patient, brachytherapy in one patient, and SBRT in seven.

We labeled the treatment interval time from the primary sites to oligometastatic lung tumors as the disease-free interval (DFI). In this study, all analyses started from the day of SBRT to oligometastatic lung tumors.

The patient characteristics are given in Table 1. There were 8 men and 14 women, and the median age was 67 years (range 30–84 years). The primary cancers consisted of lung cancer ($n = 9$), head and neck cancer ($n = 4$), breast cancer ($n = 3$), colorectal cancer ($n = 2$), genitourinary cancer ($n = 2$), thymic cancer ($n = 1$), and skin cancer ($n = 1$). The primary histology consisted of adenocarcinoma ($n = 13$), squamous cell carcinoma ($n = 4$), renal cell carcinoma ($n = 1$), transitional cell carcinoma ($n = 1$), large-cell carcinoma ($n = 1$), malignant melanoma ($n = 1$), and apocrine gland carcinoma ($n = 1$). There were 13 patients who had only one oligometastatic lung tumor and nine patients who had two oligometastatic lung tumors. The median tumor size was 15 mm (range 8–47 mm). No chemotherapy was allowed until tumor progression.

2.2. SBRT Technique. All patients received SBRT to oligometastatic lung tumors as the definitive radiotherapy. Nine patients received SBRT using a real-time tumor-tracking radiotherapy (RTRT) system, and 13 patients received SBRT without RTRT.

The RTRT system has been described in detail elsewhere [12, 13]. In brief, 1.5 to 2.0 mm gold markers were implanted near the tumor by means of image-guided procedures. CT scans were taken with the patients holding their breath at the end of normal expiration. The gross tumor volume (GTV) was contoured in axial CT images. The clinical target volume (CTV) was defined three-dimensionally as the GTV on CT with a 5 mm margin for metastatic lung tumors and was considered to be equal to the internal target volume (ITV). The planning target volume (PTV) was three-dimensionally defined as the CTV plus a 5 mm margin with optimal reduction near the organ at risk (OAR).

SBRT without RTRT was described as follows. To determine the ITV margin, CT scans were performed three times, with breath holding at the expiratory and inspiratory phases and with free breathing. The three GTVs on CT at three phases were superimposed on the radiation treatment system to represent GTV + ITV. The CTV was defined three-dimensionally as the GTV + ITV on CT with a 5 mm margin. The PTV was three-dimensionally defined as the CTV plus a 5 mm margin with optimal reduction near the OAR.

We administered 48 Gy in four fractions at the isocenter calculated by Clarkson algorism or 40 Gy in four fractions to the 95% volume of PTV by superposition algorism with a treatment period of 4 to 7 days. Patients were treated with 4- or 6-MV photons. SBRT was delivered using multiple noncoplanar static ports.

2.3. Followup after SBRT. Follow-up visits were usually every 3 months after SBRT. CT scans were usually performed every 3–6 months after SBRT. Local progression was diagnosed on the basis of histologic confirmation or enlargement of the local tumor on CT that continued for at least 6 months. FDG-PET was recommended when local recurrence was suspected, but this was not mandatory.

Table 1: Patient characteristics (22 patients).

Characteristics	Value
Age (years)	
Median	67
Range	30–84
Gender (n)	
Male	8
Female	14
Primary cancer (n)	
Lung	9
Head and neck	4
Breast	3
Colorectal	2
Genitourinary	2
Thymic	1
Apocrine gland	1
Primary histology (n)	
Adenocarcinoma	13
Squamous cell carcinoma	4
Others	5
Treatment for primary cancer (n)	
Resection	13
SBRT	7
Conventional radiation therapy	1
Brachytherapy	1
Number of oligometastatic tumors (n)	
1	13
2	9
Tumor diameter (n)	
<20 mm	25
21–30 mm	4
>30 mm	2

SBRT: stereotactic body radiotherapy.

2.4. Ethical Considerations. Written informed consent to receive SBRT was obtained from all patients. This retrospective study was performed in accordance with the 1975 Declaration of Helsinki, as revised in 2000.

2.5. Statistical Analysis. The overall survival (OS) and progression-free survival (PFS) rates were calculated from the date of SBRT to oligometastatic lung tumors using the Kaplan-Meier method. The log-rank test was used to identify significant differences. R version 2.14.2 with the survival packages (R project for statistical computing, Vienna, Austria) was used for the statistical analyses. A value of $P < 0.05$ was considered significant.

Table 2: Patterns of disease progression (9 patients).

Pattern	*n*
New pulmonary metastases	4
Liver metastases	1
Bone metastases	1
Multiple metastases	3

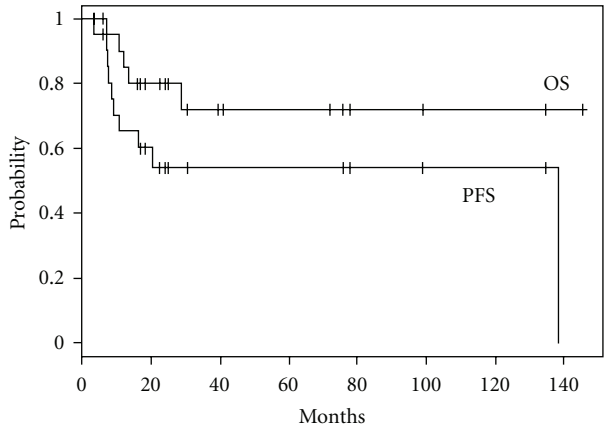

Figure 1: Kaplan-Meier actuarial overall survival (OS) and progression-free survival (PFS) rates.

3. Results

3.1. Survival. With a median follow-up period of 25 months (range 4–146 months) from the day of SBRT to oligometastatic lung tumors, the 3- and 5-year overall survival and progression-free survival rates were 72% and 54% (Figure 1). The median DFI between the treatment of the primary site and SBRT to oligometastatic lung tumors was 41 months. The primary tumor of all patients was locally controlled when SBRT to oligometastatic lung tumors was performed; the patients were thus in the state of "oligo-recurrence."

3.2. Patterns of Failure. Disease progression was observed in nine patients (Table 2). All irradiated lesions by SBRT were controlled. New intrapulmonary metastases were observed in four patients, bone metastases were observed in one patient, and liver metastases were observed in one patient. Multiple metastatic lesions including regional lymph node, brain, bone and/or liver were observed in three patients.

3.3. Toxicities. Adverse effects were graded according to the Common Toxicity Criteria for Adverse Events, version 3.0. Grade 2. Intercostal neuralgia occurred in one patient. No radiation pneumonitis of grade 3 or more was observed.

3.4. Prognostic Factors. We also analyzed the survival differences stratified by DFI duration. DFI duration was divided into <36 or ≥36 months. The OS of patients with a DFI ≥ 36 months ($n = 13$) was significantly longer than the OS of those with a DFI < 36 months ($n = 9$) ($P = 0.02$). For patients with a DFI ≥ 36 months, the 3- and 5-year OS rates were both 88%, compared to 50% for patients with a DFI < 36 months (Figure 2).

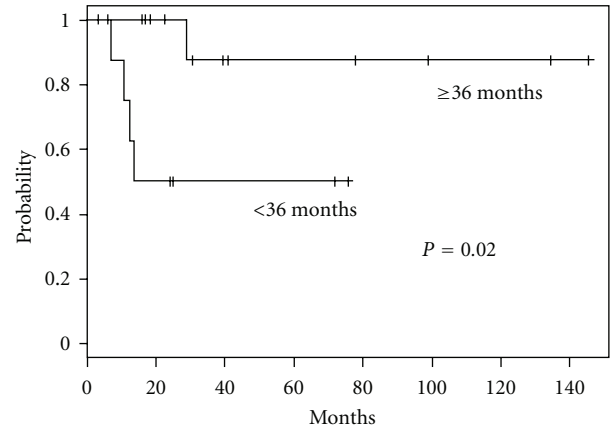

Figure 2: Kaplan-Meier curve of overall survival rates for patients with a disease-free interval (DFI) <36 months ($n = 9$) or ≥36 months ($n = 13$). The groups' survival rates differed significantly ($P = 0.02$).

4. Discussion

In this patient population, the 3- and 5-year overall survival and progression-free survival rates were 72% and 54%, respectively, which was equivalent to or better than those in previous studies of oligometastatic lung tumors as follows. Norihisa et al. reported the results of SBRT for oligometastatic lung tumors [14]. The OS rate and PFS rates at 2 years were 84.3% and 34.8%. Rusthoven et al. recently reported the results of multi-institutional phase I/II trials of SBRT for lung metastases [15]. The actual local control rates at 1 and 2 years after SBRT for oligometastatic lung tumors were 100% and 96%, respectively, and the median survival time was 19 months.

A landmark study of more than 5,000 patients by the International Registry of Lung Metastases (IRLM) demonstrated that long-term survival can be achieved in a proportion of patients with lung metastases treated with metastasectomy [16]. The actuarial survival after complete metastasectomy was 36% at 5 years. With the exclusion of the apparently favorable tumors, the survival outcome at 2 years was approximate 70%.

We previously reported the clinical outcomes of stereotactic brain and/or body radiotherapy for patients with oligometastatic lesions. The organs affected by oligometastatic lesions were the brain, lung, and/or adrenal gland [17]. For patients with oligometastatic lung disease, the 3- and 5-year OS rates were both 63%, significantly better than the 22% and 14% of those with brain/adrenal metastases.

In the present study, the DFI between the treatment of primary site and SBRT to oligometastatic lung tumors was the prognostic factor. Norihisa et al. also reported that patients with a longer DFI had a greater overall survival rate

[14]. Patients with a DFI ≥ 36 months had significantly greater OS compared to those with a DFI < 36 months. In the IRLM study, a multivariate analysis revealed that a DFI longer than 36 months is a factor associated with improved survival [15]. In our previous study, we also found that patients with a DFI ≥ 12 months had significantly greater OS compared to those with a DFI < 12 months [17].

The IRLM study and multi-institutional phase I/II trials by Rusthoven et al. included locally uncontrolled primary tumors, so-called oligometastases [15, 16]. However, in the present study, the primary tumor of all patients was locally controlled when SBRT to oligometastatic lung tumors was performed, that is, in the so-called state of "oligo-recurrence." Therefore, the present population's outcomes were equivalent or better than those in the previous study of oligo-metastatic lung tumors. We were also curious about survival differences between patients with and without oligo-recurrence, but all of the patients in this population were in the state of oligo-recurrence. Moreover, in the present study, the median DFI between the treatment of the primary site and the SBRT to oligometastatic lung tumors reached 41 months, a very long period compared with other studies. However, it was difficult in this study to distinguish second primary lung cancers from metastatic lung cancers, and oligometastatic lung tumors from NSCLC might be second primary lung cancers, which may have better prognoses than metastatic lung cancers.

One shortcoming of the present study is the retrospective nature of the analysis. Patients with sufficient medical conditions were probably selected beforehand to receive SBRT. The large number of patients who died within a short period may have masked the possible progression of the disease and local failure. However, it is notable that there was a definite group of patients treated with SBRT for oligometastatic tumors who experienced long survival even with distant metastasis. A large prospective trial is required to establish the precise benefits of SBRT for patients with oligometastatic lung tumors. Our findings suggest that the DFI should be included in the stratification criteria in a prospective randomized trial comparing treatment with and without SBRT.

In conclusion, patients with oligometastatic lung lesions treated by SBRT had good prognoses, especially the patients with a long DFI and in the state of "oligo-recurrence."

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