small because we enforced strict selection criteria. We excluded tumors < 10 mm in diameter (their maximum diameters were measured on pulmonary window setting CT images) because we could not reliably measure the SUV_{max} in such small tumors. In addition, although we excluded some tumors that were treated with a mono-polar needle, ablated incompletely, or were also treated with radiotherapy before or after RFA, this selection was necessary to equalize the experimental conditions. If we included tumors that were ablated under different conditions, the biological behavior of these tumors might modify the study results in such a small population. In addition, the effects of radiotherapy would potentially make a significant impact on the local control of lung tumors. The third limitation is that ablation factors, such as the maximum power, the ablation time, and the number of overlapping ablations, were not evaluated in the investigation of risk factors for local tumor progression. Although our ablation algorithm varies according to tumor size (thus according to the array diameter of the electrodes), almost all tumors (38/39) were treated using the same ablation technique. Therefore, the ablation conditions for each tumor were similar. Another possible limitation is that the selected tumors included varied histological types in this study. However, Hiraki T. *et al.* reported that the tumor type *per se* did not significantly influence the local control [19]. We did not adjust any of the study data based on the differences between tumor types.

In conclusion, this study demonstrated that the SUV_{max} determined using PET/CT may be an effective new prognostic factor for tumor recurrence after lung RFA. We believe that ^{18}F-FDG PET can be performed as a pre-RFA risk evaluation for local tumor recurrence after RFA, rather than just for the detection of whole body metastasis.

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Percutaneous radiofrequency ablation of clinical stage I non–small cell lung cancer

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Objective: This study aimed at retrospectively evaluating the outcomes of radiofrequency ablation of clinical stage I non–small cell lung cancer.

Methods: This study was carried out on 50 nonsurgical candidates (29 men and 21 women; mean age, 74.7 years) with clinical stage I (IA, n = 38; IB, n = 12) histologically proven non–small cell lung cancer. A total of 52 tumors were treated with 52 ablation sessions. Radiofrequency ablation was performed percutaneously under computed tomography fluoroscopic guidance. The outcomes of radiofrequency ablation were evaluated, including toxicity, local efficacy, and patient survival. Toxicity was evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0. Local efficacy was evaluated by using computed tomography scan with a contrast medium. The overall, cancer-specific, and disease-free survivals were estimated with Kaplan–Meier analysis.

Results: Grade 2 and 3 adverse events occurred after 6 (12%) and 3 (6%) of the 52 sessions, respectively. The median follow-up period was 37 months. Local progression was observed in 16 (31%) of the 52 tumors. The 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.

Conclusions: Radiofrequency ablation of clinical stage I non–small cell lung cancer was minimally invasive and provided promising patient survival, although the local efficacy needs to be improved. (J Thorac Cardiovasc Surg 2011;142:24-30)

Primary lung cancer is the most common malignancy and the leading cause of death from cancer worldwide. Surgical resection with a lobectomy is suggested as the first-line treatment for treating early-stage non–small cell lung cancer (NSCLC). Unfortunately, certain patients are considered medically inoperable, and conventional external beam radiation therapy (XRT) has been traditionally administered to such patients. A meta-analysis of patients with stage I NSCLC treated by conventional XRT revealed mean overall and cause-specific survivals at 3 years of 34% and 39%, respectively.[1] Because such survival outcomes after XRT are unsatisfactory, various alternative modalities have been the focus of many studies. For example, stereotactic radiation therapy shows favorable survivals for patients with stage I NSCLC: 56% to 60% at 3 years.[2-4] Radiofrequency ablation (RFA) has received considerable attention as a local therapy mainly for hepatic cancer. The favorable outcomes of RF ablation of hepatic cancer have facilitated the application of this technique to lung cancer. Currently, RFA is gaining popularity as a treatment of lung cancer. The purpose of this study was to retrospectively evaluate the outcomes of RFA on nonsurgical candidates with clinical stage I NSCLC.

MATERIALS AND METHODS

Study Population

Approval from the institutional review board and informed consent from the patients were obtained to perform RFA of lung cancer. Our institutional review board also provided approval for our retrospective study. From July 2002 to September 2009, we treated 56 patients with clinical stage I primary lung cancer at Okayama University Medical School. We excluded 6 of these patients, because the tumor was also treated with adjuvant radiation therapy (n = 4), the patient was lost to follow-up (n = 1), or the tumor was not histologically proven (n = 1). Thus, this study consisted of 50 patients with histologically proven clinical stage I NSCLC. Twenty patients who were previously reported in the literature[5] were included in this study, although their follow-up information was updated. Two patients had synchronous double primary lung cancers; thus, a total of 52 tumors were treated with 52 ablation sessions.

For clinical staging, chest and abdomen computed tomography (CT) scans were performed in all patients; positron emission tomography (PET) scanning was performed in 29 patients, and brain magnetic resonance imaging was performed in 26 patients. Lymph node metastasis was considered absent, because none of the lymph nodes were larger than 1.0 cm in short-axis diameter and there was no more accumulation of ^{18}F-fluorodeoxy glucose in the lymph nodes than mediastinal structures when PET was performed. This led to the diagnosis of clinical stage IA and IB cancers in 38 and 12 patients, respectively.

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Abbreviations and Acronyms

CT = computed tomography
NSCLC = non–small cell lung cancer
PET = positron emission tomography
RFA = radiofrequency ablation
XRT = external beam radiation therapy

The characteristics of the 50 patients and the 52 tumors are summarized in Table 1. There were 29 men and 21 women (mean age, 74.7 years; range, 52–88 years). Sixteen patients had a history of surgery for the following types of cancer: lung cancer (n = 9), esophageal cancer (n = 2), cholangiocarcinoma (n = 2), hepatocellular carcinoma and pulmonary metastasis (n = 1), breast cancer (n = 1), and colon, uterus, and ureter cancer (n = 1). The mean long-axis tumor diameter was 2.1 cm (median, 1.8 cm; range, 0.7–6.0 cm). There were 41 adenocarcinomas and 11 squamous cell carcinomas. Eleven tumors in 10 patients were adenocarcinomas showing pure ground-glass opacity on CT images.

Patients were first referred to the department of thoracic surgery. All patients were determined to be nonsurgical candidates by a surgeon because of one or more of the following reasons: poor pulmonary function (predicted forced respiratory volume in 1 second $\leq$ 1000 mL), poor cardiac function (New York Heart Association class $\geq$ III), advanced age ($\geq$80 years), poor performance status ($\geq$2), substantial comorbidity, or refusal to undergo surgery. Fourteen patients had poor pulmonary function, 1 patient had poor cardiac function, 7 patients had advanced age, 1 patient had poor performance status, 7 patients had substantial comorbidity, and 9 patients had combinations of 2 of those reasons. The remaining 11 patients were deemed operable but refused to undergo surgery. For the 27 patients whose vital capacity was examined before RFA, the mean value was 2.53 L (range, 1.06–3.97 L); for the 30 patients whose forced expiratory volume and volume percentage in 1 second were examined before RFA, the mean values were 1.68 L (range, 0.41–3.19 L) and 68.6% (range, 42.3%–96.3%), respectively. No patient received concurrent or adjuvant therapy.

Radiofrequency Ablation Technique

RFA was always performed percutaneously using CT fluoroscopy (Asteion; Toshiba, Tokyo, Japan). Intraprocedural pain was treated by using local anesthesia or epidural anesthesia along with conscious sedation with an intravenous drip infusion of 0.3 mg fentanyl and an intramuscular injection of 25 mg hydroxyzine. In the case of expected severe procedural pain, for example, when the tumor was close to the pleura, or if the patient asked for it, epidural anesthesia was administered. Thus, epidural anesthesia was used in 15 sessions (15 patients). General anesthesia was not used for any of the patients.

Patients were placed in a supine or prone position according to the location of the tumor, and grounding pads were placed on their thighs. An initial CT examination was scanned to identify the precise location of the tumor and decide the pathway of electrode insertion. The skin at the entry site of the electrode was sterilized. After the administration of anesthesia, the electrode was introduced into the tumor and connected to a generator. The electrodes that were used for the ablation included a multitined expandable electrode (LeVeen; Boston Scientific, Natick, Mass) with an array diameter of 2 cm (n = 15), 3 cm (n = 15), 3.5 cm (n = 4), or 4 cm (n = 2); a single internally cooled electrode (Cool-tip; Valleylab, Boulder, Colo) with a 1-cm (n = 3), 2-cm (n = 7), or 3-cm (n = 4) noninsulated tip; or a cluster internally cooled electrode (n = 2) (Cool-tip; Valleylab). In the case of the Valleylab device, radiofrequency energy was applied with an impedance control algorithm for 12 minutes during the internal cooling of the electrode. The temperature of the tumor at the electrode tip was measured immediately after the generator was turned off. When the temperature failed to reach 60°C, additional application at the same site was then required. When using the Boston Scientific device, the energy was applied until the impedance showed a rapid increase or an automatic shut-off occurred after 15 minutes; this was repeated once at each site. To obtain the ablative margin, multiple overlapping ablation zones were created whenever deemed necessary.

A chest CT scan was performed immediately after the procedure to evaluate ablation zone and procedural complications. A chest radiograph was obtained 3 hours later and the following morning to assess the occurrence of complications, such as pneumothorax, hemothorax, and pleural effusion. A complete blood count and blood biochemistry were examined at 1 and 3 days after RFA.

Follow-up

The patients were followed up, whenever possible, at 1, 3, 6, 9, and 12 months, and thereafter at 6-month intervals. At every follow-up session, a chest CT scan was performed with 5-mm collimation before and 30 and 90 seconds after the intravenous administration of a contrast medium (iopamidol, Iopamiron 300; Nihon Schering, Osaka, Japan) at a rate of 3 mL/s to assess local efficacy. The size of the ablated lesion usually exceeds the preprocedural tumor size on CT images for the first 3 months after RFA, because the ablated lesion is detected together with the ablated marginal parenchyma.[6] During this period, thus, the effectiveness of RF ablation cannot be determined by comparing the tumor size but can be determined by contrast enhancement. That is, the tumor is considered to be completely treated when the entire ablation zone is not contrast-enhanced or when the ablation zone exhibits contrast enhancement; however, the enhancement zone is peripheral, concentric, symmetric, and uniform with smooth inner margins. Such enhancement zone is considered to correspond to reactive hyperemia, inflammation, or granulation at the marginal parenchyma.[7] Thereafter, local efficacy was evaluated by comparing the size and geometry of the ablation zone in the previous CT images. Local progression was defined as tumor progression at the ablation zone and considered to have occurred when the ablation zone was circumferentially enlarged or an irregular, scattered, nodular, or eccentric focus in the ablation zone appeared. The focus generally exhibited some degree of contrast enhancement, and thus contrasted against the unenhanced necrotic tumor tissue.

For the assessment of hematogenous metastasis, an abdominal CT scan was generally performed with a contrast medium at 6-month intervals. Although PET was not included in our routine follow-up modalities, for 29 patients, PET examinations were also performed to evaluate the outcomes of RFA and hematogenous metastasis. When symptoms suggesting brain or bone metastasis were observed, a radiologic examination such as magnetic resonance imaging or a bone scintigram was performed.

Study End Points and Statistical Analysis

The study end points included toxicity, local efficacy, and patient survival. Toxicity was evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0, and adverse events of grade greater than 1 were noted. The forced expiratory volume in 1 second 1 to 3 months after RFA was compared with that before RFA by using the paired *t* test. Local efficacy was evaluated by the presence of local tumor progression, which was diagnosed with the aforementioned criteria. The overall local progression rates and the local progression rates according to tumor size were calculated. Further, the local progression rates according to type of electrode used (internally cooled electrode or multitined expandable electrode) were compared by using the log-rank test. In addition to local progression, parenchymal recurrence (defined as recurrence in the same lobe but away from ablation zone), regional recurrence (defined as hilar and ipsilateral mediastinal lymph nodes recurrence), and distant recurrence (all other recurrences) were also evaluated.

The overall, cancer-specific, and disease-free survivals were estimated with Kaplan–Meier analysis. For estimation of cancer-specific survival

TABLE 1. Characteristics of the 50 patients and the 52 tumors

	Patients (n = 50)
Age (y)	
Mean	74.7
Range	52–88
Gender	
Male	29
Female	21
Vital capacity (L)*	
Mean	2.53
Range	1.06–3.97
Forced expiratory volume in 1.0 s (L)†	
Mean	1.68
Range	0.41–3.19
Stage	
IA	38
IB	12
History of surgery for cancer	
Yes	16
No	34
Tumors (n = 52)	
Diameter (cm)	
Mean	2.1
Range	0.7–6.0
Histology	
Adenocarcinoma	41
Squamous cell carcinoma	11
Lobar location	
RUL/RML/RLL	10/2/12
LUL/LLL	15/13
Electrode used for ablation	
Internally cooled	16
Multitined expandable	36

RUL, Right upper lobe; *RML,* right middle lobe; *RLL,* right lower lobe; *LUL,* left upper lobe; *LLL,* left lower lobe. *Data are available in 27 patients. †Data are available in 30 patients.

and disease-free survival, the terminal event was cancer-related death and any death or cancer recurrence, respectively. The survivals were also estimated according to cancer stage (IA or IB), type of electrode used, and procedure period (first 4 years or later years), and compared between the 2 groups by using the log-rank test. Statistical analyses were performed using the Statistical Package for the Social Sciences software (version 11.0; SPSS Inc, Chicago, IL).

RESULTS

The case of a 79-year-old woman with clinical stage IA NSCLC is shown in Figure 1. Grade 1 pneumothorax occurred after 22 sessions. Grade 2 and 3 adverse events occurred after 6 (12%) and 3 (6%) of the 52 sessions, respectively, whereas no grade 4 or 5 adverse events occurred. The grade 2 adverse events included pneumothorax that required chest tube placement after 1 session, pneumonitis that required medical therapy after 3 sessions, and both of those after 2 sessions. The grade 3 adverse events included pleural effusion that required chest tube placement after 1 session, bronchopleural fistula that required surgical intervention to cover the pleural orifice of the fistula in 1 session, and pleural infection that required radiologic chest tube placement after 1 session.

Among the 30 patients in whom forced expiratory volume in 1 second was examined before RFA, this test was repeated 1 to 3 months after RFA in 22 patients. The mean forced expiratory volume in 1 second after RFA for the 22 patients was 1.58 L (range, 0.68–2.74 L); the volume was not significantly different ($P = .17$) than the volume before RFA. Local progression was observed in 16 (31%) of the 52 tumors at a median of 15 months after the session. Five of the 16 locally progressing tumors were confirmed by biopsy. The local progression rate according to tumor size was 33% (10/30) for tumors 2.0 cm or less, 40% (4/10) for tumors 2.1 to 3.0 cm, and 17% (2/12) for tumors greater than 3.0 cm. The local progression rates were not significantly different according to type of electrode ($P = .10$). Six of the 16 locally progressing tumors were treated again in 1 or 2 repeat sessions; 4 tumors were completely treated and the other 2 tumors progressed again. Finally, local control was achieved in 40 (77%) of the 52 tumors at the time of this report. Regional, parenchymal, and distant recurrence occurred in 2, 7, and 8 patients, respectively.

The median follow-up period of the 50 patients was 37 months (mean, 39 months; range, 2–88 months). The survival outcomes of the 50 patients are summarized in Figure 2. Of the 50 patients, 19 died and 31 were surviving at the time of this report. Of the 19 patients who died, 12 died of cancer progression and the remaining 7 died of other causes. Of the 7 patients who died of other causes, 2 had local progression and 5 were free from cancer. Of the 31 patients who survived, 20 were free from cancer since RFA. Local progression or intrapulmonary metastasis developed in 5 patients, who were then completely treated with a partial resection or repeat RFA. At the time of this report, these 5 patients were free from cancer. The remaining 6 patients showed recurrence, such as local progression, intrapulmonary metastasis, or lymph node metastasis.

The median and mean survival times were 67 months and 59 months, respectively. The overall survivals were 94% at 1 year, 86% at 2 years, 74% at 3 years, 67% at 4 years, and 61% at 5 years (Figure 3). The survivals for stage IA and IB cancers were 95% and 92% at 1 year, 89% and 75% at 2 years, 83% and 50% at 3 years, 73% and 50% at 4 years, and 66% and 50% at 5 years, respectively (Figure 4). The survivals were not significantly different between the 2 groups ($P = .057$). The survivals were not significantly different according to type of electrode ($P = .35$) or procedure period ($P = .77$). The cancer-specific survivals were 100% at 1 year, 93% at 2 years, 80% at 3 years, 80% at 4 years, and 74% at 5 years (Figure 3). The disease-free survivals were 82% at 1 year, 64% at 2 years, 53% at 3 years, 46% at 4 years, and 46% at 5 years (Figure 3). The median and mean disease-free survival times were both 42 months.

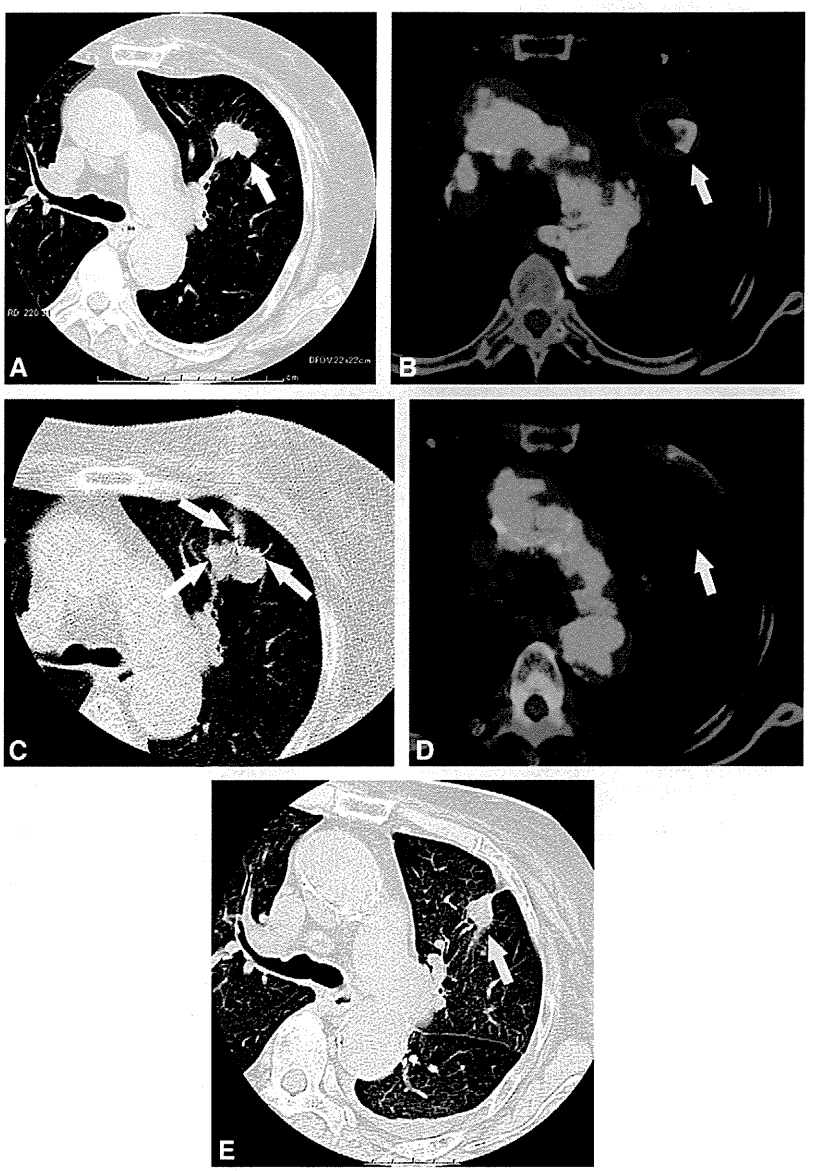

FIGURE 1. RFA for a 79-year-old woman with clinical stage IA NSCLC. A, CT image before the procedure shows a tumor (*arrow*) of 29 mm in maximum diameter in the left upper lobe. B, PET/CT image before the procedure shows marked accumulation of ^{18}F-fluorodeoxy glucose into the tumor (*arrow*). C, CT-fluoroscopic image during the procedure shows that a multitined expandable electrode (*arrows*) is introduced into the tumor. D, PET/CT image 3 months after the procedure shows no obvious accumulation of ^{18}F-fluorodeoxy glucose into the tumor (*arrow*). E, CT image 31 months after the procedure shows considerable tumor involution (*arrow*).

DISCUSSION

RFA is increasingly being used as an alternative local therapy for nonsurgical candidates with lung cancer. A prospective multicenter study of RFA on 106 patients with primary or secondary lung cancer noted technical success in 99% of patients and no procedural-related deaths.[8] An international survey reported that mortality after RFA of lung tumors was 0.4%.[9] Our study also confirmed that RFA was a safe procedure with no mortality, only a 6% grade 3 adverse event rate, and no significant effect on pulmonary function.

The local progression rates and survival data after RFA of clinical stage I NSCLC in the literature are summarized in Table 2. Approximately 30% to 40% of the treated tumors progressed locally,[10-13] which was also observed in our study. A number of studies showed that local efficacy depends on tumor size, that is, larger tumors are at a higher risk of local recurrence.[10,13-15] In our study, however, the local progression rate did not seem to depend on tumor size. The exact reason for this observation cannot be determined, but 3 groups divided by their tumor size were heterogeneous in terms of the

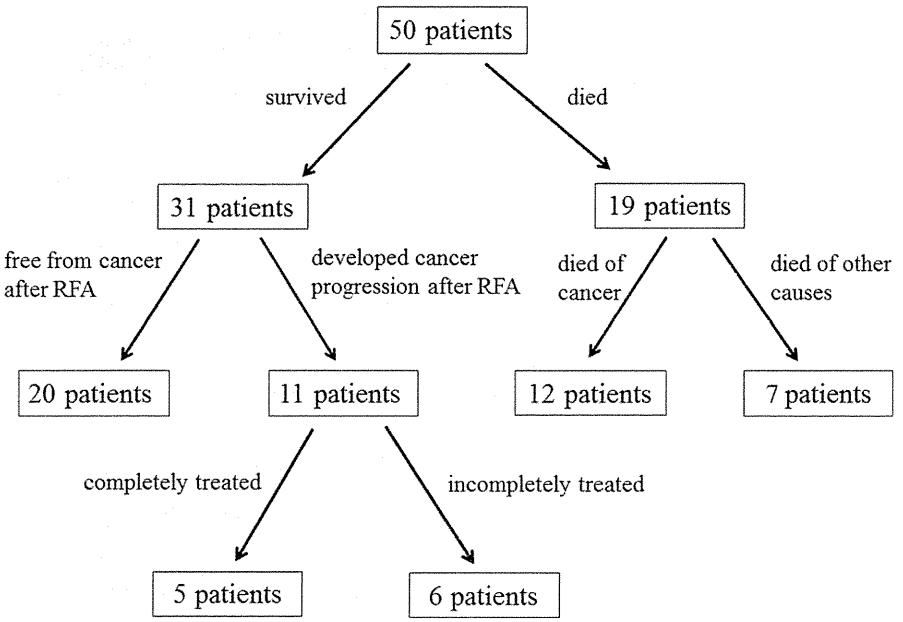

FIGURE 2. Summary of survival outcomes of 50 patients with clinical stage I NSCLC treated with RFA. *RFA,* Radiofrequency ablation.

type of electrode used, the period in which the procedure was performed (ie, the issue of a learning curve), and the follow-up period. These factors might bias the outcomes of local efficacy according to tumor size. In view of the relatively high local progression rate, the use of RFA should be limited to patients who are inoperable or operable but refuse to undergo surgery. Further, in the case of RFA, patients should be followed frequently to find local progression as early as possible.

The survivals after RFA of clinical stage I NSCLC were reported as 78% to 100% at 1 year, 57% to 84% at 2 years, and 36% to 74% at 3 years,[8,10-14] and the overall survivals in our study seem to be equivalent to these results. As expected, the survival of patients with stage IA cancer seemed to be better than the survival of patients with stage IB cancer, but this did not reach statistical significance in our study, probably because of the small size of the patient population. Although the overall and cancer-specific survivals were promising, the disease-free survival was limited to 53% at 3 years, mainly because of the relatively high rate of local tumor progression. Further, the promising overall and cancer-specific survivals may be partly attributable to the relatively high rate (10/50, 20%) of patients with pure ground-glass opacity adenocarcinoma, which is slow-growing with a doubling time of more than 800 days.[16,17]

Stereotactic radiation therapy shows favorable local control and survivals for patients with stage I NSCLC, and may rival RFA. According to a Japanese multi-institutional study on the use of stereotactic radiation on 257 patients,[2] the

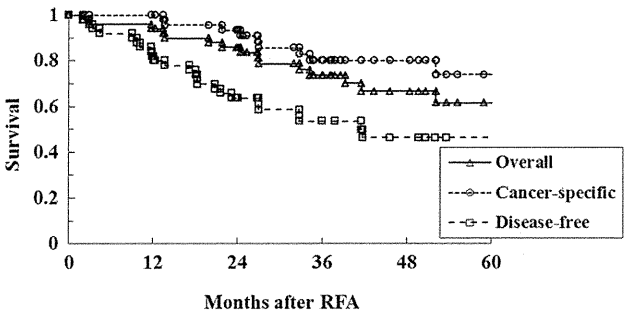

FIGURE 3. Overall survivals are 94% at 1 year, 86% at 2 years, 74% at 3 years, 67% at 4 years, and 61% at 5 years. The cancer-specific survivals are 100% at 1 year, 93% at 2 years, 80% at 3 years, 80% at 4 years, and 74% at 5 years. The disease-free survivals are 82% at 1 year, 64% at 2 years, 53% at 3 years, 46% at 4 years, and 46% at 5 years. *RFA,* Radiofrequency ablation.

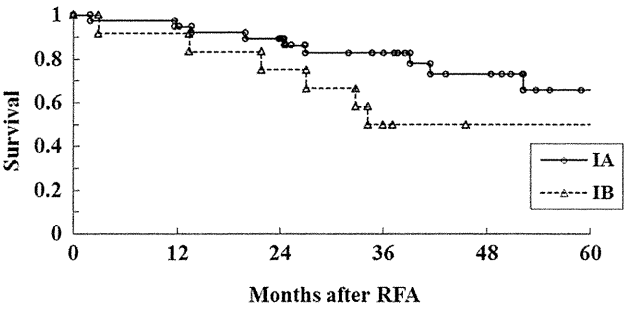

FIGURE 4. Survivals of stage IA and IB cancers are 95% and 92% at 1 year, 89% and 75% at 2 years, 83% and 50% at 3 years, 73% and 50% at 4 years, and 66% and 50% at 5 years, respectively. Survivals are not significantly different between the 2 groups ($P = .057$). *RFA,* Radiofrequency ablation.

TABLE 2. Summary of data by radiofrequency ablation of clinical stage I non–small cell lung cancer

Author	No. of patients	Follow-up period (mo)	Local progression rate (%)	Survival (%) 1 y	2 y	3 y	4 y	5 y	Survival time (mo)
Lencioni and colleagues[8]	13				75				
Lee and colleagues[10]	10	14 (median)	40	100					
Pennathur and colleagues[11]	19	29 (mean)	42	95	68				
Hiraki and colleagues[12]	20	22 (median)	35	90	84	74			42 (mean)
Lanuti and colleagues[13]	31	17 (median)	32	85	78	47	47		30 (median)
Simon and colleagues[14]	75			78	57	36	27	27	29 (median)

complication rate for tumors more than grade 2 was 5%, the proportion of patients with local recurrence was 14%, and the overall and cause-specific survivals were 57% and 77% at 3 years and 47% and 73% at 5 years, respectively. A phase 2 North American multicenter study including 55 medically inoperative patients[3] showed that the incidence of adverse events for grade 3, 4, or 5 tumors was 13%, 4%, or 0%, respectively, the estimated 3-year primary tumor control rate was 98%, and the disease-free and overall survivals at 3 years were 48% and 56%, respectively. According to another multicenter prospective phase 2 trial including 57 patients in Nordic countries,[4] grade 3 and 4 toxicity occurred in 28% and 2% of the patients, respectively, the estimated local control rate was 92% at 3 years, and the overall, cancer-specific, and progression-free survivals were 60%, 88%, and 52% at 3 years, respectively. In the future, it would be interesting to compare RFA with stereotactic radiation therapy in a randomized controlled study.

At Okayama University Medical School, stereotactic radiation has been another available therapy for lung cancer. Although selection of the 2 modalities may be difficult sometimes because of the lack of data suggesting which is better, roughly speaking, RFA is performed when performing stereotactic radiation seems hazardous, that is, when a tumor is located near (<3 cm) the hilum, mediastinum, lung apex, and vertebral body, and a tumor is located in the lower lobe in patients with considerable respiratory motion. Given that stereotactic radiation seems more toxic mainly because of radiation pneumonitis, RFA is apt to be selected in patients with severe pulmonary dysfunction. In contrast, considering the limited local efficacy of RFA, especially for tumors greater than 2 cm,[15] such tumors are likely to be treated with stereotactic radiation.

Notable advantages of RFA include its low invasiveness, the preservation of pulmonary function, the freedom to perform the procedure regardless of any previous therapy, and the ability to repeat the procedure whenever required. In contrast, a substantial limitation of this procedure may be its limited local efficacy. To secure favorable long-term survival, the local efficacy needs to be improved. In animal experiments, various attempts have been made to enhance the efficacy of RFA. In the lung, thermal and electrical conductivities are limited because of alveolar air, and they may be further limited by blood perfusion and ventilation. Thus, successfully enlarged coagulation necrosis was obtained by the modulation of conductivity by infusing saline into the lung[18] and decreasing blood perfusion[19] and ventilation.[20]

Combining RFA with other therapies may enhance its effects. Dupuy and associates[21] performed RFA followed by conventional XRT in 24 patients with stage I cancer (mean size, 3.4 cm). The local progression rate of 8% seemed promising despite the relatively large tumor sizes. The continuous evolution of the technology used in RFA may aid in the development of this procedure. Navigation devices that use electromagnetic tracking may facilitate more accurate electrode insertion.[22] In addition, other ablative technologies, including microwave ablation and cryoablation, are also being developed.[23,24] Furthermore, a recent study showed that RFA may be carried out by using a transbronchoscopic approach.[25]

Study Limitations

Our study had several limitations. This was a retrospective study with possible selection biases. We used 2 types of ablation device, although a previous study indicated that a multitined expandable electrode provided better local efficacy than an internally cooled electrode.[15] PET was not used for cancer staging in 21 patients, which may have affected the reliability of clinical cancer staging. Finally, the follow-up period was not long enough to determine the long-term outcomes.

CONCLUSIONS

RFA of clinical stage I NSCLC is minimally invasive and provides promising patient survivals, although the local efficacy needs to be improved.

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CLINICAL STUDY

Percutaneous Radiofrequency Ablation for Pulmonary Metastases from Hepatocellular Carcinoma: Results of a Multicenter Study in Japan

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ABSTRACT

Purpose: To retrospectively evaluate technical success, effectiveness, complications, patient survival, and prognostic factors with percutaneous radiofrequency (RF) ablation for pulmonary metastases resulting from hepatocellular carcinoma (HCC).

Materials and Methods: Thirty-two patients from six institutions were included, with a total of 83 pulmonary metastases treated in 65 sessions. RF ablation was always performed percutaneously with computed tomography (CT) guidance. Primary endpoints were technical success and technique effectiveness. Technique effectiveness was evaluated based on sequential follow-up CT images. Secondary study endpoints were complications, patient survival, and determination of prognostic factors. Complications were classified as major or minor. Prognostic factors were determined by analyzing multiple variables with the log-rank test.

Results: Technical success rate was 100%. Primary technique effectiveness rates were 92% each at 1, 2, and 3 years. Major and minor complications occurred after 16 (25%) and 23 (35%) of the 65 sessions, respectively. The median follow-up period was 20.5 months. Overall survival rates were 87% at 1 year and 57% each at 2 and 3 years (median and mean survival times, 37.7 mo and 43.2 mo, respectively). Significantly better survival rates were obtained in cases of (i) no viable intrahepatic recurrence ($P < .001$), (ii) Child-Pugh class A disease ($P < .001$), (iii) absence of liver cirrhosis ($P < .001$), (iv) absence of hepatitis C virus infection ($P = .006$), and (v) α-fetoprotein level of 10 ng/mL or lower ($P = .007$) at the time of RF ablation.

Conclusions: RF ablation appears effective, with an acceptable safety profile, in selected patients with pulmonary metastases resulting from HCC.

ABBREVIATIONS

AFP = α-fetoprotein, HCC = hepatocellular carcinoma, RF = radiofrequency

Recurrence of hepatocellular carcinoma (HCC) after treatments such as resection, locoregional therapy, and transplantation is an important concern. Recurrence most frequently occurs in the liver, whereas the lung is the most common site for extrahepatic spread (1–3). Although 66% of patients with extrahepatic metastasis die of hepatic causes, 22% of those patients die because of the progression of extrahepatic metastasis (1). Surgical resection may be performed in selected patients with pulmonary metastasis, and several studies have noted its effectiveness (4–10).

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Table 1. Demographic and Treatment Details in 16 Surviving Patients

Pt. No.	Age (y)/Sex	Largest Metastasis Diameter (mm)*	Pulmonary Metastases*	Etiology of Liver Disease	Cirrhosis*
1	63/M	11	2	HBV	No
2	37/F	8	1	HBV	No
3	70/F	11	1	Undetermined	No
4	58/M	25	6	HBV	No
5	35/F	10	3	HBV	No
6	59/F	13	3	HBV	No
7	55/M	39	1	HBV	No
8	82/F	15	2	HCV	No
9	44/M	10	1	HBV	No
10	59/M	7	2	HBV	Yes
11	58/F	5	2	AIH	Yes
12	58/M	14	1	Undetermined	No
13	70/M	9	1	Undetermined	Yes
14	55/M	26	2	HBV	No
15	65/M	16	1	HCV	Yes
16	47/M	14	5	HBV	No

Note.—AFP = α-fetoprotein; AIH = autoimmune hepatitis; HBV = hepatitis B virus; HCV = hepatitis C virus.
* Evaluated at the time of RF ablation.

Percutaneous radiofrequency (RF) ablation is increasingly being used as a local treatment for lung cancer. The reported midterm survival rates after this treatment seem to be promising: 68% at 2 years (11), 74% at 3 years (12), and 75% at 2 years (13) for patients with clinical stage I non–small-cell lung cancer; and 66% at 2 years (13) and 46%–48% (14–16) at 3 years for patients with metastatic colorectal cancer. These favorable survival outcomes have encouraged the use of this technique for the treatment of pulmonary metastasis resulting from other cancers.

The purpose of this multicenter study was to retrospectively evaluate the technical success and technique effectiveness of percutaneous RF ablation for pulmonary metastases from HCC. In addition, the study aimed to evaluate complications and side effects from the procedure, patient survival, and prognostic factors.

MATERIALS AND METHODS

This is a retrospective, multicenter study. At all institutions (N = 6), approval from the institutional review board and informed consent from the patients were obtained for the performance of RF ablation of lung tumors.

Patient Sample

Inclusion criteria for this study were the intent to treat and eliminate all pulmonary metastases seen on computed tomography (CT) images before RF ablation, maximum tumor diameter of less than 4.0 cm, platelet count no lower than 30,000/L, International Normalized Ratio of prothrombin time no greater than 1.5, Child-Pugh class A or B disease, and Eastern Cooperative Oncology Group performance status no greater than 2. Exclusion criteria were intent to treat pulmonary metastases solely for palliation or cytoreduction; presence of extrahepatic metastasis; presence of intrahepatic recurrence that could not be treated with some kind of therapy such as surgery, transcatheter therapy, ablation, and/or systemic therapy; maximum tumor diameter of 4.0 cm or greater, platelet count lower than 30,000/L, International Normalized Ratio greater than 1.5, Child-Pugh class C disease, and performance status greater than 2.

Thirty-two patients (24 men and eight women; mean age, 61.9 y; age range, 35–82 y) at six institutions were included in this study. At the time of RF ablation, these 32 patients had a total of 83 pulmonary metastases from HCC, which were treated with a total of 65 ablation sessions. This population included two cases that were previously reported in the literature (17), with follow-up information updated. The mean and median long-axis diameters of the 83 pulmonary metastases were 1.4 cm and 1.1 cm, respectively (range, 0.3–3.9 cm). The etiologies of underlying liver disease were hepatitis B virus (n = 13), hepatitis C virus (n = 12), autoimmune hepatitis (n = 1), alcohol-related (n = 1), and undetermined (n = 5). The Child-Pugh classes of disease at the time of RF ablation were A and B in 27 and five patients, respectively. The characteristics of patients are summarized in **Tables 1 and 2**.

Primary HCC had been treated with surgical resection in 29 patients, a combination of transcatheter arterial chemoembolization and RF ablation in two patients, and transcatheter arterial chemoembolization alone in one patient. After treatment for primary HCC, intrahepatic recurrence developed in 13 patients and did not develop in eight.

Child-Pugh Grade*	Viable Intrahepatic Recurrence*	AFP (ng/mL)*	Follow-up (mo)	Viable Recurrence at Study End
A	No	≤ 10	14.9	None
A	No	≤ 10	19.8	None
A	No	> 10	21.8	Lung
A	No	> 10	25.5	Lung, lymph node
A	No	> 10	21.8	None
A	No	> 10	36.7	None
A	No	≤ 10	57.7	None
A	No	> 10	97.9	None
A	No	≤ 10	88.4	None
A	No	≤ 10	10.7	Lung, liver, peritoneum, lymph node
A	Yes	> 10	20.0	Bone
A	No	≤ 10	29.6	Lung, liver, adrenal grand, bone
A	No	≤ 10	28.5	Lung
A	No	≤ 10	29.1	Lung
A	Yes	> 10	11.0	Lung
A	No	≤ 10	19.9	Lung

Table 2. Information on 16 Deceased Patients

Pt. No.	Age (y)/ Sex	Largest Pulmonary Metastasis Diameter (mm)*	Pulmonary Metastases*	Child-Pugh Score	Viable Intrahepatic Recurrence*	AFP (ng/mL)*	Time from RF Ablation to Death (mo)	Cause of Death
1	73/M	12	2	A	Yes	NA	20.2	Intrahepatic recurrence
2	37/M	14	3	A	Yes	> 10	3.8	Intrahepatic recurrence
3	76/F	14	1	B	No	> 10	12.8	Intrahepatic recurrence
4	75/M	23	≥ 10	A	Yes	> 10	14.6	Intrahepatic recurrence
5	52/M	13	1	A	Yes	> 10	10.9	Bone metastasis
6	70/M	34	1	B	No	> 10	12.9	Pulmonary metastasis
7	70/M	25	1	B	Yes	> 10	4.1	Intrahepatic recurrence
8	73/M	15	2	A	Yes	> 10	8.0	Intrahepatic recurrence
9	78/M	14	2	A	No	> 10	37.7	Intrahepatic recurrence
10	60/M	26	2	B	Yes	> 10	20.8	Intrahepatic recurrence
11	74/M	36	1	B	Yes	> 10	13.9	Intrahepatic recurrence
12	71/M	38	1	A	Yes	> 10	24.0	Intrahepatic recurrence
13	79/M	15	5	A	No	NA	43.9	Intrahepatic recurrence
14	50/M	35	1	A	No	> 10	20.0	Intrahepatic recurrence
15	54/M	10	4	A	No	≤ 10	39.4	Pulmonary metastasis
16	75/F	17	2	A	No	≤ 10	38.1	Progression of cirrhosis

Note.—AFP = α-fetoprotein; NA = not available.
* Evaluated at the time of RF ablation.

The intrahepatic recurrence was then completely treated, ie, there was no viable intrahepatic recurrence at the time of RF ablation. Another 11 patients with intrahepatic recurrence, despite treatment, still had viable intrahepatic lesions at the time of RF ablation. These patients were scheduled to undergo additional treatment of the intrahepatic lesions.

Pulmonary metastases were diagnosed based on the results of serial CT images: new nodules or masses detected were diagnosed as pulmonary metastases without histopathologic confirmation. The diagnosis was not confirmed histopathologically in any of the tumors. The median time to progression, defined as the time between the first therapy for primary HCC and that for pulmonary metastasis, was

16.3 months (mean, 27.1 mo). The first therapy for pulmonary metastasis was surgical resection and systemic chemotherapy in seven and six patients, respectively. For these 13 patients, RF ablation was performed a median period of 8.7 months (mean, 9.3 mo) after the aforementioned other therapies. For the remaining 19 patients, RF ablation was performed as the first therapy for pulmonary metastasis. Concurrent systemic chemotherapy was not given to any patient, although adjuvant systemic chemotherapy was given to two patients.

RF Ablation

The present study included a total of 65 RF ablation sessions. Conscious sedation was administered, and pain during the procedures was treated with local anesthesia alone (n = 51) or a combination of local and epidural anesthesia (n = 14). Prophylactic antibiotic agents were used in 46 sessions (71%). The electrodes used for the 83 tumors included multitined expandable electrodes with arrays 2 cm (n = 25), 3 cm (n = 11), 3.5 cm (n = 3), or 4 cm (n = 1) in diameter (LeVeen; Boston Scientific, Natick, Massachusetts) and a single internally cooled electrode with noninsulated tips of 1 cm (n = 5), 2 cm (n = 30), or 3 cm (n = 8; Cool-tip; Covidien, Mansfield, Massachusetts). Each procedure was performed percutaneously under CT guidance. We aimed to create at least 5-mm ablation margin around each tumor.

For patients treated with single-electrode devices, RF energy was applied using an impedance control algorithm for 10–12 minutes during internal cooling of the electrode. In case treated with multitined-electrode devices, initial RF power was set at 10–40 W and then increased by 5–10 W every 1–2 minutes. Energy was applied until the impedance showed a rapid increase or an automatic shutoff was reached at 15 minutes; this was repeated once at each site. As a result, mean RF application time at each site was 12 minutes (median, 11 min). To obtain an adequate ablative margin, multiple overlapping ablations were performed for 48 tumors. Immediately after the procedure, CT images without a contrast agent were obtained.

Study Endpoints and Outcome Measures

The primary study endpoints included technical success and technique effectiveness. The procedure was deemed technically successful when the tumor was treated according to the protocol and the entire lesion was included in the ablation zone with at least a 5-mm margin (18). Technique effectiveness was defined by complete ablation of the macroscopic tumor at imaging follow-up (18).

Imaging follow-up was performed every 3–4 months with contrast-enhanced chest and abdominal CT. We considered complete ablation to have been achieved when the entire ablation zone did not show enhancement after contrast agent administration or when the ablation zone exhibited contrast enhancement that was peripheral, concentric, symmetric, and uniform, which was considered to correspond to the ablated marginal parenchyma (19). In contrast, local progression of the tumor was indicated by the appearance of an irregular, scattered, nodular, or eccentric enhancement focus in the ablation zone or when the ablation zone was circumferentially enlarged with contrast enhancement. A new pulmonary tumor outside the ablated zone was considered to represent a new recurrence.

Secondary study endpoints included complications and side effects from the procedure, patient survival, and the determination of prognostic factors. Complications were classified as major or minor according to Society of Interventional Radiology (SIR) guidelines (18,20). Survival was estimated from the time of RF ablation to the last follow-up visit or death from any cause.

Statistical Analysis

The primary and secondary technique effectiveness rates were calculated by Kaplan–Meier analysis. The primary effectiveness rate was defined as the percentage of tumors that were successfully eradicated after the initial procedure (18). The secondary effectiveness rate was defined as the percentage of tumors that underwent successful repeat ablation after identification of local tumor progression (18). The primary technique effectiveness rates were also estimated separately according to the type of electrode (single or multitined) used for RF ablation and tumor size ($\leq$ 2.0 cm or $>$ 2.0 cm), and these two rates were compared using the log-rank test. Patient survival rates were estimated by Kaplan–Meier analysis.

To determine the prognostic factors, we analyzed multiple variables, including sex, age, new pulmonary metastasis after RF ablation, new metastasis in sites other than the liver and lung after RF ablation, time between (first) therapy for primary cancer and RF ablation, etiology of underlying liver disease, number of pulmonary metastases, maximum diameter of the (largest) pulmonary metastasis, viable intrahepatic recurrence, Child-Pugh class, liver cirrhosis, and serum α-fetoprotein (AFP) level. The latter six variables were evaluated at the time of RF ablation. The survival rates after RF ablation were compared between groups divided for each variable by using the log-rank test. Variables that were significantly different between the groups were considered to represent prognostic factors.

For all analyses, a P value lower than .05 was considered to indicate a significant difference. Statistical analysis was performed with SPSS software (version 11.0; SPSS, Chicago, Illinois).

RESULTS

Technical Success and Technique Effectiveness

The procedure was technically successful in all 83 tumors. The median follow-up period for the 83 tumors was 16.2 months (mean, 21.1 mo). Local progression was observed

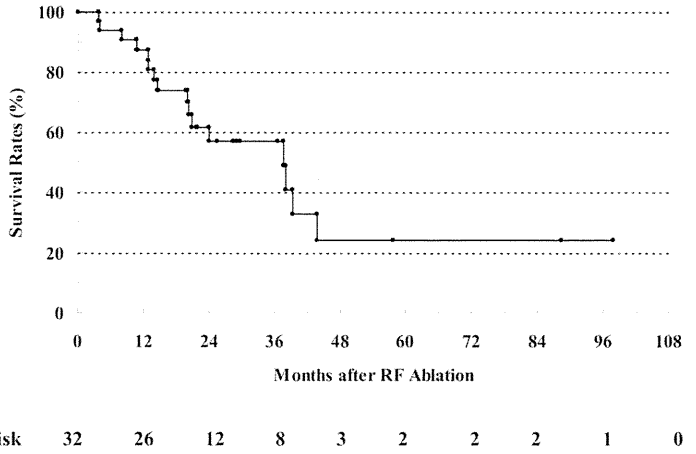

Figure. Overall survival rates of 32 patients after RF ablation of pulmonary metastases from HCC were 87% at 1 year and 57% each at 2 and 3 years.

in six of 83 tumors (7%) after RF ablation. All local tumor progression was demonstrated within 1 year. The primary technique effectiveness rates for all 83 tumors were 92% each at 1, 2, and 3 years. The primary technique effectiveness rates for the 43 tumors treated with internally cooled single-electrodes were 89% each at 1, 2, and 3 years, and those for the 40 tumors treated with multitined electrodes were 95% each at 1, 2, and 3 years. These two rates were not significantly different ($P = .41$). The primary technique effectiveness rates for the 69 tumors 2.0 cm or smaller in diameter were 93% each at 1, 2, and 3 years, and those for the 14 tumors larger than 2.0 cm were 84% each at 1 and 2 years. These two rates were not significantly different ($P = .26$). Three of the six tumors with local progression were treated with repeat RF ablation; thereafter, one tumor showed local progression again. The secondary technique effectiveness rates for all 83 tumors were 94% each at 1, 2, and 3 years.

Complications and Side Effects

No procedural mortality (ie, SIR class F complication) occurred. Major or minor complications occurred after 39 of the 65 RF ablation sessions (60%). The incidence of major complications was 25% (16 of 65). Fifteen of the 16 major complications were pneumothoraces that required chest tube placement (SIR class C or D). The one other major complication was a case of massive hemoptysis caused by a pulmonary pseudoaneurysm 9 days after the procedure. The case was successfully treated with transcatheter embolization (SIR class D). The details of this case have been published elsewhere (21). The incidence of minor complications was 35% (23 of 65). All minor complications were pneumothoraces that was treated conservatively (SIR class A or B). Side effects included asymptomatic pleural effusion (n = 11), asymptomatic small hemothorax (n = 1), and high fever (≥ 38°C; n = 16). High fever continued for a median of 2 days (mean, 3.1 d; range, 1–9 d).

Patient Survival

The median follow-up period was 20.5 months (mean, 26.8 mo; range, 3.8–97.9 mo). At the end of the study, 16 patients were alive and 16 were deceased. Data for the 16 patients who survived are shown in **Table 1**. Of these 16 surviving patients, seven were free from cancer at any location, including one patient who developed new tumors in the lung after RF ablation that were then successfully treated. Notably, four patients survived without cancer for more than 3 years after RF ablation. In contrast, nine patients had viable cancer recurrence at some location at the end of the study.

Data for the 16 deceased patients are shown in **Table 2**. The patients died at a median of 17.3 months (mean, 20.3 mo; range, 3.8–43.9 mo) after RF ablation. The cause of death was related to cancer recurrence in 15 of the 16 patients, including intrahepatic recurrence (n = 12), pulmonary metastasis (n = 2), and bone metastasis (n = 1). In the two patients who died from pulmonary metastasis, one died of respiratory failure because of the development of numerous new pulmonary metastases and the other died from hemoptysis because of pulmonary metastasis that progressed locally after RF ablation. The remaining one patient died of hepatic failure caused by progressive liver disease unrelated to malignancy. The overall survival rates after RF ablation were 87% (95% CI, 76%−99%) at 1 year and 57% (95% CI, 38%−76%) each at 2 and 3 years (**Fig**). The median and mean survival times after RF ablation were 37.7 months and 43.2 months, respectively.

Prognostic Factors

The results of analyses to determine prognostic factors are shown in Table 3. The factors that were significantly associated with better survival rates were the absence of viable intrahepatic recurrence ($P < .001$), Child-Pugh class A disease ($P < .001$), absence of liver cirrhosis ($P < .001$), absence of hepatitis C virus infection ($P = .006$), and AFP level no greater than 10 ng/mL ($P = .007$) at the time of RF

Table 3. Univariate Analyses to Determine Prognostic Factors

Variable	No. of Pts.	Survival (%)			*P* Value
		1 y	2 y	3 y	
Sex					.17
Male	24	83	48	48	
Female	8	100	88	88	
Age (y)*					.069
< 65	17	88	70	70	
≥ 65	15	87	42	42	
Pulmonary metastases*					.74
Single	14	86	43	43	
Multiple	18	89	68	68	
Maximum pulmonary metastasis diameter (cm)*					.19
≤ 2.0	22	86	74	74	
> 2.0	10	90	30	30	
New pulmonary metastasis after RF ablation					.70
Yes	16	100	68	68	
No	16	75	46	46	
New metastasis at other site after RF ablation					.32
Yes	10	89	53	53	
No	22	86	58	58	
Time from primary cancer therapy to RF ablation (y)					.15
0–2	19	95	64	64	
> 2	13	77	46	46	
Viable intrahepatic recurrence*					< .001
Yes	11	64	0	0	
No	21	100	84	84	
Liver cirrhosis*					< .001
No	13	100	100	100	
Yes	19	79	27	27	
Child-Pugh class*					< .001
A	27	89	69	69	
B	5	80	0	0	
Etiology of liver disease					.006
HBV and others	20	90	84	84	
HCV	12	83	19	19	
AFP level (ng/mL)*†					.007
≤ 10	11	100	100	100	
> 10	19	79	35	35	

Note.—AFP = α-fetoprotein; HBV = hepatitis B virus, HCV = hepatitis C virus.
* Evaluated at the time of RF ablation.
† Two patients with missing data were excluded from the analysis.

ablation. The survival rate among the 13 patients who did not have liver cirrhosis was 100% at 3 years, as was that of the 11 patients with an AFP level no greater than 10 ng/mL. Conversely, the survival rate of the five patients with Child-Pugh class B disease was 0% at 2 years, as was that of the 11 patients with viable intrahepatic recurrence.

DISCUSSION

According to a risk analysis of 1,131 patients who underwent medical treatments for HCC (22), extrahepatic metastasis developed after treatments more frequently in patients with positive viral markers, a larger HCCs, multiple HCC nodules, vascular invasion, and/or increased levels of tumor markers. After curative resection of HCC, risk factors for the development of extrahepatic metastasis have been reported to be invasion into the tumor capsule and the hepatic vein and absence of inflow vessel occlusion during hepatectomy (23). Another study (24) showed young age, solitary and large HCC tumors, high hepatitis activity, large amount of intraoperative blood loss, and large requirement for blood transfusion as risk factors of extrahepatic recur-

Table 4. Published Survival Results after Surgery for Pulmonary Metastasis from HCC (4–10)

Study	No.	Survival (%)				Survival (mo)	
		1 y	2 y	3 y	5 y	Median	Mean
Lam et al (4)	9	100	78	–	67	42	–
Tomimaru et al (5)	8	–	–	–	–	–	29
Nakawaga et al (6)	25	80	–	61	36	52	–
Nakajima et al (7)	20	45	–	24	–	–	–
Koide et al (8)	14	71	45	–	27	–	22
Kuo et al (9)	34	–	65	–	28	56	–
Kwon et al (10)	16	56	–	–	26	20	–
Present study	32	87	57	57	–	38	43

Note.—HCC = hepatocellular carcinoma.

rence after hepatic resection. Several studies (1,3,25) have described poor survival outcomes for patients with extrahepatic metastasis from HCC: 20% (1) and 25% (3) rates at 1 year, 6% rate at 3 years, and 0% rate at 5 years (25); and median survival times of 4.6 months (1) and 7 months (3). The most common site of extrahepatic recurrence is the lungs (1–3), and the reported incidences of antemortem pulmonary metastasis in patients with HCC range from 6% to 13% (3–5).

Invasive treatment is rarely used for extrahepatic metastasis, mainly because of the multifocal nature of the disease and poor hepatic reserve. However, surgical resection may be beneficial for patients with pulmonary metastasis if the intrahepatic tumor is controllable and there is no extrathoracic metastasis. Several investigators (4–10) have presented survival outcomes after surgical resection for pulmonary metastasis from HCC (**Table 4**) (4–10). Relatively favorable survival outcomes after surgical resection of pulmonary metastasis from HCC seem to justify the use of local therapy for pulmonary metastasis from HCC in similar patients.

The present study suggests that RF ablation for pulmonary metastasis from HCC is a safe procedure without related mortality and with a limited number of severe complications. The most common complication was pneumothorax, but the majority of these cases could be treated conservatively; this is similar to the results of a previous study (26). The present study also shows that RF ablation provided favorable local control for pulmonary metastases resulting from HCC. This is partly because the study population mainly consisted of patients with small tumors (mean long-axis diameter, 1.4 cm). A previous study (27) showed that local control of pulmonary metastasis resulting from HCC by RF ablation was similar to that of other lung cancers, including primary lung cancer and pulmonary metastasis from colorectal cancer, renal-cell carcinoma, and primary lung cancer. The present study shows that local tumor control did not significantly depend on electrode type and tumor size, which is in contrast with the results of a previous study (28). However, statistical analyses in the present study might suffer from a lack of statistical power in view of the small number of tumors that showed local progression. When considering the survival data obtained in the present study, it should be noted that 41% of patients (13 of 32) had already undergone other treatments for pulmonary metastasis, and RF ablation was performed a median of 8.7 months after these treatments. Therefore, it is difficult to compare the survival data in the present study with previously reported survival data after surgery, because surgery is usually performed as a primary therapy.

Although the prognostic factors for patients with extrahepatic metastasis are poorly understood, Natsuizaka et al (3) showed that Child-Pugh class, serum AFP level, and metastasis to multiple extrahepatic organs were prognostic factors. Nakagawa et al (6) investigated prognostic factors for patients with pulmonary metastasis but without uncontrollable intrahepatic recurrence or metastasis at other sites, and found that cancer-specific survival was significantly better in patients with a disease-free interval of at least 12 months and serum AFP level lower than 500 ng/mL. Kuo et al (9) showed that disease-free interval was an independent prognostic factor after the resection of pulmonary metastasis from HCC. Kwon et al (10) showed that there were no significant independent prognostic factors after pulmonary metastasectomy in patients with HCC. The present study indicates that survival after RF ablation of pulmonary metastasis depended mainly on hepatic factors, including the control of intrahepatic cancer and hepatic reserve. In fact, of the 16 patients who died, 13 died because of hepatic events. One patient died of massive hemoptysis because of locally progressing pulmonary metastasis after RF ablation, suggesting the importance of the control of pulmonary metastasis, in addition to that of hepatic factors. AFP level greater than 10 ng/mL indicated a poor prognosis in the present study because it was associated with the presence of liver cirrhosis, intrahepatic recurrence, and hepatic C virus infection.

The present retrospective study has several limitations. The data were derived from a small patient sample. The diagnosis of pulmonary metastasis from HCC was not confirmed histopathologically, and therefore nonmetastatic lesions might have been included in the tumor group. The

diagnosis of local progression of six tumors after RF ablation was also not confirmed histopathologically. The treatment strategies for pulmonary metastases were not uniform, which resulted in difficulty in drawing conclusions regarding the ultimate role of RF ablation in the treatment. The ablation systems used were heterogeneous because this is a multicenter study. Because of the broad patient population with various degrees of hepatic reserve, intrahepatic recurrence and treatment modalities for it, and pulmonary metastasis, overall survival data in this study may be complicated. RF ablation was performed to improve survival by providing local control and thereby preventing fatal pulmonary complications. However, when considering survival data in this uncontrolled study, it remains to be determined whether a survival benefit was obtained by RF ablation, or if survival data were a simple reflection of natural history in such a population.

In conclusion, RF ablation appears to be effective, with an acceptable safety profile, for local tumor control in selected patients with pulmonary metastases resulting from HCC. Better survival rates should be expected in patients with an absence of viable intrahepatic recurrence, Child-Pugh class A disease, absence of liver cirrhosis, absence of hepatitis C virus infection, and AFP level no greater than 10 ng/mL at the time of RF ablation.

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ORIGINAL ARTICLE

Analysis of various malignant neoplasms detected by FDG-PET cancer screening program: based on a Japanese Nationwide Survey

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Abstract
Objective The most distinctive feature of FDG-PET cancer screening program is the ability to find various kinds of malignant neoplasms in a single test. The aim of this survey is to clarify the range and frequency of various malignant neoplasms detected by FDG-PET cancer screening performed in Japan.
Methods "FDG-PET cancer screening" was defined as FDG-PET or positron emission tomography and computed tomography (PET/CT) scan with or without other tests performed for cancer screening of healthy subjects. This survey was based on a questionnaire regarding FDG-PET cancer screening. We analyzed the situation of 9 less frequently found malignant neoplasms including malignant lymphoma, malignancy of head and neck, esophagus, hepatobiliary and gallbladder, pancreas, kidney, cervical and uterine, ovary, and bladder.
Results The detailed information of subjects with the suspected 9 kinds of malignant neoplasms mentioned

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above in the FDG-PET cancer screening program was studied in a total of 1,219 cases from 212 facilities. A statistical significance between PET/CT and PET was found in relative sensitivity and PPV for renal cell cancer. Malignant lymphoma was frequently of indolent type, suspected head and neck cancers had many false-positive results, and pancreatic cancer detected in this program was often in the advanced stage even in asymptomatic subjects. The recommendation of combined screening modality to PET or PET/CT was as follows: gastric endoscopy for assessing early esophageal cancer; abdominal ultrasound for screening hepatobiliary and gallbladder cancer; pelvic magnetic resonance imaging for assessing gynecological and pelvic cancers; and the CA125 blood test for screening ovarian cancer. Delayed image was helpful depending on the type of suspected malignant neoplasm.

Conclusion We analyzed various types of malignant neoplasms detected by the FDG-PET cancer screening program and presented recommended combination of examinations to cover FDG-PET and PET/CT.

Keywords Cancer screening · FDG · PET · Delayed imaging · Combined examination

Introduction

FDG-PET and PET/CT scans were valuable for management of various types of malignancy because glucose metabolism is generally activated in malignant neoplasm [1]. The cancer screening program using FDG-PET or PET/CT, which is called "FDG-PET (including PET/CT) cancer screening program" has started since 1995 at HIMEDIC Imaging Center at Lake Yamanaka, Yamanashi, Japan and the detection of various types of malignancies has been reported [2]. Since then, FDG-PET cancer screening has become widespread and it is now estimated to be held in over 100 facilities in Japan.

This cancer screening program is based on FDG-PET or PET/CT, and includes additional combined test to cover PET-negative malignant neoplasms. In our analysis of 43,996 subjects who underwent FDG-PET cancer screening program, 500 cases of malignant neoplasms (1.14%) were found [3]. The most distinctive feature of this FDG-PET cancer screening program is the ability to find various kinds of malignant neoplasms at one time. The most commonly found malignant neoplasms were those of the thyroid (107 cases), colon/rectum (102 cases), lung (79 cases), and breast (35 cases). These malignant neoplasms showed high relative sensitivity of PET (88% for thyroid, 90% for colon/rectum, 80% for lung, and 92% for breast). The malignant neoplasms with low PET sensitivity were prostate cancer and gastric cancer [3]. During the survey between 2005 and 2008, we obtained detailed data of malignant neoplasms other than the six kinds of malignant neoplasms mentioned above. We examined the less frequently found malignant neoplasms in the FDG-PET cancer screening program and we suggested recommended combinations of examinations to support FDG-PET and PET/CT.

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Materials and methods

The Japanese Society of Nuclear Medicine and The Clinical PET Promoting Committee published "The Guidelines of FDG-PET Cancer Screening" in 2004 [4] and revised it in 2007 [5], with the aim of improving the quality of the FDG-PET cancer screening program. All facilities performed the FDG-PET cancer screening program following these guidelines.

Subject for investigation

Questionnaires regarding the FDG-PET cancer screening were sent to facilities in which FDG-PET tests were performed. Replies were obtained from 68 out of the 99 facilities in 2005, 98 out of the 156 facilities in 2006, 69 out of the 174 facilities in 2007, and 64 out of the 163 facilities in 2008. FDG-PET cancer screening was performed in 46 out of the 68 facilities in 2005, 68 out of the 98 facilities in 2006, 63 out of the 69 facilities in 2007, and 61 out of the 64 facilities in 2008. The total number of subjects who underwent FDG-PET cancer screening was 50,558 (27,862 men, 20,740 women, 1,956 not specified) in 2005, 46,857 (27,719 men, 18,938 women, 200 no specified) in 2006, 44,271 (26,173 men, 17,359 women, 739 not specified) in 2007, and 43,253 (25,539 men, 17,070 women, 644 not specified) in 2008. Reliable results of thorough examinations for the subjects who had a positive test in FDG-PET and one or more of the combined screening tests were obtained from 38 facilities in 2005, 59 facilities in 2006, 57 facilities in 2007, and 58 facilities in 2008. The total number of subjects from whom reliable results were obtained was 43,996 (25,193 men, 18,803 women) in 2005, 43,061 (25,594 men, 17,467 women) in 2006, 39,867 (23,948 men, 15,919 women) in 2007, and 38,929 (23,055 men, 15,230 women) in 2008.

Contents of the investigation

The data analyzed from the questionnaire survey were as follows: (1) sex; (2) age group; (3) FDG-PET (including FDG-PET/CT) imaging findings and delayed imaging findings; (4) results of combined cancer screening tests; (5) final results of further examination ("proved malignant neoplasms", "excluded malignant neoplasms," and "strict follow-up because of excluded malignant neoplasms"); and (6) "clinical stage" and "pathological stage" of each malignant neoplasms, along with "the degree of differentiation of malignant neoplasm", if the case was proved to have malignant neoplasm.

Definition of terms

FDG-PET cancer screening is defined as a cancer screening program using FDG-PET (including FDG-PET/CT) aimed at the detection of malignant neoplasm at an early stage. Any PET or PET/CT cameras, any method of FDG-PET testing, any combined screening tests, and any method of further examination are allowed. In cases with a past history of malignant neoplasm, screening for recurrence requested by the attending physician or by the patient is excluded from the definition of FDG-PET cancer screening. However, when the malignant neoplasm was considered to have been cured and FDG-PET was performed to screen other malignant neoplasm, FDG-PET testing was included in the definition of FDG-PET cancer screening.

If a screening test other than FDG-PET was performed at another facility in the same period and its results were provided to the PET center, it was defined as a "combined screening test." If further examination is judged necessary on the basis of the obtained PET information, any additional test other than the screening program fixed in each PET center is not considered to be a combined screening test. If a cancer screening test was performed using a PET/CT scanner, regardless of the method used or the method of interpretation, the information obtained from the CT integrated in the PET/CT system was regarded not as a combined screening test, but as PET/CT modality itself, because the CT findings were inseparable from PET findings in PET/CT. "PET-positive" was defined as positive findings on dedicated PET or PET/CT. Accordingly, the cases with PET-negative and CT-positive findings on screening tests performed by PET/CT were defined as PET-positive.

Statistical analysis

The chi-square test for independence was performed to compare the detection rates, sensitivities, and positive predictive values between dedicated PET and PET/CT, and a P value < 0.05 was considered to be significant.

Results

Analysis of detected malignant neoplasms

Reliable results of thorough examinations of subjects performed in the FDG-PET cancer screening were obtained from a total of 212 facilities during 4 years. The number of performed FDG-PET cancer screenings was 165,853 in 212 facilities; 7,470 cases were reported to manifest positive findings suggesting possible malignant neoplasm, and malignant neoplasms were found in 1,979 cases.

The malignant neoplasms found most frequently in this program were colon/rectum cancer, thyroid cancer, lung cancer, breast cancer, prostate cancer, and gastric cancer; these were excluded from the present analysis because details of these malignant neoplasms had already been reported [3]. The number of suspected various malignant neoplasms other than these six kinds of malignant neoplasms was 1,623 cases (dedicated PET, 792 cases; PET/CT, 831 cases) and malignant neoplasms were found in 400 cases.

In this study, we analyzed the details of the 9 kinds of less frequently found malignant neoplasms: malignant lymphoma, head and neck cancer, esophageal cancer, hepatobiliary and gallbladder cancer, pancreatic cancer, renal cell cancer, uterine cancer, ovarian cancer, and bladder cancer. The number of malignant neoplasms found in each age group was as follows; 20–29 years: 0 case, 30–39 years: 9 cases, 40–49 years: 39 cases, 50–59 years: 111 cases, 60–69 years: 107 cases, 70–79 years: 78 cases, and 80 year and greater: 5 cases.

The detection results with dedicated PET and PET/CT are shown in Table 1, the results with FDG-PET and combined screening tests are shown in Table 2, and the results of delayed imaging are shown in Table 3.

Malignant lymphoma

In this survey, suspected malignant lymphoma was found in 137 subjects. In addition, 10 cases of lymphoma were found in stomach (3 cases), lung (2 cases), spleen (2 cases), colon (1 case), parotid grand (1 case), and testis (1 case) were proved, which was result in suspicion of malignant neoplasms in each region. We analyzed a total of 147 subjects (80 men and 67 women), and 58 cases (37 men and 21 women) of malignant lymphoma and 44 cases of benign disease were found. The most frequently found benign diseases with dedicated PET- or PET/CT-positive results were lymph node swelling without malignancy