Original article

Radiofrequency Ablation of Pulmonary Metastases from Sarcoma: Single-Center Retrospective Evaluation of 46 Patients

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Abstract

Purpose

This retrospective, single-center study evaluated radiofrequency (RF) ablation for pulmonary metastases of sarcoma.

Materials and Methods

Forty-six patients with sarcoma (144 pulmonary metastases) underwent 88 RF ablation sessions. Data regarding local tumor progression, efficacy, procedural adverse events (AEs; National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0), overall survival (OS), and OS-associated prognostic factors were retrospectively evaluated using univariate analyses.

Results

Local progression occurred in 22 of 144 tumors (15.3%). Primary and secondary efficacy rates were 83.5% and 90.0% at 1 year, and 76.3% and 81.4% at 2 years, respectively. Seventy-three grade 1 AEs, 33 grade 2 AEs, and no grade ≥3 AEs were observed. Twenty-eight patients (60.9%) remained alive and 18 died, yielding 1-, 2-, and 3-year OS rates of 80.6%, 70.1%, and 47.1% (median survival time, 31.7 months). Univariate analysis revealed extrapulmonary metastasis (P = 0.005), non-curative RF ablation (P = 0.009), and a post-RF ablation disease-free interval ≤12 months (P = 0.015) as significant negative prognostic factors.

Conclusion

RF ablation is safe, offers good local control, and may be a viable treatment option for pulmonary metastasis of sarcoma.

Key Words

Radiofrequency ablation; Lung metastasis; Sarcoma

Introduction

Sarcomas are malignant neoplasms arising from various organs and tissues, including bone, muscle, adipose, fibrous and vascular tissues. These lesions are relatively rare, with an estimated incidence of 1–4.5 per 100,000 individuals [1, 2]. Approximately half of all sarcoma patients will develop distant metastases during the course of their disease [2]. The lung is the most common metastatic site, and approximately 30–40% of sarcoma patients have pulmonary metastases [3, 4]. Pulmonary metastases are the primary cause of death from bone and soft-tissue sarcomas [5], and treatment of these metastases appears important for survival prolongation. Pulmonary metastasectomy has been established as a standard of care [6, 7]; in particular, improved survival rates have been reported after complete pulmonary metastasectomy [6]. However, patients with poor respiratory function and/or medical comorbidities may not be candidates for surgery. Furthermore, recurrent pulmonary metastases sometimes occur after metastasectomy [8]. For such patients, minimally invasive and repeatable local therapy may be more efficient and desirable.

In recent years, percutaneous radiofrequency (RF) ablation has been used to treat both primary lung cancers and various types of pulmonary metastases (e.g., metastases of colorectal cancer, esophageal cancer, hepatocellular carcinoma, and renal cell carcinoma), mainly in candidates not indicated for surgery [9-14]. Promising survival rates have been reported among patients treated with RF ablation for

pulmonary metastases [9-14], and accordingly, similar treatment has been encouraged for other types of pulmonary metastases.

The purpose of this study was to retrospectively evaluate the outcomes, including technique efficacy, safety, survival, and factors associated with survival, of RF ablation for pulmonary metastases of sarcoma.

Materials and methods

Informed consent was obtained from all patients prior to RF ablation. The institutional review board approved this retrospective study and waived the requirement for informed consent requirement to use the patients' medical data.

Patients and tumors

Between August 2001 and August 2013, 53 sarcoma patients underwent RF ablation for pulmonary metastases at our institution. From this group, patients who met all of the following criteria were included in the study: i) patient follow-up period >2 months, ii) maximum pulmonary metastasis diameter ≤50 mm, and iii) unsuitability for surgery or patient refusal of surgery. Forty-six patients (11 men and 35 women; mean age, 54.5 years ± 12.9 [standard deviation]; range, 24–79 years) with 144 pulmonary metastases (mean diameter, 13.5 mm ± 9.0; range, 3–50 mm) were included in this study; 7 were excluded because they did not meet the above inclusion criteria. Three

tumors in 3 patients were histologically confirmed as pulmonary metastases based on computed tomography (CT)-guided lung biopsy. The remaining 141 tumors were diagnosed based on serial CT images in which newly detected and/or enlarged nodules were diagnosed as pulmonary metastases. Among these 144 tumors, 48 were included in a previous publication that reported the impact of the electrode array diameter on local progression after lung RF ablation [15], and their follow-up data were updated for this study.

The clinical diagnoses of primary tumors were as follows: leiomyosarcoma (n = 27), chondrosarcoma (n = 4), synovial sarcoma (n = 3), malignant fibrous histiocytoma (n = 3), osteosarcoma (n = 2), and others (n = 7). The primary sites included the bone and soft tissue (n = 19), uterus (n = 17), retroperitoneum (n = 3), and others (n = 7). The mean and median intervals between the date of treatment of the primary lesion and the date of initial lung RF ablation were 55.6 and 31.9 months (range, 2.4–306.8 months), respectively. Thirty-one patients had metastases only in the lung, whereas 15 also had metastases in extrapulmonary organs, including the bone, liver, lymph node, and others. Additionally, some patients received other treatments (e.g. surgical resection, RF ablation, radiation therapy, cryoablation, and/or systemic chemotherapy) for extrapulmonary metastases after lung RF ablation. Before lung RF

ablation, 9 patients had no history of therapy for pulmonary metastases, whereas 20, 10, 6, and 1 had undergone surgery, chemotherapy, surgery and chemotherapy, and surgery and radiation therapy, respectively. The patient characteristics are summarized in Table 1.

RF ablation techniques

RF ablation was always performed percutaneously using CT fluoroscopy (Asteion or Aquilion; Toshiba Medical Systems Corporation, Otawara, Japan). The electrodes used for ablation included a multi-tined expandable electrode (LeVeen; Boston Scientific, Natick, MA, USA) and a single internally cooled electrode (Cool-tip; Covidien, Mansfield, MA, USA). Although the multi-tined expandable electrode was preferred, the internally cooled electrode was employed when the use of multi-tined expandable electrodes was deemed hazardous (e.g., in cases of apical or hilar lesions). The procedure aims were tumor ablation and at least a 5-mm margin. The above-mentioned RF ablation procedure used at our institution was similar to procedures that were previously described in the literature [16].

Chest CT with a slice thickness of ≤5 mm was performed immediately after the RF ablation procedure to evaluate the ablation zone and procedural adverse events (AEs). All AEs were evaluated based on the National Cancer Institute Common

Terminology Criteria for Adverse Events Version 4.0.

Follow-up examinations

Chest CT images with a slice thickness of ≤5 mm were usually obtained before and after intravenous contrast administration to assess technique efficacy at 1, 3, 6, 9, and 12 months post-treatment and every 6 months thereafter. The RF ablation technique efficacy was defined as the absence of local tumor progression after RF ablation on follow-up images [17]. Technique efficacy was evaluated by comparing the size and geometry of the ablation zone with observations on previous CT images. All ablated tumors were evaluated by at least two experienced radiologists, including a lung RF ablation operator. Local tumor progression was indicated when the ablation zone exhibited a continued increase in size after reduction. The appearance of an irregular, scattered, nodular, or eccentric enhancement focus in the ablation zone was also considered to indicate local progression [13].

Statistical analyses

The overall survival (OS) rate was calculated using the Kaplan–Meier method. OS was measured from the time of initial RF ablation for pulmonary metastases to death from any cause.

To determine the prognostic factors of OS, data variables (sex, age, histology,

primary site, extrapulmonary metastases, number of pulmonary metastases, treatment result by RF ablation, treatment before RF ablation, treatment after RF ablation, local recurrence after RF ablation, disease-free interval [DFI] after therapy for primary lesion, and DFI after RF ablation) were accumulated. The study cohort was divided into subgroups based on each variable. A log-rank test was performed to compare survival rates among the groups.

The primary and secondary technique efficacy rates were calculated using the Kaplan–Meier method. The primary efficacy rate was defined as the percentage of the tumor that was successfully eradicated after the initial procedure [17]. The secondary efficacy rate was defined as the percentage of the tumor that underwent successful repeat ablation after identification of local tumor progression [17].

For all analyses, P values <0.05 were considered to indicate a statistically significant difference. Statistical analyses were performed using SPSS software (version 22.0; IBM, Armonk, NY, USA).

Results

RF ablation was technically successful [17] in all 144 tumors. Eight tumors were treated twice, and 1 tumor was treated 3 times with RF ablation because of local

progression after RF ablation. Therefore, a total of 154 ablations in 88 sessions were performed using a multi-tined expandable electrode with a 2-cm (n = 86), 3-cm (n = 30), 3.5-cm (n = 1), or 4-cm (n = 3) array diameter or a single internally cooled electrode with a 1-cm (n = 4), 2-cm (n = 21), or 3-cm (n = 9) non-insulated tip. The mean numbers of treated tumors were 3.1 (range, 1–9) per patient and 1.8 (range, 1–5) per session. In 15 patients, all pulmonary metastases were ablated (i.e., curative treatment group); in the remaining 31 patients, RF ablation was performed to reduce the number of pulmonary metastases, although not all pulmonary metastases were ablated (i.e., non-curative treatment group).

The mean and median tumor follow-up periods were 16.9 months and 10.8 months (range, 0–93.3 months), respectively. Local progression occurred in 11 patients with 22 tumors (15.3%). The primary and secondary technique efficacy rates were 83.5% (95% confidence interval [CI], 75.1–89.4%) and 90.0% (95% CI, 82.6–94.4%) at 1 year and 76.3% (95% CI, 65.7–84.4%) and 81.4% (95% CI, 70.1–88.8%) at 2 years, respectively.

Seventy-three grade 1 and 33 grade 2 AEs occurred in 57/88 sessions (64.8%) and observed (Table 2). The worst AE grades per session were grade 1 (n = 36; 40.9%) and grade 2 (n = 21; 23.9%). No AEs of grade ≥3 were observed. None of the patients

died as a result of the procedure.

By the conclusion of the study, 28 patients (60.9%) remained alive and 18 had died; of the latter, all except 1 died because of tumor progression. The mean and median patient follow-up periods were 23.9 and 16.7 months (range, 2.1–103.3 months), respectively. OS rates were 80.6% (95% CI, 65.6–90.0%) at 1 year, 70.1% (95% CI, 53.0–83.0%) at 2 years, and 47.1% (95% CI, 27.5–67.6%) at 3 years (mean survival time, 48.9 months; median survival time, 31.7 months; Fig. 1).

Univariate analysis revealed the presence of extrapulmonary metastases (P = 0.005), non-curative treatment by RF ablation (P = 0.009), and DFI after RF ablation ≤12 months (P = 0.015) to be significant negative prognostic factors (Table 3).

After initially planned consecutive lung ablation sessions, 35 patients underwent various local therapies such as RF ablation, surgery and radiation therapy, and/or systemic therapies for new and/or remnant metastases. The other 11 patients had no history of additional therapies. The outcomes after initially planned consecutive RF ablation are shown in Fig. 2.

Discussion

For sarcoma patients with pulmonary metastases, surgical treatment is

considered one of the most effective treatments, and systemic chemotherapy has not yet been established for patients with multiple metastases. Despite the use of multiple regimens, however, the reported median survival time after chemotherapy is only 8–12 months [18].

A systematic review of 18 published results reported 5-year survival rates after pulmonary metastasectomy of 34% and 25% for bone and soft-tissue sarcomas, respectively [7]. However, even after pulmonary metastasectomy, recurrences were detected in 45–83% of patients [19]. Each resection of pulmonary metastases reduces the lung volume, and multiple tumor resection carries a potential risk of worsening respiratory function. Therefore, multiple pulmonary metastasectomy is contraindicated for patients with poor pulmonary function. Only 25–30% of patients with pulmonary metastases benefit from metastasectomy because of the multiplicity of pulmonary metastases, associated recurrences at other sites, and comorbid diseases [20].

Recently stereotactic radiation therapy (SRT) has been used as an alternative local treatment for pulmonary metastases of sarcoma [21–24]. This procedure has yielded OS rates of 96.2% at 2 years [21], 72% at 4 years [22], and 50–60.5% at 5 years [21, 23]. Although this therapy seems promising, its repeatability is usually limited because of the increased risk of radiation-induced lung toxicity.

Investigators have also reported the outcomes of RF ablation for patients with pulmonary metastases of sarcoma [1, 14, 20, 25]. The reported OS rates vary widely with ranges of 58–94.1% at 1 year [14, 20], 29–85% at 3 years [1, 15, 21, 26], and 41.5% at 5 years [14], consistent with our findings. This local therapy may be a useful treatment option for patients with pulmonary metastases of sarcoma. Previous reports have described the complete ablation of all lung tumors [20] and prior DFI as factors associated with improved survival [25]. In our study, the presence of extrapulmonary metastases, non-curative RF ablation treatment, and DFI ≤12 months after RF ablation were found to be significant negative predictors in a univariate analysis. Therefore, patients with sarcoma who lack extrapulmonary metastases and can be curatively treated are favorable candidates for the RF ablation of pulmonary metastases. A prospective study with a larger population is needed to determine the long-term survival outcomes after RF ablation treatment and the prognostic factors associated with OS.

According to previous reports, lung RF ablation for lesions <2 cm yields local control rates >90% [26, 27]. RF ablation has some potential advantages over other treatments, including feasibility, safety, reduced invasiveness, and repeatability. This therapy was technically feasible and could be performed under local anesthesia for all 144 tumors in our cohort. The reported major complication and mortality rates

associated with RF ablation of metastatic lung disease range from 0% to 2.6% and from 9.8% to 22.6%, respectively [28–31].

Lencioni et al. [28] reported no significant worsening of pulmonary function at 12 months after lung RF ablation. Repeat RF ablation is possible for the treatment of local progression after RF ablation [32], as well as new lesions [33]. In this study, grade ≥3 AEs did not occur. Therefore, RF ablation seems to be a feasible, safe, and less invasive local treatment for patients with pulmonary metastases of sarcoma. In addition, these occasionally require combination treatment with various local therapies. Many of our patients received other treatments before and/or after RF ablation. RF ablation can be safely and effectively combined with other treatments in this patient population.

This retrospective study had some limitations. The small study population was derived from a single institution, and some of the cases had a fairly short follow-up interval. Not all patients were treated with RF ablation alone; therefore, the effects of other therapies on survival could not be assessed. The mean tumor diameter (13.5 mm) was small, and a majority of ablated lesions were diagnosed as pulmonary metastases based only on the results of serial CT images, without histopathological confirmation. However, we conclude that despite these limitations, RF ablation of pulmonary metastases of sarcoma appears to be a safe, viable treatment option that offers good

local control.

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Figure Legends

Figure 1. Overall survival curve in 46 patients.

Figure 2. Outcomes after radiofrequency ablation of lung metastases in 46 patients.

Table1

Table 1.Characteristics of 46 patients and 144 tumors

Variable		Value
Patient characteristics		
Sex	Man	11 (23.9)
	Woman	35 (76.1)
Age (y)	Mean ± SD	54.5 ± 12.9
	Range	24–79
Histology of primary lesion	Leiomyosarcoma	27 (58.7)
	Others	19 (41.3)
Primary site	Bone and soft tissue	19 (41.3)
	Uterus	17 (37.0)
	Others	10 (21.7)
Extrapulmonary metastases	Yes	15 (32.6)
	No	31 (67.4)
Number of pulmonary metastases	≤5	31 (67.4)
	>5	15 (32.6)
Treatment results by RF ablation	Curative	15 (32.6)
	Non-curative	31 (67.4)
Treatments before RF ablation	Yes	37 (80.4)
	No	9 (19.6)
Treatments after RF ablation	Yes	35 (76.1)
	No	11 (23.9)
Local recurrence after RF ablation	Yes	11 (23.9)
	No	35 (76.1)
DFI after therapy for primary lesion (mo)	Mean ± SD	38.3 ± 60.3
	Range	0–290.5
DFI after RF ablation (mo)	Mean ± SD	11.0 ± 23.0
	Range	0-98.9
Tumor characteristics		
size (mm)	Mean ± SD	13.5 ± 9.0
	Range	3–50
Histology of primary lesion	Leiomyosarcoma	91 (63.2)
	Others	53 (36.8)
Primary site	Bone and soft tissue	51 (35.4)
	Uterus	64 (44.4)
	Others	29 (20.1)

Values in parentheses are percentages.

SD = standard deviation: RF = radiofrequency: DFI = disease free interval

Table 2. Adverse events of radiofrequency ablation in 88 sessions

	Number		
Adverse events	Grade 1	Grade 2	Grade ≥3
Pneumothorax	28	16	0
Pleural effusion	17	1	0
Fever up	22	6	0
Pulmonary hemorrhage	2	2	0
Pleuritis	1	4	0
Pneumonia	0	4	0
Others	3	0	0
Total	73	33	0

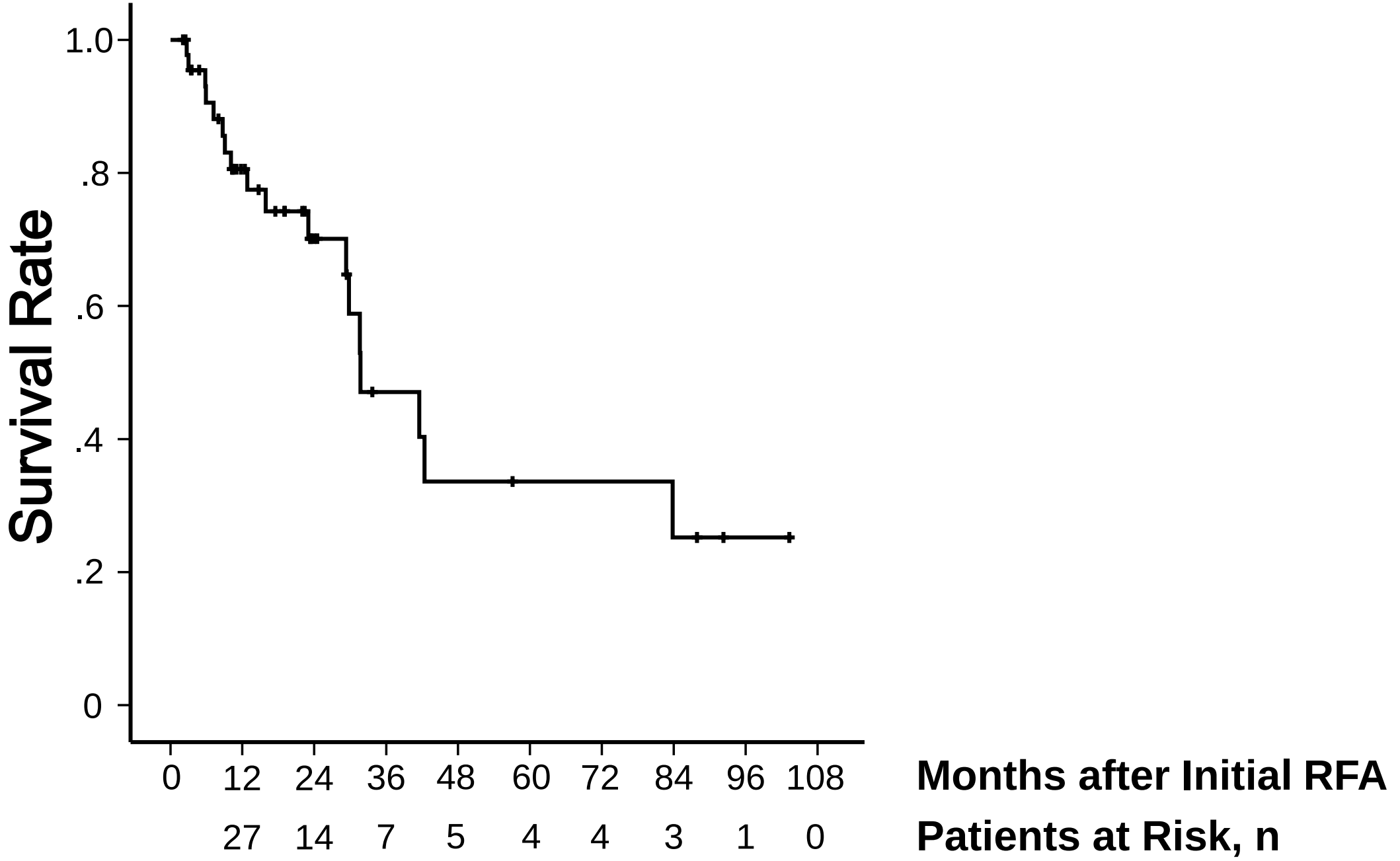
Table3

Table 3. Overall survival rates based on variables in 46 patients

	Patient number	Survival rate (%)			MST (months)	P value
		1-year	2-years	3-years		
Sex						
Man	11	63.6	50.9	50.9	NA	0.807
Woman	35	86.8	76.8	43.2	31.7	
Age						
<50	13	80.0	68.6	68.6	41.5	0.538
≥50	33	80.6	71.2	43.2	31.7	
Histology						
Leiomyosarcoma	27	79.7	74.4	62.0	31.6	0.592
Others	19	81.6	65.3	37.3	42.4	
Primary site						
Bone and soft tissue	19	83.3	68.2	39.0	31.6	0.964
Uterus	17	80.4	64.3	32.1	29.3	
Others	10	76.2	76.2	76.2	42.4	
Extrapulmonary metastases						
Yes	15	63.5	38.1	38.1	15.9	0.005
No	31	88.9	83.3	53.5	41.5	
Number of pulmonary metastases						
≤5	31	86.0	79.9	55.9	41.5	0.070
>5	15	67.5	48.2	24.1	15.9	
Treatment results by RF ablation						
Curative	15	100.0	88.9	63.5	83.8	0.009
Non-curative	31	70.4	60.3	37.7	29.8	
Treatments before RF ablation						
Yes	37	78.9	69.6	47.0	31.7	0.998
No	9	87.5	72.9	48.6	31.6	
Treatments after RF ablation						
Yes	35	78.6	65.1	43.9	31.7	0.169
No	11	88.9	88.9	59.3	NA	
Local recurrence after RF ablation						
Yes	11	71.6	71.6	43.0	31.6	0.830
No	35	83.9	68.6	50.0	31.7	
DFI after therapy for primary lesion						
≤12 mo	20	73.1	51.2	34.1	31.7	0.633
>12 mo	26	84.6	79.9	53.9	41.5	
DFI after RF ablation						
≤12 mo	39	76.5	63.0	32.0	29.8	0.015
>12 mo	7	100.0	100.0	100.0	NA	

MST = median survival time: NA = not applicable: RF = radiofrequency: DFI = disease free interval

Figure1


Survival Rate
1.0
.8
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Months after Initial RFA
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Figure2

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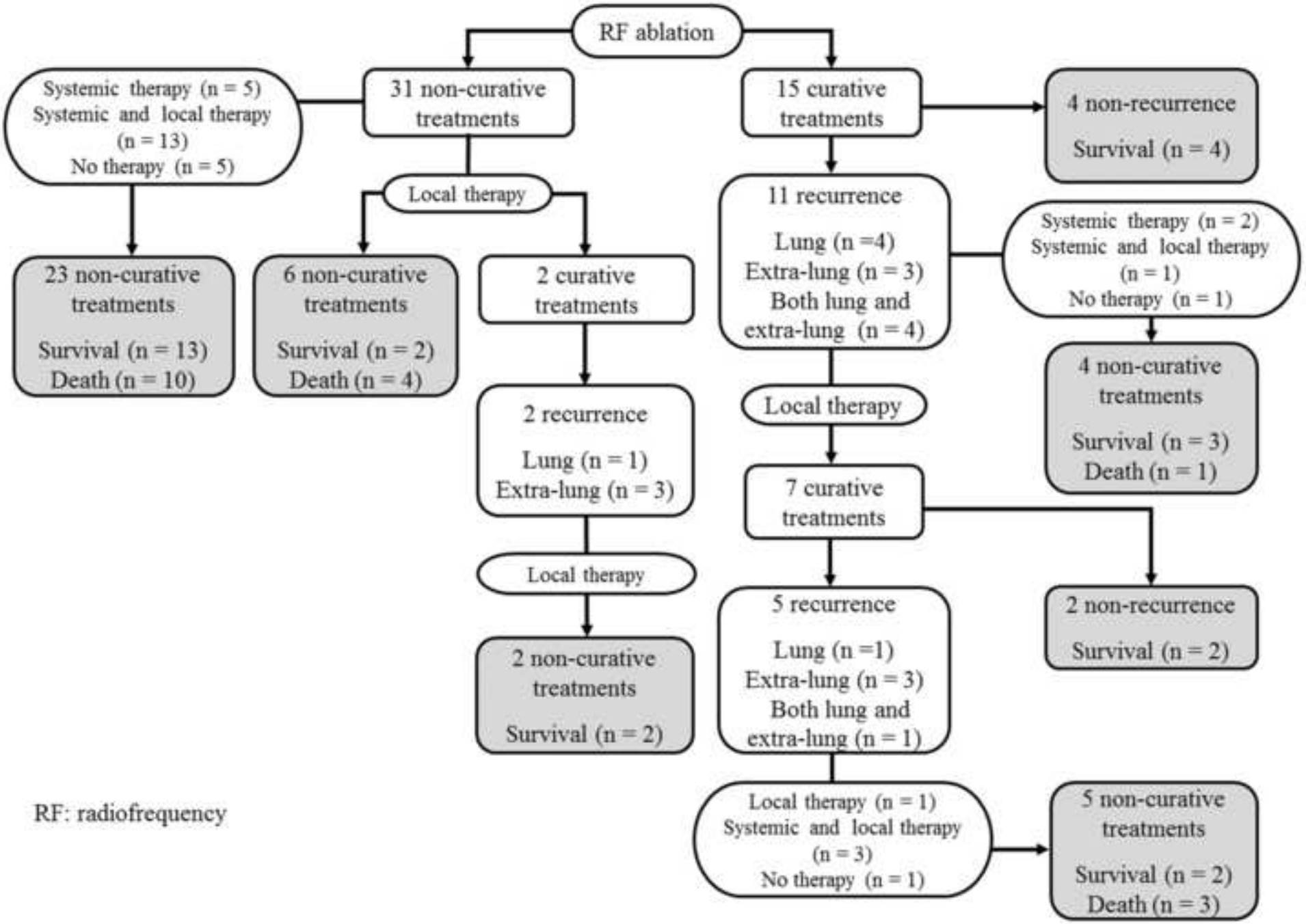

RF: radiofrequency

Prerequisites for Publication

Authorship: The Editors of *Japanese Journal of Radiology* adhere to recommendations of the International Committee of Medical Journal Editors [http://www.icmje.org] regarding criteria for authorship.

Accordingly, each person listed as an author or coauthor for a submitted report (excepting Review articles) must meet all three criteria. An author or coauthor shall have:

1. Conceived, planned, and performed the work leading to the report, or interpreted the evidence presented, or both;
2. Written the report or reviewed successive versions and participated in their revision;
3. Approved the final version.

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Authors' names: Takuya Sato, MD , Toshihiro Iguchi, MD , Takao Hiraki, MD , Hideo Gobara, MD , Hiroyasu Fujiwara, MD , Jun Sakurai, MD , Yusuke Matsui, MD , Toshiharu Mitsuhashi,MD , Junichi Soh, MD , Shinichi Toyooka, MD , Susumu Kanazawa, MD

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