データセンターFAX 番号 03-3547-6096

プロトコール名 JIVROSG-0702 (LRFA-II) 肺悪性腫瘍に対する経皮的ラジオ波凝固療法についての第 II 相臨床試験	治療後観察項目報告書

症例登録番号＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

標的病変以外の新病変の出現

□無 □有

	検査日	確認方法	出現部位	出現内容
1	20 年 月 日	□造影 CT □FDG-PET □その他 [ ]	[ ]	[ ]
2	20 年 月 日	□造影 CT □FDG-PET □その他 [ ]	[ ]	[ ]
3	20 年 月 日	□造影 CT □FDG-PET □その他 [ ]	[ ]	[ ]
4	20 年 月 日	□造影 CT □FDG-PET □その他 [ ]	[ ]	[ ]
5	20 年 月 日	□造影 CT □FDG-PET □その他 [ ]	[ ]	[ ]

有効性評価

		時期	検査日	検査方法	有効性
1	標的病変 1	6 か月目	**20 年 月 日**	**FDG-PET**	□**CR*** □**non-CR**** □評価不能 ⇒ 理由[ ]
2	標的病変 2	6 か月目	**20 年 月 日**	**FDG-PET**	□**CR*** □**non-CR**** □評価不能 ⇒ 理由[ ]

*標的病変に悪性病変と診断される異常集積が認められない。
**標的病変に悪性病変と診断される異常集積が認められる。
またはプロトコール治療 3 ヵ月後の CT で明らかに前回 CT と比較して病変の再増大を認めた場合。
「異常集積」とは、標的病変の FDG 集積が胸椎周囲軟部組織以下の集積

総合評価の評価方法（総合評価は記入不要）

		標的病変 2		
		CR	Non-CR	評価不能
標的病変 1	CR	CR	Non-CR	評価不能
	Non-CR	Non-CR	Non-CR	Non-CR
	評価不能	評価不能	Non-CR	評価不能

注：二つの標的病変があり、その評価が異なる場合は悪い方の評価とする。(例;CR と non-CR の場合 non-CR、CR と評価不能の場合は評価不能、non-CR と評価不能の場合は non-CR とする。)

プロトコール名 JIVROSG-0702 (LRFA-II) 肺悪性腫瘍に対する経皮的ラジオ波凝固療法についての第 II 相臨床試験	治療後観察項目報告書

症例登録番号＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

併用療法/支持療法

酸素投与　□無　□有　(詳細を以下に記入)

	投与日	投与量
1	年　月　日	＿＿＿＿L/分
2	年　月　日	＿＿＿＿L/分
3	年　月　日	＿＿＿＿L/分

プロトコール治療 29 日目以降の標的病変以外の病変治療　□無　□有 (詳細を以下に記入)

	治療日	治療病変数
1	年　月　日	＿＿＿＿か所
2	年　月　日	＿＿＿＿か所
3	年　月　日	＿＿＿＿か所

プロトコール治療後に開始された化学療法　□無　□有 (詳細を以下に記入)

	治療開始日	薬剤の種類あるいはレジメン名
1	年　月　日	
2	年　月　日	
3	年　月　日	

資料 3

データセンターFAX 番号 03-3547-6096

プロトコール名 JIVROSG-0702 (LRFA-II) 肺悪性腫瘍に対する経皮的ラジオ波凝固療法についての第 II 相臨床試験	治療後観察項目報告書

症例登録番号＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

記入日 20[　]年[　]月[　]日　施設名 [　　]　記入者名 [　　]

資料 3

データセンターFAX 番号　03-3547-6096

プロトコール名 JIVROSG-0702 (LRFA-II) 肺悪性腫瘍に対する経皮的ラジオ波凝固療法についての第 II 相臨床試験	イベント発生報告書

症例登録番号＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

以下に該当するイベントが発生

イベント発生確認日　＿＿＿＿＿＿年＿＿＿月＿＿＿日

☐ 臨床的に明らかな病変の増大

☐ 死亡

☐ **IVR 後 30 日以内**

AE/AR/ADR 急送報告書にも記入し、48 時間以内に事務局に報告

☐ **IVR 後 31 日以降**

☐ **IVR との因果関係が否定できない**

AE/AR/ADR 報告書にも記入し、15 日以内に事務局に報告

☐ **IVR との因果関係が否定できる**

☐ 原病死　☐ 他病死（　　）

☐ 事故　☐ その他（　　）

記入日 **20**＿＿年＿＿月＿＿日　施設名＿＿＿＿＿＿＿＿　記入者名＿＿＿＿＿＿

データセンターFAX 番号 03-3547-6096

プロトコール名 JIVROSG-0702 (LRFA-II) 肺悪性腫瘍に対する経皮的ラジオ波凝固療法についての第 II 相臨床試験	追跡調査報告書

症例登録番号＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

イベント発生 ☐ 無 ☐ 有 (下記に記入)

イベント発生確認日 ＿＿＿＿＿＿年＿＿＿月＿＿＿日

☐ 臨床的に明らかな病変の増大

☐ 死亡

☐ **IVR 後 30 日以内**

AE/AR/ADR 急送報告書にも記入し、48 時間以内に事務局に報告

☐ **IVR 後 31 日以降**

☐ **IVR との因果関係が否定できない**

AE/AR/ADR 報告書にも記入し、15 日以内に事務局に報告

☐ **IVR との因果関係が否定できる**

☐ 原病死 ☐ 他病死 (　　)

☐ 事故 ☐ その他 (　　)

9 ヶ月目以降のデータがある症例については、次ページ以降も記入してください。

記入日 **20**＿＿年＿＿月＿＿日 施設名 ＿＿＿＿＿＿＿＿ 記入者名 ＿＿＿＿＿＿＿＿

プロトコール名 JIVROSG-0702 (LRFA-II) 肺悪性腫瘍に対する経皮的ラジオ波凝固療法についての第 II 相臨床試験	追跡調査報告書

症例登録番号＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

標的病変以外の新病変の出現

□無 □有

	検査日	確認方法	出現部位	出現内容
1	20 年 月 日	□造影 CT □FDG-PET □その他 [ ]	[ ]	[ ]
2	20 年 月 日	□造影 CT □FDG-PET □その他 [ ]	[ ]	[ ]
3	20 年 月 日	□造影 CT □FDG-PET □その他 [ ]	[ ]	[ ]
4	20 年 月 日	□造影 CT □FDG-PET □その他 [ ]	[ ]	[ ]
5	20 年 月 日	□造影 CT □FDG-PET □その他 [ ]	[ ]	[ ]

有効性評価

		時期	検査日	検査方法	有効性
1	標的病変 **1**	**12** か月目	**20** 年 月 日	**FDG-PET**	□**CR*** □**non-CR**** □評価不能 ⇒ 理由[ ]
2	標的病変 **2**	**12** か月目	**20** 年 月 日	**FDG-PET**	□**CR*** □**non-CR**** □評価不能 ⇒ 理由[ ]

*標的病変に悪性病変と診断される異常集積が認められない。
**標的病変に悪性病変と診断される異常集積が認められる。
「異常集積」とは、標的病変の FDG 集積が胸椎周囲軟部組織以下の集積

プロトコール名 JIVROSG-0702 (LRFA-II) 肺悪性腫瘍に対する経皮的ラジオ波凝固療法についての第 II 相臨床試験	追跡調査報告書

症例登録番号＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

資料 4

JIVROSG-0702（LRFA-II）　重篤な有害事象の急送報告書（48 時間以内）

FAX 送付先：086-235-7313　　(全＿＿＿枚)

JIVROSG-0701 研究代表者：岡山大学大学院病態制御学専攻腫瘍制御学講座　金澤　右(TEL:086-235-7313)

研究代表者への報告日　　年　　月　　日

施設名　　FAX　　TEL

施設研究責任者名　　記入者名

I. 症例に関する情報

JIVROSG 試験番号　　症例登録番号

II. 有害事象の転帰

有害事象発生日　　年　　月　　日　　IVR 治療日　　年　　月　　日

- ☐ 治療中及び治療完了日から 30 日以内に発生したすべての死亡
- ☐ 治療に関連して発生した、重篤で、予期していない grade 4 の有害事象
- ☐ その他　（＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿）

有害事象の概要（有害事象の具体的内容、関連する治療歴や検査データを含む）

III. 有害事象と因果関係が疑われる治療

☐ IVR 治療　☐ 薬物療法　☐ 放射線治療　☐ その他の治療

治療の概要

IV. プロトコール治療との因果関係についての報告者の評価

- ☐ definite　明確な
- ☐ probable　多分、十中八九は
- ☐ possible　ありそうな

→ 死亡との因果関係があると思われる有害事象

- ☐ unlikely　ありそうにない
- ☐ not related(unrelated)　関係ない
- ☐ unassessable　評価不能

→ 「腫瘍増悪,急死,事故,自殺,殺人,不明」から死因選択

V. 研究代表者の記録欄

1) 報告受領日　＿＿＿年＿＿＿月＿＿＿日　　研究代表者署名＿＿＿＿＿＿＿＿

2) グループ代表者への報告日＿＿＿年＿＿＿月＿＿＿日

3) 本有害事象への研究代表者としての対応

参加施設への通知日　＿＿＿年＿＿＿月＿＿＿日

症例登録一時中止日（データセンターへの連絡日）　＿＿＿年＿＿＿月＿＿＿日

効果・安全性評価委員会への審査依頼日　＿＿＿年＿＿＿月＿＿＿日

資料 5

JIVROSG　重篤な有害事象の通常報告書（15 日以内）

FAX 送付先：086-235-7313　　(全＿＿＿枚)

JIVROSG-0207 研究代表者：岡山大学大学院病態制御学専攻腫瘍制御学講座　金澤　右(TEL:086-235-7313)

研究代表者への報告日　　年　　月　　日

施設名　　**FAX**　　**TEL**

施設研究責任者名　　記入者名

I. 症例に関する情報

JIVROSG 試験番号　　症例登録番号

II. 有害事象の分類

有害事象発生日　　年　　月　　日　　**IVR 治療日**　　年　　月　　日

- ☐ 死亡　　(**IVR 治療日より、**☐ **30 日以内** ☐ **31 日以降**)
- ☐ 生命を脅かすもの　　(☐ 予期していないもの　　☐ 予期されるもの)
- ☐ 予期していない **grade 2,3** の有害事象
- ☐ 永続的または顕著な障害/機能不全
- ☐ その他　(＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿)

III. 有害事象の内容とプロトコール治療の因果関係

AE/ARの内容	Grade	因果関係が疑われる治療法・薬物	因果関係の程度*	発生時期（何日目）	転帰

*因果関係の程度：definite(明確な)、probable(多分、十中八九)、possible(ありそうな)、unlikely(ありそうにない)、not related(関係ない)、unassessable(評価不能)のいずれかを記載。死亡の場合、死因が有害事象と「unlikely」、「not related」場合、「AE/AR の内容」に「腫瘍増悪、急死、事故、自殺、殺人、不明」のいずれかを記入。

IV. 症例報告の詳細　(別紙添付＿＿枚)

V. 研究代表者の意見書（別紙添付＿＿枚)

VI. 研究代表者の記録欄

1) 報告受領日　　年　　月　　日　　研究代表者署名＿＿＿＿＿＿＿＿

2) グループ代表者への報告日　　年　　月　　日

3) 本有害事象への研究代表者としての対応

参加施設への通知日　　年　　月　　日

症例登録一時中止日（データセンターへの連絡日）　　年　　月　　日

効果・安全性評価委員会への審査依頼日　　年　　月　　日

4) 当該企業への「副作用自発報告」の提出確認日　　年　　月　　日

(付表 6)ラジオ波凝固アルゴリズム参照案 (JIVROSG-0701 RRFA-Ⅰ/Ⅱ)

1. Cool-tip システム

(ア) 電極針の選択

active-tip の長さは腫瘍最大径よりも 10mm 大きなものを選択するのが。ただし刺入予定方向から見た腫瘍径が最大径と著しく異なる場合、胸壁、縦隔構造、血管などを避ける上で必要不可欠である場合最大腫瘍径よりも小さな active-tip を選択することが許容される。

(イ) 通電アルゴリズム

インピーダンスコントロールモードで通電する。

1焼灼個所につき12分間通電する(後述する場合は12分以上の通電となる)。

最大出力は140W とする。

通電出力

	2-cm active tip	3-cm active tip
開始出力	30 or 40W	40 or 50 or 60W
出力上昇率	10W/分	10W/分

ブレークダウンが生じた場合もそのまま通電を継続する。ただし再開する場合は 10-20W 出力を低下させる。あるいはブレークダウンが生じた出力の半分から再開する。

12 分間の通電終了後先端温度を測定し、60℃以上であった場合その焼灼個所の治療は終了とする。

ブレークダウンが 12 分間で生じなかった場合あるいは先端温度が 60℃未満であった場合は適宜焼灼を追加する。めやすは最大出力で 3-6 分の通電。この場合は 1 焼灼部位の通電時間が 12 分を超えることになる。

強度の疼痛に対しては鎮痛剤の追加で対処する。疼痛のため一旦通電を中断した場合、疼痛対策ののち、はじめから再開する。

(ウ) オーバーラップ

15mm までの腫瘍の場合は中央を穿刺して焼灼する。穿刺が中央をはずれた場合は反対側に追加焼灼することが望ましい。

15mm を超える場合は複数カ所の焼灼を計画することが望まれる。

(三重大の方法)

中央を穿刺して焼灼し、すりガラス影の不足している部位に追加穿刺、焼灼する。

(岡山大の方法)

当初から 3 個所あるいは 4 個所の辺縁穿刺を計画し、焼灼を実施する。

2. LeVeen システム

(ア) 電極針の選択

展開径は腫瘍最大径よりも 10mm 以上大きなものが原則。ただし刺入予定方向から見た腫瘍径が最大径と著しく異なる場合、胸壁、縦隔構造、血管などを避ける上で必要不可欠である場合上記基準よりも小さな展開径を選択することが許容される。

(イ) 通電アルゴリズム

1焼灼個所につき 2 回の通電を基本とし、1 回の通電はそれぞれ最大15 分間通電する。

最大出力は190W とする。

通電出力

	2cm 展開径	3cm 展開径	3. 5cm 展開径	4cm 展開径
開始出力	10W	20W	30W	40W
出力上昇率	5W/分	5W/分	10W/分	10W/分

1 回目の通電でロールオフが生じた場合、ロールオフが生じた最大出力の半分の出力から 30 秒後に 2 回目を開始する。

1 回目の通電でロールオフが生じなかった場合、その最終出力から 30 秒後に 2 回目を開始する。2 回目の通電でロールオフが生じなくても 15 分間の通電で終了する。

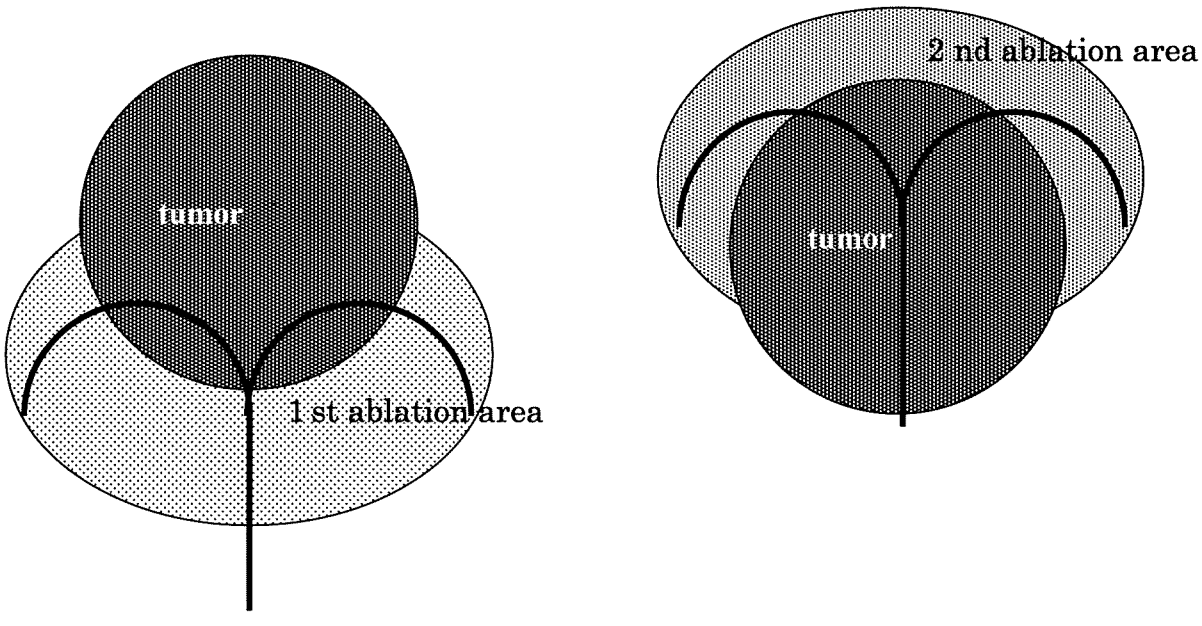
以上のごとく 2 回の通電を 1 セットとして 1 焼灼部位の通電を終了する。

強度の疼痛に対しては鎮痛剤の追加で対処する。疼痛のため一旦通電を中断した場合、疼痛対策ののち、はじめから再開する。

(ウ) オーバーラップ

(岡山大の場合)

以下のごとく、腫瘍の近位(穿刺方向から見て)で一度展開し焼灼、腫瘍の遠位(通常肺門側)に電極針を進め焼灼。以上 2 個所での通電を行う。



別添 4

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書 籍 名	出版社名	出版地	出版年	ページ
該当無し							

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Sano Y ,et al.	Feasibility of Percutaneous Radiofrequency Ablation for Intrathoracic Malignancies. A Large Single-Center Experience.	CANCER	109(7)	1397-1405	2007
Hiraki T, et al	Percutaneous Radiofrequency Ablation for Pulmonary Metastases from Colorectal Cancer: Midterm Results in 27 Patients.	J Vasc Interv Radiol.	18(10)	1264-1269	2007
Higaki F, et al.	Preliminary retrospective investigation of FDG-PET/CT timing in follow-up of ablated lung tumor.	Ann Nucl Med.	22	157-63	2008
Hiraki T, et al	Repeat radiofrequency ablation for local progression of lung tumors: does it have a role in local tumor control?	J Vasc Interv Radiol.	19	706-11.	2008
Hiraki T, et al	Does tumor type affect local control by radiofrequency ablation in the lungs?	Eur J Radiol	74	136-141	2010
Sakurai J, et al	Radiofrequency Ablation of Small Lung Metastases by a Single Application of a 2-cm Expandable Electrode: Determination of Favorable Responders	J Vasc Interv Radiol	21	:231-236	2010

Feasibility of Percutaneous Radiofrequency Ablation for Intrathoracic Malignancies

A Large Single-Center Experience

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BACKGROUND. Radiofrequency ablation (RFA) has become an accepted alternative for treating intrathoracic malignancies; however, the incidence and characteristics of peri- and postprocedural complications are not well described. The purpose of the study was to assess the safety and technical feasibility of percutaneous RFA in unresectable intrathoracic malignancies.

METHODS. Percutaneous RFA was performed in patients with intrathoracic malignancies between June 2001 and December 2004. In total, 366 tumors were treated in 137 patients in 211 sessions. All patients were nonsurgical candidates or had refused surgery. Three hundred and thirty-six lesions were subjected to RFA for the treatment of metastases and 30 lesions for primary lung carcinoma.

RESULTS. Although no procedural mortality occurred, 2 patients died during the course of the study because of intractable pneumothorax and massive hemoptysis (0.9%). The overall major complication rate was 17.1% (pneumothoraces requiring tube drainage in 25, pleuritis in 6, pleural effusion requiring tube drainage in 4, lung abscess in 1, and intrapulmonary hemorrhage with hemothorax in 1). Minor complications included pneumothoraces not requiring tube drainage in 108 sessions, pleural effusion without drainage in 34, hemosputum in 9, nausea and/or vomiting in 3, subcutaneous emphysema in 3, cough in 2, skin burn in 2, atelectasis in 1, and subileus in 1. High fever and/or chest pain were seen in 33.8% and 39.3% of patients, respectively.

CONCLUSIONS. With over 200 procedures, RFA appears to be a safe and minimally invasive option with negligible mortality and little morbidity in selected patients with unresectable intrathoracic malignancies. ***Cancer* 2007;109:1397–405.** © *2007 American Cancer Society.*

KEYWORDS: radiofrequency ablation, intrathoracic malignancy, lung cancer, lung metastasis, complications.

Intrathoracic malignancies, especially primary lung carcinoma and metastatic lung tumors, are among the principal causes of cancer deaths throughout the world. Whereas surgical resection of lung malignancies in patients without metastases of other organs may provide a long-term survival benefit compared with nonsurgical therapies, only a few patients can obtain benefit from surgical resection because of advanced age, poor performance status, poor pulmonary function, or the number and location of tumors.

For patients with seemingly unresectable malignant tumors, radiofrequency ablation (RFA) has become recognized as a leading minimally invasive therapy for malignancies of various organs, especially liver tumors[1–4]; however, it is unclear whether this relatively

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novel therapy is really minimally invasive when applied to intrathoracic malignancies.

We conducted a retrospective study to determine the feasibility and safety of RFA for intrathoracic malignancies. To our knowledge, this is the first report demonstrating the feasibility of this procedure for intrathoracic malignancies focused on the complications and side effects, with over 200 procedures being performed at a single institution.

MATERIALS AND METHODS

Percutaneous RFA was performed in consecutive patients with intrathoracic malignancies between June 2001 and December 2004 using a Cool-tip RF system (17-gauge internally cooled electrodes; Radionics/ValleyLab, Boulder, CO) or a LeVeen Needle Electrode (17-gauge multitined expandable electrodes with an RF 3000 Generator; RadioTherapeutics, Sunnyvale, CA, distributed by Boston Scientific, Natick, MA) in our institution. The type of electrode used was determined mainly by tumor location, size, and the physicians' preference. Briefly, an internally cooled electrode was preferred for tumors located adjacent to the pleura or pulmonary hilum. Multitined expandable electrodes were mainly used for small nodules but not for tumors adjacent to the pleura or pulmonary hilum. A total of 137 patients underwent 211 RFA sessions. Patient and tumor characteristics are shown in Table 1. Three hundred and fifty-six pulmonary parenchymal, 6 pleural, and 4 hilar tumors were treated in 137 patients (mean age, 62.9 years; range, 34–88 years; 135 men and 76 women) in 211 sessions. All patients were nonsurgical candidates because they were medically unable to tolerate surgery or had refused surgery, or because of the extent of their disease. The study was conducted with the approval of our institutional human studies committee and written informed consent was obtained from all patients.

Of the 366 lesions considered, 336 underwent RFA for the treatment of presumed metastatic lesions, whereas 30 underwent RFA for primary lung carcinoma. The long-axis diameter of the tumor ranged from 3 to 98 mm with a mean diameter of 21.0 mm.

All ablations were performed percutaneously with computed tomography (CT) fluoroscopic guidance. Only 2 of 211 (0.9%) treatments were done under general anesthesia. Fifty-two of 211 (24.6%) treatments were performed using local anesthesia only. Eighty-eight (41.7%) were given a combination of local anesthesia and intravenous fentanyl. Depending on the tumor location (pleural or subpleural lesions), we added epidural block (32.7%). Patients were monitored with continuous pulse oximetry, electrocardiograph (ECG), and blood pressure during the procedure.

TABLE 1
Demographics and Tumor Characteristics of Study Population (N = 137)

Characteristics	No. (%) [Range]
Mean age	62.9 [34–88 y]
Sex	88 male/49 female
Mean tumor long-axis diameter	2.1 cm [0.3–9.8 cm]
$T \leq 10$ mm	88 (24.0)
$10 < T \leq 20$ mm	148 (40.4)
$20 < T \leq 30$ mm	66 (18.0)
$30 < T \leq 40$ mm	26 (7.1)
$40 < T \leq 50$ mm	17 (4.6)
50 mm < T	21 (5.7)
Total number of lesions	366, mean, 2.67/patient
Tumor location, tumors	
Parenchymal	356 (97.3)
RUL	70
RML	26
RLL	89
LUL	86
LLL	85
Hilar	4 (1.1)
Pleural	6 (1.6)
Diagnosis	
Metastases	336 (91.8)
Primary lung carcinoma	30 (8.2)
Maximum power, watts	54.2 [10–188]
Duration of ablation, min	29.0 [3–164]

RUL indicates right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe.

The RFA technique has been previously described.[5] Briefly, the electrode was introduced into the tumor and connected to an RF generator. Ablation time and the number of RF applications at each site were determined by tumor size, number of tumors, and the patient's complaints regarding pain. The endpoint of tumor ablation was considered to have occurred when ground glass attenuation of the normal lung parenchyma surrounding the tumor was seen on a CT scan. The measured maximum power output applied during these procedures was 10 to 188 watts (mean, 54.2 watts) and total duration time of ablation was 3 to 164 minutes (mean, 29.0 minutes).

After the procedure patients were instructed to stay in bed for 4 hours. Chest radiographs were obtained 4 hours and about 24 hours after the end of the procedure. The hospital observation period after RFA was 24 hours for most patients without any complications.

The Fisher exact test was used for categorical variables and the *t*-test was used for continuous vari-

TABLE 2
Mortality and Major Complications After Radiofrequency Ablation (RFA)

Event	No.
Mortality	2 Cases, mortality rate = 0.9%
1. Intractable pneumothorax and pneumonia	1 Postpneumonectomy
2. Massive hemoptysis	1 RFA for hilar lymph nodes
Major complications	Rate of major complications, 36/211 sessions = 17.1%)
1. Pneumothoraces (required tube drainage)	25
2. Pleuritis	6
3. Pleural effusion (required tube drainage)	4
4. Lung abscess	1
Minor complications	Rate of all complications, 137/211 sessions = 64.9%)
1. Pneumothoraces (no drainage)	85
2. Pleural effusion (no drainage)	34
3. Hemosputum	9
4. Nausea and/or vomiting	3
5. Subcutaneous emphysema	3
6. Cough	2
7. Skin burn	2
8. Atelectasis	1
9. Subileus	1

ables. All tests were 2-sided and a P value $<.05$ was considered significant. Statistical analysis was conducted with StatView 5.0 (SAS Institute, Cary, NC).

RESULTS

The technical success rate of RFA in this series was 100%. There were 2 cases in which we had to control the output because of severe pain; however, it was possible to perform complete ablation for a longer period. Mortality and morbidity are described in Table 2.

Mortality

Although no immediate death occurred, 2 patients died in the hospital after RFA (0.9% of procedures). A 76-year-old man (Patient 1) with severe pulmonary emphysema and lung cancer—who had undergone right pneumonectomy 12 months previously—in whom recurrence of lung cancer was treated by RFA (3 nodules, maximum diameter 22 mm, Cool-Tip needle, maximum power 100W) because of poor pulmonary function, which developed an intractable pneumothorax, resulting in pneumonia and respiratory failure (Fig. 1). Despite maximal supportive therapy, he died 53 days after RFA. The second patient, a 67-year-old man (Patient 2) with pulmonary metastases of renal cell carcinoma, developed a massive hemoptysis from the ablated lesions and died 28 days after RFA (maximum diameter 35 mm, Cool-Tip needle, maximum power 90W) for hilar lymph nodes (Fig. 2).

Morbidity

Adverse events were divided into 3 groups: major complications, minor complications, and side effects, according to the criteria of the Society of Interventional Radiology Technology Assessment Committee and the International Working Group on Image-Guided Tumor Ablation. A major complication is defined as an event that leads to substantial morbidity and disability, increased level of care, or results in hospital admission or substantially lengthened hospital stay. This includes any case in which a blood transfusion or interventional drainage procedure is required. All other complications are considered minor. Side effects were considered undesired consequences of the procedure that, although occurring frequently, rarely would result in substantial morbidity. These included pain, postablation syndrome, asymptomatic pleural effusions, and minimal or blood collections observed during imaging.[6,7]

Thirty-six major complications (major complication rate 17.1%) occurred in our series: pneumothoraces requiring tube drainage in 25, pleuritis in 6, pleural effusion requiring tube drainage in 4, and lung abscess in 1. In addition, some minor complications were seen after these procedures. Pneumothoraces developed during or soon after the procedure in 110 sessions (52.1%), requiring aspiration in 19 sessions (9.0%) and chest tube placement in 25 sessions (11.8%). Pleural effusion requiring aspiration or chest tube placement occurred in 5 sessions (2.4%). Other minor complications included hemosputum in 9, nausea and/or vomiting in 3, subcutaneous emphysema in 3, cough in 2, skin burn in 2, atelectasis in 1, and subileus in 1 (Table 2). High fever and/or chest pain were the most common side effects seen in 33.8% and 39.3% of patients, respectively; however, most of them were cured within a few days without antibiotic treatment (Table 3). There were a total of 137 complications per session (64.9%) after RFA in our series; however, no patient suffered from respiratory failure after RFA.

Next we assessed the factors that have caused these major complications (Table 4). We conducted univariate analysis of the risk factors responsible for major complications after RFA. Only older age was shown as a statistically significant risk factor, whereas tumor size, distance from tumor to pleura, number of ablation, and duration time of ablation

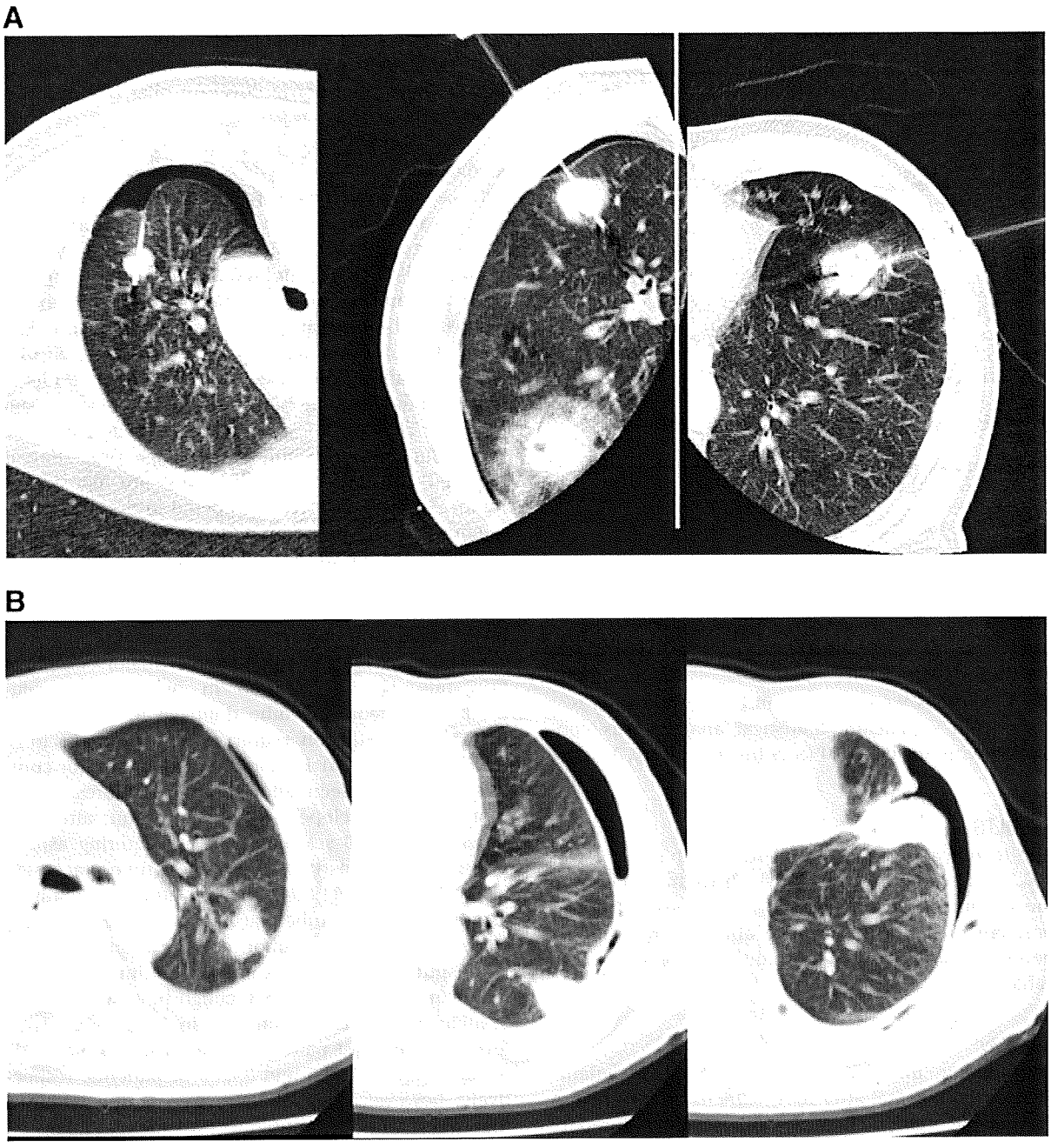

FIGURE 1. (Top) A 76-year-old man who previously had a right pneumonectomy for lung carcinoma with 3 lung metastases (Left S1 + 2, Left S6, and Left S8). Intraprocedural computed tomography (CT) scans demonstrated puncturing of 17-gauge internally cooled electrodes to these nodules. (Bottom) A 76-year-old man who previously had a right pneumonectomy for lung carcinoma with 3 lung metastases (Left S1 + 2, Left S6, and Left S8). CT scans of 38 days after radiofrequency ablation (RFA) demonstrated postprocedural pneumothorax and thickening of the visceral pleura.

were not considered as risk factors, although there was a tendency for the use of expandable electrodes and high power output to have a higher risk of major complications (Table 4).

DISCUSSION

RFA for primary and metastatic malignancies, especially in the liver, has become an accepted option because of its low morbidity and mortality, and the

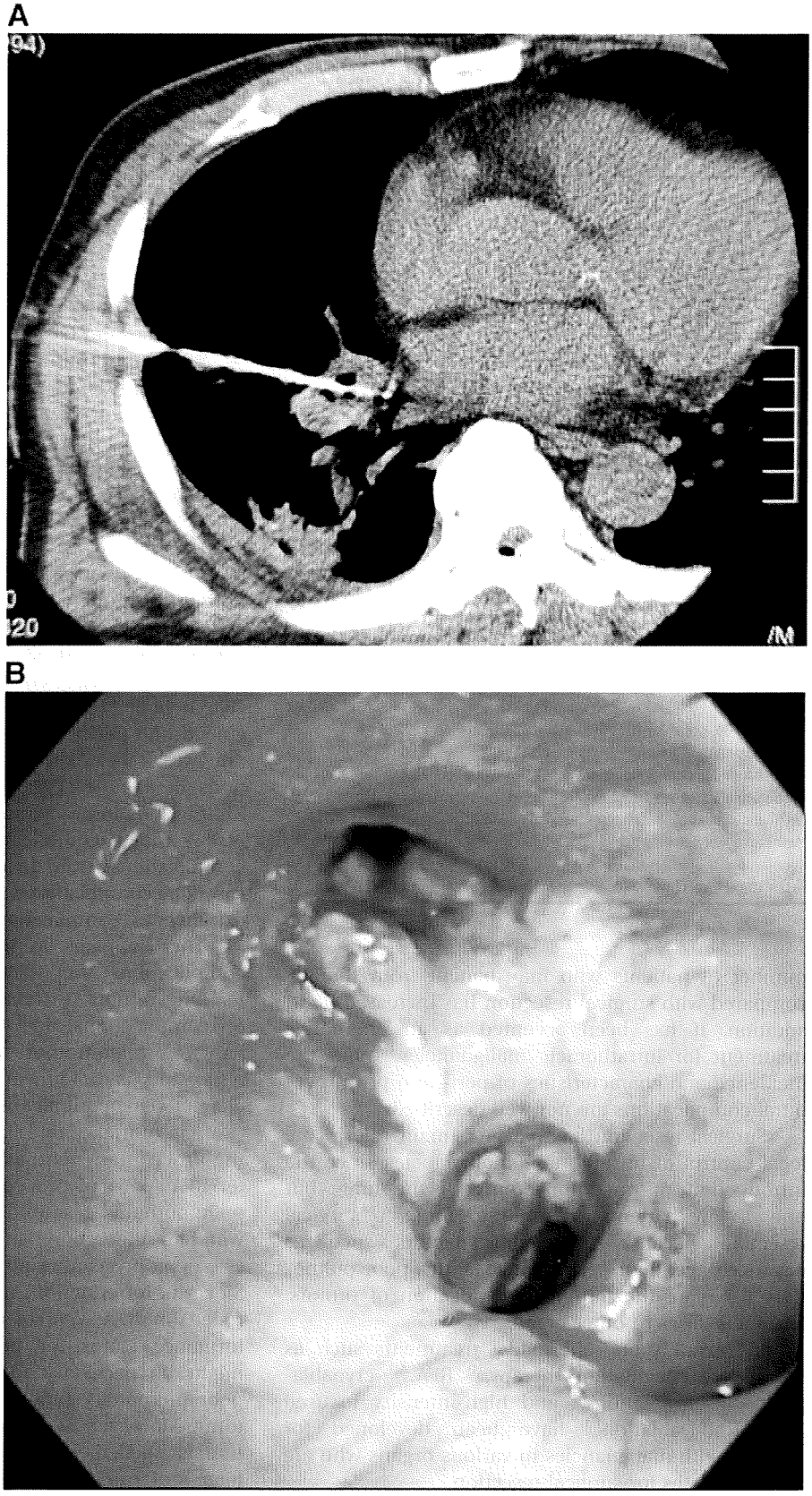

FIGURE 2. (Top) A 67-year-old man with pulmonary metastases of renal cell carcinoma. Intraprocedural computed tomography (CT) scans demonstrated puncturing of 17-gauge internally cooled electrodes to the right hilar lymph nodes. (Bottom) A 67-year-old man with pulmonary metastases of renal cell carcinoma. Image of the bronchoscopic examination 7 days after radiofrequency ablation (RFA) showed the mucosa of the spur of the right middle lobe and lower lobe bronchus was destroyed.

TABLE 3
Chest Pain and Body Temperature After Radiofrequency Ablation (RFA)

Event	No. (%)
Chest pain	
None	125 (59.2)
Mild	68 (32.2)
Severe (required NSAIDs)	18 (8.5)
Body temperature (BT)	
BT < 36.9°C	57 (27.4)
37.0 < BT < 37.9°C	92 (44.2)
38.0 < BT < 38.9°C	49 (23.6)
39.0°C < BT	10 (4.8)
Mean temperature (highest)	37.5°C

NSAID indicates nonsteroidal anti-inflammatory drug.

TABLE 4
Analysis of Risk Factors for Major Complications After Radiofrequency Ablation (RFA)

	Major complications		
Outcome parameters	No n = 170	Yes n = 41	*P*
Age, y	62.2 (34–88)	66.1 (38–82)	.03
Sex, male	108 (63.5%)	27(65.9%)	.86
Tumor size, mm	21.0 (3–98)	21.0 (4–73)	.99
Distance from tumor to pleura, mm	8.9 (0–65)	8.4 (0–36)	.70
Ablation, total no. of times	2.9 (1–15)	2.7 (1–11)	.68
Electrodes, expandable	63 (23.4%)	23 (29.9%)	.17
Maximum power output, watts	52.7 (10–188)	61.5 (15–168)	.19
Duration time of ablation, min 3	1.8 (6–164)	23.6 (3–134)	.10
Pleurocenteses, no. of times	1.5 (1–9)	1.3 (1–3)	.28

number of patients who may benefit from therapy compared with surgical resection has increased.[1–4] In addition, it has been accepted as an alternative treatment for intrathoracic malignancies,[8,9] but the incidence and characteristics of peri- and postprocedural complications are not well described.

Surgical resection has played a main role in the local control of intrathoracic malignancies since the introduction of pneumonectomy of the lung, but only a few patients are able to undergo surgical resection because of various factors such as advanced age, poor performance status, poor pulmonary function, the number and location of tumors, and metastases in other organs.

In recent years, alternative treatments such as microwave coagulation therapy,[10] RFA,[2,3] cryoablation,[11] laser ablation,[12] and high-intensity focused ultrasound ablation[13] have been developed for patients with malignancies in various organs who are not candidates for surgical resection.

RFA is a recently developed thermoablative technique that has been spreading worldwide, especially for the treatment of hepatic tumors. This relatively new therapy involves the induction of coagulation using an electromagnetic energy source with a frequency of less than 30 MHz, although most of the currently available devices function in the 375–500 kHz range. It causes temperature changes by high-frequency alternating current applied via electrodes placed within the tissue, generating areas of coagulative necrosis and tissue desiccation.[6,7]

When performing new alternative techniques that are considered "minimally invasive," one of the most important issues is whether they can be performed safely; however, there have been few reports on the safety of RFA, based on hundreds of cases.

As mentioned above, RFA has been mainly developed for liver malignancies. However, there have been several reports on complications after RFA for liver tumors. Buscarini and Buscarini[14] reported no mortality among 151 patients, 4.6% of whom had early major complications, 1.9% with delayed major complications, and 32.5% had minor complications. Chen et al.[15] reported a series of 338 patients with 763 hepatic tumors who underwent ultrasound-guided RFA (565 procedures); the major complication rate was 2.5%. Akahane et al.[16] reported complications in a large series of 1000 RFA treatments for 2140 lesions in 664 patients. There were a total of 40 (4.0%) major complications and 17 (1.7%) minor complications. They divided these complications into vascular complications, biliary complications, and extrahepatic complications.

There appears to be a difference between the complications after RFA for liver tumors and those for lung tumors. In our series, and in other reports on complications after RFA for intrathoracic malignancies, pneumothoraces, hemosputum (hemoptysis), and pleural effusion are the most frequent and characteristic complications.

The mortality rate in this series was 0.9% that of the procedures. Two patients died in the hospital after RFA (0.9% of procedures) because of intractable pneumothorax resulting in pneumonia in a patient who had undergone right pneumonectomy, and massive hemoptysis after ablation for hilar lymph nodes. Since its introduction, most of the patients who enrolled for RFA were of older age, or had poor performance status, or poor pulmonary function. It might be necessary to exclude patients with very poor pulmonary function, such as postpneumonectomy. Moreover, we have learned that careful attention is needed when ablating tumors close to the hilar structures. In addition, morbidity occurred in

137 of 211 sessions (64.9%) after RFA in our series, and 36 of these were major complications (rate 17.1%) on the basis of the criteria of the Society of Interventional Radiology Technology Assessment Committee and the Working Group on Image-Guided Tumor Ablation.[6,7] However, 26 of these patients had pneumothoraces or retention of pleural effusion, which necessitated hospitalization for only a few days—except 3 cases that required repeated pleurodesis to prevent persistent air leakage. Therefore, it may be considered that the actual rate of major complications of our series was just 4.7% (10/211 sessions).

From the previous literature on RFA in the lung, Ambrogi et al.[17] reported no mortality among 79 sessions of RFA for lung malignancies. The morbidity rate was 15.2% of procedures. Rossi et al.[18] reported that a total of 39 RFA sessions with 42 electrode insertions were required to treat 36 tumors without any major complications or deaths. Fernando et al.[19] reported 1 perioperative death. One patient, who had undergone open RFA of a right upper lobe lesion with right lower lobectomy, developed a pulmonary embolus followed by pneumonia with subsequent sepsis and multisystem organ failure. Moreover, morbidity occurred in 10 patients (55.6%) but was minor in most cases. Steinke et al.[20] reported that clinical complications were based on the RFA treatment of 46 patients (111 lung tumors) to date without any periprocedural deaths and with a modest complication rate. Lee et al.[21] reported 3 (10%) major complications directly attributed to the procedure; minor complications (60%) included small pneumothoraces, subcutaneous emphysema, obstructive pneumonia, pleural effusion, fever, mild hemoptysis, and severe myalgia. There is little in the literature on mortality and morbidity in large series. Here, the morbidity rate of about 65% appeared to be slightly high, but most of these complications and side effects did not require further treatment.

Pneumothorax is one of the most common complications during or after ablation, but many cases can be treated conservatively. We have had pneumothoraces develop during or soon after RFA in 51.2% of sessions, but the only interventions required were aspiration in 9.0% of sessions and chest tube placement in 11.8% of sessions. In the study by de Baere et al.[22] pneumothorax occurred during or at the end of 54% of 74 RFA sessions. In 31% of the sessions the pneumothorax was minor and no treatment was required; in the other 23% of sessions the pneumothorax was aspirated. A chest tube was left in place after the procedure in 9% of these cases of recurrent pneumothorax after no aspiration. Ambrogi et al.[17] reported complications consisting of 10 cases of partial pneumothorax (12.7%), 6 of which required pleural drainage. Rossi et al.[18] referred to pneumothorax revealed by posttreatment CT in 11.9% of cases, but all were self-limiting and did not require drainage. Fernando et al.[19] reported that the most common complication was the need for a chest tube or pigtail catheter for pneumothorax in 38.9% of cases; however, pneumothorax was usually minor in nature and the tube was removed on the first day after RFA. For all patients the median duration of chest tube placement was less than 24 hours. Gadaleta et al.[23] mentioned that pneumothorax requiring pleural drainage was observed in 16% of treatment sessions. Vansonnenberg et al.[24] reported 8 intraprocedural pneumothoraces. Needle aspiration was used to evacuate the pneumothorax (25%) in another patient after the RFA was completed. No therapy was required for 3 other patients. Steinke et al.[20] reported that the pneumothorax rate for their patients was 28%, and a third of these required a chest tube. In the study by Lee et al.[21] pneumothorax occurred more frequently in patients with central tumors (50%) than in patients with peripheral tumors (12%). Interestingly, the occurrence of pneumothorax was not related to the presence of emphysema, the type of electrode used, or the number of electrode insertions through the mass.

In our series we experienced a case of massive hemoptysis, and this patient died 29 days after RFA. In addition, hemosputum was observed in 9 patients (4.3%). De Baere et al.[22] reported that alveolar hemorrhage during the puncture was found in 11% (8 of 74) of the procedures and was minor in all but 1 patient (1%). Such hemorrhage never required specific treatment. Postprocedure hemoptysis was recorded in 7 (10%) of 74 procedures, but never required any treatment. Rossi et al.[18] reported that 4.7% of cases had mild transient hemoptysis. Vansonnenberg et al.[24] reported that 13.3% of patients developed mild hemoptysis, but no further bleeding occurred in these patients, and no patient required a blood transfusion. Steinke et al.[20] reported that the rate of intraparenchymal hemorrhage was 6% for their patients.

In our experience, pleural effusion requiring aspiration or chest tube placement occurred in 5 sessions (2.4%). Perhaps this number could be accepted as representing minimally invasive therapy. De Baere et al.[22] reported that a minor pleural effusion was present in 9% (7 of 74) of CT studies obtained immediately after treatment completion and on 60% (45 of 74) of CT studies obtained 24 to 48 hours after treatment. Steinke et al.[20] reported that sympathetic pleural effusion to a degree that does not require tapping

is often seen after ablation, and symptomatic effusions requiring tapping occur in less than 5% of procedures and are often hemorrhagic.

As mentioned above, various kinds of complications have been reported; however, the relation between risks and complications has not been reported. We conducted univariate analysis of the risk factors responsible for major complications after RFA and the following results were obtained. Only older age was shown as a statistically significant risk factor. Although the difference did not reach statistical significance, there was a tendency for using expandable electrodes and high power output to have a higher risk of major complications.

Other minor complications that we experienced included nausea and/or vomiting in 3 cases (1.4%), subcutaneous emphysema in 3 (1.4%), cough in 2 (0.9%), skin burn in 2 (0.9%), partial lung atelectasis in 1 (0.5%), and subileus in 1 (0.5%). Some comparatively rare complications have been also reported, such as chest wall hematoma,[17] atrial fibrillation, skin burn, hoarseness,[24] subcutaneous emphysema with pneumomediastinum,[25] pleural tumor seeding,[26] and microemboli.[27]

In addition, various side effects may be caused by RFA. Fever and pain, especially chest pain, are very common during the days after this therapy. In our series they occurred in 33.8% and 39.3% of patients, respectively, but most of these cases resolved within a couple of days without any treatment. Rossi et al.[18] reported side effects including 4 cases (9.5%) of isolated low-grade fever lasting 2 to 3 days. Steinke et al.[20] reported that a slightly raised temperature was observed in nearly all patients for 1 week after ablation. Lee et al.[21] reported that most patients treated had mild to moderate pain during the procedure. Vansonnenberg et al.[24] reported that pain was ameliorated in 11 of 11 patients, with relief varying from total (4 patients) to partial (7 patients). Steinke et al.[20] stated that most patients experienced some pain, usually pleuritic in type, that was typically treated with nonopioid analgesics, although less than 5% of patients required stronger pain medication.

In conclusion, with over 200 procedures performed to date, percutaneous RFA appears to be a safe and a minimally invasive option with negligible mortality and slight morbidity in selected patients with unresectable intrathoracic malignancies. However, it is very important to distinguish high-risk cases, not only based on the patient's physical status but also on tumor location, before the procedure. In addition, it is important to choose suitable electrodes and output for each case to avoid complications.

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