Review

Radiofrequency Ablation for Stage I Non-Small Cell Lung Cancer: An Updated Review of Literature from the Last Decade

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Abstract

This review summarizes the current findings on radiofrequency ablation (RFA) for stage I non-small cell lung cancer (NSCLC) from relevant literature published in the last decade. While most earlier studies included small populations and had short follow-up periods, more robust data have become available owing to prospective or large cohort studies. The reported overall survival rates after RFA for stage I NSCLC were 83-96%, 40-74%, and 23-61% at 1, 3, and 5 years, respectively, in recent studies. Furthermore, many comparative studies on the outcomes of RFA and stereotactic body radiotherapy have been performed. Most of these studies report no significant difference in survival outcomes between the therapies. Currently, major guidelines define RFA as a reasonable alternative treatment for stage I NSCLC in non-surgical candidates.

Key words: non-small cell lung cancer, early stage, radiofrequency ablation, survival, stereotactic body radiotherapy

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Introduction

Lung cancer remains the most common cancer and is the leading cause of cancer mortality worldwide [1]. Non-small cell lung cancer (NSCLC) accounts for 80% of all lung cancers [2]. According to the 8th edition of the TNM staging system of the Union for International Cancer Control, stage I NSCLC corresponds to T1 (i.e., tumor of size ≤ 3 cm and confined to the lung) or T2a (i.e., tumor size ranging from > 3 cm to ≤ 4 cm, involving the main bronchus or visceral pleura or associated with atelectasis or pneumonitis) tumors and shows no lymph node involvement or distant metastasis [3]. For such early-stage NSCLC, surgical resection is the cornerstone of treatment [2, 4]. The 5-year survival rate of patients after undergoing resection for stage I NSCLC is reportedly 66-91% [5]. However, up to one-fourth of patients with stage I NSCLC are unable to undergo surgery owing to severe comorbidities [6].

Percutaneous ablative therapies are an accepted alternative for the treatment of patients with stage I NSCLC who are not amenable to surgical resection. For the treatment of lung cancer, multiple ablation modalities including radiofrequency ablation (RFA), microwave ablation (MWA), and cryoablation are currently available [7]. Among these, RFA has been the most commonly studied ablative therapy [7]. Since the first report on RFA for lung tumors by Dupuy et al., the safety and efficacy of RFA for NSCLC have been evaluated in many studies [8, 9]. Earlier, most studies included a limited number of patients with short follow-up periods [9]. However, recently, more robust data have become available, including those coming from a few prospective or large co-

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Table 1. Summary of Recent Studies on RFA for Stage I NSCLC

Author	Publication Year	Study Design	No. of Patients	Stage	Tumor Size [mm]	Follow-up [mo]	Local Tumor Control [%]	Overall Survival [mo]	Overall Survival [%] (Cancer-specific Survival [%])				
									1-year	2-year	3-year	4-year	5-year
Lam et al. [10]	2018	NCDB study	967	IA	< 30	62.5 (Median)	-	33.1 (Median)	85.5	-	45.3	-	22.5
Paulussière et al. [11]	2018	Multicenter, Prospective	32	IA	20.7 (Mean)	-	81.25	-	91.67	-	58.33	-	-
Huang et al. [12]	2018	Single-center, Retrospective	50	IA	22 (Mean)	46.9 (Mean)	78.9	47 (Median)	96.0	86.5	67.1	-	36.3
Liu et al. [13]	2015	Single-center, Retrospective	29	IA or IB	31 (Mean) 30 (Median)	25 (Mean) 19 (Median)	79.0	57 (Mean)	90.5 (95.2)	76.4 (86.6)	65.5 (74.2)	-	-
Dupuy et al. [14]	2015	Multicenter, Prospective	51	IA	20 (Median)	-	62.7	-	86.3	69.8	-	-	-
Lanuti et al. [15]	2012	Single-center, Retrospective	45	IA or IB	20 (Mean)	32 (Median)	67	44.3 (Median)	-	-	67	-	31
Ambrogi et al. [16]	2011	Single-center, Prospective	57	IA or IB	26 (Mean)	47 (Mean) 45.5 (Median)	59.3	33.4 (Median)	83 (89)	-	40 (59)	-	25 (40)
Hiraki et al. [17]	2011	Single-center, Retrospective	50	IA or IB	21 (Mean)	39 (Mean) 37 (Median)	69	59 (Mean) 67 (Median)	94 (100)	86 (93)	74 (80)	67 (80)	61 (74)

RFA = radiofrequency ablation, NSCLC = non-small cell lung cancer, NCDB = National Cancer Database

hort studies with relatively long follow-up observations. Furthermore, more data are available on the comparison between RFA and stereotactic body radiotherapy (SBRT), another important treatment option for NSCLC.

In this article, we review the current findings available on RFA for stage I NSCLC from the relevant literature published during the last decade.

Literature Search

A literature search was performed using PubMed in July 2019 using the following key words: "lung cancer" and "radiofrequency ablation." In total, 299 articles were found in the initial search. Of those, 213 were published in the last decade (2010 or later). The titles and abstracts of articles obtained from the initial search were scrutinized to identify relevant studies. In this review, we focused on studies evaluating the outcomes of RFA for stage I NSCLC. Meta-analyses and prospective or retrospective clinical studies with a fair-sized study population ($n \geq 25$) were included for review. Case reports and case series with small study populations, and articles written in non-English languages were excluded. Furthermore, a few more recent relevant publications were added during the manuscript preparation and revision process.

Treatment Outcomes after RFA for Stage I NSCLC

Table 1 shows a summary of the studies that evaluated the treatment outcomes of RFA for stage I NSCLC [10-17]. When multiple reports were published from the same institution or by the same research group, a representative study was selected.

Although most studies were retrospective, Ambrogi et al. reported the results of a prospective single-center study including 57 patients with inoperable NSCLC [16]. The overall survival (OS) and cancer-specific survival (CSS) rates at 1, 3, and 5 years were 83% and 89%, 40% and 59%, and 25% and 40%, respectively [16]. More recently, the results from two prospective multicenter studies were reported. In 2015, Dupuy et al. reported the results of the American College of Surgeons Oncology Group (ACOSOG) Z4033 Trial that prospectively evaluated RFA for stage IA NSCLC in medically inoperable patients [14]. The primary objective of their study was to assess the 2-year OS rate after RFA. In 51 eligible patients, the OS rates at 1 and 2 years were 86.3% and 69.8%, respectively, with the local recurrence-free survival rate at 1 and 2 years of 68.9% and 59.8%, respectively [14]. Paulussière et al. reported results from a prospective multicenter trial on RFA for stage IA NSCLC in 2018 [11]. For the 32 assessed patients, the 1- and 3-year OS rates were 91.67% and 58.33%, respectively, while the 1- and 3-year progression-free survival rates were 71.76% and 25%, respectively [11].

Among the retrospective studies, a recent study conducted using the National Cancer Database (NCDB) had the largest cohort and the longest follow-up period performed to date [10]. This study included 967 patients with stage I NSCLC who were treated with RFA without chemotherapy or radiotherapy. The 1-, 3-, and 5-year OS rates were 85.5%, 45.3%, and 22.5%, respectively, with a median OS of 33.1 months [10]. The other retrospective studies included up to 50 patients with stage I NSCLC, with mean or median follow-up

periods of 19-47 months [12, 13, 15, 17]. In those studies, the median or mean OS was reported to be 44.3-67 months [12, 13, 15, 17]. The 1-, 3-, and 5-year OS rates were 90.5-96%, 65.5-74%, and 31-61%, respectively [12, 13, 15, 17].

The published reports consistently indicate that local tumor progression (LTP) was the most common type of recurrence after RFA for NSCLC [11, 12, 14-17]. The LTP rates in the reported studies ranged from 19% to 37% [11-17]. Tumors larger than 3 cm can be associated with higher risk of LTP [15]. Studies published in the late 2010s showed relatively low LTP rates of approximately 20% [11-13]. Considering that the reported LTP rates were 32-42% for similar-sized tumors (mean 20-26 mm) in the earlier studies published before 2010 [18-20], the LTP rates seem to be reduced in the most recent studies. This may be due to more adequate patient selection and a learning curve effect. Paulussière et al. achieved a 3-year local control rate of 81.25% using multitined expandable electrodes sized at least 10 mm larger than the diameter of the target tumor [11]. This method was chosen on the basis of the results of a previous study showing that the application of such a large electrode array was significantly associated with better local efficacy [21].

Prognostic Factors

As expected, a longer survival could be achieved using RFA in patients with stage IA (T1N0M0) than in those with stage IB (T2aN0M0) tumors. Ambrogi et al. reported that the median OS after RFA was 35 and 20 months in patients with stage IA and IB tumors, respectively, with a significant difference [16]. Liu et al. and Hiraki et al. also showed a tendency of better survival rates in patients with stage IA tumors, but the difference was not significant, presumably because of the small population [13, 17].

In the prospective study conducted by Dupuy et al., a tumor size of < 2 cm and a performance status of 0 or 1 were significantly associated with better 2-year OS in patients with stage IA who underwent RFA [14]. Huang et al. also showed that tumor size was a prognostic factor after RFA for early-stage NSCLC [12]. In their retrospective study, OS rates in patients with tumors ≤ 2 cm (94.7%, 89.5%, 78.9%, 36.8%, and 10.5% at 1, 2, 3, 5 and 10 years, respectively) were significantly better than those in patients with tumors > 2 cm (93.5%, 83.2%, 58.1%, 24.2%, and 3.2% at 1, 2, 3, 5, and 10 years, respectively) [12].

Patient comorbidities also seem relevant to survival. Simon et al. showed that the Charlson Comorbidity Index (CCI), a measuring tool for comorbidities, was a significant predictor of survival in patients who underwent RFA for NSCLC [22]. Most (88%) of the patients included in their study had stage I tumors. Patients with stage I or II tumors who have a CCI score of < 5 had a much longer median survival (55.6 and 37.78 months for CCI 1-2 and 3-4, respectively) than patients who had a score of ≥ 5 (11.67 months) [22].

Furthermore, treatment at a high-volume center may contribute to better survival. Lam et al. compared survival after RFA for stage IA NSCLC between patients treated at high-volume and non-high-volume centers using NCDB [10]. After propensity score adjustment, significantly better 1-, 3-, and 5-year OS rates (89.4%, 51.2%, and 27.7%, respectively) were observed in patients treated at a high-volume center than in those treated at a non-high-volume center (85.2%, 41.5, and 19.6%, respectively) [10].

Comparison of the outcomes of RFA and SBRT

SBRT is another treatment option for patients with stage I NSCLC who are not amenable to surgical treatment [23]. As SBRT and RFA compete with each other, the differences between these therapies have attracted significant interest. Comparative studies between RFA and SBRT are summarized in **Table 2** [24-29].

A few researchers have previously attempted to compare these two therapies using published data on the outcomes of each therapy. Bi et al. performed a pooled analysis to compare the outcomes of SBRT and RFA in medically inoperable patients with stage I NSCLC using data from trials published until 2012, including 13 and 31 studies on RFA and SBRT, respectively [27]. The pooled local tumor control rates were higher with SBRT (97%, 88%, and 86% at 1, 3, and 5 years, respectively) than with RFA (77%, 55%, and 42% at 1, 3, and 5 years, respectively); the difference remained significant even after adjustment for age and percentage of stage IA [27]. On the other hand, OS rates were not significantly different between the two therapies (1-, 3-, and 5-year OS rates after RFA vs. SBRT were 85% vs. 85%, 53% vs. 56%, and 32% vs. 40%, respectively) [27]. Bilal et al. reviewed studies published until 2011 on both RFA and SBRT in inoperable patients with early-stage NSCLC and showed that survival outcomes up to 3 years were similar for RFA and SBRT (3-year OS: 36-87.5% and 42.7-56%, respectively), whereas 5-year survival rates were lower after RFA (20.1-27%) than after SBRT (47%) [30]. The incidence of LTP tended to be higher after RFA (23.7-43%) than after SBRT (3.5-14.5%) [30]. Crabtree et al. compared short-term outcomes of the prospective clinical trials on RFA (ACOSOG trial Z4033), SBRT (Radiation Therapy Oncology Group trial 0236), and sublobar resection (ACOSOG trial Z4032) for stage I NSCLC [31]. The authors showed that the incidence of grade 3 or greater adverse events was not significantly different among these therapies [31].

Several later studies aimed to directly compare the outcomes of the two therapies. Safi et al. compared the outcomes of sublobar resection, RFA, and radiation therapy including SBRT (57%) or conventionally fractionated radiotherapy (43%) for stage I NSCLC [28]. They found no significant difference in OS rates between patients treated with RFA and those treated with radiation therapy: the 1- and 2-

Table 2. Summary of the Comparative Studies on RFA and SBRT

Author	Publication Year	Study Design	No. of Patients (RFA vs. SBRT)	Local Tumor Control [%]			Overall Survival [%]		
				RFA	SBRT	*p*-value	RFA	SBRT	*p*-value
Iguchi et al. [24]	2020	Single-center, Retrospective	38 vs. 58	-	-	-	59.7 at 5 years	63.7 at 5 years	0.701
Lam et al. [25]	2018	NCDB study	335 vs. 4454	-	-	-	89.3/52.7/27.1 at 1/3/5 years	85.5/54.3/31.9 at 1/3/5 years	0.835
Uhlig et al. [26]	2018	NCDB study	1102* vs. 27732	-	-	-	85.4/47.8/24.6 at 1/3/5 years	86.3/45.9/26.1 at 1/3/5 years	0.694
Bi et al. [27]	2016	Pooled analysis including 44 studies	328 vs. 2767	77/55/42 at 1/3/5 years	97/88/86 at 1/3/5 years	< 0.001	85/53/32 at 1/3/5 years	85/56/40 at 1/3/5 years	> 0.05
Safi et al. [28]	2015	Single-center, Retrospective	25 vs. 49	-	-	-	86/74 at 1/2 years	93/69 at 1/2 years	0.67
Ochiai et al. [29]	2015	Single-center, Retrospective	48 vs. 47	93.6/90.4 at 1/3 years	93/93 at 1/3 years	0.746	86.4 at 3 years	79.6 at 3 years	0.738

RFA = radiofrequency ablation, SBRT = stereotactic body radiotherapy, NCDB = National Cancer Database
*Including RFA and other ablative therapies

year OS rates after RFA vs. RT were 86% vs. 93% and 74% vs. 69%, respectively [28]. Ochiai et al. compared the outcomes of RFA and SBRT for solitary lung tumors sized ≤ 5 cm [29]. In their study population, 100% and 44.7% of tumors in the RFA and RT groups, respectively, were pathologically proven NSCLC. The cumulative 3-year LTP and OS rates in the RFA vs. SBRT groups were 9.6% vs. 7.0% and 86.4% vs. 79.6%, respectively, with no significant difference [29]. More recently, Iguchi et al. performed propensity score-matched analyses to compare survival rates after RFA, SBRT, and sublobar resection for stage I NSCLC in their single-center retrospective study [24]. After propensity score correction, OS and progression-free survival (PFS) rates were not significantly different between RFA and SBRT (5-year OS [PFS] was 59.7% [35.9%] vs. 63.7% [55.7%] after RFA vs. SBRT, respectively) [24].

Furthermore, two large comparative studies examining ablative therapy and SBRT have been recently published [25, 26]. The studies used NCDB to compare mid- to long-term survival between the two therapies. Lam et al. performed a propensity score-matched analysis using NCDB to compare OS rates after RFA for stage I NSCLC with that after SBRT [25]. No significant difference in OS rates was found between the RFA cohort including 335 patients (1-, 3-, and 5-year OS: 89.3%, 52.7%, and 27.1%, respectively) and the SBRT cohort including 4454 patients (1-, 3-, and 5-year OS: 85.5%, 54.3%, and 31.9%, respectively) [25]. Uhlig et al. selected patients with stage I NSCLC who were treated with thermal ablation including RFA and other ablative therapies (n = 1102) and SBRT (n = 27732) from the NCDB to compare their outcomes [26]. The thermal ablation group was associated with more comorbidities and a smaller tumor. OS rates in the propensity score-matched cohort were not significantly different between thermal ablation (1-, 3-, and 5-year OS: 85.4%, 47.8%, and 24.6%, respectively) and SBRT (1-, 3-, and 5-year OS: 86.3%, 45.9%, and 26.1%, respectively) [26].

To date, there have been no randomized trials comparing RFA and SBRT for stage I NSCLC. Although some studies have suggested better local tumor control with SBRT, no apparent superiority of either therapy has been shown regarding the survival outcomes. The repeatability of RFA may contribute to the comparable survival with SBRT [29]. In current clinical practice, patients may be selected for each therapy on a case-by-case basis, considering not only the treatment efficacy but also the difference in other factors between those therapies, including adverse events, treatment cost, duration of therapy, effect on pulmonary function, and quality of life after treatment. The common adverse events of RFA include pneumothorax, pleural effusion, and hemorrhage [32]. On the other hand, the common toxicities of SBRT include fatigue, dyspnea, chest pain, pneumonitis, and pneumonia [33]. Most of the RFA-related adverse events occur shortly after treatment and may cause a higher risk of unplanned readmission during an early postoperative period, while the toxicities of SBRT may manifest over a prolonged post-treatment period [25, 26]. Further studies are warranted for optimal patient selection with a better understanding of the relative efficacy and safety of each therapy.

Comparison of the outcomes of RFA and the other ablative therapies

MWA is another heat-based ablative treatment modality for lung cancers. MWA devices create an electromagnetic field to cause frictional heat through the rotating water molecules, depending less on electric and thermal conduction into tissues [34]. Therefore, the heat sink effect may be less in MWA than in RFA [34]. In a retrospective study including 47 medically inoperable patients with stage I NSCLC, the local control rates at 1, 3, and 5 years after MWA were 96%, 64%, and 48%, respectively [35]. In the same study, the 1-, 3-, and 5-year OS rates were 89%, 43%, and 16%, respectively [35]. Currently, comparative studies

between RFA and MWA for lung cancers remain sparse. Only a few recent studies have compared the outcomes of RFA for primary lung cancer with those of MWA. Narsule et al. compared LTP and survival between patients who underwent RFA (n = 21) and MWA (n = 4) for stage IA NSCLC [36]. They found no significant difference in median time to local progression (35 months vs. 50 months after RFA vs. MWA) or median survival (36 vs. 17 months after RFA vs. MWA) [36]. Yuan et al. compared survival outcome after RFA and MWA for primary lung cancer by meta-analysis [37]. They found no significant difference in median OS between the RFA (28.4 months) and MWA (24.4 months) groups [37]. Although other studies have shown comparative data between RFA and MWA, they used heterogeneous populations comprising patients with primary lung cancer and various metastatic lung tumors [38, 39].

Cryoablation has also been applied for the treatment of NSCLC [40, 41]. Cryoablation involves the use of low temperatures of -20℃ to -40℃ to destroy tumor cells through multiple mechanisms, including cell dehydration due to osmotic shifts in intracellular and extracellular water, disruption of cell membranes and organelles by intracellular ice formation, ischemia caused by microvascular thrombosis, and so forth [40, 41]. Yamauchi et al. retrospectively evaluated the midterm results of cryoablation in 22 patients with medically inoperable stage I NSCLC [42]. The 2- and 3-year OS rates in their study population were 88% and 88%, respectively, with LTP observed in 3% of the treated tumors [42]. Another retrospective study conducted by Moore et al. showed the long-term survival after cryoablation for stage I NSCLC [43]. In their study including 45 patients, the 1-, 3-, and 5-year OS rates were 89.4%, 78.1%, and 67.8%, respectively, with LTP observed in 14.9% of the tumors [43]. Zemlyak et al. compared survival outcomes among patients with stage I NSCLC who underwent sublobar resections, RFA, and cryoablation [44]. The 3-year OS rates for sublobar resections (n = 25), RFA (n = 12), and cryoablation (n = 27) groups were 87.1%, 87.5%, and 77%, respectively, with no significant difference among the three groups [44].

The common adverse events of MWA and cryoablation are similar to those of RFA, including pneumothorax, pleural effusion, and hemorrhage [37, 40]. In the meta-analysis performed by Yuan et al., the incidences of pneumothorax and pleural effusion were not significantly different between the RFA and MWA groups [37].

To date, robust comparative data regarding the difference in the efficacy and safety of RFA, MWA, and cryoablation for the treatment of early-stage NSCLC are still lacking, and this topic remains to be investigated.

Statements on RFA for stage I NSCLC in Current Clinical Guidelines

The American College of Chest Physicians (ACCP) evidence-based clinical practice guidelines suggest that RFA may be considered for peripheral tumors less than 3 cm in inoperable patients with stage I NSCLC [45]. Similarly, the consensus statement of the ACCP and Society of Thoracic Surgeons defines RFA as a reasonable treatment option for high-risk patients with stage I NSCLC who have a tumor less than 3 cm, while also indicating that inferior primary tumor control limits the use of RFA to patients who are not candidates for SBRT or sublobar resection [6].

The European Society for Medical Oncology clinical practice guidelines for NSCLC published in 2017 indicate RFA as a reasonable alternative for patients with stage I NSCLC who have strong contraindications for surgery and SBRT, noting that the evidence comes from observational studies only [4].

In the National Comprehensive Cancer Network guidelines version 1.2020, definitive radiation therapy including SBRT is recommended for medically inoperable patients with stage IA NSCLC, and image-guided thermal ablation is noted as an option for selected patients [46].

Conclusion

The usefulness of RFA in treating patients with stage I NSCLC has been shown in many studies in approximately 20 years, since its introduction for the treatment of lung cancers. Although most studies conducted in the earlier years were small observational ones, data from prospective or large cohort studies have become available in the last decade. Currently, representative guidelines define RFA as a reasonable alternative for stage I NSCLC in non-surgical candidates. Continuous data accumulation through further studies, e.g., prospective comparative trials with SBRT, is needed to determine the role of RFA in the management of stage I NSCLC based on high-level evidence.

Conflict of interest: The authors declare that they have no conflicts of interest concerning this manuscript.

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