

Radiofrequency ablation is a valid treatment option for lung metastases: experience in 566 patients with 1037 metastases

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Background: Minimal invasive methods are needed as an alternative to surgery for treatment of lung metastases.

Patients and methods: The prospective database of two cancer centers including all consecutive patients treated with radiofrequency ablation (RFA) for lung metastasis over 8 years was reviewed. RFA was carried out under general anesthesia, with computed tomography guidance using a 15-gauge multitined expandable electrodes RF needle.

Results: Five hundred sixty-six patients including 290 men (51%), 62.7 ± 13.2 years old with primary tumor to the colon (34%), rectum (18%), kidney (12%), soft tissue (9%) and miscellaneous (27%) received 642 RFA for 1037 lung metastases. Fifty-three percent of patients had 1 metastasis, 25% had 2, 14% had 3, 5% had 4 and 4% had 5–8. Metastases were unilateral (75%), or bilateral (25%). The median diameter [extremes] of metastases was 15 mm (4–70). Twenty-two percent of patients had extrapulmonary disease amenable to local therapy including 49 liver, 16 bone and 60 miscellaneous metastases. Median follow-up was 35.5 months. Median overall survival (OS) was 62 months. Four-year local efficacy was 89%. Four-year lung disease control rate was 44.1%, with patient retreated safely up to four times. Primary origin, disease-free interval, size and number of metastases were associated with OS in multivariate analysis. Progression at RFA site was associated with poor OS [$P = 0.011$, hazard ratio (HR): 1.69 (95% confidence interval 1.13–2.54)]. In the 293 colorectal cancer metastases, size >2 cm (HR = 2.10, $P = 0.0027$) and a number of metastases ≥ 3 (HR = 1.86, $P = 0.011$) remained significantly associated with OS. A prognostic score made of three groups based on the four above-mentioned prognostic factors demonstrated 3-year OS rates of respectively 82.2%, 69.5% and 53.6% (log-rank test, $P \leq 0.0001$) among the three groups in the overall population, and of 81.3%, 72.8% and 57.9% (log-rank test, $P = 0.005$) in the colorectal cancer patients.

Conclusion: Radiofrequency is an option for treatment of small size lung metastases, namely the ones below 2–3 cm.

Key words: lung metastases, colorectal cancer, radiofrequency ablation, thermal ablation

Introduction

Radiofrequency ablation (RFA) aims at destroying small tumor deposits by applying thermal energy under image guidance. When compared with other organs, there are organ-specific differences favoring RFA in the lung, the same quantity of energy results in larger ablation volume in lung [1], due to heat insulation and low electric conductivity provided by the lung around the tumor. A clinical study demonstrated 100% necrosis at

histopathology for nine of nine lung metastases targeted with RFA [2]. Lung RFA has been reported first in man in 2000 [3].

The aim of this study was to evaluate results of RFA of lung metastases in terms of overall survival (OS), disease-free survival (DFS), local ablation efficacy, and to define the parameters associated with better outcomes.

Material and methods

Patients

The common prospective database of two French cancer centers (Gustave Roussy, Villejuif and Bergonie, Bordeaux) included all consecutive lung RFA carried out from January 2002 to December 2010. The first 51 metastatic

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patients have been previously reported elsewhere [4, 5]. This study was approved by our institutional review boards.

Indication, feasibility and safety of the schedule lung RFA procedure were discussed by a tumor board of surgeons, medical oncologists, radiation therapists and interventional radiologists. Patients were referred for RFA either because they were deemed unable to tolerate lung resection (insufficient respiratory reserve or comorbidities) or RFA was preferred to surgery by the tumor board, or patients refused surgery.

RFA procedure

A platelet level above 100 000 per mm³ and a prothrombin time >70% were required to receive RFA. When applicable, anticoagulation and antiplatelet medications were stopped before the procedure.

All procedures were carried out by a senior staff interventional radiologist with at least 2 years of experience in RFA. All patients were administered general anesthesia, excepted six patients who received conscious sedation when general anesthesia was contraindicated.

The patients were positioned in prone, lateral or supine position on the computed tomography (CT) table according to the location of the tumor. A 4- or 16-row multidetector CT was used for guidance of the RF electrode.

A 15-gauge multitined expandable RF needle electrodes (Leveen CoAccess needle, Boston Scientific, Nattick, MA) was used in all patients excepted 3% of patients treated with a straight cooled tip needle (Covidien, Boulder, CO). A needle measuring 4 cm in diameter when electrodes are expanded was used to treat tumor 2 cm or larger, and a needle measuring 3 cm was used to treat tumors smaller than 2 cm. An RF generator (RF2000, Boston Scientific) was used with stepwise increase in power as described elsewhere in details [4, 6].

Each RFA session attempted to treat all metastases located in one lung during a single session. When impossible, a second session targeting the same lung was re-scheduled 2–6 weeks later. In case of bilateral disease, after completion of treatment on one lung, subsequent treatment of the other lung during the same session was attempted if neither pneumothorax, nor major alveolar hemorrhage were present as described in details elsewhere [7].

follow-up

A RFA treatment cycle could be one or two sessions of lung RFA, targeting one lung after the other or targeting twice the same lung. The RFA efficacy was evaluated with a follow-up CT obtained at 1, 3, 6, 9 and 12 months for a total of 1 year follow-up. After 1 year, the follow-up was left to the discretion of the physician in charge of the patient. The RF ablation zone measurements on CT obtained within 1 month after RFA were used as the baseline value for follow-up imaging. Morphologic features of RFA failure (also named local tumor progression) are an increase in the overall size of the ablation zone. Stability or decrease in size of the ablation zone at CT was considered as complete ablation. Assessment of follow-up CT imaging was completed independently by two senior radiologists, each with more than 4 years of experience interpreting CT follow-up after RF ablation. One of the readers was not involved in any RF ablation procedures. In case of discordance, diagnosis was obtained by consensus. The potential complications such as pleural effusion, alveolar hemorrhage, pulmonary artery occlusion, false aneurysm and bleeding were monitored and reported if present.

results

demographics

Five hundred sixty-six consecutive patients with 1037 lung metastasis treated with RFA included 290 men (51%) and 276 women (49%), aged 62.7 ± 13.2 years old (17–92) (supplementary Table S1, available at *Annals of Oncology* online). Location of the primary tumor was colon in 191 patients (34%), rectum

in 102 (18%), kidney in 68 (12%), soft tissue sarcoma in 51 (9%), thyroid in 19 (3%), breast in 16 (3%), and other miscellaneous origins in 119 (22%). Three hundred patients had 1 metastasis (53%), 139 had 2 (25%), 77 had 3 (14%), 29 had 4 (5%), 17 had 5 (3%), and 4 patients had 6–8 (1%). Metastases were unilateral in 424 patients (75%), and bilateral in 142 patients (25%).

The median diameter [extremes] and the mean (standard error) of metastases targeted for RFA were 15 mm (4–70) and 17.4 mm (9.3), respectively. The diameter of the largest tumor was less or equal to 1 cm in 134 patients (24%), more than 1 cm and less or equal to 2 cm in 252 patients (46%), more than 2 cm and less or equal to 3 cm in 122 patients (22%), more than 3 and less or equal to 4 cm in 31 patients (6%), and more than 4 cm in 11 patients (2%). One hundred twenty-five patients (22%) had extrapulmonary active disease amenable to local therapy (RFA or surgery) including 49 liver, 16 bone and 60 miscellaneous metastases.

procedure

Overall a total of 642 RFA sessions were carried out. RFA treatment cycle consisted of a single RFA session in 490 patients, including 53 (37%) of the 142 patients with bilateral disease. All metastases located in one lung could be treated during a single session excepted in five patients.

outcomes

The median follow-up was 35.5 months (interquartile range = 20–53 months). One hundred seventy-six patients died. At the time of analysis, 390 patients were alive, including 235 who were followed more than 2 years. Among 566 patients enrolled in this study, 227 demonstrated no pulmonary disease progression. A total of 339 patients demonstrated lung tumor progression, including 112 who died and 227 who were alive at their latest follow-up.

overall survival

Median OS was 62 months, and 1-, 2-, 3-, 4- and 5-year OS rates were 92.4% [standard error (SE) = 1.2], 79.4% (SE = 1.9), 67.7% (SE = 2.4), 58.9% (SE = 2.8) and 51.5% (SE = 3.3), respectively (supplementary Figure S1, available at *Annals of Oncology* online). Specific OS according to origin of the primary is given in Table 1. Gender, age, unilateral or bilateral location and extrapulmonary disease were not associated with OS. Location of primary disease, disease free interval (DFI), size and number of metastases were associated with OS in univariate analysis and remained independently associated with OS in multivariate analysis (supplementary Table S2, available at *Annals of Oncology* online). In a Cox model using local tumor progression as a time-dependent variable and adjusted for these four prognostic factors, local tumor progression at the site of RFA was associated with poor OS { $P = 0.011$, hazard ratio (HR): 1.69 [95% confidence interval (CI) 1.13–2.54]}.

When looking at the subpopulation of 293 colorectal cancer metastases, only size >2 cm (HR = 2.10, $P = 0.0027$) and a number of metastases ≥ 3 (HR = 1.86, $P = 0.011$) remained significantly associated with OS.

Table 1. Rates (standard error) of overall survival, progression-free survival and treatment failure according to the primary

	Primary				
	Colon (N = 191)	Rectum (N = 102)	Kidney (N = 68)	Sarcoma (N = 51)	Other (N = 154)
Overall survival					
1 year	92.9% (1.9)	93.6% (2.5)	95.5% (2.6)	94.1% (3.3)	89.0% (2.6)
3 years	76.1% (3.7)	64.9% (6.3)	73.5% (6.5)	58.0% (8.2)	59.1% (4.6)
5 years	56.0% (6.0)	49.6% (8.4)	53.8% (9.1)	41.5% (9.3)	49.4% (6.4)
Progression-free survival					
1 year	37.6% (3.6)	30.4% (4.8)	39.7% (5.9)	43.0% (7.0)	49.0% (4.1)
3 years	17.0% (3.0)	8.6% (3.2)	13.8% (4.9)	26.5% (6.6)	17.6% (3.4)
5 years	14.8% (3.0)	6.4% (3.0)	9.2% (5.0)	15.9% (6.2)	7.6% (3.9)
Treatment failure					
1 year	10.9% (2.4)	14.5% (3.7)	7.4% (3.2)	6.1% (3.4)	9.9% (2.5)
2 years	16.2% (3.0)	30.7% (5.7)	13.0% (5.0)	8.3% (4.0)	16.4% (3.5)
3 years	16.2% (3.0)	30.7% (5.7)	25.1% (9.3)	8.3% (4.0)	16.4% (3.5)

progression-free survival

PFS rates were 40.2% (SE = 2.1), 23.3% (SE = 1.9), 16.4% (SE = 1.7) and 13.1% (SE = 1.7) at 1, 2, 3 and 4 years, respectively (supplementary Figure S1, available at *Annals of Oncology* online). Age, gender, uni/bilateral location and DFI were not associated with PFS. Rectal primary tumor, metastases larger than 2 cm, number of metastases and extra pulmonary disease (supplementary Table S3, available at *Annals of Oncology* online) were associated with lower PFS in univariate analysis and remained independently associated with PFS in multivariate analysis (supplementary Table S4, available at *Annals of Oncology* online). When looking at the subpopulation of colorectal cancer metastases, size >2 cm (HR = 1.34, $P = 0.054$), number of metastases ≥ 3 (HR = 1.70, $P = 0.0005$), rectal origin (HR = 1.24, $P = 0.12$) and extrapulmonary disease (HR = 1.28, $P = 0.11$) remained significantly or borderline significantly associated with PFS.

prognostic score

A 3-category prognostic score based on the aforementioned prognostic factors of OS and DFS is presented in Figure 1 and supplementary Figure S2, available at *Annals of Oncology* online for the overall population and in supplementary data for colorectal cancer patients (supplementary Tables S5 and S6, available at *Annals of Oncology* online).

ablation local efficacy

Eighty-two patients had local tumor progression at the site of RFA, 54, 21, 5 and 2 were diagnosed during the first, second, third and fourth or fifth year of follow-up, respectively. Rates of local tumor progression per patient were 10.4% (SE = 1.3), 15.5% (SE = 1.7), 17.5% (SE = 1.9) and 18.1% (SE = 1.9) at 1, 2, 3 and 4 years, respectively. Age, gender, DFI and extrapulmonary disease were not associated with local efficacy. In univariate analysis, rectal primary tumor, uni/bilateral location, metastases size and number of metastases were associated with local efficacy. Only rectal primary tumor, uni/bilateral location and metastases size remained independently associated with local efficacy in multivariate analysis (supplementary Table S7 and Figure 3, available at *Annals of Oncology* online). Among the

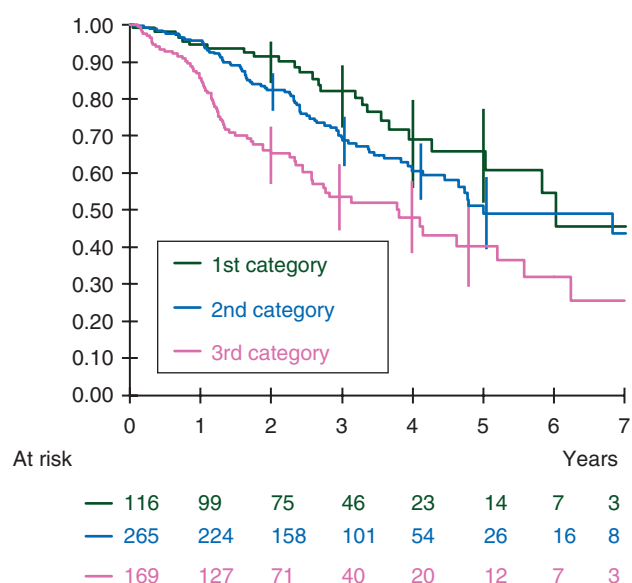


Figure 1. Overall survival rate in the complete population according to 3-category OS prognostic score based on the 4 OS prognostic factors: primary disease other than colon or kidney, DFI less or equal to 1 year, size higher than 2 cm, more than two lung metastases. 1st category: no unfavorable factor. 3rd category: at least one of the disease factors (primary disease other than colon or kidney or DFI less or equal to 1 year) and one of the lung metastasis factors (size higher than 2 cm or more than two lung metastases). 2nd category: the others.

1037 treated metastases, there was 86 local progressions with rates of local tumor progression per tumor of 5.9% (SE = 0.8), 8.5% (SE = 1.0), 10.2% (SE = 1.1) and 11.0% (SE = 1.2) at 1, 2, 3 and 4 years, respectively. Size of tumor was predictive of local tumor progression ($P < 0.0001$).

new treatments after lung progression

One hundred thirty-six (24%) patients were subsequently retreated with RFA for failure on the initially treated lesions ($n = 37$), or occurrence of new distant lung metastases ($n = 99$). Among the 136 retreated patients, 113 had 2 RFA sessions, 19 had 3 RFA sessions and 4 had 4 RFA sessions. The rates of patients

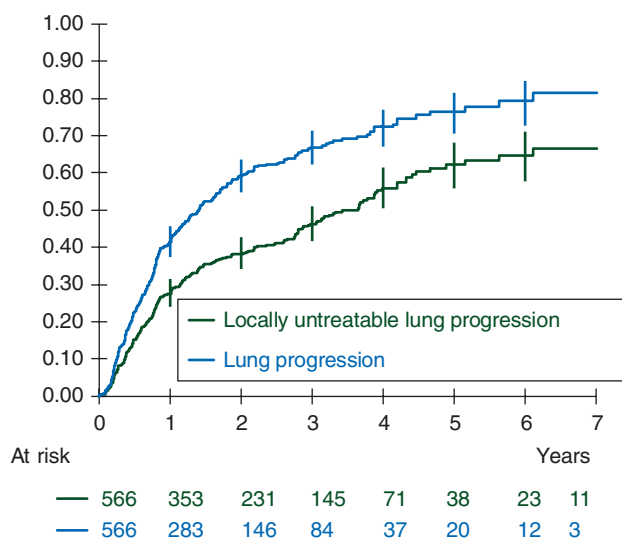


Figure 2. Lung progressions and locally untreatable lung progressions.

with locally untreatable lung progression at 1, 2, 3 and 4 years were, respectively, 27.6% (SE = 1.9), 38.3% (SE = 2.2), 46.3% (SE = 2.4) and 55.9% (SE = 2.8) whereas the rates of lung progressions were, respectively, 41.5% (SE = 2.1), 59.3% (SE = 2.3), 66.9% (SE = 2.4) and 72.4% (SE = 2.6) (Figure 2). The OS rates of the retreated patients were, respectively, 89.8% (se = 2.9) and 82.0% (se = 4.1), 2 and 3 years after the first pulmonary progression retreated by RFA.

side-effects

Hospital stay was below 4 days in 75% of RFA sessions, and above 9 days in 11 patients (1.7%). Two patients died within the 30 days postoperative period. One died at 21 days from decompensate cardiorespiratory function and the other at 16 days from cerebral stroke.

At the time of the procedure, we encountered pneumothoraces in 67% of the procedures. No treatment was needed in 28% of pneumothorax cases, simple aspiration during the RFA procedure in 14% and chest tube in 58%.

Two hemothoraces related to intercostal artery puncture were treated with embolization during the same procedure. Four minor skin burns occurred.

discussion

Our median OS of 62 months compares favorably with previously published data on RFA of lung metastases. Indeed, the largest lung metastases RFA series published today reports 148 patients with a median OS of 51 months (95% CI 19–83) [8]. Another relatively large study, 122 patients with 398 metastases reports 41 months OS [9]. Our impressive results might be explained by the very restricted inclusion criteria, resulting in more favorable predictive factors (size of metastases, number of metastases, extrapulmonary disease, DFI). Indeed, our inclusion criteria of tumor 4 cm or smaller resulted in a median diameter of metastases of 15 mm, while tumors were larger than 40 mm in 40% of cases in the largest study mentioned earlier [8]. Moreover, mean number of metastases per patient was 1.8 in our

series, versus 3.3 metastases for Gillams et al. [9]. Extrapulmonary disease represented 22% of our population, versus 51% for Gillams et al. At last, DFI shorter than 12 months accounts for 21% of our patients versus 12% and 52% for Chua et al. and Gillams et al., respectively.

Because RFA of lung metastases is a surrogate of surgery, we will try to compare our results with those of surgical series. Our 5-year OS rate of 51% is within the range of the best results obtained by surgery. Indeed, the 5-year OS rates reported after lung metastasectomy for ColoRectal cancer (CRC) metastases are 53.5% for Iida et al. in a multicenter registry [10], in between 27% and 68% in a meta-analysis by Gonzalez et al. In a literature review by Pfannschmidt looking at 11 publications with 1307 patients, the 5-year OS rates were in between 32.7% and 56%, and increasing to 39.1% and 67.8% after R0 resection [11]. These excellent results of lung RFA can be explain by inclusion criteria for lung RFA mimicking the selection criteria for surgical candidates [12]. Indeed, even if nonsurgical candidates were treated within this series, they were nonoperable due to comorbidities contra-indicating surgery, but they do not present any oncologic contra-indication to surgery. Moreover, pre-RFA imaging workup was identical to the one carried out before surgery including at least thoraco-abdomino pelvic CT, and positron emission tomography (PET)/CT, when it became easily available in the more recent years. These excellent results of lung RFA when compared with surgery can be explained by the low 11.1% rate of local tumor progression per tumor at 4 years obtained with RFA, which appears similar to what reported after surgery [13, 14].

Predictive factors of OS after surgery were complete resection, location of primary disease, and DFI in 5206 patients [15], DFI, number of metastases and positive lymph nodes at pathology in a meta-analysis 2925 patients [16], and number of metastases, completeness of resection and pre-resection CarcinoEmbryonic (CEA) level in 1030 patient with CRC lung metastases [10]. If we assimilate incomplete ablation by RF and incomplete resection at surgery, it is noteworthy that all our predictive factor of OS match predictive factors reports in major surgical series, excepted CEA level and lymph node involvement that were not available in our series.

Challenge of disease control in lung metastatic patients is more linked to the occurrence of new metastases distant from the ablation site than to local recurrences as demonstrated with lung progressions in 72.4% of patients. In such setting, RFA allows for possible retreatment due to good tolerance and lung parenchyma sparing with no change in respiratory function after RFA [4, 17]. Indeed, 24% of the initially treated patients were retreated by RF up to four times, resulting in 44.1% 4-year control rate of lung metastatic disease. Even if, RFA is mostly used today as a stand-alone technique, with the main objective of complete destruction of tumor cells in the targeted volume, its good tolerance might render easier pre-RFA or post-RFA systemic therapy feasible in an effort to decrease recurrences.

Composite scores reported in this study for PFS and OS will help to select the patients that would likely benefit from local treatment, and potentially may or may not need combined treatment including neoadjuvant or adjuvant therapy associated with RFA according to the risk of recurrence. The possibility of performing biopsy at the time of RFA should be used more extensively in the future to help to define such strategy according to molecular biology of the targeted tumor.

limitations

Our study has some limitations. No confirmatory biopsy was carried out on a routine basis. Because of a previous known primary carcinoma in these patients, new discovery or enlarging focal pulmonary tumor and a standard uptake value >4 at PET/CT was considered diagnostic of malignant disease. Another limitation is that we included in this analysis different location of primary tumor, even if only metastasis of the rectal origin demonstrated differences and colonic metastases are analyzed separately. Another limitation is that our data were analyzed without taking into account the chemotherapy delivered before or after RFA that obviously may impact on PFS and OS.

conclusion

We demonstrated in this report on a large series of RFA for lung metastases that OS after lung RFA is comparable with what reported in the surgical literature for lung metastasectomy, with superimposable predictive factors. RFA demonstrated a 53.7% 3-year, and a 44.1% 4-year control rate of lung metastatic disease in part due to the low invasiveness of RFA that allowed to repeat the procedure up to four times when needed. These results advocate RFA as an option for treatment of small size lung metastases, namely the ones below 2–3 cm.

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disclosure

The authors have declared no conflicts of interest.

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