

## Review

# Lung ablation: Best practice/results/response assessment/role alongside other ablative therapies



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## ARTICLE INFORMATION

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Today, in addition to surgery, other local therapies are available for patients with small-size non-small-cell lung cancer (NSCLC) and oligometastatic disease from various cancers. Local therapies include stereotactic ablation radiotherapy (SABR) and thermal ablative therapies through percutaneously inserted applicators. Although radiofrequency ablation (RFA) has been explored in series with several hundreds of patients with pulmonary tumours, investigation of the potential of other ablation technologies including microwave ablation, cryoablation, and irreversible electroporation is ongoing. There are no randomised studies available to compare surgery, SABR, and thermal ablation. In small-size lung metastases, RFA seems to produce results very close to surgical series with >90% local control and 5-year overall survival of 50%. In primary lung cancer, the technique is reserved for non-surgical candidates. In future, the low invasiveness of thermal ablative therapies will allow for a combination of ablation and systemic therapies in order to improve the outcomes of ablation alone. Another major advantage of thermal ablation is the possibility to treat several metastases in close proximity to one another and retreatment in the same location in case of failure, which is not possible with SABR.

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## Introduction

Today, in addition to surgery, other local therapies are available for patients with small-size non-small-cell lung cancer (NSCLC) and oligometastatic disease, including stereotactic ablation radiotherapy (SABR) and thermal ablative therapies through percutaneously inserted

applicators. Early reports, including case series and small clinical trials, have demonstrated the potential of various thermal ablation technologies including radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation, and irreversible electroporation for the treatment of pulmonary tumours.<sup>1–7</sup>

In NSCLC, surgical resection is the current standard of care for patients with Stage I or II, mainly due to the benefit of associated lymphadenectomy; however, image-guided ablation and radiation therapy are increasingly offered as alternative therapies in non-surgical candidates.<sup>3,8–12</sup> In lung metastases, local treatments have been accepted since

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the late 1990s, when an international registry reported actuarial 5-, 10-, and 15-year survival rates of 36%, 26%, and 22%, respectively,<sup>13</sup> despite the fact that the evidence for surgical metastectomy remains controversial because the practice has never been subjected to randomised trials and carries some risk of short-term morbidity, can be responsible for permanent loss of function, and has major cost implications.<sup>14</sup> In oligometastatic lung patients, evidence for the superiority of surgery over other local ablative techniques is weak, as the benefit of lymphadenectomy has not been demonstrated.

## Rationale for thermal ablation in the lung

The lung has some organ-specific differences favouring thermal ablation. Indeed, the heat insulation and low electrical conductivity provided by the lung around the tumour is responsible for a larger volume of ablation in the lung than in subcutaneous tissues or in the kidney for a given quantity of radiofrequency current.<sup>15</sup> Indeed, a tumour surrounded by lung parenchyma is highly electrically and thermally insulated by the air-filled lung parenchyma and will require less energy deposition for a given volume of ablation. Because impedance before ablation differs significantly for tumours with >50% of the tumour abutting the pleura ( $86.5 \pm 29.9$  Ohms), and those tumours not abutting the pleura ( $121.3 \pm 42.8$  Ohms),<sup>3</sup> RFA delivery must be adapted to tumour location.

Several studies have demonstrated that RFA can completely destroy an area of healthy lung or malignant lung tumours in an animal tumour model.<sup>16,17</sup> A clinical study of RFA before resection demonstrated 100% necrosis at histopathology for nine of nine lung metastases.<sup>18</sup>

## Local efficacy of RFA in the lung

A review of 17 of the most recent publications of lung RFA including NSCLC and lung metastases demonstrated a median rate of complete ablation of 90%, with a variability from 38% to 97%.<sup>19</sup> Tumours <2 cm can be ablated in 78–96% of cases according to several reports after a minimum follow-up of 1 year,<sup>3,12</sup> and mean follow-up of 12 months.<sup>20–22</sup> A statistically significant lower success rate of ablation is reported for tumours ranging from 2 to 3 cm.<sup>3,20–22</sup> A ratio >4 in between the area of RFA induced ground-glass opacity (GGO) and total tumour volume has a rate of complete ablation of 96% at 18 months, versus 81% ( $p=0.02$ ).<sup>3</sup> Margins of GGO induced by RFA of incompletely ablated tumours have been reported to be absent in 85% of patients at post-RFA computed tomography (CT), and the receiver operating characteristic (ROC) analysis confirmed the usefulness of the ablation zone as a predictor of recurrence, with an estimated cut-off of 4.5 mm for a specificity of 100%; i.e., no local recurrence.<sup>23</sup> Histopathological studies demonstrated that a 5 mm margin covers 80% of the microscopic extension for lung adenocarcinoma and 91% for squamous cell carcinoma, and that 8 and 6 mm margins are needed to cover 95% of the microscopic extension, for adenocarcinoma and squamous cell carcinoma,

respectively.<sup>24</sup> In metastases, arogenous dissemination is the most frequent pattern of tumour spread beyond the macroscopic border responsible for local recurrence after surgery.<sup>25</sup> The above-mentioned results clearly emphasise that there is a need for oversizing the ablation zone relative to the tumour volume in order to obtain safety margins that guarantee success.

## Recent ablation technologies

New technologies have been developed to overcome the limitations of RFA by extending the volume of ablation or lowering convective cooling close to the bronchi or vessels. RFA provides a volume of ablation with a maximal shortest diameter of 4–5 cm and only one probe that can be activated at a time; consequently, overlapping the ablation zone with subsequent probe replacement is needed to create a larger volume of ablation. Both MWA and cryoablation allows for simultaneous delivery of energy through several probes activated at the same time with a synergistic effect versus subsequent activation of the same probe. In an animal study, a single probe provided a mean ablation diameter of  $32.7 \pm 12.8$  mm perpendicular to the feeding point of the MWA antenna while simultaneous activation of three antenna provided an ablation zone of  $54.8 \pm 8.5$  mm.<sup>26</sup> Such a large ablation volume gives hope for improvement of local control for larger tumours and is under evaluation in clinical practice.

Contact between the targeted tumour and a vessel or bronchi >3 mm in diameter have been reported by several authors as a predictive factor of incomplete local treatment.<sup>20,27</sup> Percutaneous balloon occlusion of the segmental pulmonary artery involved during lung RFA has been reported in five patients with 100% local efficacy at 12 months using combined positron-emission tomography (PET) with CT for follow-up; however, tolerance was poor.<sup>28</sup> MWA, by working at higher temperatures,<sup>29</sup> has been demonstrated to lower convective cooling close to large vessels in animal studies,<sup>30,31</sup> but the benefit in lowering incomplete ablation has not been demonstrated in clinical practice. Early MWA systems seem to suffer from non-reproducibility and non-spherical ablation zones, with disappointing results for tumours >3 cm.<sup>5</sup> More recent technology seems to improve the reproducibility and sphericity of the ablation zone.<sup>32</sup>

Cryoablation allows placement of several probes that can be activated at the same time. Cryoablation of lung metastases has been reported using a mean of 1.7 probes per patient with a promising 94.2% local tumour control at 12 months in a phase 2 multicentre study comprising 40 patients with 60 metastases measuring  $1.4 \pm 0.7$  cm (range 0.3–3.4).<sup>33</sup> Cryoablation enables inserting the probe into the tissue/tumour and providing moderate freezing and moving the probe away from vulnerable neighbouring organs when required. An advantage of having the probe stuck in the tumour is that probe displacement will not occur during treatment as is the case with expandable RFA electrodes, which are very popular in lung ablation.

Electroporation is a non-thermal ablation process that causes apoptosis by irreversible opening of cell pores due to an electric pulse of high voltage (1500 V/cm) and short duration,<sup>34</sup> with excellent preservation of vulnerable lung structures in animal studies<sup>35,36</sup>; however, early clinical results in lung ablation with irreversible electroporation of tumours close to large vessels have been disappointing with 61% local recurrence in a multi-institutional study of 20 patients.<sup>37</sup> These unexpected high recurrence rates were hypothesised to be due to high differences in electric conductivity between the lung parenchyma and tumour tissue.

## Clinical results

### Lung metastases

A 4-year local efficacy of 89% has been reported by both Lencioni *et al.*<sup>12</sup> and de Baere *et al.*<sup>11</sup> in 61 and 566 patients, respectively, at 15 and 35.5 months of follow-up.<sup>11,12</sup> This high local rate of control is driven by strict selection criteria with extensive pre-RFA imaging work-up to guarantee a low rate of local tumour progression, which is similar to the rate reported after surgery.<sup>25,38</sup> The largest reports today of lung RFA for metastases includes 566 patients with 1,037 lung metastases (53% of patients had one metastasis, 25% had two, 14% had three, 5% had four, 4% had five to eight) including 52% with primary tumours from the colon or rectum, a median diameter of 15 mm [4–70].<sup>11</sup> Median overall survival (OS) was 62 months; OS rates at 1-, 2-, 3-, 4-, and 5-years were 92.4% (SE=1.2), 79.4% (SE=1.9), 67.7% (SE=2.4), 58.9% (SE=2.8), and 51.5% (SE=3.3). Location of primary disease, disease-free interval (DFI), size >2 cm, and three or more metastases were associated with OS in univariate analysis and remained independently associated with OS in multivariate analysis. In a Cox model using local tumour progression as a time-dependant variable and adjusted for these four prognostic factors, local tumour 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). The 62-month OS rate of this series compared favourably with previously published data with a median OS of 51 months (95% CI: 19–83) in 148 patients,<sup>39</sup> and of 41 months in 122 patients.<sup>40</sup> The better outcomes obtained by de Baere *et al.*,<sup>11</sup> are explained by the very restricted inclusion criteria, resulting in more favourable predictive factors (size of metastases, number of metastases, extrapulmonary disease, DFI). Extra-pulmonary disease represented 51%, for Gillams *et al.*<sup>40</sup> versus 22% of de Baere *et al.*<sup>11</sup> The DFI of <12 months accounts for 52% of patients for Gillams *et al.*,<sup>40</sup> and 21% for de Baere *et al.*<sup>11</sup> The OS rates after RFA of lung metastases are within the range of the best results obtained by surgical resection with very similar predictive factors for OS compared with RFA. Indeed predictive factors for OS have been reported as complete resection, location of primary disease, and DFI have been reported in 5,206 patients<sup>41</sup>; DFI, number of metastases, and positive lymph nodes at histopathology in a meta-analysis of

2,925 patients<sup>42</sup>; and number of metastases, completeness of resection, and pre-resection carcinoembryonic antigen (CEA) level in 1,030 patients with CRC lung metastases.<sup>43</sup>

The low rate of complete local treatment of 62.5% in 32 tumours measuring up to 3.5 cm were obtained when RFA was guided by preoperative manual palpation during thoracotomy without any image guidance.<sup>44</sup> This result emphasises the pivotal role of CT guidance and multiplanar reconstruction (MPR) due to the high contrast ratio between the air density of the lung parenchyma, tissue density of the target tumour, and metallic density of the RF needle, which enable optimal visualisation, and likely accuracy, in treatment targeting and delivery. Cone-beam CT is under evaluation for lung RFA.<sup>45</sup> It allows for puncture at any angle but suffers from lack of the real-time or nearly real-time imaging capability that is available with CT where an image can be acquired and reconstructed with a second. Such a delay in imaging can be problematic if the target is moving, either due to needle insertion or pneumothorax.

### NSCLC

One of the early reports included 75 primary NSCLC patients (75% stage IA and 25% stage IB) and demonstrated a median survival of 29 months (95% CI: 20–38 months) with a 1, 2, 3, 4, and 5-year OS of 78%, 57%, 36%, 27%, and 27%.<sup>46</sup> The median survival for stage IA was 30 months and 25 months for stage IB. Better survival was reported for tumours  $\leq 3$  cm with a survival rate close to 50% at 5 years.<sup>46</sup> More recent reports tend to demonstrate improvement in survival, which can be due to technical improvement, more experienced operators, and better patient selection. Indeed, impressive 1-, 3-, and 5-year overall survival rates of 97.7, 72.9, and 55.7% have been reported in 44 consecutive patients treated with RFA for 51 recurrent NSCLCs after surgery with a mean diameter of  $1.7 \pm 0.9$  cm (range: 0.6–4).<sup>47</sup> In this report, the 1-, 3-, and 5-year OS rates were 100%, 79.8% (95% CI: 61.8–97.8), and 60.5% (95% CI: 32.5–88.4) in patients with tumours measuring <3 cm, compared to 1- and 3-year OS rates, of 83.3% (95% CI: 27.4–97.5%) and 31.3% (95% CI: 1.3–73.3%) in patients with tumours measuring 3.1–4 cm. One of the largest series reported 87 NSCLC, with a mean tumour size of 21 mm (range 10–54 mm), with local tumour progression of 11.5%, 18.3%, and 21.1% at 1, 2, and 3 years, respectively.<sup>48</sup> The 5-year OS and DFS were 58.1 and 27.9%. In multivariate analysis, histopathology ( $p=0.033$ ) and tumour size >2 cm ( $p=0.032$ ) were independent prognostic factors for DFS. RFA for NSCLC is usually performed in non-surgical patients with severe comorbidities, and it is noteworthy to notice that most reported deaths in NSCLC RFA series are not related to cancer progression but comorbidities. Simon *et al.*<sup>48</sup> reported 40 deaths during the follow-up of 82 RFA treatments for NSCLC, with only 19 deaths related to tumour progression. Gender, stage, histology, and Charlson comorbidity index (CCI) score were each associated with significantly impaired survival ( $p<0.001$  in all cases).<sup>48</sup> (The CCI is one of the most widely used clinical indexes for the evaluation of comorbidities as detailed elsewhere.<sup>49</sup>) After

co-varying for age, tumour stage >IB, squamous histology, and gender, multiple Cox regressions showed that an increasing CCI score was significantly associated with an increased risk of death (HR: 1.3, 95% CI: 25.5, 58.2). A CCI score of  $\geq 5$  (OS=10.43 months; 95% CI: 7.61, 19.85) was associated with significantly impaired mortality, compared with patients who had a CCI grade of 1–2 (OS=55.5 months; 95% CI: 39.46, 64.02) or a CCI grade of 3–4 (OS=36.62 months; 95% CI: 25.54, 58.29). No significant difference was observed between CCI grades 1–2 and 3–4.

## Response assessment

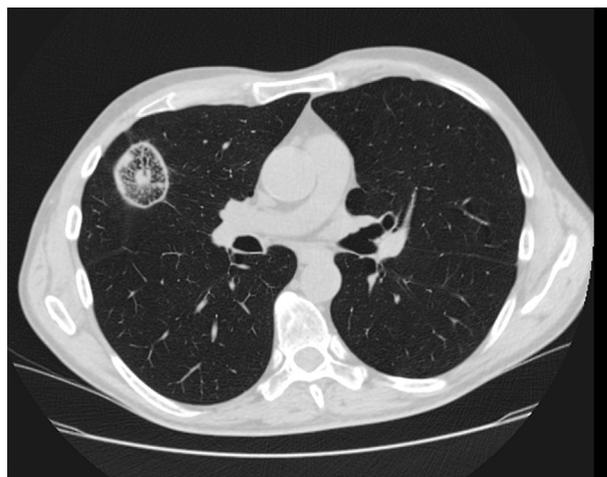
Lung metastases and primary NSCLC are very different diseases and the overall follow-up might be very different; however, these differences will not impact much on imaging follow-up for local evolution of ablated lung tumour deposit, and both metastatic deposits and primary NSCLC will be referred to as tumours in the following section. During or within a few minutes following ablation, CT images of the ablation zone will demonstrate an area of central dense opacity enclosed by an extensive area of GGO, thus enlarging the initial diameter of the hyperattenuating targeted tumour<sup>8</sup> (Figs 1–3). This area of GGO, slightly overestimates the actual size of the zone of cell death induced by RFA<sup>50</sup> and cryotherapy,<sup>51</sup> but this GGO is an early indicator of treatment success. Indeed, local tumour progression has been reported more frequent at the point on the tumour surface where there is no GGO peripheral to the tumour (i.e., no ablation margin), or when this ablation margin is <4.5 mm all around the tumour.<sup>23</sup> Local tumour progression has been demonstrated to occur within GGO margins of 3 mm, but no local tumour progression was found when the GGO extended >5 mm beyond the tumour margins.<sup>52</sup> Such GGO extension beyond the tumour margins, and its extension must be reported when evaluating the technical effectiveness of lung ablation. As early as 24 hours post-treatment and during the first 3 weeks, the entire ablated region usually appears as a well-demarcated homogeneous dense opacity on CT that corresponds to necrotic tissue and



**Figure 1** CT image of right upper lobe lung metastases from colon cancer.



**Figure 2** CT image of right upper lobe lung metastases from colon cancer after placement of a 4 cm LeVein radiofrequency needle.



**Figure 3** CT image of right upper lobe lung metastases from colon cancer obtained 30 minutes after end of treatment with RFA of 60 W over 14 minutes showing a GGO around the tumour including a safety margin of healthy lung parenchyma.

its surrounding rim of granulation tissue on histopathological examination. This zone of ablation is considered to be the “baseline post-ablation imaging” for follow-up (i.e., the time point when any increase in size will be linked to local tumour progression).

During further follow-up, there will be a relatively slow involution of the ablation zone after RFA, with a reported decrease in size of 0.7%, 11.4%, 14.3%, 40%, and 40% at 3, 6, 9, 12, and 15 months, respectively<sup>53</sup> (Figs 1–4). Cryoablation has the unique behaviour of rapid involution in the size of the ablation zone on CT that facilitates identification of local treatment failure with most local tumour progression, or incomplete ablation visualised by 6 months.<sup>54</sup> The involution of the ablation zone after RFA can follow various patterns, including: “nodular” (the ablation zone remains



**Figure 4** CT image of right upper lobe lung metastases from colon cancer obtained 3 months after RFA treatment showing shrinkage of the ablated zone.

spherical with no signs of retraction and more or less rapid decrease in size); “fibrosis” (the ablation zone loses its sphericity and becomes elongated and linear with or without peripheral spicules); “disappearance” (the ablation zone is impossible to depict); “cavitation” (an air-filled cavity with thick or thin walls appearing in the location of the ablation zone, cavitation may be incomplete and only in one part of the ablated volume), “atelectasis” (ventilatory disturbance in a segment, usually wedge-shaped, with increased attenuation surrounding the ablated tumour, thus preventing accurate analysis of the ablation zone itself).<sup>55</sup> Over time of follow-up an ablation zone can change its pattern; for example, ablation zone can be nodular at 1 month, then cavitated, and later retract to form fibrosis. Nodular and fibrosis are the most common patterns after RFA with  $\geq 80\%$  of ablation zones displaying these patterns at any stage of follow-up.<sup>55</sup> Cavitation of the ablation zone have been reported to occur in up to 31% of lung RFA, and more commonly when the area of ablation was in contact with a segmental bronchus.<sup>56</sup> After cryoablation, at 1 week, 92% of ablation zones showed the nodular pattern, and between 1- and 6-months follow-up, 52% of ablation zones began to show fibrosis.<sup>54</sup>

Follow-up evaluation with CT depicts only 50% of cases of local progression during the first year of follow-up. Indeed, among 86 local progressions in 1,037 metastases treated with RFA, reported rates of local tumour progression were 5.9%, 8.5%, 10.2%, and 11% at 1, 2, 3, and 4 years, respectively.<sup>11</sup> The follow-up of 79 NSCLC revealed 10.1% incomplete local treatment at 1 year and 28% at 2 years.<sup>57</sup>

Suh *et al.*<sup>6</sup> used quadruple-phase CT with CT acquisition at 45, 90, 180, and 300 seconds after contrast medium injection to demonstrate a drop in enhancement of the treated lesion at 1 month, but some re-increase of enhancement at a later stage with enhancement at least 50% below the pre-treatment values.<sup>6</sup> After cryoablation, internal and marginal enhancement of the ablation zone

within the 3-month follow-up did not show a direct relationship with local progression.<sup>54</sup> Consequently, most of the reports of lung thermal ablation use CT for follow-up imaging of the ablation zone and rely mainly on morphological changes for evaluation of treatment efficacy.

PET-CT has been evaluated in order to try to overcome limitations of morphological imaging using CT (i.e., late discovery of incomplete local ablation). Several authors have investigated PET-CT at different time points after RFA in order to determine the best timing for PET-CT after lung tumour ablation. Yoo *et al.*<sup>72</sup> performed PET-CT in 30 patients with Stage I NSCLC within 4 days after, and 6 months after RFA. Patients with a complete metabolic response at early PET-CT, and 6 months PET-CT had a 1-year “event” rate of 43%, and 0%, respectively (“event” being death, progression, or repeat ablation). Patient with a positive PET at 6 months had an overall event rate of 75%. Suzawa *et al.*<sup>58</sup> reported a total of 469 PET-CT studies performed at four time points (3, 6, 9, and 12 months) after lung RFA in 143 patients with 231 tumours.<sup>58</sup> After a median follow-up of 24 months, local tumour progression was identified in 20.4% of tumours (47/231). The area under the ROC curve of PET diagnostic performance was significantly higher than that of CT at all four time points (0.71 versus 0.55 at 3 months, 0.82 versus 0.60 at 6 months, 0.84 versus 0.66 at 9 months, and 0.92 versus 0.68 at 12 months). Inflammatory FDG uptake were depicted in mediastinal lymph nodes and in the needle path of the RFA needle in 15%, 21%, and 15% of patients and in 19%, 11%, and 15% of patients at 24 hours, 1, and 3 months, respectively.<sup>59</sup>

Consequently, it is likely that PET-CT is able to discover incomplete ablation earlier than CT and may help to re-treat these patients, if needed, at a stage when the disease remains small. PET-CT should be included in the follow-up strategy of lung ablated tumours, but early evaluation (before 3 months) is at risk of either false-positive results due to early inflammation processes mimicking or active tumour, or false negative results due to early inflammation masking active tumour foci. Due to this constraint and the costs involved, it cannot be performed at every follow-up examination and CT remains the imaging technique of choice for follow-up.

## Thermal ablation versus other local therapies

Comparative studies of lung RFA and other treatments are rare, with numerous biases and small series. Sixty-four patients with biopsied Stage I NSCLC who were medically unfit for standard resection were offered sublobar resections ( $n=25$ ), RFA ( $n=12$ ), and percutaneous cryoablation ( $n=27$ ) with no difference in 3-year OS (87.1%, 87.5%, and 77%), 3-year cancer-specific (90.6%, 87.5%, and 90.2%) and cancer-free survival (60.8%, 50%, and 45.6%).<sup>60</sup> The hospital stay was significantly higher for sublobar resections (6 days), than for RFA (1.8 days), or cryoablation (2 days). In the treatment of patients with Stage I NSCLC, a study matched 14 surgical resections with eight RFA on

variables such as gender, age, tumour node metastasis stage. The mean OS for RFA and surgery were  $33.18 \pm 7.9$  and  $45.49 \pm 7.21$  months ( $p=0.054$ ), respectively.<sup>61</sup>

One drawback of thermal ablation versus surgery is that it does not allow for regional control of the disease and specifically for the lymph nodes. This is not a major disadvantage in the treatment of lung metastases in which lymph node resection has not been demonstrated to improve survival, even if positive lymph nodes are a negative predictive factor of OS<sup>62,63</sup>; however, lymph node resection is mandatory during surgery for NSCLC, where lymphadenectomy has demonstrated a survival benefit. SABR has the same drawback as thermal ablation concerning lymph nodes and the need for an ablation margin around the targeted tumour; however, in order to deliver the full dose to the target volume, it is obvious that radiation has to go through the surrounding body, and the effect versus benefit of peritumoural irradiation, may include the lymph nodes and a larger margin even if the dose is low. A theoretical, never demonstrated advantage of SABR over thermal ablation in the treatment of NSCLC could be the irradiation at low dose of some adjacent lymph nodes.

For lung metastases, OS rates after RFA are within the range of the best results obtained at surgical resection of lung metastases, with 5-year OS rates of 53.5% for Lida *et al.*<sup>43</sup> in a multicentre registry, in between 27% and 68% in a meta-analysis by Gonzalez *et al.*,<sup>42</sup> and increasing to 39.1 and 67.8% for patients who benefit from R0 resection in a literature review comprising 11 publications with 1,307 patients.<sup>64</sup> In lung metastatic patients, the challenge of disease control is more linked to the occurrence of new metastases distant from the ablation site than to local recurrence, as demonstrated in a study reporting 4-year progression-free survival (PFS) of 13.1% with 72.4% of patients progressing in the lung, who had been re-treated by RFA up to four times in 24% of the initially treated patients producing a 4-year control rate of lung metastatic disease of 44.1%.<sup>11</sup> Good tolerance and lung-sparing thermal ablation as demonstrated by the absence of post-lung RFA changes in respiratory function tests,<sup>3,12</sup> allows for high feasibility of re-treatment when needed. Repeatability is definitely higher with thermal ablation than with any other local treatment including surgery or SABR. The drawbacks of surgery are higher complication rates and lower tolerance by patients, sacrifice of lung function mainly for centrally located metastases, as well as increased technical difficulty for subsequent surgery in the same lung. The drawbacks of SABR are some difficulty in treating several metastases in the same region with overlapping irradiation fields and the near impossibility to re-treat local progression with SABR after previous SABR treatment. Moreover in the authors' experience, attempts to treat local progression after radiation therapy were responsible for an increase in post-thermal ablation complications including death. Reports of large series of SABR for lung metastases are scarce. One large series comprising 321 patients with 587 metastases (201 colorectal cancer metastases) treated with SABR over 13 years reported a median OS of 2.4 years (95% CI: 2.3–2.7) with 80%, 39%, 23%, and 12% OS at 1, 3, 5, and 7.5 years.<sup>65</sup>

Performance status (0–1; HR=0.49;  $p<0.001$ ), solitary metastasis (HR=0.75;  $p=0.049$ ), metastasis  $<30$  mm (HR=0.53;  $p<0.001$ ), metachronous metastases (HR=0.71;  $p=0.02$ ), and pre-SABR chemotherapy (HR=0.59;  $p<0.001$ ) were independently related to favourable OS. Three deaths were possibly treatment-related. It is noteworthy that SABR is considered as a non-invasive technique even though some complications are directly related to the treatment, but often difficult to depict because they usually occur late after treatment as is the case for most post-radiation toxicity. Moreover, it has been reported that placement of fiducial needed for SABR in 105 patients with tumours to the lung have resulted in 33.3% pneumothoraces (13.3% major, 20% minor) with 30.5% of small peri-tumoural alveolar haemorrhage, and 2.9% of major bleeding,<sup>66</sup> which makes SABR invasiveness close to that of RFA in terms of pneumothoraces.

In NSCLC, two independent randomised Phase 3 trials assigning patients in a 1:1 ratio to SABR or lobectomy (STARS and ROSEL registered with [ClinicalTrials.gov](http://ClinicalTrials.gov)) in patients with T1–2a ( $<4$  cm), N0M0, operable NSCLC closed early due to slow accrual. Pooled analysis from these 31 patients assigned to SABR and 27 patients assigned to surgery revealed an OS at 3 years of 95% for SABR and 79% for surgery (HR=0.14, 95% CI: 0.017–1.190;  $p=0.037$ ). Recurrence free survival (RFS) at 3 years was 86% (95% CI: 74–100) in the SABR group and 80% (65–97) in the surgery group (HR=0.69, 95% CI: 0.21–2.29;  $p=0.54$ ). SABR resulted in 10% Grade 3 adverse events, including chest wall pain, dyspnoea, cough, fatigue, and rib fracture. Surgery resulted in one death and 44% Grade 3–4 adverse events, including dyspnoea, chest pain, and lung infections.<sup>67</sup> Such pooled analysis was subject to many criticisms and letters to the editor.<sup>68</sup>

## Future developments

Currently, thermal ablation of lung tumours is mostly used as a standalone technique. Pre- or post-ablation systemic therapy might improve outcomes of thermal ablation. The excellent tolerance of thermal ablation might render such a combination highly feasible, whereas peri-surgical systemic therapies are reported to be achievable in only 70% of patients who are able to complete the scheduled regimen after lung surgery due to the long recovery time.<sup>69</sup> Such a combination of thermal ablation and chemotherapy has been reported in a recent study where 74 patients with stage IIIB or IV NSCLC were assigned to MWA/chemotherapy or chemotherapy alone. Complete ablation was observed in 84.8% patients in the MWA/chemotherapy group with a median time to local progression of 27 months. PFS for MWA/chemotherapy combination was 10.9 months (95% CI: 5.1–16.7), and 4.8 months (95% CI: 3.9–5.8) ( $p=0.001$ ) in the chemotherapy group, whereas OS was 23.9 months (95% CI: 15.2–32.6) and 17.3 months (95% CI: 15.2–19.3;  $p=0.140$ ), respectively. Multivariate analyses showed that MWA was an independent prognostic factor of PFS and primary tumour size was an independent

prognostic factor of OS.<sup>70</sup> Patient selection for combined or adjuvant systemic therapy should take into account progress in histology, immunohistochemistry, and molecular biology, to define a personalised strategy for each patient. It has been demonstrated that MWA as a local therapy for oligometastatic NSCLC should be considered in patients with acquired resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) drugs.<sup>71</sup>

In the future it is likely that lung surgery for small-size oligometastatic lung disease will be replaced by low-invasive techniques. The optimal technique will have to demonstrate efficacy, tolerance, and cost effectiveness, even if randomised studies will be difficult, as highlighted by the early closure of RCTs trying to compare surgery and SABR in NSCLC (STARS and ROSEL) due to slow accrual.<sup>67</sup>

Currently, size of the target tumour remains the main driver of success and proper patient and tumour selection enables a 89% local control rate, even if new technologies may increase the size of the tumour amenable to local ablation.

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