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CHEST RADIOLOGY

Radiofrequency ablation of thoracic tumours: lessons learned with ablation of 100 lesions

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Abstract
Purpose Our aim was to analyse the results of our first 100 radiofrequency ablation (RFA) procedures, of primary (nonsmall-cell lung cancers, NSCLC) and secondary (MTS) lung cancers to assess what lessons could be learned from our experience.
Materials and methods We analysed 100 lesions (mean size 23 mm) in 81 patients (25 NSCLC/56 MTS). On the basis of the clinical–radiological evolution, we analysed complete ablation (CA) versus partial ablation (PA) at the first computed tomography (CT) scan and during the follow-up (mean 23 months), time to progression (TTP) and survival. Possible predictive factors for local effectiveness and survival were sought.
Results At the first CT scan CA was obtained in 88 %; the difference between the mean diameter of lesions achieving CA and PA was significant (20 versus 38 mm; $p = 0.0001$). A threshold of 30 mm ($p = 0.0030$) and the histological type (NSCLC 75 %/MTS 94 %; $p = 0.0305$) were also predictive of CA. A total of 18.4 % of the CA recurred (average TTP 19 months). Survival at 1, 2 and 3 years was 84.5, 65.4 and 51.5 %, respectively. The predictors of survival at 3 years were the coexistence of other MTS ($p = 0.0422$) and a diameter <20 mm ($p = 0.0323$), but not the local effectiveness of RFA.
Conclusion RFA for thoracic malignancies is accurate for lesions up to 30 mm, especially if metastatic; survival is more closely related to staging factors than to the local effectiveness of RFA.

Keywords Radiofrequency · Thermal ablation · Tumour · Lung · Thorax

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Introduction

Primary tumours of the lung are the leading cause of cancer mortality worldwide, amounting to 1.2 million deaths each year [1]. Improving survival in nonsmall-cell lung cancer (NSCLC) requires early diagnosis and effective treatment. Lobectomy with hilar and mediastinal lymph node sampling is still the gold standard treatment for NSCLC in stages I and II. Unfortunately, many patients are not good candidates for lobar resection [2].

Pulmonary metastases (MTS) are present in 25–30 % of patients suffering from different types of cancer; for some patients with oligometastatic pulmonary disease, metastasectomy seems to be associated with improved survival [3]. Radiotherapy (RT) has been offered as an alternative to surgery for both NSCLC and MTS; however, the 5-year survival after traditional RT remains low (15–20 %), with a high rate of local recurrence (LR) [4].

The last few decades have seen an increase in the detection of smaller neoplasms (in part as a result of low-dose CT screening for NSCLC [5]) and, at the same time, the development of new local therapeutic possibilities, e.g. ablative therapies. Radiofrequency ablation (RFA) represents one of these [6]. Initially applied to other solid tumours, it has been also used in the chest to increase the possibility of local control of the tumour in inoperable patients [7].

This study discusses the safety, efficacy and clinical utility of thermal ablation of NSCLCs and pulmonary MTS (mainly from colorectal cancer—CRC) by presenting our results in terms of survival and prognostic factors and comparing them with the literature data.

Materials and methods

Of a total of 1,591 patients who underwent RFA at our Institution since the late 1990s, 94 (5.9 %) were treated for thoracic cancers. To assess the significance of RFA in this type of cancers, we conducted a retrospective study on a series treated between 2002 and 2011, consisting of 81 consecutive patients who underwent RFA for 100 thoracic lesions.

The study was carried out in accordance with the guidelines on retrospective analyses established by our hospital's institutional review board.

Patients and lesions

Each patient was referred for treatment on the basis of clinical indications, after a multidisciplinary assessment by an interventional radiologist, a thoracic surgeon, a medical oncologist and an anaesthesiologist. The RFA technique was established based on the interventional radiologist's technical evaluation.

The lesions treated with RFA were not candidates for surgery due to the following reasons:

- reduced pulmonary function;
- compromised general and/or cardiovascular condition;
- advanced age of the patient;
- location of the lesions in both lungs;
- presence of extrapulmonary disease, but of limited extent;
- refusal of the patient to undergo surgery.

Depending on the histological type of neoplasm, our patients can be divided into two groups: a group suffering from primary lung cancer (NSCLC) and a second group with pulmonary MTS, mainly from CRC.

At the time of RFA, 61 of the 81 patients were male (75 %) with a mean age of 61.6 years (median 66) and 20 were females (25 %) with a mean age of 68.7 years (median 70.5); overall the average age was 61.7 years (range 17–88 years; median 66).

Fifty-five of the eighty-one patients (67.9 %) had received other treatments prior to thoracic RFA (including six liver RFA); nine patients suffering from MTS from CRC underwent liver RFA synchronous to the pulmonary RFA. Thirty-four of the eighty-one patients (42 %) were also affected by extrapulmonary MTS.

One hundred lesions were treated: 30 NSCLC (30 %) and 70 MTS [51/70 from CRC (72.8 %), 6/70 from sarcomas (8.5 %), four from hepatocellular carcinoma, two from gastric carcinoma and the remaining seven from cholangiocarcinoma, laryngeal, breast, ovary, parotid, prostate and kidney cancer, respectively]. The average diameter of treated lesions was 2.3 cm (range 0.8–8 cm; median 2 cm). Specifically 79 lesions (79 %) a diameter <3 cm, and 40 lesions (40 %) had a diameter <2 cm.

The lung lesions were solitary in 48 cases (48 %) and multiple in 52 cases (52 %).

Preprocedural assessment

Before treatment, general and cardiorespiratory condition (performance status) was evaluated. In addition, preprocedural CT or positron-emission tomography (PET)–CT staging was requested, preferably not more than 1 month before the procedure.

Pathological diagnoses were available for all of the NSCLCs; the MTS were mostly recognised as such on the basis of their clinical evolution and imaging characteristics; in a few cases only (e.g. those with atypical imaging appearance) biopsies were performed.

For each patient we requested clotting tests (in case they needed correction of thrombocytopenia or INR or PTT elongation) and electrocardiogram. Subsequently, an anaesthesiological consultation was held. Finally, any anticoagulation or antiplatelet therapy was modified or suspended.

The indications, potential benefits and risks of the procedure were discussed with the patients, who always signed a consent form.

Procedure

The RFA was performed percutaneously in all 81 patients. The needle electrodes used for thoracic RFA were always of the expandable type. In particular, the systems used were RITA (RITA Medical Systems, USA) (15/100 cases), LeVeen (Boston Scientific Corporation, USA) (75/100) and Meditalia (Meditalia Biomedica, Italy) (10/100), with different opening diameters. The RITA system is regulated by the temperature reached in the tissues (based on the application time), the LeVeen system is impedance based, and the Meditalia system can be based on either impedance or temperature. The generators used had a maximum power of 200 W.

The total number of RFA sessions was 100, equal to the number of lesions.

All RFA procedures were performed in the CT or interventional radiology room, under conditions of

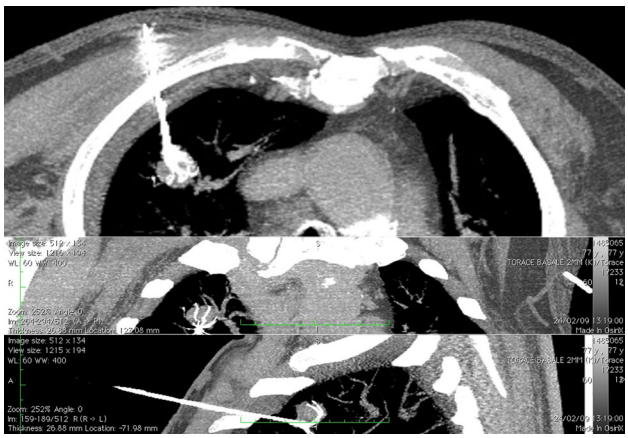

Fig. 1 Utility of the volumetric acquisition with multiplanar reconstructions to evaluate the placement of the needle towards the tumour: the needle appears correctly positioned in the axial plane, but the multiplanar reconstructions demonstrate its laterality

cutaneous sterility, with the use of a local anaesthetic at the site of entry of the needle electrode (10 ml of lidocaine hydrochloride 2 %) and with the patient under conscious sedation administered by an anaesthesiologist, who was always present in the room. During each procedure the ECG, arterial oxygen saturation, heart rate and blood pressure were constantly monitored.

The procedures were performed under CT guidance in 88 cases (88 %) and under US guidance in the remaining lesions (12 %), in which the peripheral location with extensive pleural contact afforded good sonographic visualisation (including one case performed under US guidance with CT monitoring).

Patients were placed in the most suitable position for insertion of the needle electrode, based on the location of the lesion in relation to the anatomical structures of the lung; in particular, to make up for the inability to place the patient in a prone position under conscious sedation (the anaesthesiologist would lose access to the airways), we used the lateral decubitus position to treat lesions that could not be adequately reached in the supine position.

The average RFA time was about 20 min, with differences imposed by the characteristics of the tumours, but also by the different protocols of the various RFA systems used (generator and needle electrodes).

As we did not have a CT fluoroscopy room, during insertion of the needles in the CT-guided procedures we performed serial thin axial acquisitions, with orthogonal multiplanar reconstructions (MPR) to assess the proper placement of the electrodes in relation to the tumour margins on all planes; after needle insertion, a volumetric acquisition was performed to better display the three-dimensional relationship between the needle electrode and the tumour (Fig. 1).

At the end of the procedure, the risk of complications (e.g. pneumothorax, haemorrhage, seeding, etc.) was prevented using different techniques depending on the system used: with the RITA system the "track ablation" protocol was applied, while with the LeVeen and Meditalia systems we used a coaxial needle for insertion. This, in addition to preventing neoplastic seeding, allows drainage of any pneumothorax during withdrawal.

Four hours after the procedure, a chest X-ray was obtained in all cases. In any case, patients were kept under observation for one night after treatment to monitor their clinical condition and blood count, and follow the possible evolution of pneumothorax.

All adverse events were recorded, categorised according to the SIR criteria into minor events (clinically relevant) and major complications (requiring interventional radiological or surgical intervention) [7], and counted in terms of numbers and percentages.

Follow-up

The result of the RFA was evaluated by performing contrast-enhanced CT 1 month after the procedure, to highlight the possible presence of residual viable tissue. In the case of complete ablation (CA) at the first CT scan, patients were placed on a protocol of follow-up with 4 monthly CT studies (but for patients with MTS, follow-up intervals were sometimes changed on the basis of the evolution of metastatic disease and/or in relation to systemic therapy); doubtful cases were examined by PET–CT to establish possible LR.

The possible local or general evolutions of pathology were considered as:

- no evidence of residual/local recurrence of disease (CA);
- evidence of residual local disease (partial ablation, PA);
- evidence of local recurrence of disease (LR);
- death.

In particular, the CT appearance of CA was assessed by applying the five possible patterns indicated in a recent classification by Palussiere et al. [8] (atelectasis, cavitation, disappearance, nodule and fibrosis).

Based on these parameters, it was possible to calculate: local effectiveness (CA versus PA) at the first CT scan; local effectiveness at follow-up (range 1–115 months; mean 23 months) (CA versus PA + LR), time to progression (TTP), and mid-term survival. In this regard, since there was a problem of patients being affected by two different neoplasms (NSCLC and MTS), we were unable to carry out a study of cancer-specific survival (to be further divided, in the case of MTS, according to the different primary tumours), because the numbers would be so small

as to undermine any statistical calculation; given that the end-points were limited to local effectiveness and mid-term survival, the difference in histology was thus tested as the first variable in our search for factors predicting lesion or patients outcomes.

As possible prognostic factors for local effectiveness, we analysed:

- histological type of the lesions (NSCLC versus MTS);
- size of the lesions (diameter in mm).

As potential predictors of survival we considered:

- histological type of the lesions (NSCLC versus MTS);
- solitary versus multiple lesions at the time of treatment;
- size of the lesions (diameter in mm);
- absence versus presence of extrapulmonary disease;
- maintained CA after RFA.

Statistical analysis

All variables were entered in a Microsoft Excel (Microsoft Inc., Redmond, WA) worksheet. Some data (such as percentages or averages/medians, e.g. TTP) were processed using nonstatistical calculations, whereas the statistical programme Statistical Analysis System (SAS v. 8.2, SAS Institute, Cary, NC, USA) was used to assess:

- correlations between the variables mentioned above and local effectiveness (CA), using univariate analysis;
- curves of overall survival stratified for possible predictors, processed according to the Kaplan–Meier method.

Results

Technical success, described as completion of the procedure as planned, was obtained in all cases, with the exception of one procedure (99 %) which was suspended due to haemoptysis and minimum haemothorax not requiring prolonged hospitalisation and successfully repeated after about a month.

Complications

The rate of periprocedural mortality was zero. After the first RFA, adverse events occurred in 31/100 procedures. There were seven (7 %) major complications, represented by: an apical fluid collection, accompanied by pain and fever probably due to suppuration, requiring prolonged hospitalisation and prolonged antibiotic therapy; six cases of pneumothorax with the need to place a thoracic drainage for a few days (Fig. 2). The other 24 adverse events were minor: eight cases of pneumothorax with rapid resolution, six cases of reactive pleural effusion, five cases of haemoptysis, two cases of minimum haemothorax, one case of diaphragmatic paralysis due to irritation of the phrenic nerve, one case of subcutaneous emphysema, one entirely asymptomatic pneumatocele (Fig. 3).

Local effectiveness

CA of the tumour was obtained in 89 of 100 lesions (89 %) after the first treatment, in particular at the first CT scan (Fig. 4); in 11 lesions only a PA was achieved because of varying extents of residual tumour (Fig. 5). Stratifying the result on the basis of lesion size, local success was complete in 38/40 tumours with a diameter <2 cm (95 %) and in 69/79 tumours (87.3 %) with a diameter lesser than 3 cm. Comparing the average diameter of lesions in achieving CA (20 mm) with that of lesions with PA (38 mm), the difference was very significant ($p = 0.0001$). At univariate analysis, even the "threshold" of 30 mm was highly statistically significant as a predictor for CA versus the PA ($p = 0.0030$). Only at univariate analysis (not considering at the same time the impact of other variables, such as the size of NSCLC versus MTS), statistical significance as a predictive factor for local effectiveness was also achieved for the different histological types: CA was obtained in 75 % of NSCLC and in 94 % of MTS ($p = 0.0305$).

In 10 of 89 cases (11.2 %) CA progressed to LR at follow-up (Fig. 6), with an average TTP of 19 months.

Outcome

During the follow-up there were no cases of worsening of lung function due to ablative treatment; 29 patients dead, even if only in part due to the tumour.

Overall survival at 1, 2 and 3 years after treatment was 84.5, 65.4 and 51.5 %, respectively (Fig. 7).

Stratifying the survival curves for the predictive factors described above, it was found that, among the factors analysed, the different histological type (NSCLC versus MTS: 80, 66 and 53 % versus 87, 66 and 52 %) and the solitary nature of the lesions at the time of treatment (versus multiplicity) were not statistically significant; the absence of extrapulmonary MTS ($p = 0.0261$) (Fig. 8) and the diameter <20 mm ($p = 0.0174$) (Fig. 9) were found to be predictive factors of survival at 3 years (61 versus 46 % and 65 versus 39 %, respectively); obtaining persistent CA (i.e., local effectiveness of ablation) did not reach statistical significance in relation to that timeframe but the observation of the two survival curves (maintained CA versus PA + LR) suggests a favourable trend for patients with CA maintained at shorter terms (90 versus 75 % at 1 year and 69 versus 62 % at 2 years) (Fig. 10).

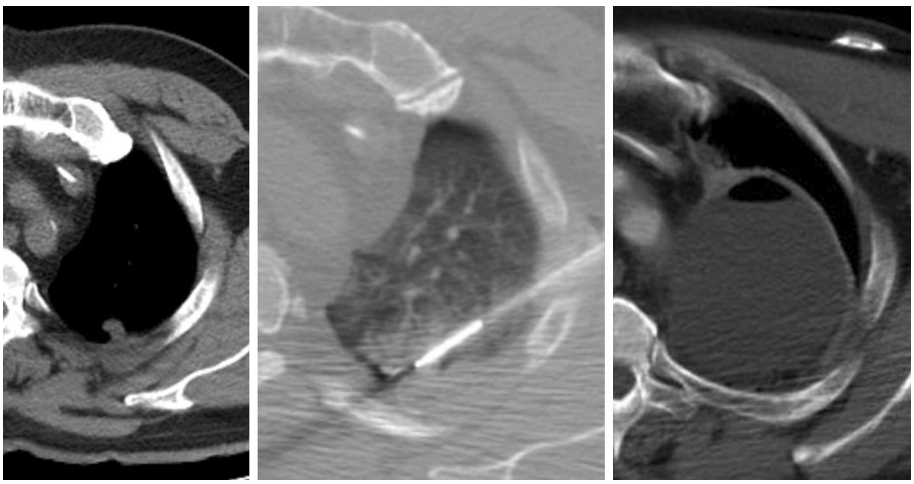

Fig. 2 Major complications. Subpleural pulmonary metastasis in the left upper lobe, treated with radiofrequency ablation. At the follow-up CT scan, appearance of a fluid collection, with a small air-fluid level: the patient required prolonged hospitalisation and antibiotic therapy

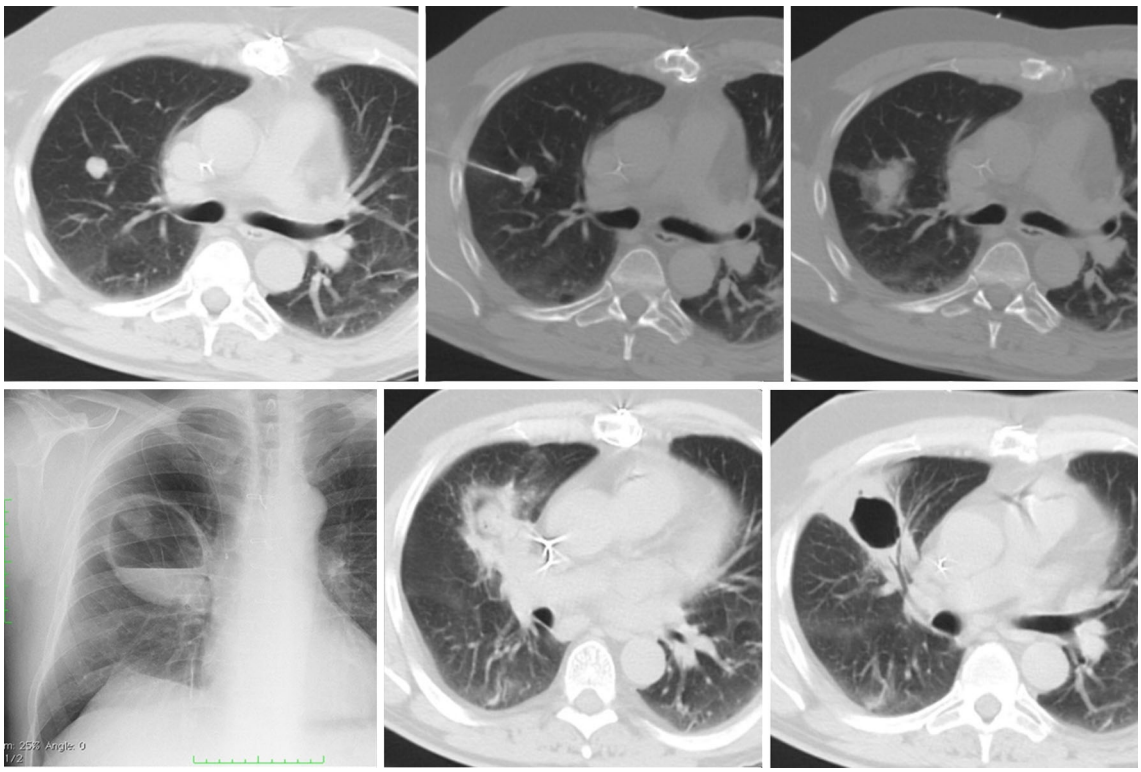

Fig. 3 Centre-parenchymal pulmonary metastasis in the right upper lobe, treated with radiofrequency ablation. At a follow-up chest X-ray, occurrence of a large, asymptomatic pneumatocele with air-fluid level. At CT scan 1 month later, favourable appearance of the ablated area ("mixed" nodular-atelectatic evolution), and regression of the pneumatocele

Discussion

Among all the RFA applications, the indication for treatment of thoracic tumours is still marginal, as attested by our experience (only 6 % of all patients undergoing RFA at our Institution, despite it receiving referrals from important regional thoracic surgery and oncology centres) and the fact that the SIR reporting standard for these procedures was only published in 2009, while more general ones were issued in 2003. Furthermore, with regard to NSCLC, no evidence-based approach is available to date which clarifies the role of various treatments in general or the specific indications for RFA [7].

RFA is therefore suggested in patients with primary lung cancers or MTS (especially from CRC) who are considered inoperable due to medical conditions or to the unfavourable position of the tumour [9, 10]. In our experience all NSCLC treated were deemed ineligible for surgery. As

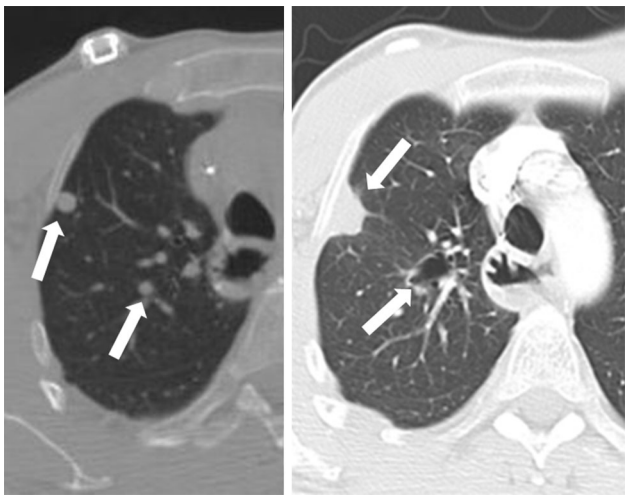

Fig. 4 Pulmonary metastases in the right upper lobe, one subpleural, the other central parenchymal. At the follow-up CT scan, complete ablation (CA) of the two nodules and evolution into peripheral atelectasis and cavitation, respectively

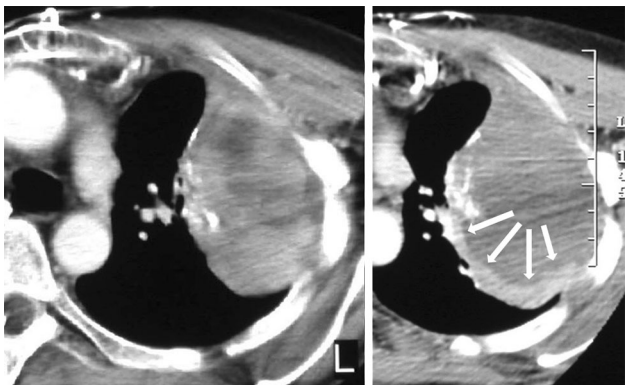

Fig. 5 Bulky metastasis from humeral osteosarcoma at the apex of the left lung: at the follow-up CT scan, after multiple needle placements, an enhancing ring of viable tissue can still be seen, due to partial ablation (PA)

regards the treatment of MTS, the choice was the result of a multidisciplinary assessment and it was included in a multimodal therapeutic strategy.

During the RFA sessions, all patients were treated using conscious sedation rather than general anaesthesia. This implies some advantages, such as the partial respiratory collaboration of the patient and the possibility of using the usual radiological room. Not being able to place the patient in a prone position constitutes the main disadvantage, which can be overcome by having patients lie in the lateral position. In the literature, comparisons of general anaesthesia and conscious sedation during thoracic RFA did not show significant differences in terms of feasibility, technical success and complication rate [11].

RFA of thoracic tumours is an excellent option to preserve lung function, without sacrificing healthy

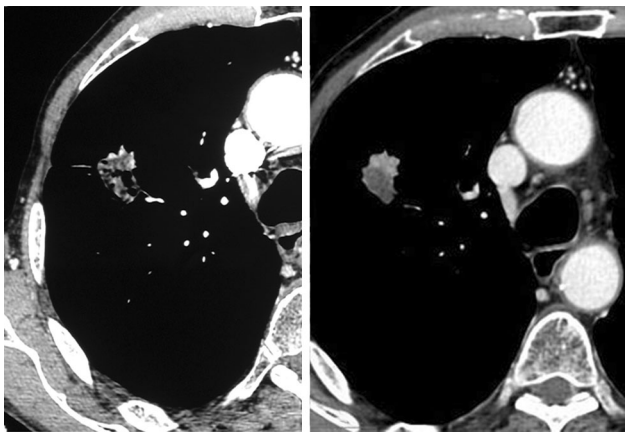

Fig. 6 Local recurrence after radiofrequency ablation of nonsmall-cell lung cancer in the right upper lobe. At the first follow-up CT scan, complete ablation is diagnosed on the basis of the absence of contrast enhancement; a subsequent CT scan shows evidence of local progression of the tumour on the anterior–medial side of the lesion

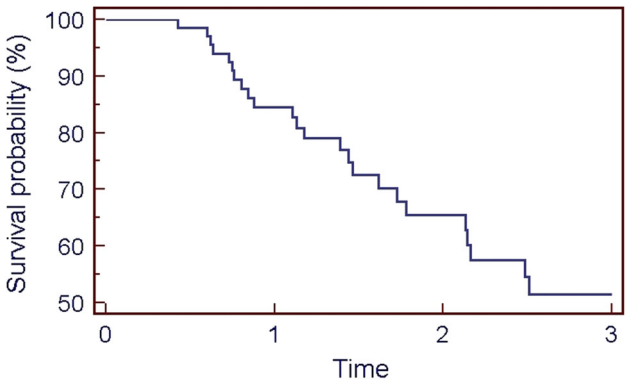

Fig. 7 Overall survival at 3 years. Overall survival at 1, 2 and 3 years was 84.5, 65.4 and 51.5 %, respectively

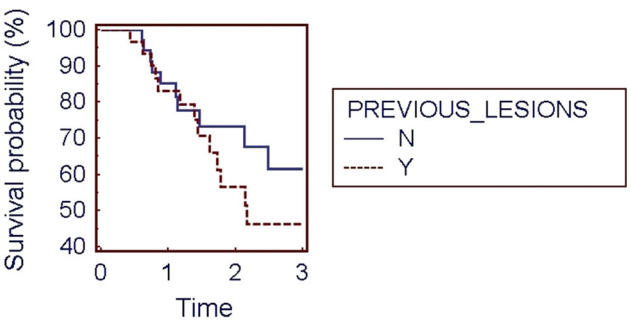

Fig. 8 3-year survival stratified by absence of extrapulmonary metastases. The absence of extrapulmonary metastases was a favourable predictive factor for survival at 3 years ($p = 0.0261$)

parenchyma, and it is a relatively safe procedure, with low mortality (about 0.4 %) [12]. In the literature, the periprocedural morbidity ranges from 15.5 to 55.6 % (median 35.7 %), with a major complication rate that varies between 8 and 12 % [13, 14]. In terms of adverse events,

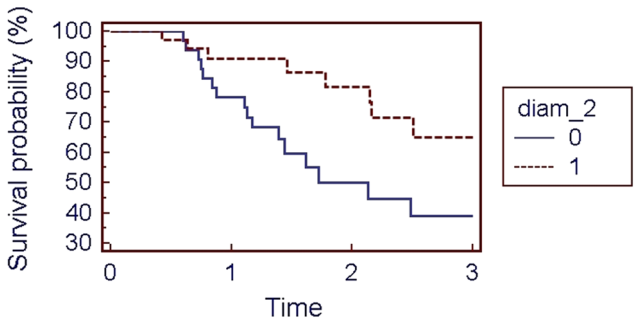

Fig. 9 3-year survival stratified by diameter <20 mm. A lesion diameter ≤20 mm was also favourable for survival at 3 years ($p = 0.0174$)

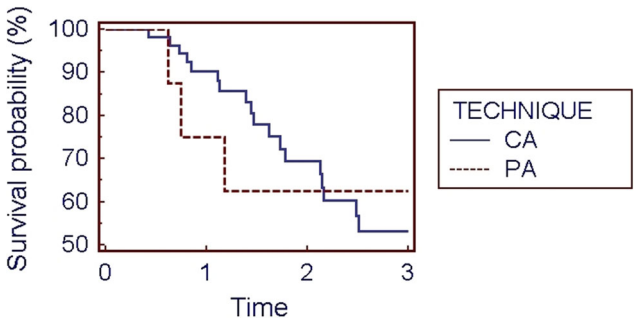

Fig. 10 3-year survival stratified by local efficacy. The local efficacy of radiofrequency ablation was not significant for survival at 3 years, but the observation of the two survival curves suggests an advantage for patients with maintained CA at shorter intervals

our results are in line with those of the best series reported in the literature, in particular as regards the rate of major complications (7 %); in fact, the development of a limited pneumothorax, which affects a large percentage of patients, often resolves without any medical intervention or with a simple drainage and could therefore be counted among the minor complications [15].

In the literature, while a consensus regarding the definition of CA has been reached, there are different definitions for PA. In practice, however, as in the rest of the oncological radiology, PA is defined as not achieving negative findings on imaging. When there is radiographic evidence that CA has been reached at the first follow-up after RFA, CA shall be deemed to be maintained until the new development of viable tumour during the follow-up, in which case it is commonly called LR, even though the term "local tumour progression" should be preferred, since the LR is essentially a lesion not completely ablated [16].

In our study, we used univariate analysis to evaluate possible variables that can influence the effectiveness of local RFA. In a recent review on thoracic RFA, de Baere et al. [17] indicated, as favourable factors for local effectiveness, a tumour size threshold of 2 cm and the use of expandable needle electrodes; conversely, proximity with the vascular structures (<3 mm) proved to be a negative predictive factor. Many other authors have set this goal; in particular Hiraki et al. [15] described the results obtained on 342 lung cancers: the risk factors associated with local progression were male sex, tumour diameter >2 cm, central location of the lesions, contact with vascular or bronchial structures and the use of internally cooled electrodes; at multivariate analysis, independent risk factors for the development of local progression were large size and the use of internally cooled electrodes.

In our series, as well as for tumours with smaller diameter (similarly to the above-mentioned studies), univariate analysis also revealed a greater local effectiveness for the treatment of MTS compared NSCLC: given the equality of the average diameter of the two histological types (23 mm), this result could be due to a greater aggressiveness of NSCLC or to the fact that, after RFA, the MTS were often treated with systemic therapies, which could lead to underestimate any residual viable tumour. MTS with residual tumour or local progression were in fact only 11/70 (15.5 %), while the NSCLC were 10/30 (33.3 %). These data are similar to those reported by de Baere [17], who described a higher rate of local control for MTS from CRC compared with NSCLC, renal cell carcinoma or hepatocellular carcinoma ($p = 0.023$); however, multivariate analysis showed that the relative risk of local progression of a particular type of cancer was comparable to that of other histological types. Even Hiraki et al. [15] showed a better local control in the treatment of MTS from CRC compared to NSCLC (and also to MTS from other types of cancer), but without reaching a statistically significant correlation.

In our study, overall survival at 1, 2 and 3 years after treatment was 84, 65 and 51 %, respectively.

The first stratification curves, based on the different tumour histological types, showed no statistically significant differences between NSCLC and MTS, but this finding could be affected by the relatively short average follow-up and by the limited sample size, especially for NSCLC. In the literature, the survival rates after RFA for NSCLC range from 70 to 83 % at 1 year and 48 to 83 % at 3 years [18, 19], consistent with our results (80 % at 1 year and 53 % at 3 years); the survival rates at 1 year after RFA of pulmonary MTS range from 78 to 89 % at 1 year and 46 to 57 % at 3 years [19–22], in line with our findings (87 and 52 %).

Stratifying the survival curves for the other prognostic factors analysed, we found that the predictors of survival at 3 years were only the absence of other MTS ($p = 0.0261$) and the diameter <20 mm ($p = 0.0174$). Simon et al. [22] conducted a study on 153 patients: the basic result of this study was the difference between patients with small tumours (progression-free survival rates at 1 and 3 years

were 83 and 57 %, respectively) and patients with larger tumours (45 % at 1 year and 25 % at 3 years). Remembering that diameter is one of the cornerstones of tumour staging, at least for NSCLCs, the better survival rate of patients with smaller lesions is believed to be partly related to the natural history of the disease. To verify the real impact of the RFA on survival, we therefore stratified the patients by local effectiveness of RFA: the difference between the survival curves at 3 years of CA versus treatment failures (PA and LR) was not statistically significant, consistent with what was reported until the last decade [23]; the observation of a trend in favour of effective treatment in the first 2 years, however, lets us hope that the clinical utility of these treatments can be demonstrated later, preferably by randomised trials.

Conclusions

The growing experience with RFA of thoracic tumours, including our first 100 cases, demonstrates the safety and efficacy of local treatment for small tumours; the predictive factors for a longer survival are mainly related to staging (tumour diameter and presence of extrapulmonary disease), as for the other cancer therapies. The initial evidence of an impact of RFA on survival, at least in the short term, prompts the performance of prospective studies to compare the results with modern radiotherapic techniques for inoperable NSCLC and MTS, and with surgical resection for MTS, with special attention to quality of life and costs.

Conflict of interest I. Garetto, M. Busso, D. Sardo, C. Filippini, F. Solitro, M.L. Grognardi, A. Veltri declare no conflict of interest.

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