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Percutaneous radiofrequency ablation using internally cooled wet electrodes for the treatment of patients with lung tumors

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Abstract. – OBJECTIVE: To assess the safety and feasibility of computed tomography-guided radiofrequency ablation (CT-guided RFA) in unresectable lung neoplasms, using a new 15G monopolar internally cooled wet electrode.

PATIENTS AND METHODS: 15 consecutive patients with lung neoplasms (< 4 cm), both primary and secondary, unsuitable for or refusing surgery, underwent percutaneous CT-guided RFA using a 15G electrode with a 3-cm exposed tip. The prevalence and grade of adverse events and technical success were evaluated, as well as the extension of the ablation zone, the complete response rates, and the time to progression, determined at CT examination performed 1, 6, and 12 months after the procedure.

RESULTS: A total of 22 lung neoplasms were treated (mean diameter: 28 mm; range: 20-39 mm). Technical success was obtained in all patients, without major complications or intraprocedural deaths. Mild or moderate pneumothorax was registered in 46.7% of patients, while a perilesional hemorrhage was observed in 5/15 cases. During the follow-up period, a complete response was obtained in 19 out of 22 lesions (86.4%) with three partial response, two of them successfully retreated with the same technique.

CONCLUSIONS: Percutaneous RFA using a 15G internally cooled wet electrode is a safe and feasible treatment for unresectable lung neoplasms, with high complete response rates.

Key Words:
Radiofrequency ablation, Lung cancer, Primary pulmonary tumor, Secondary pulmonary tumor, Precision medicine, Personalized medicine.

Introduction

In the last years, percutaneous ablation has become an acceptable alternative for the treatment of patients with inoperable lung malignancies. Advantages of this technique include its low invasiveness, cost-effectiveness, reduced morbidity and mortality in respect to surgery, preservation of more lung tissue and pulmonary function, and repeatability with fast recovery[1-6]. However, the monopolar radiofrequency ablation (RFA) has the major limitation of inducing a thermal ablation zone with limited size, which is less than that desirable to include both the tumor and peritumoral safety margin and to

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contain the local recurrence[7,8]. In the lung, the energy of RFA can be effectively delivered within the tumor while protecting the adjacent lung parenchyma, due to the heat insulation and low electric conductivity of the air surrounding the tumor[9,10]. Although this effect can be protective of the normal lung parenchyma, it is associated with high rates of local recurrence due to the limited safety margin of ablation. Furthermore, unlike most classical hepatocellular carcinomas, lung tumors are not usually encapsulated, making more complex to obtain at least an additional 8-10 mm of ablation beyond the visible tumor margin in all directions. These background issues could explain why a high rate of complete response to RFA is obtained only in tumors less than 2 cm in size. In larger tumors, a statistically significant lower success rate, due to residual or recurrent disease, has been demonstrated, with variable results[11-16]. In the attempt to overcome the limitation of a small-sized lung ablated zone, it would be possible to increase the tissue heating and coagulation power with radiofrequency (RF) by altering electrical and/or thermal conduction through the injection of saline into the tissues, as previously demonstrated[17]. This technologic advance in RF generators could be combined with a larger inner diameter of the electrode (15 Gauge) that would increase the delivery power and consequently the depth and the area of the direct volume heating.

Based on this knowledge, the current study describes our case series of inoperable primary and secondary pulmonary tumors treated with computed tomography-guided RFA (CT-guided RFA) by using a 15Gauge (G) monopolar internally-cooled wet electrode. The aim of the work was to assess the safety and technical success of this new approach to CT-guided RFA procedure.

Patients and Methods

Design of the Study

A prospective single-center multidisciplinary study, enrolling patients with primary and secondary lung cancer, was conducted. The research was approved by our Ethics Committee Board, and written informed consent, depicting the treatment and its risks, was obtained by every patient. The study was conducted in respect of the Declaration of Helsinki, according to the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice.

In the pre-treatment workup of every patient, a routine physical examination, laboratory tests, and imaging studies, including unenhanced and contrast-enhanced chest CT, were performed for procedural planning. A multidisciplinary team composed by the thoracic surgeon, pathologist, pulmonologist, clinical oncologist, chest radiologist, nuclear medicine specialist, radiation oncologist, and interventional radiologist gave the indication to the mini-invasive percutaneous ablative treatment of the lesions, based on inclusion/exclusion criteria (Table I).

Safety was evaluated in terms of rate, type, and gravity of peri- and post-procedural complications. Efficacy was assessed in terms of procedural technical success, and, during the follow-up, in terms of complete response to treatment, according to the modified response evaluation criteria in solid tumors (mRECIST), and local disease control (LDC) rate[18].

Table I. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Age > 18 years	Oral anticoagulant drugs in the 5 days before the procedure.
Signed informed consent	Known allergy to iodinated contrast medium
1-6 lung lesions	Need of urgency/emergency treatments
2-4 cm lesion	Moderate/severe kidney function impairment (assessed by the MDRD or by Cockcroft-Gault formula: Glomerular Filtration Rate < 60 mL/min/1.73 m^2)
Platelet count >50,000/mm^3	Pregnant or lactating women
International Normalized Ratio < 1.5	Previous pneumonectomy
Prothrombin time < 15 s	Active enrolment in other studies
Thromboplastin time < 45 s	

Treatment

All thermal ablation treatments were performed in the radiology department by CT guidance, via a percutaneous approach, with patients under conscious sedation and local anesthesia. The procedure equipment consisted of a 15G monopolar internally-cooled wet (ICW) electrode RFA system (Jet-tip, RF Medical, Seoul, Korea) with a 3-cm exposed tip and a multi-purpose ablation generator having tissue-specific algorithms (M-3004, RF Medical) suitable to administer a core temperature close to 100°C. For internal cooling, isotonic saline at 2-5°C was diffused into the internal lumen of the electrode with a peristaltic pump (RFP-300, RF Medical, Seoul, Korea) to maintain a perfusion rate of 100-110 mL/min. A single needle per-patient was inserted and positioned along the longitudinal axis of the lesion, with the tip on the tumor margin. A pre-determined ablation time of 12 min was decided. No more than 2 lesions per session were treated and only one lung per session was treated. At the end of the procedure, an unenhanced chest CT examination was performed to assess the technical success, the volume of tumor necrosis and eventual complications. Every patient underwent chest radiography examination and blood laboratory tests performed 3 and 24 h after the treatment, before being discharged. Intra/peri-procedural morbidity and mortality rates were evaluated, based on the prevalence of minor and major complications, or death, in the first 7 days after the treatment. Complications were classified as minor or major according to the patient's outcome, as stated by the Society of Interventional Radiology. Major complications were defined as events requiring a high level of care or prolonged hospitalization and determining high morbidity or disability or death. All other events were classified as minor complications. Complications were graded in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute[19].

Imaging Evaluation

The following parameters were considered: tumor histology (primitive versus secondary), lesion location, tumor transverse diameter, ablation zone two perpendicular transverse diameters, technical success, and technical efficacy. Technical success was defined as the correct electrode placement within the lesion and the adequate tumor coverage throughout the ablation zone, as assessed at the final intra-procedural CT imaging. Technical efficacy was defined as still adequate tumor coverage throughout the ablation zone.

In the follow-up, chest contrast-enhanced CT examinations were performed 1, 6 and 12 months after RFA for evaluating the treatment response. The ablation zone was assessed on contrast-enhanced CT scan performed 1 month after the procedure by measuring, on the axial image, the two perpendicular largest transverse diameters of the zone, including parenchymal consolidation and peripheral ground-glass rim. This evaluation provided a transverse roundness index (the ratio of the two diameters) as an approximation for ablation zone sphericity in one plane. A roundness index of 1 was determined as ideal roundness.

Treatment response to RFA treatment was defined based on the mRECIST criteria: the complete absence of contrast enhancement in the target lesion was considered as complete response (CR), whereas a reduction of the enhancement area of more than 30% was considered as partial response (PR)[20]. Local TTP (time to progression) was also evaluated.

Lymph node, locoregional and/or distant tumor progression did not affect the primary end-point and thus were not considered.

Statistical Analysis

All described variants are given via Mean ± Standard Deviation (SD) if continuous, or via percentages if non-continuous. Statistical analysis also included adverse events, and coagulative and blood chemical parameters. Kaplan-Meier method was used to analyze patient survival. Pre- and post-treatment diameters of the lesions and ablated zones were compared using a paired-sample *t*- tests.

Results

From October 2017 to April 2018, 15 patients (mean age: 66.1 ± 10.2 years, age range: 45-88 years) with primary non-small cell lung cancer (NSCLC; 5 patients) or secondary (10 patients) pulmonary tumors underwent 18 RFA sessions using a monopolar 15G ICW electrode under CT scan guidance for the treatment of a total of 22 lesions. Technical success and efficacy, as previously defined, were obtained in all patients.

In all patients, the diagnosis of pulmonary tumors with histologic characterization was obtained following a transbronchial or percutaneous transthoracic needle biopsy. All the enrolled

patients were not candidates for surgery because of the advanced disease stage associated with a poor cardiopulmonary status (n= 4), coexistent medical problems or advanced age (n = 4), concomitant extrapulmonary diseases (n= 6) or refusal to undergo surgery (n = 1). Mean tumor size was 2.8 ± 0.6 cm (range: 2-3.9 cm). One needle electrode insertion into the tumor mass was always obtained, with a fixed duration of ablation therapy of 12 min.

No unexpected adverse reactions were neither noted nor major complications and treatment-related deaths were observed. Minor complications were detected in 7 patients (7/15, 46.7%) and were mainly represented by pneumothorax. In 5 patients pneumothorax was classified as mild and did not require any treatment and in 1 it was classified as moderate and resolved with percutaneous aspiration. In another patient a moderate pneumothorax increased at chest radiography, performed after 3 h, and required a chest tube placement with subsequent resolution (1/15, 6.7%). In 1 patient was also described as a minimal pleural effusion during the procedure (1/15, 6.7%), which spontaneously resolved. In 5 patients a perilesional alveolar hemorrhage was described (5/15, 33.3%) and classified as mild, without any evidence of hemoptysis. All these complications were completely recovered without any surgical treatment and without increasing hospital stay. Mean hospitalization time was 2.5 days.

Mean maximum diameter of the ablated zones, obtained at 1-month follow-up CT, was 43.7 ± 4.3 mm, with a transverse roundness index of 0.84 ± 0.06.

Based on the mRECIST criteria, a complete response was observed in 19 out of 22 lesions (86.4%) and partial ablation was achieved in the remaining 3 (3/22, 13.6%; Figure 1). Among the latter lesions, two were re-treated with RFA, whereas one secondary pulmonary tumor, associated with the appearance of a new extra thoracic secondary lesion in the follow-up, was treated with chemo-radiotherapy. When considering the pre-treatment size of the lesions (range: 2-3.9 cm), a complete ablation was achieved for all tumors with a mean diameter < 3 cm (13/13, 100%) and for 6 out of 9 tumors with a mean diameter larger than 3 cm (6/9, 66.7%). Two patients showed a recurrence in the follow-up, one NSCLC primary lesion and one breast metastasis. Two patients died during the follow-up, 8 and 11 months after RFA respectively, one for distant metastasis and the other for acute exacerbation of the chronic obstructive pulmonary disease, One-year overall survival of 86.6% (13/15) and local tumor progression of 9.1% (2/22) were obtained.

Discussion

Pulmonary radiofrequency ablation (RFA) has become an increasingly adopted treatment option for primary and metastatic lung tumors, mainly performed in patients with unresectable lung neoplasms, due to advanced age or medical comorbidities. However, review of the literature demonstrated high variability in reaching a complete ablation, in the range of 38-97%[8,21-25]. Negative predictive factors for a complete tumor ablation are tumor size larger than 2 cm and its location in proximity to bronchi or large vessels[8,26-28]. These limitations and heterogeneous results are mainly related to relevant technical deficiencies in the delivery of RF energy to the lung. In detail, inflated lung tissue creates a high-impedance path for RF current flow that can be several times greater than the impedance encountered in the normal liver, even when considering a solid tumor within the lung[21]. Higher impedance reduces the energy deposition by RF generators, causing a lower temperature increase in lung tumors and, potentially, an increase in treatment failure rates[29,30]. The intrinsically high impedance of normal lung tissue is aggravated by other relevant limitations in RF ablation, such as the inability to heat carbonized or dried tissue or to overcome even moderate heat sinks (e.g., vessels larger than 3 mm in diameter)[31,32]. To solve these inherent issues of RFA in the treatment of lung malignancies, ablation should produce a larger coagulation area, including the lesion and a safety margin. Internally cooled (IC) electrodes have been demonstrated to decrease tissue impedance by avoiding charring and to increase the size of the necrotic area significantly compared with conventional electrodes. However, the zone in which these electrodes prevent overheating is limited[33]. Several investigators demonstrated the possibility of increasing RF tissue heating and coagulation by altering electrical and/or thermal conduction through the injection of saline into the tissues during RF ablation. With this method, the saline solution is injected into the tumor through the side hole of the needle electrode, perfusing the neoplastic tissue around

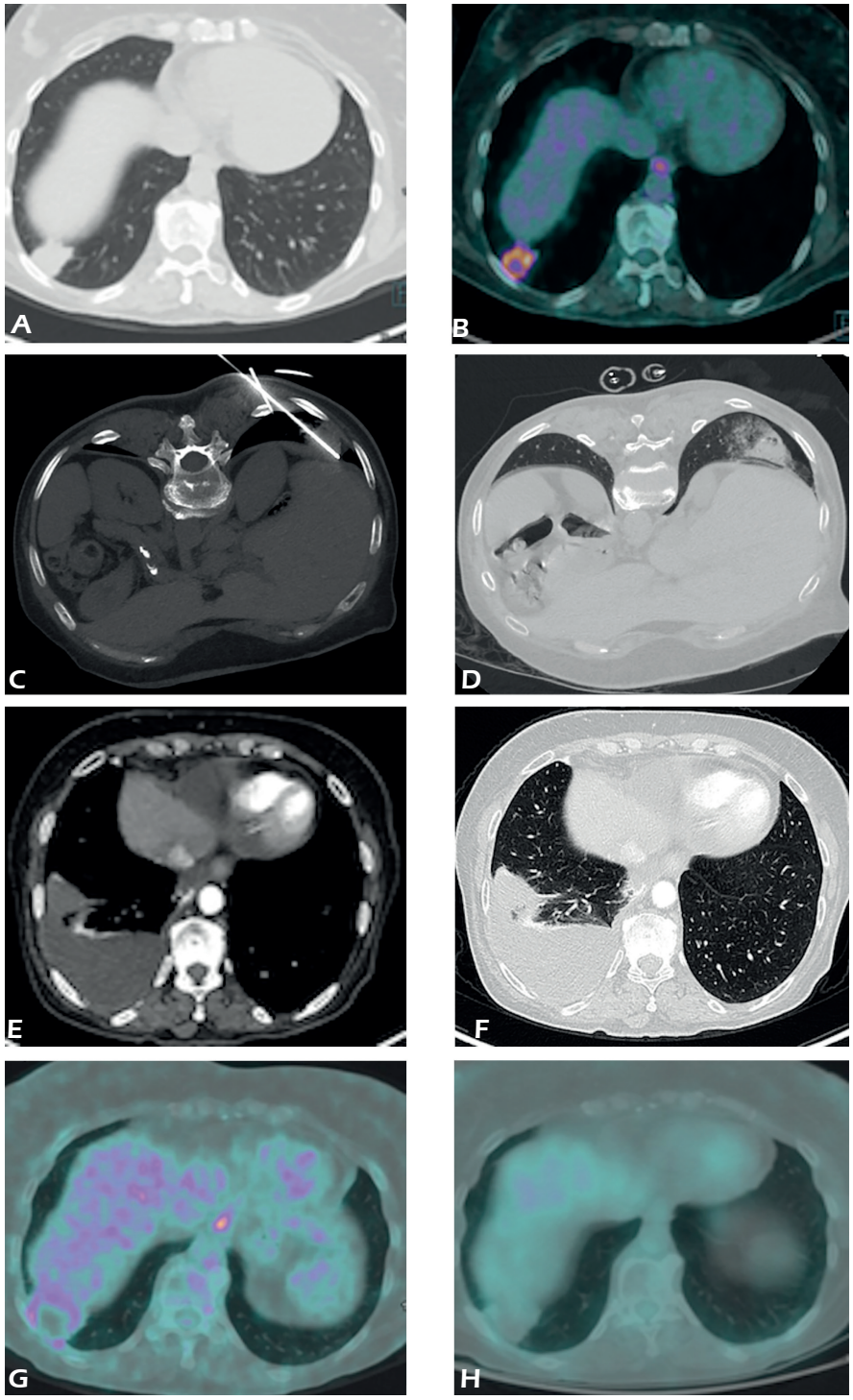

Figure 1. 58-year-old woman with single lung metastasis from parotid gland cancer. CT image in axial plane ***(A)*** shows a 32 × 24 mm lung parenchymal nodule in right lower lobe, with high FDG uptake on PET-CT ***(B)***. Pulmonary ablation of the lesion using a 15G jet-tip electrode, after creating iatrogenic pneumothorax to displace lung far away from diaphragm, was performed ***(C)***. Immediate post-procedural unenhanced CT-scan shows peripheral lesion ground-glass opacity due to edema, inflammation and mild hemorrhage ***(D)***. 1-month contrast-enhanced CT axial images ***(E-F)*** show diffuse hypoattenuating necrotic nodule with intralesional air bubble and peripheral mild, thin and smooth enhancement and pleural omolateral suffusion, as sign of pleural reaction. PET-CT exam performed 3 months after treatment ***(G)*** shows photopenic central area with mild peripheral hypermetabolic component, due to inflammatory reaction, without residual vital tumor, as confirmed by complete absence in FDG uptake at 6-month PET-CT scan follow-up ***(H)*** (metabolic complete response).

the needle tip. The electrical conductivity of the RF in the targeted tissue is increased and tissue vaporization and charring are prevented, thus increasing the volume of coagulation necrosis[34-36]. However, the uneven diffusion of large amounts of the saline solution may increase the risks of distal heating and ablation of non-tumoral areas. ICW electrodes, which simultaneously provide internal cooling and interstitial saline solution infusion, have been developed to overcome the limitations of IC and saline-perfused electrodes, preventing any rapid increase in impedance, with higher current delivery. Furthermore, the microhole of ICW electrodes permitted a controlled rate of saline infusion resulting in consistent and large ablation volumes[37]. There are few reports evaluating ICW electrodes for the treatment of hepatic or pulmonary malignancy in humans[32-37]. As far as we know, this study is the first to evaluate the safety and efficacy of 15G ICW electrodes in primary or secondary pulmonary malignancies. In detail, the diameter of an electrode is clearly known to be associated with the size of the ablation zone. Theoretically, as the diameter of an electrode becomes larger, the contact surface of the electrode with the surrounding tissue becomes bigger thereby increasing the active electric field[38]. As a result, an electrode with a larger diameter is likely to create a larger ablation zone. In our case series, the combination of these technologic advances was safe and effective, without major complications. Minor complications, mainly represented by spontaneously resolved mild pneumothorax, were detected in 46.7% of patients. This technique also resulted in consistent and large ablation volumes, regardless of the location of the lesions, not influenced by surrounding tissue or bronchial and/or vascular structures. It could be attributable to the delivery of a greater energy power by this type of electrode into the lung tissue, secondary to the larger diameter and the low impedance due to the diffusion of saline solution around the electrode. We found that RFA using such electrodes afforded a high technical success rate, with a complete ablation at 1 month achieved for 86.4% of tumors (19 out of 22 tumors). It is also relevant to underline that in regards to lesion size, a complete response was obtained in all the pulmonary lesions smaller than 3 cm in size, as well as in 66.7% of the lesions larger than 3 cm. These results seem to demonstrate that such electrodes have the potential to overcome the above-mentioned limitations of a standard RFA approach, also in the treatment of pulmonary lesions larger than 3 cm. Furthermore, combining cooling and saline perfusion effects it was also possible to obtain a predictable necrotic treated area, as demonstrated by the low standard deviation of mean maximum diameter of the ablated zones obtained (43.7 ± 4.3 mm), and a spherical necrotic area, as demonstrated by the transverse roundness index obtained, close to 1 (0.84 ± 0.06). These results were consolidated by the evidence observed in the follow-up, with a high overall survival rate (1y: 86.6%) and a low local tumor progression rate registered (1y: 9%).

The main limitations of the current research are the inclusion of patients treated at only one single center and the small number of patients and lesions included. However, it was a preliminary study mainly aimed to assess the safety and feasibility of this advanced electrode system used in RFA treatment of pulmonary malignancies, to adequately sample a future larger multicenter prospective trial. Furthermore, the work is lacking a control group. As a matter of fact, it would be very interesting to compare 15G ICW electrodes with multiple electrode ablation systems as well as with microwave ablation electrodes that claim to create larger lesions. It would be interesting to perform a randomized trial in terms of safety, repeatability, and efficacy in pulmonary malignancies larger than 2 cm in size, to clearly define the best procedural technique to be used.

Conclusions

We showed that percutaneous RFA using 15G ICW electrodes seems to be a safe and effective treatment option for patients with unresectable primary or secondary pulmonary malignancies for advanced age or medical comorbidities, providing larger and spherical necrotic ablated area than the conventional technique, with successful local tumor control and high overall survival rate.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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