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Introduction. *Recently, percutaneous thermal ablation of focal malignancy has received much attention due to its promising results in the treatment of primary and secondary neoplasms. Its feasibility, toxicity and efficacy on lung tumors have been evaluated through a research program, started in January 2001, whose first three preliminary phases and their results are reported herein.*

Methods. *Radiofrequency thermal ablation (RFA) was initially performed on lung tissue in an animal model (rabbit) and on lung tumors in two human models. A 150 W automatic generator (Model 1500, RITA Medical System, Mountain View, CA) and multiple electrode device (StarBrust XL, RITA Medical System, Mountain View, CA) were utilized for all the phases. It consists of a 15-gauge needle with nine deployable electrodes which open laterally in the flower-like manner up to 5 cm. The percutaneous approach was utilized in the animal model, under fluoroscopic guidance. In the human models, instead, radiofrequency ablation of a lung tumor was performed on the bench just after surgical resection in the first model, and via open thoracotomy just before surgical resection in the second model. The target temperature was 90°C in all the cases. It was maintained for 4 minutes in the animal model (with electrodes deployed 1 cm) and 20 minutes in the human models (with electrodes deployed 5 cm). Animals were euthanized at programmed intervals (day 0, 1, 3, 15, 30) and their specimens, as well as those of the human models, underwent pathological study.*

Results. *Radiological and pathological examinations on 15 rabbits assessed the efficacy in producing a limited lesion without significant toxicity and permanent damage to peripheral parenchyma. In the human models, pathological study assessed complete ablation*

A preliminary study on thermal ablation of lung tumors

Wstępne badania oceniające skuteczność termoablacji w guzach płuc

Marcello Carlo Ambrogi[1], Gabriella Fontanini[3], Riccardo Lencioni[2], Olivia Fanucchi[1], Laura Crocetti[2], Pinuccia Faviana[3], Chiara Franchini[2], Alfredo Mussi[1], Carlo Alberto Angeletti[1]

[1]Thoracic Surgery – Cardiac and Thoracic Department and [2]Radiology – Department of Oncology Transplants and New Technologies, Via Paradisa 2, 56124 – Pisa, Italy; [3]Pathology, Department of Oncology Transplants and New Technologies, Via Roma, 56100 – Pisa, Italy

INTRODUCTION

Percutaneous radiofrequency ablation is an emerging technique to induce thermal injury in several kinds of tumors. This method has been successfully used for the treatment of hepatocellular carcinoma [1], hepatic metastases [2] and osteoid osteoma [3]. Moreover, many studies report the feasibility of this technique on lytic vertebral metastases [4], renal cancer [5, 6] and brain primary and secondary lesions [7]. Thin, metallic probes, similar to aspiration biopsy needles, are percutaneously inserted into the lesion using computed tomography scanning (CT) or ultrasound guidance. An alternating current operating in the frequency of radio waves is emitted from the tip of the needle-electrode, which is placed directly into the tissue, in order to achieve a target temperature (in most cases 90°C). Thus coagulative necrosis is induced in a limited rounded area of tissue and in a controlled manner. Recent technologic improvements have permitted the creation of thermal necrosis volumes up to 5 cm in diameter with a single percutaneous insertion of new multiple electrode devices, thus enabling successful ablation in a single treatment session [8].

This paper discusses the first three preliminary experimental phases of a more extended state financed research program. The aims of this complex research program were to verify the possibility to transfer RFA technique to the lung and its tumors, to assess efficacy and safety of the procedure in three experimental models before we proceed to a clinical trial (which is started and still in progress). Moreover we evaluate a new device with multiple deployable electrodes.

MATERIALS AND METHODS

This study was led with the approval of the local ethical committee for human research and animal care (approval code number 1265/2001 and 02/133-2001).

of the tumor on 7 out of 10 treated cases. Instead, in 3 cases the residual clusters of neoplastic cells were seriously damaged.

Conclusions. *RFA seems to be safe and efficacious in the treatment of lung tumors. An array with deployable electrodes seems to be preferable to avoid multiple insertion. Now, clinical trials of percutaneous CT-guided RFA are required to confirm these preliminary results and to define which patients qualify for this treatment.*

Key words: lung cancer, pulmonary tumors, radiofrequency ablation, percutaneous thermal ablation.

Research design

The purpose of the study was to progressively investigate feasibility, safety and efficacy of RFA on the lung parenchyma and its tumors, by means of three experimental samples. An animal model, rabbit, was adopted to take familiarity with the procedure and to verify its feasibility and safety. Two human models were utilized to confirm feasibility and safety, and to assess effectiveness of the technique.

Radiofrequency generator

In all the phases of the study, we utilized the new model of a generator able to provide monopolar radiofrequency (RF) energy to perform coagulation and ablation of soft tissues (Model 1500, RITA Medical system, Mountain View, CA). This is an automatic apparatus with a maximum power output of 150 W (460 Hz). It has multiple temperature displays as well as impedance and power monitoring. The energy is transferred into the tissue by means of a new disposable array (StarBrust XL, RITA Medical system, Mountain View, CA). It consists of a 15-gauge needle with nine deployable electrodes which open like a flower up to 5 cm (Fig. 1). Five electrodes are equipped with a thermocouple in order to continuously measure the temperature inside the tissue. Two dispersive electrode pads are available to ground the current and to reduce risks of skin heat injuries. Once the system is powered up, the physician can set the parameters of the ablation, such as, the mode of operation, the target temperature, the ablation time at target temperature and the maximum power delivery level, which can be modified at any time during the procedure.

Fig. 1. The array with the nine electrodes completely deployed (StarBrust XL, RITA Medical system, Mountain View, CA)

Animal model

RFA was performed on pulmonary tissue of fifteen rabbits (White New Zealand) whose weight ranged from 3.8 to 4.1 kg. Ketamine (50 mg/kg) and xylazine (5 mg/kg) were administered to provide initial anesthesia. Booster injections (1/10 of the initial dose) were administered as necessary. Respiratory activity was kept in a spontaneous manner. Two grounding pads were placed on each shaved leg of the animals. After a small skin incision, using an aseptic technique and under radioscopic guidance, the probe was inserted in the right lung of each rabbit. The needle-electrode was inserted between the 7th and 9th intercostal space, in the right lower lobe, using a posterior approach in the effort of minimizing the number of pleural surfaces to traverse. After radiological confirmation of the needle position, the 9 electrodes were deployed for 1 cm in the lung parenchyma (Fig. 2). Radiofrequency was then applied for 4 minutes at the target temperature of 90°C. During the procedure, the rabbits were carefully monitored for signs of discomfort. Wattage, tissue impedance and probe tip temperature were continuously controlled and recorded every 30 seconds during the entire

Wstęp. *W ostatnim czasie przezskórna termoablacja ognisk nowotworowych stała się popularna głównie z powodu obiecujących wyników uzyskiwanych zarówno w przypadku nowotworów pierwotnych, jak i wtórnych. Funkcjonalność, toksyczność i skuteczność termoablacji w leczeniu guzów płuc były oceniane w badaniu klinicznym rozpoczętym w styczniu 2001r. W niniejszej pracy opisano wyniki trzech wstępnych faz badania.*

Metody. *Początkowo termoablacja przy użyciu fal o częstotliwościach radiowych nowotworów płuc oceniana była w modelu zwierzęcym (króliki) oraz w dwóch układach u ludzi. We wszystkich badaniach wykorzystywano automatyczny generator o mocy 150 W (Model 1500 RITA Medical System, Mountain View, CA, USA) oraz układ elektrod (StarBrust XL, RITA Medical System, Mountain View, CA, USA) składający się z igły w rozmiarze 15 oraz dziewięciu elektrod otwierających się bocznie na kształt kielicha kwiatowego (do 5 cm). Terapia przezskórna była stosowana w modelu zwierzęcym po naprowadzeniu fluoroskopowym. U ludzi natomiast, w jednym układzie ablacja guza nowotworowego falą o częstotliwości radiowej była przeprowadzana bezpośrednio po jego resekcji, a w drugim układzie poprzez torakotomię tuż przed resekcją. Temperatura docelowa we wszystkich przypadkach wynosiła 90°C i była utrzymywana przez 4 min w modelu zwierzęcym (elektrody obejmowały obszar 1 cm) i przez 20 min w modelach ludzkich (elektrody obejmowały obszar 5 cm). Zwierzęta były poddawane eutanazji w określonych punktach czasowych (dzień 0, 1., 3., 15., 30.), a uzyskane od nich preparaty, równolegle z preparatami uzyskanymi w modelach ludzkich, były poddawane badaniom histopatologicznym.*

Wyniki. *W modelu zwierzęcym wykazano, że termoablacja miała działanie ograniczone do określo-*

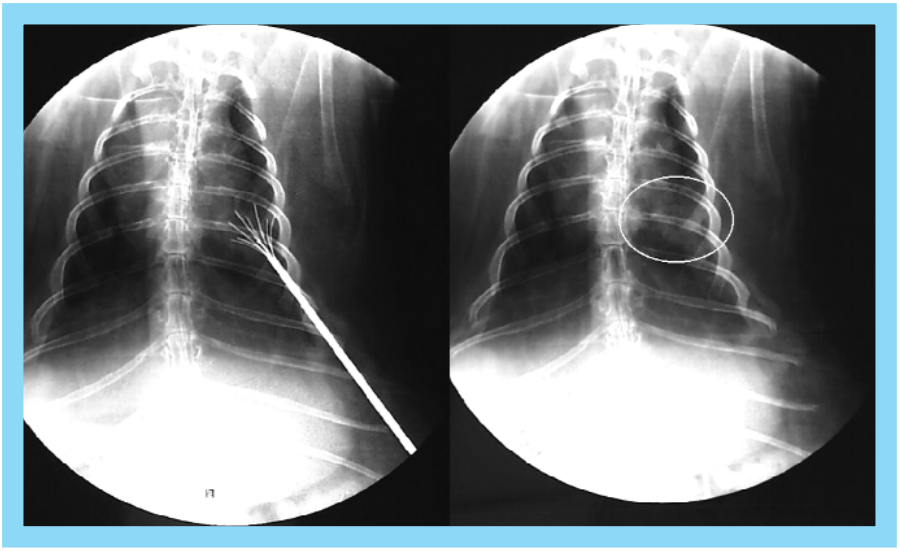

Fig. 2. The array is inserted in the right lower lobe of the rabbit lung under radioscopic guidance and the electrodes deployed for 1 cm. After ablation a rounded opacity is visible in the site of radiofrequency application

procedure. The total time of thermal ablation (the time at target temperature plus the time to reach target temperature and the time stopped due to higher impedance) was 7 minutes on average. At the end the electrodes were retracted and the needle was drawn out slowly with a rotatory motion, at the temperature of 75°C (track ablation mode), to minimize the risk of pneumothorax and haemothorax. Then a radioscopic control was performed to assess the presence or absence of complications, as well as the extension of the thermal lesion that appeared as a rounded opacity in the lung parenchyma (Fig. 2). The rabbits were euthanized with a pentobarbital overdose: three rabbits after the procedure, three after 24 hours, three after 3 days, three after 15 days and other three after 30 days. After the euthanasia, the right lungs were harvested in toto and processed for the anatomopathologic study.

Human models

RFA was performed on lung tumors in two experimental human models. The second one was close to physiologic conditions. All the treated lesions were lung carcinomas and their maximum diameter was 35 mm (mean 27 mm, range 25-35 mm).

The ex-vivo model

Three adenocarcinomas and two squamous cell carcinomas in five freshly removed pulmonary lobes underwent RFA. After the surgical resection, the lobar or segmental bronchus was intubated with an orotracheal pediatric tube and then ventilated manually by ambient air using an ambu balloon. On the bench the lobes were placed on a grounding pad and, by digital palpation guidance, the needle was inserted into the tumors. Once the system was powered up, we settled the parameters of the ablation, such as the ablation time, the target temperature and the power delivery level. Then the electrodes were gradually deployed to the maximum diameter of 5 cm and the target temperature of 90°C maintained for 20 minutes, in order to induce a coagulative necrosis area at least 1 cm larger than that of the tumor diameter. After thermal ablation, pulmonary lobes were immediately processed for the anatomopathologic study.

The in-vivo model

Four adenocarcinomas and one squamous cell carcinoma were treated with radiofrequency

nego obszaru, nie wiążące się z toksycznością oraz z trwałym uszkodzeniem parenchymy. W modelu ludzkim wykazano całkowitą ablację guzów w 7 z 10 badanych przypadków. W pozostałych 3 ogniska komórek nowotworowych były silnie uszkodzone.

Wnioski. *Termoablacja przy wykorzystaniu fali o częstotliwości radiowej wydaje się być bezpieczną i skuteczną strategią leczenia guzów płuca. Wykorzystanie systemu z rozchodzącymi się elektrodami umożliwia przeprowadzenie termoablacji bez potrzeby wprowadzania szeregu pojedynczych elektrod. W tej chwili konieczne jest przeprowadzenie badań klinicznych oceniających skuteczność przezskórnej termoablacji pod kontrolą KT.*

Słowa kluczowe: rak płuca, guzy płuc, ablacja falami o częstotliwości radiowej, przezskórna termoablacja.

thermal ablation in 5 patients during open surgery, just before the surgical resection. The electric current was grounded by means of two pads, which were placed on each patient's legs. A thoracotomy, with the patients under general anesthesia and selective tracheobronchial intubation, was performed to allow surgical resection. After the isolation of the lobar hilum, in order to permit quick surgical resection in the case of complications, the needle was inserted into the tumor by digital palpation guidance and the electrodes were deployed. Then, introducing into the tumor the multiple electrode array by digital guidance, at the same target temperature of the ex-vivo model and with the same ablation parameters, RFA was performed. The lung was ventilated and vital signs of the patients recorded. At the end of the procedure, the electrodes were retracted and the needle was withdrawn slowly with a rotatory motion. A lobectomy was then completed as programmed. The specimens were sent for the anatomopathologic study.

Anatomopathologic study

Animal and human tissue specimens were sectioned across the maximum diameter and macroscopic findings recorded. Then they were preserved in formalin solution for microscopic analysis. Multiple sampling was performed in the treated area: two samples 1 cm from the treated area; two samples 2 cm from the treated area and other two in the surrounding parenchyma far from the thermal lesion. The sections, by microtome, underwent hematoxylin-eosin staining and they were examined by light microscope using low (4-10x) and high (400x) zoom lenses.

RESULTS

Animal model

We had no mortality or major complications. Only one case of partial pneumothorax was observed.

The values of impedance were remarkably elevated in this model (450 Ω on average) and often exceeded 999 Ω determining the stop of the generator. In these cases the ready manual relighting avoided reductions of the target temperature below 70°C.

The anatomopathologic study was performed on the right lung of all the 15 rabbits, sacrificed after RFA at the established times (as previously described). On gross examination thermal lesion's diameter was 12 mm on average (range of 9-17 mm). The lesions examined within three days were on average 5 mm larger than those examined on the 30th day. The lesions appeared spherical with a central cavitation rounded by black carbonized and white coagulated tissue. A peripheral red band-like zone well demarcated the thermal lesion from the surrounding normal-appearing parenchyma. After 15 days, a thin rim of light fibrous scar tissue was observed at the periphery of the lesion, replacing the red damaged area. On the 30th day this red area, surrounding the residual central thermal coagulum, was completely replaced by light scar tissue. A peripheral area of hemorrhage, surrounding thermal lesion, was observed in two of the 7 lungs harvested within 72 hours, probably due to direct vessel damage by the electrodes before radiofrequency applications. Such complication was not observed in the lungs of animal euthanized later, suggesting a complete resolution with time.

In the specimens harvested immediately, 1 and 3 days after RFA, the histopathologic exam

showed a central area of bloodless and devitalized tissue with coagulation necrosis. At the periphery, there was a well-demarcated 1-centimeter reddish area of early inflammation with edema and hyperemia, probably due to vascular mechanism in response to the heat. Tissue congestion with acute inflammatory cells infiltration characterized this surrounding area, with the alveolar spaces filled with proteinaceous fluid. No anatomopathologic alterations, instead, were visible in the distant parenchyma (two centimeters or more from the periphery of the necrotic area). The specimens obtained on the 15th day showed the central coagulative necrosis surrounded by granulation tissue while the inflammatory cells were cleaning up damaged tissue and leading the scar tissue synthesis. The specimens obtained on the 30th day showed a central bloodless necrotic area well demarcated from peripheral light granulation tissue, while the new connective tissue formation had completely replaced the red damaged area.

Human ex-vivo model

Gross analysis showed spherical bloodless necrosis lesions with a diameter of 58 mm on average (range of 52-61 mm). The lesion was composed of a central probe hole in a tan thermal coagulum characterized by the presence of carbonized tissue in some cases. The central necrotic lesion was surrounded by tissue congestion area. This hyperemic reddish area was well demarcated from surrounding normal-appearing parenchyma. Histopathologic examination showed coagulated tissue with cellular debris. Clusters of viable but injured tumor cells were found in one case, surrounded by a wide necrotic area. Early inflammation, edema and damaged alveoli were seen within 1 cm peripheral from the necrotic nodule. No anatomopathologic alterations were seen in the surrounding distant parenchyma (two centimeters or more from the periphery of the necrotic area).

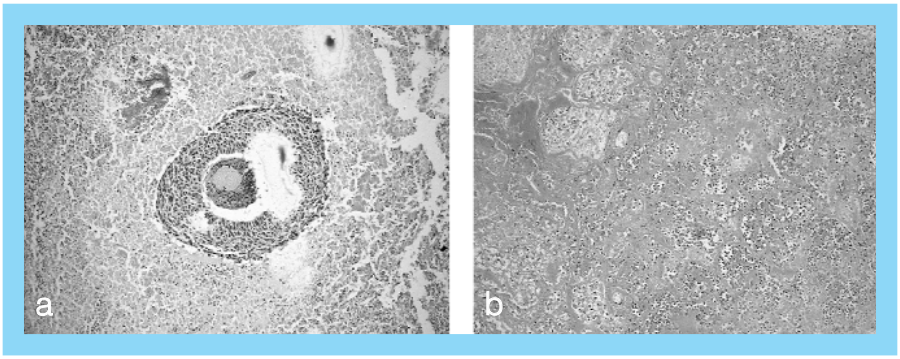

Fig. 3. The anatomopathologic examination with hematoxylin-eosin staining show a cluster of neoplastic cells still viable but significantly damaged and surrounded by necrotic tissue (a), and a completely destroyed tumor with coagulative necrosis (b)

Human in-vivo model

On macroscopic examination lesions appeared as a rounded bloodless necrotic tissue with a diameter of 52 mm on average (range of 50-57 mm). Lesions observed in this group were on average 0.6 cm smaller than those of the ex-vivo model with the same electrodes deployment. A central cavitation was rounded by white coagulated tissue partially carbonized in some cases. A peripheral reddish rim was well demarcated from both central coagulated tissue and the surrounding normal-appearing parenchyma. Microscopic examination showed the presence of coagulative necrosis with necrotic cells, characterized by pyknotic or cardiocinetic nuclei and cytoplasmatic hypereosinophilia (Fig. 3b). Clusters of viable but injured tumor cells were observed in two cases. They were completely surrounded by necrotic tissue, without blood supply (Fig. 3a).

DISCUSSION

The first experience of thermal ablation of a pulmonary tumor using radiofrequency was described by Lilly and his colleagues in 1983 [9]. The study, pre-clinical on an animal model (dog), was aimed to induce a coagulative necrosis in a bronchogenic tumor of 5 cm. The authors noticed that an important increase of the temperature could be obtained by introducing an electrode inside the tumoral mass and applying radiofrequency energy. The result was satisfactory without meaningful damage to the surrounding pulmonary parenchyma. This study first demonstrated the efficacy of radiofrequency in ablating a lung tumor in an animal model.

But it was Goldberg et al., in 1995, who first experienced the feasibility of the percutaneous application of radiofrequency to induce a thermal injury in the lung parenchyma [10]. Like in our animal model, they examined the possibility of thermal ablation of pulmonary parenchyma in a healthy rabbit by means of radiofrequency as an energy source. Using an aseptic procedure and by computed tomography (CT) guidance, the electrodes were inserted in the lower lobe of the right lung of eight rabbits. As in our experience, the lower lobe of the right lung was chosen because of its largest size and to minimize the number of pleural surfaces that were transgressed with the needle-electrode. Our rabbits' dimensions, instead, were bigger because of the necessity to introduce a larger needle. The target temperature, like

in our experience, was 90°C, maintained for 6 minutes in Goldberg's experience. We used a new array furnished with nine extensible electrodes which allowed the time of thermal ablation to be reduced to 4 minutes, inducing lesions with larger dimensions. In Goldberg's experience, the radiological control of the procedure was obtained with CT, while we used the radioscopic imaging. We chose the radioscopic guidance for its dynamical features that were helpful during introduction of the needle-electrode. Besides, with CT scanning Goldberg could study the correlation between the imaging and the anatomopathologic analyses, demonstrating correspondence of the lesion's dimensions. Anatomopathologic features described by Goldberg are in accordance with our own results and early coagulative necrosis was substituted by fibrosis within 30 days. The diameter of the lesions was 8 mm on average in Goldberg's experience and 12 mm in our experience, even if the time at target temperature was 2 minutes shorter. The multiple electrodes array, as expected, allows a better diffusion of radiofrequency energy and consequently extension of the thermal injury. But the most important aspect, similar in both experiences, is the auto-limitation of the thermal injury itself, which does not affect peripheral parenchyma. Furthermore, Goldberg observed that the dimensions of the lesion induced in pulmonary parenchyma were lower than those induced in other solid organs like the liver. He related these facts to the high impedance of the inflated lung that reduces propagation of radiofrequency waves. This behavior could prove to be useful in RFA of solid pulmonary neoplasms. In fact the energy would be adequately propagated in the solid tissue obtaining coagulation and necrosis, while the surrounding healthy parenchyma would be protected from air inflation with a kind of physiologic auto-delimitation of the thermal damage. On the other hand, air flow in the lung tissue could significantly reduce temperature to the periphery of the tumor resulting in incomplete ablation. These considerations stress how useful a multiple deployable electrodes array may be. It is able to better distribute the energy, and as a consequence the heat, to the periphery of the tumor too. Instead, multiple insertions of a single electrode device, described to achieve larger thermal lesions in solid organs, must be avoided in the lung due to the increasing possibility to develop complications such as a pneumothorax. This underlines again the advantage of a multiple deployable electrodes array which achieves larger thermal lesions with a single procedure.

Application of a multiple electrodes array in the lung was first performed by Putman et al. [11], in an big animal model (pig). First of all, he confirmed the possibility to induce radiofrequency thermal ablation of pulmonary parenchyma in a reproducible and controlled manner. They focused the study on anatomopathologic features. The thermal lesions turned out smaller than the expectations, with the surrounding pulmonary tissue undamaged except for a rim of reactive inflammation. He noticed that shape and size of the thermal lesion was influenced by the probe size, as well as blood and air flow. Similar anatomopathologic findings were observed in our in-vivo experience in the human model. Comparing the results of the in-vivo model with those of the ex-vivo one, it is noticed how blood supply is important to reduce and limit the thermal lesion. Lesions of the ex-vivo model, in fact, were larger than those of the in-vivo model, probably due to the absence of blood flow in the first one. Two cases of the in-vivo model showed persistence of clusters of viable neoplastic cells against one case in the ex-vivo model, probably underlining again the protective effect of blood flow against thermal injury. These findings suggest a different behavior of the different kind of tumors during thermal ablation treatment. It is expected that the more vascularised tumors will be best protected from thermal injury and consequently they will require more energy and longer application. In practice, these results suggested increasing time at target temperature from 20 minutes, as in the human pre-clinical models, to 27 minutes in the outstanding clinical trial.

First percutaneous radiofrequency thermal ablation of pulmonary neoplasms was again described by Goldberg on rabbits with pulmonary tumor induced by means of an injection of suspension of sarcomatous cells VX2 [12]. Seven rabbits with a tumor (diameter of between 6 mm and 12 mm) were treated for six minutes at 90°C, as in the previous study. The anatomopathologic examination, executed at several intervals of time from the treatment, showed the presence of a necrotic area with absence of neoplastic cells in 95% of the cases. Our ex-vivo and in-vivo human model substantially confirmed such results, with a complete necrosis of the tumor in 70% of cases. The residual clusters of vital neoplastic cells observed in 3 cases were sensitively injured, completely surrounded by necrotic tissue, and therefore probably destined to die themselves. Moreover, Goldberg observed that the area of induced necrosis, which had a medium diameter of 11 mm, was larger than the lesion produced in healthy pulmonary tissue (8 mm),

as it was expected for the lower electrical impedance offered in the solid neoplastic tissue.

CONCLUSIONS

The results of our experience, as well as those reported in the literature, assess feasibility, effectiveness and safety of RFA in the pulmonary parenchyma and its neoplasms. Particularly, our human in-vivo model by reproducing physiologic conditions with air ventilation and blood supply, assessed the efficacy in producing a necrosis area in a primary lung cancer without toxicity for the patient.

Moreover, multiple deployable arrays like the one utilized in our experience, with the same safety of a single electrode device, seems to be preferable for the greater loss of heat in the lung (due to blood and air flow). In this case it is possible to avoid multiple insertions of the needle, thus reducing the possibility of risky complications.

Obviously, such experimental models should be the first step to securely reproduce the procedure in clinical trials via the percutaneous access, as it usually happens in the liver and other tissues. Recently, as it was expected, a few papers reported the first clinical experiences of percutaneous RFA of lung tumors, generally showing good results [13-16]. We also carried on a clinical study, which is still outstanding and whose first promising results will be published as soon as they reach the programmed number of patients as well as an adequate follow-up [17]. Actually our preliminary clinical experience and the one of other authors seem to confirm feasibility of the procedure associated with very low toxicity and a good effectiveness in tumors smaller than 5 cm. But, to asses efficacy, above all in the long period, and to define correct indications and selection criteria, more patients and a longer follow-up are needed.

Despite all that, it seems realistic to foresee that in the future this technique will become another arrow to the arc of those physicians who fight against cancer, thus increasing therapeutic options for those patients with primary and secondary lung cancers.

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CORRESPONDING ADDRESS

Dr. Marcello Carlo Ambrogi
Dipartimento CardioToracico
via Paradisa 2
56124 - Pisa
Italy
tel. 0039-050-995211
fax 0039-050-577239
e-mail: m.ambrogi@med.unipi.it