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State of The Art in Alternative Treatments for Lung Cancer: Thermal Ablation Therapy

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ABSTRACT

Surgery is considered the best choice for stage I non-small cell lung cancer therapy and for selected patients with lung metastasis. However, surgery is often a high-risk procedure because of severe medical co-morbidities affecting this cohort of patients. Thermal Ablation **(TA)** has been recently proposed to achieve destruction of lung tumors whilst avoiding the use of general anesthesia and parenchyma resection, thereby limiting the invasiveness of the procedure. Two technique of TA based on tissue heating have been described: Radio Frequency Ablation **(RFA)** and Microwave Ablation **(MWA)**. Both are mini-invasive procedures, delivering energy to the tumor through single or multiple percutaneous needles introduced under guidance of computed tomography. The procedure may be performed under conscious sedation or general anesthesia to avoid pain caused by needle insertion and tissue heating. We have reviewed the literature and

reported our experience with the aim to understand whether these techniques are successful and should be proposed. In summary, we found that local efficacy is directly correlated to tumor target size: concerning RFA, tumors smaller than 2 cm can be completed ablated in 78-96% of cases; concerning MWA, according to the largest available study, 95% of initial ablations are reported to be successful for tumors smaller than 5 cm. Very few series provide survival data beyond 3 years. For nodules smaller than 3 cm, the registered survival rate is higher: 50% at five years. Data collected in the last 10 years allow to conclude that TA is an established alternative treatment for patients whose cannot undergo surgery because of compromised general condition. In the case of pulmonary metastasis, most authors agree to offer TA only if lesions are smaller than 5 cm.

INTRODUCTION

The preminent role of surgery as best therapy in stage I NSCLC has been universally accepted based on favorable outcomes [1]. In case of regional disease (stage II/IIIB) the combination of surgery, chemotherapy and/or radiotherapy is the standard protocol. On the contrary, the role of surgical resection for pulmonary metastasis has been discussed for years. Now a days, in case of few nodules and specific histology such as colorectal and kidney metastasis [2,3], surgery is widely considered a safe and effective treatment modality when complete resection is achievable and primary carcinoma is controlled.

However, surgery is often a high risk procedure because of severe medical (cardiac, respiratory, etc) co-morbidities affecting these cohort of patients: only 15% of patients with stage I/II meet the physiologic criteria for parenchyma resection [4].

Starting with these assumptions, any successful non-invasive local treatment allowing to avoid functioning parenchyma resection and prolonged general anesthesia, could be the key point in the management of patients not eligible for surgery. Traditionally, external beam Radio Therapy **(RT)** was considered the treatment of choice in these selected cases. Recently, based on excellent results, many Authors have suggested that overall survival after Stereotactic Body Radiation Therapy **(SBRT)** could be comparable to surgery [5]. However, most of the series concerning RT outcomes in terms of survival are less desirable when compared with surgery at 5 years [6].

In the last decades different innovative mini invasive therapies, alternative to surgery, have been developed to obtain tumor destruction without the use of general anesthesia and parenchyma resection.

Thermal Ablation **(TA)** is probably the most interesting among these options. At the beginning, TA was used in the treatment of bone, kidney and liver cancer; it has been introduced in the lung cancer management from 2000.Available techniques involve tissue freezing (cryoablation) or heating [Radio Frequency Ablation **(RFA)** or Microwave Ablation **(MA)**]. This chapter is limited to RFA and MA, which are the most commonly used methods.

There are no data available comparing TA with SBRT. However, in a recent literature review there was clear support for SBRT in the treatment of early NSCLC [7]. This review concluded that sterotactic ablative therapy offered a 5-year local control rate of 83.0-89.5% as opposed to 58-68% with RFA, which had a short follow up of only 18 months. Both overall survival and cancer-specific survival were also better with stereotactic ablative therapy with a 3-year overall survival ranging from 38% to 84.7%, and a cancer-specific survival of 64-88%, whereas overall survival data were only available for two radiofrequency studies and reported as 47-74%.

Lung thermal ablation can be used to treat both primary and secondary thoracic malignancies. The aim of treatment is generally to ablate all of the visible disease with the intention of achieving complete disease remission. Before treatment, it is obviously desirable to have histologic diagnosis, but this is often not possible, particularly for small lesions. In patients with a known malignancy, clinical context is usually sufficient evidence to progress to ablation of new metastases. In primary tumors or where there is clinical doubt, lung biopsy is performed prior to ablation.

MATERIAL AND METHODS

The Ablative Techniques

The ablative technologies utilize several sources of energy and different devices to damage the target tissue. Both RF and MW are mini invasive procedures since they deliver the energy to the tumor through single or multiple percutaneous needles.

RF ablation consists in an alternating electrical current with 10-200 W of power applied to the tumor via an interstitial electrode. Current delivered leads to ions agitation inducing the tissue heating. Heating is directly proportional to current density and is in inverse proportion with increasing distance from the electrode. When temperature between 60 and 100 °C is reached a coagulative necrosis of the target tissue is obtained.

To increase the ablation size different kinds of electrode have been developed such as cooled, clustered or multipolar electrodes [8]. However it is remarkable that independently by the needle characteristics, only one probe can be activated at one time. That brings an increasing in the procedure duration.

MW uses electromagnetic waves at frequency between 915 and 2450 MHz to rapidly accelerate the polar water molecules rotation and obtain energy conversion into heat. MW has several theoretical advantages over RF since energy is deposited over a larger active zone and higher temperatures are produced in less time. Moreover MW needle electrode has multiple antennae activated simultaneously increasing the ablation zone size and determining a procedure duration shorter than RF.

TA and Lung Tissue

TA determines a parenchyma thermal destruction without any specificity for cancer. The goal of TA is to induce a tissue damage of the target by heating cells to > 60°C such as to obtain a complete tumor and surrounding tissue necrosis. The extension of achieved ablation depends upon the unique characteristics of the tissue. As concerning lung parenchyma the presence of continuous blood-flow and air-flow adjacent to the target are the most important factor to be considered. In particular thermal conductivity and "heat sink effect" are the main obstacles in determining the procedure efficacy. Thermal conductivity is lower than in other organs, because of high air percentage, and create a difficulty to reach ablations with sufficient surrounding margins. "Heat sink effect" causes heat dissipation away from the target tissue due to blood and air flow thus limiting intended tissue damage. These two factors influence the effects of TA and have to be always considered before to decide which nodule to treat and the ablation modality.

Treatment Procedure

TA may be performed under either conscious sedation or general anesthesia to avoid pain due to needle insertion and tissue heating. Some Authors showed how general anesthesia is related to better outcomes probably correlated to the easier achievement of complete ablation [9].

Today CT is the only accurate image guidance modality for lung TA. It is real time and allows an adequate needle position. Moreover CT guarantees a direct post procedure evaluation of the ablation.

The patient is positioned on the CT couch to allow a safe access route. CT fluoroscopy with single shot axial image acquisition is the routine approach. Full CT helical imaging is used to confirm the position of the electrode with regard to both the lesion and any adjacent structures. Needle positioning is planned such that the predicted ablation zone encompasses the mass with an adequate margin. It is not necessary to pass the electrode directly through small lesions and a final position with the tip immediately adjacent to the metastasis is usually enough, providing the predicted ablation zone yields an adequate margin of safety. Larger lesions should be punctured as near to their centre as possible. Sometimes, it may be necessary to induce a pneumothorax or instill a fluid buffer using 5% dextrose to prevent thermal damage to adjacent structures. Depending on the size of the lesion, it may be necessary to perform several overlapping ablations to achieve an adequate treatment. We suggest to perform an immediate post-ablation chest CT, mainly to check for complications and to assess the adequacy of the ablation zone.

Imaging Follow-Up

Immediately after TA, lung tumor appears surrounded by a ground-glass opacity enlarging the diameter of tumor itself Figure 1. It represents a zone of ongoing necrosis. Ablation can be considered complete if ground-glass opacity margins are present and encircle all around the tumor target for a rim of at least 5 mm. Therefore ground glass opacity is an indirect predictor of future recurrence.

Over a period of a week, the GGO usually changes to more dense airspace opacification [10]. GGO represents a transition from vital to non-vital parenchyma, and the outer margin of the shadowing probably overestimates the zone of complete ablation by 3-4mm, emphasizing the need for an adequate treatment margin, analogous to the surgical margin in a resected cancer. It is suggested that the ablation zone should be at least 1 cm larger than the lesion [11]. De Bae`re et al. [12] showed that the ratio of post-treatment GGO to the pre-treatment tumor area was predictive of success. If the ratio was at least four, the rate of complete ablation at 4 months was found to be 96%. For a ratio of three or less, the success rate was 61%. Distant follow-up for lung cancer, according to the Response Evaluation Criteria in Solid Tumors **(R.E.C.I.S.T.)**, is usually based on changes in diameter of the nodule at CT scan. These criteria are obsolete to evaluate tumor treated with TA since ablation zones are intended to be larger than the target itself after the treatment. Moreover is known that tumor size increase in the first weeks after the procedure because of tissue arrangements. On the opposite, contrast enhancement and its post ablation changes may differentiate malignant from necrotic tissue. Between 1 and 3 months, the margin of the ablation zone becomes better defined and denser, due to organizing fibrosis. Centrally, a variety of appearances can be present. Cavitation is common, occurring with an incidence of 14% at 1.5 months. At 3 months, the ablated lesion is usually slightly larger than baseline because of the residual edema, but by 6 months, the ablation zone is usually starting to decrease in size. After this period, any increase in volume is very suspicious of recurrence [13]. In our experience the enhancement above baseline density is unusual after 6 months, and when present should again raise the suspicion of re-vascularization and thus local recurrence. Between 3 months and 1 year, the ablation zone usually shows retraction Figure 2. The end appearances are variable and can range from a rounded area of relatively dense scarring to a barely perceptible region of atelectasis or fibrosis. In our experience, the track of the ablation electrode is often clearly visible, sometimes persisting in excess of 6 months. In conclusion, second CT should be performed 4-8 weeks after the ablation to determine the baseline for future comparisons. Subsequent evaluations should show a progressive decrease in size of the tumor until a definitive disappearance or replacement by a scar. CT densitometry is also valid criteria to determine ablation completeness or tumor progression. PET/CT evaluate metabolic activity of tumor. It is not useful in the first weeks after the procedure since tissue arrangements may create false positive findings, but at subsequent follow up SUV of the ablated tumor is expected to decrease. Based on these criteria PET/CT has the highest sensitivity among the imaging techniques for the evaluation of treatment response [14]. When the ablated zone presents an increased SUV or a nodular growth in size beyond 3 months from the procedure, relapse of disease has to be considered. In these cases a biopsy is recommended. PET-CT may detect recurrence earlier than does conventional CT, but there is limited evidence to support this [14-17]. In a study of 68 patients, a SUV of 8 was found to be a predictor of improved disease-free survival. After treatment, reduced recurrence-free survival correlated with an unfavorable fluorine-18 fludeoxyglucose uptake pattern, the absolute value of the post-RFA SUV and increases in SUV over time after ablation [18]. To conclude, we suggest to determine the ground glass rim immediately after the procedure in order to appreciate the obtained effect. Then, follow-up is based on CT scan one month after the ablation to obtain a baseline in size and to determine contrast enhancement. Then we use periodic CT/PET scan every 3 months to determine both local and distant disease control.

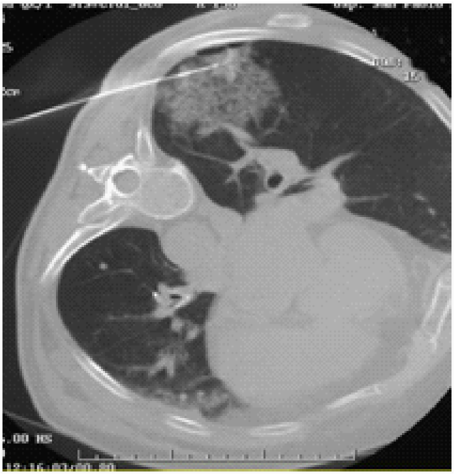

Figure 1: after the procedure, a ground glass area around the nodule appears and guarantees the completeness of the necrosis.

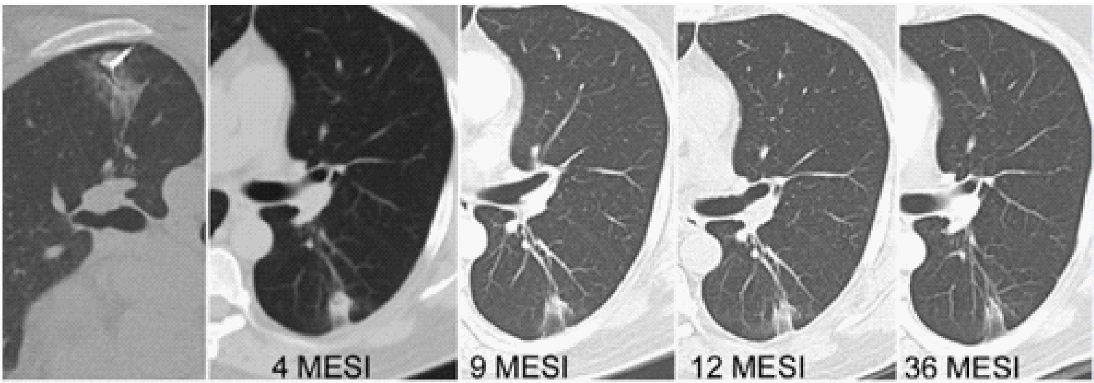

Figure 2: post procedurale edema and progressive decrease in size of the tumor until a definitive disappearance or replacement by a scare in 36 months

RESULTS

Outcomes

The use of ablation in primary lung tumors is due to the evidence that one-third of Non-Small-Cell Lung Cancers **(NSCLCs)** are unsuitable for surgery and to the evidence of similar outcomes when thermal ablation and sublobar resection was compared. As yet, there is no data available comparing ablation with SBRT. However, in a recent review of the literature, there is clear support for SBRT in the treatment of early NSCLC [7].

To evaluate outcomes after TA treatment, local efficacy and survival are the priority data. Is universally accepted that local efficacy is directly correlated to tumor target size. As regarding RFA, tumor < 2 cm can be completed ablated in 78-96% of cases [19,20]. As concerning MW, according to the largest available study [21], 95% of successful initial ablation are reported in a population of 66 treatments for < 5 cm lung cancer.

Long survival data for both RFA and MW are scarce and not mature since these technique have been demonstrated efficacy and introduced in lung cancer management in the year 2000. Few series provide survival beyond 3 years. Simon [22] in a series of 75 NSCLC treated with RFA, demonstrated a median survival of 29 months with an overall survival of 78, 57, 36, 27 and 27% in the first 5 years. Better survival was registered for nodules < 3 cm with a survival rate of 50% at 5 years. Wolf [23] in a series of 66 MW ablation sessions for primary and secondary lung cancer, found that 26% of patients had residual disease, predicted by using index size of larger than 3 cm ($p = 0.01$). Actuarial survival was 65, 55 and 45 % at 1, 2 and 3 years from ablation. Survival was not affected by index size of 3 cm and by residual disease.

In our personal experience of 26 cases of primary (16 patients) and secondary (10 patients) lung cancer treated with RFA, the median survival was 30 months. Survival was 100% at 6, 95, 2% at 12, 71.9% at 24 and 21.6% at 32 months. There were relapses in every patient with lesions bigger than 3 cm, in 4 with primitive cancer smaller than 3 cm and in 3 with metastasis. Disease-free survival was 25 months divided as follow: 100% at 6, 86.3% at 12, 47.4% at 24 and 17.8% at 32 months [24].

As concerning TA in lung metastasis treatment, its use is indirectly supported by The International Registry of Lung Metastases reported in 1997 that patients with completely resected lung metastases had a 5-year survival of 36% as opposed to 13% for patients with no surgery. It was also noted that those patient with fewer metastases and a long disease-free interval had an improved survival [25]. These data are the main driver for the use of aggressive local ablative therapy for metastatic disease. The Response to Radiofrequency Ablation of Pulmonary Tumors (RAPTURE) multicentre prospective trial, which reported in 2008 and included patients with both primary and secondary tumors, showed a 99% technical success rate and a 2-year overall survival rate of 48% in patients with NSCLC and 66% in patients with pulmonary metastases from a colorectal primary [9]. Many small observational studies suggest a survival advantage when small volume disease is treated by ablation.

As observed in NSCLC, local control for all tumor types does seem to be influenced by the size of the treated lesions, with lesions in excess of 3 cm at the time of treatment having a much higher incidence of local progression [26].

A study of 71 patients with 155 unresectable colorectal lung metastases showed an overall survival of 46% at 3 years. Three-year survival data for patients with lung metastases from a colorectal primary have recently been reported as 57–77% [27,28]. The presence of treated liver metastases, the number of pulmonary metastases ablated, previous treatment with systemic chemo- therapy or prior lung resection did not appear to alter outcome.

Lee et al. [29]. Described success rates of only 38% for tumors= 50mm in diameter. In a study of 198 colorectal lung metastases, the 1, 3 and 5-year local tumor progression rates were found to be 10.1%, 20.6% and 20.6%. 1, 3 and 5-year survival rates were 83.9%, 56.1% and 34.9% with a median survival of 38 months. In this study, a maximum tumor diameter of 3cm, single lung disease, lack of extra-pulmonary metastases and normal carcino embryonic antigen were associated with a better prognosis [30].

Local ablation has been used in multiple other tumor types, including sarcoma, kidney, hepato cellular carcinoma, breast and neuro endocrine tumors.

A recent article reported a median 2-year progression-free survival of 23% in patients with low volume sarcoma metastases treated with ablation [31].

In a small retrospective study of 39 patients with unrespectable renal cell carcinoma pulmonary metastases, the Authors found a possible survival advantage for those treated with RFA. Patients were divided into two groups, one where treatment was with curative intent and a second group where there was extra pulmonary disease or other adverse features. The overall survival rates in the curative and palliative groups were 100% and 90% at 1 year, 100% and 52% at 3 years and 100% and 52% at 5 years, respectively [32].

Hiraki et al. [33] reported results on the outcome of patients with lung metastases from hepato celluar carcinoma. In 32 patients where RFA was preformed with curative intent, the overall survival was 87% at 1 year and 57% at 2 and 3 years with a median follow up of 20.5 months.

Palliation Therapy

The role of ablation in tumor cytoreduction is controversial. Early reports of debulking hepatic metastases from breast carcinoma suggest that the technique is feasible, but it is difficult to draw any firm conclusions with regard to survival advantages. There are case reports of symptom relief after debulking of thoracic malignancy, but this remains an area where further investigation is required. There may be a role for the debulking of small renal cell carcinomas in the context of metastases.

Tumor Recurrences

Local recurrence is the commonest pattern of relapse after treatment. Tumor type is a strong predictor of recurrence with higher control rates seen in metastases from colorectal cancer than those of primary lung cancer, renal cell carcinoma and hepato cellular carcinoma. In a large review, local recurrence was reported in 12.2% of patients with a mean period to relapse of 13 months (range, 3-45 months) [34]. Risk factors include size of tumor and stage of disease at presentation. Masses close to blood vessels 3 mm in diameter have a higher rate of relapse owing to under treatment because of the so called "heat sink" effect, where tissue is cooled by flowing blood. MW, by virtue of its direct heating and more predictable heat profile, may offer an advantage over RFA for lesions close to vessels, but as yet, there is no good evidence to support this.

Signs of relapse can be very subtle, particularly on early follow-up CT. Any change in lesion contour, increase in volume or contrast enhancement after 6 months is highly suspicious; however, there are no well-defined criteria to assess post-ablation appearances on CT. A recent study has described the following features as being most useful: a change in dynamic enhancement (increasing contrast material uptake in the ablation zone, nodular enhancement measuring 10mm, any central enhancement .15HU and enhancement greater than baseline at any time after ablation) and growth of the treatment zone after 3 months, peripheral nodular growth and change from GGO to solid opacity.

Modalities other than CT have been used to follow-up ablated tumors. Several studies exploring the role of Positron Emission Tomography **(PET)** have been published, and these suggest a characteristic set of findings in the successfully ablated tumor, including a large decrease in the Standardized Uptake Value **(SUV)** in the ablated area. PET-CT may detect recurrence earlier than does conventional CT, but there is limited evidence to support this [15, 14,16,35].

COMPLICATIONS

Pneumothorax

PNX is the most common complication after percutaneous TA, with an incidence between 30 and 60% of the procedures [22,23]. Usually in asymptomatic cases radiologic control is adequate. Otherwise patients are treated with chest tube insertion. The incidence of pneumothorax requiring a chest drain seems to be related to the number of lesions treated and the length of the procedure. 20-50% of these cases require chest tube placement [23]. A higher incidence of delayed pneumothorax was seen in patients, where the post-treatment GGO reached the pleura [36].

Pleural Effusion

Pleural fluid is often a response to thermal injury; the percentage of cases treated by thoracentesis is usually 1-7% [14]. The number of pleural punctures and previous systemic chemotherapy are significant risk factors [37]. Large pleural effusions are relatively uncommon and are usually reactive.

Haemothorax is also rare but should obviously be suspected in the context of rapid accumulation of fluid

Parenchyma Hemorrhage

Seven-eight percent of patients present self limited parenchyma hemorrhage. Mild pulmonary parenchymal haemorrhage is a universal finding on the immediate CT. This usually settles, and significant haemoptysis is uncommon. Patients occasionally report a cough productive of "dirty" or blood-stained sputum in the weeks after ablation, but this is usually self-limiting. Parenchyma haemorrhage is often asymptomatic.

Pneumonia

Same cases of pneumonia have been reported after RFA [30]. Pneumonia occurs in 1.8% of treated patients with an increased risk in patients who have received prior radiotherapy. Lung abscess is rare, with a reported incidence of 1.6% patients [38]. It is more common in the context of pre-existing inflammatory lung disease. Pre or post-procedure antibiotics are not recommended routinely, but some centers advocate their use in high-risk patients.

Lung Inflammation

Acute interstitial pneumonitis has been reported although its etiology is uncertain. The risk is greater in patients with tumors of 2 cm in diameter and in those individuals who had previously received external beam radiotherapy [39].

Thoracic Wall Injury or Seeding

With lesions near to the pleura, there is a risk of pleural and chest wall injury [41]. Damage to intercostal nerves can lead to persistent neuralgia, and these symptoms can be difficult to manage. However, the pain is almost always self-limiting. Superficial skin burns can occur but should be avoided with careful multiplanar pretreatment measurement of the electrode tip distance from the chest wall.

Needle tract seeding is rare. In a review of 661 procedures, an incidence of 0.2% has been reported [40]. Care should be taken when manipulating the needle not to withdraw the electrode through tumor before adequate treatment. Similarly, if a second needle is used to deliver local anesthetic or induce a pneumothorax, special attention is needed to ensure that it does not pass through tumor tissue.

CONCLUSION

Today a definitive opinion on long terms outcomes after TA for primary or secondary lung cancer is limited because few series composed by an homogenous population and providing survival beyond 3 years are available. However data collected in the last 10 years allow to conclude that TA is an established alternative treatment for patients who cannot undergo surgery because of comprised general conditions. Main indications are represented by early stage (I/IIN0) lung cancer. In case of pulmonary metastasis the most of Authors agree to offer TA only if lesions are fewer than 5 cm.

Tumor size is a predictive factor of complete ablation, independently by the technique used, with an accepted limit of 3 cm for both primary and secondary lung cancer.

RFA is a safe procedure with reduced cost and short hospital stay that guarantees high success rate of complete ablation allowing the opportunity of a curative treatment in patient not eligible for surgery.

MW presents the substantial advantage to guarantee a bigger ablation zone that could lead to a better local disease control and long term survival. Relationship between lesion size and survival needs further studies; however there are several early clinical studies showing interesting rates of local control even in larger than 3 cm tumors. Nowadays data about outcomes for pulmonary tumors treated with MW are relatively scarce.

There are several studies with animal models that compare the effectiveness of MW and RFA for lung cancer showing a larger and more circular zone of necrosis obtained with MW [41]. Further studies will be needed to address optimization of TA protocols; these should include prospective randomized clinical trials comparing RFA and MW to determine the most effectiveness technique of local tumor control [42].

Despite some Authors [43] have presented encouraging results comparing survival between sublobar surgical resection and TA, surgery is still the treatment of choice for early stage lung cancer.

Prospective

Multidisciplinary approach is the standard treatment for patients who undergo surgical resection for lung cancer, with the intent to improve outcomes by a synergistic effect. Today TA is mostly used as stand-alone technique. In the future it will be necessary to determine the impact of induction and adjuvant therapy also in patients treated with TA. Dupuy reports 24 cases treated with RFA and RT showing better local control and survival than with RT alone [44]. These encouraging data needs to be confirmed by multicentral trials. The hypothesis to improve local control and survival using TA associated with other conventional local or systemic treatments should be the aim of future studies.

The management of loco regional recurrences after RFA is topic recently proposed by Lanuti [26]. In his paper different local, regional and distant recurrences, treated with repeated RFA, RT, CT or CT/RT are reported. These series suggest that recurrences treatment should be managed based on an accurate evaluation of the their distinctive features. The diagnosis between incomplete ablation, local relapse or systemic disease should be the rationale to determine a salvage therapy. More data about recurrences treatment are requested in future.

Some Authors have proposed RFA for symptoms palliation in thoracic cancer. Some interesting data are available in the treatment of painful thoracic tumor involving the chest wall [45]. Another field of interest is the treatment of symptomatic osseous metastasis. We have also suggested the use of RFA in the management of recurrent hemoptysis due to unresectable lung cancer [46]. These experiences suggest that tumor palliation could further enlarge the use of percutaneous thermal ablation in thoracic oncology.

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