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MICROWAVE ABLATION OF MALIGNANT CENTRAL AIRWAY STENOSES

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DOTTORANDO
Dr.ssa Michela Bezzi

TUTOR
Prof. Federico Lavorini

_____ _____

COORDINATORE
Prof. Lorenzo Cosmi

_____

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MICROWAVE ABLATION OF MALIGNANT CENTRAL AIRWAY STENOSES

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1. INTRODUCTION

Minimally invasive thermal ablation of tumours has become common since the advent of modern imaging. From the ablation of small, unresectable tumours to experimental therapies, percutaneous radiofrequency ablation, microwave ablation, cryoablation and irreversible electroporation have an increasing role in the treatment of solid neoplasms.

Thermoablative techniques induce tumour cell death through different mechanisms which are discussed in rapidly developing areas of research in the field, including combinatorial ablation and immunotherapy, synergy with conventional chemotherapy and radiation, and the development of new ablation modalities such as irreversible electroporation (1).

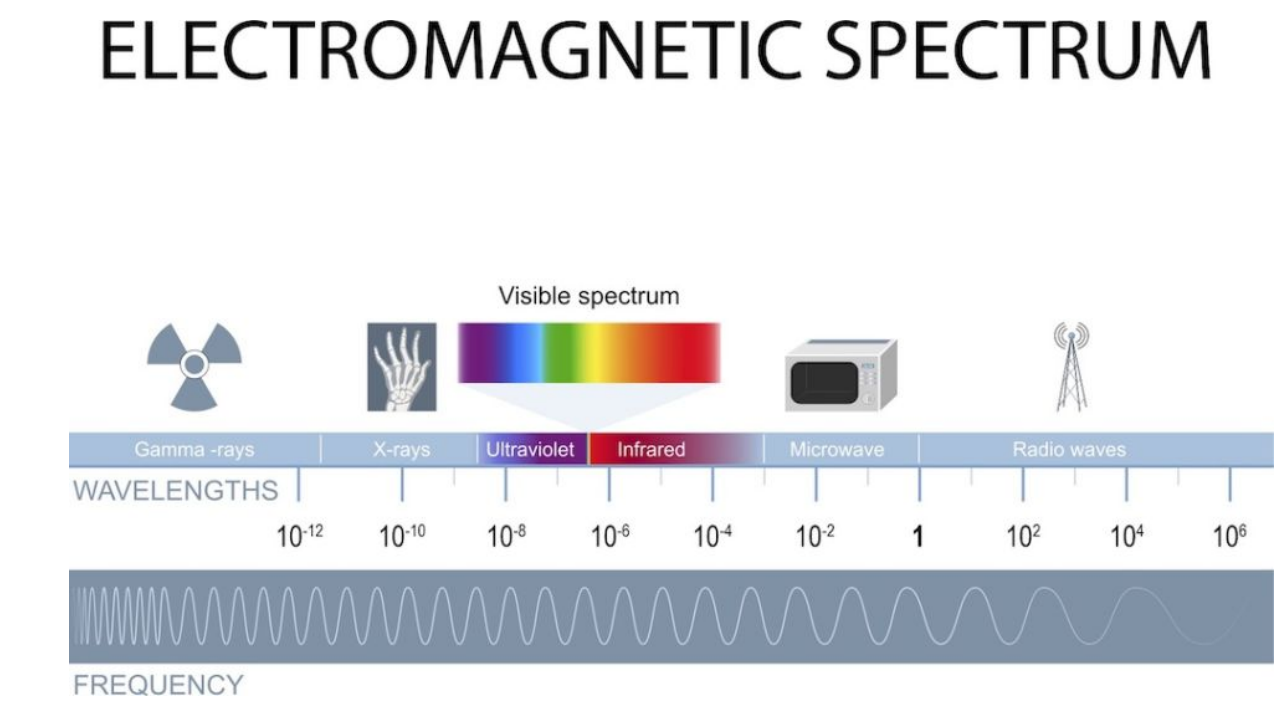
Thermal ablation techniques, namely radiofrequency ablation, microwave ablation and cryotherapy, are minimally invasive treatments that consist of creating local tissue necrosis (by respectively heating or freezing the tissue) around the tip of a needle. This needle is currently inserted percutaneously into the centre of the tumours under CT guidance.

These techniques are very effective for curing small (<3 cm) primary or metastatic lesions in the liver (2, 3), kidney (4, 5) and lung (6, 7). They are also very effective for curing benign bone tumours, such as osteoid osteomas (8, 9). However, they are currently mainly used for palliation in patients with bone metastases (10-13).

Thermal ablation offers an intriguing therapeutic option for Lung cancer. It can increase local tumor control and survival in patients with early stage NSCLC or with limited metastatic disease from nonlung primaries who are not surgical candidates because of poor cardiopulmonary reserve, anatomic constraints limiting resection, failure of traditional therapies, or refusal of operative approaches. Most preclinical and clinical trials have focused on demonstrating the feasibility of three modalities for pulmonary thermal ablation, namely radiofrequency (RF) ablation, microwave (MW) ablation, and cryoablation (14).

2. MICROWAVES

Microwaves are a type of electromagnetic radiation, as are radio waves, ultraviolet radiation, X-rays and gamma-rays. Microwaves have a range of applications, including communications, radar and, perhaps best known by most people, cooking. Electromagnetic radiation is transmitted in waves or particles at different wavelengths and frequencies. This broad range of wavelengths is known as the electromagnetic spectrum (EM spectrum). The spectrum is generally divided into seven regions in order of decreasing wavelength and increasing energy and frequency. The common designations are radio waves, microwaves, infrared (IR), visible light, ultraviolet (UV), X-rays and gamma-rays. Microwaves fall in the range of the EM spectrum between radio and infrared light.



The electromagnetic spectrum, from highest to lowest frequency waves. (Image credit: Shutterstock)

Microwaves have frequencies ranging from about 1 billion cycles per second, or 1 gigahertz (GHz), up to about 300 gigahertz and wavelengths of about 30 centimeters

(12 inches) to 1 millimeter (0.04 inches), according to the Encyclopedia Britannica. This region is further divided into a number of bands, with designations such as L, S, C, X and K, according to Ginger Butcher's book "Tour of the Electromagnetic Spectrum."

One of the most common uses of microwaves is to heat food quickly. Microwave ovens are possible because microwaves can be used to transmit thermal energy. The discovery of this phenomenon was purely accidental. In his book, "They All Laughed...: From the Light Bulbs to Lasers: The Fascinating Stories Behind the Great Inventions That Have Changed Our Lives" (HarperCollins, 1992), author Ira Flatow recounts the story of the invention of the microwave oven: "Shortly after World War II, Percy L. Spencer, an electronics genius and war hero, was touring one of his laboratories at the Raytheon Company. Spencer stopped in front of a magnetron, the power tube that drives a radar set. Suddenly he noticed that a candy bar in his pocket had begun to melt." Further investigation led him to make the first batch of microwave popcorn as well as the first exploding egg.

The first microwave ovens were quite large and expensive, but they have since become so affordable that they are common in homes worldwide. Microwave heating systems are also used in a number of industrial applications, including food, chemical and materials processing in both batch and continuous operations.

3. CLINICAL APPLICATION OF MICROWAVES

Microwaves have been widely considered for clinical applications in medicine.

Microwave Ablation (MWA) particularly has been used to treat different types of neoplasms.

In the field of thyroid nodules, MWA has been used for both benign and malignant lesions. This is a fast and safe approach, and it may reduce many side effects of standard treatments, such as surgery, medications, and radiotherapy. Feng et al. (1) applied MWA percutaneous treatment to a small sample of patients affected by cytologically benign thyroid nodules, defining it a feasible technique. In a larger sample (222 patients) Yue et al. (2) observed a significant reduction in benign nodules after a 6-months follow-up, with no major complications. These findings were confirmed by Korkusuz et al. (3), who also noted how functional imaging seems a promising technique for post-ablative and early functional evaluation of MWA efficiency.

MWA can also be used to treat invasive thyroid malignancies: Tsutsui et al. (4) have shown how bronchoscopic tumour ablation with MWA for laryngotracheal

intraluminal invasion caused by well-differentiated thyroid carcinoma can be a safe and effective procedure when accompanied by a combination of argon plasma coagulation (APC) and laser vaporization, taking full advantage of their individual characteristics.

Pancreatic adenocarcinoma is an aggressive malignancy with an extremely poor prognosis (5), which has not changed significantly during the last decades. Prolonged survival is achieved only by complete surgical resection, although most of the cases are considered inoperable at diagnosis due to local spread or presence of metastases (6). Chemoradiotherapy is not tolerated by all patients and still fails to prolong survival significantly, whereas neoadjuvant treatment also has limited results on pain control or tumour downstaging (7,8). MWA, along with radiofrequency ablation (RFA), high-intensity focused ultrasound (HIFU) and irreversible electroporation (IRE) offer a cytoreductive measure in an adjuvant setting, with the aim of better palliation in locally advanced pancreatic cancer. Thermal ablation is universally recognized as effective and intentionally radical when a ‘‘safety halo’’ of necrosis is achieved around the target lesion; nonetheless, the difficulty to obtain that without running excessive risks of perioperative complications is the most important limitation of any thermal ablative technique in the pancreas (9). Furthermore, considering its anatomic relationship with adjacent organs and vessels, MWA can decrease heat-sink effect and can guarantee optimal heating of cystic masses and tumours close to the vessels, taking shorter intra-operative time and, using multiple antennae simultaneously, reducing the need for multiple treatment sessions and therefore decreasing the rate of incomplete treatments

of larger tumors. In addition, MWA is associated with a lower amount of intra-procedural pain and complications (10, 11, 12, 13). In selected patients, MWA may be performed as a percutaneous procedure (14), even in the management of insulinomas, for example in those patients who are not suitable for surgical removal (15).

As far as breast cancer is concerned, there has been a trend toward less aggressive treatment of small breast cancers, leading to the development of less invasive alternatives. Many patients are not satisfied with the cosmetic outcome after breast-conservation therapy, and surgical side-effects are not rare. Moreover, less aggressive treatment options would be extremely useful in patients older than 70 years with comorbidities that make surgery a difficult and sometimes life-threatening treatment. MWA may have a predominant role: Zhou et al. (16) described an ablate and resect study of ultrasound-guided microwave coagulation of small breast cancers performed under general anaesthesia. Results similar to those of RFA were found: complete tumour coagulation in 95% of cases (36 of 38). However, complications included thermal injuries to the skin and pectoralis major muscle. Barral M et al. (17) also found a possible application of MWA in the treatment of oligometastatic breast cancer patients.

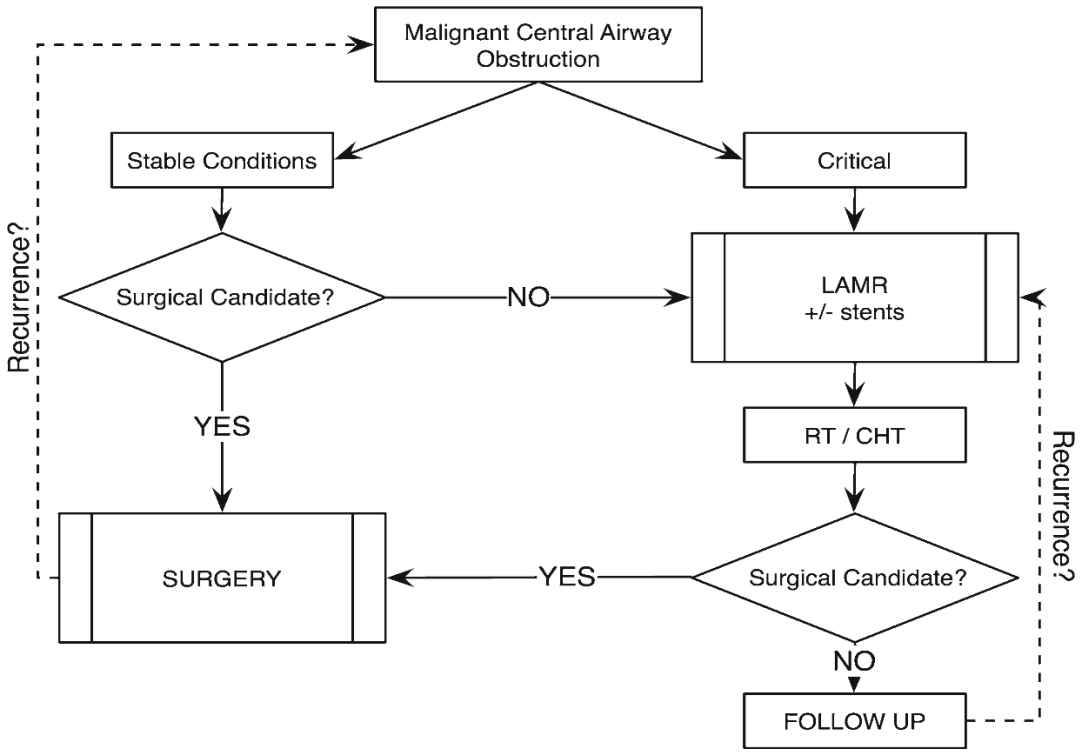
MWA has also been successfully used in the treatment of kidney masses, achieving a similar effect and lower rate of complication compared with laparoscopic radical nephrectomy and open radical nephrectomy (18, 19, 20), and of the focal hepatocellular carcinoma with single or up to three nodules (<3 cm) (21). Finally, MWA may play an important role in the treatment of localized prostatic cancer (22).

4. RIGID BRONCHOSCOPY AND TECHNIQUES

Central airway obstruction can occur secondary to a number of lung primary, adjacent or metastatic malignancy and benign processes. It may be extrinsic or intrinsic. Interventional options for central airway obstruction are subject to the availability of experienced personnel and equipment. In addition, the degree of obstruction and severity of symptoms, the nature of the underlying problem, and the patient's overall prognosis and quality of life impact the choice of intervention [1-5].

Endobronchial therapy for malignant tumors is purely palliative and should only be performed in non-surgical cases.

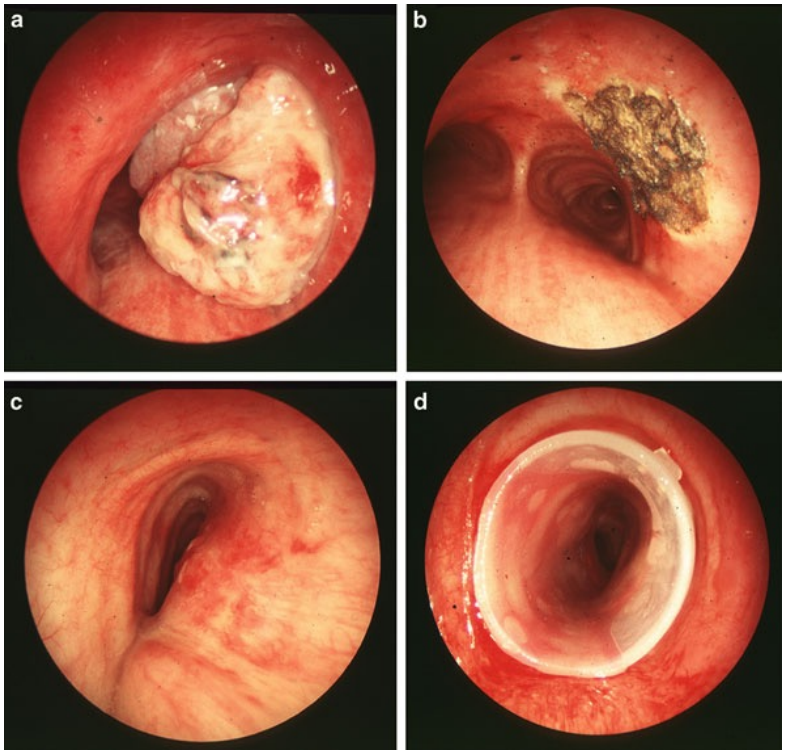
Algorithm for the management of malignant central airway obstruction



Surgical resection is feasible only in about 25% of patients with lung cancer and less than 30% of these survive longer than 5 years. Thus, more than 90% of these patients require palliative treatment. Thirty per cent of lung cancers cause obstructions of the trachea and main bronchi [6] with consequent respiratory distress, bleeding and infection. The technique of endobronchial coagulation and disobstruction plays a pivotal role in all these situations, since conventional treatment with chemo- and radiotherapy is often performed with unsatisfactory results with regard to the endobronchial component of the tumor [7, 8]. Endoscopic coagulation and debulking allow restoring of airway patency, palliation of symptoms and improvement of quality of life. However, palliation with endoscopic techniques is to be reserved to inoperable obstructive central tumors in symptomatic patients.

No controlled trials have been published that compare the various modalities that can perform endobronchial procedures. As a result, current practice is based upon local influences, available resources and equipment, the bronchoscopist's training and preferences, and uncontrolled studies. Of all options, only Bronchoscopic Laser Resection, Argon Plasma Coagulation (APC) and Electrocautery produce rapid tissue destruction in a single session and are therefore appropriate to treat lesions that are producing acute respiratory distress or hemoptysis. Bronchoscopic laser resection has to be considered as a part of a more complete treatment called “Laser Assisted Mechanical Resection/Dilation – LAMR/LAMD. Bronchoscopic LAMR/D is used to relieve malignant or benign intraluminal airway obstructions. It is of no use when the obstruction is caused by sole extrinsic compression. In case of significant (>50% of the

lumen) extrinsic compressiona airway stenting is commonly used. It is rapid, effective, repeatable and may be complementary to other therapies.



Endoscopic view before (a) and after (b) Laser Assisted Mechanical Resection of an endoluminal mass causing tracheal stenosis. Before (c) and after (d) stent implantation in an extrinsic stenosis of the trachea

Endobronchial electrocautery and APC are frequently seen as less expensive alternatives to laser therapy with similar effects and as such similar indications. Similarly to laser, these treatment modalities are indicated for any benign or malignant tissue destruction responsive to heat delivery. These indications include endobronchial malignancy, benign tumors, relief of post-intubation stenoses, and, particularly in the case of APC, treatment of stent-induced granuloma.

Clinical presentation

Central airway obstruction may cause a variety of symptoms, from shortness of breath to respiratory failure and death. The hallmark of the severe airway obstruction is impairment of oxygenation and ventilation. Patients may develop symptoms suddenly or more gradually; the onset and progression of symptoms depend upon the nature of the problem (acute with foreign bodies, slowly progressive with an expansive goiter) and the location of the lesion (tracheal versus bronchial). Symptoms and signs develop when airflow impairment reaches a critical threshold. Patients complain of shortness of breath, which is often constant and unresponsive to bronchodilators. Monophonic wheezing may be present and can be unilateral if the lesion is distal to the carina. Stridor is a sign of severe subglottic or tracheal obstruction. Breathing becomes labored in advanced phases and heralds impending respiratory failure. In the decompensated patient, immediate restoration of ventilation and oxygenation is of vital importance. Patients with minor obstruction are often asymptomatic, since airflow limitation is mild. However, rapid deterioration may occur if swelling or secretions increase the degree of luminal impingement during a respiratory tract infection. It is not uncommon for patients with subcritical lesions to be misdiagnosed as suffering from an exacerbation of asthma or chronic obstructive pulmonary disease (COPD) while the true etiology is anatomic airway obstruction. Patients with airway obstruction also frequently have pneumonia; if symptoms and/or radiographic infiltrates do not resolve within four to six weeks, bronchoscopy should be considered.

A number of studies are employed to confirm the presence of central airway obstruction and to estimate its magnitude: plain chest radiographs are rarely diagnostic. If an airway lesion is suspected and time permits, a high resolution chest computed tomography (CT) can prove helpful [1]. In a stable patient spirometry can show the characteristic changes of airway obstruction on flow volume loops, frequently before abnormalities in the spirometric volumes are noted.

Direct bronchoscopic visualization is the gold standard for confirming the presence of airway obstruction and also aids in discerning its underlying etiology. Often the differentiation of endobronchial or extrinsic lesions can be discerned only with bronchoscopy.

Management of central airway obstruction requires initial stabilization of the patient with secure access to the airways which guarantees ventilation. Airway interventions can then be considered.

In a stable patient, imaging studies and pulmonary function tests should be obtained as mentioned above. A patient with severe tracheal or mainstem obstruction and marginal lung function requires initial stabilization to secure ventilation and oxygenation. Flexible bronchoscopy can be performed after the airway has been secured (orotracheal tube/deep sedation or general anaesthesia) and appropriate gas exchange documented. During the bronchoscopic examination, the airway is inspected, lesions are assessed, distal secretions are suctioned, and diagnostic tissue is obtained if needed. This information is used to plan further interventions aimed at opening an airway and

maintaining patency. After the patient has been stabilized he should be transferred to a specialized center where a dedicated airway team is available. In case of severe tracheal obstruction, use of the open ventilating rigid bronchoscope is the preferred method of airway control. The rigid bronchoscope not only provides a secure airway during visualization, but is also a therapeutic tool. In emergency cases, the rigid bronchoscope is the preferred instrument for unstable patients and when significant bleeding is expected. The airway can be dilated with the barrel of the scope [2]. During this procedure, the patient is intubated with the instrument under general anesthesia. The optical telescope is advanced through the stenotic airway opening and the barrel then pushed through the obstruction in a rotating motion. Bleeding is usually minimal due to compression of the lesion by the rigid instrument. In one session, using the rigid bronchoscope under general anesthesia, immediate good results can be achieved: bronchial recanalization with improvement of ventilation and/or drainage of post-stenotic secretions. Dilation is immediately effective for intrinsic and extrinsic lesions, but the results are usually not sustained. For this reason, multimodality approaches featuring a combination of several interventions are preferred for their mucosal sparing effects and long term success over dilation alone [1-3]. The number and scope of therapeutic options has increased dramatically, and a given intervention must be chosen carefully in the context of an individual patient's situation. They can be devided into “slow methods” such as photodynamic therapy, cryotherapy and brachytherapy, and into “fast methods”: laser, argonplasma coagulation and electrocautery. Fast methods will be the topic of this chapter.

Laser therapy normally integrates rigid bronchoscopic resection; this procedure is known worldwide as Laser Assisted Mechanical Resection (LAMR) and represents the safest and most effective way to obtain all potential effects of laser in bronchoscopy. Some operators use laser with the flexible bronchoscope with limited safety and efficacy when compared to LAMR. The tissue-light interaction leads to thermal tissue damage with vaporization, coagulation, resection or incision of obstructing lesions [10,11].

Laser therapy was originally indicated for short endobronchial central airway lesions with a visible distal lumen. Bronchoscopists who become familiar with the technique can use it even in complete stenoses where the distal bronchial tree can only be reached using the suction tube and the rigid bronchoscope based upon precise knowledge of the anatomy and preferably with the support from CT scan images. In these cases the combination of rigid bronchoscopy and laser firing is crucial. The technique is most commonly applied in cases of malignant intrinsic airway obstruction or in postintubation tracheal stenosis. The effects upon airway lumen size are usually immediate and accompanied by excellent control of bleeding.

Electrocautery and argon plasma coagulation also rely on thermal tissue destruction. With electrocautery, a high-frequency current is applied to the lesion with bipolar probes. When the current is directly applied to the tissue, heat develops and leads to tissue necrosis. Electrocautery is traditionally defined “the poor man’s laser” since it

can mimic the effects of laser firing when vaporization or resection are needed with less expensive equipment.

Argon plasma coagulation is a related therapeutic intervention. Argon gas is emitted through a flexible Teflon tube. This gas is ionized because of exposure to an high-frequency current and an electrical arc is formed, which allows for desiccation and tissue destruction. It is a valuable tool in treating superficial bleeding and debulking granulation tissue and tumors.

Indications, equipment, applications and outcomes of these techniques will be extensively discussed hereafter.

Laser Assited Mechanical Resection

- History and historical perspectives

Until the early eighties the endoscopic treatment of central airway obstructions was hazardous and often inadequate. Mechanical resection was performed using the rigid bronchoscope and rigid biopsy forceps with high risk of bleeding. Even when successfully managed it often provided only short-term results. Endoscopic electrosurgery and cryotherapy were then introduced to reduce the risk of bleeding and prolonge palliation. Nonetheless these methods provided only delayed recanalization, carrying an unpredictable risk of damage to adjacent healthy tissue. The advent of laser immediately proved very useful in reducing hemorrhages. Once an appropriate technique for the treatment of the implantation base was developed, laser coagulation in depth also proved to be quite effective in prolonging palliation in central airway

obstruction due to lung cancer. Bronchoscopic mechanical resection then turned into Laser Assisted Mechanical Resection (LAMR).

- Indications and contraindications

Bronchoscopic laser resection (LAMR) can relieve malignant and benign intraluminal tumors, particularly exophytic proximal airway lesions, but it is of no use when the obstruction is caused by extrinsic compression [12,13]. Laser is also useful in the treatment of benign diseases such as cicatricial tracheo-bronchial stenoses.

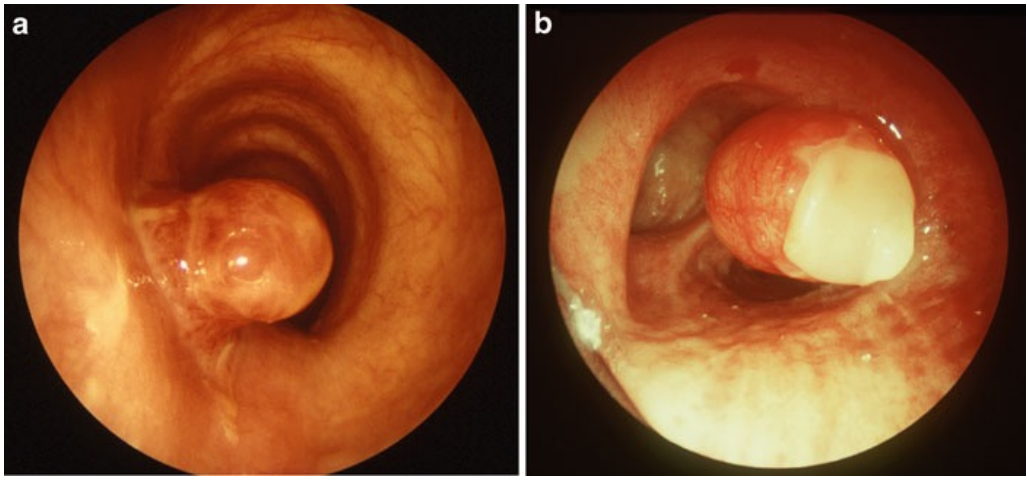
Although rare, benign tumors are the best indication for laser therapy. If exclusively endoluminal, endoscopic laser resection should be the first therapeutic choice for such tumours, as they are usually polypoid and rarely recur if the tumour base can be well photocoagulated with the laser. Surgery should be limited to those cases with partial or exclusive extrabronchial growth.

Airway obstruction from bronchogenic carcinoma is the most frequent indication for laser resection. It is typically employed in patients who have exhausted their therapeutic options, although some may be eligible for salvage chemotherapy, brachytherapy, or surgical resection [2,3,14].

Other malignant causes of central airway obstruction that have been managed by laser resection include the so-called “low grade malignancy” such as adenoid cystic carcinoma, mucoepidermoid carcinoma, bronchial carcinoids, but also endobronchial metastases from melanoma, colon, kidney, and breast cancer [15,16].

The major aim of laser therapy in case of malignant central airway obstruction is to recanalize the tracheobronchial tree and restore adequate ventilation and/or drainage of post-stenotic secretions. It is the location and macroscopic appearance of a tumor, rather than its histological type, which determine whether or not laser therapy can be carried out. Because of accessibility, the best results are obtained in tumors located in the trachea or main bronchi, which is also where obstruction causes the greatest respiratory distress. On the contrary, tumors obstructing segmental bronchi do not impair ventilation to the degree that severe symptoms are produced. Furthermore, reduced accessibility with the laser fiber and the thin walls of these bronchi increase the difficulty of laser delivery and the risk of perforation. The sole indications for laser disobstruction of segmental bronchi are for those cases requiring drainage of distal purulent secretions (post-obstructive pneumonia) and for the cure of benign tumors.

It is very important for the endoscopist to identify the base of the obstructing endobronchial tumour. Polypoid tumors are easy to remove and often completely resectable.



Polipoid bronchial tumours

Intraluminal tumors which infiltrate the bronchial wall cannot be treated completely. However, if the airway lumen is not seriously reduced by tumor infiltration, ventilation is usually not impaired appreciably and laser resection may not be necessary.

For occluding endobronchial tumors with an extraluminal component or with significant mediastinal growth, laser treatment alone is frequently unsuccessful. Although the endoluminal growing component may be initially successfully removed, the airway is quickly re-obstructed as a result of further growth, extrinsic compression and endoluminal migration of the tumour. In these cases, laser treatment is to be considered as preliminary to stenting or, if the extra-luminal component is only peribronchial, to brachytherapy. Pure extrinsic compression is a major contraindication for endoscopic laser treatment.

Regardless of impact on ventilation, location or macroscopic appearance, vascular tumors producing haemoptysis represent a good indication for laser bronchoscopy. Although the tumor is often not completely resected, short term reduction or ceasing of bleeding occurs systematically after laser coagulation.

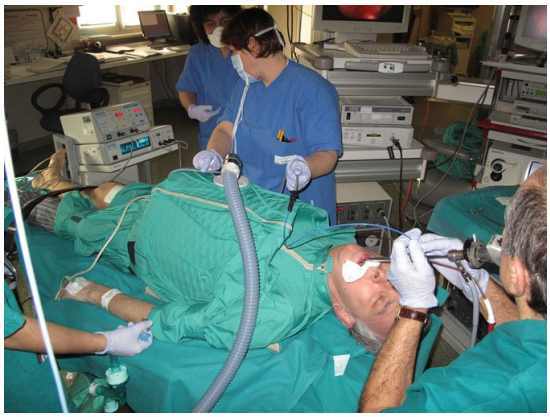
In all of the previous conditions, endoscopic resection allows a precise assessment of the extent of the tumor thus shifting patients to surgery who were originally considered to have inoperable disease or allowing lung-sparing resections [17].

The combination of endobronchial laser therapy with other palliative therapies is possible and can be extremely advantageous. The addition of radiotherapy is particularly useful either by external beam radiation or endobronchial brachytherapy, resulting in the extention of the palliation. When indicated, laser resection should be

performed before radiotherapy, because preventive laser recanalization of obstructed airways allows improved functional status. Furthermore, it is well known that radiotherapy and chemotherapy are poorly effective on the endoluminal component of the tumor [7,8]. Similar therapeutic algorythms for the management of malignant central airway obtructions have been described by different authors [18-20]. Here is how we procede (Fig. 1).

- Application of the technique

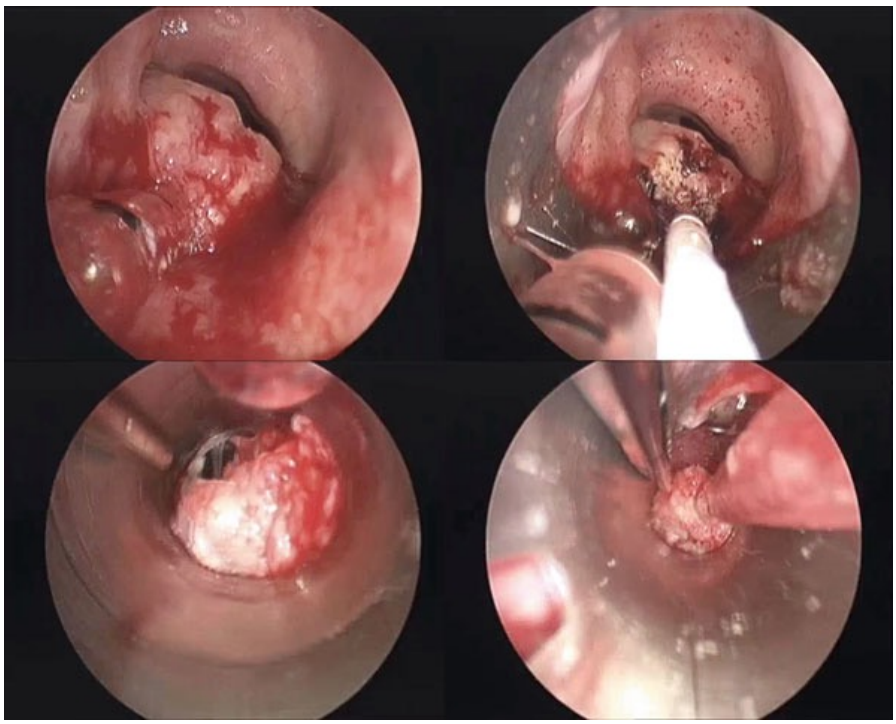
Most bronchoscopic laser resection will be performed via rigid bronchoscopy in the operating room with general anesthesia [28-30]. In fact, laser therapy normally integrates rigid bronchoscopic resection; this procedure is known worldwide as Laser Assisted Mechanical Resection (LAMR) and represents the safest and most effective way to obtain all potential beneficial effects of laser in bronchoscopy. Some operators use laser with the flexible bronchoscope with limited safety and efficacy when compared to LAMR. It is performed in a specially equipped bronchoscopy suite with topical anesthesia and conscious sedation. LAMR is performed using general anesthesia, the patient's oxygenation and ventilation are supported through the rigid bronchoscope by spontaneous-assisted ventilation or jet ventilation [11,17,31].



Intermittent Negative Pressure Ventilation (Poncho or Cuirass) is associated with lower incidence of complications, such as acidosis due to hypercapnia [32].

Muscle relaxants and paralytic agents can be helpful during general anesthesia because they prevent the patient from coughing during resection and they facilitate insertion of the rigid bronchoscope. The four main effects laser can provide are *Coagulation, Resection, Vaporization* and *Incison* .

Laser Resection is generally facilitated by the use of the rigid scope in the so-called Laser Assited Mechanical Resection already mentioned before.



Laser Assited Mechanical Resecion (LAMR) of a bronchial tumour

It follows *Laser Coagulation,* which involves directing the laser at the target lesion, devitalizing the lesion via photocoagulation of the feeding blood vessels, so that the devitalized tissue can be more easily removed with the beveled edge of the bronchoscope, forceps or suction, minimizing the risk of bleeding. Coagulation is possible because the laser penetrates tissue to a depth of up to 10 mm in an inverted cone fashion and provides reliable photocoagulation at this depth. Its power density

can be altered by moving the laser closer to, or farther from, the target tissue. *Laser Vaporization* is possible because energy from the laser is relatively well absorbed by water. It involves aligning the laser parallel to the bronchial wall and aiming at the edge of the intraluminal lesion (the laser should never be discharged perpendicular to the airway wall because of an increased risk of perforation). It can also be performed through the flexible scope. In this setting, laser pulses of only one second or less are used to vaporize the tissue preventing thermal injury to the scope and airways. On the contrary, when performed through the rigid scope, laser can be used for longer periods of time reaching higher temperatures with higher power densities. This is possible because laser debris and smokes can be effectively suctioned by the suction tube inserted through the scope, minimizing the risk of injury. Laser vaporization applied using a fiberoptic bronchoscope should be limited to small non-bleeding lesions, to refine and complete treatments previously performed with the rigid scope, and, through a tracheal tube, for treating neoplasms in the upper lobe bronchi, in distal locations and for distal tracheobronchial toilette.

The channel of the rigid bronchoscope is wide enough to ensure ventilation as well as the passage of telescopes, suction tubes, and the laser fiber. Simultaneous laser coagulation of a bleeding site and suction of blood and clots is very important when dealing with airway hemorrage. In addition, the rigid bronchoscope allows mechanical resection of polypoid tumours, previously coagulated with laser, which saves considerable time over laser vaporization. For all these reasons most bronchoscopists prefer rigid bronchoscopy, although a flexible bronchoscope is to be available if the

airway abnormality is within a distal segmental bronchus and also to remove blood and debris from the distal airways. In the treatment of cicatricial tracheal stenosis (eg post-intubation web-like stenoses), laser is used in contact mode to perform radial incisions before a mechanical dilatation is obtained with rigid bronchoscopes of progressive caliber. The radial incisions reduce tension with minimum heating of the adjoining tissue thus limiting recurrence [33-35]. Other authors described a different technique with repeated small radial incisions in contact mode through the flexible bronchoscope [36].

Most laser resection teams are comprised of a bronchoscopist, an anesthesiologist experienced with interventional pulmonology techniques and airway management, an endoscopy nurse familiar with the equipment, and a second endoscopy nurse who assists the bronchoscopist and controls the laser settings. General anesthesia is usually more comfortable for both the patient and the operator, it allows maximal control of ventilation and immediate management of complications. Anesthetic agents that are rapidly eliminated or readily reversed should be used so that the patient can be rapidly re-awakened and postoperative mechanical ventilation avoided. Regardless of the type of anesthesia, the laser endoscopist and the anesthesiologist need to work in close agreement throughout the procedure, adapting to their mutual needs.

For endobronchial tumors, the most common indication for laser treatments, the use of a rigid bronchoscope is crucial since the most evident part of the monoeuvre, i.e. the obstructing mass removal, is mechanically performed. In this setting, Laser is more efficiently used to coagulate the endoluminal mass before the mechanical resection to

avoid or reduce bleeding. It is also used to treat in depth the implantation base of the tumor in order to delay recurrences or to achieve cure in case of benign tumors, selected typical carcinoids, early cancers and carcinoma in situ.

A proposed technique for laser treatment of endobronchial tumors consists in initial low power Nd:YAG laser firing (<30 W) to coagulate the tumor followed by removal of the endoluminal portion of the lesion with the tip of the rigid bronchoscope, the biopsy forceps and the suction tube. High-power settings (50-60 W) are then employed to vaporize the residual endoluminal tumor. At the end of the procedure, the base of the lesion is exposed to low-power settings with long pulses (20 to 30 W for 4 to 5 s; 2000J /cm2) to obtain a cytocidal effect in depth within the airway wall.

Dark colored tissues (eg, charred or hemorrhagic tissue) and large lesions require special consideration. With respect to dark tissues, laser coagulation in depth is limited because the dark color enhances tissue absorption, limits deep tissue penetration, and reduces deep photocoagulation. To avoid charring and vaporization due to radiation absorption on the surface and to obtain coagulation in depth, the laser fiber must be kept at a sufficient distance from the tumor surface and directed a little bit more tangentially to the bronchial wall, thus obtaining, due to the divergence of the beam, an increase of the diameter of the spot and, thus, a reduction of the power density.

With respect to large lesions, firing with laser in full tumor is not advisable. It is time-consuming and uselessly risky to reduce the whole endoluminal mass by charring and vaporizing it with laser. Bronchoscopic laser resection should only be performed by bronchoscopists who have advanced training and experience. Bronchoscopists and

team members should remain familiar with techniques, potential complications, and necessary precautions [37]. To minimize the risk of combustion

- The fraction of inspired oxygen should be kept below 40 percent during laser firing [38].
- Power settings should not exceed the maximum recommended for the laser being used (60 watts for the Nd:YAG laser)
- Flammable materials (including silicone stents) should be kept far away from the operating field
- Adequate suction must be available to remove the combustible laser plume (the smoke caused by vaporization of tissues) [39].
- If a flexible bronchoscope is employed, the laser must be kept a sufficient distance beyond the tip of the bronchoscope

Video systems allow all personnel to observe the procedure, which makes it easier for assistants to anticipate the needs of the bronchoscopist and the patient. Many bronchoscopic laser resection procedures are performed in less than one hour [40].

- Evidence based review

Outcome data regarding bronchoscopic laser resection are sparse. However, it appears to be a rapid and safe method to relieve airway obstruction. A case series that included 2610 laser resections in 1838 patients with malignant airway obstruction found that airway patency improved and symptoms were palliated in over 90 percent of patients

[17]. In this series, the rigid bronchoscope was used in 92% of the treatments that were performed almost always under general anaesthesia. The fiberoptic bronchoscope – alone – was used in less than 10%. In 93% of the patients with endobronchial malignant obstruction, Nd:YAG laser therapy allowed the patency of the central airways and avoided the most distressing symptoms of the disease, enhancing the patient's quality of life. The location and macroscopical appearance of the lesion plays the greatest role in determining the success of the procedure: for tumors involving the trachea and main bronchi immediate results were almost always excellent (> 95%). The median time between a first and second palliative treatment was 102 days. Mortality was less than 1 percent within seven days of the procedure.

Smaller series have reported similar results [11], while a larger series reported that death occurred in only 15 out of 5049 patients (0.3 %) and serious complications occurred in only 119 out of 5049 patients (2.4 %) [41].

In 38 typical carcinoids and in more than 150 benign tumors, in which the base of the lesion was reached, laser therapy was curative. These results were achieved in exclusively endoluminal polypoid tumors in which coagulation of the lesion and mechanical resection were followed by a systematic treatment of the base of the tumor with low power settimg and long exposure time, avoiding tissue loss while still obtaining a cytocidal effect in depth. Overall mortality rate was 0,25 % (42)

In benign stenoses and particularly in post-intubation tracheal stenoses, laser assited mechanical dilation can guarantee cure in up to 66% of cases, 100% when only cicatricial web-like stenoses are considered [9].

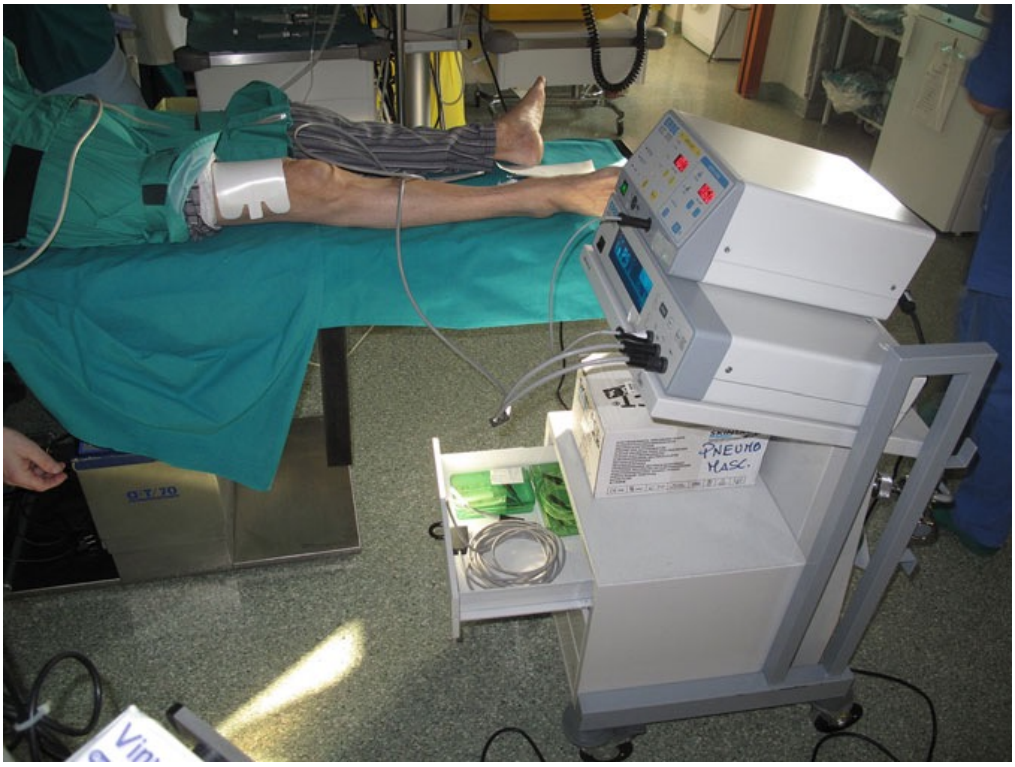
Complications of bronchoscopic laser resection are infrequent but they include hypoxia, hemorrhage, airway wall perforation, airway wall necrosis, and fistula formation. Hypoxia, whether due to general anesthetic or to major bleeding, may lead to irreversible cardiovascular complications and thus must be corrected promptly by bleeding suction and ventilation control. Adequate control of hemorrhage and ventilation can only be assured with the rigid bronchoscope. Other possible complications include perforation of the airway with resulting mediastinal emphysema, pneumothorax or infection. Perforation is unlikely if the procedure is performed by experienced endoscopists familiar with rigid bronchoscopy. Airway fires have been reported, particurarly when flexible fiberoptic instruments are used. Fortunately this complication is quite rare. Arterial air embolism has been anedoctically reported as a complication of bronchoscopic laser resection. Studies of laser procedures performed during continuous transesophageal echocardiographic monitoring suggest that air emboli may be caused by coolant gas (which exits the bronchoscope under high flow and pressure conditions to cool the laser probe) entering the pulmonary venules and gaining access to the systemic circulation [43]. The frequency of this complication may be reduced by maintaining the laser fiber coolant airflow at the minimum level and avoiding direct contact between the laser probe and tissue.

Endobronchial Electrocautery And Argon Plasma Coagulation

- Introduction and definition of the procedure

Several techniques are available for the bronchoscopic treatment of obstructing tissue in the tracheobronchial tree. Of these options, only Laser Assisted Mechanical Resection (LAMR, already discussed above), Argon Plasma Coagulation (APC) and electrocautery produce rapid tissue destruction in a single session, and are therefore appropriate to treat lesions that are producing acute respiratory distress or hemoptysis. The neodymium yttrium aluminum garnet (Nd:YAG) laser is commonly used in this situation, but expense limits the availability of laser equipment in many parts of the world. Endobronchial electrocautery and argon plasma coagulation (APC) are alternative modes of thermal tissue destruction that may be used via the flexible or rigid bronchoscope. Electrocautery has been referred to as "the poor man's laser" because it also produces rapid thermal destruction of tissue, but does so relatively inexpensively by means of electric current rather than laser light [44,45]. Argon plasma coagulation (APC) is also an electrosurgical technique used to resect an obstructing lesion and/or to achieve hemostasis [46,47]. The history, principles, equipments, and techniques of endobronchial electrocautery (also referred to as electrofulguration, diathermy, electrocoagulation, thermocoagulation, or electrosurgery) and Argon plasma coagulation (APC) will be reviewed here. In addition, their indications, contraindications, and complications are presented.

- Application of the technique

- 

Argon Plasma Coagulation (APC)

Endobronchial electrocautery and APC are thermal tissue-destructive modalities that use electricity to generate heat. They differ in the fact that APC does not make contact with the tissues it destroys, and has a penetration depth of just a few millimeters. For these reasons, it is more suitable for the treatment of superficial and spreading lesions. Once gas is released through the catheter tip, it is ignited through electrical current; an arc is formed if the probe is close enough to the mucosal surface, causing heat destruction and desiccation of the tissue. The arc can be moved back and forth (painting) and can even be aimed around bends, making it very suitable for hard to reach lesions. When electric current flows through human tissue a *thermal* effect is observed, due to the resistance of the tissue to the flow of electrical current. The rise in temperature is proportional to the square of the applied electrical current times the

intrinsic resistance of the tissue; the latter is largely a function of vascularity and water content, with bone and fat having a higher resistance than skin and muscle [62]. Resistance and thermal effects are also increased by reducing the area of contact between the electrical probe and the patient, since the same quantity of current must then flow through less conducting tissue. The temperature rises at different rates in different areas within a given tissue due to inhomogeneity of tissue density and the irregular distribution of electrical current. As a rule, the density of the electric current is largest, and the rise in temperature greatest, in the contact area between the coagulation electrode and tissue, and decreases with greater distance from this point. Thermal destruction of tissue can be used to effect coagulation or resection:

- Evidence based review

No controlled trials have been published that compare the various modalities that can perform endobronchial procedures. As a result, current practice is based upon local influences, available resources and equipment, the bronchoscopist's training and preferences, and uncontrolled studies. Endobronchial electrocautery and APC are frequently seen as a less expensive alternative to laser therapy with similar effects and, as such with similar indications. These treatment modalities are indicated for any benign or malignant tissue destruction responsive to heat delivery. These indications include endobronchial malignancy, benign tumors, relief of postintubation stenoses, and, in the case of APC, treatment of stent-induced granuloma.

5. THE RATIONALE FOR MICROWAVE ABLATION IN INTERVENTIONAL PULMONOLOGY

MWA is an emerging technology in the field of tumour thermal therapy, used in minimally invasive surgery or percutaneous interventions. It is applicable for the thermal ablation therapy of different kinds of tumours where it is emerging as a valuable alternative to radiofrequency ablation (RFA).

The goal of treating tumours with MWA is thermal degeneration of proteins and a consequent coagulative necrosis.

Lung cancer remains the leading cause of cancer death. Pneumonectomy or lobectomy with hilar and mediastinal lymph node sampling is the gold standard treatment and offers the best option for cure of stage 1/2 non-small cell lung cancer (NSCLC) (1). Unfortunately, only 15% of patients present with stage 1/2 disease, and many of these patients do not meet the pulmonary physiologic guidelines for lobar resection (2).

In addition to lung cancer, pulmonary metastases are present in 25% to 30% of patients dying from all types of cancer (3). For some patients with oligometastatic pulmonary disease, metastectomy is associated with an improvement in survival (4). External beam radiation traditionally has been offered as the alternative to surgical resection for NSCLC or pulmonary metastatic disease. Unfortunately, the 5-year survival following radiation for stage 1 and 2 NSCLC remains low at 15% to 20%, with local recurrence being the most common mode of failure (5,6).

Thermal ablation offers an intriguing therapeutic option to increase local tumor control and survival in patients with early stage NSCLC or with limited metastatic disease from nonlung primaries who are not surgical candidates because of poor cardiopulmonary reserve, anatomic constraints limiting resection, failure of traditional therapies, or refusal of operative approaches.

Up to now MWA of lung cancer has been performed by radiologists through a percutaneous approach with an “antenna insertion technique”.

The size and shape of the ablation zone created by MWA is the complex result of multiple factors such as the MW frequency, the design and cooling system of the antenna, the power setting and the total ablation time.

There have been several early clinical studies of percutaneous MW ablation for lung tumors in people, which have shown promising rates of local control even with tumors larger than 3 cm (7,8). Thus far, though, MW ablation has demonstrated high pneumothorax rates which may be related to the large antenna size and may improve with the development of smaller antenna (8).

Although the complication rate varies and can be expected to be higher in patients who have poor underlying pulmonary reserve, a minor complication rate of approximately 50% and a major complication rate of approximately 8% can be expected. In MW percutaneous ablation, pneumothorax rates up to 39% have been reported (8). This relatively high pneumothorax rate may be secondary to the larger, 14.5-gauge antenna currently available.

Less commonly reported complications following ablation include thermal damage to the phrenic nerve, intercostal nerves and brachial plexus.

Patients undergoing thermal ablation are also at risk for air embolism and tumor track seeding similar to what is seen with needle lung biopsy (9,10).

With MW percutaneous ablation, there have been several reports of severe skin burns, possibly requiring skin grafting (8). This is likely related to either shaft heating caused by inadequate cooling, or propagation of the MW energy along the shaft with multiple antenna ablations, resulting in nontarget tissue ablation. This issue should be addressed with the development of improved shaft cooling paradigms on future systems.

In order to reduce the complication rate a transbronchial approach through a dedicated flexible antenna to be inserted into the working channel of a flexible bronchoscope has been developed and is currently under investigation.

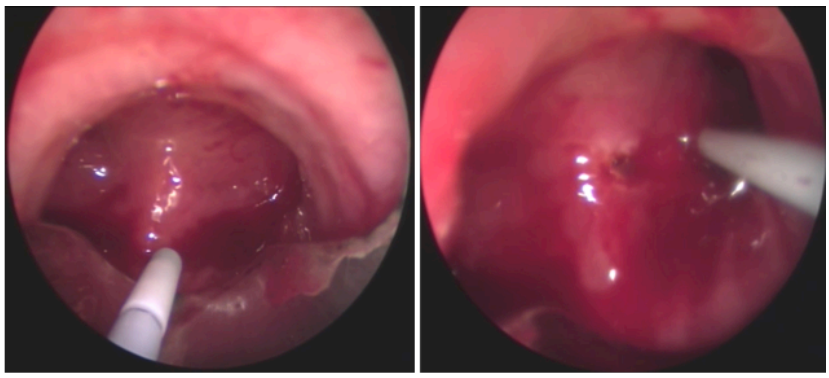
Besides, our intuition and the aim of this project was to investigate the potential of endobronchial MicroWave Ablation (eMWA) through the available 14 or 17 gauge needle to treat central airway obstruction for immediate airway patency restoring. In the design of this project this can be done through the rigid bronchoscopy technique in experienced centers.

Central airway obstruction can occur secondary to a number of lung primary or metastatic malignant and benign processes.

The degree of obstruction and severity of symptoms, the nature of the underlying disease and the patient's overall prognosis and quality of life impact the choice of intervention. The techniques of endobronchial coagulation and disobstruction allow restoring of airway patency, palliation of symptoms and improvement of quality of life.

The rigid bronchoscope is the preferred method of airway dilation with immediate improvement of ventilation. Multimodality approaches featuring a combination of several interventions are needed for long-term success. They can be distinguished into “slow methods” such as photodynamic therapy, cryotherapy and brachytherapy, and “fast methods” like laser, argonplasma coagulation and electrocautery.

The newly proposed technique of Endobronchial MicroWave Ablation through the rigid bronchoscope can be considered among the latter for rapid airway disobstruction and control of bleeding.



Endobronchial MicroWave Ablation (eMWA) in rigid bronchoscopy

The choice of one technique depends on the characteristics of stenosis, the condition of the patient, available techniques and the operator’s expertise.

6. TERMAL ABLATION OF LUNG TISSUE - LUNG NODULES

- Percutaneous trans-thoracic
- Transbronchial (bronchoscopy)

Surgery is universally accepted as the best choice of therapy in stage I non-small cell lung cancer (NSCLC). This is based on the favorable outcomes, according to pathologic stage, observed in patients who have been surgically treated. Therefore, non-invasive local treatments that make it possible to avoid resection of functioning parenchyma or prolonged general anesthesia represent a key point in the management of patients who are not eligible for surgery. External beam by Stereotactic Body Radiation Therapy (SBRT) has been traditionally considered as the treatment of choice in these selected cases despite the survival rate is less favorable when compared with surgery at 5 years. This treatment frequently is complicated by post-actinic pneumonitis which can worsen patient's clinical conditions. Over the last few decades, various innovative mini-invasive therapies have been developed as alternatives to surgery and thermal ablation is probably the most interesting. For pulmonary malignancies two main methods are used: radio frequency ablation (RFA) and microwave ablation (MWA) (1,2).

Microwave ablation (MWA) is a heat-based ablation technique in which coagulation occurs through dielectric hysteresis in which alternating electromagnetic waves, at frequencies of typically 915 and 2450 MHz with maximum power output of 45 and

140W respectively, agitate water molecules in tissue causing them to oscillate and rotate rapidly and thereby increasing their kinetic energy and converting the applied energy into heat and elevating tissue temperature to cytotoxic levels (> 60°C) (2-4).

In lung parenchyma, the presence of continuous blood flow and airflow adjacent the target is the most important factor to be considered. In particular, thermal conductivity and "heat sink" effect are the main obstacles in determining the efficacy of the procedure. Thermal conductivity is lower than in other organs because of the high percentage of air which makes it difficult to create ablations with sufficient margins. "Heat sink" effect causes heat dissipation away from the target tissue due to blood- and airflow, thus limiting the intended tissue damage (2,3).

MWA produces larger ablation zones than radiofrequency ablation (RFA) as it is not affected by the insulating effect of the normal lung, desiccated or charred tissue or by the heat sink effect from the adjacent vessels. In fact, MWA offer less susceptibility to heat sinks, faster heating to higher temperatures, larger ablation zones and the ability to penetrate high impedance tissues (i.e. aerated lung tissue) cause are not limited by lower thermal conductivity of lung or the increased impedance of charred tissues. MW energy also has been shown to effectively treat perivascular tissue and coagulate large vessels with improved efficacy near heat-sinks (2,3).

Furthermore, MWA allows for shorter periods of application by producing higher intra-tumoral temperatures than with RFA and these factors may account for the improved performance of MWA over RFA with larger tumor ablation zones. MWA operates at higher frequencies on the electromagnetic spectrum and, unlike with RFA, the energy

is not distributed through electrical currents. Thus, the microwave antennas do not require grounding pads, are not affected by pacemakers and multiple antennas can be simultaneously operated. The performance of MW ablation is highly system dependent and factors such as system frequency, total energy delivery and relative phase alternating fields produced by each antenna can greatly affect the resulting ablation zone size.

Although no studies have been performed in human to compare the relative effectiveness of MWA and RFA ablation in lung, there have been several promising studies performed in animal models. In particular, one study in swine model looked at a prototype 17 Gauge internally cooled MW antennae and showed that it produced ablation zones that were 25% larger in diameter and 50% larger in cross-sectional area than the ablation zones achieved with a similarly configured internally cooled RF ablation electrode (5).

Percutaneous transthoracic approach

The size, location and number of tumors were evaluated by conventional CT scan. The procedure requires mild sedation and analgesia by administration of Midazolam and Morphine intravenously. This procedure is performed using TC-guide under local anesthesia. A needle catheter called “MW antenna” is internally cooled by water or, in a recent prototype, by gas as CO2 that allow to control the overheating of the catheter, avoiding side effects. The MW antenna is inserted percutaneously under TC guide and

placed into the lesion. The microwave applicator is introduced along the same direction as the line connecting the puncture point and tumor center. The patients are instructed to hold their breath and microwave antenna is directly inserted until it reaches the predetermined location. CT scanning is performed again to confirm the location of the antenna tip and subsequently connect the antenna with the microwave ablation instrument and water-cooling device. The average operating time is 8 mins.

Feng W et Al have demonstrated, in their study to evaluate the clinical effects, CT image changes and side-effects of percutaneous MWA coagulation therapy for peripheral lung cancer, an overall response rate of 57.1% with an ellipsoid shadow 3.5 x 2.5 cm across in lesions immediately after coagulation; gasification within the coagulated area was observed in a week with a high density in the peripheral region and consolidation at 3 months. The lesion disappeared 1 year later with a complete tumor necrosis proved by biopsy without side-effects or complication.

The majority of complications is pleural-related as pneumothorax which may be due to the large antenna size and occurs about in 30-60% of patients with up to 19% requiring placement of a chest tube and up to 2% develops a persistent bronchopleural fistula necessitating prolonged pleural drainage. Additional complications related to the transthoracic puncture during percutaneous ablation include pleural effusion (0-34%), hemoptysis (up to 30%) and alveolar hemorrhage (0-45%), hemothorax, empyema and infection (0-18%), pain, skin burns (up to 9%) and tract seeding [6-7].

Percutaneous trans-thoracic MWA has been shown to be a safe and feasible technique for the treatment of peripheral lung cancer. It seems that its effect is largely determined

by the lesion size (worse outcomes for tumors > 3 cm) (5-8) and location in relation to the hilum (better outcomes for more peripheral tumors). Local control rates with MWA at 1 year are 78-96%; superior to RFA (about 77%) and approaching those with SRBT but 3-year survival is similar (29-56%) (8,9).

Nelson DB et Al by a systematic review (12) have analyzed the local recurrence of lung malignancies after MWA and the study showed a median incidence of recurrence from 9 to 37% and tumor size was consistently correlated to increase this risk, in particular, among tumors smaller than 3 to 4 cm was 5% to 19%.

In a retrospective analysis, Healey et al have demonstrated that the odds of primary technical success were 11.1 times higher for tumors < 3 cm (P = 0.0003) and for every millimeter increase in original tumor maximal diameter (OMD) the odds of not attaining success increased by 7%. Median time to tumor recurrence was 62 months and the rates were estimated at 22%, 36% and 44% at 1, 2 and 3-years respectively.

Transbronchial (tMWA) by flexible bronchoscopy approach

tMWA was described as early as 2013 (10). To date, in the literature, no studies have been performed to evaluate feasibility and efficacy of microwave ablation in central airway tumor and few recent studies, only in animal model, with new technical approach by gas (CO2)-cooled MW antenna (Neuwave ®), have demonstrated efficacy and safety of procedure.

In the ex vivo swine model study, Yuan H.B. et al achieved an effective (therapeutic) temperature of 60°C using power settings of 80 and 90 Watts with treatment times of 480 and 360 secs respectively at the distance of 20 mm from the antenna implying this would equate to an approximately 4 cm ablation zone determining cell death and necrosis coagulation. These results were significantly different in vivo model (diameters 22.7x15 vs 19.3x12.2 mm) and the range of effects was decreased sharply far from 20 mm radius due to respiratory motion and pulmonary blood flow "heat-sink". Histological evaluation of bronchial mucosa and cartilage demonstrated the maintenance of original organization structure, intact, without apoptosis of cartilage and presence plenty of fibrous scar tissue in the ablation area. No serious complication occurred. They demonstrate feasibility and safety of flexible bronchoscopy-guided water-cooled MWA (11).

A recent case report (13) described simultaneous treatment of multiple bilateral high-risk pulmonary nodules (without hilar or mediastinal lymph nodes enlargement) in a 47-year-old female that underwent MWA in the right lung and VATS segmentectomy in the left lung. They explained a multimodal approach based on performing lung biopsy of lesion by electromagnetic navigation bronchoscopy (ENB), pathology evaluation by ROSE with confirmed presence of malignant cells (adenocarcinoma in situ) and immediate MWA treatment and following the thoracoscopic procedure.

7. THE TATO SYSTEM

Background

The field of image-guided microwave ablation (MWA) therapies is very rapidly growing, both in technical development and clinical adoption. Since electromagnetic wave propagation is not limited by desiccated tissue, water vapour, or low-water content tissues, MWA may be the natural evolution of radiofrequency (RF) ablation, offering a more effective modality for tumors in the lung, bone, or cystic lesions.

Recent researches show a fundamental advantage in using multiple MWA antennas [1,3]: power distribution in a multiple-probe system is more effective, even compared to that of a single antenna providing the same amount of energy. Heating produced simultaneously by multiple nearby synchronous (coherent) or asynchronous (un-coherent) arrays of radiating sources can create larger ablation areas than what we might expect from a single applicator radiating the same amount of energy, by means of the effect called *thermal synergy*. This ability to perform multiple ablation simultaneously may allow the treatment of large tumors with concurrent overlapping thermal lesions or the ablation of several anatomically separate tumors at once. Furthermore properly assembled linear or conformal arrays of applicators can be used as surgical resection devices to reduce blood losses and to assist in coagulation of liver tissue during intraoperative and laparoscopic surgical procedures.

Multi-probe MWA ablations reduce the need to repeat treatments, decrease inadequate treatments of larger tumors, and increase the speed of the therapy, thereby decreasing the complication rate.

Tumor dimensions

The median liver tumor diameter currently being targeted by thermal ablation is approximately 25 mm [4]. Therefore, a > 30 mm ablation zone is recommended to treat an average tumor with an appropriate 5-10 mm radial margin, aiming at a lower probability of local tumor progression [5].

Although the tumor diameter can vary in the 8 to 60 mm range, more than 70 % of the diagnosed tumors have D < 30mm and this percentage is increasing thanks to the continuous advances in image technologies (US, CT, MR), that allow to discover tumors in their early stage.

TATO system operating mode

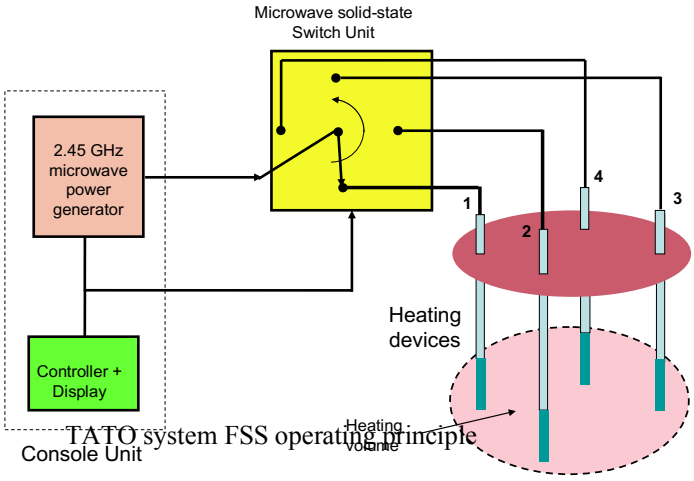
TATO has been conceived as an advanced state of the art multi-applicator system for treating isolated or multiple metastatic tumors of different sizes and shapes in liver, lung, kidney, breast, bone and prostate.

The TATO unique asynchronous operating mode [6,7], called Fast Sequential Switching (FSS™) provides many advantages in terms of system complexity reduction, robustness and operational flexibility without suffering any significant

power losses and maintaining a high overall energy efficiency that allows to operate with a maximum MW power of only 100W.

The TATO system is highly innovative and stands out for its compactness and portability, offering intuitive and rapid touch screen setting of the treatment parameters that can be easily updated also during the procedure.

TATO system view



TATO system FSS operating principle

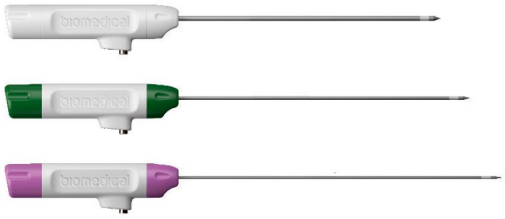
TATO Switching Unit capable of feeding up to four heating devices (applicators)

TATO applicator innovative technology

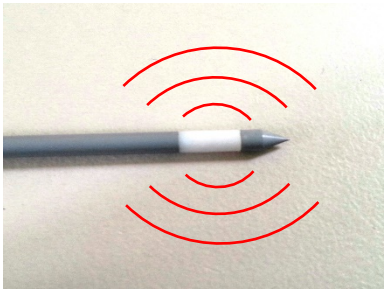
TATO's Very Low Loss (VLL™) applicator technology [6] (patent pending) has been developed within a strict academic-industry collaboration that leaded to a solution unique for its simplicity, robustness and very high energetic efficiency. This novel dimension-scalable device opens the possibility of performing tumors thermal ablation without applicator's cooling, thus dramatically simplifying the procedure and assuring very high reliability and reproducibility of the ablation dimensions and volume.

Using this innovative device the physician is allowed:

- to choose the optimum applicator size for the best treatment procedure (laparoscopic, open surgery, robotic surgery);
- to operate with single or multiple uncooled applicators, with great advantages in term of usability, reproducibility and procedural safety;
- to quick connect or disconnect the feeding cable through a microwave snap-on connector, easing applicator's insertion and placement under CT, US and MR guidance;
- to combine MWA with PEI (Percutaneous Ethanol Injection) and infuse drugs and contrast media by way of the same device before, after or during the ablation procedure.

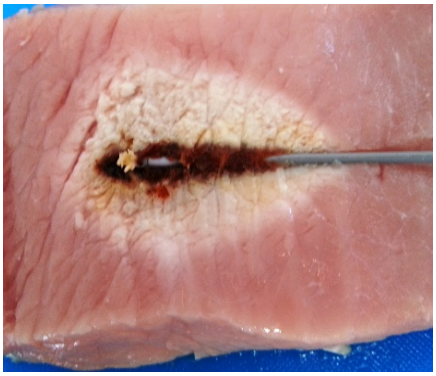


13G (white), 14G (green) and 17G (violet) TATO uncooled applicators

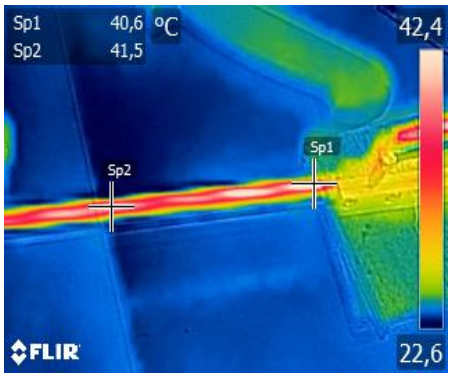


14 G radiating applicator Tip

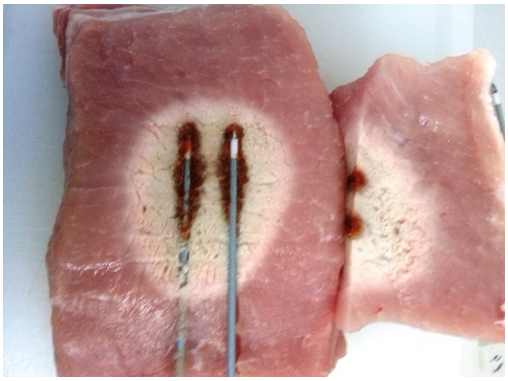
Ex-vivo ablation results



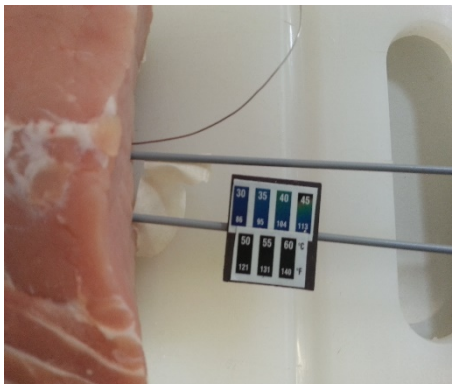
Typical ablation performed on ex-vivo swine tissue using an uncooled 14 G applicator.
Ablation dimensions: 4x5.6 cm.
Pin=50W T=10 min.



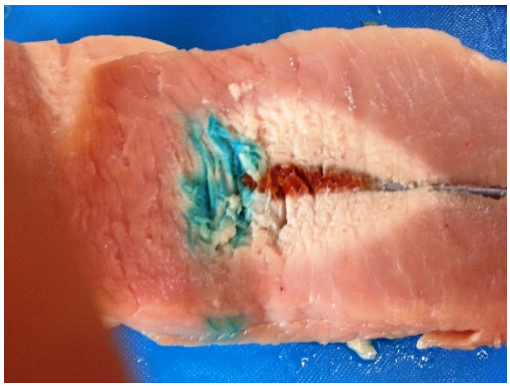
Thermal image showing temperature distribution along the shaft.
Pin=50 W T=10 min



Typical ablation performed on ex-vivo swine tissue using a couple of uncooled 17 G applicator.
Ablation dimensions: 4.8x5.2 cm.
Total Pin=50W T=10 min.



Thermocromic magnetic label clamping a 14 G applicator's shaft.
Green colour indicates a temperature well below 50 °C.
Pin=50 W T=10 min



Example of the infusion of a contrast media through the applicator's tip

Experiments have been made employing selected pieces of swine loin because:

1. ex-vivo loin and liver have practically the same electrical and thermal properties;
2. ex-vivo loin is more homogeneous than liver and the ablation border (T>60°C) is better highlighted.

It is worth noting that moving from ex vivo to in vivo tissues the electromagnetic and thermal properties vary significantly due to the presence of the blood perfusion, becoming also time and temperature dependent.

Tables of ablation dimensions in ex vivo liver tissue

Tables are obtained by interpolating results of an experimental campaign performed on many (>200) fresh ex-vivo swine liver pieces at ambient temperature.

Table 1: Single applicator, 10 min treatment time

Applicator Gauge	**Maximum power without cooling (W)**	**Ablation diameter D (cm)**	**Ablation length L (cm)**
14	**50**	3.8±0.3	5±0.5
17	**30**	3±0.3	4.5±0.6
18	**15**	1.5±0.2	2.5±0.5

Table 2: Multiple applicators, 10 min treatment time

Applicator number	**Configuration**	**Suggested inter-applicator spacing (cm)**	**Ablation cross-section (cm)**	**Ablation length (cm)**
2	couple	1.5	(1.4 D) x (1.3 D)	L
3	equilateral triangle	1.6-1.8	(1.5 D) x (1.5 D)	L
4	square	1.6-1.8	(1.6 D) x (1.6 D)	L
4	linear array	1.5-2.5	(2 D) x (1.2 D)	L

Table 2 allows to estimate the cross-section and length of the multiple applicators ablation from the dimensions D and L of the single applicator ablation in the hypothesis that the total applied power is a multiple of that of a single applicator.

The dimensions given in the Tables 1 and 2 should be conservatively reduced of 30% to 40% when operating on living in-vivo tissues to take into account blood perfusion

that produces a thermoregulatory heat sink effect. Targeted embolization procedures can significantly reduce blood perfusion and increase ablation volumes.

It is worth nothing that D and L dimensions increase of about 10% by increasing treatment time to 15 min.

An increase in power beyond the limits specified in Table 1 may cause overheating of the shaft with potential damage to the crossed healthy tissues.

Applicator reflection coefficient and temperature control

The reflection coefficient Γ of a MW applicator is a basic parameter that describes how much of the applied input power is reflected back to the generator and therefore does not contribute to the tumor heating. For example a too high values of Γ will be exhibited by an applicator damaged or not properly inserted into the tissue.

The temperature T of the applicator's shaft is strictly dependent on the Γ coefficient, in fact an increase of Γ always causes an increase of shaft temperature and a more pronounced comet effect.

In the TATO system the Γ parameter is continuously monitored and an automatic control loop provides to turn off the MW power if a too high Γ is detected, giving an acoustic alert and a failure message.

A direct temperature monitoring can be made using a magnetic thermochromic label clamped to the shaft that can also act as a sliding reference element to adjust and limit the needle insertion depth.

Applicator cooling

For high power (>50 W) single applicator treatments the device needs cooling in order to maintain shaft temperature below 50 °C and reduce comet effect and tissue carbonization.

TATO applicators are designed for an efficient air or gas (CO2) cooling through a luer lock pneumatic connector; a separate unit. provides to the distribution of the cooling fluid.

Conclusions

Combining the Fast Sequential Switching (FSS) and Very Low Loss (VLL) proprietary technologies, TATO is the only MWA multi-applicator system that allows to treat single and multiple tumor lesions using very safe uncooled ablation devices; in fact, if the power limits of Table 1 are not exceeded a thermal damage will be never produced to the healthy tissues.

Practically thermal ablations having 3 cm maximum diameter can be produced in vivo using a single uncooled applicator, while larger ablations up to 6 cm diameter require the use of 2 to 3 applicators depending on the ablation length and shape. Elongated ablation, useful for the resection of pieces of organs without bleeding (typically the liver) require 2 to 4 uncooled applicators.

We can conclude that solitary tumors having < 2.5 cm diameter can be ablated using a single uncooled applicator with an appropriate radial margin. Larger tumors, in particular those of irregular or elongated shape or placed very near to large vessels

require a well-planned multi-applicator approach to reduce the risk of a runaway ablation.

High power single applicator ablations having D>5cm are also possible but require device cooling, fast temperature control loop and very high caution in applicator placing for avoiding unexpected thermal damage to the nearby healthy tissues and organs.

8. ORIGINAL RESEARCH
THE CENTRAL AIRWAYS (RIGID BRONCHOSCOPY)

Introduction

MWA is an emerging technology in the field of tumour thermal therapy, used in minimally invasive surgery or percutaneous interventions [10]. It is applicable for the thermal ablation therapy of different kinds of tumours where it is emerging as a valuable alternative to radiofrequency ablation (RFA).

The goal of treating tumours with MWA is thermal degeneration of proteins and a consequent coagulative necrosis.

Up to now MWA of lung cancer has been performed through a percutaneous approach with an “antenna insertion technique” that is almost identical to that of CT-guided biopsies. Different MWA systems are presently on the European and American markets without considering those that are available only on Asian markets. Each device differs from the others considering low-frequency (915 MHz) or high frequency (2450 MHz), with the maximum output power varying between 32W and 140 W and some of them allowing the concomitant use of up to three antennas. The size and shape of the ablation zone created by MWA is most likely the complex result of multiple factors such as the MW frequency, the design and cooling system of the antenna, the power setting and the total ablation time [9].

Aim of This Project

The purpose of this project is to determine the feasibility and safety of the endoscopic use of microwave ablation (eMWA) through rigid bronchoscopy in central airway obstruction secondary to a number of lung primary, adjacent or metastatic malignancy not eligible for surgery.

Endpoints

Feasibility

- Movability of the antenna into the bronchoscope and in relation to other instruments (rigid optic, aspiration catheter)
- Definition of airway generation limit (lobar/segmental or subsegmental level) at which the rigid antenna of MW can be used
- Proof of penetration of the needle-antenna into the airway wall
- Proof of penetration of the needle-antenna into the tumor mass
- Proof of feasibility of continuous oxygenation during the whole procedure

Efficacy

- Changes in lesion volume on CT scan before and 1 week after treatment (endobronchial MWA, eMWA) and when a CT scan of the thorax is performed according to standard follow up.

- Changes in airway lumen area before and after endobronchial MWA treatment as assessed endoscopically and by Chest HRCT at 1 week and whenever a CT scan of the thorax is performed according to standard follow up.

- Timing of palliation (recurrence of airway stenosis requiring new treatment)

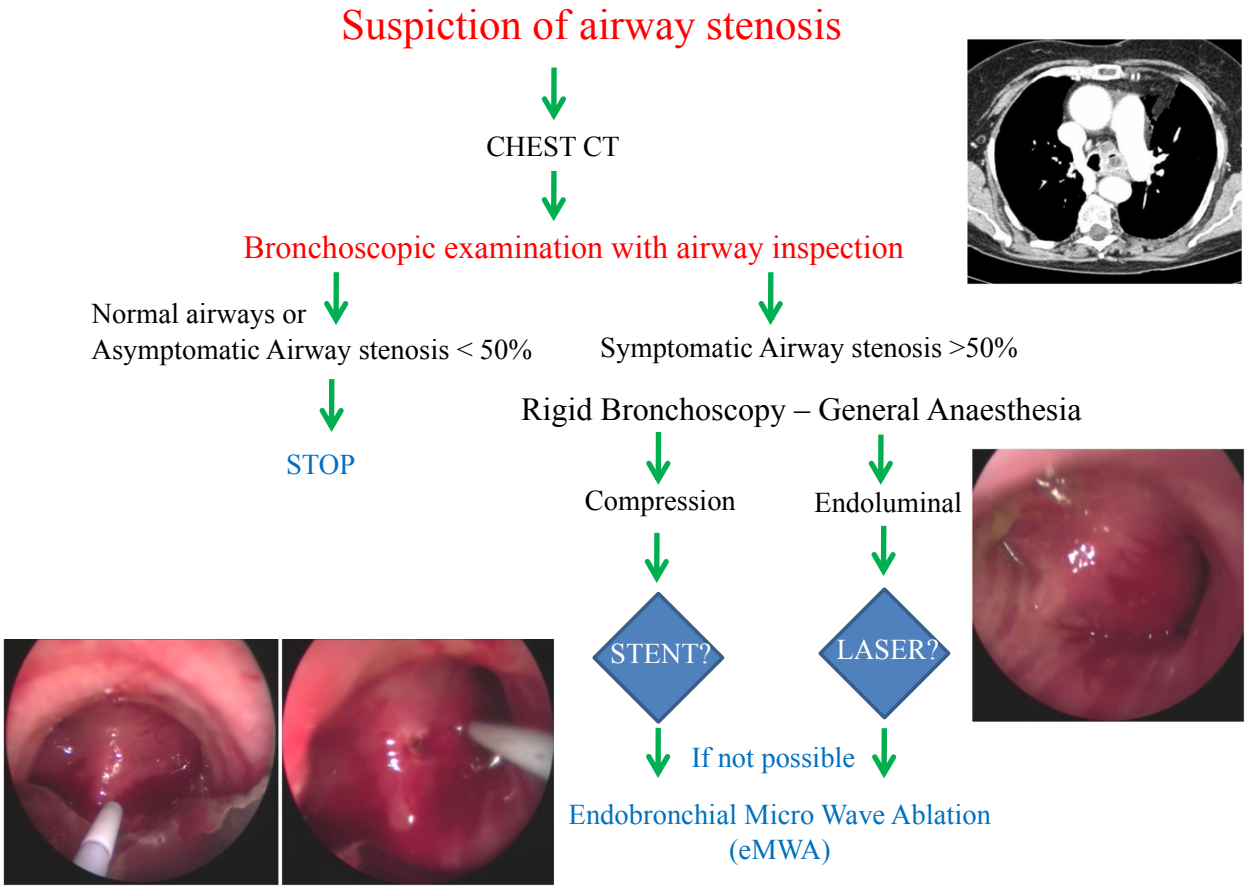
Safety

- Rate of expected adverse events such haemorrhage, pneumothorax, pneumomediastinum, fistula between tumour and airway lumen, excavation of the lesion, infections.
- Description and rate of unexpected adverse events.

ANTICIPATED ADVERSE EVENTS:

- haemorrhage
- pneumothorax
- pneumo-mediastinum
- fistula between tumour and airway lumen
- excavation of the lesion
- infections

Study Plan



Suspiction of airway stenosis Diagnostic&Therapeutic flowchart

Consecutive patients who have been evaluated for recanalization of malignant central airway stenosis were recruited from the Interventional Pulmonology department at Careggi University Hospital in Florence and from the Pulmonary Endoscopy Department of the University Hospital ASST Spedali Civili in Brescia, Italy.

Written informed consent was obtained from all patients.

Inclusion criteria:

- Inoperable primary lung cancer, endobronchial metastatic lesions or extrinsic tracheal or bronchial compressions due to enlarged mediastinal lymph nodes or adjacent masses.
- Endobronchial lesions causing more than 50% reduction of airway lumen in symptomatic patients for dyspnea or mucus retention with post-obstructive infections.
- Airway stenoses with more than 50% reduction in lumen caused by extrinsic compression in symptomatic patients for dyspnea or mucus retention with post-obstructive infections.

Exclusion criteria:

- Asymptomatic patients
- Operable lung cancer
- Severe coagulation dysfunction
- Severe respiratory insufficiency or other organ failure

Procedures

Bronchoscopic resection using MWA was performed through rigid bronchoscopy with general anesthesia [28-30] in a specially equipped bronchoscopy suite. The patient's oxygenation and ventilation are supported through the rigid bronchoscope by

Intermittent Negative Pressure Ventilation (Poncho or Cuirasse) which is associated with lower incidence of complications, such as acidosis due to hypercapnia, compared to spontaneous-assisted ventilation or jet ventilation [32]. Oxygen delivery never stops neither during the activation of MWA.

MWA systems generate an ellipsoidal microwave field around a needle-like applicator that is introduced into the tissue. Microwaves are part of the electromagnetic spectrum with frequencies between 300 MHz and 300 GHz. Since water molecules have a positively and negatively charged pole, they tend to align with the electromagnetic waves. The oscillation of the electromagnetic wave therefore causes a rapid flip motion of the water molecules which results in heating of the adjacent tissue through the mechanism of dielectric hysteresis. If the MW frequency perfectly matched the molecule-specific resonance frequency of the water molecules, all energy would be transformed into heat, but the penetrability into the tissue would be low. The frequency used by current MW manufactures (915 MHz and 2450 MHz) only partially matches the resonance frequency of the water molecules and therefore MWs assure efficient energy conversion into heat with satisfactory tissue penetrability [9].

Endobronchial lesions: During the procedure MWA is performed inserting a 14 or 17 gauge dedicated needle into the endobronchial lesion to obtain tissue devascularisation and necrosis. The lesion is then resected using the barrel of the rigid scope (Storz or Dumon-Efer) and removed with the aspirator and/or rigid, optic forceps.

Pure compressions: During the procedure MWA is performed inserting a 14 or 17 gauge dedicated needle into the bronchial/tracheal wall at the level of the obstruction in order to obtain immediate volume reduction of the compressing mass. MWA is delivered stepwise until sufficient airway calibre is obtained.

Follow up

Chest XR was performed in the first 24 hours after the procedure.

Chest CT scan was performed at 1 week and then according to standard follow up (three to six months intervals) and patients overall conditions

FOLLOW UP

- Chest XR in the first 24 hours after the procedure
- Chest CT at 1 month
- Chest CT whenever clinically necessary
- Chest CT according to standard follow up (three to six months intervals)
- Bronchoscopy whenever clinically necessary

Results

Starting December 2017 all patients referred to the Center of Interventional Pulmonology of the University Hospital Careggi in Florence and after December 2018 to the Pulmonary Endoscopy Department of the University Hospital ASST Spedali Civili in Brescia, Italy, for Laser Assisted Mechanical Resection and/or stenting of lung malignancies were considered for eMWA whenever conventional laser and stent dilation was not feasible.

Patients who required treatment with eMWA generated by TATO were affected by primary lung tumors (Small Cell or NSCLC) or lung metastasis with no indication for surgical treatment. The most common indication was extraluminal compression of tracheal or bronchial lumen.

eMW were administered using a dedicated 14 Gauge needle catheter inserted through the bronchial and/or tracheal wall in rigid bronchoscopy in one single session.

eMW were administered in the range from 40 to 50 watts for a total of 25 to 140 sec divided in 2 to 6 applications.

Ten patients underwent eMWA of lung primary or secondary tumors between December 2017 and December 2019.

AGE	site TRACHEA	Site CARENA	LMS bronchs	RMS bronchs	COMPRESSION	ENDOLUMINAL	STENOSIS %	Stent TRACHEA	Stent LMS	Stent RMS
82	X	-	-	-	X	X	60	X	-	-
54	-	X	X	X	X	X	70	-	X	-
75	X	-	-	-	X	-	50	X	-	-
82	-	X	-	X	X	X	80	-	-	X
49	-	X	X	X	X	X	75	-	X	-
56	-	-	-	X	X	X	80	-	-	-
77	X	-	-	-	X	X	80	X	X	-
82	-	X	X	-	X	-	80	-	X	X
71	X	-	-	X	X	-	75	-	-	-
53	X	-	X	X	X	X	85	-	-	X

Five tracheal and 5 bronchial stenoses were treated. In 8 cases infiltration of the bronchial mucosa was also present and in one case eMWA was performed through a fully covered metallic stent which was implanted several years earlier. In 7 patients a silicon airway stent was inserted in the same procedure after eMWA treatment. In one patient two stents were necessary to maintain airway patency. The reduction of the stenosis-infiltration after treatment with eMWA was confirmed after 1 month by bronchoscopy and chest CT in all patients who survived. In 3 cases the endobronchial stents could be removed.

In 2 cases eMWA could reduce the granulomatous reaction given by the metallic stent, allowing an easy substitution with a silicon one.

Radiology - follow up

Pt	X ray 1w	CT 1mo	CT 3mo	CT 6mo	CT 1yr
1RA	x	x	-	-	-
2GF	x	x	x	-	-
3LG	x	-	-	-	-
4PL	x	x	x	x	-
5CI	x	x	x	-	-
6FA	x	x	-	-	-
7BA	x	x	x	x	-
8PN	x	x	x	x	x
9MC	x	x	-	-	-
10BE	x	-	x	-	-

Only one patient completed the 12-month follow up, 6 patients died during the 3 months follow up and 3 patients completed the 6 months follow up. None of the patients' deaths was directly related to the eMWA treatment. Causes of death were

sepsis in 3 patients, one empyema, one cerebral ischemia, one myocardial infarction and 3 respiratory failure, 2 of these were due to pulmonary lymphangitis and one to Sars-Cov2.

CAUSES OF DEATH

- 3 sepsis
- 1 empiema
- 1 cerebral ischemia
- 1 myocardial infarction
- 2 respiratory failure in pulmonary lymphangitis
- 1 respiratory failure due to Sars-Cov2

Standard CT follow up (three to six months) was performed in 9 of the 10 patients during the 1 to12 month follow up. Seven patients out of 10 had a follow up bronchoscopy one month after eMWA. Three patients had a second flexible diagnostic bronchoscopy mainly for mucus retention and to re-evaluate airway patency. Neither bronchoscopic nor CT follow up was ever performed in one of the patients who died 2 weeks after the procedure due to cancer progression and respiratory failure.

Bronchoscopy - follow up

Pt	1w	1mo	3mo	6mo	1yr
1RA	x	x	-	-	-
2GF	x	x	x	-	-
3LG	x	-	-	-	-
4PL	x	x	x	-	-
5CI	x	x	x	-	-
6FA	x	x	-	-	-
7BA	x	x	x	-	-
8PN	x	x	x	-	x
9MC	x	-	-	-	-
10BE	x	x	-	-	-

When CT scan was performed in this stage 4 cancer patients systemic progression of the disease was systematically reported, but the treated tumour mass volume was systematically reduced without any recurrence of severe airway stenosis.

No adverse events were reported either during the procedures or in the follow up, In particular no fistula in the site of needle puncture was detected, no severe bleeding or excavation of tumor mass.

None of the patients required a new endobronchial treatment of the stenosis. (The reduction of the lesion's volume permitted the maintenance of an adequate airway lumen preventing the occurrence of dyspnoea and respiratory failure related to the stenosis).

Discussion and Conclusions

Although the one described in this research project is only a very limited experience, in one single center, by a single operator, with no other such treatments described in the literature to date, endobronchial Microwave Ablation (eMWA) appears to be a feasible and safe technique to restore airway patency in patients with neoplastic airway infiltration and compression causing severe lumen reduction and shortness of breath, atelectasis and mucus retention.

No precise data about treatment efficacy are available since this project is based on the compassionate use of the newly proposed technique in an otherwise "standard of care" setting and no extra-exams such as CT scans or bronchoscopies aimed at measuring the volume of the tumour mass before and after eMWA or bronchoscopies aimed at measuring the exact size of the airway lumen. Nonetheless quite interesting and significant data are described in the result paragraph regarding immediate airway lumen restoration and persistence of the effect which has even led in some cases to

stent removal after prolonged tumor mass reduction thanks to MW mediated tissue denaturation.

Due to its apparently good safety profile, particularly regarding absence of complications but also prevention of tumor bleeding, which is very common during laser assisted mechanical resection of lung primary or secondary tumors, eMWA could be considered as an alternative to Laser Assisted Mechanical Resection even when this technique is available and feasible.

The significant, immediate but also progressive reduction in volume of the treated extraluminal mediastinal compressing tumor mass makes it possible to consider eMWA also as an alternative to airway stenting, especially when sacrifice of bronchial branches can’t be avoided.

PUBBLICATIONS AND FUTURE DIRECTIONS

(Multicenter Clinical Trial)

Uptodate results of this project have been presented and published at the most important international respiratory conferences: European Respiratory Society Congress (ERS Congress) 2017, American Thoracic Society Conference (ATS Conference 2018). An original research paper is to be submitted for publication to one of the most relevant journals in the respiratory field.

A multicenter prospective clinical trial has been proposed with the support of Biomedical, Italy and Terumo, Japan. It is meant to further investigate feasibility, efficacy and safety of endobronchial Microwave Ablation of central airway tumour masses in the most experienced centres of Interventional Pulmonology and Rigid Bronchoscopy in Europe (Ancona, Italy; Brescia, Italy; Marseille, France; Barcelona, Spain; Heidelberg, Germany)

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