Techniques Used in Lung Metastasectomy

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It is generally agreed that the object of surgery is not achieved without complete removal of all pulmonary metastatic tumor. In current practice, pulmonary metastasectomy may be performed more than once so conservative resections are recommended. Preservation of as much functioning lung parenchyma is an agreed principle while removing a centimetre of the surrounding pulmonary tissue. For nodules located peripherally, stapled wedge resection is generally the preferred treatment but for large or central lesions, segmental resections, lobectomy, or occasionally, pneumonectomy may be required. Other techniques have been proposed as an alternative, both to save as much surrounding lung as possible and reduce trauma to patients with a low cardiopulmonary reserve. The following techniques are described in this literature:

1. Cautery resection (precision resection)
2. Laser resection
3. Ligasure system
4. Ultracision scalpel
5. Saline enhanced thermal sealing system
6. Image—guided ablative therapies
7. Stereotactic radiosurgery (CyberKnife)

CAUTERY RESECTION (PRECISION RESECTION)

This type of resection has been proposed to reduce the amount of parenchymal resection in patients with multiple lesions (metastases) or in patients who are not considered good candidates for segmentectomy or lobectomy. Deep-seated lesions or nodules located on the broad surface of the lung may be excised by coring them out of the parenchyma using cautery. This method was initially described by Perelman[1] and subsequently proposed with Cooper et al.[2]; it consists of painstakingly slow coagulation of the surrounding lung parenchyma with individual ligation of small vessels and bronchi in the depth of the resultant cavity.

When the precision cautery dissection technique is used, the lung must be inflated. If deep seated lesions are to be excised, the procedure is begun on the surface of the lobe nearest to the lesion. The electrocauthery is used to outline a circle on the pleural surface corresponding to the size of the core of lung to be excised. Using fine-tipped cautery forceps, very small bites of tissue are coagulated and incised with scissors. Thus, the lung tissue to be excised is separated from the surrounding lung without bleeding or major leakage of anesthetic gas. Blood vessels or bronchi are isolated and divided between ligatures. This technique is not ideally suitable for the video-assisted thoracoscopic surgery approach since it requires the lung to be in an inflated state. Electrocautery on a high setting generates smoke, charred tissue sticks to the electrode, and moderate sized blood vessels bleeding before coagulating. It is difficult to cope with these thoracoscopically.

LASER RESECTION

Laser has three major advantages: it permits limited excision of deep-seated lesions sparing lung tissue as much as possible; there is minimal deformity or damage to the adjacent lung tissue; for lesions located near a major bronchus or vessel a maximum margin of tissue around the lesion can be taken without injury to these adjacent structures. The major disadvantage is that the technique is tedious and time consuming.[2] In 1985, LoCicero et al.[5,6] reopened the debate on the use of lasers in open thoracic surgery. His initial research was performed with a CO_2 laser; however, this is a pure absorption or cutting laser and is inadequate for lung surgery. As a result, a number of centers in the United States, Japan, and Europe began experimenting with 1064 nm Nd:YAG lasers, using bare fibers and sapphire tips to perform superficial resections but failed with central tumors.[7–12]

On the basis of that initial experience, further research on laser devices and wavelengths have been promoted to improve results. The lung parenchyma has a typical water content of 80% but a very low tissue density (only one-fifth of the liver parenchyma), a very low heat capacity, and variable air content and is an ideal organ for photothermal

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laser applications. Giving the high vessel density, resecting lung parenchyma requires laser wavelengths with powerful coagulation capability and excellent cutting properties to prevent bleeding and prolonged air leakage. For these reasons, the 1318-nm laser is the only one to be considered to work on the lung parenchyma; this is due to its 10 times higher absorption of water, with a still sufficient laser light scatter related to its proximity to the beginning infrared spectrum, able to satisfy the vital coagulation requirements.[7] The disadvantage of this promising wavelength was related to the difficulty in developing a laser device able to deliver a satisfactory power output. The only laser device able to produce this wavelength in the 1980s was the Nd:YAG laser delivering 25 Watt power output on a second wavelength level; this was sufficient to start with clinical application. Ten years later, in 1996, a Nd:YAG laser system has been developed delivering a power output of 40 Watts; this improvement was obtained by increasing the system's efficiency to a maximum but the main disadvantage, that is a time consuming resection process remained. Finally, in 2007, due to nanotechnology a pure high power diode laser was developed; this device is now able to deliver 100 Watts of the 1318 nm wavelength. This laser device, configured as a bare fiber on a handpiece, delivers power densities of 80 kW/cm^2 at tissue level, reducing the resection time to one-third. Thirty metastases in one lung ranging between 1 and 2 cm (60% peripheral–40% central) can now be resected in an hour. The benefit of the improvement for the patient is a significant reduction of postoperative photo thermal edema of lung tissue due to the lower heat exposure time.

Laser metastasectomy is usually performed through a muscle sparing anterolateral thoracotomy (staged 3–4 weeks for bilateral lesions) after fulfilling the standard indication criteria for pulmonary metastasectomy. All visible and palpable nodules are noted; in the collapsed lung the nodules are dissected from the residual lung by the most direct route with 2 to 3 mm tumor margins (plus a 5-mm rim of residual lung necrosis secondary to laser energy dispersal). In comparison with electrocautery, ultrasonic or ligasure incisions the 1318-nm noncontact laser resection can be performed from the periphery up to the center of a lobe without bleeding. In this way metastases up to diameters of 8 cm can be resected; up to 100 metastases per lung have been removed.[13] Within one-thousandth of a second, heat dissipation reaches the volume of 20 to 30 alveoli triggering their shrinking. The interstitial space, capillaries, small lymphatic and blood vessels are closed avoiding tumor cell spread. Exposed bronchial branches at the segmental level are usually over sewn with absorbable suture and the segmental vessels are ligated. The lung architecture and orientation is reconstructed after each nodular resection by reapproximating the visceral pleura with a running absorbable suture. This technique avoids distortion of the lung tissue.

The group that has dedicated more efforts to the development of this technique is the one of Rolle et al.[14] In their initial experience with the first 100 patients, overall survival for complete curative resection was 82% at 1 year, 66% at 3 years, and 30% at 5 years. In 2006, this group published the results on 328 patients with a 5-year survival of 41% following laser resection of a mean of eight metastases per patient (range 1–124).[15] They recommended laser resection of 20 metastases and more because a 5-year survival of 26% was observed.

The new 1318-nm laser demonstrates a significant influence on parenchyma sparing during metastasectomy and seems to minimize complications; it may expand the indications for surgical treatment for pulmonary metastases; allowing more complete resection; patients at present not considered ideal candidates because of poor residual lung function or multifocal pulmonary disease may be included in the future. The disadvantages of a laser system are the initial financial investment, staff education and training in security and handling of this special technology, the additional need of a high performance evacuation system and other unpleasant things like wearing goggles.

USE OF THE LIGASURE SYSTEM

The LigaSure Vessel Sealing-System[16–19] is an electrothermal bipolar tissues sealing system proposed for nonanatomic staplerless pulmonary resection. The LigaSure Vessel Sealing-System allows local hemostasis by vessel compression and obliteration through the emission of a bipolar energy determining the fusion of collagen and elastin in vessel walls and subsequent tissue reformation with creation of a permanent seal zone. The system automatically detects the thickness of tissue to be coagulated defining the amount of energy required to minimize the effect on surrounding tissue (1.0 mm–1.5 mm). The vessel and airways sealing capabilities of the LigaSure system have been assessed detecting the burst pressure for each anatomic structure using a pig lung model[19] indicating it is effective for vessels less than 7 mm in diameter but for bronchi only up to 4 mm.

The experience with LigaSure System is limited in thoracic surgery. Clinical series[18,19] totaling 84 wedge resections in 36 patients, through video-assisted thoracoscopic surgery and thoracotomy indicate it is effective. Surgical parameters (operating time, bleeding, intrapostoperative complications; postoperative drainage stay, hospitalization) are similar to those observed using staplers and it allows better tailoring of resection margins with minimal thermal damage. With a thoracoscopic approach, the Ligasure system avoids the difficulty encountered in manipulating the stapler within the thoracic cavity and avoids the use of multiple reloadable cartridges, thus reducing the costs of disposable surgical supplies.

The major disadvantages encountered using this system are the longer operative time required to perform the resection of deeply located pulmonary lesions and the impossibility of safety excising lesions near the hilum or the great vessels.

ULTRACISION SCALPEL (HARMONIC SCALPEL)

Ultracision works by liberating energy at the tip of the instrument as an ultrasonic wave with a frequency of 55.5 kHz. The longitudinal waves coagulate by denaturing proteins. Tissue is separated by forming steam bubbles with a

temperature not exceeding 100°C. Further advantages include reduced lateral spreading of heat, which allows operating near vulnerable structures, and minimal smoke production. The velocity of tissue separation can be controlled very well by variation of manual pressure. The coagulative and cautering effect on tissue has been verified clinically by the excellent control of bleeding,[20] and histologic examination of the resected lung tissue[20–23] in lung parenchyma of animals and humans.

SALINE-ENHANCED THERMAL SEALING

It was recently shown that the familiar diathermy with a continuous flow of electrically conductive saline between the tissue and the diathermy electrode results in marked changes in the coagulative property of the diathermy on living tissue. Two new devices, a monopolar floating ball device and a bipolar sealing forceps, provide a continuous flow of electrically conductive saline to the interface between a metal electrode and tissue. The saline couples radiofrequency electrical energy into tissue in which it is converted into thermal energy. The flow of saline provides cooling to limit peak tissue temperatures to 100°C or less. This is different from other conventional electrosurgical devices in which tissue temperature can easily exceed 300°C, resulting in tissue desiccation, char formation, smoke generation, electrodes sticking to tissue, and undesired lateral thermal damage. The new technology avoids these undesirable tissue effects, while producing the levels of tissue temperature required to achieve both hemostasis and pneumostasis of lung tissue. These two devices have been used to perform both nodulectomies (floating ball) and wedge resections (bipolar sealing forceps).[30] The resected specimens were carefully examined to assess thermal injury at the margins; the thermal spread averaged 2.5 mm (range 2.2–3.6 mm), and there was no difference in the depth of coagulative necrosis between the floating ball device and the sealing forceps. The surgeon needs to individually divide the coagulated vessel and bronchiole and more time is needed compared with the conventional electrocauthery or laser procedures. Also, as the operated lung is deflated, there is a tendency to remove more functional lung tissue than would be necessary or desirable. This drawback can be overcome by experience. Pathologic interpretation of the resection margin is not a concern since the depth of the coagulative necrosis caused by thermal spread averaged only slightly more than 2 mm. This compares favorably with the conventional technique using staplers, which must be removed before cutting microscope sections. Both instruments can be used in open and thoracoscopic procedures.

IMAGE—GUIDED ABLATIVE THERAPIES (THERMOABLATIVE THERAPIES)

Less invasive therapies have been proposed. There is a question though about whether they accomplish complete eradication. The margins are not amenable to histologic proof. Their attraction is that they do not required general anesthesia.

Three distinct thermoablative therapies are currently available:

- Radiofrequency ablation
- Microwave ablation
- Cryoablation

Radiofrequency Ablation

Percutaneous thermal tissue ablation is performed with electrodes inserted into the lesion under imaging guidance; the tip has a non-insulated portion that generates medium frequency electromagnetic waves of 400–500 kHz. Adhesive grounding pads are applied to the thighs or back. The insertion technique is similar to a routine percutaneous biopsy. The mechanism of tissue heating for radiofrequency ablation is frictional or resistive energy loss caused by the motion generated by the ionic current. Alternating radiofrequency current agitates ions in the tissue surrounding the needle creating frictional heat, which denatures and destroys tissue at predictable temperatures, in a relatively predictable volume.

The electrode is inserted directly into the tumor with the use of ultrasound for chest wall and pleural based masses; computed tomography (CT) or magnetic resonance are used for lesions located deep in the lung parenchyma.

Lung tumors seem to be good targets for radiofrequency ablation because the surrounding air in the adjacent normal lung parenchyma provides an insulating effect, thus concentrating the energy within the tumor.[33] As a result, less radiofrequency energy deposition is required to achieve adequate tumor heating than with intrahepatic pathology. Conversely, if there is a large vessel nearby heat is conducted away. Interest in this procedure in the treatment of lung neoplasms is demonstrated by the increasing number of reports published.[35–42] There is heterogeneity in these studies, including various approaches (percutaneous or open), type of device, patient characteristics and duration of follow-up.

It is reported to be low risk and well tolerated but the most frequent complication, pneumothorax, occurs in up to 43% of the patients[35] when the transcutaneous approach is used. Other reported complications were intraprocedural pain, hemorrhage, hemoptysis, persisting air leaks, acute respiratory distress syndrome, reactive pleural effusions, damage to the adjacent anatomic structures, skin burns, and infections or abscess formation. The authors agree that lesions larger than 3.5 cm are difficult to destroy.[43] There are currently three commercially available systems. Of these systems, two (Radio-therapeutics, Boston Scientific and RITA Medical Systems, Inc) use a deployable array electrode that consists of 10–16 small wires deployed through a 15–17 gauge needle. The third system (Valleylab, Inc, Boulder, CO) uses a single or triple cluster perfused electrode. This internally cooled electrode can increase the volume of the induced thermocoagulation by between 4 and 7 cm in diameter, as reported in the liver,[44] but it may be greater in the lung due to the insulative effect of aerated tissue.

Objective results are more difficult to assess. Imaging techniques such as contrast – enhanced CT or positron emission

tomography have been used to determine the therapeutic response and to plan further treatment.[36,40,45,46] Gadalata et al.[47] in 2004 reporting on 63 primary or metastatic lung cancers with percutaneous CT-guided radiofrequency ablation claimed a complete tumor necrosis response rate in 92% with a mean follow up period of 9 months. Steinke et al.[35] reported on 23 patients with 52 colorectal pulmonary metastases treated with radiofrequency ablation; 10/23 had a pneumothorax (43%), and five patients died of diffuse metastatic disease in the first year after the intervention (22%). Short-term local control rates metastatic lung tumors less than or equal to 3 cm have been shown by multiple investigators; however, studies with longer term control rates are necessary.

Microwave Ablation

Microwave ablation refers to the use of all electromagnetic methods for inducing tumor thermocoagulation using devices with frequencies more than or equal to 900 MHz.[48,49] This technique is similar to radiofrequency ablation, because it is a heat-based tumor ablation method. As with radiofrequency ablation, microwave ablation may be performed either percutaneously (under either conscious sedation or general anesthesia) or through open surgical approach. CT guidance is the most widely used approach.

Unlike radiofrequency ablation, microwave ablation induces thermocoagulation via an electromagnetic wave, which causes marked oscillation of water molecules in the tissue surrounding the active tip.[50] Because of the inherent properties of the electromagnetic wave (no electrical current being produced) the device doesn't need to be grounded, avoiding the risk of grounding pad burns. Intratumoral temperatures can be accurately measured by the separate placement of a thermocouple adjacent to the active antenna. Given the poor electrical conduction of air, microwave energy may provide better heating around soft tissue nodules as compared with radiofrequency energy, although this has not been scientifically proven yet.

Microwave ablation offers many of the benefits of radiofrequency ablation but has several advantages that may result in an improved tumor thermocoagulation, with greater energy deposition in the aereated lung and greater heating near the blood vessels.[50] During radiofrequency ablation the zone of active tissue heating is limited to a few millimeters surrounding the active electrode, with the remainder of the ablation zone being heated via thermal conduction. Owing to the broader field of power density deposition, microwave ablation results in a much larger zone of active heating.[52] This has the potential to allow for a more uniform tumor kill in the ablation zone, both within the target zone and next to blood vessels. Radio frequency ablation is limited by the increase in impedence with tissue boiling and charring,[53] since water vapor and char act as electrical insulators. Because of their electromagnetic nature, microwave ablations are not subject to this limitation, with an intratumoral temperature considerably higher and a larger ablation zone with a shorter ablation period.

Indications are still limited and use should be restricted to local control. In patients with metastatic disease not amenable to surgery either for concurrent contraindications or because the patient refused it this type of treatment could be indicated.

Cryoablation Technique

Cryoablation technique (also known as cryotherapy) can be performed with an argon-based Cryoablation system (Endocare, Irvine, CA). The patient undergoes a 10 minutes freeze followed by 8 minutes active helium thaw followed by another 10 minutes freeze. The number of freeze-thaw-freeze cycles remains dependent on the individual clinical case. A post treatment CT scan is usually performed with the low density changes within the target measured and approximated to the size of the ablated region. Because the margin of the cytotoxic temperatures may not have been achieved, a 1-cm margin is subtracted from the diameter of the low density ablated region to better approximate the true volume of the necrosis.[54]

Cryotherapy exerts its ablative effects via a number of tumoricidal pathways, including direct cytolysis via intra and extracellular ice crystal formation causing protein denaturation, intracellular dehydration and pH changes, ischemic necrosis via vascular injury, cellular edema and vessel disruption during the thaw phase, activation of antitumor immune responses, and induction of cellular apoptosis. Endothelial damage leads to platelet aggregation and microthrombosis.[43]

A frequently mentioned benefit of cryoablation over other heat-based ablative techniques is the apparent ability to preserve collagenous and other structural cellular architecture in frozen tissues.[43] Another potential benefit would include the ability to visualize lower attenuation ice as it covers a soft tissue mass during the freeze cycles.

The use of this technique within the respiratory system has been widely popularized through the rigid bronchoscope in the treatment of endobronchial neoplasms.[55] With the development of newer argon-based cryoablation systems, cryotherapy applicator diameters have significantly decreased, making percutaneous utilization feasible. Recently, it has also been proposed to ablate lung tumors[55]: Wang reported on 217 sessions in 187 patients with lung cancer. The short follow-up does not allow estimates of survival but quality of life increased significantly.

STEREOTACTIC RADIOSURGERY FOR LUNG TUMORS (CyberKnife)

The most frequently used system for stereotactic radiosurgery is the CyberKnife System (Accuracy Inc, Sunnyvale, CA). It involves a 6-MV x-band linear accelerator mounted on a computer-controlled robotic arm. The means of targeting is based on two ceiling-mounted diagnostic x-ray sources with table-mounted flat-panel detectors.[58] For precise image localization, percutaneously placed metal marker (fiducials) are inserted in, or adjacent to the tumor. This maneuver is usually accomplished using an 18- or 19-gauge needle under CT guidance and local anesthesia; 2 to 4 cylindrical gold metal fiducials (1 mm in diameter by 3 mm in length) are inserted. A radiation therapy immobilization device is custom made for each patient to minimize non respiratory motion

during treatment. Patients undergo contrast-enhanced CT scan of the chest and a radiosurgical treatment plan is developed using a nonisocentric, inverse-planning algorithm based on tumor geometry and location. The tumor is outlined in sequential axial CT images and the gross tumor volume is calculated. Adjacent structures within 5 cm of distance are identified to avoid incidental radiation. The radiation to be delivered is prescribed to the maximum isodose line that completely covers the gross tumor volume, and the imaging set is processed for radiosurgery. The system coordinates the radiation treatment plan with the mechanical delivery therapy by dividing the dose into approximately 100 beam directions (called nodes).

The problem of tumor motion due to respiration may be addressed either by a breath holding technique or by tracking light emitting diodes placed on the patient's skin. The movements of the light emitting diodes are correlated with tumor movements using a ceiling-mounted light detector; the robotic arm and linear accelerator are able to track respiratory motion of the tumor.[59]

Treatment planning is usually done with a proprietary system allowing inverse planning and nonisocentric radiation delivery. After determining the total radiation dose to be delivered to the tumor and defining the boundaries to protect the adjacent critical structures, the software determines the targeting positions and dose to be delivered from the targeting positions. Radiation is then delivered for a calculated period of time from specific orientations and directions, each of which is called a node. The current CyberKnife device allows for up to 12 different beam directions from up to 110 robot arm locations, for a total of 1320 possible beam paths.

The greatest limitation to a more widespread use of this technique is the low overall efficacy when compared with surgical resection (notwithstanding the fascinating term "radiosurgery"). In fact, a complete radiologic response (that does not correspond to an histologically proven complete response) has been reported in only 9% of the patients with lung tumors and partial response in 65% of them.[60] Additional studies are under design and evaluation to investigate the optimal radiation dose, best motion-compensation technique, and overall treatment efficacy.

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