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Palliative Therapy

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Lung cancer is the most common neoplastic disease in men while in women is the 5th most common type of cancer (men account for 19-21% of all new cases, women account for 5%).

About 13% of all new diagnosis are cancer originating in the lung with a 3% growth rate per year [1]. Prognosis at 5 years, despite prevention campaigns, early diagnosis and the new chemotherapy agents combined with new treatment strategies, stands at about 3%. Lung cancer accounts for 30% of all cancer deaths in men [1].

At the time of diagnosis only 20-25% of lung cancers can be radically treated with surgery [2], for the majority of cases, therefore therapy is essentially palliative and aimed substantially at alleviating symptoms and consequently improving quality of life [3]. 20-30% of cases present an obstruction of the main airway (trachea and bronchi) which may lead to severe dyspnoea. Massive haemoptysis and complications of the trachea-oesophageal fistula may also lead to the death of these patients [2].

Several endoscopic techniques to relieve the obstruction to the airway and restore good ventilation have been available to pneumologists for over 20 years. Such techniques can be further complemented by additional treatments such as chemotherapy and radiotherapy. Numerous clinical studies have proved that endoscopic therapy is indeed useful to limit disease progression and consequently improve quality of life [3-10]. It has been deemed unethical to carry out double blind protocols in these disease stages *(Level of evidence: III)*.

Indications for palliative bronchoscopic therapy

The main indication for palliative endoscopic therapy in patients with lung cancer is obstruction of the main airway [3-8] caused by:

1. endoluminal growth of the cancer;
2. ab extrinseco stenosis of the main airway;
3. endoluminal growth associated to extrinsic compression.

This occurrence, based on severity of stenosis, may cause dyspnoea of varying severity leading ultimately to life threatening asphyxial crisis.

Haemoptysis and trachea-oesophageal fistula are further indications for endoscopic palliative therapy *(Level of evidence: IV)*.

The main objective endoscopic treatment is to resolve airway occlusion and to maintain airway patency, providing consequently a better quality of life.

Endoscopic treatment techniques

There are currently several palliative treatment techniques indicated for airway obstruction:

1) techniques with immediate mechanism of action
   - Coring out
   - Laser
   - Conventional and high frequency electro scalpel
   - Radiofrequency diathermy
   - Argon plasma coagulation (APC)
   - Stent
2) techniques with delayed mechanism of action
   - Cryotherapy
   - Brachytherapy
   - Photodynamic therapy (PDT).

These techniques may be used alone or in combination and they may be repeated; they may be associated with conventional radiotherapy, chemotherapy or before surgery [6-9]. There is no literature as to controlled randomised studies and the long-term results are scarce. Patients eligible to this therapeutic approach should be assessed by a multidisciplinary medical team and treated in a centre with adequate experience. Endoscopic palliative therapy for obstruction of the main airway should be preferably carried out with a rigid bronchoscope (general anaesthesia) as it allows maximum operativeness and control of ventilation [12, 13] *(Level of evidence: III)*.

The fiberbronchoscope may be used for peripheral lesions at the level of the upper lobe bronchi although still with rigid equipment at hand [14]. Improvement of ventilation is, in cases like this, not usually significant but the relief of airway obstruction may be indicated in case of post obstructive infections. Laser or electrocauterious treatment may be indicated for coagulation purposes in haemoptysis [6, 8, 11].

After the relief of the obstruction it is advisable to repeat an assessment and staging of the disease, since patients who have already been deemed inoperable may well be eligible for surgery or to a more limited exeretic treatment [15-17] *(Level of evidence: IV)*.

Several factors dictate which treatment is the most suitable:

- urgency of treatment based on severity of dyspnoea: life-threatening imminent asphyxia;
- nature and extent of obstruction (endoluminal or extra bronchial);
- availability of equipment, operators' experience, organization of endoscopy service.

Pre-operative tests

As with any other surgical procedure, the techniques for the relief of bronchial obstruction require an in-depth pre-operative assessment, included diagnostic bronchoscopy and a radiological study of the lesion which allow a correct assessment of the lesion, its extent and the relation with surrounding structures, bronchial patency as well as stenosis.

Diagnostic bronchoscopy is a serious and delicate test as its primary purpose is to define the site, extent and endoscopic features of the lesion. In high risk patients it is advisable to avoid any procedure that may cause bleeding and consequently worsen respiratory function. The biopsy of the lesion, for instance, can be performed during endoscopic resection *(Level of evidence: III).* The histological typing is absolutely necessary in order to confirm clinical radiological diagnosis, plan a treatment regimen and establish a prognosis, it is not indispensable in the case of urgent endoscopic relief of bronchial obstruction.

Radiological study of the trachea and the main bronchi is crucial both for a laser assisted endoscopic resection and for a safe stent positioning in patients with tracheal-bronchial tumour.

An in depth radiological study is not always possible as many patients require emergency treatment; the radiological tests that can be performed based on conditions of patient and the type of disease are as follows:

- *Standard chest x-ray:* it provides crucial information as to the site and extent of the lesion. Especially if atelectases are present, it may be subsequently used for comparison an after treatment.
- *Chest CT:* it allows a study of the tracheobronchial tree, of the mediastinum and of vascular structures. It can't often be administered as emergency treatment, even though last generation CT are very quick and cause little discomfort to the patient. Lastly volumetric "rendering" techniques enable the so-called CT bronchography and Virtual Bronchoscopy [18, 19]. The CT bronchography is a segmentation of the lumen-wall interface of the airway which enables a three-dimensional volumetric reconstruction of the tracheal-bronchial tree up to the 7th order of division. Virtual Bronchoscopy, on the other hand provides an internal rendering of the walls and of the tracheal-bronchial lumen simulating an interactive endoscopic vision with the possibility to reconstruct endoluminal lesions with a good correlation with fiberoptic bronchoscopy as to the site, the shape and the extent. Furthermore it allows visualisation of the bronchial tree beyond the obstructing lesion, almost like a 'retroscopy' thus providing indications on downstream patency, a pre-requisite in order to perform an endoscopic resection with laser.

Together with the endoscopic and imaging tests described before, it is also important to carry out a complete peripheral blood hemochromocitometer and chemistry screening of the coagulation test, a respiratory function assessment (arterial blood gas analysis at least for urgent cases) and a cardiologic assessment considering that the majority of patients have serious co-morbidities such as COPD and cardiovascular diseases [11] *(Level of evidence: III).*

Techniques with immediate mechanism of action

Coring out

Mechanical resection with the distal tip of the rigid bronchoscope or with resection tongs (coring out) may well be considered the first endoscopic resection technique in case of obstruction of the main airway caused by endoluminal vegetation with an immediate threat to life.

Even though this technique allows an immediate recanalisation it presents a discrete risk of causing haemorrhage [8]. Furthermore gas flow during ablation therapy can cause gas emboli to the heart [20].

The technique has evolved with time thanks mainly to the availability of laser equipment and the new resection techniques subsequently developed by Toty, Dumon and Cavaliere [12, 13, 15, 17, 21].

Mechanical resection must be preliminarily preceded by coagulative procedures which can be proved with thermal lasers or with electrocoagulator as an alternative [22, 23].

Some authors have proposed a new resection technique using a special balloon covered with an hexagonal mesh structure that cut and destructs the tumoural tissue [24].

Laser

Nearly all laser assisted endoscopic resection treatments described in literature case history have been carried out with the ND:YAG (other types of thermal lasers suitable for endobronchial treatment are available on the market: diodes, thulium). Laser provides an immediate de-obstruction in 90% of cases and it is therefore the most suitable technique in emergency situations. Laser may well be useful during preparation for stent positioning.

Though rare, the most serious complications are bleeding with immediate effect on respiratory exchange (1-10%) and perforation (3%) [12, 13, 15]. When operated by expert hands, it is however rightly considered the gold standard in palliative treatment of the main airway [17] *(Level of evidence: III).*

Electrocauterization

Conceptually similar to the laser, electrocauterisation relies on the heat transmitted to the tissue by unipolar probes of different type, capable of transmitting electric current generated by a high frequency electric generator.

It can be used with both flexible and rigid equipment, bearing in mind however the usual operativeness differences in favour of the rigid bronchoscopes. The number of case histories documented by literature data is however markedly smaller compared to laser ones. The advantage compared to laser is undoubtedly financial [22, 23] *(Level of evidence: IV).*

Radiofrequency diathermy

This technique relies on the effect produced by the impact on the tissue of the waves emitted by the electrode with subsequent molecular excitement and the generation of thermal energy (resistive heat).

Stent

The positioning of the stent at the tracheal-bronchial level is indicated primarily for *ab exstrinseco* compression (trachea and main bronchi) and for stabilisation of the airway further to laser therapy [16].

There are several stent models currently available: silicon, metal and mixed [25-30]. The most widely used are silicon prosthesis developed by Dumon [30] which are easy to position and to remove, they are available in different sizes and models, such as the upside down Y(s), which are particularly useful when the tracheo-bronchial bifurcation is involved [31]. The no-covered metallic prosthesis are not indicated for neoplastic stenosis with infiltration of the tracheal-bronchial wall, considering that the cancer growth tends to enclose them; furthermore they may cause granulomatous reactions [28, 29].

Stents can be positioned both with rigid bronchoscope (all silicon prosthesis) and with fiber-bronchoscope (self expandable metallic ones) with fluoroscopic guide, if needed. Complications of silicon stents include dislocation and occlusion caused by secretions. Even though some centres prove regular endoscopic test, a piece of work by Matsuo and Colt [32] suggests that this procedure is useless *(Level of evidence: III).*

Argon Plasma Coagulation (APC)

It is a non contact electrocoagulation technique [33] which exploits the effect generated by a ionized argon flow, generated by a high frequency electrode which acts substantially as an electricity conductor between the electro-scalpel and the tissue which is coagulated as a result.

It is safer and more superficial but less effective than the laser ND:YAG or the electro-scalpel. It is in fact more suitable for coagulation purposes in superficial lesions [33, 34] than as an de-obstruction technique *(Level of evidence: IV).*

Techniques with delayed mechanism of action

Cryotherapy

Cryotherapy resorts to extreme cold (-80 °C) to destroy the tissue. This techniques combines two mechanisms: fast freezing which in turn generates intracellular crystals with subsequent cell death, combined with a halt of microcirculation which is the result of the thrombosis caused by endothelial damage.

Necrosis of a greater tissue volume (compared to the one directly frozen) [35, 36] is thus achieved at a later stage and can be removed after hours or days during following sessions. The very characteristics of the above mentioned technique do not allow for it to be used in emergency situations. Cryosensitive tissues are rich in water whilst all the others are cryoresistant (fibrose tissues and cartilage) and this is why the technique should not lead to perforation.

A further advantage is the contained cost [36]. Indications: non critical tracheal bronchial obstructions, haemoptysis *(Level of evidence: IV).*

Brachiterapy

Endobronchial radiation is achieved by inserting radioactive probes at tracheal-bronchial level (Iridium 192) with a catheter (after loading) and with the help of a fiberoptic bronchoscope thus allowing a precise positioning (brachitherapy).

High Dose treatment (HDT) is usually carried out in 6 fractions with intervals of 1-3 weeks and with doses varying between 2-30 Gy per fraction at about 1 cm from the probe's axis [37]. To date no definite agreement has been reached on optimal dosage. The therapy is used both as a palliative and as a cure for early cancer and for inoperable bronchial carcinomas. In palliative treatment specifically, brachitherapy is aimed at restoring and stabilizing bronchial patency.

It can be carried out at ambulatory level but it is however marred by high costs for equipment and facilities. Amongst the most serious complications it is worth mentioning haemorrhages, at times fatal (when the dose of 15 Gy is exceeded) *(Level of evidence: IV).*

Photodynamic Therapy (PDT)

Photodynamic therapy uses photosensitive substances (haematoporphyrin and its by products) which, when inserted systemically can stick to the tissues with a high mycotic index such as cancer tissues [38, 39].

The illumination of cancer tissues (48-72 hours after administration) with a special light (630 nm wavelength, low potency) triggers a series of photochemical reactions (photodynamic effect) which cause the necrosis of the tissue with a high hemotoporphyrin concentration.

The effects of PDT can be seen at 5-15 mm deep in the cancer areas whilst they are pretty much absent in healthy tissues.

Recommendations

- **Obstruction of the main airway caused by cancer leads to dyspnoea, at times severe and can seriously threaten patient's survival even in the early stage of the disease. This is why it must be diagnosed and treated at a very early stage (Grade B).**
- **Fiberoptic bronchoscopy and imaging techniques are particularly important in defining degree and type of obstruction (endoluminal or *ab extrinseco* compression) hence in selecting the most suitable type of the treatment (Grade B).**
- **The best techniques to restore airway's patency are assisted endoscopic resection (laser or electrocauterious) and stent insertion with rigid bronchoscope. They are to be used especially in emergency situations and by expert personnel in a suitably equipped environment (Grade C).**
- **Other techniques to relieve obstruction of the airway (cryotherapy, brachitherapy and PDT) are effective but they can not be used in emergency situations (Grade C).**

Haemoptysis

This symptom affects 7-10% of patients with lung cancer and it is the cause of death in 3% of cases.

Prognosis is usually bad for cancer based massive haemoptysis and mortality ranges between 50-100% [40]. The chances to manage such a dramatic event are scarce and they are initially aimed at maintaining an adequate control of ventilation which in turn requires the endotracheal intubation and the constant suction of haematic secretions and of coagula [11]. Bronchoscopy is crucial in order to identify the site of bleeding. During this procedure, which is not always easy, cold saline solution, adrenaline and other vasoactive drugs can be used to reduce haemorrhage [41, 42]. Balloon catheters may also be used and they can be left in the site for 24-48 hours in order to tampon the site of the bleeding. When the haemorrhage is caused by a visible cancer lesion laser, electrocauterious, APC and criotherapy may be useful. Once the bleeding has been addressed, conventional radiotherapy may be indicated as palliative treatment [11]. Some literature data refers to sporadic treatments with embolisation of bronchial arteries [43, 44] *(Level of evidence: IV).*

Recommendations

- **During a massive haemoptysis episode it is primary to intubate the patient and preserve patency of the airway (suction of blood and coagula). In the majority of cases bronchoscopy can identify the site of the bleeding, it can guide intubation and aid the positioning of balloon catheters if needed (Grade C).**
- **If the bleeding is caused by an endobronchial cancer lesion laser, electrocauterious, cryotherapy and APC may be useful (Grade C).**

Oesophago-tracheal fistula

The oesophagus-tracheal fistula affects about 5-10% of patients with oesophagus cancer. The cancer can infiltrate the tracheal bronchial mucosa and thus lead to necrosis and subsequent fistula formation. The lesion may well be as a result of radiotherapy. Surgery in this case has a palliative significance, the mortality percentage is high and hospitalisation is generally prolonged [45, 46].

Satisfactory results, though limited in time, have been achieved with the implant of a prosthesis in the oesophagus; Colt and Freitag have proved that the double implant (oesophagus and airway) allows for a better control of the fistula and its consequences in particular (longer survival and better quality of life). In some cases the implant of a second prosthesis is made necessary by the critical stenosis that may occur further to positioning of the stent in the oesophagus [47]. It is worth remembering however that the double implant can determine an erosion with a second fistulisation in the membrane portion of the trachea due to the ischemic necrosis determined by the compression exerted by the two stents. In cases like this the prosthesis must stick to the tracheal or bronchial mucosa even if there is no stenosis. This is why covered metallic prosthesis are best suited to perform this task: Ultraflex in particular, given their tolerability, can be rightfully considered the gold

standard (Type IV Evidence). The creation of an oesophageal by-pass may be taken into consideration as it is effective in ensuring patient's nourishment [11] *(Level of evidence: IV).*

Recommendation

- **In patients with oesophago-tracheal fistula prosthetic implant (simple or double) may be taken into consideration especially in case of critical tracheo-bronchial stenosis (Grade C).**

Summary of Recommendations

- **Obstruction of the main airway caused by cancer leads to dyspnoea, at times severe and can seriously threaten patient's survival even in the early stage of the disease. This is why it must be diagnosed and treated at a very early stage (Grade B).**
- **Fiberoptic bronchoscopy and imaging techniques are particularly important in defining degree and type of obstruction (endoluminal or *ab extrinseco* compression) hence in selecting the most suitable type of the treatment (Grade B).**
- **The best techniques to restore airway's patency are assisted endoscopic resection (laser or electrocauterious) and stent insertion with rigid bronchoscope. They are to be used especially in emergency situations and by expert personnel in a suitably equipped environment (Grade C).**
- **Other techniques to relief airway obstruction of the airways (cryotherapy, brachitherapy and PDT) are effective but they can not be used in emergency situations (Grade C).**
- **During a massive haemoptysis episode it is of primary importance to intubate the patient and preserve patency of the airway (suction of blood and coagula). In the majority of cases bronchoscopy can identify the site of the bleeding, it can guide intubation and aid the positioning of balloon catheters if needed (Grade C).**
- **If the bleeding is caused by an endobronchial cancer lesion laser, electrocauterious, cryotherapy and APC may be useful (Grade C).**
- **In patients with oesophago-tracheal fistula prosthetic implant (simple or double) may be taken into consideration especially in case of critical tracheo-bronchial stenosis (Grade C).**

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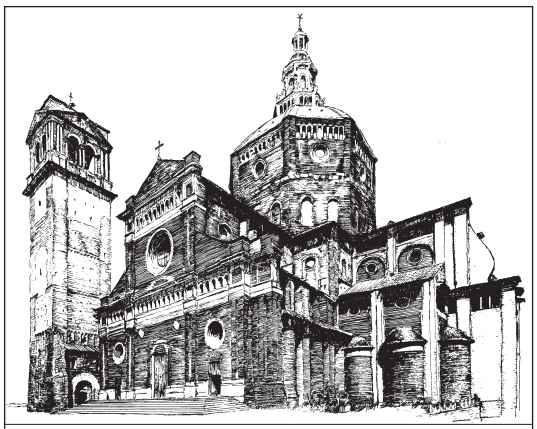

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