The GEC ESTRO Handbook of Brachytherapy

SECOND EDITION

PART II: CLINICAL PRACTICE

29

Bronchus Cancer

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1. Summary 3
2. Introduction 3
3. Anatomical Topography 4
4. Pathology 4
5. Work Up 4
6. Indications, Contra-indications 5
7. Tumour and Target Volume 6
8. Technique 6
9. Treatment Planning 9
10. Dose, Dose Rate, Fractionation 14
11. Monitoring 15
12. Results 15
13. Adverse Side Effects 18
14. Key messages 20
15. References 21

1. SUMMARY

Brachytherapy is one of the most efficient methods in overcoming difficulties in breathing that is caused by endobronchial obstruction in palliative treatment of bronchus cancer. Depending on the location of the lesion in some cases brachytherapy is the treatment of choice often combined with a recanalisation procedure. Because of uncontrolled local or recurrent disease, patients may have significant symptoms such as: cough, dyspnea, hemoptysis, obstructive pneumonia or atelectasis. Efforts to relieve this obstructive process are worthwhile, because patients may experience improved quality of their life.

Brachytherapy plays a limited but specific role in definitive treatment with curative intent in selected cases of early endobronchial disease as well as in the postoperative treatment of small residual peribronchial disease.

Indications for intraluminal brachytherapy include:

1. Palliative treatment of dyspnoea, obstructive pneumonia or atelectasis, cough or haemoptysis resulting from endobronchial or endotracheal tumour growth, usually by primary lung cancer but occasionally also by metastatic disease.
2. Retreatment of endobronchial or endotrachel recurrent tumour growth in previously irradiated areas.
3. Curative treatment as a boost for minor residual disease within a combined non-surgical radical approach. This may apply to small cell lung cancer after remission induction by chemotherapy and external radiotherapy or for non-small cell lung cancer as a boost after remission induction by external beam radiotherapy (with or without chemotherapy).
4. Curative treatment for small tumors by definitive external beam radiotherapy combined with brachytherapy or by brachytherapy alone.

One of the positive aspects of BT is a possibility to perform it on outpatients basis with a short treatment time.

2. INTRODUCTION

Bronchial carcinoma is an ever-increasing health problem, smoking habits being responsible for a major increase in incidence in recent decades, and with five-year survival rates reaching only 10 - 12% during the last 20 years.

Most patients with lung cancer present with distant metastases at diagnosis. Approximately 80 % of patients with small cell lung cancer (SCLC) have overt metastatic disease at diagnosis [16], and 50 % of non-small cell lung cancer (NSCLC) patients have detectable distant metastases at the time of presentation [84]. Even after treatment with curative intent, most patients will die of lung cancer the first 3 years after diagnosis. Local recurrences occur as first site of failure in about 30% of locally advanced NSCLC patients, whether treated with concurrent chemotherapy and radiotherapy, or with induction chemotherapy followed by resection [6]. Similar local recurrence rates are observed in stage I-III SCLC treated with concurrent chemo-radiotherapy. The cumulative local recurrence rates approach 60%.

It is therefore clear that there is an obvious need for palliation of symptoms caused by intra-thoracic tumour growth. Radiotherapy is a standard and efficacious way to achieve improvement of symptoms in 70-80% of patients [57]. Importantly, 50% of patients remain free of the symptoms for which they were treated during their lifetime [75]. Re-irradiation is possible in case of recurrent symptoms.

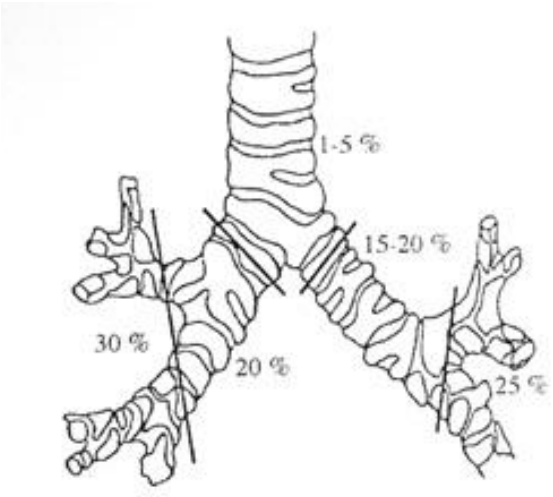


Fig. 29.1: The tracheal-bronchial tree and incidence of non small-cell lung cancer (Fraser, Paré, Fraser and Genereux. Diagnosis of Diseases of the Chest, Saunders, 1989: 1368).

The most common symptoms in those patients suffering from endobronchial obstructive disease are: coughing (45 - 75%), haemoptysis (25 - 35%), dyspnoea due to atelectasis (40 - 60%) or retro-obstructive pneumonia (25%).

Brachytherapy plays an important role in the palliative treatment of obstructive disease, sometimes in conjunction with endobronchial laser therapy or stent implantation. Removal of endobronchial obstruction leads to quick improvement of clinical status and Quality of Life (QoL). Brachytherapy is one of the most efficient methods in overcoming difficulties in breathing that is caused by endobronchial obstruction in palliative treatment of tracheal and lung cancer. Depending on the location of the lesion in some cases brachytherapy is the treatment of choice. Efforts to relieve this obstructive process are worthwhile, because patients may experience improved QoL in hours or days after treatment [66, 77]. Brachytherapy plays a limited but specific role in definitive treatment with curative intent in selected cases of early endobronchial disease, in selected advanced inoperable tumours combined with external beam radiation therapy (EBRT) or in the postoperative treatment of small residual peribronchial disease. A relatively rare indication is interstitial brachytherapy of peripheral tumours using permanent implants. For peripheral tumours stereotactic external RT usually is the method of choice, in particular for limited size tumours [83,77].

3. ANATOMICAL TOPOGRAPHY

The tracheo-bronchial system is a tree-like tubular structure (Fig. 29.1), divided into anatomical sub-units with progressively narrowing lumen diameter and wall thickness. Lumen diameters take up 90% and wall thickness 5% of the whole diameter. The trachea has a lumen diameter of 18 mm, the right and left primary bronchus of 14 mm, the secondary bronchi of 11 mm, the tertiary bronchi of 9 mm (Fig. 29.1).

The walls consist of a fibro-muscular skeleton, reinforced by cartilaginous rings in the trachea and primary bronchi and covered by respiratory mucosa endobronchially. The wall thickness (5% of the diameter) decreases from 1 mm in the trachea, to 0.8 mm in primary, 0.6 mm in secondary and 0.5 mm in tertiary bronchi.

4. PATHOLOGY

The most common primary malignant tumours occurring in the respiratory tract arise from the endobronchial epithelium. They are subdivided into small cell lung cancers (+/- 25%) and non-small cell lung cancers (+/-75%).These are further subdivided into squamous cell carcinoma, adenocarcinoma, and undifferentiated large cell carcinoma. The cancer growth frequently leads to endobronchial obstruction, which represents the classical indication for palliative endobronchial brachytherapy. In selected early cases cancer growth is very limited and superficial and is confined to the dimensions of the bronchial wall. These cases may be considered for definitive treatment with curative intent with brachytherapy playing a major role, often in combination with photodynamic therapy.

Lung metastases from other primary sites such as e.g. renal cell carcinoma, breast cancer, soft tissue sarcoma, osteosarcoma, or malignant melanoma only represent an indication for intraluminal brachytherapy if there is endobronchial obstruction caused by intraluminal tumour growth, which is rather rare.

5. WORK UP

The definitive decision for brachytherapy, which is mainly palliative, is taken by the pneumologist and/or radiation oncologist. It is based on clinical examination, flexible bronchoscopy with precise documentation of the location and the amount of obstruction, and X-ray of the chest, which in some cases is supplemented by computed tomography or endobronchial echography. Each case should be biopsy proven. It is important to determine tumour extent as clearly as possible.

The tumour dimensions should be noted in mm, along the axis of the tracheal-bronchial tree and in the radial axis, always related to reproducible topographic landmarks. In addition, the minimum and maximum diameter of the involved part of the bronchial tree is measured and recorded in mm. If possible, the thickness of the bronchial wall should also be indicated.

To evaluate the response to treatment objective criteria should be used before and after treatment. Assessment of the grade of dyspnoea, haemoptysis, pneumonia and the amount of obstruction by using for example Speiser and Spratling scale [73] and lung function tests is helpful to obtain quantitative information on the functional impact of the obstruction (see Table 29.1). It makes quantitative assessment of functional improvement after brachytherapy or after a combined approach possible.

Table 29.1: Speiser and Spratling Scale for assessing palliative response in endobronchial brachytherapy [73].

PRIMARY TUMOR (T)

DYSPNEA	
Score 0	None
1	on moderate exertion
2	with normal activity, walking on level ground
3	at rest
4	requires supplemental oxygen
Cough	
Score 0	None
1	intermittent: no medication necessary
2	intermittent: non-narcotic medication
3	constant or requiring narcotic medication
4	constant or requiring narcotic medication, but without relief
Haemoptysis	
Score 0	None
1	less than 2 x per week
2	less than daily, more than 2 x per week
3	daily, bright red blood or clots
4	decrease of Hb/Ht > 10%, more than 150 cc, requiring hospitalisation, leading to respiratory distress, or requiring > 2 units transfusion
PNEUMONIA/ ELEVATED TEMPERATURE	
Score 0	normal temperature, no infiltrates, WBC less than 10.000
1	temperature greater than 38.5° AND infiltrate, WBC less than 10.000
2	temperature greater than 38.5° AND infiltrate and or WBC over 10.000
3	lobar consolidation on radiograph
4	pneumonia or elevated temperature requiring hospitalisation

For curative treatments a comprehensive work up as usual for lung cancer should be performed, including in each case CT and/or MRI of the chest and appropriate investigations such as PET CT to exclude distant and lymph node metastases.

6. INDICATIONS, CONTRA-INDICATIONS

- The main indication for palliative treatment is dyspnoea, obstructive pneumonia or atelectasis, cough or haemoptysis resulting from endobronchial or endotracheal tumour growth, usually by primary lung cancer but occasionally also by metastatic disease. Extra bronchial tumour extension cannot be adequately treated by intraluminal brachytherapy. If obstruction is severe, endobronchial brachytherapy is usually preceded by endobronchial disobliteration techniques e.g. laser, cryocoagulation, electrocautery or endobronchial stenting in selected cases [4,41]. This may induce rapid relief from symptoms. The combination with brachytherapy aims to achieve long lasting intraluminal tumour control. Intraluminal treatment may be combined with external radiotherapy, particularly as almost all tumours are too large for brachytherapy alone. Nevertheless, as this is mainly a palliative treatment, brachytherapy alone may be justified, if disappearance of symptoms can be achieved by these means long enough for the patient's remaining life span.

- Intraluminal brachytherapy alone can also be considered for the palliative treatment of endobronchial or endotracheal recurrent tumour growth in previously irradiated areas [20,38,78].

- In the palliative treatment for tracheal cancer brachytherapy may be one of the effective methods of controlling dyspnoea due to the location of the lesion inside the tracheal tube, the degree of clinical advancement, and patient's general condition. In some patients brachytherapy carried out on an out-patient basis, takes a short time and leads to a small number of early complications [23-25,51,61,69,71].

- Postoperative external radiotherapy and/or intraluminal brachytherapy of the bronchial stump after resection with positive resection margins [70].

- Endobronchial brachytherapy with curative intent is considered as a boost for minor residual disease within a combined non-surgical radical approach. This may apply to small cell lung cancer after remission induction by chemotherapy and external radiotherapy or for non-small cell lung cancer as a boost after remission induction by external beam radiotherapy (with or without chemotherapy) [32,78].

- Definitive external beam radiotherapy and brachytherapy [17,60] or brachytherapy alone for small tumours (T1 - T2) [2,27,45,56,79-81].

- In peripheral tumors, inoperable for different reasons and inaccessible in bronchofiberoscopy some percutaneous techniques may be applied. Potential treatment options for these high-risk or medically inoperable patients include sublobar resection with or without I-125 lung brachytherapy [82]. Permanent implantation of I-125 seeds can be safely used in areas where the total dose of radiation received is usually limited by significant late toxicity, such as directly on pulmonary tissue or in close proximity to the spinal cord. Interstitial brachytherapy of bronchus cancer is not recommended outside of clinical trials. Published material refers to small inoperable peripheral tumours or not radically excised lung tumours [1,11,76,82].

Contraindications for endobronchial brachytherapy are obstruction by extra-bronchial or extra- tracheal tumour growth, and peripherally located tumours not visible and accessible by bronchoscopy.

7. TUMOUR AND TARGET VOLUME

The intraluminal target volume is usually determined by bronchoscopy findings. Proximal and distal margins of the intraluminal gross tumour volume must be carefully assessed and the distance from both margins to the tracheal carina measured. In completely obstructing lesions, assessment of the distal margin may not be possible by endoscopy. Additional information from chest X-ray or CT imaging may be helpful then to estimate the length of the obstruction.

Since in *palliative* brachytherapy the extraluminal part of the tumour is usually rather large, and therefore not treatable by brachytherapy, there is only limited need for a precise assessment of the extraluminal tumour dimensions for target definition.

In the longitudinal direction, a safety margin of 20 mm is usually added to both sides of the macroscopic tumour to define the target volume (CTV and PTV). If there is doubt about the distal margins an extra 20 to 30 mm should be added to be sure to cover the whole endobronchial tumour extension.

In contrast, in curative brachytherapy the whole area at risk must be included. This is the GTV and the CTV margin in the adjacent wall in superficial spreading tumours, and tumour depths of a few mm in limited T1-tumours. Autofluorescent bronchoscopy is very helpful in this situation, determining exactly the margins of the infiltrating tumour. The same applies for adjuvant treatment after radical resection with positive margins and for minimal residual disease after chemotherapy and/or external beam therapy.

CT scans with the applicator in place allow a better estimate of the tumour topography in relation to the applicator. CT-based planning enabling more precise target volume definition (GTV and CTV) and volumetric dose information can improve the therapeutic ratio of brachytherapy. Potential benefits and limitations of using "CT-assisted brachytherapy" can be characterized by the following:

1. Use of CT imaging to supplement the findings of bronchoscopy, particularly in determining the distal extent of the target volume;
2. Visualization of the position of the applicator in relation to the tumour and target volume;
3. Facilitation of dose prescription to the bronchial mucosa by identifying the position of branching of the different subsegments of the bronchial tree and allowing the use of actual measurements of the diameter of each segment and the depth of the target volume;
4. Visualisation and delineation of the oesophagus, particularly in tumours of the trachea and the left primary bronchus;
5. Generation of a 3D dosimetric database for correlation with toxicity [39,45,64,65,67].

8. TECHNIQUE

The technique for introducing the applicator depends on the size of the endobronchial applicator. Small applicators [5 to 6 French) which are nowadays most often used can be introduced directly via the working channel of the bronchoscope (Fig. 29.2). Larger applicators (beyond the size of the working channel) are introduced using a flexible guide wire (Seldinger Technique) through the bronchoscope or via an extra tube introduced by the bronchoscope. This technique is less frequently used.

In a widely open tracheal or bronchial lumen (e.g. after laser-photo resection) a precise central and fixed position can be achieved using a specific applicator with an expanding outer cover which fixes the tube to the walls without obstruction of the respiratory system [15]. This expansion is mechanically achieved after introduction and positioning. Using this applicator can reduce high contact doses to the mucosa. (Fig. 29.3). Centring is also achievable by adding endoluminal spacing catheters (Fig. 29 4).

With decreasing size of the available sources and catheters (5 to 6 French i.e. 1.7 to 2 mm-outer diameters) it is possible to take tighter bends and to enter tertiary bronchi (Fig. 29. A, B). It has also become possible to treat lesions at the carina or on a bronchial division by sandwiching the tumour between two or even three inserted applicators (Fig. 29.2 C,D). Using multiple catheters also for mono luminal lesions can increase the degrees of freedom in source positioning and lead to better target coverage and/or better wall sparing.(Fig. 29.3).

However, in most cases the target is approached by a single endobronchial catheter that can cover up to 25-cm target length.

8.1 Patient preparation and monitoring

The application can usually be performed on an outpatient basis. The patient must have an empty stomach and an intravenous access must be prepared.

Ideally, the whole procedure should be performed in the endoscopic room placed in Brachytherapy Department, since it is easy for the pneumologist or brachytherapists to bring along and return the instruments for flexible bronchoscopy there and difficulties may arise, if the patient has to be taken after placement of the brachytherapy application from the Pneumology Department to the Brachytherapy Department. In some centres bronchoscopy is performed by a qualified brachytherapist.

The application itself is performed under local anaesthesia, supplemented by sedatives and vagolytic drugs. It is important to suppress coughing and prevent displacement of the inserted applicator. Specific drug contraindications should be documented before the procedure. If indicated, cardiac function is monitored using ECG. Oxygen saturation is measured e.g. by a pulse oxymeter.

8.2 General application procedure

Flexible bronchoscopy and insertion of the brachytherapy applicator is performed with the patient in a sitting or supine position. The bronchoscope is usually advanced through the nose or mouth. Local anaesthesia to the nasal cavity and the nasopharynx is given before inserting the bronchoscope and then continuously via the dedicated channel of the bronchoscope.

Direct application through the working channel of the bronchoscope is possible in applicators with a small diameter of 5 or 6 French. In applicators with a large diameter but with an open end, the Seldinger technique is used. An oral route of intubation is necessary for applicators with a large diameter and a closed end (see below).

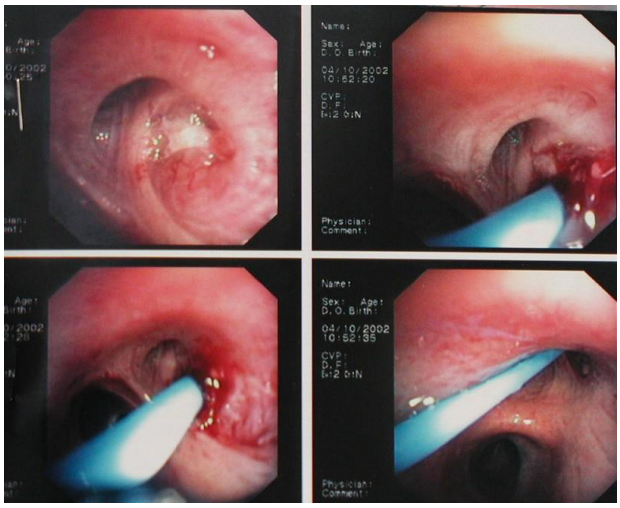


Fig. 29.2 A: Endobronchial brachytherapy with a small (<2mm, 5 to 6 French) endobronchial applicator, fixed into a tertiary bronchus for treatment of a small lesion in the right secondary bronchus of the lower lobe

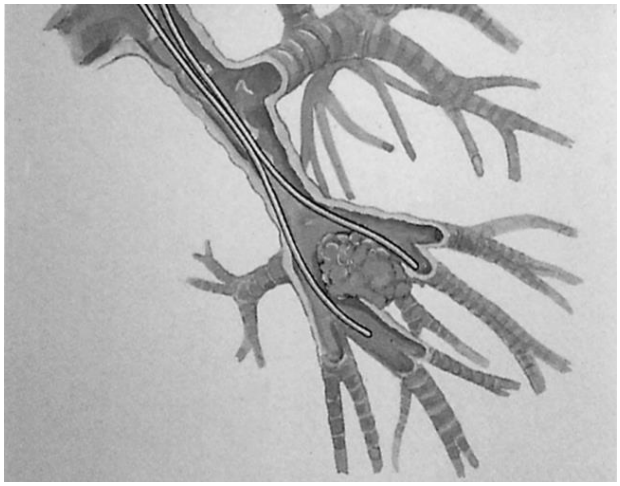


Fig. 29.2 C: Intraluminal treatment of endobronchial lesions with 2 tubes Schematic anatomical diagram showing the ideal situation with two tubes encompassing a small tumour located in the carina of two tertiary bronchi in the left lower lobe.

Fig. 29.3. The Fritz Adjustable intraluminal applicator (Elekta –Nucletron) endobronchial catheter with inflatable centring balloon to avoid over and underdosage of the tumour and/or bronchial mucosa

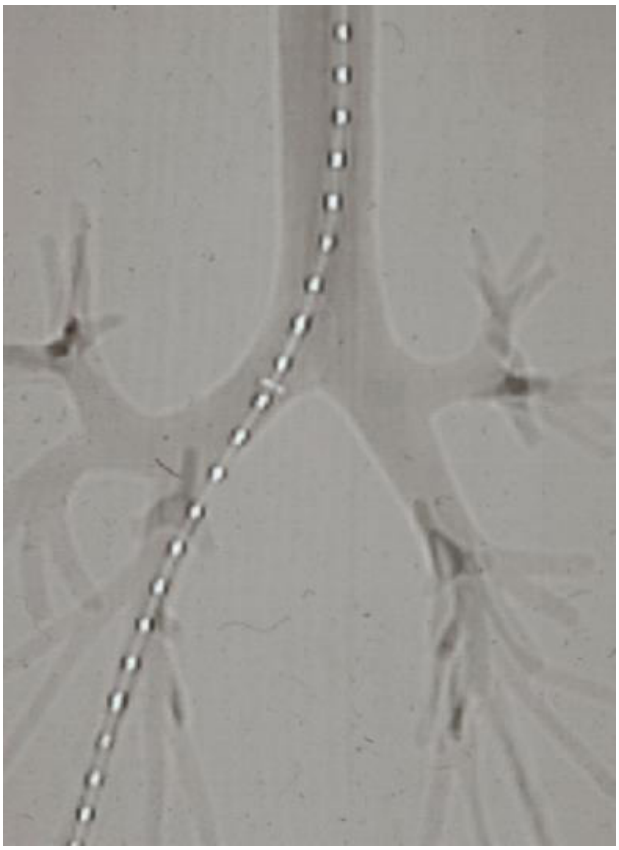
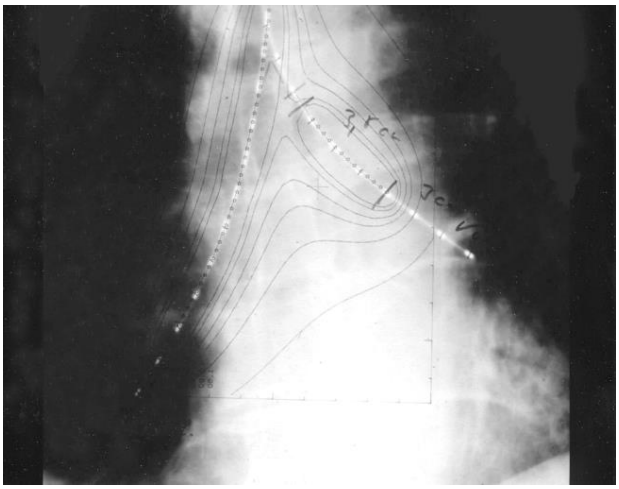


Fig. 29.2 B: 2 D visualisation of the inserted catheter.: PTV is GTV +20mmm



D: Anterior-posterior localisation radiographs in an extensive tumour growing into both main stem bronchi including the main carina. The two intraluminal tubes diverge at the main carina.

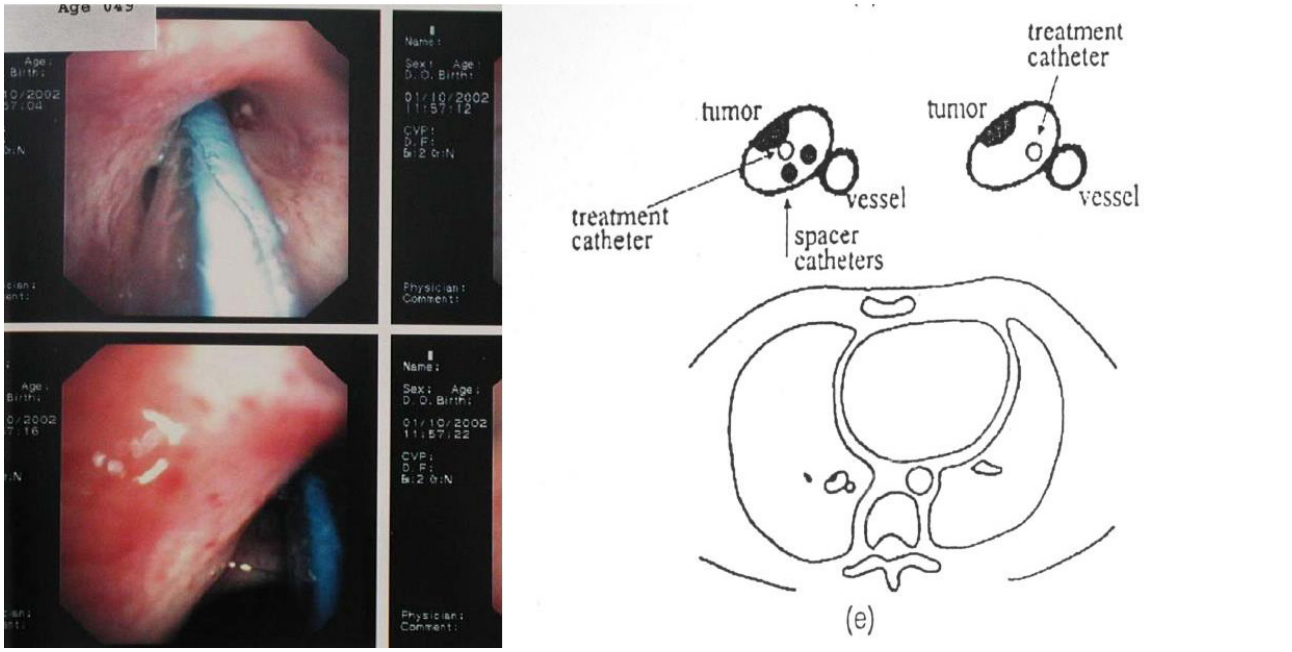


Fig. 29.4 Insertion of extra dummy catheters to push the treatment catheter to the GTV while lowering the dose to the non-invaded mucosa (with courtesy to Hugo Marsiglia et al [45])

The tumour is inspected by the chest physician and/or radiation oncologist and localised. The distance from the carina to the proximal and distal edges of the macroscopic tumour is measured by moving the bronchoscope. It can also be accurately documented on two anterior-posterior X-rays in the treatment (supine) position with the tip of the bronchoscope at the distal and proximal end of the GTV. If the tumour obstruction does not allow passage of the bronchoscope, a flexible guide wire, which is introduced through the biopsy channel, can be used to radiologically mark the distal end.

8.3 Specific applicators

Small 5 to 6 French applicators
These small applicators can be placed under direct view via the working channel of the bronchoscope. The applicator should be pushed several centimetres beyond the tumour using endobronchial friction to anchor.The bronchoscope can then be withdrawn over the applicator with the applicator remaining in the defined position. If the position is unsatisfactory (e.g. wrong lobar or segmental bronchus), the bronchoscope may be introduced again through the opposite side of the nose and the adequate position can be controlled and corrected if necessary. Using this procedure, several catheters can fairly easily be introduced. If there is difficulty in placing the applicator in the right place - in particular in the right superior bronchus – a special pigtail like ended guide wire may be used to take tight bends.

Finally, the catheter(s) are carefully taped to the patient's nose and a fixation neck collar is applied.

Applicators (> 3 mm in diameter)
Applicators with a larger diameter than the diameter of the working channel, cannot be introduced through the bronchoscope. Two possibilities of introducing these larger applicators into the tracheo-bronchial tree can be chosen:

- *Open tip applicators* with a large diameter can be inserted using a modified Seldinger technique. First, a flexible guide wire is introduced through the working channel of the bronchoscope and placed with its tip at least at the distal end of the tumour obstruction or further beyond, if possible under direct bronchoscopy vision. The long guide wire is fixed and then the bronchoscope is withdrawn leaving the guide wire in place. The applicator is then advanced using the guide wire as a glide path and positioned correctly. If there are uncertainties in accurate positioning, the bronchoscope can be introduced again parallel to the applicator and the final placement can be performed under direct bronchoscopic vision. At the end of the procedure the applicator is taped to the patient's nose.

  In both techniques using the bronchoscope channel, the catheter should be more than twice as long as the bronchoscope to allow withdrawal of the bronchoscope over the catheter. If the catheter is not long enough, at least the flexible guide wire should have the sufficient length to withdraw the bronchoscope over it without losing its end.

- Applicators with a large diameter and a *closed end* have to be introduced beside the bronchoscope. After oral intubation of the bronchoscope (continuously injecting local anaesthesia via the dedicated channel) a tube is advanced over the bronchoscope. The tube is placed within the glottis and into the proximal part of the trachea and the bronchoscope is then withdrawn. The applicator is advanced through the tube into the trachea and then the tube is removed. Parallel to the applicator the bronchoscope is introduced again and now the applicator can be precisely placed at the tumour obstruction under direct bronchoscopic view. At the end of the procedure the applicator is carefully taped to the patient's nose.

This type of large applicators are used less and less frequently.

8.4 Interstitial brachytherapy

Interstitial brachytherapy may be used in subpleural, peripheral tumours or Pancoast tumour [1,9,11,14,28- 30,52,76,82].

Patients are qualified to sublobar resection with I-125 seeds placed at the suture line. The implant techniques permitted in the study are to either suture two rows of I-125 seeds directly into the lung tissue around the suture line or place the seeds into mesh which is then placed over the suture line [76].

Seeds can be placed directly into a tumor as a volume implant, or woven in a grid pattern in a planar implant. Volume implants require the use of an applicator which transfers the seeds from a storage magazine directly into the tumor site, or preloaded needles which drop the seeds into the tumor individually or in a line. A planar implant is custom-made intraoperatively, securing seeds to a Vicryl mesh or other platform custom-sized to cover the area in question. The steps of planar implant construction using I-125 seeds set into Vicryl suture with 10 mm spacing between seeds [76]. Careful suturing of the platform must be performed to prevent migration and to assure that the platform is flat and approximates all portions of the area in question, because the areas of implant overlap or variable distance between the implant and the target will greatly affect the dose received [76].

Most frequently isotopes I-125, Pd-103 and Cs-131 (dose rate 0.01 to 0.3 Gy/h) are used. Physical characteristics of them shows low-energy, small size and short half-life decay time. Treatment time doesn't exceed 30 – 45 minutes. Isotopes are implanted into tumour in general anaesthesia. Special elastic applicators are used for implantation. Nominal total activity is 0.5 – 1 Gy/h, total summarized dose is 100 – 160 Gy in CTV (Clinical Target Volume). Recommended diameter of the tumour should not exceed 50 - 60mm.

Some clinical experience has been recently reported for CT guided fractionated HDR brachytherapy in thoracic malignancies including lung cancer [83].

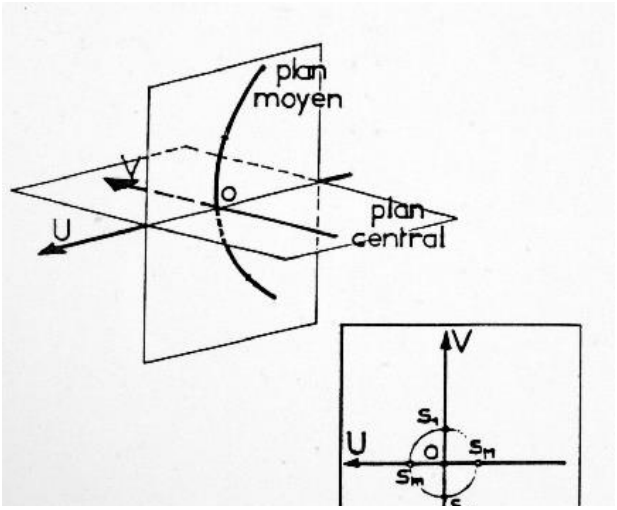


Fig. 29.5: Dose prescription for intraluminal brachytherapy with a curved source line in a small sized applicator. Prescription is done at the depth considered to be adequate for curative or palliative treatment purposes. Recording and reporting should also be at 10mm of the source axis in the central plane. In case of a curved source the recording dose should be the mean of two dose points perpendicular to the curvature. Dose points at 10mm at the convex site underestimate the dose, at the convex site overestimate it. (After Bucciarelli 1993 [7]).

9. TREATMENT PLANNING

9.1 2D Dose Planning

For final radiographic evaluation a flexible calibrated guide wire or a set of radiographic markers is inserted into the brachytherapy applicator (Fig. 29.2B). Orthogonal localisation films with or without a reference frame are taken for documentation and dose planning. The position of the applicator on these radiographs must be checked and compared with the clinical and/or radiographic documentation of the tumour extent at bronchoscopy at the beginning of the application. The tip of the visible guide wire should always pass at least 20 mm beyond the distal tumour edge. On the radiograph, the target is drawn taking into account all diagnostic findings from bronchoscopy and X- ray examinations (computed tomography) as well as the X-ray documentation of the tumour extent during the bronchoscopy.

Appropriate (for example 20 mm) safety margins are indicated proximally and distally from the tumour (see definition of target volume).

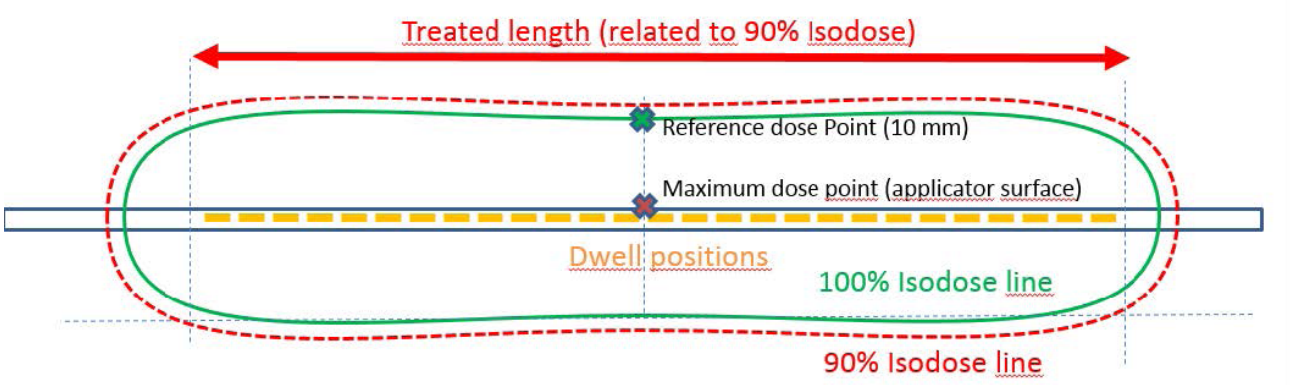
The dose, as well as the depth at which the dose is prescribed is at the discretion of the brachytherapist. It may depend on whether the tumour is central or peripheral, on the endobronchial radial extent and the treatment policy. The use of CT is recommended, even in palliative treatment planning. It allows for better coverage of (stenotic) GTV/CTV, to reduce radiation doses to critical organs (especially esophagus in primary bronchus lesions) and thereby reduce the toxic effects of treatment [40].

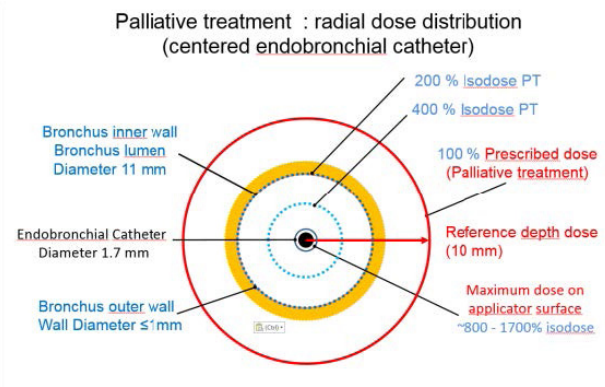
In curative situations the prescription isodose should encompass the target volume completely. 3 D CT dose planning (see below) is mandatory nowadays as it may help to define the exact target depth and the OARs.

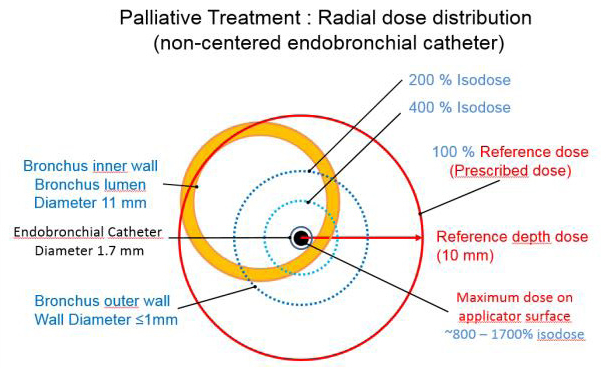
In palliative treatments intraluminal brachytherapy cannot encompass the whole large tumour extent and the dose is prescribed at a certain distance (e.g. at 10 mm depth) from the source axis as recommended for small applicators, or at a fixed distance (5 mm) from the applicator surface as recommended for large size applicators. Usually when stepping source technology is available, the dose is prescribed either at a fixed distance, or at a varying distance from the source axis or the applicator surface, taking into account the diminishing bronchial diameter along the target. The reference points that indicate the target volume must then be drawn on the orthogonal radiographs and entered into the planning system.

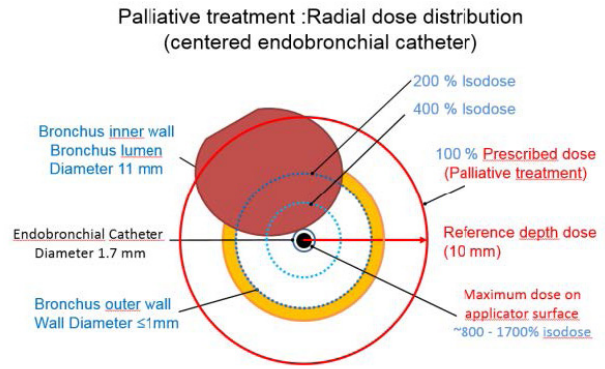
For a curved source the dose at 10mm will vary depending on the direction of the curvature: the dose will be higher at 10 mm at the concave side than at the convex side. This problem is solved by taking the mean of the doses at 2 points situated in the central plane at 10mm and perpendicular to the plane of the main curvature [6] (Fig. 29.5).

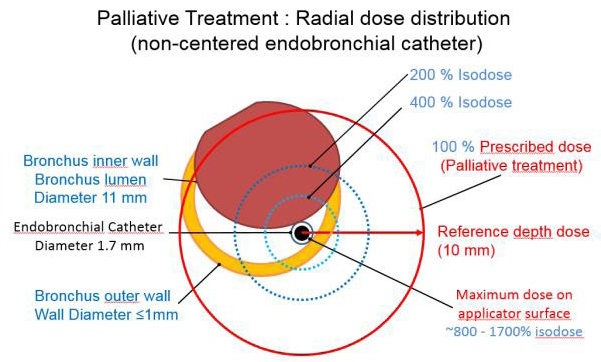
However, according to the ICRU recommendations (ICRU report 58), the dose should, for reasons of comparability, be reported











Lumen diameter: trachea 18mm, primary bronchus 14mm, secondary 11mm, tertiary 9mm Wall thickness: trachea 1mm to 0.5 mm tertiary bronchus

Fig. 29.6: Dose distribution and reporting for palliative endobronchial treatment The prescribed dose (PD) at 10mm, the reference depth (RD) at 10mm and the applicator surface dose (AS) are indicated beside the Applicator Diameter (AD 1.7mm). The dose to the tumor and to the bronchial mucosa are strongly dependent on the positioning of the catheter (centred or not centred). The Treated Length (TL) is defined as the length of the 90%-isodose at the reference depth of 10mm.

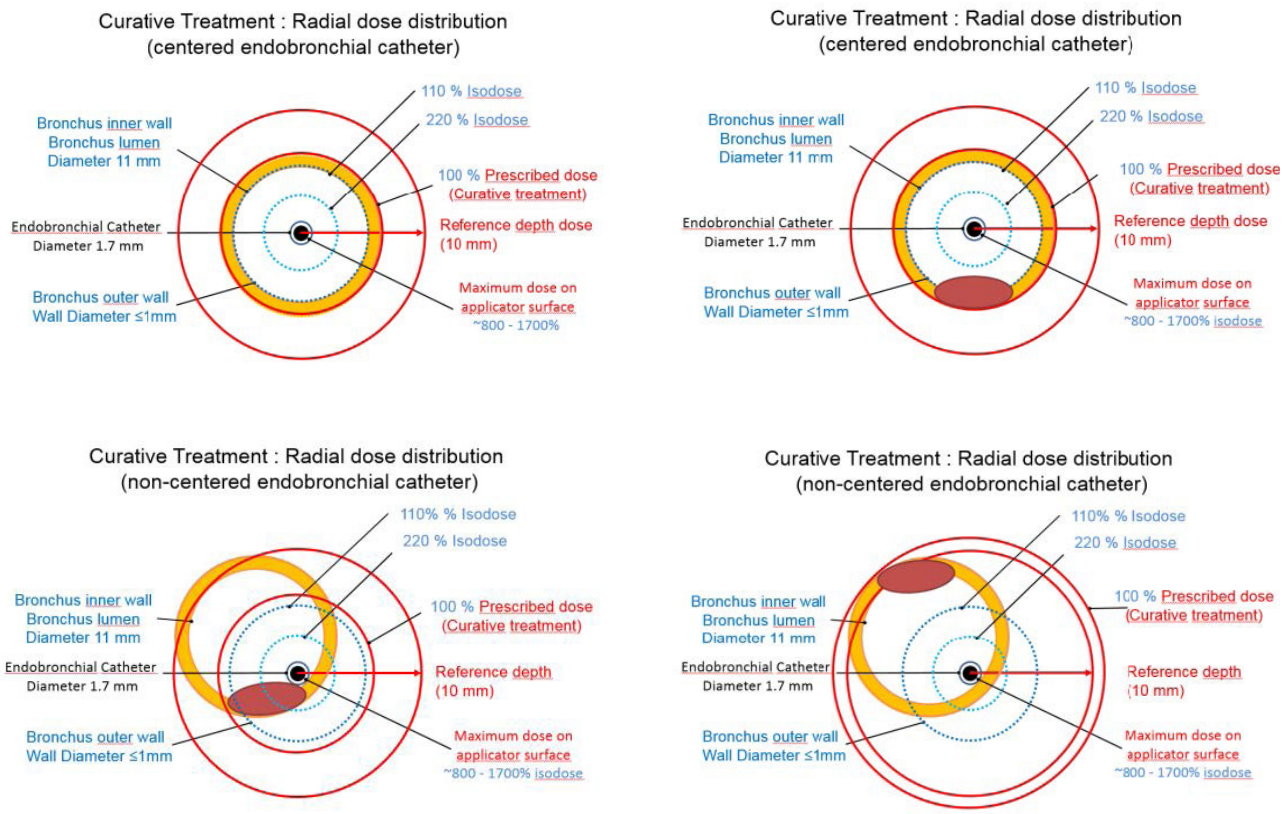


Fig. 29.7: Dose distribution and reporting for curative endobronchial treatment. The prescribed dose (PD) at the outer bronchial wall (basis of the target), the reference depth (RD) at 10mm from the catheter and the applicator surface dose (AS) are indicated beside the Applicator Diameter (AD 1.7mm).
The dose to the tumor and to the bronchial mucosa are strongly dependent on the positioning of the catheter (centred or not centred). Therefore it is extremely important to position the treatment catheter as close as possible to the bronchial lesion (see C and D).
The Treated Length (TL) is defined as the length of the 90%-isodose at the reference depth of 10 mm (see Fig. 29.6).

in the central plane at 10mm from the source. In addition the Treated Length (TL) should be reported, which is the length along the bronchus where the 90% isodose cuts the prescription depth (10mm).

Since the position of the endobronchial catheter is usually eccentric, the applicator surface dose should be reported, indicating the potential maximum dose that could be delivered to the tumour surface or to the bronchial mucosa (Fig. 29.6). In particular in curative treatment care has to be taken to put the catheter(s) as close as possible to the target. Endoscopists are able to direct the catheter(s) within the bronchus through a specific steering technique so that it lies closeto the target (Fig. 29.7).

For 2 or 3 diverging sources dwell times should be adjusted in such a way so that the dose at 15 mm from the intersection does not exceed the prescribed dose at 10 mm around the single sources. (Fig. 29.8)

9.2 3D Dose Planning

Nowadays 3D dose planning is increasingly used in brachytherapy and should be advocated in curative brachytherapy for small bronchus cancers. Sectional imaging with CT allows to delineate the GTV, which usually becomes easily detectable when combining the measured distances from the main carina to the tumour on the images of 3 mm slice thickness CT (Fig. 29. 9). Then the CTV extending 10 mm along the bronchial wall, and the PTV extending another 10 mm along the bronchial tree can be delineated to account for source position uncertainties during breathing.

It is important to delineate the bronchial wall and not the outer wall, to get meaningful DVH's to correlate with dose/ volume related complications. It can be done either by extending the GTV with 10 mm and erasing endo and extrabronchial air and tissues (e.g. oesophagus, vessels...) from the CTV.

In case of lesions in the trachea, or in the central parts of the primary bronchi the oesophagus, which risks to receive important dose, has to be delineated.

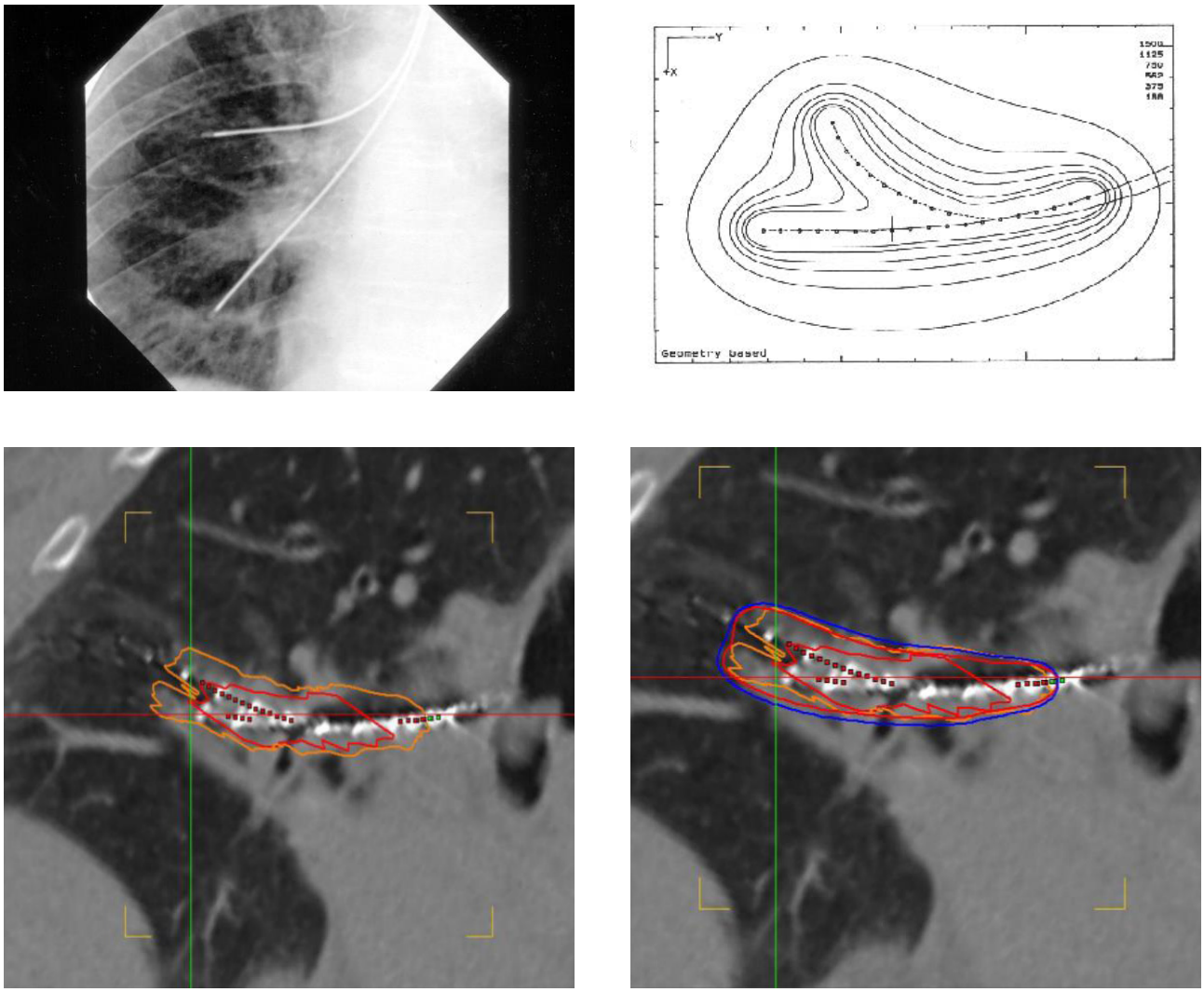


Fig. 29.8:
A. Anterior-posterior localisation radiograph in a tumour growing around the carina of the intermediate and lower lobe bronchus with two intraluminal tubes introduced into the intermediate and lower lobe bronchus.
B. Dose distribution in case of a fork application with a stepping source afterloader. Individual dwell times should be programmed in such a way that the dose at 15 mm from the fork will not exceed the dose prescribed at 10 mm from the individual source lines.
C. 3D target delineation for treatment of a bronchus tumour located at the bifurcation of a tertiary carina of the right inferior lobe
D. 3D dose planning for the same patient

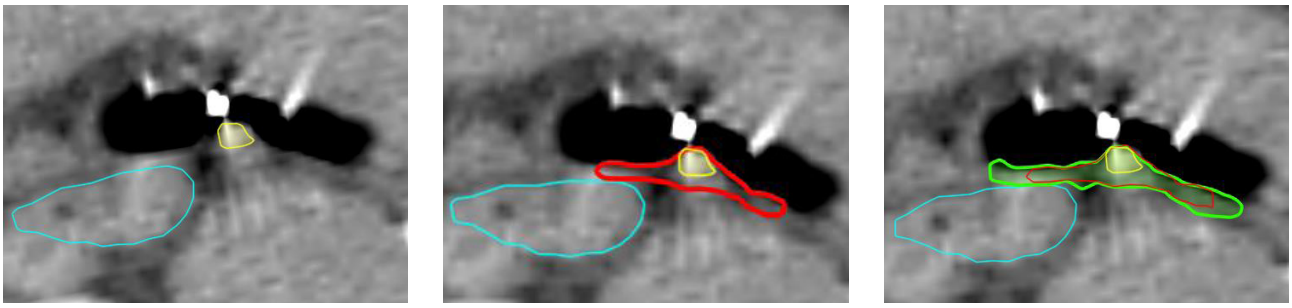


Fig. 29. 9: Sectional image of a small tumor of 8mm in the left primary bronchus.
In yellow the delineated GTV, in red the delineated CTV extending 10 mm into the bronchial wall.
In blue the delineated oesophagus. In green he PTV is drawn by adding another 10 mm both sides of the CTV

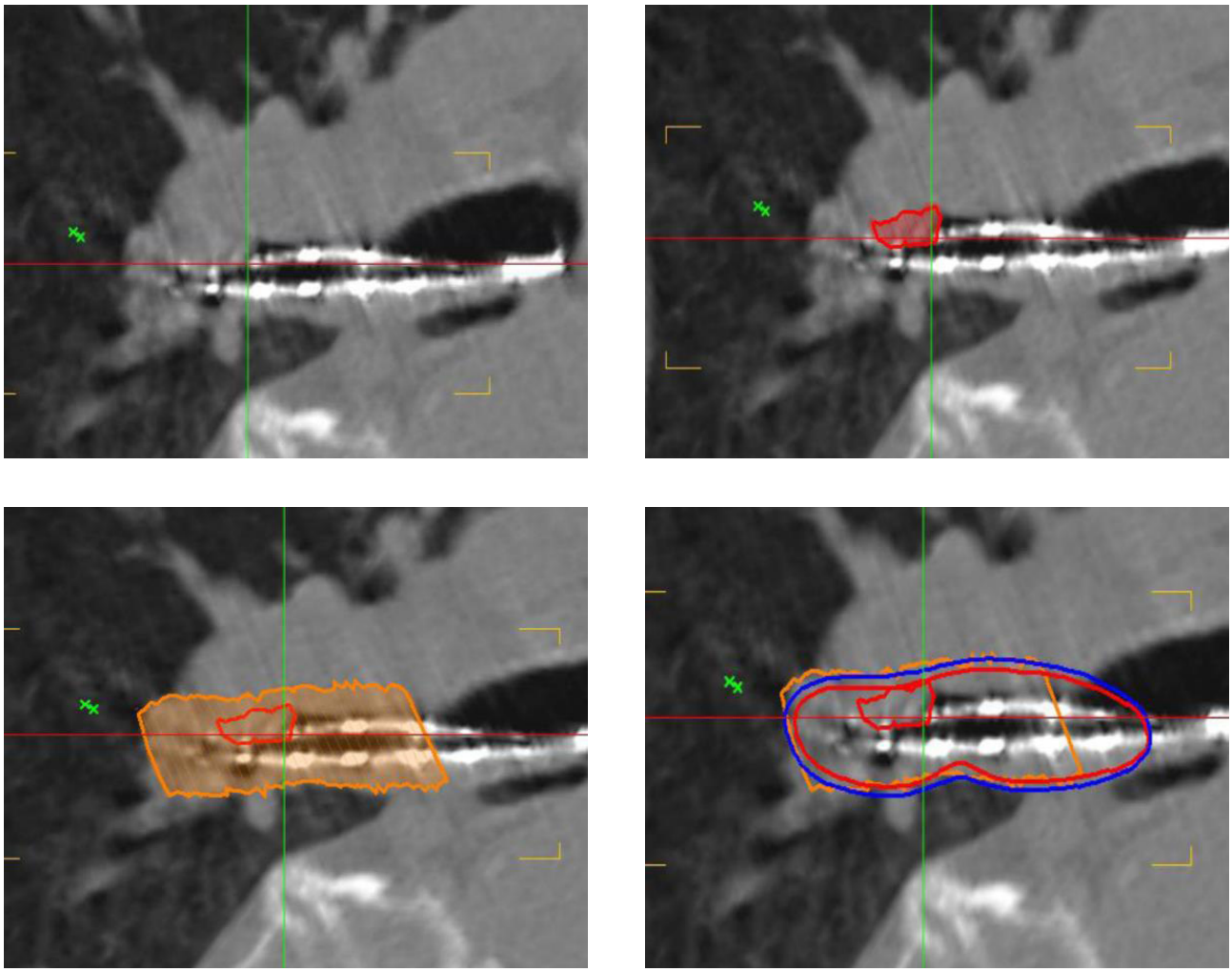


Fig. 29.10: Placement of 2 endoluminal bronchus catheters instead of one in the right primary bronchus to increase the possibilities for more conformal target covering: in red the delineated GTV, in orange the delineated PTV. The covering isodose lines 6 Gy in red and 5 Gy in blue are displayed

Fig. 29.11: Placement of 2 endoluminal bronchus catheters instead of one in the left secondary bronchus to increase the possibilities for more conformal target covering and better sparing of the OAR (oesophagus in dark blue). The GTV in red receives 10Gy the CTV in orange 8 GY

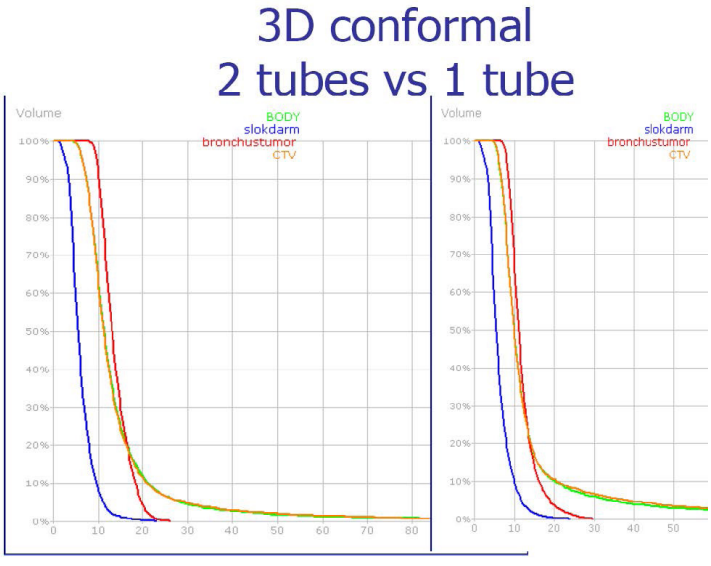


Fig. 29.12: DVH comparison of loading 1 versus 2 endoluminal bronchus catheters in the left secondary bronchus to increase the possibilities for more conformal target covering (GTV in red, CTV in orange and better sparing of the OAR (oesophagus in blue)

The systematic placement of a second intraluminal catheter in case of a 3D planning (Fig. 29.10) increases the degrees of freedom, to improve as well target covering as sparing OAR (Fig. 29.11 and Fig. 29.12).

10. DOSE, DOSE RATE, FRACTIONATION

For the patients´ comfort and to minimise source displacement during treatment, HDR brachytherapy is nowadays the preferred treatment for intraluminal bronchial brachytherapy. Only a few minutes are required for the treatment because of the high specific activity of the source.

The total dose depends on the aim of treatment and - if previous radiotherapy has been given - on the dose already delivered. There is some variation in dose specification and diameters of applicators in the literature. Taking a lateral distance of 10 mm from the axis of the source, the dose per fraction varies between 5 - 10 Gy. Larger doses per fraction may lead to adverse side effects (ulcer, necrosis, haemorrhage), in particular as the volume of overdose is significant. This applies in particular for small diameter applicators (e.g. 2 mm) where the mucosal surface dose can be extremely high [46]. This effect becomes even more pronounced as central positioning of the applicator is often difficult.

The total dose of HDR brachytherapy usually does not exceed 25 to 30 Gy at the reference point.

The treatment interval between the single fractions should be up to one week. The treatment time for one fraction is several minutes with a single catheter application using an Ir-192 HDR source with an activity between 5 and 10 Ci.

Intraluminal brachytherapy can be performed concomitant with external beam radiotherapy with 1 fraction given by brachytherapy and 4 fractions by external beam therapy in one week [30]. Commonly used treatment schemas are listed in Table 29.2.

Table 29.2: Suggested brachytherapy treatment schedules (indications, doses) based on published literature [17,18,19,23,45,53,66,68,73]

Indications for brachytherapy	Step I	Step II	Step III	Step IV	EQD2 α/β 10	EQD3 α/β 3 Gy
Radical combined treatment: schema I, clinical stage T1-3 N1-3 M0	EBRT: 44 Gy in 2 Gy Fx	1HDR BT fr. x 6 Gy, ref. point 5 - 10 mm	EBRT 16 Gy in 2Gy fr. (changed fields)	1 fr. x 6 Gy, ref. point 5 - 10 mm	76 Gy	81.6 Gy
Radical combined treatment: schema II, clinical stage T1-3 N1-3 M0	EBRT: 44 Gy in 2 Gy Fx	EBRT 16 Gy in 2Gy fr. (changed fields)	HDR-BT - in 1, 3 and 5 weeks of EBRT – 3 x 10 Gy. ref. point 0.5 - 10 mm		110 Gy	138 Gy
Radical sole BT treatment, radiologically occult cancer T1-2N0	HDR BT 36 - 42 Gy in 6 - 7 fr. with 4 - 7 days between fractions				48 – 56 Gy	64.8 – 73.6 Gy
Radical treatment after surgery, R2	After EBRT with total dose of 50 - 60 Gy	HDR. Fr. dose from 1 x 6 Gy till 3 fr. x 6 Gy (18 Gy), depending on EBRT dose ref. point 5 - 10			68 - 74 Gy	70.4 – 81.8 Gy
Radical treatment: stump infiltration	Sole BT: 4 fr. of 7.5 – 10 Gy with 4 - 7 days between fractions				49.5 – 66.6 Gy	63 – 104 Gy
Palliative treatment (one of schedules)	BT 18 Gy in 3 fr. of 6 Gy with 4 -7 days interval – in patients treated earlier with EBRT – dose > 50 Gy				24 Gy after > 50 Gy	32.4 Gy after > 50 Gy
	BT 22,5 Gy in 3 fr. of 7,5 Gy with 4 -7 days interval– in patients not irradiated or treated earlier with EBRT – dose < 50 Gy				32.8 Gy After < 50 Gy	47.25 Gy After < 50 Gy
	BT 1 x 10 Gy in case of WHO scale > 2*				16.7 Gy	26 Gy

** In single cases dose can be repeated after few weeks, in cases with clinical remission and/or visible during bronchoscopy*

11. MONITORING

Beside the standard monitoring during the bronchoscopy procedure described earlier, the main issue afterwards is cough suppression as this may lead to displacement of the applicator during brachytherapy. This problem mainly occurs during longer treatments with PDR brachytherapy. Cough suppression is achieved by administration of codeine or derivatives and by sedative drugs.

Oxygen tension is continuously monitored. ECG may also be recorded, if necessary.

12. RESULTS

12.1 Palliative endoluminal BT

A lot of investigators have used a range of prescription points and fractional doses which could not be directly compared.

As symptom relief is the main endpoint in palliative treatment, results should be described accordingly. There are subjective and objective methods (Speiser and Spratling scores, (Table 29.1) [73] for assessing the efficacy of endobronchial brachytherapy. According to several large series published [10,21,37,43,73] overall symptom relief is achieved in more than two thirds of the patients. For example in Kohek's series [37] relief from cough was obtained in 51/73, from dyspnea in 42/63, from haemoptysis in 6/8 patients. Improvement in general condition (Karnofsky scale) was noted in 69.5 to 76.5%.

Partial remission as assessed by objective measurements was achieved in 101/188, minor response in 25/188, no change in 29/188, progressive disease in 33/188 patients. Speiser and Spratling found a change in mean obstruction score (from bronchoscopy findings) before and after brachytherapy in 65 to 71% of the treated subgroups (curative, palliative, recurrent) [73].

In another study [19] results of treatment of over 100 patients of palliative intent alone were presented. Treatment consisted of three or four weekly fractions, 5 or 7.5 Gy per fraction. The median survival time was only 5.6 months. Objective response, evaluated bronchoscopically, occurred in 84%. The majority of patients had experienced symptomatic relief by the third fraction of brachytherapy. The frequency of symptomatic relief was as follows: dyspnoea 54%, cough 51%, pneumonia 86%, haemoptysis 94%. Similarly, Gustafson et al. [23] noted significant clinical improvement in 74% of 38 symptomatic patients treated with 21 Gy at 10 mm given in three HDR applications over 3 weeks. In patients

Table 29.3: Palliative HDR brachytherapy of lung cancer – treatment results

Author	N	HDR doses (Gy)*	EQD2 α/β 10 Gy	Clinical improvement (%)	Chest X- ray improvement (%)	Broncho-scopy improvement (%)	Median OS
Bedwinek [5]	38	3 x 6	24 Gy	76	64	82	10 m
Jacobson [32]		3 x 6	24 Gy	74	-	65	-
Gauwitz [20]	24	-		88	-	88	8 m
Sutedja [78]	31	3 x 10	50 Gy	82	-	-	7 m
Burt [8]	50	1 x 15-20	31.6 - 50Gy	50-86	46	88	-
Miller and Phillips [50]	88	3 x 10	50 Gy	-			-
Aygun [3]	62	3-5 x 5	18.7 – 27.1 Gy	-	-	80	-
Mehta [47]	31	4 x 4	50 Gy	79	36	76	-
Speiser and Spratling [72]	144	3 x 10	50 Gy	85-99	85	85	-
	151	3 x 5-7	18.7 – 29.75 Gy				
Zajac [85]	82	1-5 x 10	16.6- 83.3 Gy	82	-	80	-
Chang [10]	76	3 x 7	29.75 Gy	79-95	-	74	-
Delclos [13]	81	1-2 x 15	31.25 – 62.5 Gy	85	-	87	-
Gollins [21]	406	1 x 10-20	16.6 – 50 Gy	-	75	80	-
Macha [43]	365	3-4 x 5	18.7 – 25 Gy	66	-	65	-
Kelly [34]	175	2 x 15	62.5 Gy	66	-	-	6 mos
Skowronek [68]	303	3 x 7.5	32.8 Gy	88,4 (after 4 weeks), (14,5 - after 1 year) – whole group	-	78	3,7m
	345	1 x 10	16.6 Gy				

** Number of fractions and fraction size in Gy, HDR – High Dose Rate brachytherapy, mos – months, OS – Overall Survival*

without prior irradiation, there was a tendency for higher percentage of clinical and radiographic response. They concluded that a significant proportion of patients can be rendered asymptomatic for the duration of their lives. In one of the largest published studies there were 648 patients with endobronchial tumour, treated with two different protocols of HDR brachytherapy [68].

Significant and durable clinical and radiographic responses could be obtained in patients with symptoms, despite prior radiation or metastatic and non-bronchogenic primary disease. There was no statistically important difference in the results between the two groups of patients treated with different doses. The complication rate compared favourably with those reported from other institutions. The median survival time of 5.9 months was consistent with the advanced stage of this population. Multivariate analysis showed that the grade of remission after treatment, clinical stage and performance status had maintained significance for survival time as well as for treatment response. Other published results are presented in Table 29.3.

12.2 Endobronchial recurrence after EBRT – endoluminal BT

A special indication for endobronchial brachytherapy is recurrent endobronchial disease after EBRT in selected patients. Endobronchial radiation therapy, especially in previously irradiated area with dose limitations set by radiation tolerance of normal tissue represents a therapeutic option with several advantages over conventional external beam radiotherapy and other therapeutic modalities. By placing a radioactive source near or in the tumour, a high dose of radiation is given to the tumor with the dose fall off in accordance of the inverse square law. The chance of damaging healthy tissues is reduced, since only a small amount of tissue receives therapeutic dose of radiation [66]. Speiser and Spratling [73] reported the same palliative effect and survival outcome in these recurrences as was seen in patients treated primarily with palliative intent. Gauwitz [20] reported on 24 patients with recurrent disease after external beam RT of at least 55Gy. All patients had an ECOG performance less than 2. Treatment consisted of 2 HDR fractions of 15 Gy at 6mm (corresponding to 9 Gy at 10 mm). Symptomatic relief was obtained in 21/24 (88%), and relief from atelectasis in 15/18 (83%), lasting for 26 weeks on the average (7 - 40 weeks). Only 1/24 died of haemoptysis. Micke et al. [49] reported the results of HDR brachytherapy in 16 patients with recurrent lung cancer after EBRT (50 – 60 Gy). The recurrences were treated using 2 to 4 applications of 5 to 6 Gy each. The median period of remission was 4 months, whereas the median survival time was 9 months. Ornadel et al. [55] have undertaken a prospective analysis of symptom response, duration response and prognostic factors in 117 patients treated with brachytherapy. A single dose of 15 Gy was given. Ninety-two patients had received previous EBRT. The median survival time was 12 months. There was no correlation between the total dose of the prior EBRT and the survival rate or rate of fatal haemoptysis [55]. In the Bedwinek et al. [5] series, 38 patients were treated with high dose rate endobronchial brachytherapy to palliate symptoms caused by endobronchial recurrence of previously irradiated (> 50 Gy) lung cancer. Twenty-nine (76%) patients had symptomatic improvement in response to a dose of 18 Gy, given in 3 HDR sessions weekly. The median duration of symptoms relief was 7.5 months. Bronchoscopy carried out 3 months after brachytherapy revealed that 41% had complete regression and another 41% had partial regression.

Table 29.4: Endobronchial BT for radiographically occult endobronchial carcinoma (ROEC)

Author	N	Clinical stage	EBRT	Brachy-therapy schedule	EQD2 α/β 10 Gy	Ref point	OFS %	CR %	LR %
CURATIVE LDR BRACHYTHERAPY COMBINED WITH EBRT									
Fuwa [17]	17	Chest Xray neg	50 Gy (30 - 77)	22 Gy (10 – 42)	72-87 Gy	3-9mm	-	100%	12%
Saito [60]	68	Chest Xray neg	40 Gy	25 Gy	65 Gy	10mm	-	NA	13%
CURATIVE MDR BRACHYTHERAPY COMBINED WITH EBRT									
Fuwa et al. [18]	39	-	45 Gy (22-66)	28 (10-46)	76- 85 Gy	-	-	97	10%
CURATIVE SOLE HDR BRACHYTHERAPY									
Tredaniel [81]	14	Limited to wall	-	3 * 7 Gy	29,8 Gy	10mm	-	84%	14%
Ardiet [2]	28	< 10mm CTneg	-	3-5 * 7 Gy	29.8-49.5 Gy	10mm	-	84%	24%
Perol [56]	19	<10 mm CTneg	-	3-5 * 7 Gy	29.8-49.6 Gy	10mm	58 - 2y	83%	5%
Taulelle [80]	22	Limited to wall	-	3-5 * 7 - 10 Gy	+/- 50 Gy	10mm	46 - 3y	96%	18%
Hennequin [27]	73	< 20mm CTpos	-	5-6 * 7 Gy	49.6-59.5 Gy	5-15 mm	45 - 2y	NA	41%
Marsiglia [45]	34	2 - 40mm	-	6 * 5 Gy	37.5 Gy	5-15 mm	78 - 2y	94%	27%

In selected small tumours, palliation may be more successful and long term survivors have been described. At Manchester's Christie Hospital, 37 patients with small tumours less than 20 mm, were treated with a single dose of 15 - 20 Gy delivered at 10 mm from the source [21]. Symptom relief lasting for up to 12 months after treatment was obtained for haemoptysis in 96%, relief of pulmonary collapse in 69%, relief of cough in 55% and of dyspnoea in 52%. The median survival was 709 days, 2-year survival 49.4 % and 5-year survival 14.1%.

12.3 Definitive endoluminal BT

Survival after palliative treatment in M0 patients seems to be dependent on the degree of remission achieved. Macha [43] reported a mean survival of 7.5 months in M0 patients ranging from 8.5 months in PR to only 2.5 months (NC+ PD). However, the impact of endobronchial brachytherapy on survival is still debatable. Speiser and Spratling [73] reported that patients treated with curative intent with external beam radiotherapy and a brachytherapy boost did not have a significantly longer survival than patients treated with external beam radiotherapy alone.

The Munich group [32] conducted a prospective randomised trial on central lung tumours. Patients received 60 Gy with external beam therapy and received either no further treatment or a boost of two 4.8 Gy endobronchial HDR fractions at 10 mm from the source axis. The median local control in these advanced cases was increased with the boost from 12 weeks to 21 weeks (p=0.052). In the 68 patients with squamous cell carcinoma the impact of the boost was more important with a significant increase in local control (p=0.007) Survival time seemed to be longer (40 versus 33 weeks), but did not reach statistical significance (p=0.09).

A specific subgroup to be considered is radiographically occult endobronchial tumours (ROEC) in medically inoperable patients. Although these cases are rare, they could be the best indications for endobronchial brachytherapy, as brachytherapy alone or combined with EBRT. BT alone with curative intent is possible, because in these cases brachytherapy might be able to cover the whole ROEC target volume. The reported outcome in this selected group of patients is encouraging (Table 29.4).

Fuwa et al. [17] treated 17 cases of ROEC with the combination of EBRT and intraluminal LDR brachytherapy. Although doses of EBRT and LDR BT varied considerably, no severe late toxicity was observed and 5-year cause specific survival was about 90%.

In a larger Japanese series reported by Saito [60] 64 patients with ROEC (68 lesions) were treated with external beam RT to 40 Gy followed by 25 Gy LDR intraluminal brachytherapy. Five year survival was 72.3%, and disease free survival 87.3% with acceptable acute toxicity with 6 % grade 2 pneumonitis and 29 % grade 1 late stenosis, but without any grade 2 or greater deterioration of respiratory function due to radiotherapy. Nine (14%) local recurrences were seen, five of them rescued by surgery and EBRT. In Europe studies were performed on medically inoperable patients

Table 29.5: Curative HDR brachytherapy combined with EBRT: in IIIA and IIIB lung cancers

Author	N	Clinical stage	EBRT (Gy)	Brachy-therapy schemas (Gy)	EQD2 α/β 10 Gy	LC (%)	OFS %
Mantz et al. [44]	39	T1-2 < 5 cm	54 – 75.6	1.: 2 - 4 x 5 - 7 Gy	79.-95.6 Gy	5 y: EBRT + BT - 58% EBRT - 32%	NS
				2: no BT	54-75.6 Gy		
Huber et al. [31]	68	advanced central lung tumors	60	Trial: 1: 2 x 4.8 Gy	71.8 Gy	5 vs 3 mos (p=0.052)	10 vs 8 mos (p=0.09)
				2: no BT	60 Gy		
Reddi et al. [58]	32	IIIA – IIIB	60	3 x 7.5 Gy	71.9 Gy	-	8 mos
Aygun et al. [3]	62	IIIA – IIIB	50 – 60	3-5 x 5 Gy	78.8-81.2 Gy	-	13 mos
Mehta et al. [48]	22	IIIA – IIIB	60	4 x 4 Gy	878.7Gy	-	8.5 mos
Chang et al. [10]	54	IIIA – IIIB	20 – 70	3 x 7 Gy	23.3-97.8 Gy	-	-
Cotter et al. [12]	65	IIIA – IIIB	55 – 66	2-4 x 2.7-10 Gy	77.4-99.3 Gy	86%	8 mos
Speiser and Spratling [73]	50	IIIA – IIIB	60	3 x 7.5-10	81,9- 110 Gy	80%	11 mos
Kohek et al. [37]	39	III	50 – 70	1-5 x 5.6	77.3-86.4 Gy	67%	13 mos
Zajac et al. [85]	24	III	50 – 61.2	3 x 5-10	80-100 Gy	82%	12 mos

LC – local control, OFS – overall free survival, BT – brachytherapy, LDR – Low Dose Rate, MDR – Medium Dose Rate, HDR – High Dose Rate, EBRT – external beam radiation therapy, y – years, Gy – Grey, mos – months

with HDR-brachytherapy alone [2,27,45,56,80,81]. Most patients received 3 - 6 fractions of 7 - 10 Gy at 10 mm from the source axis. Over 80% had a complete response and a good survival outcome. Local recurrences were noted in 5-40% of cases (Table 29.4). Acute toxicity was tolerable, but fatal haemoptysis and bronchial necrosis were reported, especially in those patients who received more than 35 Gy HDR brachytherapy [27,45,56,81]. Groups of patients qualified for combined treatment (EBRT and BT) are heterogeneous (Table 29.5)

12.4 Interstitial BT

In early-stage of non-small-cell lung cancer (NSCLC), the addition of intraoperative brachytherapy to sublobar resection improved predicted rates of local control and overall survival compared to sublobar resection alone. In more advanced disease with residual tumor or positive lymph nodes at surgery, the addition of thoracic brachytherapy resulted in favorable rates of local control and survival. When planar I-125 implants were placed following resection of metastatic and locally invasive paraspinal tumors, excellent local control rates with minimal toxicity were seen, despite high localized doses to the spinal cord [52,66].
Interstitial brachytherapy as an independent radical brachytherapy was used so far in small groups of patients. Three presented in Table 29.6 reports come from studies of one group of researchers. They described in each of these papers different groups of patients in clinical stage I and II, III and a group of patients with Pancoast tumor [28-30]. In the last group especially noteworthy are good clinical results - 70% local control in 5-years follow-up, 10 years survived 20% of patients [28].

13. ADVERSE SIDE EFFECTS

Acute side effects related to the treatment procedure itself are reported in 3 % of applications [21,73] consisting of pneumothorax, bronchospasm, haemoptysis, pneumonia, cardiac arrhythmia, cardiac arrest or hypotension.

Some problems arise in assessing the incidence of late complications occurring weeks to months after brachytherapy, as it is sometimes difficult to differentiate between complications due to tumour progression or from radiotherapy.
Risk factors for severe haemoptysis include: received high dose of

Table 29.6 Clinical results of interstitial brachytherapy

Author	Number of patients, clinical stage	Isotope, technique	Local control	Overall survival
Hilaris [30]	322, stage III - N0	I -125, residual tumor after surgery	71% - 2 y	20% - 2 y
Hilaris [28]	55, stage I and II	I -125, 24 patients - additional EBRT	T1N0 - 100% (5 y) T2N0 - 70% T1-2N1 - 71%	33% - 5 y
Hilaris [29]	127, superior sulcus tumors - Pancoast tumors	preoperative EBRT + partial resection + I -125 or Ir-192	70% - 5 y	20% - 10 y
Fleishman [14]	stage I	I -125	71% - 1 y	median - 15 mth
Burt [8]	stage III: 1. S only – 49 2. S incomplete + BT – 33 3. BT only - 101	I -125	-	2 y; 3 y: 1 - 29%, 21% 2 - 30%, 22% 3 - 21%, 9%
Chen [11]	23, I stage NSCLC, high risk group	video-assisted thoracoscopic resection (VATR) + I -125	median follow-up – 11 mos	3 – metastases 3 – perioperative deaths 1 - recurrence
d'Amato [1]	14, T1N0, NSCLC	video-assisted thoracoscopic (VATS) wedge; resection + I -125 (Vicryl)	median follow-up – 7 mos	no recurrences
Trombetta [82]	278	gross total resection of a non small-cell lung cancer using segmental resection, wedge resection, or sublobar resection + I -125	median follow-up – 45.3 mos	-

Y – years; EBRT – External Beam Radiation Therapy; mos – months; S – Surgery, BT – Brachytherapy; NSCLC – Non Small Cellular Lung Cancer

EBRT, several brachytherapy fractions, the location of the tumour in the left upper lobe, long sections of irradiated bronchi (clinical stage). The rate of fatal haemoptysis reported in the literature varies from 0% to 32% (Table 29.7). However, it is recognised by most authors that most fatal haemorrhage is not due to brachytherapy, but to tumour progression [5,27] and the rate is comparable to the incidence of haemoptysis after laser coagulation alone. Hennequin [27] found no correlation with site of the treatment, technical factors, fraction size or association with external beam therapy as has been reported by others [21], but only with the length of endobronchial tumour spread. In the randomised trial conducted by the Munich group [31] however, fatal haemoptysis occurred more frequently after 2 x 4.8 Gy HDR boost than in patients who did not receive a boost after 60 Gy external beam RT (18.9% versus 14.2% fatal haemoptisis), but results were not statistically significance (p=0.53).

The rate of tracheo-oesophageal fistula leading to death in the Macha [43] series is 5.3% (mean 3.5 months after start of radiotherapy). To prevent fistula, it seems to be important to examine the bronchial wall (e.g. flat ulceration) and the oesophageal wall (oesophagoscopy) carefully in central tumours growing in this area. Oesophageal tumour infiltration carries a higher risk of developing fistula. Summarized observations are presented in Table 29.8.

Late effects such as chronic radiation bronchitis, bronchial stenosis and tracheomalacia are of course only seen in long term survivors, most of them with lesions of the trachea or primary stem bronchus [27]. The incidence rates reported in the literature vary between 4 and 13%. Speisser and Spratling [73] related chronic bronchitis to dose and dose rate. (9% in MDR and 13% in HDR). Hennequin et al [27] found a relation between chronic bronchitis and trachea and main stem sites (p=0.002), total dose (p= 0.04) and irradiated volume (p=0.02), the latter being the only significant parameter in multivariate analysis.

Table 29.7: Incidence of massive haemoptysis after HDR endobronchial brachytherapy

Author	N	Dose HDR* (Gy)	EBRT** (n)	EQD2 of BT α/β 3 Gy	Reference point (mm)	Haemoptisis (%)
Nori [54]	32	3-4 x 4-5	32	22.4-24 Gy	10	0
Speiser and Spratling [73]	295	3 x 10, 3 x 7.5	156	47.2-78 Gy	10	7
Chang [10]	76	3 x 7	59	42 Gy	10	4
Gollins [22]	406	1 x 15-20	82	54 -92	10	7.9
Gustafson [23]	46	3 x 7	12	42 Gy	10	7
Hennequin [27]	149	4-6 x 7	112	56-84 Gy	5-15	7.4
Huber [31]	56	2 x 4.8	56	15 Gy	10	18.9
Tredaniel [81]	51	1-6 x 7	32	14-84 Gy	10	10
Ornadel [55]	117	1 x 15	92	54 Gy	10	11
Taulelle [80]	189	3-4 x 8-10	117	70.4-78 Gy	10	7
Kelly [34]	175	1-4 x 15	160	54-216 Gy	6-7.5	5
Miller and Phillips [50]	88	3 x 10	(-)	78 Gy	10	0
Aygun [3]	62	3-5 x 5	62	24-40 Gy	10	15
Bedwinek [5]	38	3 x 6	38	32.4 Gy	10	32
Mehta [47]	31	4 x 4	9	22.4 Gy	20	3
Sutedja [78]	31	3 x 10	31	78 Gy	10	32
Seagren [63]	20	1 x 10	(+)	26 Gy	10	28
Roach [59]	17	30 Gy (LDR)	(+)	30 Gy	10	0
Khanavakar [35]	12	2-8 x 8	(+)	35.2-140.8 Gy	5	50

** number of fractions and fraction size in Gy, ** EBRT before BT or simultaneously, EBRT – external beam radiation therapy, BT – brachytherapy, LDR – low dose rate*

Table 29.8: Incidence of fistulas after brachytherapy

Author	n	Clinical stage	EBRT (Gy)	Brachytherapy schemas	Fistulas (n,%)
Macha [42]	188	recurrence after EBRT	(-)	3 x 7.5 Gy	15/188 (8.0%)
Harms [26]	1. 21	1. recurrence after EBRT, metastases	1. (-)	1. 5 - 27 Gy	1/55 (1.2%)
	2. 34	2. inoperable tumors	2. 30 -60 Gy	2. 10 - 20 Gy	
Delclos [13]	81	recurrence after EBRT	(-)	1-3 x 1.5 Gy (reference point at 6 mm)	1/81 (1.2%)
Cotter [12]	65	inoperable tumors	55 - 66 Gy	2-4 x 2.7-10 Gy	3/65 (4.6%)
Kohek [36]	39	IIIA – IIIB	50 - 70 Gy	1-5 x 5.6 Gy	(2.5 %)
Zajac [85]	24	IIIA – IIIB	50 – 61.2 Gy	3 x 5-10 Gy	(8%)
Mehta [47]	23	III	61 Gy	LDR - 48 Gy	(6%) - TV (3%) – TE
Sutedja [78]	31	inoperable tumors	(-)	3 x 10 Gy	3/31 (9.7%)
Schray [62]	40	inoperable tumors	(-)	LDR - 30 Gy	2/40 (5%)

TV – tracheovascular fistula, TE – tracheoesophageal fistula, EBRT – external beam radiation therapy, LDR – Low Dose Rate

14. KEY MESSAGES

- Brachytherapy is an efficient method for palliative treatment in advanced lung cancer resulting in improvement of quality of life in most patients.
- Brachytherapy is easy to perform on outpatients basis.
- Brachytherapy plays a limited but specific role in definitive treatment with curative intent in selected cases of early endobronchial disease as well as in the postoperative treatment of small residual peribronchial disease.

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