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## 1. INTRODUCTION

This is a retrospective study of patients treated with stereotactic body radiation therapy (SBRT) for centrally located lung tumours. The primary purpose of the study is to quantify the doses to the bronchi (the airways) in a series of patients treated for tumours located close to the hilum of the lungs with SBRT that had significant doses to the bronchi. The reason of studying this is that high dose irradiation of the bronchial tree can cause significant damage of the bronchi and lead to atelectasis (Timmerman and Lohr, 2005), collapse of a part of the lung.

The secondary purpose of this study is to relate the dosimetric information of the bronchi with clinically documented complications after radiation therapy of the patients, to get a dose-response relation. The endpoint was radiation induced atelectasis. The aim with this is to have a better knowledge of the bronchi tolerance when planning a phase I study of SBRT of centrally located lung tumours.

### 1.1. LUNG CANCER AND RADIATION THERAPY

Lung cancer is the most common type of cancer in the world and about 1.35 million people were diagnosed during year 2002 (Parkin *et al*, 2005). Lung cancer is the kind of cancer with highest mortality, year 2002 1.18 million died due to that disease (Parkin *et al*, 2005). What causes lung cancer is not completely known but the main reason is past exposure to tobacco smoking, and other reasons are asbestos, radon and air contamination (Cancerfonden och Socialstyrelsen, 2005).

Cancer in the lungs can either be primary lung tumours or pulmonary metastases. There are a couple of different types of primary lung tumours: Non small cell lung cancer (NSCLC), small cell lung cancer and mesotheliom (bronchial cancer) (ROC, 2006). Metastases in the lungs can be caused by various types of primary cancer in different organs. The different choices for treatment of lung tumours are surgery, chemotherapy and radiation therapy (RT). Some factors to consider for the choice of treatment method are the histopathology of the tumour, stage of the cancer, medical condition and age of the patient (Hansen *et al*, 2003), but also the location in the lungs (possibly close to

radiosensitive organs), previous radiation therapy to the same region in the body and previous chemotherapy. The primary treatment method is surgery, but if the tumour is unresectable, if the patient is medically inoperable (for instance in case of heart-disease) or if the patient refuses surgery then radiation therapy or chemotherapy, or a combination of these two, are the choices of treatment. The major cause of failure in conventional radiation therapy of medically inoperable or locally advanced NSCLC is local recurrence but also distant metastases (Baumann *et al*, 2001). As a consequence of that the treatment needs to be intensified, without increasing normal tissue complications (Baumann *et al*, 2001). One way of intensifying the radiation is hypofractionation in stereotactic radiation therapy (SRT) (Lax and Blomgren, 2005).

#### **1.1.1. Radiation induced complications following radiation therapy in the lungs**

Radiation induced complications when irradiating tumours in the lungs are divided into three groups depending on the time after treatment the complication appears. There are early/acute, intermediate/delayed and late complications. Early complications are esophagitis and fatigue (ROC, 2006). The intermediate complications can be radiation pneumonitis (after 2-6 months) and Lhermitte's syndrome (a feeling of electric shocks when bending the neck) (ROC, 2006). The late complications are lung fibrosis (a very common complication after high dose irradiation), pericarditis (accumulation of fluid in the pericardium, can occur if the whole pericardium receives >55 Gy), esophagus stricture (narrowing of esophagus, occurs at doses >60 Gy) (ROC, 2006) and as mentioned before bronchial damage leading to atelectasis (Timmerman and Lohr, 2005). Radiation myelopathy (damage to the spinal cord like Lhermitte's syndrome) and chronic radiation damage to the heart can both be classified as intermediate and late complications (Baumann *et al*, 2001), as can lung fibrosis.

#### **1.1.2. Atelectasis**

The lung complication atelectasis is when a small volume, a segment, a lobe or even a whole lung appears hyperinflated followed by absorption of air, resulting in a shrinkage or collapse of that part of the lung (Mayer *et al*, 1956). Potential reasons for a person to develop atelectasis are:

- Intrinsic obstruction of the airways caused by for example foreign bodies, tumours, secretion or mucous plugs (Faber and Piccione, 2000)
- External compression of the airways, caused by space occupying lesions like tumours, enlarged lymph nodes and abnormal amount of fluid or air in the pleural space (Faber and Piccione, 2000), another cause can be collapsed alveoli due to fibrotic lung tissue (Travis and Komaki, 2000)
- Defective production or capacity of the liquid substance coating the alveoli, which normally prevents them from collapsing (Faber and Piccione, 2000)
- Collapse of the bronchial lumen after high-dose irradiation of the airways (Timmerman and Lohr, 2005)
- Inadequate blood supply to the region beyond a place in the lung tissue of intense irradiation (Timmerman and Lohr, 2005)

A reason that a part of the lung collapses after an occlusion is that the air in the alveoli distal to the blocked airway is absorbed into the blood and that causes the alveoli to collapse (Faber and Piccione, 2000). The collapsed lung can be replaced with blood cells, serum and mucous and lead to varying degree of inflammation (Mayer *et al*, 1956).

Common symptoms of atelectasis are shortness of breath, dyspnea, cough and decreased oxygen level in the blood which can cause increased heart rate (Faber and Piccione, 2000). If inflammation is developed in the atelectasis region, fever and pain in the chest can occur (Baciewicz, 2000). However, the symptoms depend on the size of the affected lung volume. Most people have more respiratory capacity than needed, which constitutes a reserve in lung function (Timmerman and Lohr, 2005). If the lung function of the atelectatic volume is less than the reserve function no symptoms of complication will be noticed by the patient (Timmerman and Lohr, 2005).

## **1.2. STEREOTACTIC BODY RADIATION THERAPY**

Stereotactic body radiation therapy (SBRT) is a methodology that gives the possibility to improve the geometrical accuracy in the dose delivery and as a consequence the

possibility to treat tumours with very high doses without increasing the toxicity (Lax and Blomgren, 2005). With SBRT the patient's reference system is defined with an external three dimensional (3D) reference system (the stereotactic system) used both for target definition and set-up at the treatment unit. In conventional radiation therapy, on the other hand, anatomical reference systems are used (Lax *et al*, 1998).

The stereotactic treatment method began with radiation therapy of intracranial tumours, with the gamma knife, and has been used at the Karolinska University Hospital since 1974 (Lax *et al*, 1994). The treatment with the gamma knife of intracranial tumours is a single high-dose irradiation of a small volume in the brain with beams from up to 201 directions (Lax *et al*, 1994).

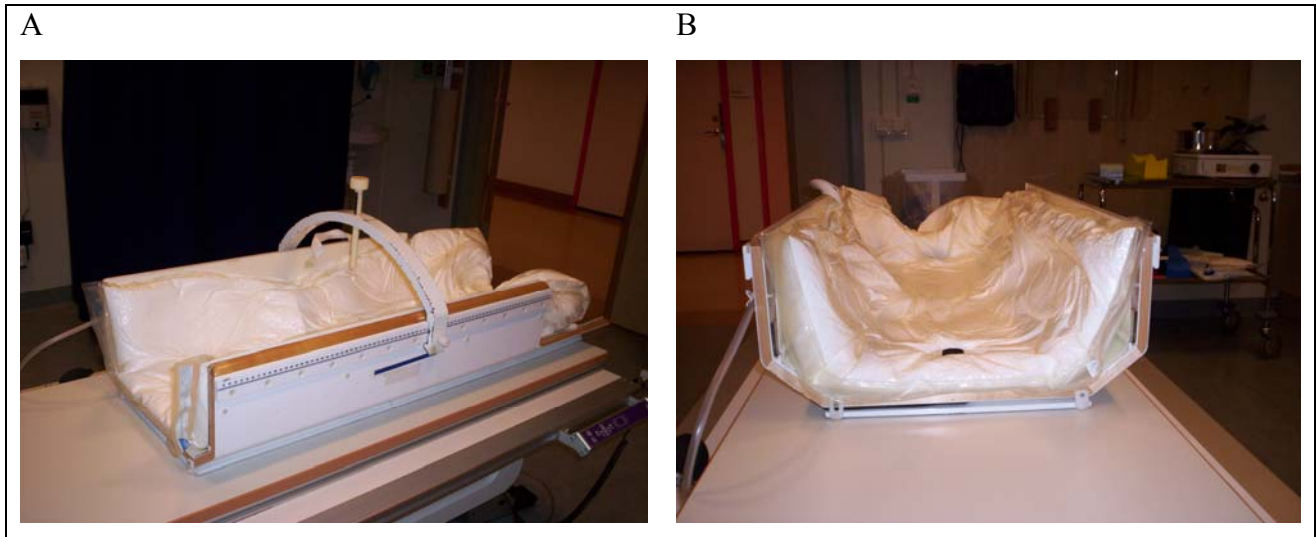
### **1.2.1. The stereotactic body frame**

At the Karolinska University Hospital a special stereotactic body frame (Figure 1) used for stereotactic body radiation therapy, has been developed (Lax *et al*, 1998). This frame is primarily used when treating small localised targets in the abdomen (Lax *et al*, 1994), but also for boost treatment of the gross tumour in targets with microscopic spread (Lax *et al*, 1998). At the Karolinska University Hospital this frame was taken in clinical use during 1991 (Lax and Blomgren, 2005). The patient is placed in this frame during both the preparatory CT scan and during all the treatment occasions. With this method it is possible to get a stereotactic treatment for tumours in the thoracic, abdominal and pelvic regions.

The patient is placed on a custom fitted vacuum pillow (Figure 1) from the head to the thighs (Lax *et al*, 1994) placed in the stereotactic body frame both at the diagnostic and therapeutic units. With the vacuum pillow the contact area between the patient and the body mould is large to obtain good reproducibility of the patient's position in the frame (Lax *et al*, 1998). The vacuum pillow can be used for the patient during the whole treatment period and after that be refitted to another patient.

To improve the reproducibility of the tumour in the stereotactic coordinate system the position of the patient in the frame is decided not only by the custom fitted mould but

also with laser markers adjusted to small tattoo points on the patient's skin (Lax *et al*, 1998).



**Figure 1:** The stereotactic body frame developed at the Karolinska University Hospital, with abdominal pressure device (A) and without (B).

Since the lungs of the patient expand and compress during breathing the position of tumours in the lungs or in the abdomen changes during the breathing cycle, mainly in the longitudinal (cranial-caudal) direction (Lax *et al*, 2006). The movement of the tumour in the cranial-caudal direction is commonly up to 20 mm but can sometimes be more than 30 mm for tumours located in the base of the lungs (Lax *et al*, 2006). This movement adds an extra geometrical uncertainty. To take this into account, the motion of the tumour is measured in fluoroscopy. If the tumour motion is more than 10 mm an abdominal pressure device (Figure 1A) is used to reduce the movements. This abdominal pressure makes the patient breathe more intercostally than diaphragmatically (Lax *et al*, 1998). In case the tumour is not visible in fluoroscopy, the motion of the diaphragm is measured. With this device the longitudinal movements of the tumour is generally reduced within 10 mm (Lax *et al*, 1994).

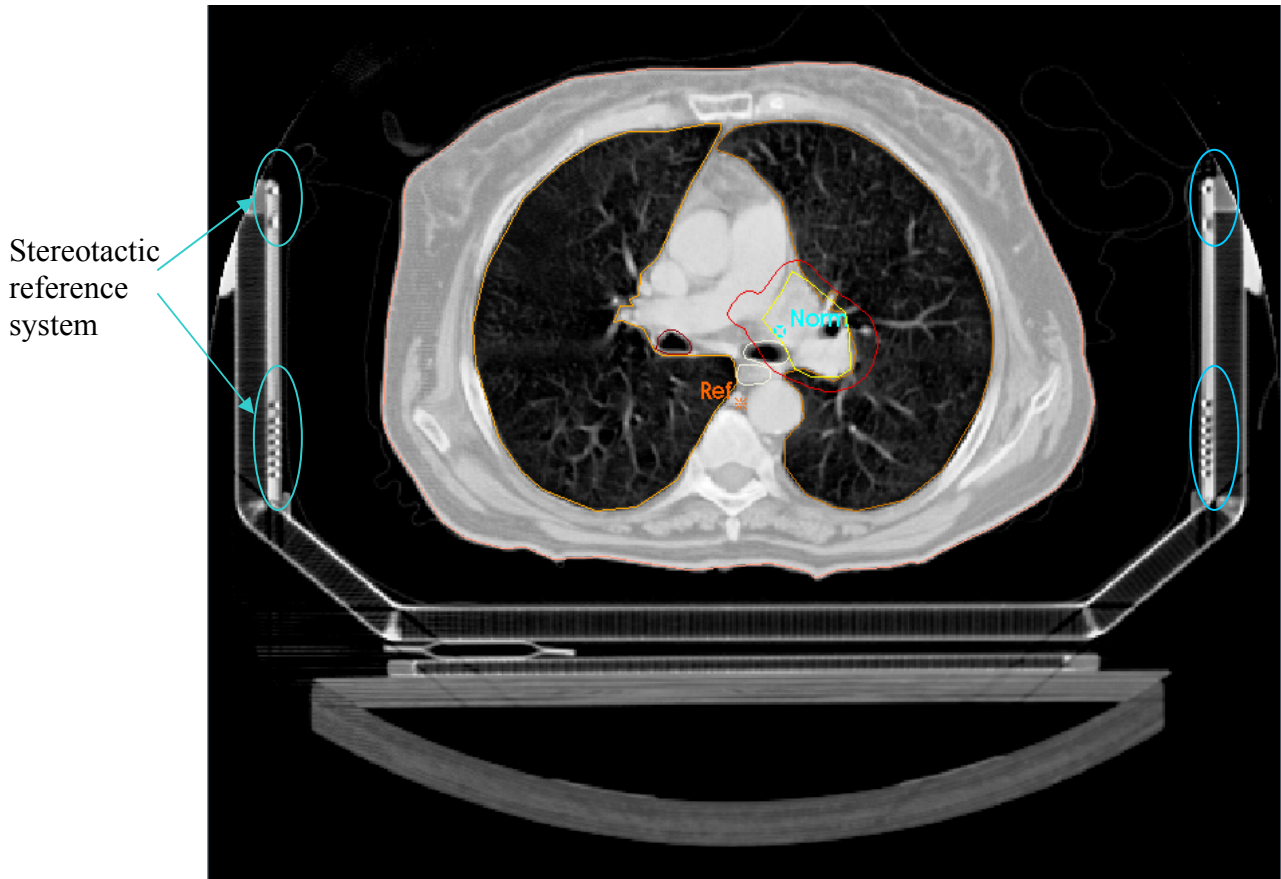
Other alternative ways of handling the respiratory motions are breath-hold devices, respiratory gating and measuring the respiratory variations with one CT scan at inspiration and another at expiration (Song and Blomgren, 2005).

The walls of the stereotactic frame are made of low density materials like plastic to give minimal artefacts on the tomographic images (Lax *et al*, 1998). These materials also make it possible to irradiate through the walls with just a small correction for the attenuation (Lax *et al*, 1998).



**Figure 2:** The stereotactic body frame with indicators on the inner walls and a scale on the outer walls.

On the inner walls of the frame there are indicators (Figure 2) made of glass fibre coated with copper film, these indicators can be seen on CT images (Figure 3), and on MR images with indicators of a copper sulphate solution. The indicators define the stereotactic reference system on the images (Lax *et al*, 1994).



**Figure 3:** A computer tomography image of a cross section through the lungs where the stereotactic body frame with its stereotactic reference system can be seen.

### 1.2.2. Geometric verification in SBRT

To verify the position of the target in the stereotactic system in SBRT repeated CT examinations are done. The verification CT images are compared with the first reference CT images, from which the dose planning is done, and a quantitative difference of the target position in the stereotactic system is calculated with a matching function in the dose planning system (Lax *et al*, 1994).

The difference between the CT-verification method used in SBRT and the portal imaging verification method used in conventional radiation therapy, is that the CT verification verifies the tumour position in the stereotactic system while in portal imaging, where soft tissue and gross tumour not is visible, only the position of the skeleton is verified (Lax *et al*, 1998). An advantage with this is that the patient system is avoided in CT verification, only the stereotactic and the tumour systems are used. The stereotactic methodology together with the CT-verification method makes is possible to



have small margins between clinical target volume (CTV) and planning target volume (PTV). Clinical experience of measurements at the Karolinska University Hospital has showed that a margin of 5 mm in the transverse plane and 10 mm in the longitudinal direction are generally sufficient (Lax *et al*, 1998).

When adjusting the stereotactic system to the isocenter coordinates in the treatment unit the set-up uncertainty has during repeated measurements been estimated to be within 1 mm (Lax *et al*, 1998).

### **1.2.3. Treatment intention for lung tumours**

When treating primary lung tumours with conventional radiation therapy there is a curative intention and because of that high doses are given. For patients with metastases in the lungs, radiation therapy has not traditionally been used with curative intention since the prognosis has been poor for these patients (Song and Blomgren, 2005). The intention has commonly been palliative since there might have been several metastases spread in different organs in the body and due to that there is a poorer prognosis. With a palliative intention lower doses are generally given, to prevent toxicity. If the prognosis for a patient with pulmonary metastases is good, i.e. if the patient is not suspected to have several rapidly growing metastases, the treatment intention is to prolong the survival time or even cure the patient. These patients as well as patients with primary lung tumours are treated with an intention of local tumour control and because of that given high doses to all these tumours. The patients chosen for SBRT are those who have one or a few small localised tumours and not patients with several metastases spread in the body.

### **1.2.4. Fractionation in conventional RT of the lungs**

In radiation therapy the sizes of the fractionation doses and the number of fractionations during a treatment period can be chosen in different ways. There are a few different fractionation schedules to choose between, the most common are conventional fractionation, hyperfractionation, accelerated fractionation and hypofractionation. In conventional fractionation the fractionation doses are of sizes between 1.8-2.0 Gy and it

is common with 5 fractions per week up to a total dose of 60 Gy or higher (Baumann *et al*, 2001). In hyperfractionation there are smaller doses per fraction (1.1-1.3 Gy) than with conventional fractionation, usually given in two fractions each day but the overall treatment time is often the same as with conventional treatment. The hypothesis of hyperfractionation is that a low dose per fraction will reduce late toxicity. Accelerated fractionation has shorter overall treatment time, the fractions can often be given twice a day, and each fractionation dose is often decreased but the average dose per week is higher than with conventional fractionation (Baumann *et al*, 2001). This fractionation pattern may be used when the probability for repopulation in the tumour is high when a long treatment time is used. With hypofractionation there are higher doses per fraction ( $>2$  Gy) and shorter overall treatment time, often no more than 5 fractions given within two weeks. The total dose is often decreased, otherwise it leads to a higher incidence of late normal tissue complications (Baumann *et al*, 2001). This fractionation pattern may be used in organs with parallel radiobiological response, in which very high biological doses can be given to the target while the toxicity still is acceptable.

### **1.2.5. Fractionation in SBRT of the lungs**

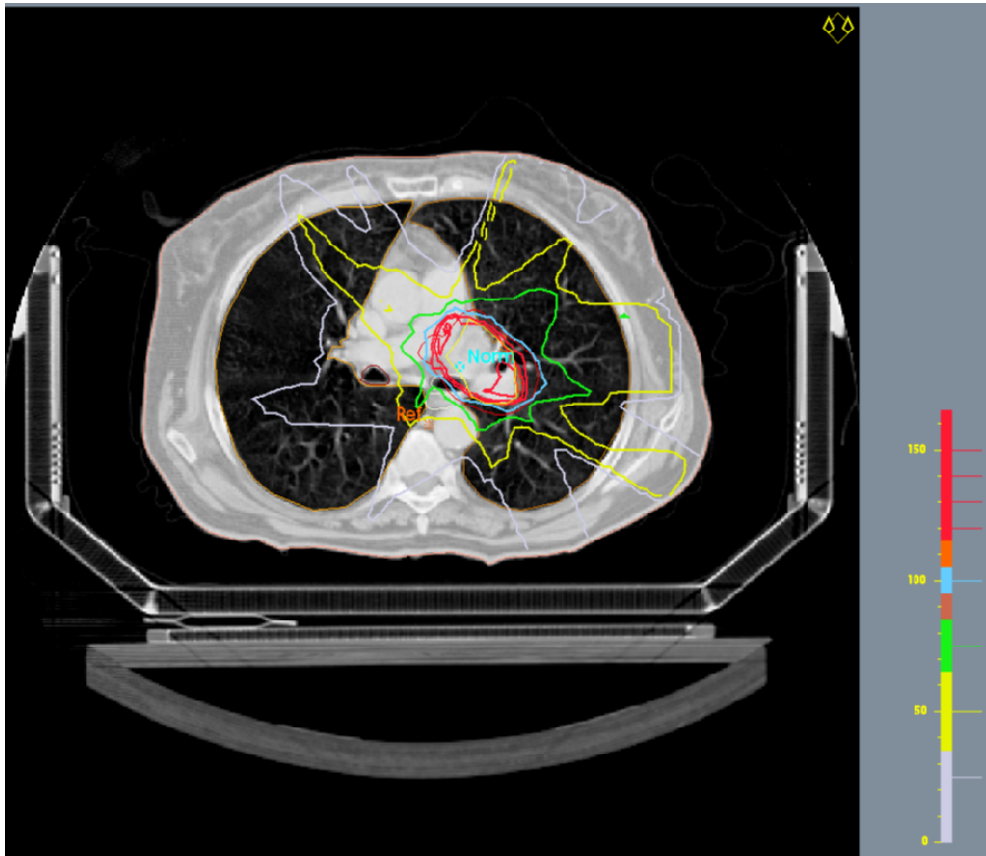
Since the geometrical accuracy in the dose delivery is enhanced with SRT compared with conventional external irradiation the margins between CTV and PTV can be decreased. In SBRT at the Karolinska University Hospital the margin is generally 5 mm in the transverse plane and 10 mm in the longitudinal direction (Lax *et al*, 1998), the difference in the two directions is depending on differences in the breathing motions. However, for small tumours in the lungs, not adherent to mediastinum or pleura the transverse margin is 10 mm. Besides the breathing motions of the tumour, also geometrical uncertainties and inaccuracy in reproducibility of placing the patient in the frame are included in the margins. Because of the reduced margins with SBRT the normal tissue around the target is spared and the fractionation schedule can be tougher than with conventional therapy. The type of fractionation chosen in stereotactic irradiation is therefore hypofractionation. From the beginning the intention with SBRT was to treat with one single fraction as with intracranial SRT, but the tumour control was not satisfying (Lax and Blomgren, 2005). After empirical development a new fractionation schedule was proposed and consisted of a few fractions of 8-20 Gy every

second day. The toxicity turned out to be acceptable and the tumour control was satisfying (Lax and Blomgren, 2005). The main advantage with hypofractionation in stereotactic radiation therapy is that there is no repopulation of the tumour cells during the total treatment time which improves the biological effect in the tumour. The hypofractionated treatment in SBRT also offers economical and practical advantages, due to the limited number of treatments. Besides the increased convenience for the patient with fewer fractions it is also possible to put larger effort into set-up accuracy at each treatment occasion and then decrease the margins around the tumour even more (Lax *et al*, 1994).

The fractionation standard for small tumours (<3 cm) are 2-3 fractions of 15-20 Gy, while for larger tumours 4-6 fractions of 5-8 Gy are commonly used (Lax and Blomgren, 2005). If the tumour is located close to radiosensitive organs as the hilum of the lung, the bronchi or the esophagus the fraction dose is decreased (Lax and Blomgren, 2005).

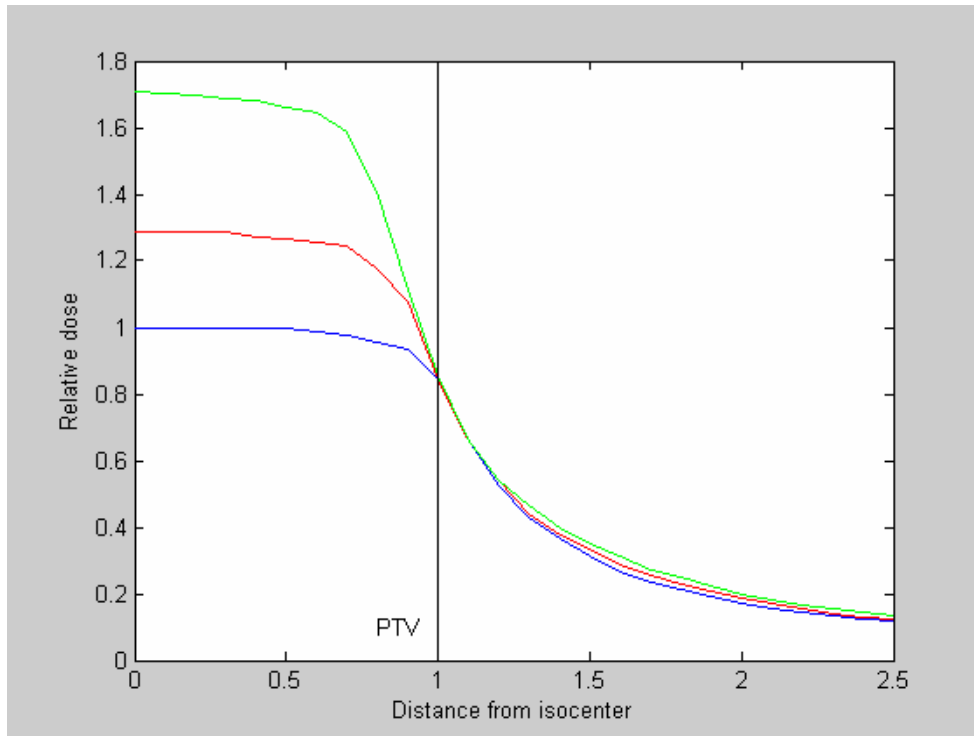
#### **1.2.6. Heterogeneous dose distribution**

When creating a dose plan for patients with SBRT at Karolinska University Hospital about 5-7 static, conformal, coplanar or non-coplanar beams are used (Lax *et al*, 1998). The 100 % isodose level is set to the periphery of PTV. An intentionally heterogeneous dose distribution is created inside the PTV with beams smaller than the size of the PTV (Lax *et al*, 1994). Outside the target, the dose gradient falls steeply, so even if the dose to the target is very high the surrounding tissue receives much lower doses. In the central parts of the target the dose can be about 50 % higher than the prescribed dose to the periphery, as shown in an example in Figure 4.



**Figure 4:** A computer tomography image of a slice through the central part of a tumour in the lungs with the isodose curves, the dose distribution, around the target calculated by the 3D treatment planning system. The different isodose levels can be seen on the scale to the right.

With a heterogeneous dose in the target it is possible to increase the delivered dose in the central parts of the target with just a slight increase in dose to the surrounding tissue, in comparison with a homogeneous dose, for a given dose to the periphery of the target (Lax *et al*, 1998) as shown in Figure 5. Cells in the centre of a solid tumour often have lower radiosensitivity due to hypoxia than normally oxygenated cells. The advantage of this method is that the dose can be increased in the centre without increasing damage of surrounded normal tissue (Lax *et al*, 1998). It has to be pointed out that even though some tumours have necrotic volumes in the middle it is not true that tumours always contain less hypoxic cells at the periphery than in the central parts (Kavanagh and Cardinale, 2005). In general, to treat tissue containing radioresistant hypoxic cells or cells in a radioresistant phase in the cell cycle the required dose is 2.5 to 3 times the dose required if these cells were not present (Fowler *et al*, 2005).



**Figure 5:** Relative dose versus the distance from the isocenter. The dose distributions are weighted to give the same dose to the distance 1.0 from the isocenter. The figure is taken from Lax *et al* (1994).

## 2. MATERIALS AND METHODS

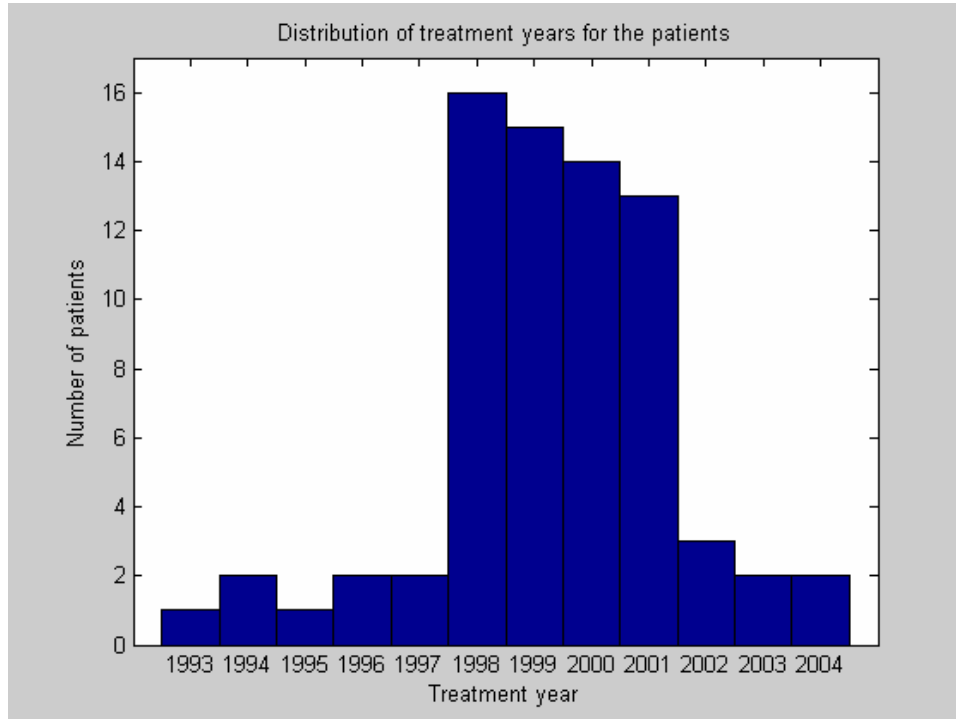
### 2.1. PATIENT MATERIAL

This study is based on data from 71 patients treated with SBRT for centrally located lung tumours for a total of 73 different treatments (two patients were treated twice for two different tumours) and 102 tumours. The patients were treated between November 1993 and March 2004, mainly during the years 1998 to 2001 as depicted in Figure 6. The patient group consisted of 36 men and 35 women with a mean age at treatment of 67 years (range 34-87). The patients were treated for primary lung tumours (45 patients with 56 tumours) or pulmonary metastases (23 patients with 40 tumours), for 5 patients with 6 tumours the diagnoses were not known. The metastases originated from several primary tumours: kidneys (11), testis (2), colon (1), ovaries (1), tonsils (1), cervix (1), esophagus (1), tubar (1), rectum (1), breast (1), liver (1) and malign melanoma (1). The patients were selected from schematic drawings in the medical records as being expected to have significant doses to the tracheobronchial tree.

The fractionation schedules varied as illustrated in Table 1, the corresponding biologically equivalent dose (BED) for each fractionation schedule calculated with  $\alpha/\beta=3$  Gy is also given.

**Table 1:** The different fractionation schedules and corresponding prescribed dose expressed in BED, with  $\alpha/\beta=3$  Gy, used for the patients in the study. The turquoise coloured rows are the most commonly used fractionations. \*Prescribed dose at the periphery of PTV.

<b>Fractionation*</b>	<b>Prescribed dose in BED (Gy<sub>3</sub>)</b>	<b>No. of patients</b>
20 Gy x 2	306.7	2
15 Gy x 3	270.0	16
15 Gy x 2	180.0	14
15 Gy x 1	90.0	1
12 Gy x 3	180.0	2
10 Gy x 5	216.7	2
10 Gy x 4	173.3	12
10 Gy x 3	130.0	9
10 Gy x 2	86.7	3
10 Gy x 1	43.3	1
8 Gy x 5	146.7	23
8 Gy x 4	117.3	3
8 Gy x 3	88.0	1
8 Gy x 2	58.7	1
7.5 Gy x 3	78.8	1
7 Gy x 5	116.7	1
7 Gy x 4	93.3	4
7 Gy x 3	70.0	2
6 Gy x 5	90.0	1
5 Gy x 5	66.7	2
4 Gy x 5	46.7	1
?		1



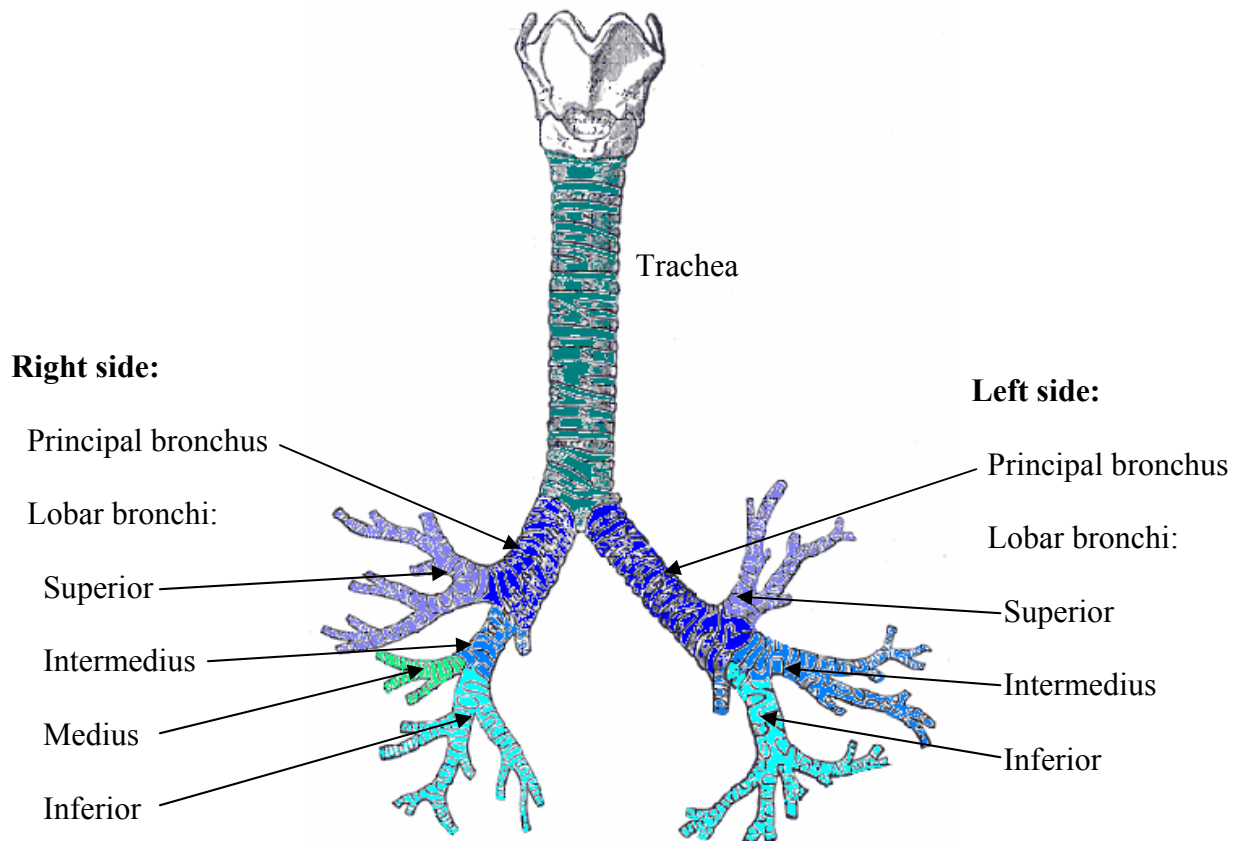
**Figure 6:** The distribution of number of patients with centrally located lung tumours treated during the years 1993 to 2004.

## 2.2. METHODS

The treatment plans for 3 of the 73 patient treatments in the study were not archived in a proper way, so for these three patients no dosimetric information were known and an analysis of the doses to the bronchi could not be done. Neither has the dosimetric analysis been done for one patient for whom information about the fractionation schedule is missing. Dosimetric analysis is done for 67 patients treated with SBRT at 69 different treatments. Patients with number 2 and 3 (see Results) is the same patient treated at two different occasions and so are also the patients with number 50 and 73.

The airways consist of the trachea and the different bronchi structures, or the tracheobronchial tree, and are structured like an ordinary tree with its branches and twigs (Figure 7). The tracheobronchial tree is probably a serially functioning tissue since the air follows a single path as a chain of function and since the clonogens (cells that have the capacity to proliferate several generations and give rise to colonies of cells (Steel, 1997)) in the airways are situated in the epithelium and can move in the bronchi without anatomic boundaries (Timmerman and Lohr, 2005).

The airways start with the trachea that divides into two parts, the right and left principal or mainstem bronchi, at the place of division called carina. The mainstem bronchi enter the lung tissue at the hilum of the lungs and divide into lobar bronchi. There are three lobar bronchi to three lobes and one intermedium bronchus in the right lung and two lobar bronchi to two lobes and one intermedium bronchus in the left lung, see Figure 7. After that the lobar bronchi divide into bronchioles that finally reach the alveoli-capillary complexes where the exchange of oxygen and carbon dioxide takes place (Timmerman and Lohr, 2005).



**Figure 7:** A schematic structure of the tracheobronchial tree and the definition of the different tracheobronchial structures in this study. The picture is taken from <http://en.wikipedia.org/wiki/Image:Gray961.png> and edited.

### 2.2.1. Outlining of the organs at risk: Trachea, bronchi and normal lung tissue

The dose plans for all the SBRT patients of the present study have been stored in the archive of the 3D treatment planning system (TPS) Helax-TMS by MDS Nordion used



at the Karolinska University Hospital. After rereading the plans and reactivating them in the TPS, the anatomical structures of interest, i.e. the trachea, the different bronchi structures and the lung tissue excluding the gross tumour volume (GTV), were outlined for each patient, all structures are listed in Table 2. A radiologist supervised this part of the work. The 3D dose distribution for each structure was then calculated. The outline of the different bronchi was the air plus the wall with a thickness of about 1-4 mm, with the thickest walls for the trachea, thinner walls for the mainstem bronchi and the thinnest walls for the lobar bronchi. The radiosensitive structure is of course the wall. It was however not considered to be practically possible to outline the walls excluding the air.

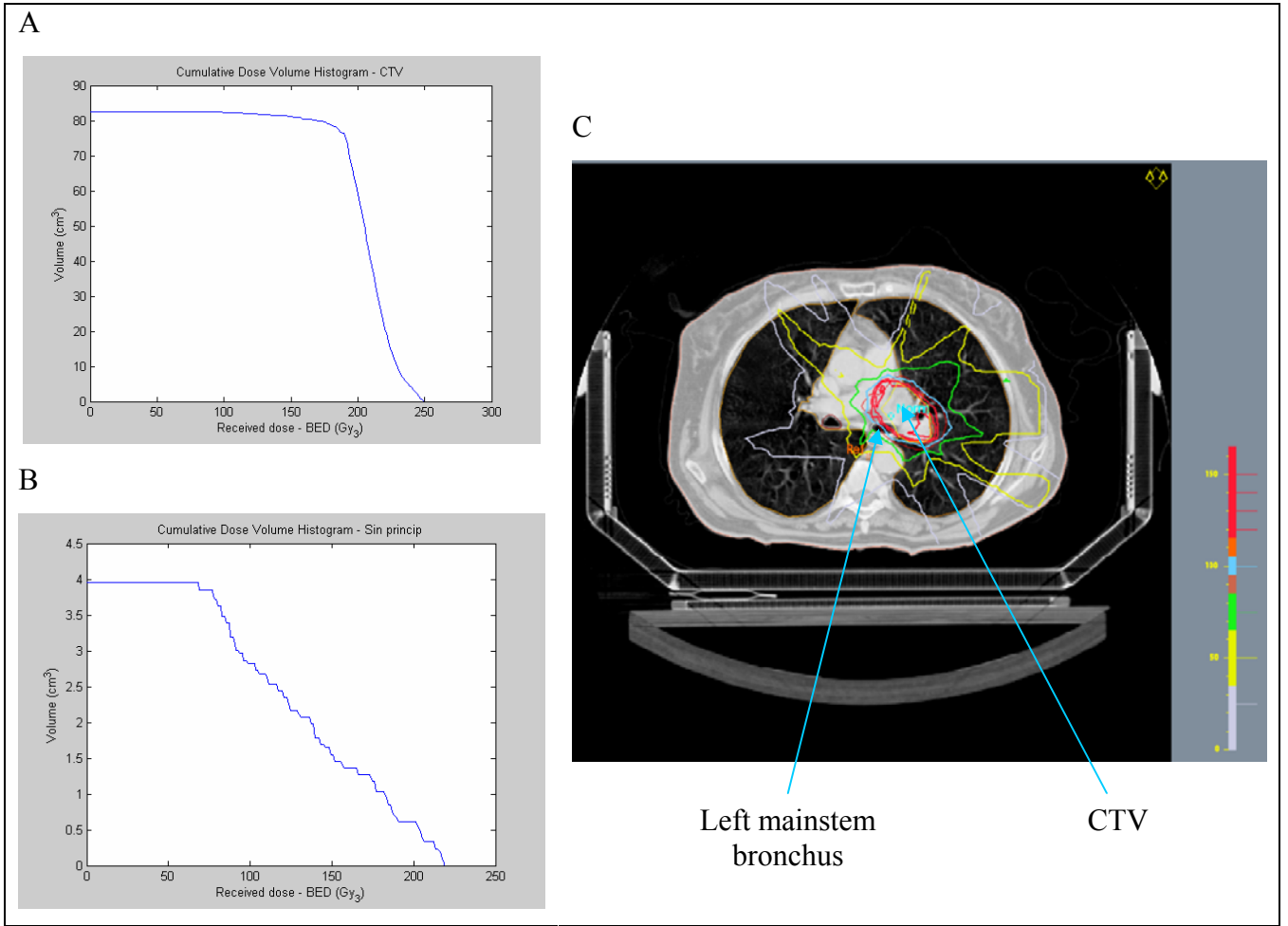
**Table 2:** The organs at risk of interest for the patients in this study.

<b>Right lung</b>	<b>Left lung</b>	
Mainstem bronchus	Mainstem bronchus	Trachea
Superior bronchus	Superior bronchus	Lung
Intermedius bronchus	Intermedius bronchus	Lung - GTV
Medius bronchus	Inferior bronchus	
Inferior bronchus		

### 2.2.2. Dose distribution in the organs at risk

For each patient, the differential DVHs of the visible structures (trachea, right mainstem, right superior, right intermedius, right medius, right inferior, left mainstem, left superior, left intermedius and left inferior) were calculated. Some patients (9) had several targets which were treated separately but with the same fractionation schedule. These plans were weighted equally and the values of the doses were given in percent of the prescribed dose. For each patient, each DVH was later converted with the value of the biologically effective dose (BED). For the patients (11) who had several targets treated with different fractionation schedules the dose plans were instead weighted by using the BED value for the fractionation schedule, at the calculation of the DVH.

From the differential DVHs the cumulative DVHs could be calculated and an example of the cumulative DVHs for a CTV and a left mainstem bronchus are shown in Figure 8.



**Figure 8:** An example of a cumulative dose volume histogram for a CTV (A) and for a left mainstem bronchus (B) and the corresponding dose distribution in one cross section in the body (C).

### 2.2.3. BED conversion

Studies of mammalian cells implies that the frequency  $f$  of the radiation effect of cells can not be described as a linear function of the dose  $d$ , at least the frequency must be described with a linear and a quadratic term (Barendsen, 1982):

$$f = \alpha d + \beta d^2 \quad (1)$$

$\alpha$  and  $\beta$  are constants decided by the cell survival curve. From this linear quadratic (LQ) model the surviving fraction (SF) of cells in a target after irradiation of the dose  $d$  are derived to be (Joiner and van der Kogel, 1997):

$$SF = \exp(-\alpha d - \beta d^2) \quad (2)$$

The linear component  $e^{-\alpha d}$  of the SF originates from a single-track event of the radiation while the quadratic component  $e^{-\beta d^2}$  comes from two-track events (Joiner, 1997). The radiation effect  $E$  after  $n$  fractions is expressed as (Joiner and van der Kogel, 1997):

$$E = -\log_e (SF)^n = n(\alpha \cdot d + \beta \cdot d^2) \quad (3)$$

After dividing this equation of the radiation effect with the linear coefficient  $\alpha$  (Barendsen, 1982) the formula of BED is received:

$$BED = \frac{E}{\alpha} = nd \left( 1 + \frac{d}{\alpha / \beta} \right) \quad (4)$$

The value of BED is the theoretical total dose required to produce the radiation effect  $E$  when using an infinitely large number of infinitesimally small dose fractions (Joiner and van der Kogel, 1997). This value is very important when analysing tissue tolerance (Barendsen, 1982).

The LQ formulation is a generally accepted model for calculating the BED to be able to compare different fractionation schedules (Song and Blomgren, 2005). The LQ formula is a description of the response to radiation (Joiner, 1997) and is intended for fractionation doses up to 8-10 Gy (Fowler, 1989), but the formula is assumed to be valid up to doses of 23 Gy per fraction (Douglas and Fowler, 1976), this is however not shown for clinical data.

BED takes the biological effect of cells after irradiation into account. Different factors affect the biological response; the overall treatment time, the dose per fraction and the proliferation of the cells after irradiation (Fowler, 1989). These factors affect late responding tissue, which have cells with slow or no proliferation, and early responding tissue and tumours, in which cells proliferate rapidly, in different ways (Fowler, 1989). The difference in proliferation time of the cells is the reason why different tissues respond at different times after irradiation. Late responding tissues react several months

or years after irradiation while early responding tissue or tumours react within a few days or weeks after irradiation (Fowler, 1989).

Since the endpoint in this study is atelectasis which is a late complication, the calculations of BED have been done for late responding tissue. Late complications are not, or very little, affected by the overall treatment time since cells in this kind of tissue do not repopulate during the treatment (Fowler, 1992). Though, late complications depend a lot of the size of the dose per fraction since larger doses per fraction make the late complications worse (Fowler, 1992). As a consequence the LQ model without time dependence can be used for BED calculations for complications in late responding tissues.

The ratio of  $\alpha/\beta$  is a tissue specific constant with the value 10 Gy or higher for early responding tissue and tumours and between 1.5 to 5 Gy for late responding tissue (Fowler, 1992). Generally the value of  $\alpha/\beta$  for late reactions is about 3 Gy (Fowler, 1989). For late complication in normal lung tissue the  $\alpha/\beta$  ratio is intended to vary between 2 and 6.9 Gy as shown in Table 3, but there is no specific data for the bronchi available. Because of that  $\alpha/\beta = 3$  Gy has been used in all calculations of BED in this report, both for normal lung tissue, the trachea and the bronchi.

**Table 3:** Published values of the  $\alpha/\beta$  ratio for late complications in lung tissue.

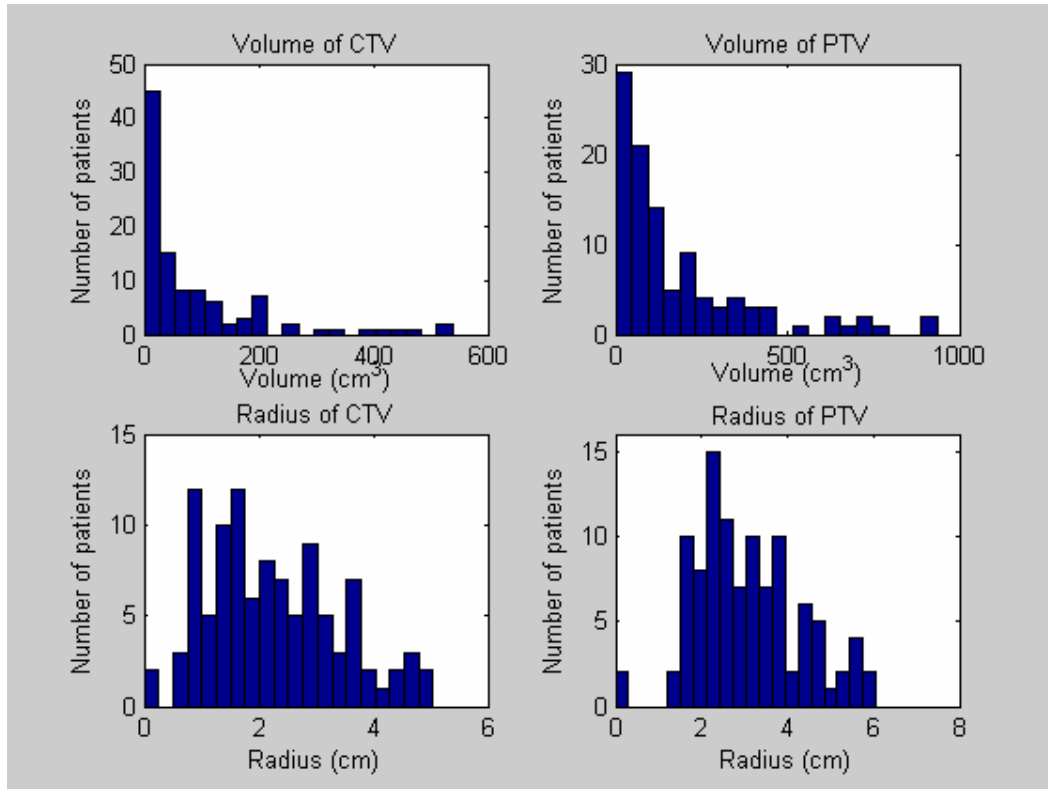
Author	End-point	$\alpha/\beta$ (Gy)
Thames and Hendry, 1987	Late effects	2.1-4.3
Bentzen <i>et al</i> , 2000	Late effects	2-3
Fowler, 1989	Late effects	3-5
Fowler, 1989	Pneumonitis	4.4-6.9
Fowler, 1989	Fibrosis (later)	3.0-3.6

### 3. RESULTS

#### 3.1. TUMOUR VOLUMES

For all patients in the present study the volumes of the clinical target volume (CTV) and the planning target volume (PTV) varied as shown in Figure 9. The radii of the CTV and the PTV volumes were also calculated assuming that each tumour had the shape of

a sphere (Figure 9). The mean volumes and the mean radii, as well as the minimum and maximum, of CTV and PTV for the patients in the study can be seen in Table 4. Information about the PTV was missing for one tumour each in two patients (patient 4 and 8).



**Figure 9:** The distribution of the volumes for CTV and PTV for the tumours included in the study, and the distribution of the radius (assuming a sphere) of these.

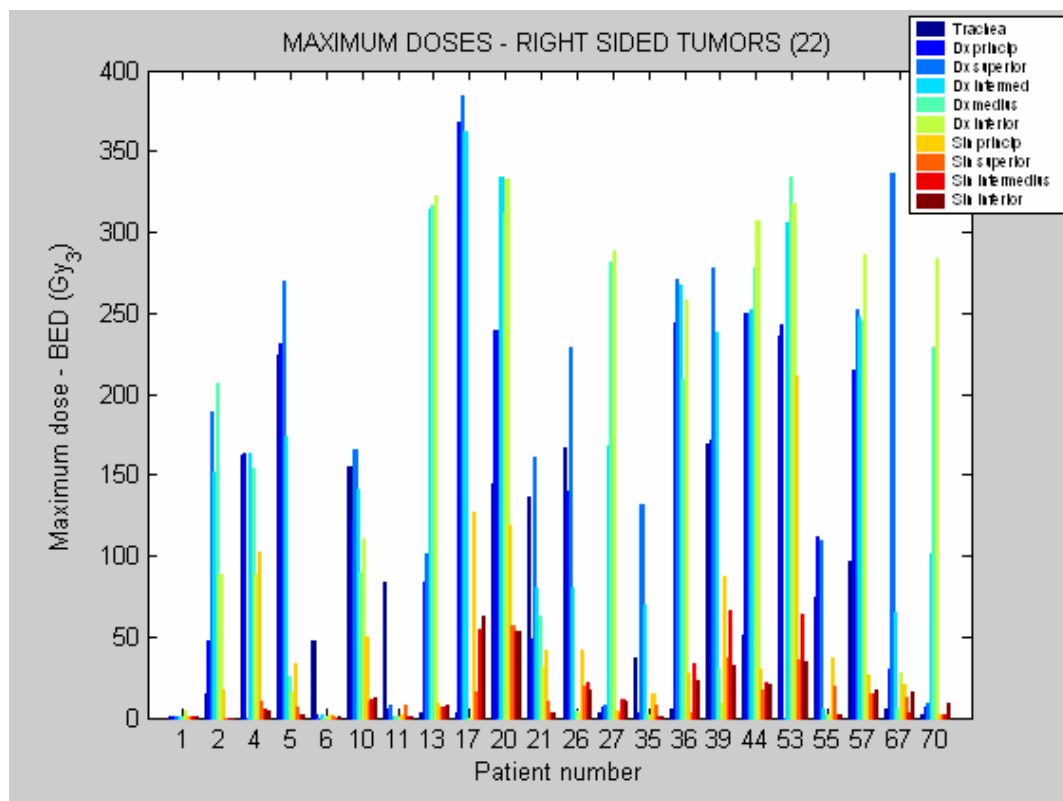
**Table 4:** The mean, minimum and maximum values of the volumes and radii of CTV and PTV for the patients in the study. \*The resolution in the dose calculation is limited for very small structures.

	Mean	Minimum	Maximum
<b>Volume of CTV (cm<sup>3</sup>)</b>	87.8	0.0*	538.0
<b>Radius of CTV (cm)</b>	2.2	0.0*	5.0
<b>Volume of PTV (cm<sup>3</sup>)</b>	185.7	11.0	935.0
<b>Radius of PTV (cm)</b>	3.1	1.4	6.1

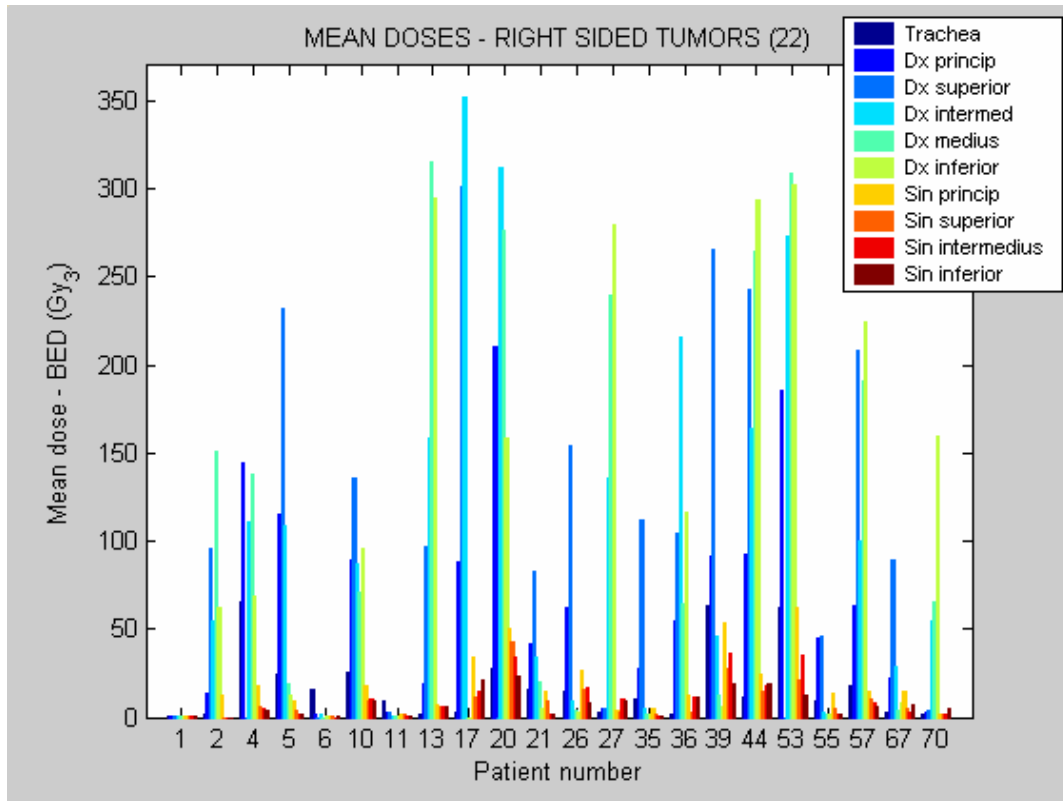
### 3.2. DOSES TO THE BRONCHI

To get an easier overview of the dosimetric data the patients were allocated to four groups: patients with right sided tumours (22), left sided tumours (14), mediastinal tumours (23) and bilateral tumours (10).

There is very little data available in the literature about the radiosensitivity of the bronchi and because of that we do not know if the maximum or the mean doses are significant to study. The maximum and mean doses to the different tracheobronchial structures for the patients with right sided tumours can be seen in Figure 10 and Figure 11 respectively. For each patient ten bars are plotted, one bar for each structure in the tracheobronchial tree. In some cases a bronchus was not visible in the CT images, and no dose could be calculated for the structure.



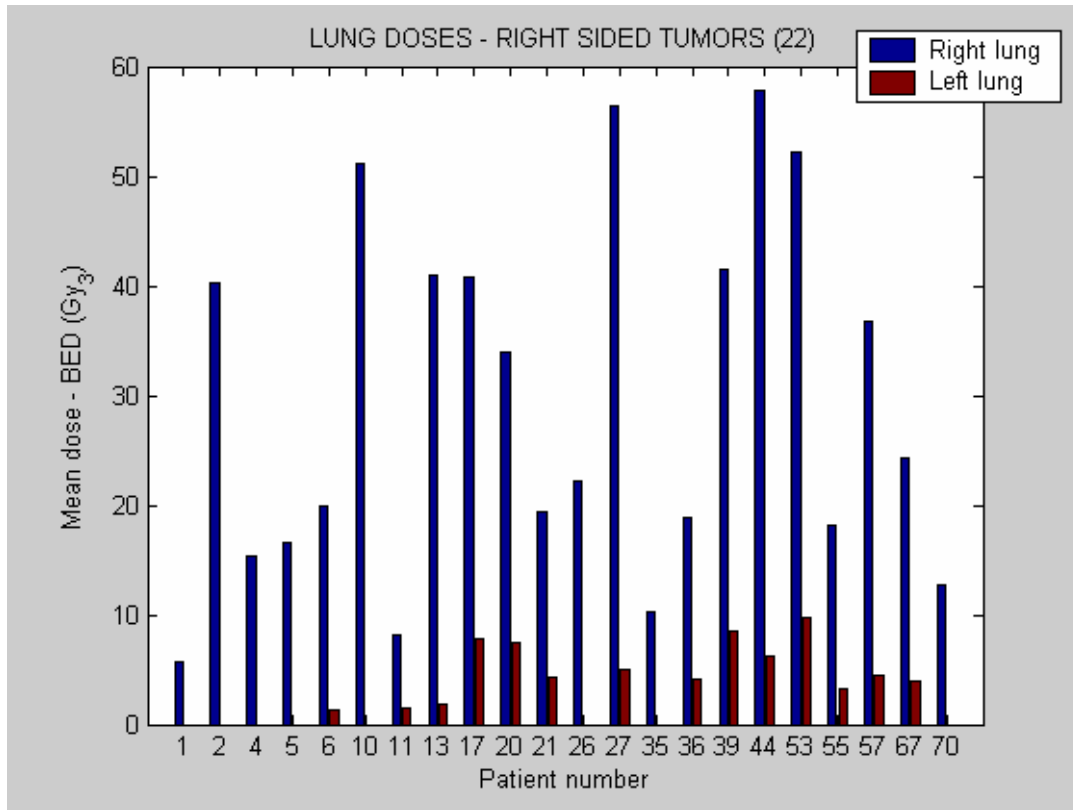
**Figure 10:** Maximum doses to the trachea and the bronchi for the patients with right sided tumours.



**Figure 11:** Mean doses to the trachea and the bronchi for the patients with right sided tumours.

### 3.3. MEAN LUNG DOSES

For parallel functioning organs, like lung tissue, clinical investigations have shown a good prediction for complications from the mean lung dose (MLD) (Kavanagh and Cardinale, 2005). Although, MLD and  $V_{20}$  (percentage of the lung volume that has received more than 20 Gy (Seppenwoolde and Lebesque, 2001)) are generally considered to be good predictors of lung complications in conventional radiation therapy, we still do not know if this is the case also in hypofractionated treatments. Lung fibrosis has been discussed as one of the causes of atelectasis. Because of that it might be interesting to study the MLD to see if it is related to atelectasis after SBRT of the lung tissue. The mean lung doses for the normal lung tissue (the lung minus GTV) for the patients with right sided tumours in this study can be seen in Figure 12.

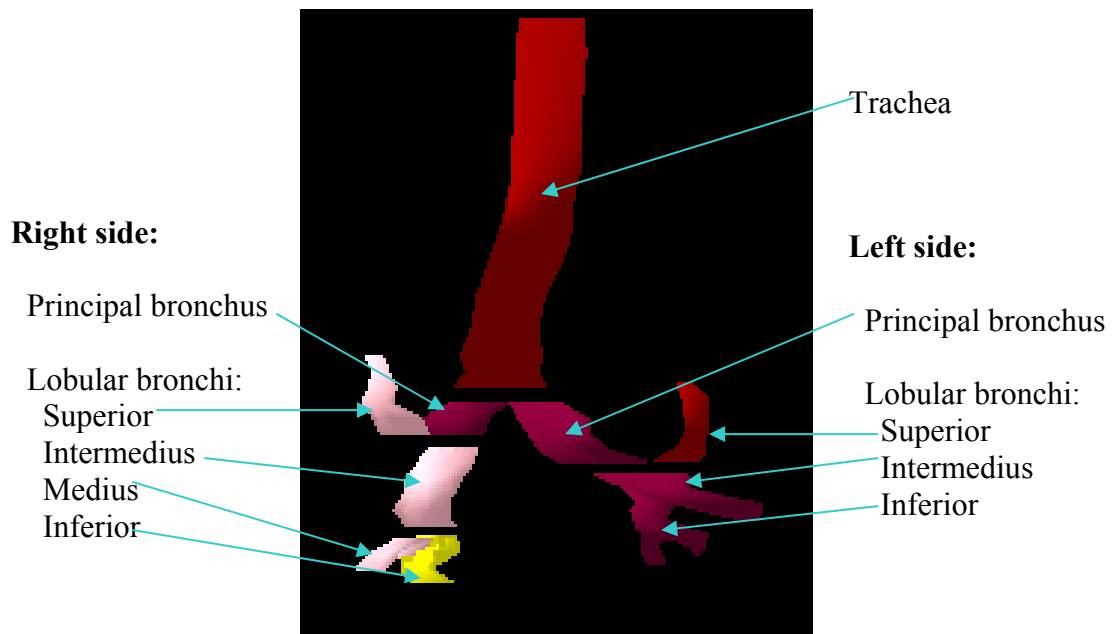


**Figure 12:** Mean doses to the lungs for the patients with right sided tumours.

### 3.4. VOLUMES OF THE BRONCHI

The figure of the tracheobronchial tree, shown in Figure 7, is a sketch of the whole tracheobronchial tree. When outlining the trachea and the bronchi on the CT images for the patients in this study it was not possible to see as much as shown on the figure. An example of what could be seen in the treatment planning system is shown in Figure 13.

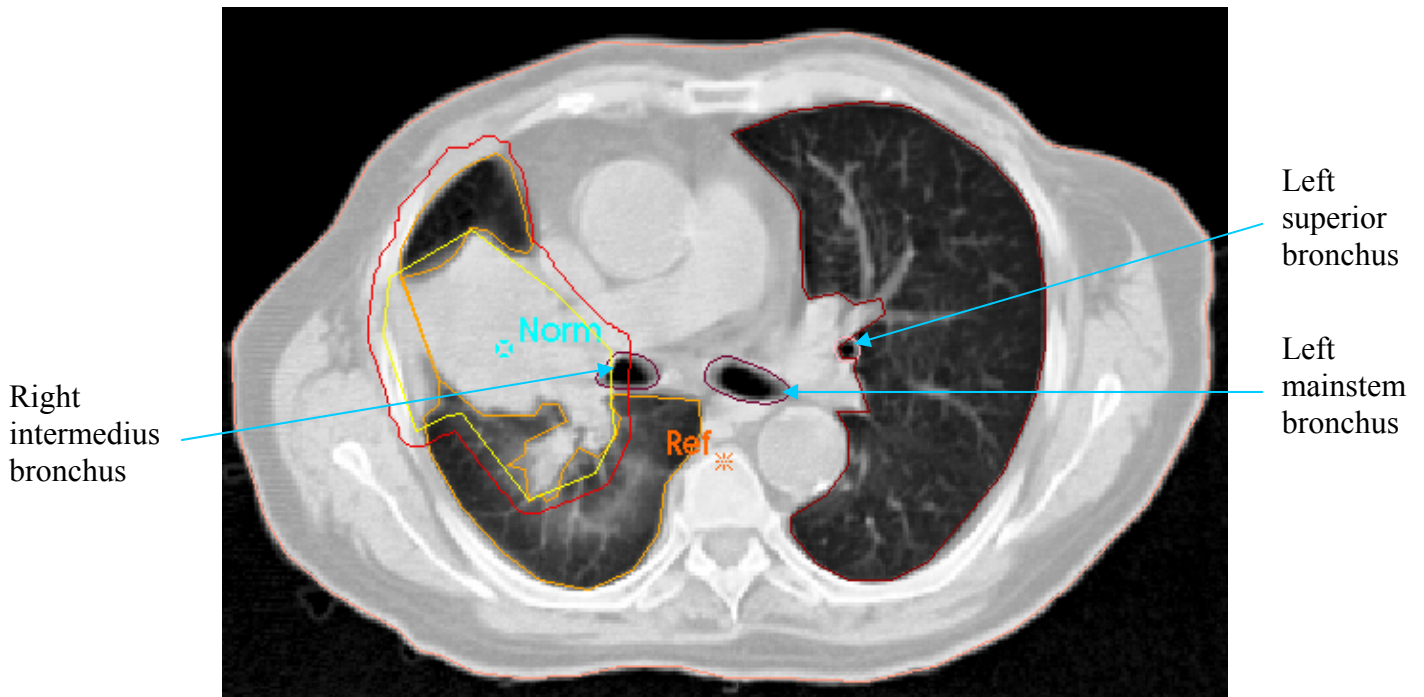




**Figure 13:** An example of what the tracheobronchial tree can look like after outlining in the treatment planning system Helax-TMS.

The outlining of the tracheobronchial tree on CT images taken in SBRT treatment position, i.e. during breathing, is very hard since all the anatomical structures is blurred due to breathing motions. Also the resolution (including the slice thickness and the size of the image matrix) of the images has an impact on the ability to outline the structures.

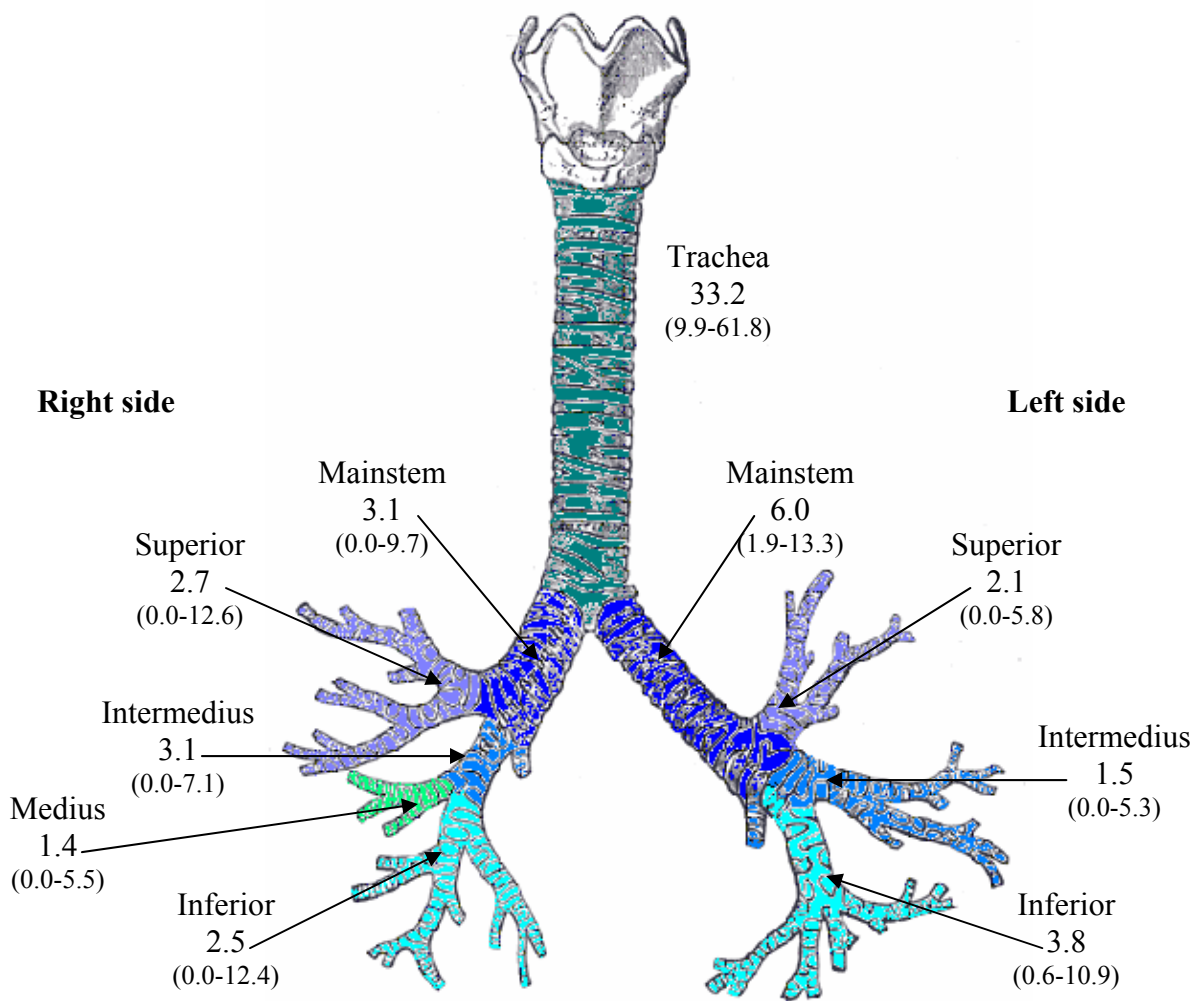
In this study the interest was to quantify the doses to the bronchi and to do that in a quite simple and time effective way the definition of the bronchi was the air filled cavity and the bronchus wall around it, as mentioned earlier. Figure 14 gives an example of the definition of the wall. For the trachea the walls were about 4 mm, the mainstem bronchi had walls about 2-3 mm and the lobar bronchi had walls about 1-2 mm.



**Figure 14:** The outlining of the bronchi is the air filled cavity with margin for the wall. Here an example in one slice of the right intermedius bronchus and the left mainstem and superior bronchus is seen.

The volumes of the trachea and the different bronchi structures varied a lot as shown in Figure 15. It has to be pointed out that in some cases the bronchus was only seen in a few slices or even in a single slice, due to the thickness of the CT slices.

For the reasons given above, quantitative volume data is not presented in this report, but will be further analysed.

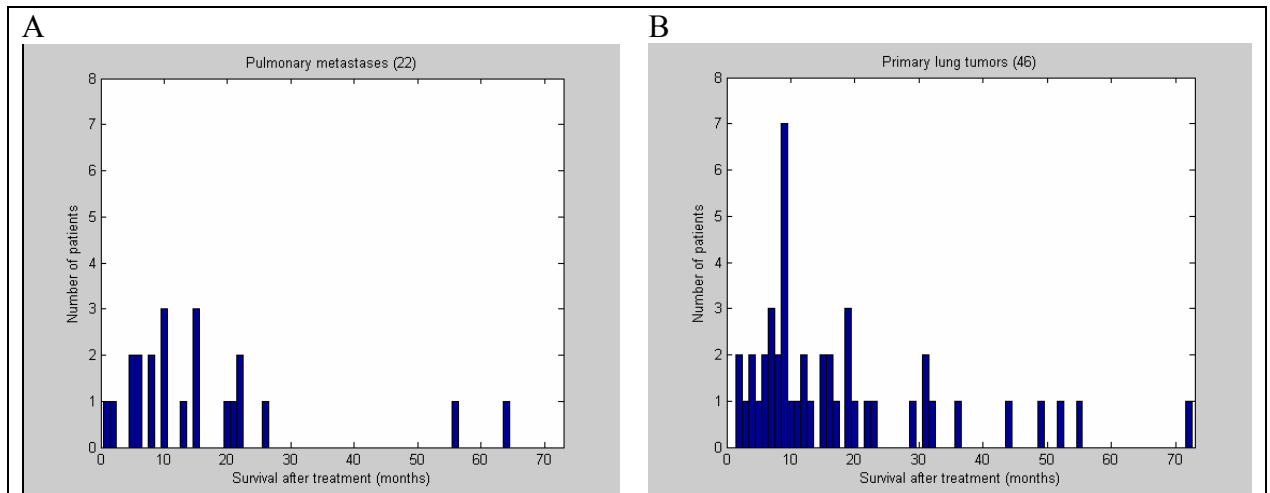


**Figure 15:** The mean volumes, in  $\text{cm}^3$ , of the different structures of the tracheobronchial tree for the patient in the present study. The picture is taken from <http://en.wikipedia.org/wiki/Image:Gray961.png>.

### 3.5. CLINICAL DATA

#### 3.5.1. Survival after treatment

For the patient group in this study the mean survival after treatment was 18 months (range 1-72), while the median survival was 13 months. The mean survival for patients with pulmonary metastases was 16 months (range 1-64), and for patients with primary lung tumors the mean survival was 18 months (range 2-72), the distribution is shown in Figure 16. At this moment (October 2006) 4 patients are still alive and information is missing about one patient. The survival data for these are not included in the calculation of the mean survival.



**Figure 16:** The distribution of survival after SBRT of pulmonary metastases (A) and primary lung tumors (B) for the patients in this study.

### 3.5.2. Atelectasis: Preliminary results

48 patients of the 69 patients treated with SBRT for centrally located lung tumours that have been dosimetrically evaluated in this study have also been clinically evaluated. The medical records were reviewed by an oncologist. The investigated endpoints were: cough, respiration complications, stenosis (narrowing) of the bronchi, fibrosis of the lung tissue, atelectasis (collapse of a part of the lung) and also tumour progression, recurrence and time of death (if dead). In this study the focus was on atelectasis.

10 of the 48 clinically evaluated patients in this study developed atelectasis after SBRT. The mean time between the treatment and the atelectasis diagnosis was 13 months (range 1-84). Since the range of survival time after treatment was between 1 and 72 months there might be that a few of the patients in the group died before developing or discovering atelectasis.

For the clinically evaluated patients the dosimetric data of the maximum doses can be seen in Appendix A. The bronchi on the contralateral side did not get significant doses for patients with right sided respectively left sided tumours, see Figure 13, for this reason they were not presented here. For the same reason the data for the trachea was not presented either.

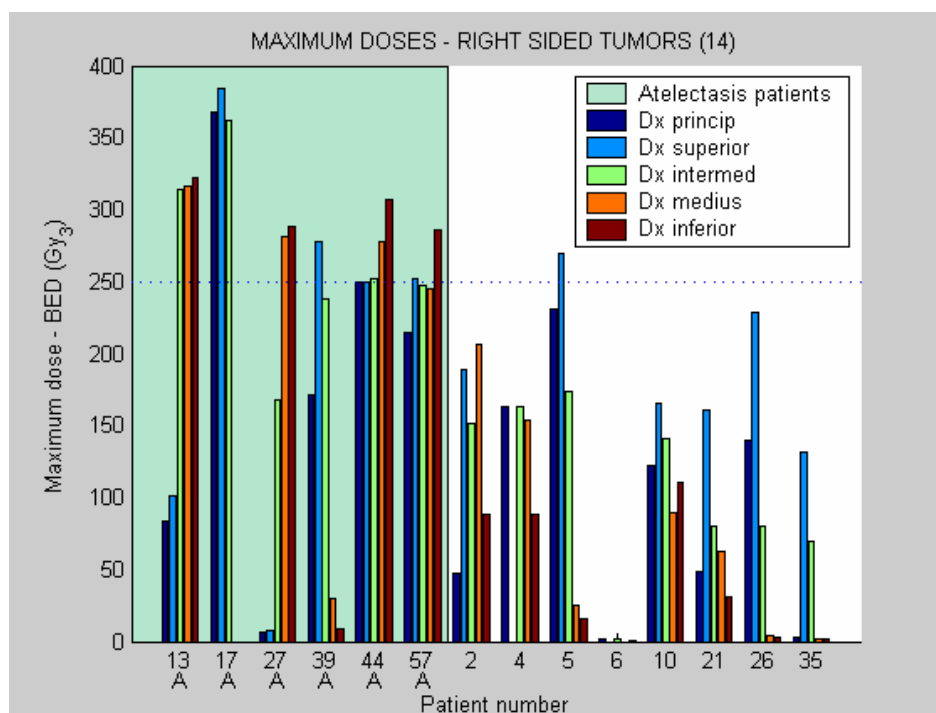
In the analysis of the maximum doses to the right sided bronchi for clinically evaluated patients with right sided tumours patient 20 and 36 were excluded since they had atelectasis before radiation therapy. Patient 53 who died 3 months after treatment (might be too short time to develop/discover atelectasis) was also excluded. That was also the case for patient 1 since the tumour was located in the base of the lung rather than centrally located, this patient should not be included in this study.

Further, for the analysis of the maximum doses in the patients with right sided tumours the patients were divided into two groups, i.e. patients with and without atelectasis, while excluding the four patients who had atelectasis before treatment, who died shortly after the treatment or who should not be included in this study. For this patient group the mean values of the maximum dose to the tracheobronchial structures were calculated, the results are reported in Table 5. However, it has to be pointed out that for 3 patients (1 with atelectasis and 2 without) some of the bronchial structures were not visible on the CT images. As a consequence of that the doses to these structures were not calculated and not included in the calculations of the mean values in Table 5.

In general it seems that for patients with atelectasis the maximum doses to the bronchi are higher in comparison with patients without atelectasis. The maximum doses to the right sided bronchi for the patients with right sided tumours are shown in Figure 17.

**Table 5:** Mean values of the maximum doses, and range of the maximum doses, expressed in BED to the trachea and the bronchi for clinically evaluated patients with right sided tumours (four patients excluded).

	<b>Mean values of maximum dose (Gy<sub>3</sub>)</b>	
	<b>Atelectasis (6 patients)</b>	<b>Non atelectasis (8 patients)</b>
<b>Trachea</b>	54.4 (2.5-168.7)	117.6 (14.2-223.42)
<b>Right mainstem</b>	182.5 (7.0-368.4)	94.5 (1.9-231.5)
<b>Right superior</b>	212.3 (7.6-384.54)	190.7 (131.0-268.1) not visible in 2 patients
<b>Right intermedius</b>	263.6 (167.5-362.0)	107.6 (1.5-173.4)
<b>Right medius</b>	230.3 (30.2-316.9) not visible in 1 patients	77.7 (1.5-206.9) not visible in 1 patients
<b>Right inferior</b>	242.2 (8.7-321.8) not visible in 1 patients	42.4 (1.1-110.6)
<b>Left mainstem</b>	47.3 (4.2-126.4)	37.7 (1.2-102.7)
<b>Left superior</b>	15.6 (2.9-36.6)	8.1 (0.0-19.8)
<b>Left intermedius</b>	29.2 (6.7-66.4)	6.4 (0.0-21.5) not visible in 1 patients
<b>Left inferior</b>	25.0 (7.7-62.7)	5.0 (0.0-16.5)



**Figure 17:** Maximum doses to the right sided bronchi for clinically evaluated patients with right sided tumours (four patients excluded).

Looking at the patients with atelectasis in Figure 17 it can be seen that the maximum dose to at least one bronchial structure each is above a BED value of 250 Gy<sub>3</sub> (that corresponds to a fractionation schedule of 14.4 Gy x 3). For the patients without atelectasis the maximum doses to the bronchial structures (except for the right superior bronchus in patient 5) are below the BED value of 250 Gy<sub>3</sub>. A visual view of the maximum doses, divided in BED above and below 250 Gy<sub>3</sub>, for all the tracheobronchial structures in each analysed patient with right sided tumours can be seen in Appendix B. The data is still too preliminary in order to suggest a tolerance dose to the bronchial structure.

## 4. DISCUSSION

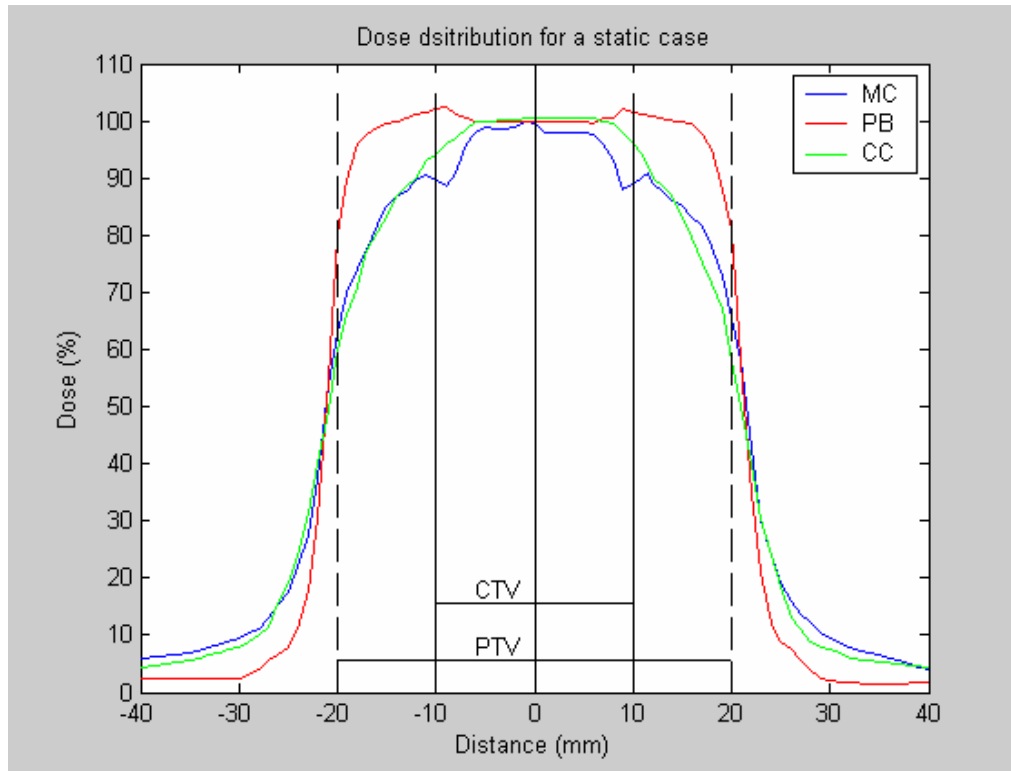
### 4.1. DOSE CALCULATIONS IN THE LUNGS

The TPS used in this study was the Helax-TMS using the pencil-beam algorithm. There are some problems with this calculation algorithm. Further more, respiration motions of the tumour make the dose estimation for the bronchi difficult (Lax *et al*, 2006).

The pencil-beam algorithm underestimates the lateral range of the Compton electrons in lung tissue, especially in the area close to the interface between the tumour and the lung tissue (Lax *et al*, 2006). The most accurate method for calculating in radiation treatment planning today is Monte-Carlo simulations. The Monte-Carlo simulations and also the collapsed-cone algorithm consider the lateral scattering of electrons in a more correct way.

A study at the Karolinska University Hospital about the differences in the longitudinal dose distribution through the centre of a target located in the lung tissue calculated with Monte-Carlo (MC) simulations in comparison with the pencil-beam (PB) algorithm and the collapsed-cone (CC) algorithm has been done, the results from these calculations in a static situation can be seen in Figure 18 (Lax *et al*, 2006). In the static situation, when respiratory movements are not taken into account (in the way the clinical dose planning is done) the dose in the CTV was overestimated with up to 10 % by the pencil-beam

algorithm. In the region between the CTV and the PTV the pencil-beam method overestimated the dose up to 30 % and outside the PTV the situation was the opposite, i.e. the dose was underestimated.



**Figure 18:** The dose distribution through the centre of a lung target calculated with Monte-Carlo (MC) simulations, the pencil-beam (PB) algorithm and the collapsed-cone (CC) algorithm. Reproduced from Lax *et al* (2006).

According to these results it may be expected that doses calculated for the bronchi located within PTV are overestimated and for bronchi located just outside PTV the doses are underestimated (cf Figure 18). For bronchi located further away from the target the doses seem to be calculated in a way more according to the Monte-Carlo simulations. A quantitative estimate of the error in dose calculation is the present study is however difficult to give.

When considering breathing movements the dose in the lung tissue between CTV and PTV was overestimated by the pencil-beam technique, the differences were about 30 % and sometimes more (Lax *et al*, 2006). Most affected by the respiration movements are tumours placed in the basal and dorsal parts of the lungs (Lax *et al*, 2006). In the present



study the uncertainties for the trachea and the mainstem bronchi probably are less since these are more centrally located in the lungs, closer to the mediastinum, where the respiratory motions are minor. But when looking at the uncertainties in the dose calculations of the lobar bronchi one has to consider that these are located more in the middle of the lung structure and the uncertainties for these should correspond to the uncertainties in the work by Lax *et al* (2006).

Independent of the uncertainty of the pencil-beam algorithm, it may be possible to get a better knowledge of the “pencil-beam dose”-response curve. This is a relevant clinical question, though not scientific.

#### **4.2. OUTLINING OF THE TRACHEOBRONCHIAL STRUCTURES**

When treating patients with SBRT the patients breathe normally during the irradiation, apart from the abdominal pressure device. As a consequence of that the CT images also include these movements when the anatomical structures move between the different slices during the scan, which adds an extra inaccuracy when outlining structures on the images.

Another uncertainty when outlining the bronchi is the resolution. Since the volumes of the different bronchi structures are very small the resolution has quite a big impact on the accuracy of outlining them. For patients treated up to the end of 1996 the sizes of the CT images were 256 pixels x 256 pixels, after 1996 the sizes were 512 pixels x 512 pixels. Also the slice thickness of the CT images has an impact on the resolution. For the earliest patients the slice thickness was 10 mm and after 1996 the slice thickness was reduced to 5 mm. The poorer resolution of the images for the earliest patients made it even harder to outline the small bronchi structures.

#### **4.3. CLINICAL DOCUMENTATION**

Since this is a retrospective study there are uncertainties in follow-up and documentation of the patients. The main question is: If there is no documented atelectasis in the medical record does this mean that the patient for sure has not had an

atelectasis or is it possible that there is undocumented atelectasis? It is likely (according to the oncologist that did the review of the medical records) that there are patients with atelectasis that is not documented in the medical records. As mentioned before the patients can be asymptomatic if the lung function of the atelectatic volume is less than the reserve function (Timmerman and Lohr, 2005). Song *et al* (2005) has reported a case where the patient had an atelectasis but was asymptomatic. Also in the present study the number of patients with atelectasis might be underreported due to lack of symptoms.

#### 4.4. DOSE TOLERANCE FOR THE BRONCHI

In the present study a level of the maximum dose at 250 Gy<sub>3</sub> (BED) was observed for patients with right sided tumours to distinguish between atelectasis and non atelectasis patients, as shown in Figure 17. This dose can be compared with doses from other studies.

The Radiation Therapy Oncology Group in the United States has proposed radiation tolerances for any point in the trachea and the ipsilateral bronchi of 30 Gy (10 Gy x 3), this value is not validated with long-term follow-up (Timmerman and Lohr, 2005). A total dose of 30 Gy given in 3 fractions corresponds to 130 Gy<sub>3</sub> in BED with  $\alpha/\beta = 3$  Gy.

Hayakawa *et al* (1996) have reported about pulmonary insufficiency, after treatment of patients with centrally located NSCLC, in 4 of 5 patients who received higher doses than 80 Gy to the hilum and developed severe stenosis of the proximal bronchi. The doses were given in 2 Gy fractionations which means that the doses to the proximal bronchi corresponded to 133 Gy<sub>3</sub> in BED with  $\alpha/\beta = 3$  Gy.

Blomgren *et al* (1995) have reported about a patient with atelectasis in a segment of the lung lobe developed 4-5 months after radiation treatment of a large lung tumour. The maximum dose delivered to the PTV was 42 Gy in 3 fractions, corresponding to 238 Gy<sub>3</sub> in BED with  $\alpha/\beta = 3$  Gy. The location of the tumour was not told, but if a bronchus was not passing through the PTV the bronchi can maximally have received 238 Gy<sub>3</sub>.

At this moment the patient material in this study has been divided according to the tumour location in the lungs. However, Schefter *et al* (2006) have indicated a possibility of lower risk of large bronchi stenosis after SBRT of pulmonary metastases than after SBRT of primary lung tumours. This indicates another interesting classification of the patient material in this study.

## 5. CONCLUSIONS

- In a first analysis the results show a correlation between atelectasis and maximum doses to the bronchi for the patients with right sided tumours
- The correlation between the maximum dose and atelectasis has not been shown for patients with non right sided tumours
- A trend in the correlation between atelectasis and mean dose has been observed

## 6. FUTURE EVALUATION

Evaluation of clinical data will continue by trying to find all the CT images taken after radiation therapy of all the patients to look for atelectasis. The aim is to try to reveal any uncertainties in the documentation of atelectasis in the patients' medical records.

What also will be done in the prolonged evaluation is:

- Correlation of DVH data of the bronchial tree to clinical data will be extended
- Correlation of DVH data of the bronchial tree with the adjacent lung tissue on one hand to the clinical data on the other hand will be performed
- Classification of the patient material between pulmonary metastases and primary lung tumours will be done

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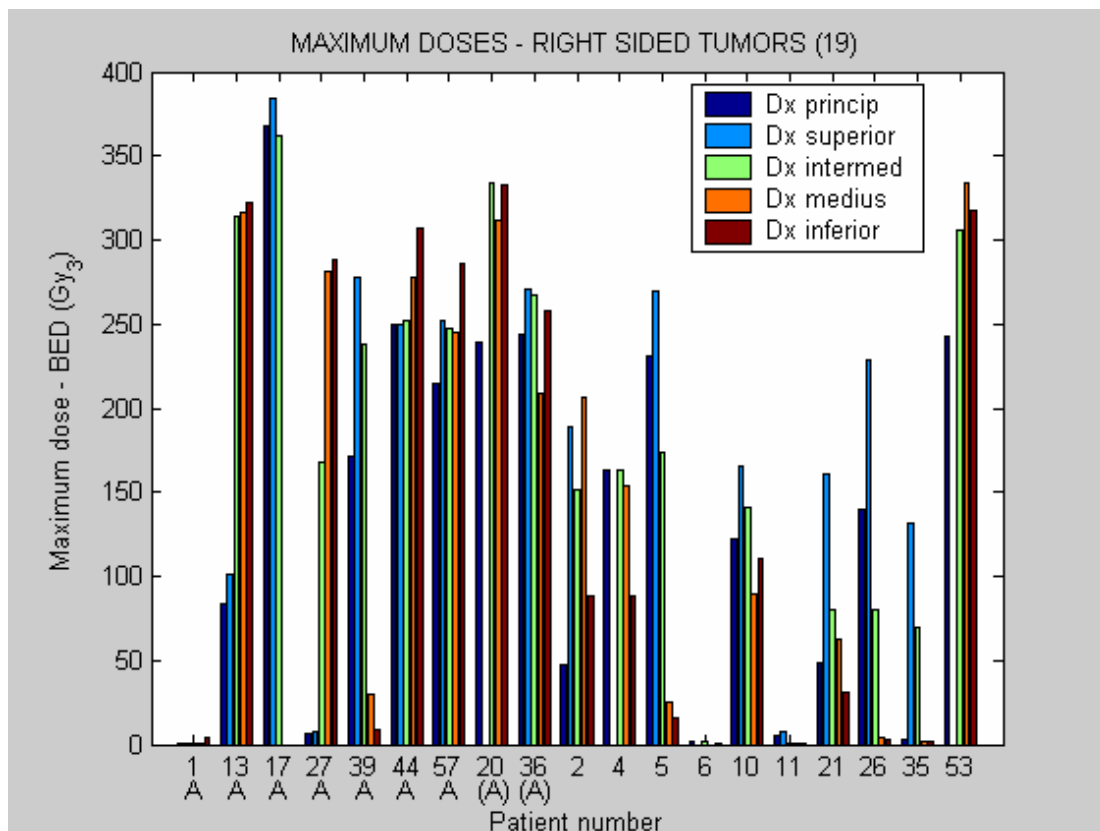
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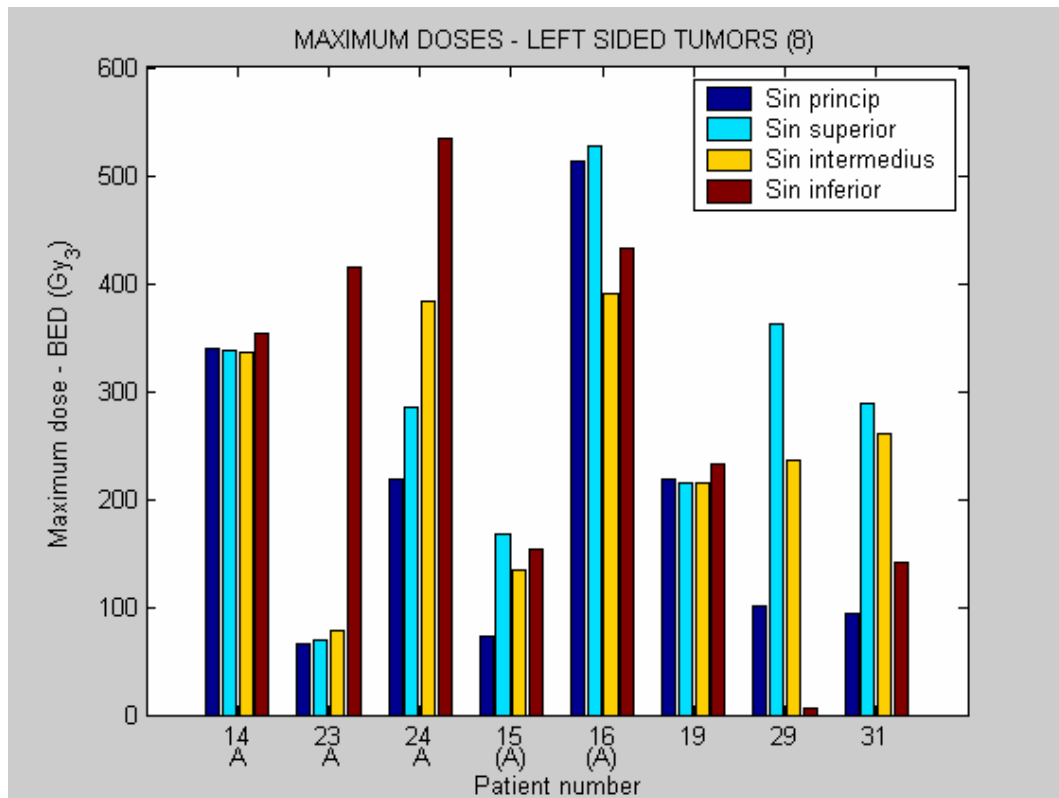
## APPENDIX A

Maximum doses to the bronchi for the clinically evaluated patients in the four different groups, right sided tumours (A), left sided tumours (B), mediastinal tumours (C) and bilateral tumours (D). The label A below the patient number denotes patients with atelectasis after the RT treatment, while the label (A) denotes patients with atelectasis even before the treatment.

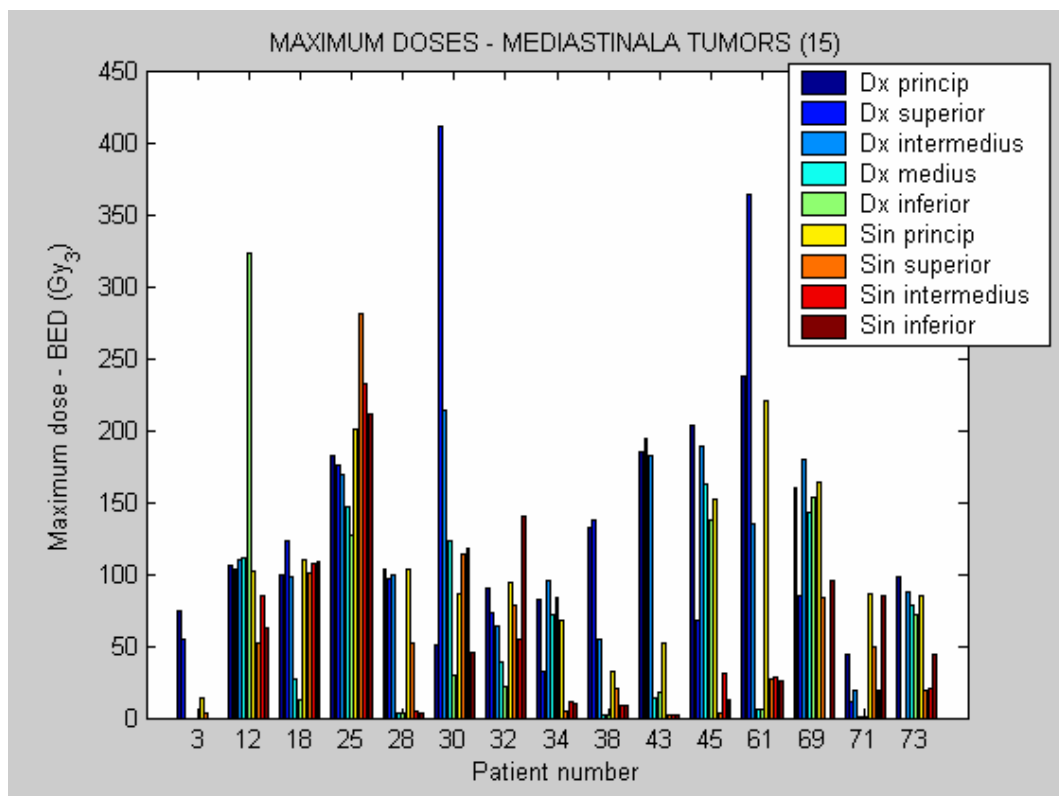
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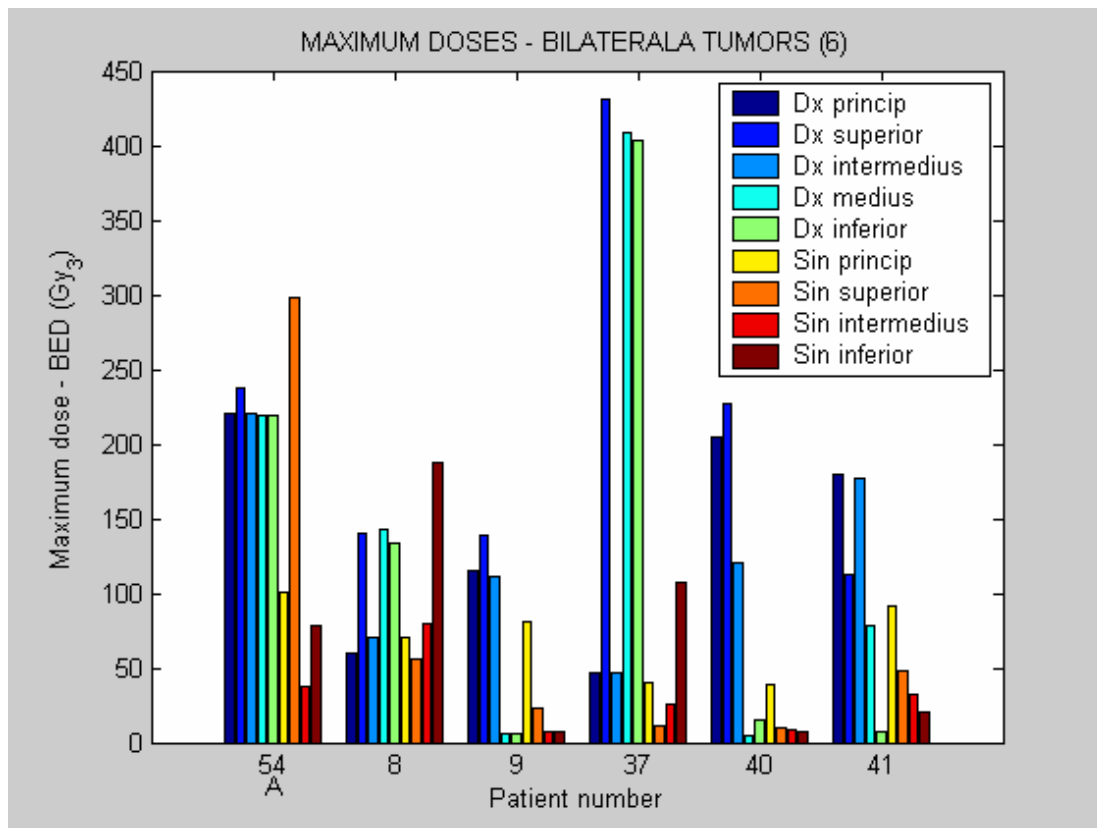
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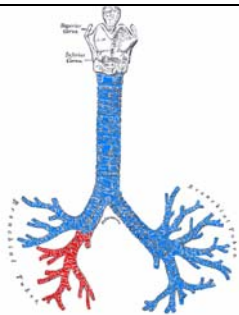
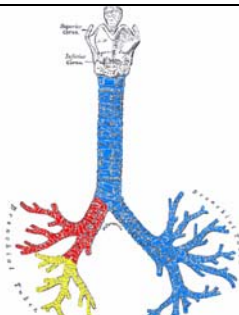
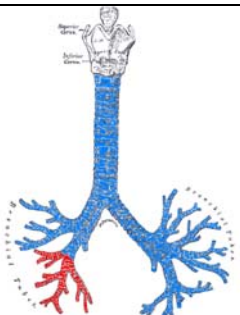
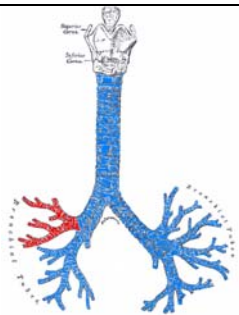
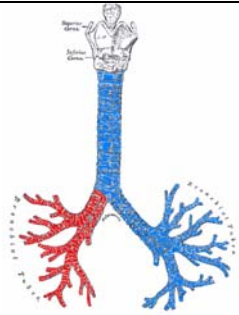
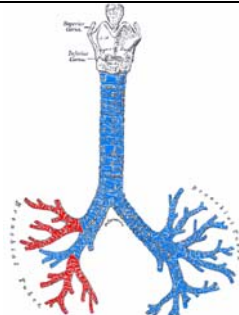
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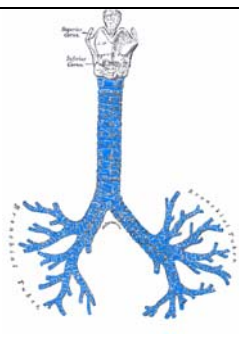
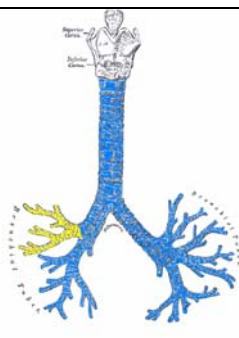
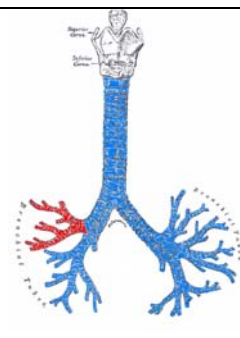
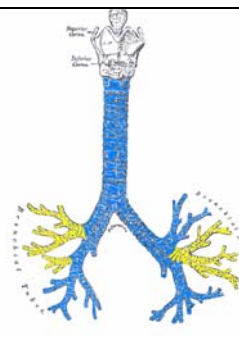
## APPENDIX B

A visual view of the doses to the different bronchi structures for all the analysed patients with right sided tumours. The bronchi coloured red indicates that they have received a maximum dose expressed in BED above 250 Gy<sub>3</sub>, blue indicates maximum dose below 250 Gy<sub>3</sub> and yellow indicates that the structures have not been visible on the CT images.

Atelectasis patients (the text in parenthesis denotes the part of the lung affected by atelectasis):

Patient 13 (lower lobe)	Patient 17 (missing information)	Patient 27 (right lower lobe)	Patient 39 (right lower lobe)
			
Patient 44 (partial right upper/middle lobe)	Patient 57 (right upper lobe)		
			

Non atelectasis patients:

Patient 2	Patient 4	Patient 5	Patient 6
			
Patient 10	Patient 21	Patient 26	Patient 35
