Chapter 8
Stereotactic Radiotherapy for Lung Tumors

Joost J. Nuyttens

Abstract Early stage lung cancer may often be not amenable for surgery due to poor underlying lung function. While conventional radiation therapy may be utilized, respiratory motion often implies inclusion of large volumes of normal lung, to cover the planning target volume with the attending morbidity. This poses a significant challenge for utilising SBRT, where sharp gradients and short treatment schedules benefit these patients. Different techniques have been utilized to address this, and SBRT has been a useful treatment option for peripheral lung tumors with excellent local control. Central lung tumors still pose challenges due to anatomical location and proximity of critical structures, emphasizing the need for careful patient selection.

This chapter outlines the role of SBRT in Lung cancer, serves as practical guide addressing the technical challenges and provides an overview of the available literature

In stereotactic radiotherapy, many different techniques have been developed to control for motion of tumors in the lung. The following methods have been applied to reduce the impact of respiratory tumor motion on dose distribution: (1) patient-specific treatment volumes based on tumor motion observed during planning CT scans (CT-based ITV), (2) forced shallow breathing with abdominal compression, (3) breath-hold methods, (4) respiratory gating methods, and (5) real-time tumor tracking. These different techniques will be reviewed in this chapter. The simulation and target definition depend on the technique.

The local control is excellent for peripheral tumors. However, the local control for central tumors varies depending on the total dose administered. The reported overall survival is excellent but depends on patient selection. The acute and late the toxicity of treatment of peripheral tumors is low. When treating central tumors, caution must be taken because the organs at risk are in close proximity and fatal toxicity has been reported by some authors.

Keywords Real-time tumor tracking • ITV • Breath hold • Forced shallow breathing • Respiratory gating • Local control • Outcome • Toxicity

J.J. Nuyttens, MD, PhD
Department of Radiation Oncology, Erasmus MC Cancer Institute,
Rotterdam, Zuid-Holland, The Netherlands
e-mail: j.nuyttens@erasmusmc.nl

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8.1 Introduction

Lung cancer is the most common cause of cancer related death. Seventy-five percent of patients with bronchogenic carcinoma will be diagnosed with non-small cell lung cancer (NSCLC). Approximately 15–20 % of NSCLC patients present with early or localized disease [1]. Surgical resection of stage I (T1–2, N0) NSCLC results in 5-year survival rates of approximately 60–70 % and remains the treatment of choice for this population [2–4]. Unfortunately, some patients with early-stage NSCLC are unable to tolerate the rigors of surgery or the postoperative recovery period due to severe comorbidity. Patients deemed medically inoperable or who refuse surgery have been treated with non surgical therapies, such as conventionally fractionated radiotherapy, or have been simply observed without any anti-tumor therapy. While some patients succumb to their comorbid illnesses, many of these patients will die of progressive lung carcinoma. Mc Garry et al. reviewed the outcome in 75 medically inoperable patients who received no specific cancer therapy at time of diagnosis for stage I NSCLC, and the cause of death was cancer in 53 % of cases [5].

To control the tumor in these patients, the dose must be increased without correspondingly increasing normal tissue toxicity. Therefore, not only is a precise dose delivery required but also a respiratory tracking method must be used to reduce the planning target volume. In a planning study, Prevost et al. compared stereotactic radiotherapy with real-time tumor tracking and three-dimensional conformal radiotherapy (3D CRT). They were able to deliver a 75 % higher mean dose with stereotactic radiotherapy and real-time tumor tracking compared to 3D CRT without increasing the dose to the lungs or other organs at risk [6]. This precise dose delivery is now achieved with the image-guided linear accelerators like the cone beam linear accelerator. Tomotherapy (Accuray Inc, Sunnyvale, CA) linear accelerators with X-ray tubes mounted on the ceiling or floor, and the CyberKnife.

Due to the precise delivery of image-guided radiotherapy, a reduction of safety margins surrounding the gross tumor volume is allowed. Sometimes GTV and CTV can be combined. Consequently, treatment volumes are reduced and treatment doses can be escalated. However, tumors can move considerably during the breathing cycle. These tumors can often move by more than 1 cm and sometimes as much as 3 cm during deep inspiration or expiration [7]. The following methods have been applied to reduce the impact of respiratory tumor motion on dose distribution: (1) patient-specific treatment volumes based on tumor motion observed during planning CT scans (CT-based ITV), (2) forced shallow breathing with abdominal compression, (3) breath-hold methods, (4) respiratory gating methods, and (5) real-time tumor tracking [8]. So, due to the combination of a precise delivery and a reduction in the impact of the motion of the tumor, the target volume can be reduced and the dose can thus be safely escalated. Due to this dose escalation, high local control rates exceeding 90 % have been reported for early-stage NSCLC patients treated with stereotactic radiotherapy (SRT) [9–11]. In this chapter, different methods to reduce the impact of tumor motion, the clinical results of the treatment of primary lung tumors, including central tumors, and lung metastases will be reviewed.

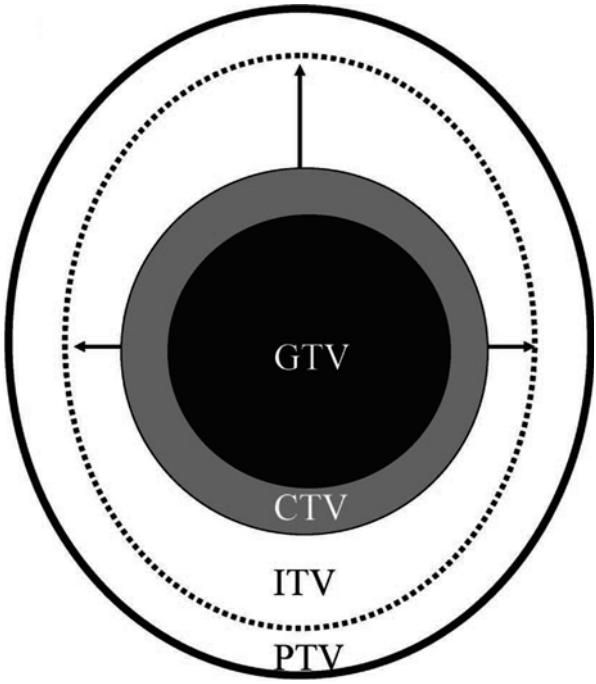

Fig. 8.1 The definition of GTV, CTV, ITV, and PTV. *GTV* gross tumor volume, *CTV* clinical target volume, *ITV* internal target volume, *PTV* planning target volume

8.2 Methods to Reduce the Impact of the Tumor Motion

8.2.1 Introduction

The ultimate goal of methods to reduce the impact of tumor motion is reducing the planning target volume margin from GTV or CTV. Reducing the target volume will reduce the radiation dose to organs at risk. However, by reducing the PTV margin, the tumor could be missed (a geographical miss). An extra margin around CTV is necessary because the tumor moves internally with respiratory motion. The ICRU reports define the margins that are necessary: the tumor as seen on a CT scan or on other examination is called the gross tumor volume (GTV) (Fig. 8.1). The GTV plus a margin to take into account microscopic extension of the tumor is the clinical tumor volume (CTV). The CTV plus a margin for the internal motion of the CTV is called the internal target volume (ITV). The ITV represents the movements of the clinical target volume (CTV) referenced to the patient coordinate system and is specified in relation to internal and external reference points, which preferably should be rigidly related to each other through bony structures. Finally a margin for positioning and motion of the patient on the table is added to the ITV and results in a planning target volume or the volume that must be used to get the correct dose within the tumor [12]. Most methods reduce all margins except the margin from GTV to CTV.

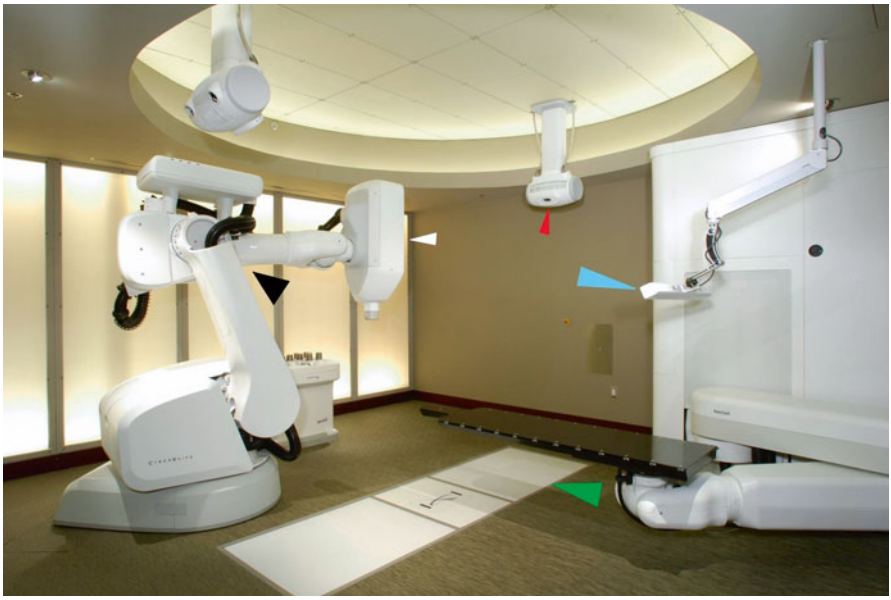

Fig. 8.2 The CyberKnife. *White arrow*, linear accelerator; *black arrow*, robot; *red arrow*, one of the 2 X-ray tubes; *green arrow*, one of the 2 flat panels; *blue arrow*, Synchrony camera

8.2.2 Real-Time Tumor Tracking

The most commonly used method of real-time online tumor tracking is the CyberKnife Synchrony system. With real-time tumor tracking, the GTV is expanded to a CTV and then to a PTV and results usually in a total margin from the GTV to PTV of 5–8 mm. An ITV is not required. The CyberKnife (Fig. 8.2) is a frameless image-guided radiotherapy system involving a 6 MV x-band linear accelerator mounted on a robotic arm, which possesses six degrees of freedom of motion. The imaging system consists of 2 diagnostic X-ray sources mounted to the ceiling paired with amorphous silicon detectors to acquire live digital radiographic images of the tumor, or tumor localizing surrogates such as the skull, spine, or fiducial markers. The Synchrony system enables 4-dimensional real-time tracking of tumors that move with respiration. An advantage of the Synchrony subsystem is that the patients can breathe normally. Synchrony combines non continuous X-ray imaging of internal fiducial markers as surrogates for the tumor position, with a continuously updated external breathing signal. In more recent system versions, it is possible to track the tumor directly in the X-ray images (in certain very specific circumstances) using the contrast between tumor and surrounding lung tissue, thereby removing the need to implant fiducial markers. A correlation model that relates the external breathing signal with the motion of the tumor provides a real-time update of the beam position that is fed to the robotic arm on which the linear accelerator is mounted. In the treatment room, the patient is placed in a supine position on the couch in the vacuum mattress. Three light-emitting diodes (LEDs) are placed on the patient's chest or abdomen to provide the external breathing signal. The

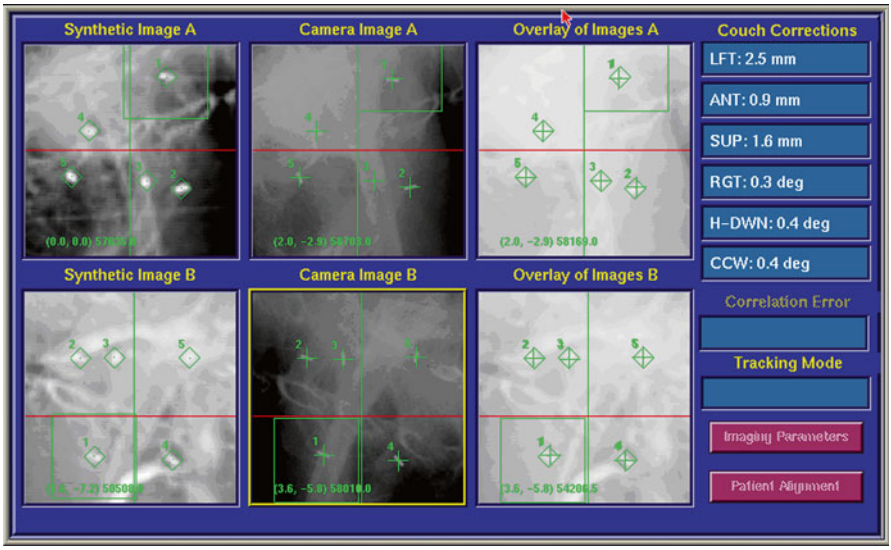

Fig. 8.3 Alignment of the tumor with the use of implanted fiducial markers. A screen dump of the digital display at the CyberKnife treatment console taken before treatment in order to align the tumor. In the *first column*, the DRR is shown. In the *green* cubes, the markers on the DRRs are shown. In the *second column*, 2 orthogonal images of the patient are shown. The *green* crosses indicate the marker positions detected automatically by the tracking software. The offsets between the target centroid position in the treatment plan and that calculated from the live X-ray images are shown under the heading "Couch Corrections." Initially this information is used to automatically adjust the couch position. Once treatment starts, the couch remains static and all tracking is performed using the robotic arm and LINAC. The *third column* shows an overlay of the DRRs and the X-ray images after the calculated offsets are applied

motion of these LEDs due to respiration is registered by a digital camera array (the Synchrony camera) (Fig. 8.2). Initial patient alignment is conducted by the X-ray image-guidance system and the remotely controlled treatment couch, such that the extent of the respiratory motion is within the translational limits of the robot. The tumor is localized by reconstructing the 3D position of the tumor or the fiducial markers, which are automatically segmented in the X-ray images. The reconstructed position is compared with the position in the planning CT scan (Fig. 8.3). Just prior to the start of the irradiation, the correlation model is built by acquiring approximately 8 X-ray image pairs at different phases of the breathing cycle (Fig. 8.4). The Synchrony system makes a correlation model that relates the movement of the tumor or the fiducial markers and the LEDs. Non linear models are used to account for hysteresis in the tumor trajectory. Using this model, the linear accelerator can continuously track the motion of the tumor via the motion of the LEDs. The correlation model is intermittently validated and updated throughout treatment by acquiring new X-ray image pairs (typically every 1–6 min at our site). After each image-pair acquisition, the correlation model error is displayed on the system console. This measures the distance between the tumor position detected from the new images and the expected position based on the current correlation model. If the correlation model error is larger than 5 mm, a system interruption is generated and the operator has to build a new model.

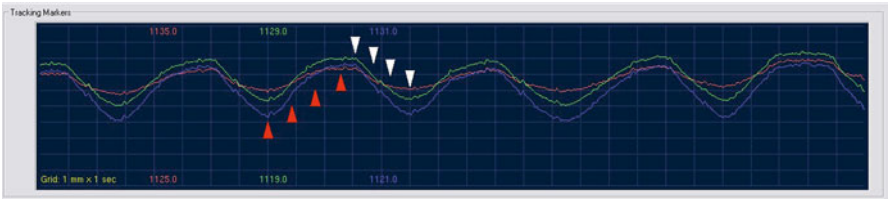

Fig. 8.4 The timing of imaging to calculate tumor trajectory in three dimensions. *Green*, *blue*, and *purple lines*: breathing cycle as recorded with the Synchrony camera; *red arrows*, imaging during expiration; *white arrows*, imaging during inspiration. In reality the image acquisitions are spaced over multiple breathing cycles and can be timed automatically by the Synchrony system to ensure that the entire respiratory cycle is evenly sampled

Otherwise, the new tumor position and corresponding LED positions are added as a new data point into the existing set of correlation model data points, and the model is regenerated such that the model adapts during each treatment fraction to changes in the internal external motion correlation [13–18]. Tumor tracking during respiration can be done in two ways using the CyberKnife system: one way is with the use of digital radiographic images of the tumor with the Xsight lung system and the other way is with the use of fiducial markers. The Xsight lung system was commercially released in 2006 and has been updated twice since then by the vendor. Clinical experience with the latest algorithms is currently limited. On the other hand, several CyberKnife users did report on the technique to place fiducials based on extensive clinical experience. In total, five different techniques are available to place markers: (1) bronchoscopic, (2) percutaneous intrapulmonary, (3) percutaneous extrapulmonary, (4) intravascular, and (5) bronchoscopic with electromagnetic navigation.

8.2.3 CT-Based Internal Gross Tumor Volume (ITV)

The movement of tumors in the lung depends on their location within the lung. These tumors often move by more than 1 cm and sometimes as much as 3 cm during deep inspiration or expiration. The reduction of margins with a CT-based ITV is based on the individual movement of the tumor. A tumor that is moving less than one centimeter will thus get a smaller margin than a tumor that is moving more than 1 cm. A CT-based ITV is preferably outlined on the expiratory phase of the 4 D images and registered with the outline on other respiratory phases to create a union of target contours enclosing all possible positions of the target (an ITV). Another method is to create an image of maximum intensity projection by combining data from the multiple CT data sets with data from the whole-breath cycle and modify tumor volume by visual verification of the target volume throughout the breathing phases. In this case, the ITV should consist of the GTV plus a margin to account for microscopic disease (8 mm). Even with 4D-CT, the free-breathing simulation is only a snapshot and a single stochastic sampling of the patient's respiratory cycle. Attention should be paid to irregular breathing and variations in the patient's breathing pattern over

the course of each treatment session and the entire treatment course and to the effects of these irregularities on the ITV margin [19]. If 4 D CT is not available, an ITV can be developed based on breath-hold spiral CT images that require the patient to hold his/her breath once during the simulation at the end of expiration and once at the end of inspiration, but not during treatment delivery. In this procedure, images are acquired through the use of a standard extended temporal thoracic CT protocol. In this protocol, patients are asked to breathe normally, and the extended temporal CT images are acquired at the beginning of the simulation; the isocenter is then set. Subsequently, images are obtained by using a fast CT simulation protocol while at the end of inspiration and expiration. Separate GTVs and CTVs should be delineated by a physician both on the end of expiration CT image set and on the end of inspiration image set. An ITV is then generated by combining the two CTVs on the extended temporal CT scan to form an ITV that includes the entire path of the CTV as it moves from inspiration to expiration. Normal tissues should be contoured in the extended temporal CT images as well. The ITV will be superimposed on the slow CT images, which will serve as the basis for treatment planning [20].

8.2.4 Forced Shallow Breathing with Abdominal Compression

The patient is immobilized in a stereotactic body frame (Fig. 8.5). This usually consists of a vacuum pillow and a rigid frame with a laser system attached for positioning and a diaphragm control device. Several small tattoos are placed on the patient's chest for repeated positioning. A pressure can be applied to the upper abdomen using the diaphragm control device. This device consists of an abdominal plate and a screw that is attached to the body frame (Fig. 8.6). The pressure on the upper abdomen is regulated by adjusting the height of the plate with the screw (Fig. 8.7). The patient is now only able to have shallow breathing. Margin reduction from CTV to PTV is possible because on one hand the tumor will move less than 1 cm due to the shallow breathing and on the other hand due to the exact immobilization with the whole body frame and the abdominal compression [21–24].

8.2.5 Breath-Hold Methods

With the breath-hold methods, the CTV to PTV margin is reduced because radiation is only delivered when the tumor is not moving during the breath hold. This method is also called the deep inspiration breath-hold technique (DIBH). Barnes et al. found that, on average, self-gated DIBH decreased the percent of lung volume receiving 20 Gy (V20) from 12.8 to 8.8 % with GTV-to-PTV margin reduction [25].

In the DIBH technique, the patient is initially maintained at quiet tidal breathing, followed by a deep inspiration, a deep expiration, a second deep inspiration, and breath hold. At this point the patient is at approximately 100 % vital capacity, and simulation, verification, and treatment take place during this phase of breath-holding.

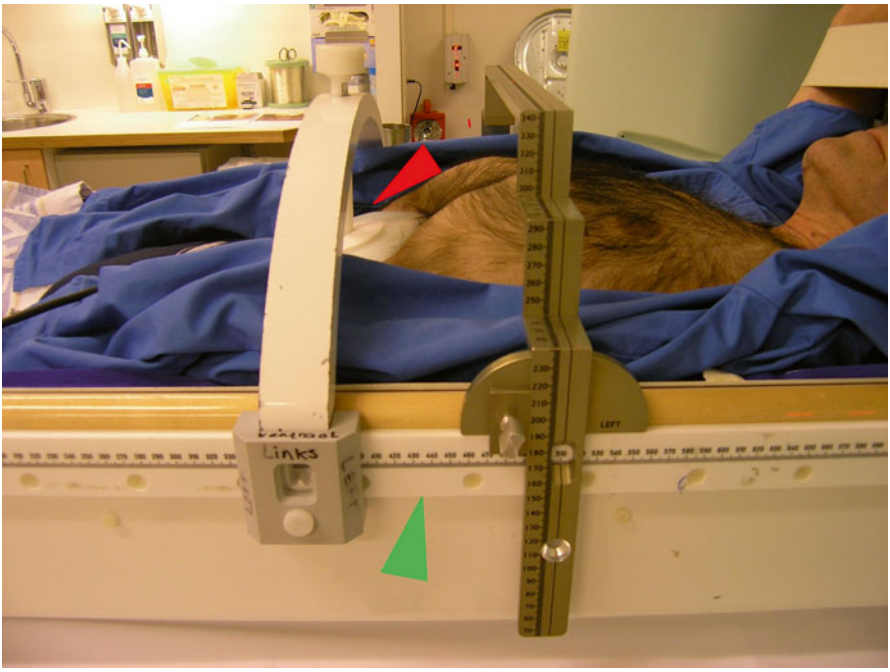

Fig. 8.5 The whole body frame with abdominal immobilization. *Green arrow*, the whole body frame; *red arrow*, the abdominal compression plate

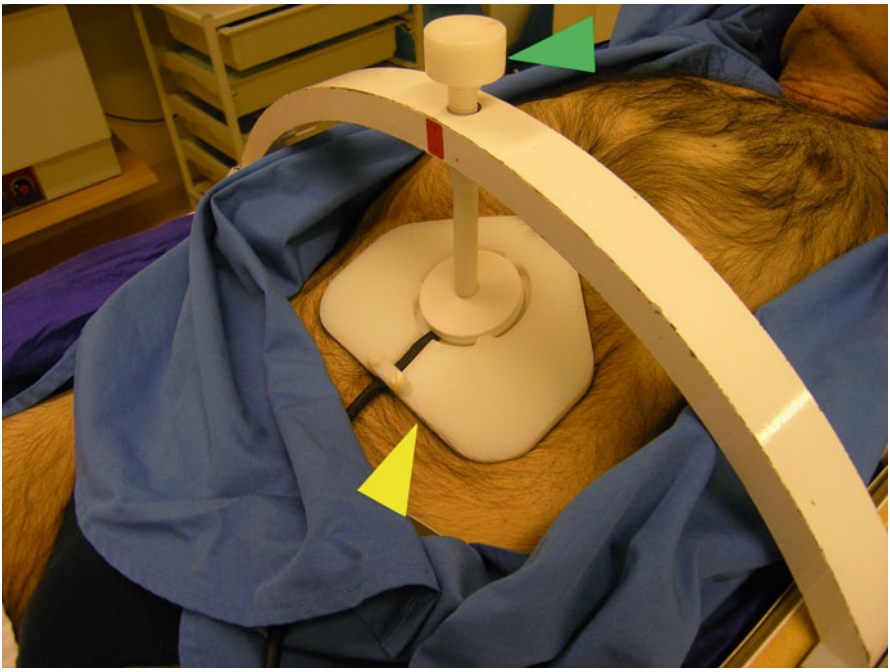

Fig. 8.6 A detailed picture of the whole body frame with abdominal immobilization. *Yellow arrow*, abdominal plate; *green arrow*, screw to regulate the degree of abdominal compression

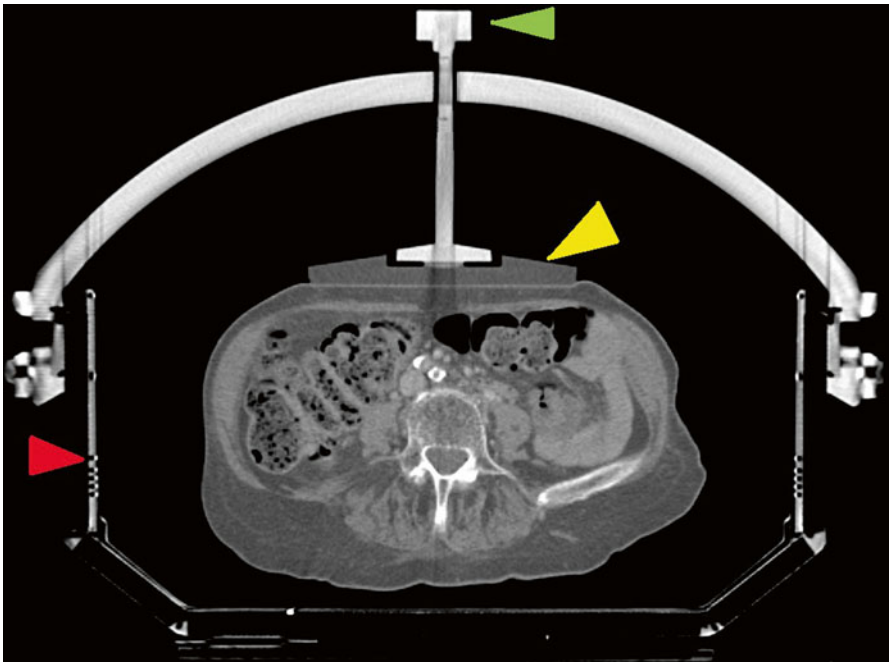

Fig. 8.7 A CT scan slice through the whole body frame. *Red arrow*, the whole body frame; *yellow arrow*, abdominal plate; *green arrow*, screw to regulate the degree of abdominal compression

Different methods have been implemented based on this principle. To monitor lung inflation levels, the patient breaths through a mouthpiece connected to a differential pressure pneumotachograph spirometer or modified ventilator interfaced to a laptop computer to monitor the air flow. A nose clip is used to prevent nasal breathing [26–28]. If the patient is at the right inspiration level, the therapist can turn on the beam. With another method, the patient controls an interlock of a modified linear accelerator if he/she reaches the right inspiration level. The therapist turns on the beam when the patient judges that he/she has attained the correct breath-hold level (=self-gated DIBH). To familiarize the patient with the procedure, a training session is given a few days before the planned simulation. Breath-holding techniques may be poorly tolerated by patients with mediocre lung function, and active patient and therapist participation is often required [29].

8.2.6 Respiratory Gating Methods

The ITV is smaller because irradiation of the tumor only occurs during a certain phase in the breathing cycle. A device monitors patient breathing and allows delivery of radiation only during certain respiratory phases, synchronous with the patient's respiratory cycle. Several devices have been developed; however, the real-time position management respiratory gating system (RPM) is most commonly used [30–32]. This system uses two passive reflective markers that are placed on the patient's chest

or abdomen. An illuminator sends infrared light to the reflective markers and the markers send the light back to a video camera. The respiratory movement is tracked by the upper marker; the lower marker calibrates the system. A computer processes the video signals and sends on-off control signals to the linear accelerator. The patient has to breathe regularly and stably during simulation and treatment. At the start of the simulation and the irradiation, the minimum and maximum position of the upper marker is determined by recording a few breathing cycles [33]. The planning CT scan must be acquired in the same phase of the breathing cycle as the treatment.

8.3 Simulation, Treatment Planning, Constraints, and Prescription

The simulation depends on the radiation therapy technique as is explained in Chap. 6. Usually, the patient is simulated and treated in the prone position with or without a vacuum mattress to minimize motion of the patient. The treatment planning CT scan is performed with intravenous contrast, usually with a wide-bore multi-slice computed tomography (CT) simulator. The use of 4D CT scans, exhale or inhale CT scan combined or not combined with a contrast enhanced planning CT scan, depends on the radiation technique (see Chap. 6). The patient is scanned from his/her teeth to the middle of his/her abdomen, and the trans axial imaging has a slice thickness of 1.5–3 mm.

The planning CT is transferred to the treatment planning system (TPS). The tumor and organs at risk (OAR) are then contoured. The gross tumor volume (GTV) is contoured using the lung window. Margins to the GTV are added depending on the radiation technique (see Chap. 6). The OAR consist of both lungs, esophagus, the heart, and the spinal cord.

Usually, inverse treatment planning is used; however, the treatment plan can also be calculated using forward planning, and depending on the radiation technique, the number of beams varies between 7 and 15 using conventional IG-IMRT techniques or up to 150 beams using stereotactic radiotherapy with the CyberKnife. The total dose is prescribed to the isodose surface that covers 95 % of the volume of the PTV. The total dose depends on the fractionation scheme (see Chap. 5 and 6). The dose to normal tissues (lungs, heart, spinal cord, etc.) should be within the constraints. An example of dose constraints to the OAR using different treatment schedules is shown in Table 8.1. Two opposite (90°) digitally reconstructed radiographs (DRRs) are generated to align the patient correctly; however, also this depends on the radiation technique.

8.4 Clinical Outcome of Primary Lung Tumors

8.4.1 Introduction

Stereotactic body radiotherapy (SBRT) targets and delivers high ablative doses of radiation to sites within the body while applying methods to reduce the effects of tumor motion to help assure accuracy and precision, as described in Chap. 6.

Table 8.1 Dose constraints

Dose constraints for		1 fraction	3 fractions	5 fractions	7 fractions
Organ	Volume	Dose (Gy/fr)	Dose (Gy/fr)	Dose (Gy/fr)	Dose (Gy/fr)
Spinal cord	Any point	12.5	6	5.5	4.5
Esophagus	Any point	13	7	7	6
Heart	Any point	15	12	10	8
Trachea and main bronchus	Any point	16	10	10	8
Plexus brachialis	Any point	14	8	6	5
Liver	Any point	30	20	12	8
Lung	V_{20} (EQD2)	<31 %	<31 %	<31 %	<31 %

V_{20} (EQD2): the volume (in %) receiving ≥20 Gy, expressed in equivalent dose of 2 Gy

However, caution must be taken if the tumor is close to organs at risk such as the trachea, mainstem bronchus, esophagus, or heart. Serious complications, including death following bacterial pneumonia, pericardial effusion, radiation pneumonitis, or massive hemoptysis, have been reported [34, 35]. Therefore, the tumors are classified into two groups: the peripheral tumors and the central tumors. Although there are several definitions, central tumors are tumors located <2 cm from the trachea, mainstem bronchus, main bronchus, or esophagus, as well as tumors located close to the heart and tumors located in the mediastinum.

SBRT to peripheral tumors has resulted in high local tumor control rates [9–11]. An example of an excellent local control in one patient is shown in Fig. 8.8. Less experience exists in SBRT for central lung tumors because they are relatively rare and because common SBRT dosing schedules, such 3 fractions of 20 Gy, cannot be safely used due to the proximity of the trachea, mainstem bronchus, esophagus, or heart. By increasing the number of fractions to 5, 8 or even 10 and reducing the fractional dose, some groups have reported successful treatment of central lung tumors with minimal complications [36]. However, some authors did report grade 5 toxicity related to the treatment [34, 37–39].

8.4.2 Peripheral Tumors

Although many articles did report the outcome of stereotactic radiotherapy of peripheral tumors, a randomized trial comparing surgery or different methods of radiation delivery has not been done. Treatment schedules with single fractions were mainly used in the beginning but are still used by some radiation centers. Whyte was one of the first to report his/her results with a single fraction of 15 Gy in a phase I clinical trial [40]. Later on, dose escalation studies were done [30, 34]. Hara et al. reported a 2-year local control rate for patients receiving a single fraction of 30 Gy or more of 83 % compared to 52 % in those treated with a single fraction less than 30 Gy [30]. However, Hof et al. concluded that single fraction SRT was a safe and effective treatment option for patients with small tumors but that the application to larger tumors was unclear [41]. While these articles did appear, other

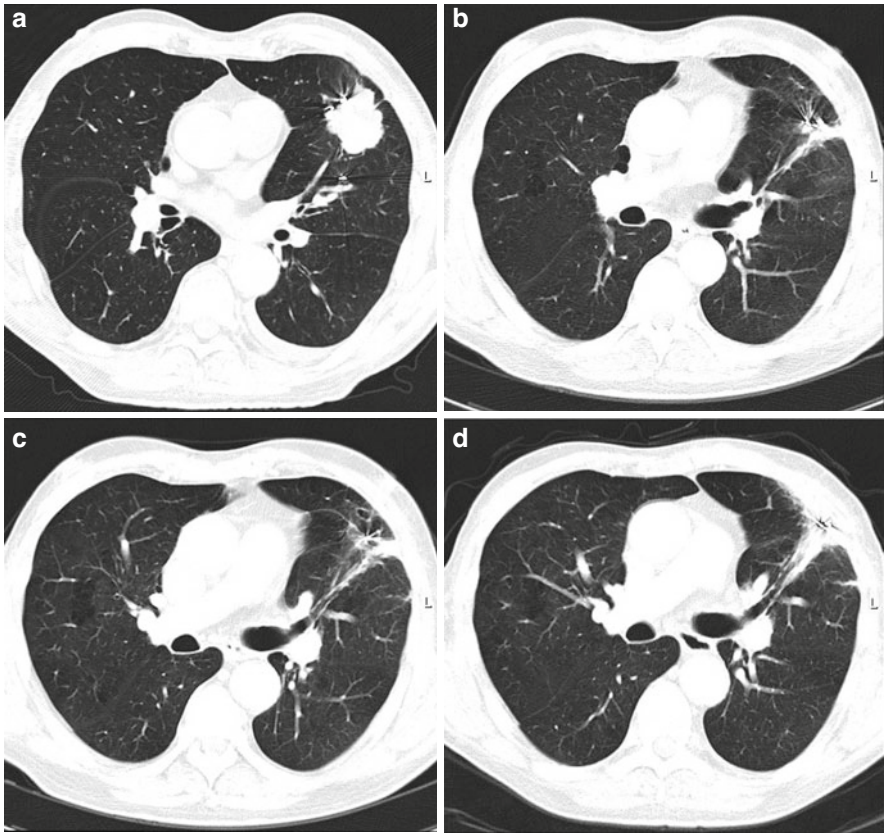

Fig. 8.8 T2 N0 NSCLC before the treatment (**a**) and the clinical result after 1 year (**b**), 2 years (**c**), and 3 years (**d**). Note pulmonary fibrotic change

articles did report the outcome of multiple fractions. The most commonly used schedule for peripheral tumors is one with 3 fractions of 18-20Gy, but schedules with 4 or more fractions also exist.

The first three most important articles are from Timmerman et al., Onishi et al., and Wulf et al. [9, 42, 43]. Timmerman et al. performed a dose escalation study with inoperable early-stage lung cancer patients. He started with 24 Gy in 3 fractions and escalated the dose at 2 Gy per fraction [42]. Patients with T1 vs T2 tumors underwent separate independent dose escalations. Thirty-seven patients were enrolled and both T-stage groups ultimately reached and tolerated 60 Gy in 3 fractions. The maximum tolerated dose for this therapy in either T-stage group was not reached. Tumors responded to treatment in 87 % of patients (complete response, 27 %). After a median follow-up period of 15 months, 6 patients experienced local failure, all of whom had received doses of <18 Gy per fraction since February 2000. One patient experienced grade 3 pneumonitis and another patient had grade 3 hypoxia. Onishi et al. reported in 2004 the clinical outcome of a Japanese multicenter

Table 8.2 Local control after treatment for early-stage lung cancer, peripherally located

Technique	Number of patients	Total dose	Number of fractions	Local control at 2 years (%)	Author
Real-time tumor tracking	70	60	3	96	Van der Voort et al. [10]
Real-time tumor tracking	20	42–60	3	95	Vahdat et al. [44]
CT-based ITV	591	60	3–5-8	93	Verstegen et al. [45]
Real-time tumor tracking	43	50	10	95	Xia et al. [46]
Whole body frame	45	48	4	100	Nagata et al. [47]
Breath hold or respiratory gating	20	45–54	3–4	94	Ng et al. [48]

study [9]. Two hundred forty-five patients with stage I NSCLC (T1N0M0, n = 155; T2N0M0, n = 90) were treated with hypofractionated high-dose stereotactic radiotherapy in 13 institutions. Stereotactic three-dimensional treatment was performed using non-coplanar dynamic arcs or multiple static ports. A total dose of 18–75 gray (Gy) at the isocenter was administered in 1–22 fractions. The median calculated biologic effective dose (BED) was 108 Gy (range, 57–180 Gy). Local progression after a median follow-up of 24 months occurred in 14.5 %, and the local recurrence rate was 8.1 % for BED ≥100 Gy compared with 26.4 % for <100 Gy ($p < 0.05$). The 3-year overall survival rate of medically operable patients was 88.4 % for BED ≥100 Gy compared with 69.4 % for <100 Gy ($P < 0.05$).

Wulf et al. compiled the results of several studies. They included both lung metastases (n = 56) and primary lung tumors (n = 36) [43]. Twenty-four patients receiving 3 × 10 Gy, 22 patients receiving 3 × 12.5 Gy, and thirty-one patients receiving 1 × 26 Gy had 2-year local control rates of 71, 92, and 100 % respectively. After a median follow-up of 14 months (2–85 months), 11 local recurrences were observed with significant advantage for higher doses. These 3 studies did show the efficacy of a biologically effective dose (BED) of 100 Gy or more, and therefore, these are the most used schedules with 3 fractions of 17–20 Gy. With the current techniques as described in Chap. 6, the 2-year local control is 93 % or more (see Table 8.2). The 2-year overall survival varies between 58 and 91 %, but depends on patient selection as most treated patients are not candidates for surgery due to their comorbidities as cardiovascular and pulmonary diseases (see Table 8.3).

8.4.3 Central Lung Tumors

The tumor-ablative effects of high-dose SBRT for lung cancer can be safely extended to lesions in the central chest if treatment is adapted to reduce the risk of OAR injury. Several studies have now shown that delivering lower doses over 4–10 fractions can considerably reduce toxicity of SBRT in the central chest [11, 39, 44,

Table 8.3 Survival after treatment for early-stage lung cancer, peripherally located

Technique	Number of patients	Total dose	Number of fractions	Survival at 2 years	Author
Real-time tumor tracking	70	60	3	63 %	Van der Voort et al. [10]
Real-time tumor tracking	20	42–60	3	90	Vahdat et al. [46]
CT-based ITV	591	60	3–5-8	65	Verstegen et al. [45]
CT-based ITV	43	50	10	91	Xia et al. [44]
Whole body frame	45	45	3	71	Nyman et al. [49]
Whole body frame	45	48	4	90 (T1N0M0)	Nagata et al. [47]
				72 (T2N0M0)	
Breath hold or respiratory gating	35	60	10	58	Onishi et al. [50]

51–54], although doses that are often used in treating peripheral lung lesions can result in serious toxicity and death when delivered to central lesions [24, 34, 35, 37] or can result in at least a higher rate of toxicity than for peripheral lesions [38]. The published studies to date have typically consisted of a mixed population of peripheral and central tumors and included a relatively small number of patients (8–27 patients) with central tumors. However, 2 studies reported on a larger group: Haasbeek et al. reported on 63 patients who were treated with eight fractions of 7.5 Gy [55]. Of these 63, 37 patients had a tumor at a central hilar location, whereas 26 patients had tumors abutting the pericardium or mediastinal structures. The median follow-up was 35 months. Three-year local control rate was 92.6 %, and the 3-year overall survival rate was 64.3 %. Nuyttens et al. reported on 58 central lesions in 56 patients (39 with primary, 17 with metastatic tumors) [56]. Fifteen tumors located near the esophagus were treated with 6 fractions of 8 Gy. Other tumors were treated according to the following dose escalation scheme: 5 fractions of 9 Gy (n = 6), then 5 fractions of 10 Gy (n = 15), and finally 5 fractions of 12 Gy (n = 22). In 21 patients, the coverage of the PTV was reduced below 95 % to protect adjacent organs at risk. At a median follow-up of 23 months, the actuarial 2-year local tumor control was 85 % for tumors treated with a BED >100 Gy compared to 60 % for tumors treated with a BED ≤100 Gy. The median volume of the main bronchus irradiated to an EQD2 of 130 Gy or a BED of 216 Gy in 29 patients was 0.4 cm^3 (range, 0.001–4.9 cm^3). The median Dmax to the esophagus was 88 Gy_3 EQD2 of 143 Gy BED.

In some studies in which lower doses per fraction were delivered, reduced toxicity seemed to come at the expense of local control. For example, Taremi et al. delivered 50 or 60 Gy in 8 fractions to 20 patients with central lesions (out of 108 patients treated overall) and observed no severe toxicity related to tumor location [54]. However, seven of the ten local recurrences were central lesions, five of which were treated with 50 Gy. Chang et al. observed low toxicity but a high recurrence rate (43 %) in seven patients treated with 40 Gy in 4 fractions [52]. A similar combination of low dose (BED < 100 Gy) with relatively low toxicity and relatively low local

control was obtained by Onimaru et al. [39] and Guckenberger et al. [57]. We treated several of our patients with doses lower than 50 Gy and found a statistical trend toward poorer tumor control in these patients, a finding that is consistent with these reports.

Other authors, however, have reported the ability to deliver doses equal to or above BED = 100 Gy, resulting in the combination of good tumor control (>85 % at 1.5–2 years) and low toxicity [11, 44, 53]. Stephans et al., for example, were able to treat central lung lesions without serious toxicity using 50 Gy delivered in 5 fractions [53]. Patients were immobilized in a stereotactic frame and abdominal compression was applied to reduce tumor motion. Tumor control at a median follow-up of 18.4 months was 98 %.

A risk-adapted treatment of central lesions requires both a consideration of the maximum overall and fraction doses and care to optimize the dose distribution to meet strict dose constraints for sensitive central structures, because several authors did report grade 4 and 5 toxicity (see Chap. 6). The fact that even doses as low as 40 Gy can cause significant complications points to the critical importance of careful treatment planning, accurate patient setup, and precise radiation delivery throughout a treatment fraction [24].

8.5 Clinical Outcome in the Treatment of Lung Metastases

Patients with metastatic disease to the lung who are referred for radiotherapy are, for a number of reasons, a very different group: they often have centrally located lesions, may have one or more lesions in each lung, have previously undergone a lobectomy or pneumonectomy, or are bad surgical candidates due to their medical condition. The presumed state of oligometastasis, as described by Hellman et al., is one in which lesions are detected prior to the widespread distribution of malignant cells [58]. In such a state, an effective local therapy such as SRT should, in theory, arrest the disease progression and extend life. If a local therapy is non invasive and associated with low toxicity, then life-extending treatment can be delivered without seriously impacting a patient's quality of life during or after treatment [59, 60]. Combined with surgical and chemotherapeutic approaches as necessary, as well as aggressive use of modern imaging to detect smaller, tumours, the potential to control disease progression over the long term with stereotactic radiotherapy makes it a powerful tool in the oligometastatic state. Stereotactic radiotherapy may also be applied in patients who cannot endure surgery, or patients who have undergone repeated systemic treatments, thus extending the potential of local treatment of oligometastases to patients who might otherwise have been treated palliatively.

Published reports of SRT for lung oligometastases reveal a wide variety of dose/fractionation schemes, approaches to image guidance and motion management, and related margins to account for microscopic disease extension and radiation delivery error. These reports typically show good long-term tumor control, but overall survival can be disappointing. For example, Milano et al. treated 121 patients with 5 or fewer

metastases in 10 fractions of 5 Gy; 41 % of patients had tumors in the lung. Overall survival was promising at the 2-year time point (50 %), but at 6 years, although local control was maintained at relatively high levels, overall survival fell to 20 % [61]. Similar outcomes have been reported frequently, with local control at 2–3 years ranging from 70 to 100 % but overall survival generally being much lower, typically due to progression outside the treated region, [62, 63] for example, in a phase I/II study in which 48–60 Gy was delivered in 3 fractions, obtained local control of 96 % at 2 years whilst median survival was only 19 months [62]. We can conclude from this and other studies that the identification of "oligometastatic" patients, who can benefit from long-term disease control, requires additional investigation.

8.6 Toxicity and Quality of Life

8.6.1 Toxicity of Treatment of Peripheral Lesions

The difficulty in distinguishing between treatment-related symptoms and the natural course of COPD may cause variation in the incidence of reported toxicity. The 2-year overall late toxicity is reported in 2–10 % of patients [9, 10]. Onishi et al. treated 245 patients and reported pneumonitis grade 3 and 4 of 2.4 %, esophagitis grade 2 and 3 of 2 %, and rib fractures in 0.8 % [9]. Grade 1 pulmonary symptoms resolved in most patients with or without steroid therapy, but continuous oxygen supply was required in three patients who displayed poor respiratory function before irradiation. Chronic segmental bronchitis and wall thickening causing atelectasis on the peripheral lung were observed in one patient. Grade 3 or 4 dermatitis was observed in two patients with tumors adjacent to the chest wall. Verstegen et al. reported the outcome of 592 patients [45]. Severe (CTCAE v3) late toxicity was uncommon. A total of 18 patients (3 %) developed grade 3 radiation pneumonitis, 10 patients showed rib fractures on follow-up scans (2 %), and three patients experienced grade 3 chest wall pain (1 %). Van der Voort et al. reported the results of 70 patients and reported no grade 4 or 5 toxicity [10]. Acute grade 1–2 toxicity occurred in 32 patients, consisting mostly of fatigue, dyspnea, and cough. One patient had acute grade 3 toxicity, requiring morphine for severe thoracic pain. Late grade 3 toxicity was observed in seven patients (10 %). Three patients had radiation pneumonitis treated with antibiotics and corticosteroids. Four patients had thoracic pain requiring morphine. They all had a tumor near the chest wall. A rib fracture was found in one of these patients. Although most authors report a low incidence of rib fractures, Nambu et al. reported that rib fractures were seen in 41 of the 177 patients (23 %) [64]. Rib fractures appeared at a mean of 21.2 months after the completion of SRT (range, 4–58 months). Chest wall edema, thinning of the cortex, and osteosclerosis were findings frequently associated with and tending to precede rib fractures. No patients with rib fracture had tumors >16 mm from the adjacent chest wall. Chest wall pain was seen in 18 of 177 patients (10 %), of whom 14 patients

developed rib fracture. Bongers et al. found on multivariate analysis that patients with chest wall pain had larger treatment volumes and shorter tumor-chest wall distances, whereas patients with rib fractures had larger tumor diameters and treatment volumes [65]. Grade 3 chest wall pain and rib fractures were associated with larger volumes of chest wall receiving doses of 30–50 Gy and rib fractures specifically with a higher maximum dose in the chest wall. Stephans et al. reported that on multivariate analysis of 134 patients, the tumor volume was no longer correlated with symptomatic chest wall toxicity and only V30 through V60 remained statistically significant [53].

8.6.2 Toxicity of Treatment of Central Lesions

The toxicity following treatment of central lesions is quite similar with the toxicity after the treatment of peripheral lesions. However, 5 publications did report death due to pulmonary complications and two due to esophageal complications. Two authors reported the death of one patient secondary to bronchial stenosis and subsequent bleeding from the bronchus [24, 38]. In one patient, the dose to the tumor was 48 Gy in 4 fractions, and in the other patient the dose was not specified (but was probably 60 Gy in 4 fractions, based on other details in the report). Milano et al. reported one death due to fatal hemoptysis after treatment of a mediastinal mass abutting the bronchus. The cumulative dose to the bronchus was 98 Gy [66]. Le et al. reported 2 deaths due to pulmonary complications [34]. Both patients were treated previously with radiotherapy to the chest. Fakiris et al. reported five grade 5 toxicities, all possibly related to the stereotactic treatment of 22 patients and three of them due to pneumonia, one to hemoptysis, and one to respiratory failure [37]. Le et al. reported the death of one patient due to esophageal fistula followed by a fatal hemoptysis from a tracheovascular fistula [34]. Brachial plexopathy has been reported in two patients: one patient developed a brachial plexopathy that was managed medically; however, the dose to the plexus was not reported [51]. The other one developed brachial plexus neuropathy and partial arm paralysis after receiving a dose of 40 Gy (in 4 fractions) to a significant volume of the plexus [52].

8.6.3 Quality of Life

Two groups of authors studied patient quality of life after treatment. Van der Voort et al. reported the quality of life of 39 patients with pathologically confirmed T1 to T2N0M0 NSCLC [59]. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) C30 and the QLQ LC13 lung cancer-specific questionnaire were used to investigate changes in quality of life.

Assessments were done before treatment, at 3 weeks, and at 2, 4, 6, 9, and 12 months after treatment, until death or progressive disease. Toxicity was evaluated using common terminology criteria for adverse events version 3.0. The emotional functioning improved significantly after treatment. Other function scores and QLQ-C30 and QLQ-LC13 lung symptoms (such as dyspnea and coughing) showed no significant changes. Widder et al. investigated changes of health-related quality of life parameters after stereotactic radiotherapy (202 patients) and 3 D treatment (27 patients) [67]. Two prospective cohorts of inoperable patients with T1–2N0M0 primary lung tumors were analyzed. Patients received 70 Gy in 35 fractions with 3D CRT or 60 Gy in three to eight fractions with stereotactic radiotherapy. The EORTC QLQ-C30 and the QLQ-LC13 lung cancer-specific questionnaire were also used. Global quality of Life and physical functioning were stable after stereotactic radiotherapy ($p=0.21$ and $p=0.62$, respectively). Dyspnea increased after stereotactic radiotherapy by 3.2 out of 100 points ($p<0.01$), which is clinically insignificant. At 1 year, physical performance status decreased by an excess of 8.7 out of 100 points ($p<0.01$) after 3D CRT compared with stereotactic radiotherapy.

8.7 Conclusion

Stereotactic radiation can minimize lung toxicity in the treatment of early stage lung cancer. However, respiratory motion of the tumors may often lead to inclusion of surrounding normal lung in the target volume. In stereotactic radiotherapy, many different techniques have been developed to control for motion of tumors in the lung. The local control is excellent for peripheral tumors. The local control for central tumors depends on the total dose administered. The reported overall survival varies but depends on the patient selection. The toxicity in the treatment of peripheral tumors is low. When treating central tumors, caution must be taken because the organs at risk are close and high toxicity has been reported by some authors.

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