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Radiotherapy in Lung Cancer

Fiona Lim Mei Ying

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Abstract

Lung cancer remains one of the top five cancers worldwide. Around 85% are nonsmall cell lung cancer (NSCLC) and only one-third present with early stage diseases. Radiotherapy had an important role both in radical and palliative treatment. With advancement in technology, newer techniques of stereotactic body radiotherapy allow delivery of much higher biologically effective dose to tumor achieving similar outcomes to radical surgery in early stage diseases. However, the usually large tumor volume together with preexiting poor lung condition makes radiotherapy challenging to deliver a radical dose to tumor while maintaining normal tissue constrains. In this chapter, different indications and techniques used in treating NSCLC will be discussed and reviewed.

Keywords: nonsmall cell lung cancer, external beam radiotherapy, stereotactic body radiotherapy

1. Introduction

According to the World Cancer Report 2014, lung cancer remains the top five most common cancers among both men and women worldwide. And it is also the leading cause of cancer deaths. Majority (around 85%) are nonsmall cell lung carcinomas [1, 2]. Incidence of adenocarcinoma had been rising and now became the most common histological subtypes in both men and women. About one-third of them are presented with early stage localized disease (stage I–II), another one-third with locally advanced disease (stage III), and remaining one-third with metastatic disease (stage IV) at diagnosis [3, 4].

2. Anatomy

Lungs are a paired structure that is separated into left and right by the mediastinum, which contains the tracheal, heart, esophagus, and lymph nodes. The left lung is divided into upper and lower lobe by oblique fissure, while the right lung is divided into three lobes (upper, middle, and lower) by oblique and horizontal fissures.

Lung cancers can arise from mucosa of the tracheobronchial tree or the alveolar lining cells of peripheral lung parenchyma. Tumor can spread locally within lung parenchyma or invading surrounding structures including mediastinum, major vessels, or chest wall (**Figure 1**). They can also spread along major airways causing obstruction, distal collapse, or atelectasis (**Figure 2**).

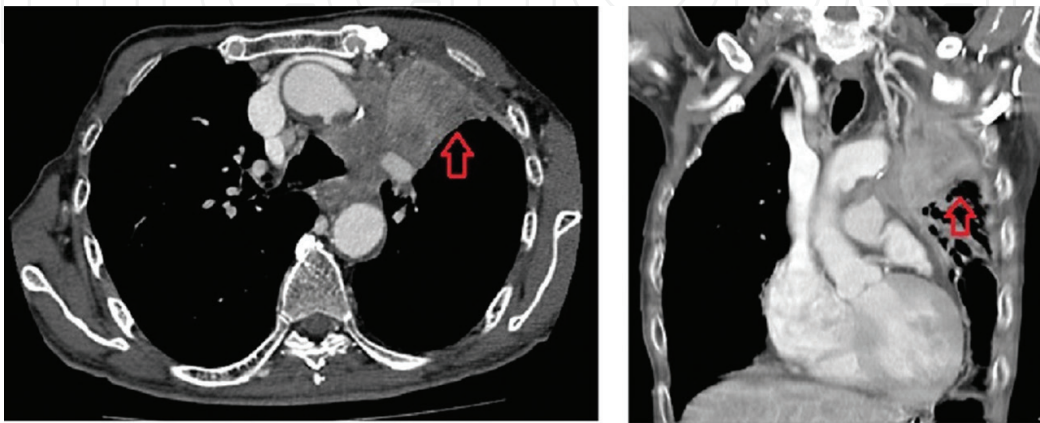**Figure 1.** Tumor invasion to chest wall.

Figure 2. Tumor over left main bronchus causing collapse of left upper lobe (red arrow).

There is rich lymphatic within the respiratory system that accounts for the high rate of nodal metastasis. The lymph node map proposed by the International Association for the Study of Lung Cancer (ISALC) in 2009 divides the lymph nodes into 14 stations and sever zones [5]. It is adopted by the latest seventh edition of AJCC and UICC Manual for N staging, with involvement of ipsilateral hila node as N1, ipsilateral mediastinal nodes as N2, and contralateral mediastinal or supraclavicular nodes as N3. Lymph nodes drainage depends on the location of tumors, with those in left upper lobe drain predominantly into subaortic node and those in right upper lobe drain predominantly into right upper paratracheal node. Middle and lower lobe tumors drain more commonly into subcarinal and lower paratracheal nodes. However, skip metastasis to mediastinal nodes bypassing hilar nodes occur in around 10–25% tumors [6]. Lymph nodes with short axis diameter ≥10 mm is considered suspicious of nodal metastasis (**Figure 3**).
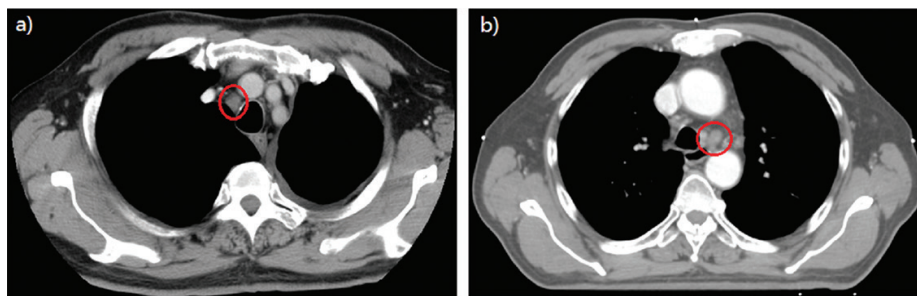

Figure 3. Enlarged mediastinal lymph node over (a) right upper paratracheal node (station 2R) and (b) subaortic node (station 5).

3. Staging and assessment

All patients with suspected lung cancer should have computer tomography (CT) of thorax with intravenous contrast for proper staging. Histological proof from primary tumors can be obtained by bronchoscopy if centrally located or by image-guided approach if peripherally located. For those patients planned for radical treatment, positron emission tomography (PET) scan is recommended to exclude any distant metastasis. Unanticipated metastasis may be detected in up to 10–20% cases. It is also more useful than CT in differentiating collapse or atelectasis from primary tumors (**Figure 4**). Any suspicious lymph nodes based on enlargement on CT or uptake in PET should be confirmed by needle technique (e.g., endoscopic ultrasound) or mediastinoscopy.
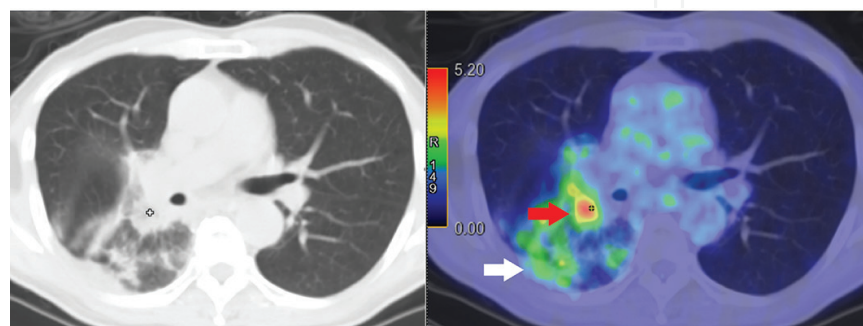

Figure 4. Use of PET in differentiating primary tumor with intense uptake (red arrow) from surrounding collapse or atetactasis (white arrow).

4. Indications of radiotherapy

4.1. Nonsmall cell lung cancer

4.1.1. Early stage I–II disease: curative treatment

Radical surgery remained the preferred treatment in early stage I–II lung cancer with 5-year overall survival rate of around 60–80%. Radical radiotherapy can be an alternative to patients who are medically unfit for surgery due to medical comorbidities or who declined surgery. Currently, there are no phase III trials to directly compare the outcomes after surgery with radiotherapy. Retrospective and historical databases showed that the long-term survival after conventional radiotherapy may be half (or even less) than that after surgery, with 5-year survival of around 20–30% in most series. But this indirect comparison is difficult due to the different population groups with more elderly, comorbidities, or poor lung function in those nonsurgical series. For elderly patients, hypofractionated scheme using 55 Gray (Gy) in 20 daily fractions is as effective as conventional radiotherapy in 2Gy per fraction.

Stereotactic body radiotherapy (SBRT) is now a newly emerging treatment option that allows delivery of a much higher radiation dose to a precise area than conventional radiotherapy. The reported local control rate in early stage lung cancer can be up to 80–90% in 2 years and is well tolerated. Therefore, it becomes the preferred radiotherapy modality for stage I lung cancer patients who are not fit for surgery. But extra care should be given when treating tumors that are centrally located around the major airways due to the potential higher complications with the hypofractionated regime.

4.1.2. Locally advanced stage III disease: curative treatment

This stage of disease was considered locally advanced either due to extensive primary tumor extension to extrathoracic structures nearby (T3 or T4) or mediastinal lymph nodes involvement (N2 or N3). It is a heterogeneous population that requires multimodality treatments. The reported 5-year survival was around 10–30%. A multidisciplinary discussion involving cardiothoracic surgeons, radiologists, and oncologists is needed to individualize and optimize the treatment plan for each patient. Patients with good performance status 0–1, no significant weight loss of >10% in the preceding 3 months and good pulmonary function (forced expiratory volume in 1 second FEV1 > 1.0 L) are candidates for radical combined modality treatment.

For potentially operable N2 disease, induction treatment with either chemotherapy alone or chemoirradiation is recommended over surgery alone. There is no solid evidence to support the superiority of either approach. Addition of preoperative radiotherapy may have the potential effect in downstaging the tumor and achieving a higher pathological complete remission rate of mediastinal disease. Special precaution should be given with its use in candidates before a planned pneumonectomy due to the higher perioperative mortalities. When preoperative radiotherapy is considered, a dose higher than 45–54 Gy in 1.8–2 Gy per fraction had not been shown to give addition survival benefit.

For infiltrative N2 or N3 (contralateral mediastinum) disease, risk of systemic micrometastases is high. Definitive chemoirradation is the commonly used approach. Addition of chemotherapy to radical radiotherapy led to a survival benefit of 5–10% at 5 years. Concomitant use of chemotherapy had a further improvement in survival by 4.5% at 5 years when compared with sequential approach, but with the expense of higher toxicities (mainly esophagitis and/or pneumonitis). Platinum-based doublet chemotherapy is the preferred regime and usually 2–4 cycles are given [7, 8]. Thus, concurrent chemoirradiation is the preferred strategy for fit patients, while sequential approach can be used for less fit patients with disease still within a treatable radical radiotherapy volume. A dose higher than 70 Gy in conventional fractionation is not recommended due to the associated higher toxicities but no added survival benefit. A continuous, hyperfractionated, accelerated radiotherapy (CHART) using 54 Gy in 36 fractions of 1.5 Gy three times per day can be considered for selected patients opting for radiotherapy alone. It had around 20% relative risk reduction in 2-year local progression rate and survival compared with conventional radiotherapy, but implementation can be challenging.

For patients with performance status 3–4, significant comorbidities and poor lung function that preclude a radical treatment approach, palliative radiotherapy may be considered for local symptoms control.

4.1.3. Metastatic stage IV disease: palliative treatment

Early radiotherapy to thorax in patients with incurable disease but no or minimal symptoms had not been shown to improve symptom control, survival, or quality of life. Hence, palliative thoracic radiotherapy can be deferred till symptoms emerged. Common indications are cough, hemoptysis, chest pain, and airway obstruction [9]. The optimal radiotherapy dose and fractionation schedule remained unclear. While there is no significant difference in symptom control with different dose schedules, a small survival improvement may be seen with higher dose radiotherapy.

For malignancy-related superior vena cava obstruction, external beam radiotherapy is effective in 60% patients with nonsmall cell lung cancers and 80% patients with small cell lung cancers [10]. Chemotherapy is another treatment option for patients with chemosensitive tumors like lymphoma, germ cell tumors, or small cell tumors. Intravascular stent insertion may be considered for patients that require rapid relief of symptoms, those who fail to response or relapse after radiotherapy.

Palliative radiotherapy can also be given to distant metastatic sites (e.g., bone, skin). Single fraction radiotherapy is as effective as longer course radiotherapy in pain and local symptom control.

4.1.4. Postoperative treatment

Adjuvant postoperative radiotherapy (PORT) helps to improve local control in patients with high risk of local recurrence after surgery, including those with pathological N2 disease and incomplete resection either microscopically or macroscopically. A careful evaluation of general conditions and remaining lung reserves is required before the start of treatment. It is not routinely given to early stage I–II disease with clear resection due to the potential detrimental

effect on overall survival from previous meta-analyses that include trials using large radiation fields and nonconformal radiation techniques. However, its role with the use of modern radio-therapy machine and conformal radiotherapy are unclear and further research is warranted.

5. Radiotherapy data acquisition

5.1. External beam radiotherapy

5.1.1. Immobilization

Patient will lie supine with arms above head holding a T-bar device and elbow supported laterally (**Figure 5**) to facilitate different beam angle entry for treatment. Knee support can be given to allow a more comfortable position when needed. Vacuum bag can be added to reduce movement if treatment time is long. For palliative setting using AP beams only, patients usually lie supine with arms beside body.
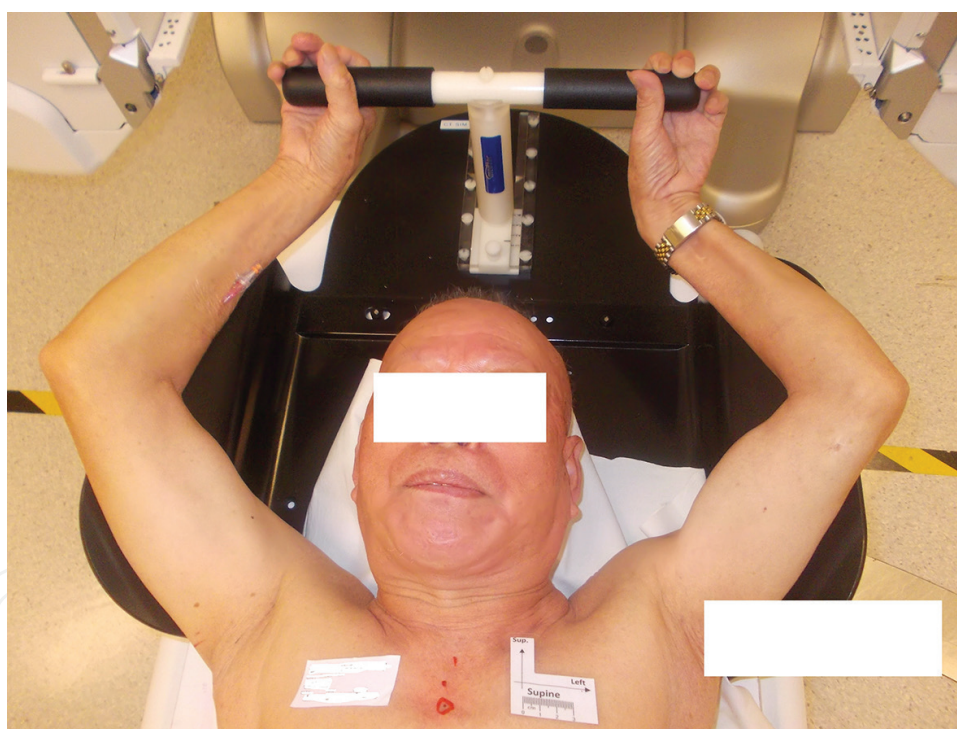

Figure 5. Immobilization for thoracic radiotherapy with T-bar and elbow support.

5.1.2. Simulation

For treatment with radical intent, computer-tomography from cricoid to lower border of L1 is needed to cover the whole lung for calculation of lung dose. Slice thickness of 3–5 mm allows better quality of images for target volume delineation. Intravenous contrast is not essential but is preferred when mediastinal disease is present so as to allow better visualization of the extent.

For treatment of palliative intent, radiation field border can be defined by simple X-ray simulation. Radio-opaque markers (e.g. lead wire) can be used to mark any clinically palpable diseases that are going to be included for radiotherapy (e.g., chest wall mass, supraclavicular lymph nodes).

To aid set-up, tattoos will be marked on beam center or isocenter, together with lateral reference points over left and right side of the body.

5.2. Stereotactic body radiotherapy (SBRT)

5.2.1. Immobilization

Patient should be immobilized in a comfortable position to avoid movement during the longer treatment length of each fraction. In this way, a supine position with arms above head immobilized by wing board and vacuum bag is commonly used (**Figure 6**).

Figure 6. Immobilization with wing board and vacuum bag for SBRT of lung cancer.

5.2.2. Breathing motion assessment and correction

Fluoroscopy can be used to visualize tumor motion. But it only allows tumor motion assessment in two dimensions and can be difficult if with indistinct border of tumors. Noncontrast four-dimensional CT (4D CT) is a better option, which is a fast scanner that acquires multiset of CT images over consecutive phases of breathing cycle. Information about patients' breathing cycle and amplitude can be recorded by infrared reflecting marker and a coupled camera (**Figure 7**). And different CT images set will be sorted according to different phases in the respiratory cycle (**Figure 8**).
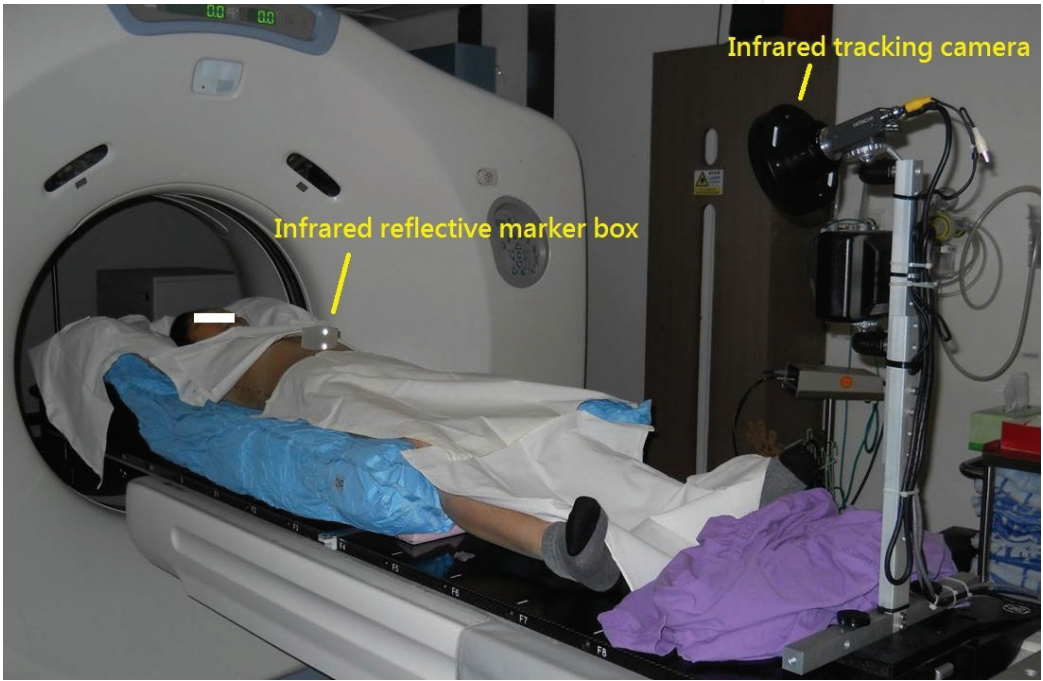

Figure 7. Infrared system including reflecting marker on patient's xiphsternum and coupled camera for tracking breathing cycle.
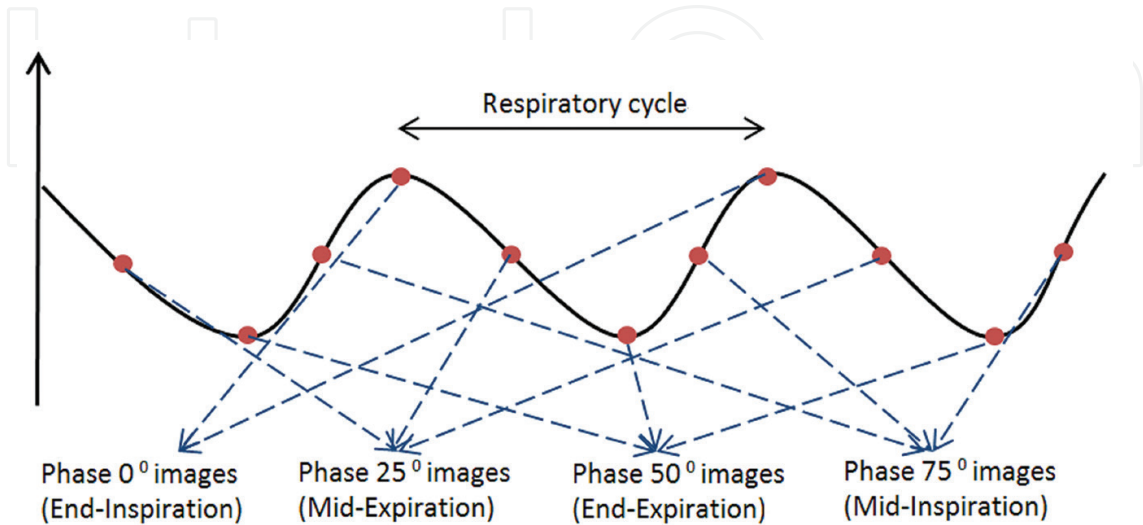

Figure 8. Sorting of 4D CT images by different phases in respiratory cycle.

Additional methods should be considered to reduce the tumor movement when it is ≥1cm, including abdominal compression, breath-hold, respiratory gating, or active breathing control. Both breath-hold and active breathing control require sufficient lung reserve to allow holding each breath for at least 20 seconds, which may be difficult for most of patients with lung cancers. Respiratory gating allows free breathing and beam on in certain phase of respiration. But it requires the use of fiducial markers to track internal tumor motion and is time consuming. Abdominal compression is the most commonly used method but reproducibility can be difficult (**Figure 9**). So the best method to be used depends on the patient's condition, tolerance, and corporation.

Figure 9. Abdominal compressor on patient's belly to reduce respiratory motion.

6. Target volume delineation

6.1. Conventional radiotherapy

Any clinical information and findings from bronchoscopy and mediastinoscopy should be gathered and correlated with diagnostic images. For postoperative cases, surgical records and pathology reports should be reviewed. And in case with doubt, discussions with surgeons and pathologists are encouraged to identify sites at risk of recurrence. Clips that are placed intraoperatively at sites with incomplete resection are useful for target identification.

An appropriate window setting should be used to delineate different targets on planning CT. Extent of primary lung tumor and mediastinal disease is best visualized by lung setting (window width 1600 and window level -600) and soft tissue setting (window width 400 and window level 20), respectively (**Figure 10**). Diagnostic imaging (e.g., CT or PET) should be coregistered with the planning of CT for contouring. PET images can help delineate area of collapse and atelectasis from tumors, but care should be taken when matching the images due to poor spatial resolution and breathing motion artifact.
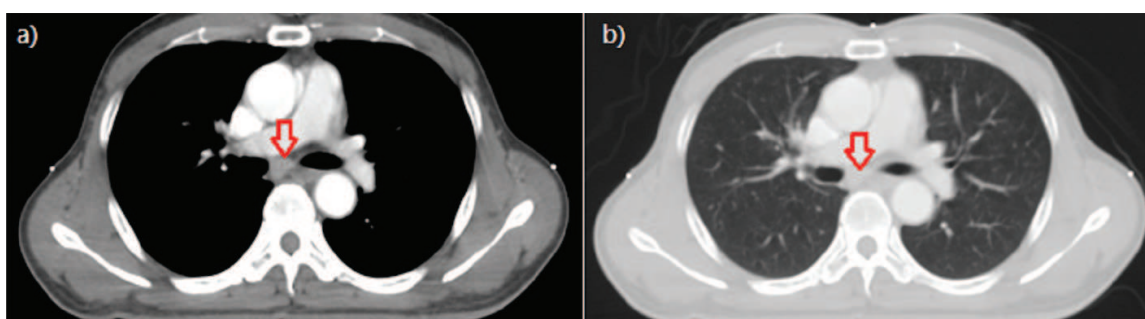

Figure 10. Soft tissue window setting (a) in planning CT to define the mediastinal lymph node (red arrow), which cannot be easily seen in lung window (b).

Gross tumor volume of primary tumor (GTV-P) is best contoured on lung window setting to include any visible tumor within lung parenchyma and the speculated border. Any local invasion to surrounding structures (e.g., chest wall, vertebra) should be included as well based on soft tissue window setting. Areas of collapse or atelectasis were excluded but can be difficult to differentiate. Input from radiologists and PET may be useful. Elective nodal irradiation is not recommended as isolated nodal recurrences are rare. So GTV of lymph node (GTV-N) will only include any pathologically confirmed lymph nodes (fine needle cytology or core biopsy) and any suspicious lymph nodes based on imaging characteristics (including short axis diameter ≥1 cm, necrotic center or PET uptake). If chemotherapy had been used before radiotherapy, all initial sites of tumor involvement should be contoured unless it exceeds a tolerable radiotherapy portal.

An isotropic margin is then added to GTV-P to cover microscopic tumor spread to form the clinical target volume (CTV-P). Usually, a 6 mm margin for adenocarcinoma and an 8 mm margin for squamous cell carcinoma are used as it had been shown to cover around 95% of microscopic tumor extension on pathological specimens [11]. Subsequent CTV-P is edited

according to the presence of natural barriers (e.g., great vessels, bone). For GTV-N, usually no additional margin is needed for CTV.

A margin from CTV to PTV (planning target volume) depends on tumor motion and daily set-up errors (**Figure 11**). Tumor motion can be quite variable from zero in cases using implanted fiducial markers in image-guided radiotherapy to certain centimeters in cases without any breathing motion control. Set-up errors are regularly measured in each department and usually within 5 mm in all directions. In common practice with free breathing treatment, a 1 cm isotropic margin is usually given to form the PTV. But a larger superior-inferior margin of 1.5 cm may be used for tumors with greater movement as long as the lung dose is within the tolerance limit.
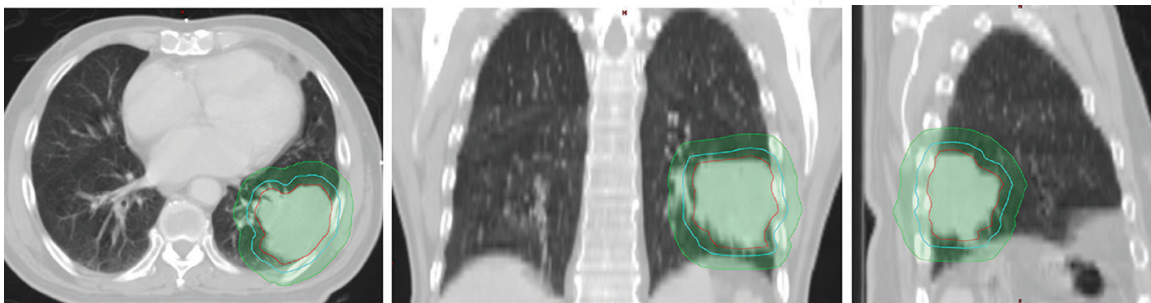

Figure 11. Target volume delineation: primary lung tumor (T) is contoured on lung window as gross tumor volume (GTV; red line); an additional 6 mm is added to form clinical target volume (CTV; blue line) to cover microscopic spread; further 1 cm margin is added to form the planning target volume (PTV; green line) to account for tumor motion and set-up error.

For palliative radiotherapy using AP beams, information about tumor extent from diagnostic imaging can be superimposed on those visible on simulator to form the GTV. And a further 1.5 cm margin from GTV can be used to define the radiotherapy field border.

6.2. Stereotactic body radiotherapy

Internal target volume (ITV) takes into account both GTV and internal tumor motion. It can be generated from the 4D CT using the maximum intensity projection (MIP) scan, maximum inspiratory, and expiratory scans, or all 10 phases of respiratory cycles (**Figure 12**). No CTV is needed. The usual CTV to PTV margin is 3–5mm, but it depends on methods of immobilization, tumor motion assessments, and treatment verification.
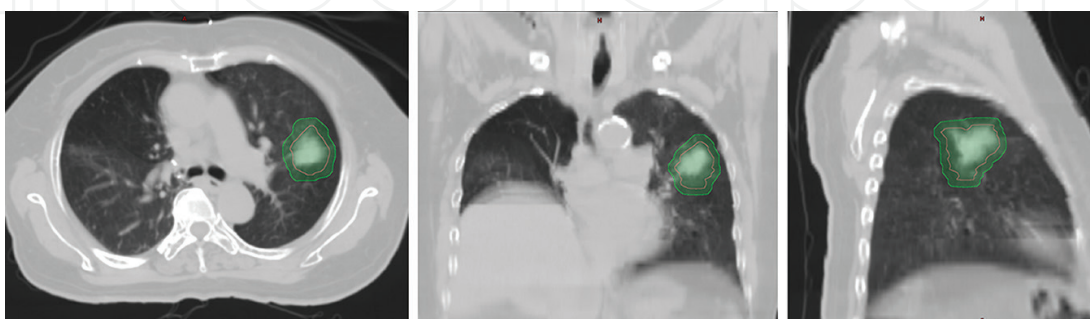

Figure 12. Target delineation on 4D CT: tumor is contoured on MIP images to form the internal target volume (ITV; red line); addition 5 mm margin was used to generate the planning target volume (PTV; green line).

7. Organs at risk delineation

Organs at risk including heart, esophagus, and spinal cord will be contoured using soft tissue window. The heart includes the whole structure within pericardial sac starting from the pulmonary artery to the apex. All layers of esophagus will be included and contoured from the cricoid cartilage to the esophagogastric junction. Spinal cord will be contoured at least 10 cm above and below PTV. For tumors over upper chest, the ipsilateral brachial plexus should also be contoured. Both left and right lungs are also contoured and then used to form a new structure called lung minus PTV after subtraction.

For SBRT, the tracheal and proximal bronchial tree should be contoured as well. Trachea will start from the level of cricoid cartilage to 2 cm above the carina, where it then continuous with the proximal bronchial tree (PBT, **Figure 13**) including the distal 2 cm trachea, main carina, bilateral main bronchi, bilateral upper lobe bronchi, lingular bronchus, intermedia bronchus, right middle lobe bronchus, and bilateral lower lobe bronchi. A 2 cm margin applied around the PTB will then be used to form a PRV (planning organ at risk volume).
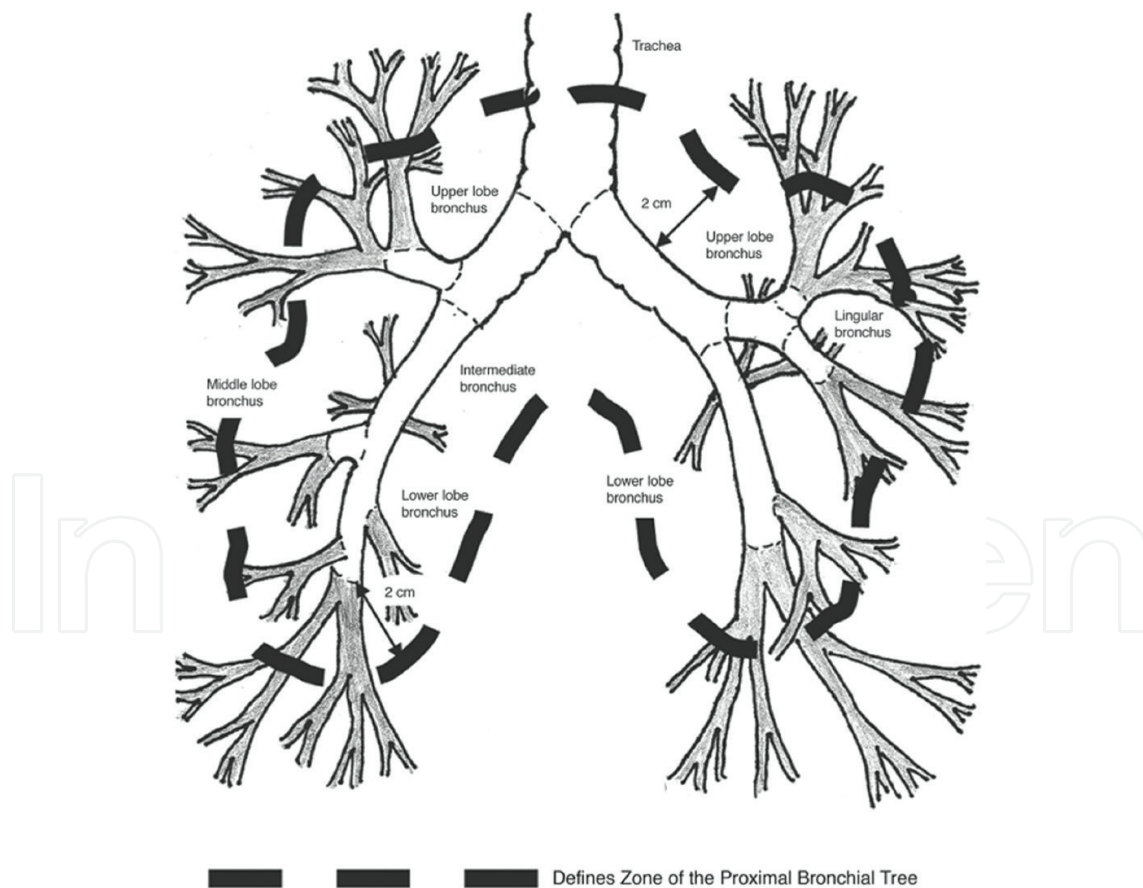

Figure 13. Definition of proximal bronchial tree.

8. Radiotherapy planning

For radical treatment, three-field conformal radiotherapy is most commonly used. The choices of beam numbers and beam angles depend on the location of the tumor and proximity to OARs. For early stage I–II tumors with lateralized target volume, a lateral, anterior, and posterior oblique beams are usually chosen to reduce irradiate contralateral lung (**Figure 14**).
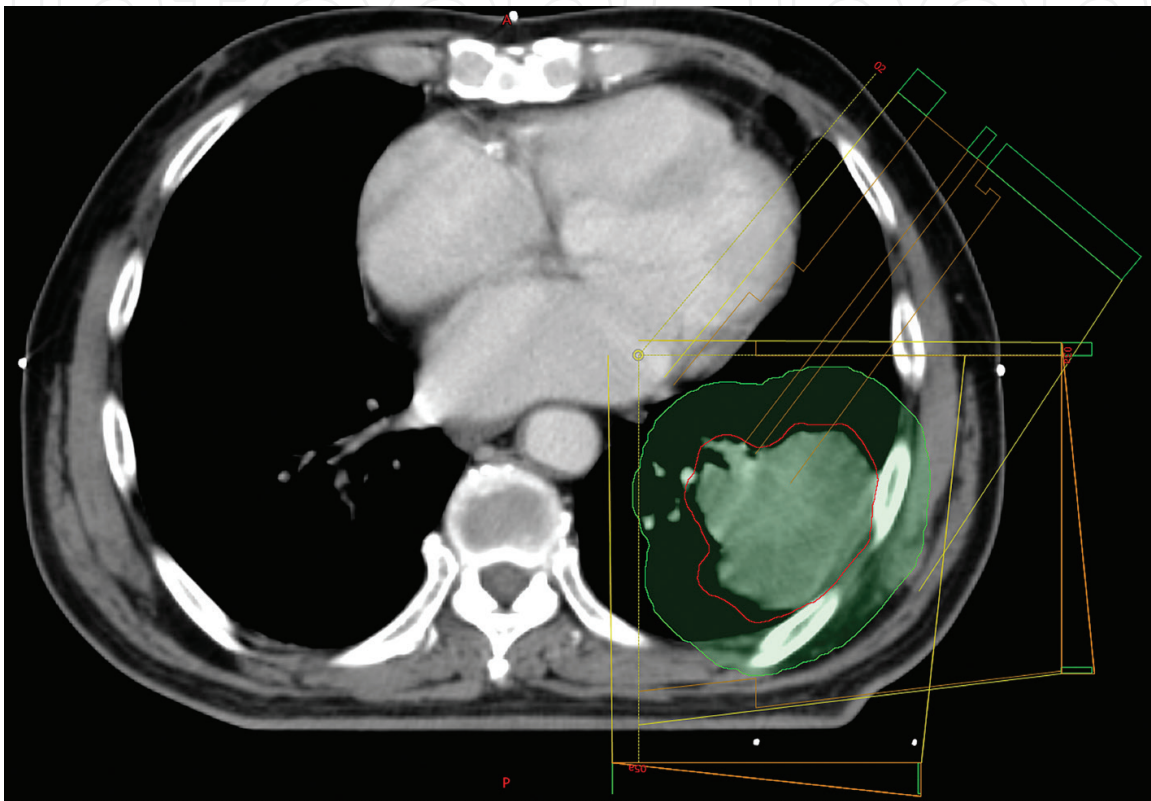

Figure 14. Beam arrangement in a three-field conformal radiotherapy for early stage lung cancer (red line = GTV; green line = PTV).

For more advanced stage disease with tumor involvement to mediastinum or across midline, the above three-field technique using ipsilateral beams only may not give good dose coverage to target, and addition of contralateral beam will increase total lung dose. In such case, two phases treatment should be considered. First phase will treat the mediastinum using AP beams shaped by multileaf collimator (MLC), while the second phase will use conformal technique to give adequate coverage to all the target volume. With this approach, total lung dose can be reduced but OARs near midline (e.g., esophagus, spinal cord) will receive higher dose.

For palliative radiotherapy, anterior and posterior fields modified by MLC are usually used with dose prescribed to midplane. Energy of photon beam used will depend on separation at the center of the field.

Radiotherapy plans should be carefully evaluated using dose-volume histogram (DVH). Optimal plan should aim at 95% PTV receiving at least 100% of the prescribed dose and 99% PTV receiving a minimum of 90% of the prescribed dose. For OARs, commonly used dose constrains for lung minus PTV is V20 (volume receiving >20 Gy) below 35%, preferably below 30%. However, a tighter constrain to reduce the risk of radiation pneumonitis should be considered when there is presence of other risk factors including preexiting lung disease and concurrent use of chemotherapy. Another frequently used limit is the mean lung dose below 20 Gy. The dose constrains for other OARs are maximum dose to spinal cord less than 45 Gy and heart V20 less than 40 Gy. Care should be given to avoid irradiation of more than 10 cm length of the esophagus due to higher long-term risk of stricture.

For SBRT, either intensity-modulated radiotherapy using 6–8 fields (IMRT) or rapidarc therapy is recommended to deliver a high and conformal dose to a precise area (**Figure 15**). Dose to skin should be minimized to avoid cutaneous and subcutaneous toxicities. Recommendations to other OARs can be made reference to that published by ROSEL study and RTOG 0813 study.
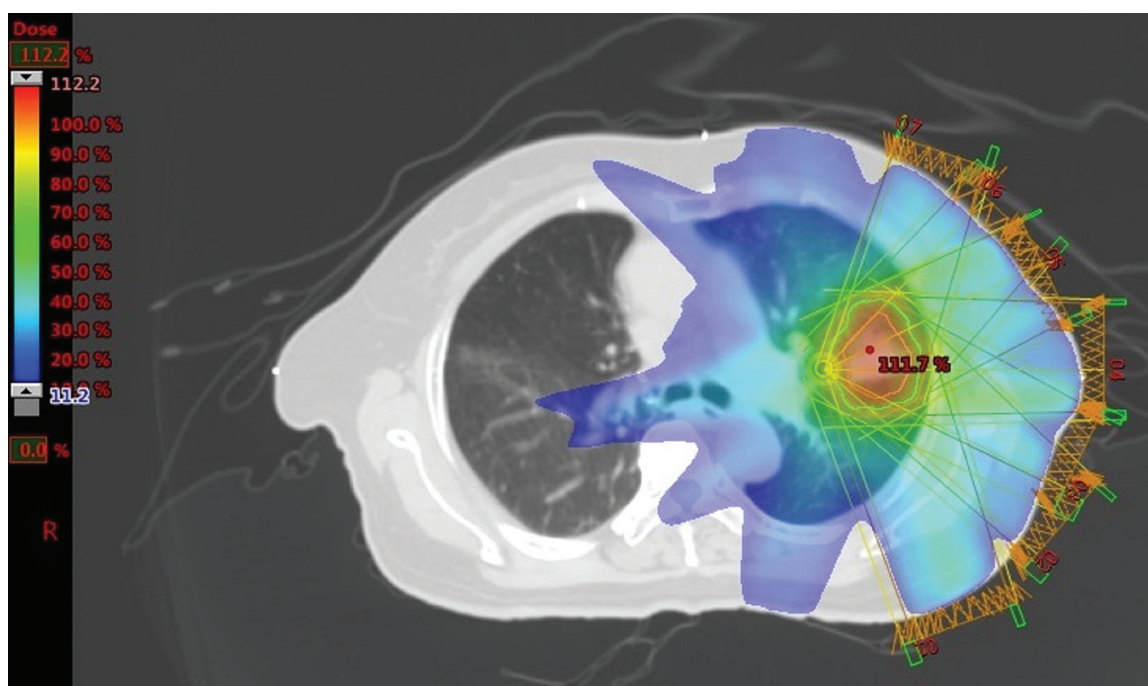

Figure 15. Beam arrangement and dose color wash from SBRT for lung cancer using IMRT technique.

9. Radiotherapy dose and fractionation

9.1. Radical treatment

9.1.1. Early stage T1-3N0 disease and fit patients: use SBRT

- For peripherally located tumor: 54 Gy in three fractions or 60 Gy in five fractions, alternate day treatment over 1–2 weeks (more conservative schedule is recommended if PTV is in contact with chest wall to avoid rib toxicities).

- For centrally located tumor (defined as GTV within 2 cm from proximal bronchial tree): 50 Gy in 10 fractions, alternate day treatment over 2 weeks.

9.1.2. Other early stage I–II disease: use conventional radiotherapy

- 60–70 Gy in 30–35 daily fractions over 6–6.5 weeks.

- Consider hypofractionated regime of 55 Gy in 20 daily fractions over 4 weeks if elderly.

9.1.3. Locally advanced stage III disease: use conventional radiotherapy

- For preoperative treatment (with or without chemotherapy): 45–54 Gy in 1.8–2 Gy per fraction over 5–6 weeks.

- For definitive treatment with concurrent chemotherapy: 60–66 Gy in 30–33 daily fractions over 6–6.5 weeks (consider treat up to 70 Gy in 35 daily fractions over 7 weeks if no chemotherapy given and within lung dose tolerance).

9.2. Adjuvant treatment

- For complete resection: 50 Gy in 25 daily fractions over 5 weeks.

- For incomplete resection: 60 Gy in 30 daily fractions over 6 weeks (consider boost up to 66 Gy in 33 daily fractions if gross residual disease).

9.3. Palliative treatment

- For PS 0–1 and life expectancy >6 months: 30 Gy in 10 daily fractions over 2 weeks (consider 39 Gy in 13 daily fractions over 2.5 weeks if spinal cord not within treated volume).

- For PS ≥ 2: 20 Gy in five daily fractions over 1 week or 10 Gy single fraction.

10. Treatment verification and delivery

Portal images by electronic portal imaging device on treatment machines are taken on first 3 days on treatment and then weekly afterwards. These are compared and registered with digitally reconstructed radiography (DRR) from CT simulations to allow offline corrections. For SBRT, cone beam CT by onboard imaging on treatment machine is done daily to allow online correction before delivery of each fraction of treatment.

During treatment period, patients should be reviewed at least once by radiation oncologists for assessment of any acute radiation side effects. Mild chest symptoms like cough or dyspnea are common but concomitant chest infection should be excluded if symptoms worsened. Dysphagia can occur due to esophagitis which usually start at around third week. Adequate analgesics and diet advice should be given to minimize severity and the impact on nutrition or weight loss.

11. Follow-up

After radical treatment, CT of thorax and upper abdomen should be done 3 monthly in the first 2 years, then half yearly till 5 years, and then annually to evaluate disease status. Long-term toxicities especially on lung function and esophageal stricture should be regularly reviewed and managed accordingly.

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