IMAGE GUIDED RADIOTHERAPY IN NON SMALL CELL LUNG CANCER (NSCLC)

Essay

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INTRODUCTION

Lung cancer represents a major health hazard worldwide. In Western countries, it is the second most common cancer in women behind breast cancer, and the third most accounts for approximately 80% of all lung cancer cases. Whereas the mortality of prostate and colon cancers decreased considerably during the past decade, the cure rates for lung cancer remained essentially unchanged and range from 10 to 14% *(Spira and Ettinger, 2004).*

Although non-small cell lung cancer (NSCLC) has the potential for cure with surgical resection, unfortunately, less than 15% of all patients and less than 25% of those who present with intrathoracic localized disease are candidates for curative surgical resection *(Hayakawa, 2003).*

Radiation therapy (RT) is recognized as one of three major treatment modalities in the management of cancer. The ratio of newly diagnosed cancer patients treated by RT is around 60% in developed countries. The only exception is Japan where only 25% of patients

receive RT. The ratio has increased by 10% in the last decade, and it is estimated that it will be up to 40% in 2015 *(Teshima et al., 2008)*.

Until the late 70s, before Computed Tomography scan (CT) became available, clear delineation of tumors from healthy tissues was difficult to achieve, and radiation treatment of tumors involved irradiation of neighboring healthy tissues at the highest tolerable dosage. Since the introduction of CT, evolution in imaging has occurred and treatment planning involves delineation on computed tomography scans of target issues to be irradiated and of healthy tissues to be spared *(Ballini et al., 2010).*

A goal of cancer treatment is to improve tumor control while minimizing normal tissue toxicity *(Okunieff et al., 2009).*

Conventional photon radiotherapy for lung cancer is associated with about 20%-30% local tumor control *(Curran et al., 2003).*

Intensity-modulated radiotherapy (IMRT) allows one to achieve a better dose conformality to the PTV (planning target volume), compared to 3D conformal

photon therapy, especially for irregularly shaped concave target volumes (*Seco et al., 2007).*

Missing the target as a result of tumor motion has been considered one of the main reasons for local failure *(Chang et al., 2008).*

Current EPID (electronic portal imaging), based verification of 3D conformal treatment only visualizes bony anatomy and therefore cannot identify movement of internal organs. These individuals are therefore at risk of geographical miss of the target if it has moved significantly from the initial localization computed tomography (CT) scan position *(Dobbs, 2006).*

Researchers have reported that ~40% of lung tumors move >5mm and that 10-12% move >1cm (*Lui et al., 2007).*

The opportunity to deliver effective high radiation doses while sparing critical neighboring organs increased the need for more precise target volume localization and for geometrical contouring before and during irradiation. Organs and tumors, in fact, show an important degree of mobility and tumor masses tend to undergo variations during the course

of the radiation treatment. A real breakthrough is thus represented by the Image Guided Radiation Therapy (IGRT) technology *(Ballini et al., 2010).*

Image-guided radiotherapy (IGRT) uses online imaging at treatment delivery in order to increase the probability that radiation is delivered as closely as possible to the original plan *(Dawson and Jaffray, 2007).*

For simplicity, an ideal IGRT system should have three essential elements:

- 3D volumetrics of soft tissues including tumors,
- Efficient acquisition and comparison of the 3D volumetrics, and
- An efficacious process for clinically meaningful intervention.

(Ling et al., 2006)

AIM OF THE WORK

The aim of this work is to overview the recent advances in technology that improved radiation planning and delivery in Non small cell lung cancer (NSCLC) discussing in depth the emerging technique of image guided radiotherapy (IGRT) in lung cancer patients treated definitively with radiation.

ANATOMY

Gross Anatomy

The right lung has three lobes as a result of a second fissure, the horizontal fissure, which separates the middle lobe from the upper lobe and extends from the anterior margin into the oblique fissure *(Boyden, 1955)*.

The left lung is composed of two lobes: an upper and lower lobe *(Boyden, 1955)*.

The lingular portion of the left upper lobe corresponds to the middle lobe on the right.

The trachea enters the superior mediastinum and bifurcates approximately at the level of the 5th thoracic vertebra *(Gray's Anatomy, 1995)*.

Functional Anatomy

- The alveolar epithelium has two types of cells: type I and type II pneumocytes.
- Type I cells are squamous and have little capacity to respond to or repair damage. The type II cells synthesize and secrete surfactant, the lipid-protein complex that prevents alveoli collapse by

reducing surface tension at the air alveolar interface. Type II cells are also the progenitor cells both during normal cell turnover and after damage.

- Other cells that normally present in the lung are pulmonary macrophages and fibroblasts, both of which are critical for pulmonary repair after damage *(Komaki et al., 2005).*

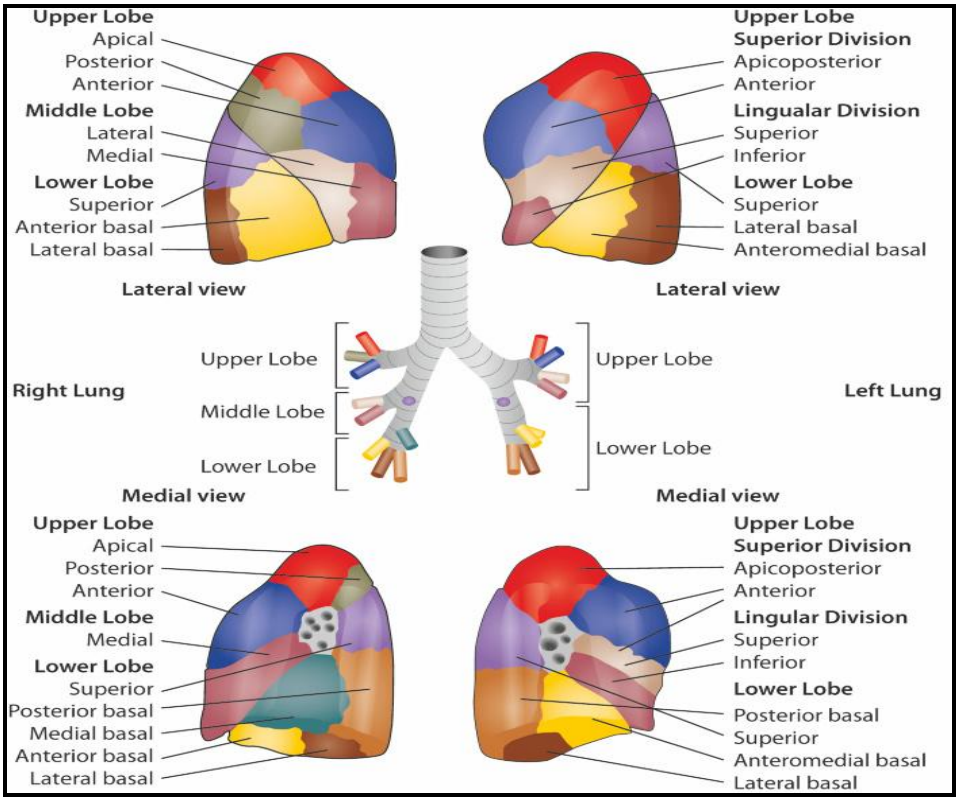

Fig. (1): Anatomy of the lung *(Komaki et al., 2005)*.

Lymphatic Drainage

- The lymph from the right upper lobe flows to the tracheobronchial lymph nodes. The lymph from the left upper lobe flows not only to the venous angle of the same side, is but also to the venous angle of the opposite superior mediastinum.
- The right and left lower lobe lymphatics drain into the subcarinal nodes and from there to the right superior mediastinum (the left lower lobe also may drain into the left superior mediastinum) and directly into the inferior mediastinal lymph nodes.
- The intrapulmonary lymph nodes are situated within the lung: the subsegmental nodes, the segmental nodes, and the lobar or interlobar nodes. They are located either at the bifurcation of the bronchi or close to the angle formed by the division of the arteries and veins.
- Hilar nodes are located at the pulmonary hilum outside of the pleural reflection.
- From a radiotherapeutic viewpoint, the bronchopulmonary lymph nodes, situated either along the lower portions of the main bronchi (hilar

lymph nodes) or at the bifurcations of the main bronchi into the lobar bronchi (interlobar nodes), are considered hilar nodes *(Borri, 1952)*.

- The mediastinal lymph nodes are divided into two groups: superior, located above the carina, including the upper paratracheal, pretracheal, retrotracheal, lower paratracheal nodes (azygos nodes), and a group of nodes located in the aortic window; and inferior, situated in the subcarinal region and inferior mediastinum including the subcarinal, paraesophageal, and pulmonary ligament nodes. The peritracheobronchial nodes are located around the trachea and the main bronchi.
- In the case of chest wall involvement, there is a risk of spread to the intercostal nodes located close to the intercostal vessels and nerves. Paravertebral nodes situated either lateral to or in front of the vertebral bodies may be located along the pathway of the intercostal lymph collector *(Komaki et al., 2005)*

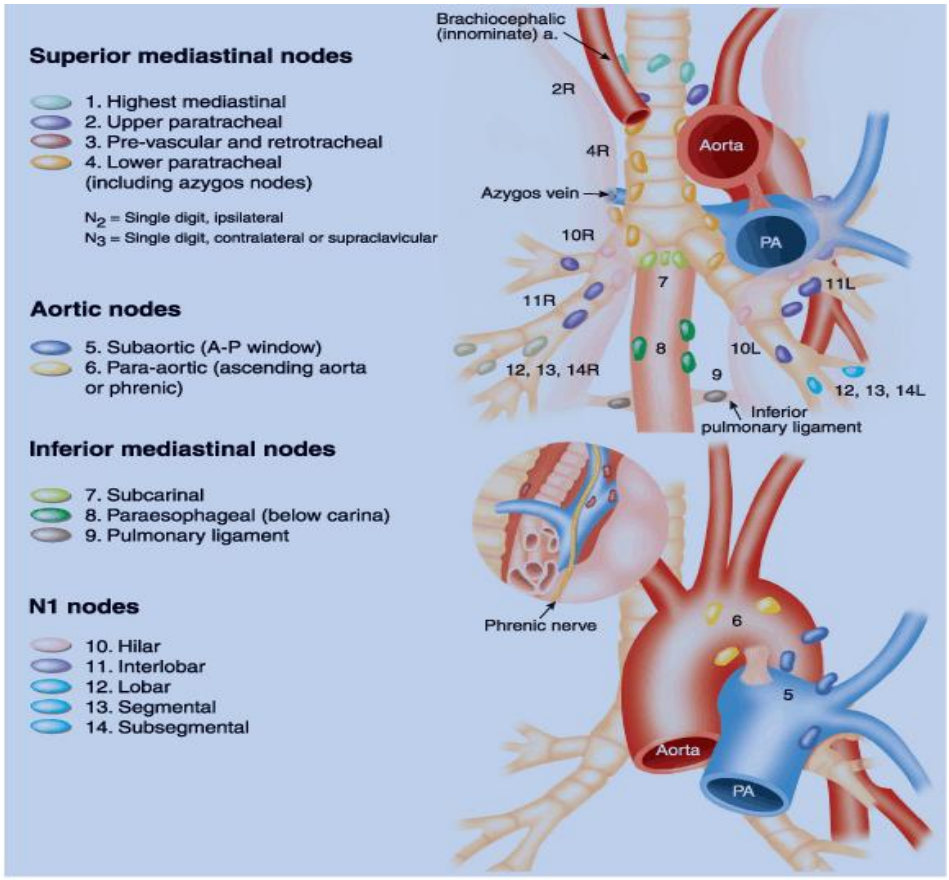

Figure (2) Lymph node stations of the pulmonary system. Stations 1–9 are designated N2 nodes; stations 10–14 are designated N1 nodes *(Mountain and Dresler., 1997)*

Pathology

Three major types of tumors are included under the NSCLC category: adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma.

Adenocarcinoma is currently the most common type of NSCLC, accounting for approximately 40% of cases. Of all the types of lung cancer, adenocarcinoma is most likely to occur in nonsmokers or former smokers. In addition, it is the most common tumor in women. Typically, adenocarcinoma presents as a small peripheral lesion that has a high propensity to metastasize to both regional lymph nodes and distant sites. Because of the tendency of the primary tumor to occur in peripheral locations, it frequently produces no symptoms ***(Robert et al., 2003)***.

Bronchoalveolar adenocarcinoma: During the last decade, it has become apparent that the incidence of the bronchoalveolar type of adenocarcinoma is increasing. This tumor appears to rise from type 2 pneumocytes, and it may present as a pneumonic infiltrate, as multiple nodules scattered throughout the lung, and occasionally, as a single nodule ***(Robert et al., 2003)***.

Squamous cell tumors comprise approximately 30% of all cases of lung cancer. This tumor tends to

occur in a central location and tends to spread to regional lymph nodes; it is the most likely of all the lung cancers to remain localized and to cavitate. In fact, autopsy studies have shown that about 15%- 30% of patients with squamous cell carcinoma may expire from local disease without evidence of distant metastases *(Robert et al., 2003)*.

Large-cell carcinoma

Accounts for approximately 10%-15% of all lung cancers. It tends to be a relatively large peripheral lesion and, like adenocarcinoma, it has a high propensity to metastasize to regional lymph nodes and distant sites *(Robert et al., 2003)*.

Carcinoids:

These neoplasms, which contain neurosecretory granules and neural filaments, are relatively rare. The classic carcinoid tumor presents as an endobronchial lesion, tends to be quite indolent, and rarely metastasizes. Some carcinoid tumors spread to regional lymph nodes and distant sites. These tumors are classified as atypical carcinoids or anaplastic carcinoids. More recently, some investigators have

suggested that the more aggressive carcinoids be called well-differentiated neuroendocrine carcinoids *(Robert et al., 2003)*.

Tab (1): WHO/IASLC Histological Classification of NSCLC

Squamous cell carcinoma	Papillary.
	Clear cell.
	Small cell.
	Basaloid.
Adenocarcinoma	Acinar.
	Papillary.
	Bronchioloalveolar carcinoma : ➢ Nonmucinous. ➢ Mucinous. ➢ Mixed mucinous and nonmucinous or indeterminate cell type.
	Solid adenocarcinoma with mucin.
	Adenocarcinoma with mixed subtypes
	Variants.
	Well-differentiated fetal adenocarcinoma.
	Mucinous (colloid) adenocarcinoma.
	Mucinous cystadenocarcinoma.
	Signet ring adenocarcinoma.
	Clear cell adenocarcinoma

Large cell carcinoma.	Variants.
	Large cell neuroendocrine carcinoma (LCNEC).
	Combined LCNEC.
	Basaloid carcinoma.
	Lymphoepithelioma-like carcinoma.
	Clear cell carcinoma.
	Large cell carcinoma with rhabdoid phenotype.
Adenosquamous carcinoma.	Carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements.
	Carcinomas with spindle and/or giant cells.
	Spindle cell carcinoma.
	Giant cell carcinoma.
	Carcinosarcoma.
	Pulmonary blastoma.
Carcinoid tumor	Typical carcinoid.
	Atypical carcinoid.
Carcinomas of salivary gland type.	Mucoepidermoid carcinoma.
	Adenoid cystic carcinoma.
	Others.
Unclassified carcinoma.	