Advances in Radiotherapy Techniques in NSCLC

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Radiation therapy plays a crucial role in the management of lung cancer. However, with two-dimensional (2-D) radiotherapy planning, the local control was poor and dose escalation was associated with increased toxicity, particularly when concurrent chemotherapy was given.

Three-dimensional (3-D) conformal radiotherapy (3-D CRT) might improve local control and possibly survival compared with 2-D therapy in stage I non small cell lung cancer (NSCLC).

In addition, dose-escalation phase I/II clinical studies have shown promising clinical outcomes in stage III NSCLC, with improvements in survival and toxicity, with the use of 3-D CRT, although a phase III study is needed to confirm the results. The three main reasons for local failure after radiotherapy are (1) geographic misses due to inadequacy of imaging tools for staging and radiotherapy planning; (2) geographic misses due to respiratory tumor motion during radiation delivery; and (3)inadequate radiation dose because of the potential for significant toxicity. Image-guided radiotherapy (IGRT), particularly radiotherapy planning based on positron emission tomography/computed tomography (PET/CT), consideration of individualized tumor motion with four-dimensional (4-D) CT, and on-board imaging-guided adapted radiotherapy during the course of treatment may allow more accurate tumor targeting and reduce side effects. IGRT with radiation dose escalation or acceleration could significantly improve clinical outcomes for patients with lung cancer. For example, image-guided stereotactic body radiotherapy (SBRT) has been shown in phase II clinical trials to improve local control and survival in early-stage NSCLC compared with historical data, and intensity-modulated radiotherapy (IMRT) may be better tolerated than 3-D CRT. As information about IGRT for lung cancer continues to emerge, standard" radiotherapy approaches for patients with NSCLC are evolving. Guidelines and step-by-step techniques for the use of IGRT in mobile lung cancers are needed to implement IGRT into daily clinical practice. Recent developments in image-guided radiotherapy are ushering in a new era of radiotherapy for lung cancer. Positron emission tomography/computed tomography (PET/CT) has been shown to improve targeting accuracy in 25 to 50% of cases, and four-dimensional CT scanning helps to individualize radiotherapy by accounting for tumor motion. Daily on-board imaging reduces treatment set-up uncertainty and provides information about daily organ motion and variations in anatomy.

Image-guided stereotactic radiotherapy can achieve local control rates exceeding 90% through the use of focused, hypofractionated, highly biologically effective doses. These novel approaches were considered experimental just a few years ago, but accumulating evidence of their potential for significantly improving clinical outcomes is leading to their inclusion in standard treatments for lung cancer at major cancer centers.

Image-Guided Target Volume Delineation

Gross Tumor Volume

The pulmonary extent of lung tumors should be delineated on pulmonary windows and level settings in CT images, and the mediastinal extent of tumors should be delineated using mediastinal windows and level settings. In general, a lymph node larger than 1 cm in its shortest dimension on CT is considered positive, because the risk of involvement is more than 15%. Functional imaging such as (FDG)-PET is quite important for disease staging and radiation treatment volume delineation in NSCLC, particularly in stage III disease. In particular, FDG-PET can help to categorize suspected mediastinal and hilar lymph node adenopathy and distinguish benign collapsed lung tissue from tumor. Currently, a standard uptake value (SUV) equal to or higher than 2.5 is suggested as a threshold. However, the SUV is determined not only by the presence of cancer but also by the size of the lesion, presence of inflammation, timing of imaging after injection of 18F-FDG, blood glucose level, etc. FDG-PET scanning usually can only detect cancer lesions larger than 5 to 10 mm. For smaller lesions, clinical judgment should be applied. Inflammation can cause false positive findings on FDG-PET scans, and biopsy is recommended in the event of questionable findings. Pre- and post treatment SUVs of FDG-PET were found to be predictive of survival in NSCLC. Recent clinical data have also shown that in NSCLC treated with standard concurrent chemoradiotherapy, an SUV higher than 13.8 was associated with a local recurrence rate of 65.5% compared with a rate of less than 25% in lesions with an SUV less than 13.8.

Tumor Motion Consideration

A major obstacle to radiotherapy target delineation has been respiration-induced target motion (also known as intrafractional tumor motion), which can add

considerable geometrical uncertainty to the radiation treatment. Such motion requires enlargement of the treatment field portals to cover the movement of the tumor during treatment. The development of 4-D CT with multislice detectors and faster imaging reconstruction has facilitated the ability to obtain images while patients breathe and to assess organ motion. 4-D CT involves acquiring over-sampled CT information and correlating these data with information about the respiratory cycle.

4-D CT-Based ITV

When 4-D CT is available for treatment planning, the use of a new concept called internal gross tumor volume IGTV, which is the envelope of the GTV throughout its motion during respiration. Delineating the IGTV from 4-D CT images involves outlining the tumor volume on the expiratory phase of the 4-D images and registering the outline on other phases of the images to create a union of target contours enclosing all possible positions of the target. 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. In this case, the ITV should consist of the IGTV plus a margin to account for microscopic disease (8 mm). Even with 4-D CT, the free-breathing simulation is only a snapshot and a single stochastic sampling of the patient's breathing.

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 .

Image-Guided Stereotactic Body Radiotherapy

The conventional radiotherapy dose (60–66 Gy) for patients with early-stage NSCLC is associated with a local recurrence rate of more than 50%. Phase II clinical studies have shown that hypofractionated SBRT provides promising local control rates (more than 85%) and survival rates with minimal toxicity in patients with stage I (T1–2 N0 M0) or select stage II (T3 N0 M0) NSCLC because of higher biologically effective dose (BEDs) and more accurate targeting. According to Onishi et al., BEDs of 100 Gy or more are associated with better local control (91.9 Vs. 73.6%) and survival rates (88.4 Vs. 69.4%) than are BEDs of less than100 Gy. However, the optimal dose regimen for SBRT is controversial.

Peripheral lesions can be subjected to higher BEDs, such as 60 Gy in three fractions developed by Dr. Timmerman' group (current RTOG phase II clinical trial regimen), but treatment of centrally located lesions with such a high-BED regimen can be associated with considerable long-term toxicity.

Because of the significantly higher fraction size used in SBRT, IGRT is crucial for optimal target coverage and sparing of normal structures.

Image-Guided Intensity-Modulated Radiation Therapy

The use of IMRT for lung cancer has been delayed because of concerns that it may deliver low, yet damaging, doses to larger volumes of normal lung tissue than does conventional 3-D CRT. Moreover, tumor movement due to respiration introduces another level of complexity to both the IMRTdosimetry and the technique used. Virtual clinical studies were conducted to compare IMRT with 3-D CRT with respect to target dose, tumor conformity, and normal tissue sparing in patients with early stage and locally advanced NSCLC. IMRT may be more suitable than 3-D CRT treatment planning for patients with advanced-stage disease with large GTVs and thus greater volumes of normal lung exposed to irradiation. Using IMRT, the median absolute reduction in the percentage of lung volume irradiated to more than 10 Gy was 7% and that irradiated to more than 20 Gy was 10%. The volumes of the heart and esophagus irradiated to about 50 Gy and the volume of normal thoracic tissue irradiated to more than 10 to 40 Gy were also reduced using the IMRT plans. A marginal increase was noted in the lung volume exposed to more than 5 Gy (V5) in the IMRT plans in half of the patients. V5 was found to be correlated with lung toxicity .To reduce the potential for delivering low doses less than 10 Gy to normal lung and to educe beam delivery time, the use of fewer beam 5–7 beams is suggested. Although IMRT may be effective in reducing normal tissue toxicity and improving tumor coverage, its high dose gradient and conformity require high levels of precision in dose delivery and tumor localization. The complexity introduced by tumor motion must also be recognized when using IMRT, and 4-D CT planning is recommended. Unlike 3-D CRT, IMRT treats only a portion of the target volume at a particular time. A great deal of concern has been expressed as to whether target motion and collimator motion during IMRT delivery have substantial interplay, thus degrading the planned dose distributions. For IMRT to be feasible and more effective in treating NSCLC, motion-reduction techniques such as breath-holding and tumor tracking should be explored further. Preliminary clinical studies indicate that IMRT may reduce toxic effects in normal tissue in selected patients, particularly for those with tumors that movement can be controlled to be less than 5 mm, such as in the case of a superior sulcus tumor with chest wall/vertebral body involvement, and may allow further dose escalation.