Review Article

Innovative technologies in thoracic radiation therapy for lung cancer

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Abstract: Radiation therapy plays a major role in the cure of patients affected with lung cancer, both in early and locally advanced disease. Local control and survival rates are still poor, even with the best combination with chemotherapy and/or targeted agents. The recent technical advances in radiotherapy changed the planning and delivery processes, enabling radiation oncologists to modify treatment schedules towards further dose intensification, while opening a new scenario for future clinical studies. In this paper we briefly review the major technical changes in the field of thoracic radiotherapy for primary lung tumors and their potential in improving clinical outcomes.

Key Words: lung cancer; radiotherapy; image-guided radiotherapy; intensity modulated radiotherapy

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Introduction

Approximately 70% of patients affected with lung cancer are diagnosed in advanced stage, with only 25-30% candidate for surgery for early stage presentation. Radiation therapy represents, in combination with chemotherapy, the most important treatment option for patients with inoperable locally advanced non-small cell lung cancer (NSCLC), and a milestone in the combined treatment of limited stage small-cell lung cancer. Despite progresses, local control rates achievable with standard thoracic radiotherapy remain unsatisfactory. Based on the classical definition of Freedom from Local Progression (on radiological imaging), a loco-regional control probability of approximately 40% is expected with a standard combination of concurrent chemo-radiotherapy in stage IIIA-B NSCLC, even if in older reports, evaluating the pathological response in bronchoscopy, the local control rates were as low as 20% (1). The expected local control rate of conventional radiotherapy for stage I inoperable tumors is in the range 30-45%, as shown by epidemiological studies (2).

A major limit for conventionally fractionated conformal radiotherapy was the inevitable exposure of high volumes of normal tissues to high doses, with low tolerance and the consequential need of lowering total doses received by the target structures. The delivery of very high biologically effective doses (by dose-escalation, acceleration or altered fractionation) plays a key role in enhancing tumor response and increasing local control (3,4), and there is an indirect evidence on the impact of increased local control on better overall and progression-free survival, as shown by previous experiences and confirmed by recent studies (5). In the last years, important technological advances in staging, imaging and radiotherapy planning and delivery (the incorporation of functional imaging in target volume definition, 4D CT, IMRT, IGRT and adaptive radiotherapy) lead towards an intensification of thoracic radiotherapy, as a consequence of a better sparing of normal structures such as spinal cord, esophagus or lungs.

Aim of this short review is to summarize the recent technical advances in the field of thoracic radiotherapy that could lead to better local control rates, lower toxicity and potentially better survival outcomes.

PET-CT in target volumes definition and response assessment

Diagnostic imaging has a major role in radiotherapy treatment planning, by permitting a correct delineation

of target volumes and organs at risk. Until recently, the only imaging method used to define and contour the volumes of interest was Computed Tomography, in most Centers performed without intravenous contrast medium. One of the limits of CT consists in its low sensibility and specificity in detecting the possible involvement of thoracic lymph nodes, with a significant inter-observer variability in defining the correct disease extension. Moreover, several conditions such as chronic obstructive lung disease, cavitation, pleural fluid, necrosis and atelectasis can obscure the exact boundaries of the tumor on CT, inducing errors in measured tumor volume and/or diameter size.

Two principal technical advances make now possible a more precise definition of the targets: one is represented by the possibility offered by many commercial software to perform advanced image fusion with deformable protocols, creating hybrid images between the diagnostic CT performed in Radiology Departments and the planning CT performed in Radiation Oncology Departments. The use of these tools increases the precision in delineation of the target, particularly for metastatic lymph nodes. The second and probably most important innovation is represented by the integration of FDG-PET imaging in the radiation therapy treatment planning process. The sensibility of FDG-PET in staging, both for NSCLC and SCLC, is very high, with values around 90%. Specificity is also high, with negative and positive predictive values of respectively 95% and 74%. Toloza *et al*. in their meta-analysis on studies investigating the role of PET in lung cancer staging reported a sensibility and specificity for mediastinal involvement of 84% and 89%, while CT alone is able to correctly identify metastatic lymph nodes with a sensibility of 57% and a specificity of 84% (6). Moreover, FDG-PET has a very high negative predictive value when evaluating the involvement of N3 stations (96%), approximately the same as mediastinoscopy (6).

The introduction of CT-PET hybrid machines made possible image fusion between high spatial resolution CT images and functional information from FDG-PET scan: the same paradigm has been extensively applied in radiation oncology by fusing FDG-PET images with planning CT images. This makes possible a unique opportunity for target delineation by merging anatomical and functional data. Several studies conducted in this field underlined that there is a significant variation in radiotherapy target volumes when PET images are integrated in the planning process. PET could improve the accuracy of GTV definition for radiation treatment planning, as shown by Munley *et al*. in a study where a pre-RT PET scan was able to modify the extension of the target volumes in approximately 15% of cases (7). Other studies showed how the volumes defined with the integration of FDG-PET with CT in approximately one third of patients affected with NSCLC can be very different if compared with volumes defined on CT scan alone (8). The integration of FDG-PET can also significantly reduce uncertainties and inter-observer variability in tumor delineation (9-11). In the majority of cases, these modifications lead to an increase of treated volumes secondary to an extension of mediastinal involvement, as evidenced by Erdi *et al*. (12). A very recent study also showed that the maximum diameter derived from CT-based delineation was overestimated compared to pathology, especially for large tumor diameters, while PET-based tumor delineation methods provided maximum diameter sizes in closer agreement with pathology, making even more attractive the possibility to include FDG-PET imaging in the planning process of all patients candidate to radical thoracic radiotherapy for primary lung cancer (13). Another important application of FDG-PET is its use for the assessment of treatment response during and after radiotherapy. So far, these applications have been mainly explored by studying FDG uptake quantitatively, by means of standardized uptake values (SUV). A study by Rosenzweig *et al*., where FDG-PET was performed in every patient at 4 months after treatment, showed that those with a SUV value after radiotherapy below 3.5 had significantly higher tumor control than patients with SUV values after treatment above 3.5 (14). Nevertheless, other parameters, such as the metabolic volume or total lesion glycolysis (product of SUV and metabolic volume), may provide additional valuable information both as prognostic value as well as for treatment response monitoring. To improve the accuracy of GTV definition, FDG-PET can also indicate areas within the tumor that are metabolically more active and that may need an additional boost dose, as strategy that is under investigation in order to increase tumor control.

Four-dimension computed tomography and respiratory gating

One of the most important uncertainties in radiotherapy planning for lung cancer is target motion secondary to respiration, or "intra-fraction" tumor motion. This phenomenon may lead to geometric errors in dose delivering, especially when highly conformal techniques are used. In a study by Liu and collaborators (15), 50% of

tumors showed an intra-fraction shift of more than 5 mm, and 11% a shift of more than 1 cm, particularly if target lesions were located closely to diaphragm. One of the most diffused technical solutions designed for compensating for tumor motion and to adapt the margins around the GTV is 4D-CT. This technique consists in the acquisition of a series of CT images concurrently with the monitoring of respiratory cycle by the mean of sensors and specific sofware. The whole process makes possible the delineation of a target volume that includes all the phases of the respiratory cycle and consequently all tumor positions during free normal breath. The final target, called Internal Target Volume (ITV), represents the sum of all contours in all phases, taking into account the time factor. In most studies, the ITV generated by 4D-CT is different from the planning target volume generated by expanding for tumor motion with standard margins, and also delineation can be different and sometimes challenging (15,16). The introduction of 4D-CT is a major advance in adapting planning margins to individual patients while avoiding to apply general standardized margins derived from population studies (17).

Other important technical options in managing tumor motion during radiotherapy include:

(I) Tumor tracking: this technique enables to track in real time tumor motion by the mean of fiducial markers and to irradiate the tumor dynamically with a moving beam.

(II) Respiratory gating: it is based on the principle that the tumor is irradiated only during a part of the breathing cycle, which is called the gating window. The respiration is measured during every treatments session by external sensors (skin markers or belt) and/or internally using fluoroscopy, in order to determine when the beam should be on and off. Gated treatment can be performed with patients in free breathing or by a breath-hold irradiation technique. Gating is generally performed in exhalation, because the exhale respiration phase is more reproducible and takes longer than inspiration.

(III) Mid-ventilation planning CT and mid-ventilation image acquisition before treatment at LINAC: the mid-ventilation CT scan represents the tumor in its time-averaged position over the respiratory cycle, and the individual margins necessary to correct for tumor motion are estimated taking into account its average position during breath. A corresponding series of images can be obtained by a dedicated 4D system in the treatment room and the two average series compared for corrections, permitting a higher precision delivery.

Intensity Modulated Radiation Therapy

Intensity Modulated Radiation Therapy (IMRT) represents a major advance in radiation planning and delivery, and consists in a completely computerized evolution of 3D-conformal radiotherapy. By modulating the intensity of treatment beams, the dose distribution is extremely improved in conformity, enabling dose escalation to target volumes and a reduction of doses received by surrounding organs at risk. Few technical and clinical data are available about the use of IMRT in lung cancer, a technique that in principle could be of high value, especially when treating locally advanced lung tumors proximal to critical structures. Schwarz *et al*. reported on a comparison of dose distribution between IMRT and 3D-CRT in 10 patients enrolled in a dose-escalation study: despite the higher dose inhomogeneity in tumors, IMRT permitted to escalate the dose to tumor volume by 20-35%, while maintaining the dose constraints to organs at risk (18). In a retrospective clinical study by Jiang *et al*. (19), on 165 patients treated with IMRT at MD Anderson Cancer Center, the median radiation dose was 66 Gy given in 33 fractions (range, 60-76 Gy) and median overall survival time was 1.8 years, superior to a control/historical group of patients treated with standard 3D-CRT. Rates of Grade 3 radiation pneumonitis were 11% at 6 months and 14% at 12 months. Due to the complexity of IMRT planning, a careful analysis of DVH and constraints to both lungs (high, intermediate and low doses) is strongly advisable in these patients, especially when radiotherapy is given concomitantly with chemotherapy.

Stereotactic Ablative Radiotherapy for early stage NSCLC

Stereotactic Ablative Radiotherapy (SABR), or Stereotactic Body Radiation Therapy (SBRT), is an advanced high-precision conformal technique able to deliver very high biologically equivalent doses to small lung tumors in single or few fractions. The sparing of adjacent structures is maximal due to the pronounced dose gradient and the rapid fall down of the dose at the periphery of the target. In most clinical studies, the maximum tumor diameter for selecting patients for SABR was below 5 cm, even if currently in few Centers patients with larger tumors are enrolled in clinical trials. From a biological point of view, the advantage of delivering higher doses combines with the advantage of a short overall treatment time, and the local control rate at 3 years after SABR is in the range 85-90% with hypo-fractionated/accelerated SABR (20). Central

lesions located close to the major vessels and/or bronchi were previously considered at a high risk of toxicity, but it is now possible to adapt fractionation and deliver high dose in 5-10 fractions. SABR has also been extensively investigated in elderly patients, often affected with cardiac or pulmonary comorbidities, and proved to have a very low toxicity profile if compared with other options such as surgery (VATS) even in patients with poor or very poor pre-treatment pulmonary function (21-23). Planning and delivery technique consisted initially in patients' immobilization by the use of a stereotactic body frame, CT scan with slow acquisition time, margins of typically 5 mm in antero-posterior and latero-lateral directions and 10 mm in cranio-caudal direction. Planning consisted of 8-10 non-coplanar conformal fields, with online checking of tumor position by the use of orthogonal digital portal imaging on every treatment session. Nowadays, frames were replaced in most Centers by lighter immobilization devices, 4D-CT scan became the standard procedure for image acquisition and target contouring and smaller margins of 3 mm are added to ITV if image-guidance is used: all these advancements made this technique easier to plan and deliver, helping the wide diffusion of SABR as a very effective treatment for early stage lung cancer. The introduction of SABR deeply modified the pattern of care of patients affected with early stage lung cancer not amenable to surgery, as indicated by many studies (24,25), and quality of life and long-term outcomes (26-28) make it a very attractive treatment modality also for operable patients.

Image guided radiation therapy (IGRT) and adaptive radiotherapy

Dose escalation made possible by the introduction of technologies such as IMRT or SABR requests higher levels of accuracy when localizing tumor volumes, planning dose distribution to organs at risk and defining margins for the compensation of set-up errors, both within the same treatment session (intra-fraction) and between the different fractions (inter-fraction). The concept of image-guidance refers to all the multi-modality imaging options that can guide radiotherapy treatments by improving the accuracy of patients positioning and the minimization of the set-up errors. Currently the main imaging modality used in thoracic radiotherapy for lung cancer is represented by kilo-voltage cone-beam CT (CBCT). By CBCT, a series of volumetric images generated at the time of treatment can be compared to the planning CT images by the use of a specific software, permitting an individualized every day correction of set-up errors by automatic shift of the treatment table positions. Several studies evaluated the use of CBCT in lung cancer patients by comparing the shifts in a series of repeated images obtained in different patients, reporting that daily CBCT substantially reduces the set-up error (29,30). The consequent reduction of PTV margins, together with 4D-CT delineation, made possible a consistent reduction of treated volumes in recent years. The possibility to perform repeated imaging during an entire fractionated radiotherapy cycle opened a new research area called "Adaptive Radiation Therapy", based on the concept that as the tumor and normal tissue anatomy are known to change in the course of treatment (resolution of atelectasis, response of the tumor and/or lymph nodes), a consequent adaptation of the radiation plan could be very useful in further reducing the exposure of normal tissue while maintaining dose intensification. A study by Schaake *et al*. (31) evaluated the quantitative variations of intra-thoracic anatomy that occur during radiotherapy for lung cancer (5-6 weeks overall treatment time) in 114 patients. Patients underwent repeated cone-beam CT and the target volumes were re-contoured weekly. The comparison with pre-treatment volumes delineated on CT scans for planning showed that significant anatomic variations are evident in 41% of patients. There are several other publications addressing volumes changes during radiotherapy and these findings strongly support the implementation of clinical protocols prospectively investigating adaptive radiotherapy strategies in lung cancer (32).

Conclusions

The combination of functional imaging, 4D-CT, intensity-modulated and adaptive radiotherapy strategies in thoracic radiotherapy permits to enhance the dose to lung tumors while keeping low the dose received by surrounding tissues: these technical advances might lead to higher control rates and a better toxicity profile both for early stage and advanced stage disease.

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