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4D PET-CT GUIDED RADIATION THERAPY*

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Tremendous technological progress in the field of imaging and computation have been revolutionizing radiotherapy of non-small cell lung cancer (NSCLC). Tumor biology can now be characterized by functional imaging for modifying treatment management and dose delivered in better accordance with the radiobiology of solid tumors and normal tissues. Specific radiation therapy (RT) strategies can further address the tumor motion issue, ensuring optimal tumor coverage with small safety margins.

Key-word: Lung neoplasms, therapy.

Radiation therapy has been long past recognized as one of the main treatment modalities of locally-advanced unresectable non-small cell lung cancer (NSCLC), as well as of early stage tumor in medically inoperable patients. Like surgery, the primary objective of RT is to locally control tumors, which is an essential prerequisite of cancer cure. However, local tumor failure remains high in patients with stage II and III NSCLC, with local progression free survival rates of about 30% (1) when conventional radiotherapy schedules are used (60-66 Gy, daily fraction of 2 Gy).

Dose intensification strategies, such as concomitant chemo-radiation, accelerated and dose-escalated schemes have been already shown to improve the tumor control and patient survival rates. Interestingly, the improved survival of stage III NSCLC patients with the concurrent delivery of chemotherapy and RT over sequential delivery is solely due to improved local tumor control (1). It is thus clear that improvement of local control leads to a better survival, even in patients with locally-advanced diseases. This justifies pursuing strategies to increase local tumor control that can be integrated with systemic treatment. Moreover, as most local recurrences have been observed in the primary tumor and not in the involved mediastinal lymph nodes, further clinical research needs to more specifically focus on the primary tumor control.

The clinical implementation of dose-intensified protocols however remains problematic. The proximity between the target volumes (TV) and highly sensitive intra-thoracic organs, such as the lungs, spinal cord, oesophagus and heart, may result in unacceptable short- and long-term toxicities when dose intensification is considered. Therefore, the recent development of new high precision radiation techniques, such as intensity modulated radiation therapy (IMRT), image guided radiotherapy (IGRT) and stereotactic body radiation therapy (SBRT) offers new perspectives.

However, high precision RT not only requires sophisticated radiation delivery techniques, but also thorough selection and delineation of TVs. In this regard, functional imaging like positron emission tomography (PET) might advantageously complement morphological computed tomography (CT) for RT planning, by providing unique molecular information about the tumor biology.

In addition, accuracy would never be achieved in NSCLC RT without optimally accounting for respiratory-correlated tumor motion. Indeed, it causes major geometric uncertainties during image acquisition, treatment planning and dose delivery, which have certainly contributed to the poor local control achieved with old RT techniques. It is thus anticipated that adequate motion-related strategies would achieve better outcome in terms of both tumor control and toxicity profile.

Thus, this paper will discuss the rational, the practicalities and the potential of modern radiotherapy strategies in NSCLC that appeal to recent imaging technologies like PET and four-dimensional (4D) imaging.

PET-guided radiotherapy

Nowadays, CT is the reference imaging modality for the treatment planning of NSCLC. It is widely available, conveys essential anatomical information, and also indicates the electronic density of the tissues used for dose calculation. Nevertheless, it offers poor soft tissue contrast between the primary tumor and the surrounding normal tissues in cases of lung parenchyma changes (i.e. fibrosis, atelectasis, pleural effusion, and pneumonia), contiguity between the primary tumor and mediastinal nodes, and tumor located close to the mediastinum or chest wall.

Alternatively, FDG-PET provides higher sensitivity and specificity than CT for the detection of primary tumor and mediastinal nodes, and is now considered as a reference for the clinical staging of NSCLC (2, 3). In the radiotherapy field, FDG-PET has already been shown to significantly modify the size, location and shape of the primary Gross Target Volume (GTV, i.e. the macroscopic disease) (4, 5), and to improve the selection of neoplastic lymph nodes in the target volume (6). FDG-PET thus leads to the opportunity to optimize both the patient selection for a given treatment through a better clinical staging, and the radiotherapy treatment planning through a better identification of the target to be irradiated (7, 8).

Even more promising, PET has the potential of identifying tumor subvolumes that are suspected of being radioresistant (high tumor burden, hypoxia…), in which an escalated, non-uniform radiation dose distribution could improve tumor control and patient's outcome (9-11). This so-called "dose-painting" strategy would possibly solve the issue that uniform dose escalation to the whole tumor would lead to too high doses to the normal tissues, with unacceptable subsequent toxicities. Restrictively boosting the parts of the tumor that show unfavourable responsiveness to radiation should thus reconcile tumor radiobiological imperatives with those related to treatment safety.

Any PET tracer identifying a metabolic pathway involved in the

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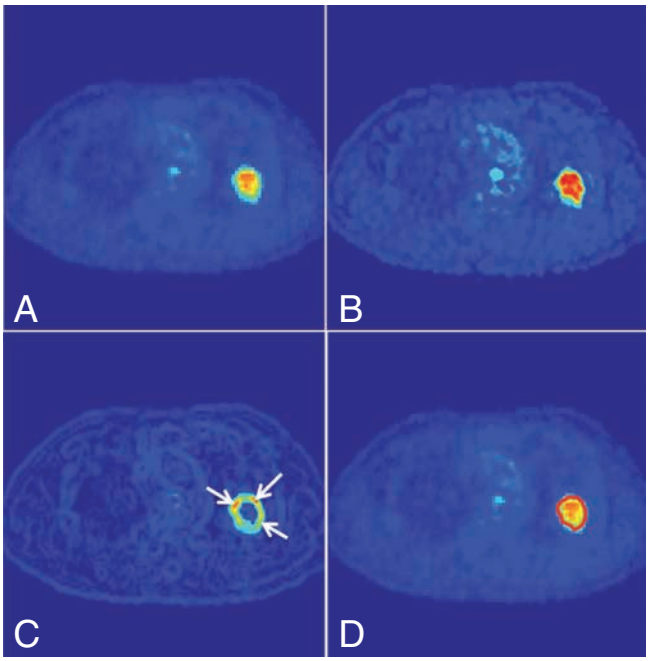

Fig. 1. — Axial PET images from a patient with a primary lung tumor. On the left panel, the PET image corresponds to the raw image reconstructed with 3D OSEM algorithm (A). The application of the bilateral filter and the deconvolution algorithm restored the gradient intensity as shown on conventional image (B). The gradient image is then generated to depict the gradient intensity peak (C, white arrows), and the tumor contour (red line) is finally generated and transferred to the raw image (D).

radio-resistance process, such as hypoxia, glucose metabolism or tumor proliferation could theoretically be selected for driving dose escalation. In NSCLC, FDG appears as pretty good candidate as demonstrated by the Maastro and NKI groups from The Netherlands: 1) it benefits from a large and long-term clinical experience, 2) it demonstrates a good signal-to-noise ratio (SNR), 3) its high uptake areas within the tumor correlate with poor local tumor control and survival (12), 4) the radio-resistant areas can be identified on the basis of the pre-treatment FDG-PET, and 5) highly metabolic areas remain at the same location throughout the course of radiotherapy (13, 14).

Although indirect evidences exists about a radiation-dose response relationship in NSCLC, the question however remains whether delivering a higher dose to the most avid FDG-uptake areas within the tumor would result in higher local control. This should thus be addressed in well-designed prospective trials that should adequately deal with specific methodological/technical aspects inherent to PET-guided RT as further described in this paper.

Delineation of the PET-based target volume

The first step consists in identifying and delineating FDG-PET-based targets, which still remains technically complex. At the moment, several delineation methods were suggested relying mainly on either manual contouring or automatic threshold-based segmentation. However, manual delineation is a subjective and non-reproducible approach, while some studies pointed out that the threshold for accurately recovers the actual PET volume substantially differ with the size, shape, heterogeneity and background uptake of the tumor (15), questioning thus the validity of thresholding itself.

From a methodological point of view, the use of a straightforward segmentation method such as a threshold-based one is driven by the low quality of PET images, in terms of resolution and statistical noise, compared with others modalities like CT or MRI. In this regard, the use of appropriate image-processing tools like denoising and deblurring techniques can address the noise and resolution issues of the images, so that a segmentation method that exploit the image gradient information could be used. These tools have been developed in our lab, and are in depth described in (16). Briefly, the segmentation process goes through 3 successive steps (Fig. 1):

The denoising step with specific edge-preserving filter aims at attenuating the statistical noise without additional smoothing of the tumor edges.

The deblurring step aims at compensating for the blur effects of the scanner point spread function. It relies on an iterative deconvolution algorithm that recovers the ideal image from the blurred one, with stepper intensity gradients between the tumor and the background (Fig. 1 B).

The intensity gradient detection on the computed gradient image is then done by means of Watershed and Clustering algorithms, and leads to the accurate identification of the object boundaries (Fig. 1 C,D).

This method has been validated on FDG-PET images from phantoms, and from patients with head and neck and lung cancers, using the surgical pathology specimen as the "ground truth" (16, 17). Interestingly, our gradient-based segmentation of FDG-PET images provided a closer estimate of the true tumor volume compared to CT, which systematically overestimated it. This method also proved to outperform the classical threshold-based approaches in terms of accuracy and robustness. Based on these facts, the gradient-based segmentation approach was considered as the reference tool for further FDG-PET-driven dose-escalation protocols.

FDG-PET guided dose escalation protocol

A pilot study was then designed to address the feasibility and the efficacy of FDG-PET-driven dose boosting in locally-advanced stages II-III NSCLC. In this prospective trial, patients are treated with state of the art concomitant chemo-radiation therapy. A total dose of 62.5 Gy is delivered in 5 weeks to classical target volumes, i.e. the primary tumor and the clinically-positive mediastinal lymph nodes, delineated on a routine contrast-enhanced planning CT.

The dose by fraction is then escalated on the FDG-PET volumes delineated with our gradient-based method. The dose escalation is performed with Simultaneous Integrated Boost (SIB) IMRT technique using tomotherapy machine, which allows to

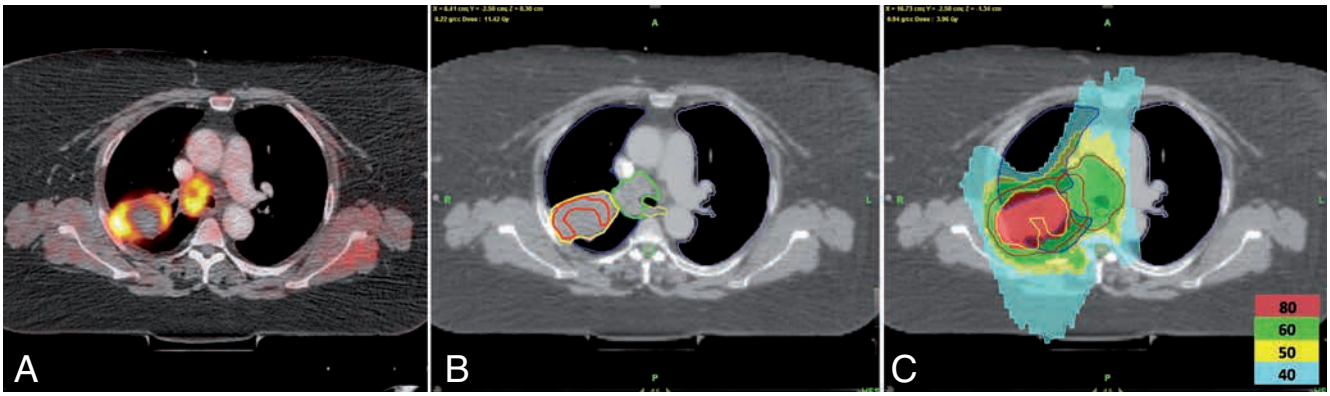

Fig. 2. — Radiotherapy planning process for FDG-PET-guided dose escalation in NSCLC. First, a combined FDG-PET-CT of the patient immobilized in treatment position is acquired (A). Gross tumor volumes (GTV) from involved lymph node (green contour) and primary tumor (yellow contour) are then manually delineated on the contrast-enhanced CT, while the FDG-avid region (red contour) within the primary tumor is automatically segmented on PET images (B). Margins are then added to these GTVs to account for microscopic extension, tumor motion and setup uncertainties. The dose is finally prescribed to reach 62.5 Gy to CT-based volumes, while being escalated for FDG-PET-based volume up to 80 Gy in this particular case (C).

deliver different dose levels to different targets (CT and PET-based volumes) during the same treatment session (Fig. 2). The dose to the PET volume is individually increased until a set of pre-defined dose-limiting normal tissue constraints is reached for lungs, heart, oesophagus, plexus brachialis and mediastinal structures (18).

Thus, all parts of the primary tumor will receive at least 62.5 Gy (CT-based volume), while FDG-avid regions will be escalated to a maximal dose of 125 Gy (25 fractions of 5 Gy). This later dose level has been set to be biologically equivalent to this achieved with a 3 times 18 Gy stereotactic body radiotherapy (SBRT) scheme used in early stage small NSCLC, which results in local tumor control rates above 85% (19). If needed, this dose is lowered for individual patient to ensure that the dose to normal structures will not exceed the current recommendations. Even in this case, the tumor control probability is expected to be much higher than what we can achieve today. This will be evaluated by the local-progression free survival, while acute and late radiation-induced toxicities will be carefully monitored and reported.

RT strategies for respiratory-related tumor motion management

Breathing induces a three-dimensional, ellipsoidal-shaped (hysteresis) tumor motion that is often significant, especially in the cranio-caudal direction and for lower lobe tumor. This motion can furthermore vary in amplitude, shape, and baseline when transient changes occur in the patient's breathing pattern. In this context, the use of a conventional free-breathing 3D-CT typically leads to several geometric distortions (image artefacts in tumor shape and position, delineation errors...). To account for these geometric uncertainties, large safety margins are needed, thereby limiting the effectiveness of radiotherapy (20). To reduce geometric uncertainties in CT images, and thus the safety margins, time-resolved four-dimensional CT (4D-CT) and PET (4D-PET) techniques have been developed. They serve as a basis of various breathing-related RT strategies. Some aspects of these strategies will be tackled in the following paragraphs.

Respiratory audio-video coaching

To ensure reliable and reproducible tumor motion and trajectory, an audio-video coaching (AVC) procedure has been developed. It aims at regularizing the patient breathing throughout all imaging and treatment sessions. Prior to any image acquisition, a training session is planned to record and characterize the breathing pattern of each individual patient. The average frequency, the relative duration of the inhalation and exhalation phases, as well as the breathing amplitude, are first determined from the signal acquired in free breathing mode. Then, the respiratory sound that best matched the specific patient's breathing pattern is selected from a large database and further used for the audio coaching procedure. The breathing amplitude is also constrained by a visual feedback of the respiratory with video-glasses. Several studies have already pointed out that audio-guidance stabilized breathing frequency and improved the external/internal correlation between the breathing and the tumor (21-23). Combining video feedback with audio-guidance further regularizes the breathing amplitude (24, 25).

4D planning imaging

In addition to the contrast-enhanced CT (CE-CT) and conventional FDG-PET used for delineation and dose calculation purposes, respiratory-correlated acquisitions are performed to capture the tumor motion. In this technique, the breathing signal coming from external surrogates (pressure belt, optical scanner, infrared camera...) is used to sort the respiratory-correlated CT or PET images in 10 equally distributed temporal bins, so that the resulting 10 respiratory CT and PET phases may provide an estimate of the tumor motion throughout the breathing cycle.

Treatment planning strategies

Based on this 4D information, various strategies can be deployed. The respiratory synchronized techniques that intend to either gate the dose delivery at a certain tumor position or track the tumor in real-time are appealing since they minimize the tumor motion contribution in the safety margin calculation (26-29). However, these approaches remain complex to implement, require sophisticated and time-consuming in-room verification procedures, and are technically unfeasible with helical tomotherapy machine. Alternatively,

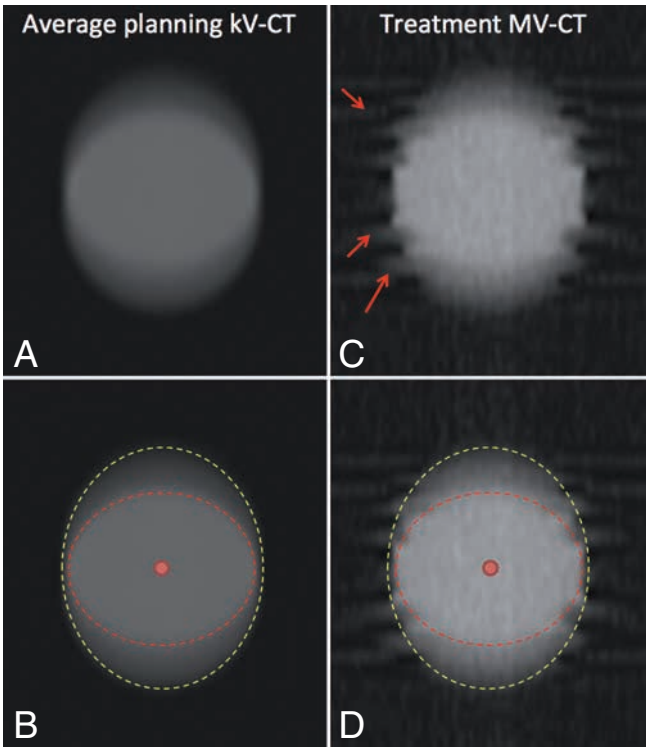

Fig. 3. — Average planning kV-CT (A,C) and MV-CT (B,D) images of a moving spherical phantom (1 cm amplitude motion in the supero-inferior direction). Although MV-CT presents geometric motion artefacts (red arrows, right upper panel), it shares similar density distribution patterns with the average kV-CT (red and yellow dotted lines). Based on that, the centres of mass (red spheres) are directly used for aligning the tumor on its average position between kV and MV-CT.

margin-based approaches, which are more suitable for tomotherapy treatment, aim at either covering the entire tumor trajectory derived from 4D information (internal target volume, ITV) (30), or at taking advantage of the geometrical time-weighted mean tumor position (MidPosition, MidP) (31).

In our setting, the internal motion is first estimated using non-rigid registration between the different 4D-CT or 4D-PET respiratory phases. The calculated deformation maps can then be used to either generate ITV or MidP:

For ITV, the gross tumor volume delineated by the experienced physician on CE-CT or automatically segmented on FDG-PET is propagated to the 10 respiratory CT/PET phases. The union of all volumes then leads to the definition of the ITV that covers all tumor positions through the whole breathing cycle. An additional margin is added to the ITV to account for setup errors.

For MidP, the deformation maps are used for generating a single 3D-CT/PET frame, i.e. the MidP CT or PET, from the 4D dataset. This image is obtained by deforming all features of each frame of the 4D dataset from their position in a certain frame to their time-weighted mean position with the estimated motion. Subsequently, averaging over the respiratory phases of the transformed 4D-CT results in the MidP CT or PET. The MidP image comprises thus all the internal structures, including the tumor, in their exact time-weighted mean position of the respiratory motion. The mean time-weighted tumor position is finally extended with an appropriate margin to account for residual uncertainties.

The MidP strategy presents several advantages (31). First, as the MidP image corresponds to an averaged image from all transformed frames, it is less noisy (better signal-to-noise ratio) than each separate time frame. This may contribute to the reduction of delineation errors. More importantly, the MidP eliminates the systematic error due to 3D sampling or tumor hysteresis. Indeed, a 3D image only represents a snapshot of the tumor motion, from which the tumor position can significantly and systematically diverge from its mean position over the whole breathing cycle. Removing this systematic error ultimately allows a substantial reduction of the safety margins, compared to conventional 3D CT and ITV strategies, margins that are actually close to those obtained with gated radiotherapy. Last but not least, the MidP is a simple method that only involves the reconstruction of a new planning CT, and leaves other treatment planning and delivery aspects unchanged. It does not require any complex 4D treatment planning nor additional verification, and is thus easy to implement in clinical routine. A complete, unique validation of this approach with tomotherapy treatment is on going in our lab, which addresses volumetric, dosimetric and dose delivery aspects with Monte Carlo calculation verification (32).

In room imaging and positioning

To ensure the adequate positioning of the patient during the treatment delivery, a daily MV-CT is performed at the tomotherapy unit. Classically, the bony anatomy is used to realign the actual patient position from the daily MV-CT with this corresponding to the planning CT (i.e. bony anatomy setup correction protocol). Unfortunately, this procedure does not correct for tumor baseline shifts, i.e. day-to-day variations in the basal position of the tumor due to pattern changes in the tumor motion. Without baseline shift correction, a significant margin extension has to be considered to compensate for. Another approach would thus consist in directly aligning the tumor between the MV-CT and the planning CT (i.e. on-line tumor setup correction protocol).

Interestingly, MV-CT may be considered as a (very) slow CT capturing the tumor motion, and thus sharing similarities in density distribution with the average kV-CT from the 4D planning CT (Fig. 3). Thanks to this property, the mass centre of the tumor in its average position can be found out and used to realign both images at the tumor level. This procedure, which should account for the possible geometric motion-related distortion within the MV-CT image, is currently under development and validation using moving phantoms and real patient images.

Conclusion

Tremendous technological progresses in the field of imaging and computation have been revolutionizing radiotherapy of NSCLC. The tumor biology can now be characterized by functional imaging for modifying the way the treatment plan is designed and the dose delivers, in better accordance with the radiobiology of solid tumors and normal tissues. Specific RT strategies can furthermore address the tumor motion issue, ensuring optimal tumor coverage with small safety margins. Although results from prospective trials are still awaited, we can expect that these progresses would translate into better patient's outcome.

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