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Review

Metabolic imaging in non-small-cell lung cancer radiotherapy

Imagerie métabolique pour la radiothérapie des cancers bronchiques non à petites cellules

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ABSTRACT

Metabolic imaging by positrons emission tomography (PET) offers new perspectives in the field of non-small-cell lung cancer radiation therapy. First, it can be used to refine the way nodal and primary tumour target volumes are selected and delineated, in better agreement with the underlying tumour reality. In addition, the non-invasive spatiotemporal mapping of the tumour biology and the organs at risk function might be further used to steer radiation dose distribution. Delivering higher dose to low responsive tumour area, in a way that better preserves the normal tissue function, should thus reconcile the tumour radiobiological imperatives (maximising tumour local control) with dose related to the treatment safety (minimising late toxicity). By predicting response early in the course of radiation therapy, PET may also participate to better select patients who are believed to benefit most from treatment intensification. Altogether, these technological advances open avenues to in-depth modify the way the treatment plan is designed and the dose is delivered, in better accordance with the radiobiology of individual solid cancers and normal tissues.

Mots clés :
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RÉSUMÉ

L'imagerie métabolique par émission de positons (TEP) offre de nouvelles perspectives en radiothérapie des cancers bronchiques non à petites cellules. D'abord, elle permet d'améliorer la sélection et la délimitation des volumes-cibles, en meilleure concordance avec la réalité de la tumeur. De plus, elle permet d'établir une cartographie spatiotemporelle de la biologie tumorale et de la fonction des organes à risque, qui peut être utilisée pour guider la prescription de la dose. Ainsi, délivrer des doses supérieures dans les régions de la tumeur les plus radiorésistances, tout en préservant mieux la fonction des organes des voisinages, devrait réconcilier les impératifs radiobiologiques de la tumeur (améliorer le taux de contrôle tumoral local) avec ceux relatifs à la sécurité du traitement (minimiser la toxicité). Ensemble, ces avancées technologiques pourraient considérablement modifier la façon dont les traitements sont planifiés et la dose est délivrée, en accord avec la radiobiologie de chaque tumeur et tissu sain.

1. Introduction

Combined chemoradiation has long been past recognized as the reference treatment of non-operable stages II-III non-small-cell lung cancer. However, local failure remains high in these patients, with local progression free survival rates of only 30% when conventional schedules are used [1]. Despite distant metastasis remains a major concern, locoregional failures are directly involved in about one third of cancer deaths. Thus, improving survival in stages I-III non-small-cell lung cancer undoubtedly necessitates more efficient local treatment on top of improved systemic therapies. In that regard, dose intensification strategies, such as dose-escalated

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schemes have already been shown to improve the tumour control and the patient survival rates. The best example comes from stereotactic ablative radiation therapy (SABR) in early stage non-small-cell lung cancer, which achieves local control as high as 90% by delivering high biological equivalent dose (BED > 100 Gy), where conventional schemes (60–66 Gy, 2 Gy/fraction) laboriously reach 40% [2]. Even more important, this benefit in local control translates into a substantial survival gain [3]. Similarly in locally-advanced diseases, the improved survival of patients with the concurrent delivery of radiation therapy and chemotherapy is solely due to the increased local tumour control [1]. Although the recent randomized phase III study (RTOG 0617) failed to confirm the role of dose intensification (74 Gy vs. 60 Gy), this finding runs counter to a large body of evidence that higher doses lead to better tumour control. This is most likely due to the non-optimal dose prescription to both target volumes and organs at risk, with increased risks of local failure and late cardiac and pulmonary toxicities.

The previous study perfectly illustrates that dose intensification in extended disease remains a huge challenge, and more than never, justifies intensive efforts from the entire radiation therapy community to improve the way radiation is planned and delivered, so that dose-intensified schedules can be safely administrated.

By answering to "how does the tumour behave" and not only to "where is the tumour", metabolic imaging like positrons emission tomography (PET) might help at solving this issue and at improving the therapeutic window between treatment efficacy and toxicity. Indeed, PET imaging has the ability to provide unique, global and in-vivo information about the tumour biology that may be exploited at least in 4 different ways:

- a better mediastinal staging for accurately selecting lymph nodes that have to be irradiated;
- an accurate delineation of the primary tumour, especially when it is close to tissues with similar densities on conventional computed tomography (CT) (atelectasis, mediastinum, thoracic wall);
- a spatiotemporal mapping of both the tumours and normal tissues biology to steer radiation dose distribution according to their responsiveness to radiation (dose-painting);
- last but not least, an early response prediction to radiation therapy, at the time when the radiation dose and/or the therapeutic option can still be adapted.

In this short review, we will focus on these recent advances made in PET in these specific fields of non-small-cell lung cancer radiation therapy. We will mainly focus on how these features may improve the patient management.

2. Elective nodal irradiation guided by PET

Fluorodeoxyglucose (FDG)-PET is more accurate than CT to detect extracerebral distant metastases in non-small-cell lung cancer, and is now part of the routine patient's workup. In addition, it demonstrates higher accuracy for mediastinal lymph node staging with sensitivity and specificity of about 90%, where CT only achieves 65% and 80%, respectively [4]. Based on recent meta-analyses, negative predictive values ranging from 85% to 95% were reported [5,6]. This means that most of metastatic regional lymph nodes are accurately detected by FDG-PET. In planning studies, the use of PET has lead to a significant reduction of the nodal target volumes compared to CT, and resulted in smaller radiation fields with lower dose levels to the adjacent organs at risk. A prospective clinical study has further confirmed that selective mediastinal node irradiation guided by FDG-PET was a safe option, which did not lead to higher isolated nodal recurrences [7]. Better sparing the dose to organs at risk would lead to fewer side effects, and thus would facilitate the implementation of dose escalation strategies with the aim to safely improve the tumour local control.

3. Primary tumour target delineation

Historically, the primary tumour has been delineating on conventional planning kV-CT with or without contrast. In peripherally located tumour surrounded by lung parenchyma, the air provides a high natural contrast allowing the appropriate tumour delineation in most cases. However, CT offers poor soft tissue contrast when the primary tumour is associated with lung parenchyma changes (fibrosis, atelectasis, pleural effusion, pneumonia), or is close to the mediastinum, chest wall or diaphragm. Alternatively, FDG-PET provides higher sensitivity and specificity for the detection of the primary tumour in these conditions, with better discrimination between tumour and non-tumour tissues.

Although promising, the tumour delineation on PET remains technically complex. Indeed, PET has a low intrinsic spatial resolution (4–7 mm) and relies on limited statistics. As a consequence, PET images look blurred and noisy, which are unfavourable image conditions for an accurate detection of the tumour boundaries. At the moment, several delineation methods were suggested relying mainly on either manual contouring or automatic threshold-based segmentation. Intrinsically, the manual contouring is a subjective approach, highly sensitive to the image display (windowing, colour scale) and the individual expertise. Alternatively, the threshold-based methods rely on the selection of an absolute (i.e. SUV 2.5) or relative threshold (i.e. 40 or 50% of SUV_{max}) above which voxels are considered to belong to the tumour. Although simple and objective, these methods suffer from important limitations: the optimal threshold actually varies according to the background activity, they are not adapted for images with low signal-to-noise ratio (inflammatory conditions and/or tumour response with FDG, non-FDG-PET tracers) and for complex-shaped tumours [8]. From a methodological point of view, improving the PET image quality should greatly facilitate the segmentation task. We have thus implemented specific image restoration tools, including denoising and deblurring algorithms. The resulting "restored" images have sharper intensity gradients at the tumour edges, which can be easily detected by Watershed and Clustering algorithms afterwards [9]. Our gradient-based method was validated on phantom material, but also on images from real head and neck and lung cancer patients treated surgically by laryngectomy and lobectomy [9,10]. The macroscopic specimen was used as the "ground truth" for further comparisons. Interestingly, our method provided a closer estimate of the true tumour volume compared to the conventional threshold-based approaches. In addition, the higher contrast resolution of PET for soft tissue led to smaller tumour volumes than CT in both head and neck, and lung tumours [9,10].

Thus, this validated and robust method provides a better estimate of the true gross target volume compared to CT and others PET segmentation methods. Reducing the target volumes will necessarily contribute to better spar the organs at risk and normal tissues from the highest radiation doses.

4. The dose-painting concept

Another exciting feature of PET is its ability to provide 3D maps of the tumour and the normal tissues, in order to prescribe a non-uniform dose according to the local radioresistance/radiosensitivity expected from the imaged biological characteristics [11]. In dose-painting, delivering higher dose to low responsive tumour areas, in a way that better preserves the