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Review

Lung cancer. Radiotherapy in lung cancer: Actual methods and future trends

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ABSTRACT

This survey is performed to update knowledge about methods and trends in lung cancer radiotherapy. A significant development has been noticed in radiotherapeutic techniques, but also in the identification of clinical prognostic factors. The improvement in the therapeutic line includes: application of the four-dimensional computer tomography (4DCT), taking advantage of positron emission tomography (PET-CT), designing of new computational algorithms, allowing more precise irradiation planning, development of treatment precision verification systems and introducing IMRT techniques in chest radiotherapy. The treatment outcomes have improved with high dose radiotherapy, but other fractionation alternations have been investigated as well.

Radiotherapy represents the basic method of treatment in lung cancer. It is used at every stage of clinical advancement, both in the non-small cell (NSCLC) and the small-cell form (SCLC) of the cancer. According to epidemiological studies, in developed countries 61–76% of all patients with NSCLC require one of radiotherapy forms at a certain stage of their disease.[1,2] At early stages of the disease advancement, in cases when the patient is not planned to undergo surgery, stereotactic radiotherapy is applied, in locally advanced stages, radiochemotherapy or radical radiotherapy are used. In cases of the disseminated disease or when the disease cannot be radically treated for various medical reasons, radiotherapy is employed as a palliative treatment. On the grounds of the analysis of data obtained from SEER-17 data base and presented during ASTRO conference, Kong et al. evaluated the effect of radiotherapy on patients' survival, comparing techniques employed before and after 2004. Application of radiotherapy was found to improve results of treatment at all stages of advancement, with better results obtained in the group treated after 2004, thus using more modern techniques.[3]

In recent years, a significant progress has been observed in radiotherapeutic techniques in general, with a significant increase in studies on the efficacy of lung cancer radiotherapy using modern tools. The areas where particular development has been detected include progress in identification of clinical prognostic factors, allowing individualization of patient's treatment as well as improved quality of anatomic imaging

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of the tumour and the regional lymph nodes, which results in a precise definition of the target volume.[4] Nevertheless, from the point of view of a radiotherapist the most important has been the improvement in the therapeutic line technological quality: application of the four-dimensional computer tomography (4DCT), taking advantage of positron emission tomography (PET-CT) studies in treatment planning, designing of new computational algorithms, allowing more precise irradiation planning, development of treatment precision verification systems and alterations in the very implementation process in administration of the recommended dose. Application of new technological solutions allowed to deliver treatment in higher biological doses with retention of treatment toxicity at a relatively low level.

1. PET-CT

In patients with lung cancer the key examination, permitting an improved quality of preliminary qualification and radiotherapy planning, is PET-CT with [18F]-FDG. Some prospective studies revealed that introducing PET-CT before planned radiotherapy disqualified radical treatment in 25–30% of the patients, most frequently due to distant metastases.[5,6] PET-CT examination manifests high sensitivity in detection of metastatic lymph nodes and distant metastases. This diagnostic accuracy allows to distinguish patients with lower stage of advancement, in whom radical treatment (surgery or local therapy) can be performed, from palliative patients. The value of PET-CT in radiotherapy planning cannot be overlooked either, as the tool which helps to define target volumes. Numerous studies have accentuated that PET-CT examination in planning of radiotherapy reduces the risk of the geographic error, particularly in outlining the mediastinal lymph nodes,[7,8] but also in distinguishing the tumour from the surrounding pulmonary atelectasis.[9] The equipment used for PET-CT examinations in radiotherapy must be appropriately calibrated.[10] The use of such imaging for planning requires compliance with certain protocols, which specify not only patient immobilization but also an appropriate interpretation of obtained results.[10,11] Quality of the image, which is supposed to be used for planning, can be improved by the use of PET-CT equipment, which additionally records patient's respiratory cycles (4DPET-CT). This causes the blurring of image patterns, resulting from patient's respiratory movements, to become reduced and in this way the region of metabolically active lesions within the lung can be better outlined. Another difficult issue is the manner in which PET-CT is used for outlining the target volume. The most frequently used method is qualitative visual evaluation of PET images (Qualitative Visual Method, QVM). The other approaches involve an automated quantitative evaluation of the result: an arbitrary SUV level can be assumed, e.g. >2.5, and on this basis the tumour can be located. However, the approach is difficult because no standard SUV value is defined for malignant tumours. Another method involves determination of a threshold SUVmax value, expressed in percents, e.g. 40%, above which the tumour region is outlined. No unequivocal data are available which may suggest an optimal character of any of these approaches. Therefore, the best solution requires the formation of an interdisciplinary team dealing with appropriate qualification and treatment planning and in this way direct cooperation with a nuclear medicine specialist. Only such a cautious approach to the obtained results allows to significantly avoid systemic errors resulting from an improper interpretation of the Images.[10,12] Radiation Therapy Oncology Group (RTOG) recommended the use of [18F]-FDG-PET-CT in radiotherapy planning of patients with non-small cell lung cancer already in 2003. Nevertheless, further investigations are necessary to define the role of this examination with higher accuracy, at least within the range of effects induced by the therapy and the effect of PET on patients' survival.

2. Role of 4DCT in RT planning

The concept of using 4-dimensional computer tomography (4DCT) for radiotherapy planning has been discussed for a long time, due to the significant and not always predictable mobility of chest organs. The idea of 4DCT involves scanning of the patient using a spiral computer tomography, which is paralleled by the reception of signals recording the respiratory cycle. Subsequently, the collected tomographic data are separated for individual respiratory phases, with the resulting grouping of CT images into a few series, reflecting shift of the tumor.[13] Treatment planning based on 4DCT images requires the use of an algorithm grouping CT images into separate image sets, in which oncologist-radiotherapist defines independent tumour contours, which subsequently can be presented as a global contour in a selected bin. At present, the use of 4DCT is recommended both in conventional fractionation,[14] and in high dose radiotherapy.[15]

Based on 4D tomography, a few concepts were introduced for PTV defining. They include *internal tumour volume* (ITV)-PTV_{ITV}, modification of ITV based on *maximum intensity projection* (MIP)-PTV_{MIP}, determination of PTV based on respiratory gating-PTV_{GATING} and the concept of *midventilation*-PTV_{MidVen}.

Determination of PTV_{ITV} involves outlining of a tumour in 6–10 individual respiratory phases.[16] Even if relatively precise, the method is time- and work-consuming and, therefore, the potential for a faster contouring has been introduced as a facilitation of the radiotherapist's every day work, based on automatic delineation of ITV using MIP. MIP projection reflects maximum values of HU ascribed to voxels in the volume restricted to tumour location while delineation of the region itself takes place with an assistance of a specific software,[17] the so-called 3D IsoConture identifying marginal HU values which detach tumour margins from the lung. This allows restricting the time-consuming procedure of outlining the tumour, but it also carries limitations in cases of tumours situated close to the chest wall or mediastinum.

Radiotherapy using respiratory gating involves irradiation of a tumour only at a certain stage of respiratory cycle, most frequently at expiration, although breath-hold techniques can also be applied. In order to implement this concept special equipment is required, which reads out respiratory movements of the patient, synchronizing them with an accelerator.[18] In order not to needlessly extend RT procedure, 20–40% of the respiratory cycle time is used to create the