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Accounting for, Mitigating, and Choice of Margins for Moving Tumors

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Tumor motion can lead to uncertainties in delivered dose to patients and undesirable outcomes. Motion management has become an integrated component of the standard of care for moving tumors in external beam radiotherapy with the development of novel imaging and treatment techniques in the past 2 decades. This article reviews the use of advanced and functional imaging to guide target delineation, considerations for margin selections, technique for accounting for and mitigation of tumor motion in treatment planning and delivery, and motion management in radiation therapy.
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Introduction

Application of advanced treatment techniques, such as intensity-modulated radiation therapy (IMRT), volumetric-modulated arc therapy (VMAT), and stereotactic body radiotherapy (SBRT), along with the introduction of novel imaging techniques, such as 4DCT and cone-beam CT, in radiation therapy have enabled the delivery of a highly conformal dose to the tumor. However, respiratory motion is a major obstacle to achieve highly precise radiation for thoracic malignancies. Failure to account for lung tumor motion can lead to underdosing of the tumor as well as excessive dose to normal lung, which in turn could lead to failure of local control or radiation-induced side effects including pneumonitis.[1] In a study on SBRT treatment of metastatic colorectal cancer in 47 patients, Van den Begin et. al.[2] suggested that inadequate respiratory motion management could lead to reduced local control of metastases in moving organs (lung and liver) compared to lesions in areas less prone to respiratory motion. This review examines imaging, treatment planning, and treatment delivery aspects of current motion management techniques.

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Extent of Tumor Motion

For lung tumors, the range of tumor motion is patient specific and depends on tumor location and staging of the disease.[3-5] In a study including 191 (94 early stage and 97 locally advanced) non–small cell lung tumors, Yu et. al.[4] correlated tumor motion characteristics with their standardized tumor locations, lobe location, and clinical staging. It was found that early-stage NSCLC tumors could have motion range up to 30 mm, while motion in locally advanced tumors seldom exceeded 10 mm. The largest tumor motions were observed in the lower lobe, in the superior-inferior direction and were associated with diaphragm motion. However, tumor volumes were found not to correlate with motion. It was also concluded from review of respiratory motion literature that there are no general patterns of respiratory behavior that can be assumed for a patient prior to observation and treatment,[6] thus individualized imaging of the tumor motion is highly desirable for patient simulation and treatment.

Imaging of Respiratory Motion

The use of 4DCT, or respiration-correlated CT, for treatment simulation has become the de facto standard for tumor motion visualization and is strongly preferred for the radiotherapy of thoracic malignancies.[7,8] A 4DCT dataset consists of multiple 3D image sets with each set representing a different portion, or phase, of the respiratory cycle. By combining all the phases, the extent of tumor and organ at risk motion for an individual patient can be analyzed. Patient breathing irregularity and variation in the patient breathing pattern during the 4DCT

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acquisition could introduce artifacts in the 4DCT[9] and should be closely monitored during the simulation. Maximum intensity projection (MIP) dataset, which is derived from the 4DCT by taking the highest intensity value for each voxel among all breathing phases, can then be used for target delineation. Similarly, an average intensity projection (AIP) images can be derived using the average intensity value for each voxel among all breathing phases. The AIP images allow the visualization of the averaged tumor location and often used as planning dataset for dose calculation.[10]

In conjunction with the 4DCT, the use of FDG-PET for the purpose of radiotherapy target delineation is recommended[11] because of the diagnostic benefit in the detection of lymph node metastases.[12] Owing to challenges of this technique that is involved in the registration between diagnostic PET/CT scan and simulation CT, acquiring a PET/CT scan in the radiotherapy treatment position for the purpose of target delineation is recommended by an IAEA report.[11] Because the time elapsed for PET imaging is much longer than the respiratory cycle, the contours generated from PET/CT usually contain the entire motion trajectory of a lung tumor.

MR imaging can also be used to image the motion of lung and abdominal tumors. Cai and Yang et al.[13,14] demonstrated that by retrospectively sorting 2D cine-MR images into respiratory phases, 4D-MRI is feasible, accurate, and could potentially offer improved tumor CNR compared to 4DCT. In addition, the absence of ionizing radiation with MRI could be favorable for continuous imaging of the patient, such as the case in real-time motion assessment and construction of motion models.[15] However, using MRI data for treatment planning purposes faces challenges such as geometric distortions,[16] and lack of electron density and attenuation coefficient determination.[17]

It has also been proposed that a pulmonary ventilation map could be extracted from 4DCT,[18-21] SPECT,[22] PET/CT[23] or MR[24] scans. The ventilation map could be used as an indication of lung function and to reduce dose to highly functional regions of the lung in the treatment planning process. Studies have shown that it is possible to significantly reduce the functional lung region dose when ventilation images derived from 4DCT, SPECT, or[3] He-MRI are used for IMRT planning.[21,24]

Margin-Based Treatment Planning

4DCTs are routinely used for target and critical structure delineations for radiotherapy and are often supplemented with other imaging techniques such as free breathing/breath hold CTs, PET/CT, MRI images, and fluoroscopy. ICRU report 62[25] described the use of an internal margin (IM) to account for expected physiologic movements and variation in size, shape, and position of the CTV during therapy and the use of an internal target volume (ITV), which represents the volume encompassing the CTV and IM, in the treatment planning. For this purpose, it is necessary to evaluate the entire 4D image sets, which contains multiple 3D image sets (phases), to account for the entirety of the tumor motion. In practice, however, because the CTV cannot be visualized using current imaging techniques, contours of gross tumor volumes (GTVs) in all phases of a 4DCT scan, or GTV in the maximum intensity projection (MIP) scan, along with GTV delineated on other imaging studies including MR or FDG-PET imaging, are often used instead to form the internal gross tumor volume (IGTV), and the ITV is then determined to be the IGTV plus a margin that accounts for microscopic disease.[26-28] Contouring on MIP is more convenient compared to contouring on all phases of 4DCT. However, MIP images may lead to uncertainty/error when mobile structures are adjacent to structures that have similar (or higher) densities. Ezhil et al.[26] found that using a MIP-based approach alone underestimated IGTV volume for lesions near the mediastinum, diaphragm, liver or chest wall and recommended that MIP-defined GTV contours should be verified (and modified as needed) for each individual phases of the 4DCT. Since the ITV approach takes the entire extent of the tumor motion into account to ensure tumor coverage, the ITV is always larger than the actual CTV at any given moment during the treatment delivery, and consequently, increases delivered dose to normal tissue surrounding the tumor.

Setup margins (SM) were added to the ITV to create the PTV, as recommended in ICRU report No. 62. SM accounts for random and systematic setup uncertainties associated with patient setup,[29] and image guidance has a strong impact on the magnitude of the setup uncertainties. In general, more frequent imaging enables better accounting of systematic and random setup uncertainties, and thus leads to margin reduction.[30,31] When daily IGRT is employed during treatment, typical PTV margins are on the order of 5-10 mm, whereas the margins should be much larger (10-20 mm) without the daily IGRT.[8] The ICRU Report No. 62 also recommends that a margin be added to an organ-at-risk from a planning organ at risk (OAR) volume (PRV) to account for variation in the OAR position.

In state of the art treatment planning systems, treatment planning and optimization can only be performed on a single 3D CT dataset. For free breathing treatments, the planning dataset could be free breathing (FB) CT, MIP, AIP or mid-ventilation CT. In a study comparing dose calculation on FB, MIP, and AIP in 20 lung cancer SBRT patients, Tian et al. suggested that while no substantially dosimetric characteristics were observed, AIP appeared to be favorable for planning and dose calculation due to concerns that FB datasets may be prone to significant image artifacts, and MIP may overestimate or underestimate the target volume when the target is closer to the denser tissue.[32] Another study by Glide-Hurst et al. showed that dose calculated on AIP yielded a close approximation to the full 4D dose calculation and outperformed dose calculation on end inhale phase or mean position CT.[33] 4D dose calculation involves dose calculation on all phases, the transformation of dose calculated on each phase to a reference phase, and dose accumulated on the reference phase. Although 4D dose calculation is considered a more accurate representation of delivered dose, the application of 4D dose calculation in clinical practice is still very limited.[34]