



Recent Advances and Challenges in Adaptive Radiotherapy for Patients with Locally Advanced NSCLC

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Abstract

Patients with locally advanced Non-Small Cell Lung Cancer (NSCLC) often show significant tumor regression and anatomical changes during the course of radiation treatment. As reaction to these changes, planned treatment parameter will be modified multiple times so that the overall treatment can be optimized. This is termed as Adaptive Radiotherapy (ART). While significant progress has been made in the past few years for development of different ART techniques, challenges still exist in implementation of this treatment modality in clinic. In this topical review, techniques used in different ART components will be briefly reviewed, and strategies to maximize the efficacy of adaptive treatment will also be discussed.

Introduction

Lung cancer is the leading cause of cancer death worldwide; it is responsible for over 1.6 million deaths a year [1]. Most patients with Non-Small Cell Lung Cancer (NSCLC) are treated either with Radiotherapy (RT) alone or by a combination with chemotherapy [2]. Technique development in radiotherapy has made significant progress in the past two decades. For example, Intensity-Modulated Radiotherapy (IMRT) has a better sparing of critical organs than 3D conformal treatment [3]; On-Board Imaging (OBI) enables real-time corrections of patient setup errors [4,5], facilitating Stereotactic Body Radiotherapy (SBRT). These techniques have increased the efficiency of radiation treatment, reduced radiation toxicity to surrounding normal tissues [6] and improved clinical outcomes for patients with early stage NSCLC [7-9].

Although the underlying mechanisms of the SBRT approach are not fully understood, the success of this regimen is likely a result of the significantly higher dose (BED's >100 Gy) delivered in a highly focused way to the tumor [10-12]. For patients with locally advanced cancer, the ability to escalate dose significantly, however, is often limited by the increased risk of normal tissue complications due to the large size of the tumor [13-15]. On the other hand, investigators have observed a significant reduction in tumor volume during fractionated radiotherapy. One study showed that the tumor volume decreased by ~41% (range: 32.9% to 49.6%) and the metabolic activities decreased by 69% on average (range: 62.2% to 76.8%) [16]; other studies reported tumor volume regression of ~1.2% daily and ~52% by the end of treatment [17,18]. The reduction in tumor volume makes it possible to use a carefully validated ART paradigm to reduce normal tissue toxicity, enable iso-toxic dose escalation to the residual tumor target, and consequently improves treatment outcomes for these patients.

Advances in Development of ART Techniques

Adaptive radiotherapy consists of multiple steps: developing an initial treatment plan for the first few fractions, evaluating treatment response using CT, CBCT or PET images, updating Gross Tumor Volume (GTV) and Planning Target Volume (PTV) based on the measured treatment response, revising the original prescription on the target volume according to an adaptive protocol such as the principle of iso-toxic dose escalation, and developing an adaptive plan through re-contouring, dose accumulation, and plan re-optimization. Because tumor and patient anatomy may change significantly after a few fractions of treatment, Deformable Image Registration (DIR) is required to help perform these tasks.

Deformable image registration

DIR plays a key role in implementation of adaptive radiotherapy. Development of an accurate, robust DIR algorithm has been an active area of research. Optical flow-based "demons" and B-spline-

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based free form are two most popular registration algorithms used in clinical RT planning systems. In the past two decades a variety of modifications have been applied to improve the performance of these algorithms. For example, the original “demons” [19] has been enhanced to be efficient [20], inverse consistent [21] and diffeomorphic [22,23]; the B-spline-based algorithm [24] has been extended to be hierarchical [25] and diffeomorphic [26], or have non-uniform knot placements [27] and simplified regularization forms [28]. Furthermore, these registration methods have been integrated with mechanical models to improve their performance in regions with low contrast intensity gradients [29] and for cross-modality deformable image registration [30]. The technical developments have greatly improved the efficiency of contour propagation [6,31,32] and dose accumulation [33,34], and advanced the research of adaptive radiotherapy.

Contour propagation

Updating an initial RT plan multiple times may help maximize the ART benefits [35]. However, it is time-intensive to contour tumor target and Organ at Risk (OAR) for each of these plan adaptations [36]. To address this issue, DIR algorithms were employed to propagate OAR contours automatically from the original planning CT images to during-RT images [37,38]. Due to limited contrasts and gradients in during-RT images, the registrations could have large errors, and the propagated volumes should be thoroughly assessed [6]. Also to minimize the influence of tumor regression on the registration of surrounding structures, it was recommended that the registration’s displacements in the tumor region be corrected with a mechanical model [33] or alternatively, image information in regions nearby the tumor be excluded from the registration [39].

Dose accumulation

Optimization of an adaptive plan requires radiation dose delivered to each image voxel to be accumulated appropriately over the course of treatment. The accuracy of dose accumulation depends on the DIR and dose mapping methods used. Currently most registration algorithms could be accurate within 2 mm to 3 mm on average [40-42], which is comparable to the resolution of dose grids often used in clinic [43,44]. The spatial uncertainties may result in dose mapping errors up to 3 Gy/mm [45], but in clinical scenarios the impact of these errors could be limited [46]. On the other hand, even with a correct registration map, dose interpolation methods still have inherent errors in regions of high dose gradient [47]; also Deformable Dose Accumulation (DDA) can be compromised by changes in the mass and volume of solid tumors and/or normal tissues over the course of treatment. To address these issues, 4D Monte Carlo-based methods such as Voxel-Warping Method (VWM) [48], Energy-Mass Congruent Mapping (EMCM) [49] and energy-conserved registration methods [33,50] were proposed to help improve the quality of dose accumulation.

Quality assurance

Adaptive treatment planning involves multiple computational tasks such as 3D dose calculation, DIR, dose warping and accumulation. Ideally these tasks could be separately verified for each patient. Unlike 3D dose calculations which can be verified with homogeneous and heterogeneous do simetric phantoms during the commissioning of treatment planning systems, the actual dose delivered to deforming organs over the treatment course is difficult to verify [51]. Since there is a lack of a gold standard to evaluate the DIR and DDA operations directly, alternative verifications must be

performed.

Landmark and contour comparisons and Dice similarity coefficients are often used as criteria to evaluate the performance of DIR in various applications including contour propagation [41,52-54]; the self or inverse consistency of deformation maps also can be used to help evaluate the accuracy of the registration [21,55,56]; computational phantoms offer another option to verify the accuracy of displacements directly at each voxel. The phantom’s deformation can be simulated using different mathematical formulae [20], and the realism of the deformation can be enhanced with patient-specific deformable models [57]. Different from computational phantoms, physical phantoms may help measure the delivered dose to verify dose accumulation operations. However, these phantoms are limited in simulation of mass changes in tumor and other organs during the course of treatment, and also do not have realistic organ deformation and mass heterogeneity as patients [58-60]. Therefore, further improvement of these phantoms is required, and the phantom-based evaluations should be supplemented by other verification methods such as the energy conservation criterion that can be applied to both deformed anatomical structures and regress tumor volumes [33,50].

Response assessment

In clinic tumor response is evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST), based on changes in measured tumor volumes [61]. Note that tumor volume may increase during the course of treatment, for example, due to internal hemorrhage, necrosis, or metabolically non-viable tumor cells miscounted in the measured volume. Also there are uncertainties when only CBCT images were used for the volume measurement [18]. Since FDG-PET images can show metabolic activities in addition to the tumor size, it has been recommended that both CT and PET images be used for measurement of mid-treatment tumor response for adaptive RT [62,63]. It should be mentioned that the Standardized Uptake Value (SUV) of PET images could be influenced by many factors [64-66], and also changes in region-specific SUVs cannot be quantified until correct deformation maps are applied [66-68]. Methods for quantitative assessments of tumor response are worth further investigations.

Prescription for adaptive planning

It has been reported that for locally advanced NSCLC, dose regimens in the range of 60 Gy to 66 Gy produce 5-year overall survival rates of 10% to 15% [69]. Although a randomized trial did not show superiority at a dose of 74 Gy vs. 60 Gy [15], the reasons for the under performance of the higher dose arm are still unclear [70-72]. Many technical factors such as respiratory motion management, treatment planning margins, type of delivery (IMRT vs. 3D-CRT), use of FDG-PET and image guidance in the treatment planning and delivery process could be further analyzed [70,73]. With improved RT planning and delivery techniques, it is possible to have the normal lung and heart better spared from radiation, and dose-intensified RT schedules safely administered [69]. It has been found that for patients with locally advanced NSCLC, ART may increase radiation dose to the residual tumor target up to 80 Gy on average, without increasing dose to normal tissue [74,75]. However, more clinical data should be collected to evaluate the impact of ART on normal tissue dose reduction.

For patients with locally advanced NSCLC, it has been reported that increasing dose from 60 Gy to 74 Gy results in predictable, deleterious effects on quality of life [76]. For these patients, RT-

induced adverse events may include pneumonitis, esophagitis and pericarditis [77], and therefore radiation dose to these organs should be minimized. Compared to dose escalation, it is of equivalent importance to develop effective treatment strategies to mitigate normal tissue toxic effects for these patients.

Decision for plan adaptation

For patients with NSCLC, initial plans were suggested to be updated if tumor regression is up to 30% within the first 20 fractions [78]. With a single adaptation at mid-treatment, approximately 65% of the potential dose escalation can be achieved [35]. Since tumor may continuously shrink during the course of treatment, there is a tradeoff between the amount of the reduced tumor volume and the number of the remaining fractions [79]. It has been reported that plan adaptation performed around fraction 15 and fraction 20 is most diametrically efficient for concurrent and sequential chemoradiotherapy, respectively [79]. Based on iso-toxic Mean Lung Dose (MLD), re-planning twice at weeks 2 and 4 may achieve an average escalation of 13.4 Gy [75], and at weeks 3 and 5 may have an average increase of 7 Gy or a reduction in MLD of approximately 8% [12]. Since tumor shrinkage depends on many factors such as tumor histology, location, stage and imaging modality used in the volume measurement, the optimal time point for plan adaptation and its dosimetric gain could be different for individual patients.

Challenges

Adaptive radiotherapy holds great clinical promise in iso-toxic escalation of radiation dose to target structures and also in reduction of normal tissue complications [80]. Tremendous progresses have been made in development of deformable dose accumulation and re-planning techniques in the past years. However, some critical issues remain to be addressed before this treatment modality is accepted generally in clinic for treatment of NSCLC patients [81].

Since tumor response is not uniform, survived tumor cells may exist sporadically. The CTV margin required for the adaptive plan could be different from that used in the original plan where the margin was designed to cover sub-clinical disease spread from the original gross tumor volume [82]. While PET images, after appropriate registrations, may help measure region-specific tumor response, the resolution of these images is limited, and the survived tumor cells cannot be detected effectively. Also as tumor response to radiation is patient dependent, it is not clear what is the optimal dose required to eliminate the remaining tumor cells, and how much doses should be delivered by the adaptive plan, respectively, to the remaining tumor and to those regions where the tumor is no longer visible from the during-RT images [70].

The accuracy of DIR remains the major concern in the clinical implementation of ART. It has been illustrated that intensity-based DIR algorithms are prone to have errors in regions with low image contrasts [40,42,83], and consequently, errors in dose reconstruction and response assessment may exist in these regions. Also due to the lack of knowledge on the pattern of tumor regression, how to deform the anatomical structures near by the tumor is still unclear [74,80]. Despite some improvements being made using mechanical models, the parameters and constraints of these models remain to be optimized and the accuracy of these algorithms in clinical settings needs to be further evaluated.

Conclusions

Patients with locally advanced NSCLC often have tumor

regression during the course of fractionated radiotherapy. Updating an initial RT plan at multiple time points may help spare normal tissue and enable dose escalation to the residual tumor target. With more clinical trials, adaptive strategies can be further optimized to improve clinical outcome for these patients, and consequently help migrate the modality of adaptive radiotherapy into general use in clinic.

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