Adaptive radiotherapy for anatomical to changes

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Adaptive Radiotherapy for Anatomical Changes

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The anatomy of cancer patients changes between radiation treatment planning and delivery as well as over the course of radiotherapy. Adaptive radiotherapy (ART) aims to deliver radiation accurately and precisely in the presence of such changes. To that end, ART uses an imaging feedback loop to quantify these changes and modify the treatment plan accordingly. This paper provides an overview of anatomical changes occurring over the course of therapy and various adaptive strategies developed to account for those. Moreover, residual uncertainties present in adaptive radiotherapy are discussed as well as required tools, potential pitfalls and remaining challenges.

Introduction

Radiotherapy aims to deliver a high therapeutic dose to the tumor while minimizing exposure to the surrounding healthy tissue. In external beam radiotherapy, patients are treated with multiple megavoltage (MV) photon beams generated with a linear accelerator (linac). The treatment plan is generally designed based on a single computed tomography (CT) scan acquired one or more weeks before treatment. The total radiation dose is typically delivered in smaller daily portions over a period of several days to weeks, to exploit the higher repair capacity of normal tissue compared to tumor cells. Between radiation treatment planning and delivery as well as over the course of radiotherapy, however, anatomical changes frequently occur. Consequently, the dose actually delivered differs from the planned dose.

The traditional approach to account for anatomical changes is to apply a safety margin around the clinical target volumes to ensure coverage of these targets.[1] Consequently, however, surrounding noninvolved tissue is also exposed to high levels of radiation, increasing the risk of unacceptable side effects.[2] To reduce these safety margins, Image-guided RT (IGRT) has been developed.[3] IGRT is the process of acquiring images of the patient's anatomy (in the treatment room), comparing the position of the tumor (or surrogate) during treatment with the planned position and correcting the treatment position. While IGRT has been widely adopted in clinical practice, it has a limited solution space as it assumes that the target has an (almost) invariable shape and the dose to the organs-at-risk (OAR) does not change considerably. Anatomical changes frequently do not match these assumptions, such as for example posture changes, differential motion between primary tumor and involved lymph nodes, shape changes of bladder or cervix, weight loss, and tumor regression. Adaptive radiotherapy (ART) aims to deliver radiotherapy accurately and precisely in the presence of such changes. To that end, ART uses an imaging feedback loop to quantify these changes and modify the treatment plan accordingly.[4] This paper describes an overview of anatomical changes occurring over the course of therapy and various adaptive strategies developed to account for those. Moreover, residual uncertainties present in adaptive radiotherapy are discussed as well as required tools, potential pitfalls and remaining challenges.

Anatomical Changes

Anatomical changes occur over various time scales, ranging from seconds for cardiac and respiratory motion, to minutes for bladder filling and peristaltic motion, days for prostate

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rotations, rectal filling, lung re-ventilation and cervical shape changes, and weeks for treatment-related changes such as weight loss, radiation-induced diarrhea and tumor regression. Adaptations to changes occurring within a treatment fraction fall out of the scope of this paper and are comprehensively discussed in Keall et al.[5]

Anatomical changes can occur in any region of the body/disease site and can affect tumors as well as healthy organs. The skull is often considered an adequate surrogate for cranial lesions, but shifts of brain metastasis up to 5 mm have been reported.[6] In head and neck radiotherapy, posture changesof 3-4 mm (systematic [Σ] and random [σ]) have been observed.[7] Additionally, tumor volume reduction at a median rate of 1.8%/d as well as parotid volume change of 0.19 cm^3/d have been reported.[8] Between simulation and the first fraction, on the other hand, a median increase of 16% was reported.[9]

In locally advanced lung cancer patients, differential motion between primary tumor and involved lymph nodes of 2.5 mm (Σ and σ) was observed.[10] Similar to head and neck cancer, a median GTV increase between simulation and planning of 35% was reported. Lung tumor regression during treatment ranges from 0.6% to 2.4%/d,[11] while also other intrathoracic changes in atelectasis and pleural effusion are regularly observed.[12]

In breast cancer, an average seroma reduction of 62% was observed affecting the size of the boost volume.[13] Additionally, position variability of the heart of about 3 mm (Σ and σ) have been reported for left sided breast cancer patients.[14]

Similar to lung cancer, in esophageal cancer radiotherapy, considerable primary tumor position variability has been reported, averaging 3-4 mm in 3D.[15] As considerable larger variability was observed for distally located lesions, considerable differential motion relative to the CTV can be inferred. Also median volume changes at fraction 20 of 22% and 34% were reported for distal and middle esophageal cancer respectively.[15] For gastric lymphoma, large interfractional deformations of the stomach have been reported up to 9.3 ± 22.0 mm in the anterior-posterior direction.[16]

For bladder cancer, interfraction bladder wall motion ranged from 1 mm (Σ and σ) at the caudal side to 12 mm (Σ and σ) at the cranial-anterior side of the bladder despite drinking protocols.[17] Variations in bladder filling also cause shape changes in cervix cancer, where displacements at the tip of the uterus up to 50 mm have been reported.[18] Cervix motion is smaller with Σ ranging from 3.4-5.5 mm and σ ranging from 2.2-4.5 mm.[19]

While for prostate cancer, IGRT approaches are effective to correct for organ motion, prostate rotations typically remain uncorrected. These are primarily observed around the left-right axis with $\Sigma = 5.1°$ and $\sigma = 3.6°$.[20] Additionally, radiation-induced diarrhea causes time trends in rectal volume over the course of treatment.[21]

For preoperative rectal cancer radiotherapy, where the mesorectum represent the CTV, the interfractional variability of the upper-cranial region ranges from 2 mm till 7 mm (Σ) at the cranial-anterior side.[22] Finally, in preoperative radiotherapy of extremity soft tissue sarcomas, volume changes ranging from −57% to 28% were reported.[23]

The overview above illustrates that large geometric uncertainties remain for many disease sites despite the use of extensive image guidance. To account for such geometric uncertainties, margins ranging from 5 mm (head-and-neck) to 40-50 mm (bladder and stomach) are required. By correcting for such anatomical changes ART has the potential to improve the quality of RT for a wide range of disease sites, reducing margins, OAR exposure and toxicity and/or facilitating dose escalation and improved tumor control.

Concepts of Adaptive Radiotherapy

The concept of adaptive radiotherapy was introduced by Di Yan[24] as an imaging feedback control strategy to include patient-specific treatment variation in treatment plan modification. “A complete implementation should include 4 key components, which are (1) treatment dose assessment, (2) treatment variation identification/evaluation, (3) treatment modification decisions, and (4) adaptive treatment modification”.[4] Frequently, however, only 2 or 3 components are used in adaptive strategies, in part depending on the type of anatomical change to be adapted to.

Roughly, 3 types of anatomical changes can be distinguished in radiotherapy. Firstly, the anatomy changes from day to day. During the acquisition of the planning (CT) scan, the anatomy is frozen in an arbitrary configuration that may not be representative of treatment delivery. Consequently, a systematic error is introduced into the process. Secondly, these day-to-day anatomical changes also occur during treatment delivery and thus represent a random error. Finally, the treatment itself can cause anatomical changes that typically increase gradually over the course of therapy. Due to these time trends, such anatomical changes have both a systematic and a random component. Different strategies have been developed to account for these types of anatomical changes as detailed below.

Average Anatomy Model

Systematic errors can be mitigated through offline corrections while random error corrections require online strategies. Systematic errors induced by freezing the anatomy in an arbitrary configuration during simulation can thus be effectively corrected for offline. To that end, the average anatomical configuration during treatment needs to be estimated. Similar to offline decision rules for setup error and organ motion,[25,28] such strategies rely on the quantification of anatomical changes over the first number of fractions of RT. Initially, such an adaptive strategy was developed to reduce systematic rotational deviations in prostate cancer patients.[26] That is, by measuring the daily prostate rotation relative to the planning anatomy during for example the first week, the average prostate rotation can be estimated and a new treatment plan in which the CTV has been rotated accordingly can be optimized.

This concept can be extended to more complex anatomical changes. An average anatomy model can be estimated by

(1) deformable registration of the planning scan to the scans of the initial fractions, (2) calculating the average deformation vector field, and (3) deforming the planning scan and corresponding structures accordingly[27] to obtain a synthetic scan representing the average anatomical configuration. A new treatment plan can subsequently be optimized on the average anatomy model. Such strategy needs to balance on the one hand the number of fractions used to make an accurate estimate of the systematic error while on the other hand leaving enough fractions that can benefit from an adapted plan. Optimal time points ranges from about 5 to 12 scans depending on the accuracy of the estimation, the balance between systematic and random errors and the total number of fractions.

The average anatomy model described above only uses two components of the general adaptive framework: variation assessment and adaptive modification. A modification decision can be added to select only patients with larger systematic error to balance workload and efficacy similar to a shrinking action level protocol.[28] Furthermore, a dosimetric assessment can be added to improve patient selection and or treatment plan modifications.

Library of Plans

To account for random anatomical changes, online approaches are required, adapting each treatment fraction to account for the anatomical changes observed on each particular day. The approach most commonly implemented consists of a library of treatment plans, created "a priori", to account for expected anatomical changes such as variations in bladder volume. Though the "library of plans" (LoP) approach is arguably easier to implement than other forms of adaptation, it is worth noting that the details of its practical implementation vary widely. The different plans are typically made on a single CT scan (eg an "empty bladder" scan) with interpolated and possibly even extrapolated contours obtained from additional scan(s) (eg a "full bladder" scan) and deformable registration.[18] Alternatively, a LoP can be made on different CT scans (eg a "full bladder" scan followed by an "empty bladder" scan [29] or using multiple CBCTs of the first few fractions.[30] Instead of creating a library based on patient specific variations, one can also design a library based on population statistics to generate different CTVs [31] or PTVs.[32]

For each treatment fraction, the best plan from the library is subsequently selected, typically using visual comparison of the daily in-room scan with the contours of the library plans. For practical reasons, only libraries containing a limited number of plans (2-5) can be generated. Consequently, the application of a LoP strategy is limited to anatomical changes that are dominated by a single variable, such as bladder filling or the associated cervix-uterus shape change. To account for more complex random anatomical changes, online replanning strategies are required as described below. A LoP approach primarily uses the treatment variation evaluation and treatment modification decisions of the general adaptive framework. Note that the case where the library is generated prior to the first fraction, the treatment plans itself are not modified based on a feedback loop.

Triggered Adaptation

To account for time-dependent changes, triggered adaptations are frequently applied. Triggered adaptation refers to the process of adapting the treatment plan when exceeding a certain "threshold," for example, when the patient experienced considerable anatomical changes such as weight loss. In its simplest form, this is arguably the most common form of offline adaptation, pre-dating the introduction of the term "adaptive radiotherapy". In most cases, the criteria for triggering an adaptation are qualitative, for example, the fixation equipment is no longer appropriate, or the anatomical changes are judged significant on visual examination (eg, Ramella et al 2017).[33] Kwint et al[12] have described a semi-quantitative traffic light protocol for intrathoracic changes. Some reports have described objective criteria, based on geometry and or dosimetry. For example, Møller et al[34] described a strict set of criteria based on a combination of changes in the position of the tumor, lymph nodes and OARs in NSCLC/SCLC patients and dosimetric impact. Adaptation is then triggered if the defined criteria are violated in 3 consecutive fractions.

Ideally, adaptive replanning is triggered based on dosimetric criteria. By recalculating the treatment plan on daily images and accumulating the dose, the delivered dose can be estimated.[35,36] Subsequently deviations compared to the planned dose can be used to identify patients who require adaptive replanning. This triggered adaptive approach thus uses treatment variation identification, treatment modification decisions, and adaptive treatment modification and can be extended with treatment dose assessment.

Scheduled Adaptation

Triggered adaptation has the disadvantage of being unpredictable: arrangements for re-scanning/replanning can only be made once a change has been observed. In contrast, scheduling the time-point(s) of the adaptive process enables departments to predict which resources need to be allocated. Rescanning can occur once (eg, halfway through the treatment course) or several times (eg, weekly during the treatment course).[37] To limit required resources, the original treatment plan can then be transferred and recalculated on the new anatomy to judge if it is still fulfilling the clinical objectives of tumor coverage and OAR sparing.[38] It is worth noting that most studies reporting on the efficiency of scheduled adaptation are retrospective and often on a limited number of patients.[23,39,40]

Online Replanning

To account for both systematic and random complex anatomical changes as well as time trends, daily online replanning can be considered. With such an approach the plan is

reoptimized every treatment fraction. The challenge is to condense the time of scanning and treatment planning traditionally spanning a few days to a few weeks, to a few minutes. To accelerate the treatment planning process, Ahunbay et al.[41] proposed a geometric approach named segment aperture morphing (SAM), where the beam/segment apertures are adjusted by applying the spatial relationship between the planning target contour and the apertures to the new target contour. Such an approach was shown to be practically equivalent to full-scope reoptimization in prostate cancer radiotherapy. Similarly, to account for 6D setup error in fractionated mask based stereotactic radiosurgery, the planned shot positions of the Gamma Knife Icon (Elekta AB, Stockholm, Sweden) can be reoptimized.[42] The introduction of MR-guided radiotherapy machines[43,44] has further illustrated the feasibility of daily online replanning. The high soft-tissue contrast of MRI is exploited for (partial) recontouring of the anatomy and full replanning at the expense of longer treatment time slots.

Tools and Requirements

Although the concept of adapting radiotherapy using in-room images is not new, the software tools required to facilitate this process are not fully mature and their performance must be continuously evaluated. Both offline and online approaches require a feedback-loop encompassing image acquisition, image evaluation, plan generation/selection and (possibly) new image acquisition for verification.

For the average anatomy model approach, the image quality should be high enough for accurate registration.[45] Software tools for subsequent processing of registration results, however, are currently not commercially available. An average anatomy model based on repeated delineations[46] does not need additional tools and could be implemented using standard treatment planning software. Similar to alternative approaches, however, automation in delineation and planning facilitates efficient workflows.

Various approaches of the library of plans strategy have been reported.[47] The approach to acquire sequential scans with different bladder filling could be implemented using standard treatment planning software. An alternative approach is to acquire 2 scans and use a motion model to interpolate between those scans. Such interpolation strategies are currently not commercially available. Finally, an approach to design a library based on the scans of the first week requires adequate image quality to delineate the target on these scans. For all approaches, proper training to select the adequate plan from the library is mandatory.[48]

Scheduled adaption has the advantage of using the standard treatment planning pathway: a new “treatment planning” quality image is acquired during the treatment, satisfying the same image quality criteria for delineation and dose calculation as the original treatment planning image. To reduce the workload for any adaptive strategy, contour propagation and automatic planning would be useful tools as described above. A major limitation of this approach is the general lack of knowledge of the optimal time point at which to schedule one or several adaptations. Such time point should balance the time that relevant changes have occurred and the remaining number of fractions that can benefit from an adaptive replan. Additionally, the efficiency of such an approach would increase with accurate selection of patient that would benefit from an adaptive intervention.[49,50]

For triggered adaptation, qualitative or semi-qualitative criteria require no dedicated software or image processing, only sufficient image quality to make a clinical judgment call. However, in order to limit interobserver variation, some guidelines and training are essential.[12] Where quantitative criteria are used, the images must be of high enough quality for manual or automatic delineation. For in-room CT this will generally be the case. The adequacy of CBCT for this purpose depends on disease site[51,52] and image quality.[53,54] Though various approaches provide a reasonably accurate dose calculation on CBCT as described below, most clinical approaches still rely on the Hounsfield units from diagnostic quality scans, either from the original treatment planning scans or from rescans acquired for this purpose. For in-room MR, image quality is expected to be adequate provided that proper sequences are used. Ideally, those images would also offer an accurate map of electron density (enabling reliable dose calculation). Note that for triggered adaptations the frequency of repeat imaging should be high enough to timely capture relevant changes.

Finally online replanning requires high image quality and both fast delineation and fast replanning within a single treatment fraction. At present, the delineations are either completely or partially manual and treatment times are typically double or longer than normal fractions.[44,55] Further acceleration is therefore warranted to implement online replanning on a larger scale.

Treatment planning systems are well equipped to perform a straightforward adaptive replanning. Frequently, also a "warm start" is available where the initial treatment plan is reoptimized using the final objectives and constraints on the new image and structures. More dedicated tools for adaptive replanning to take into account patient-specific variation, delivered dose, and adapting the objectives to the observed changes and variations[4] are typically not available.

A weak point of all approaches is the reliability of the criteria to identify patients for adaptation: a high number of false negatives can be a concern, as patients who could benefit from adaptation would go undetected) while false positives result in a high resource burden. The lack of quality assurance tools for the newly created adapted plan is a concern, especially for online approaches.

These issues could be mitigated by introducing software solutions processing all longitudinal images available for one patient instead of triggering an adaptation based on a single “image of the day”. Appropriate software tools (eg, reliable automatic delineation and dose accumulation) may also reduce the resource burden slightly as described below.

Clinical Applications of Adaptive Radiotherapy

Although adaptive radiotherapy is not widely adopted in clinical practice, various clinical applications have been described in the literature. Some characteristic examples are described below.

Prostate cancer radiotherapy was one of the first disease sites where adaptive protocols were clinically implemented. Nijkamp et al[56] described the clinical results of the first twenty patients treated with an off-line ART protocol using CBCT. Patients began treatment with a standard PTV margin. The CBCT scans acquired during the first six fractions were used to generate an average prostate CTV based on local rigid prostate registration,[26] after which a new treatment plan was generated with a reduced PTV margin. A safe margin reduction of on average 29% was reported while the volume of the rectum that received >65 Gy was reduced by 19% and the mean dose to the anal wall was reduced on average by 4.8 Gy. Park et al.[46] report on a large cohort of 992 prostate cancer patients treated with offline ART. The target motion was assessed with daily CT during the first week from which patient-specific confidence-limited PTVs were then constructed. Authors report excellent biochemical control that was independent of rectal volume/distension in contrast to de Crevoisier et al[21] while maintaining very low rates of chronic GI toxicity. The feasibility of daily online plan adaptation to account for 6 degrees of freedom of prostate motion using geometrically adapted IMRT segments was shown in a cohort of 39 patients and allowed safe margin reduction down to 5 mm in 31 of 39 patients.[57]

The nonrigid day-to-day target motion in cervix cancer radiotherapy is well suited for a library of plans approach. Heijkoop et al.[92] report on the clinical evaluation of such a protocol where full and empty bladder CT scans were acquired prior to treatment to build a bladder volume-dependent cervix-uterus motion model for establishment of the plan library. In patients showing >2.5 cm bladder-induced cervix-uterus motion, two IMRT plans were constructed, based on model-predicted internal target volume for empty-to-half-full and half-full-to-full bladder. Otherwise only a single IMRT plan was constructed based on the full predicted motion. The PTV combined the ITV(s) and nodal CTV expanded with a 1 cm margin. Additionally a 3D conformal radiotherapy (3DCRT) motion-robust backup plan was created. Daily CBCT scans were used to position the patient based on bony anatomy and nodal targets and select the appropriate plan. In 11 out of 40 patients, two IMRT plans were created. An IMRT plan was chosen in about 81% of the fractions and reduced the bowel cavity volume receiving 99% of the prescription dose by 26%-29%.

For bladder cancer radiotherapy, different adaptive approaches have shown to be feasible in clinical practice. An average anatomy model, using the first five CBCTs to generate an ITV expanded by 1 cm was used in a multi-center study and reduced the treatment volume by about 40% without compromising target coverage.[58] Tuomikoski et al.[59] evaluated a LoP approach consisting of 3 to 4 plans generated on successive planning CTs acquired over 15-30 minute intervals. In five patients, this reduced the average volume of intestinal cavity receiving ≥ 45 Gy by 46% compared to a conventional strategy while maintaining similar CTV coverage. Meijer et al.[60] used a full and voided bladder scan combined with an interpolation model to generate 6 IMRT plans with concomitant boost. Lipiodol markers were used to align the GTV, followed by plan selection to maintain full bladder coverage. In twenty patients no grade 3 urinary or gastrointestinal toxicity was observed and after a median follow-up of 28 months two local relapses occurred. A bladder LoP approach consisting of 3 plans, small, medium and large derived from CBCT in the first week has been tested in two multicenter trials[61,62] containing 54 and 20 patients respectively. Both studies demonstrate feasibility in a multicenter setting with considerable reduced course-averaged PTVs. Moreover, the integral dose was reduced despite the use of daily kV CBCT imaging.[63]

For locally advanced lung cancer, Møller et al.[34] report on a triggered ART protocol where daily CBCT scans used for soft-tissue matching were systematically evaluated. In case residual uncertainties of tumor, lymph nodes or vertebrae exceeded thresholds of 2.5 and 5 mm respectively for 3 consecutive days or when large anatomical changes in normal tissue, pneumonia, atelectasis or pleural effusion persisted for 3 consecutive days, an adaptive plan was created based on a new CT scan to corrected for these changes. In a cohort of 233 patients, 27% were adapted. The trigger criteria used, correctly identified 98% of the patients requiring adaptation with a false positive rate of 20% as evaluated on surveillance CT scans. The same group also reported an increased loco-regional control rate (65% vs 47%) without increasing treatment-related toxicity in the ART cohort compared to a historical cohort without ART and larger margins. In the prospective Lartia trial,[33] 217 patients received weekly rescanning to access clinically relevant tumor regression by 2 independent physicians. Fifty patients were replanned with a CTV reduction from 155 to 91 cc after a median of 25 fractions of 1.8 Gy. In the adapted cohort, 2% and 4% of patients experienced acute grade ≥3 pulmonary and esophageal toxicity and late toxicity in 4% and 2%, respectively. In-field, marginal and out-of-field local relapse was reported in 20%, 6%, and 4% of patients.

In a retrospective analysis, van Beek et al.[64] describe a triggered adaptation protocol based on visual assessment of daily CBCT scans in head and neck cancer patients that yielded adaptations in 37 out of 416 patients. Combined with daily IGRT, this protocol allowed for a PTV margin reduction from 5 mm to 3 mm, which reduced the severity, frequency, and duration of radiation-related toxicity without jeopardizing outcome.[65] Scheduled adaptations have been prospectively studied in head and neck cancer radiotherapy. Capelle et al.[50] report on a prospective trial including 20 head and neck cancer patients receiving a second CT scan after 15 fractions followed by a new plan from fraction 20. They observed minimal benefit of routine adaptive replanning in unselected patients, and no benefit in adjuvantly

treated patients. Patients with nasopharyngeal carcinoma or with greater weight loss or reduction in neck separation did have clinically significant dosimetric benefits. Schwartz et al.[66] report on a prospective trial of 22 patients receiving one (14) or two (8) plan adaptations. While the initial plan had PTV margins of 3-4 mm, 0 mm PTVs were utilized in the adapted plans. Single ART reduced the dose to the ipsilateral and contralateral parotid by 1.3 and 0.6 Gy respectively and could be further reduced with a second adaptation.

The availability of MR guided systems has increased the interest for daily online replanning strategies and has been explored for various disease sites.[43] Pancreatic cancer is a disease site with very poor prognosis. Bohoudi et al.[67] describe a fast and robust online adaptive planning strategy for the MRIdian system (ViewRay Inc, Cleveland, OH), where OAR (re-)contouring was done only within a distance of 3 cm from the PTV surface and demonstrate good plan quality. Rudra et al.[68] treated 36 patients with locally advanced or borderline resectable pancreatic cancer using MR guided radiotherapy. Both conventionally-fractionated as well as SBRT regimens were used. In patients treated with a BED <70 Gy, only 3.6% of fractions were adapted while in patients treated with a BED ≥70, 66% of treatment fractions were adapted. Moreover, a BED ≥70 Gy was associated with improved OS in uni- and multivariate analysis. This has led a recently opened prospective multi-center phase 2 trial (NCT03621644) to investigate the safety efficacy of MR driven adaptive high dose SBRT for pancreatic cancer patients.

Residual Uncertainties

As described above, adaptive radiotherapy provides a versatile suite of techniques to reduce geometric and possibly biological uncertainties. Inevitably, however, residual uncertainties remain due to the fact that adaptive radiotherapy has finite accuracy, is powerless to some sources of geometrical uncertainties and also induces sources of geometric uncertainties novel to radiotherapy. In this section we will give an overview of these residual geometric uncertainties in adaptive radiotherapy for anatomical changes and discuss strategies to account for them.

One of the weakest links in modern radiotherapy is target delineation. Inter and intraobserver variation in target delineation is a major source of geometric uncertainty in image guided and adaptive RT.[69] Moreover, pathology validation studies to quantify the target delineation in relation to the gold standard are scarce.[70,71] In adaptive radiotherapy, the targets are delineated on new scans and thus also susceptible to target delineation errors. Repeated delineations potentially reduce the impact of intraobserver variations with the square-root of the number of delineations being part of the adaptive protocol or even interobserver variations depending on the number of observers involved. Systematic differences between imaging and pathology, however, persist despite advanced adaptive strategies or might even increase. Similarly, ART is powerless against treatment delivery inaccuracies associated with the mechanical precision of the treatment machine.[72]

Adaptive radiotherapy also introduces new sources of geometric uncertainties. First of all, the in-room imaging systems used to drive adaptive strategies such as CBCT and MRI need to be calibrated to the linac isocenter. The finite precision of such a calibration introduces uncertainty about the exact position of the anatomy during treatment.[73] Similarly, in-room image distortions add uncertainties to the exact position of the visualized anatomy.[74-76] Following image acquisition, in-room images are typically registered rigidly or deformably to the planning scan. These registrations can be used to access, for example, setup errors, quantify anatomical changes, propagate contours and accumulate the delivered dose. All these processes are influenced by the finite accuracy of image registrations.[77-79]

The adaptive radiotherapy process itself has also limited accuracy. The average anatomy approach uses the first couple of fractions to estimate systematic misalignments relative to the planning geometry to reduce the systematic. The accuracy of such an estimate is proportional to the square-root of the number of observations. Consequently, such a protocol needs to balance the number of fractions used to estimate the systematic deviations against the number of remaining fractions that can benefit from an adaptive intervention.[27] Similarly, a library of plan approach is based on a limited number of plans (typically 2-5) and thus each plan needs to cover a range of motion.[80] Moreover, the scans underlying the library of plans are typically acquired on the same day or first week of treatment and thus do not capture the full complexity of motion present during treatment.

ART is also used to account for progressive changes such as treatment response. In an offline setting, the progressive changes before and after the adaptive intervention need to be accounted for in the initial and adaptive treatment plans. In an online setting of daily plan adaptations, slow progressive changes can be accurately accounted for. However, rapid changes that occur during a fraction following the plan adaptation such as intrafraction setup variability, bladder filling, peristalsis and respiratory motion still challenges the accuracy of adaptive radiotherapy.[81–85] Although even more frequent adaptations are being explored,[86] on- and offline adaptive strategies need to account for such intrafraction variabilities.

Table 1 provides an overview of the residual geometric uncertainties limiting the accuracy of adaptive radiotherapy. Although a number of these uncertainties are quite small, their relevance increases with increasing accuracy of treatment delivery associated with advanced adaptive protocols. The Planning Target Volume concept (PTV)[1] is most widely used to account for residual uncertainties in adaptive radiotherapy. Margin recipes to calculate the appropriate PTV margins are typically based on assumptions such as rigidity, normally distributed errors, large targets, and long fractionations schemes.[69] Residual uncertainties associated with adaptive radiotherapy frequently violate these assumptions and such recipes should thus be handled with care.[87] Probabilistic planning is a more advanced method to account for geometric uncertainties[88] but not widely available.

Table 1 Overview of Residual Uncertainties in Adaptive Radiotherapy

Type of Uncertainty	Range of Uncertainty	References
Limited number of observations	$1/\sqrt{N}$ of the systematic error, with N the number of observations	69
Limited number of plans in library	1/P of the initial motion with P the number of plans in the library	80
Intra-fraction motion	2-5 mm	81,83
Respiratory motion	Peak-to-peak amplitude 0-50 mm	85
Imaging ISOC calibrations	±0.3 mm	75
Imaging distortions	CT: <1 mm	75
	MRI: <2 mm	89
Registration	Rigid: <0.5 voxel dimension	78
	Deformable: 95% <2 mm	
Contouring	4mm (1 SD)	90
Delivery inaccuracies	0.2-2 mm	72

Potential Pitfalls

While adaptive radiotherapy represents a powerful strategy to improve the accuracy of radiotherapy, there are also some important limitations that should be acknowledged. Here we discuss some caveats associated with modern adaptive strategies.

Deformable registration between a planning and repeated scan can be utilized to propagate the contours of the planning scan to the new scan. While such an approach is uncontroversial for OAR (although careful evaluation of the contours is recommended), it should be handled with care for target volumes. First of all, tumors frequently respond to radiotherapy and thus become smaller over the course of treatment.[91,92] Contour propagation through deformable registration is likely to segment the smaller tumor volume. It is, however, unclear if it is safe to adapt to these smaller volumes as the region originally occupied by the GTV might still contain microscopic disease.[93] This will depend on whether the regression was elastic (i.e., the surrounding tissue moves inward with the regressing tumor) or eroding (i.e., the remains in its original location while the tumor regresses).[11] Safety of field size reduction following tumor regression should therefore be studied in prospective clinical trials.[33] Outside such a trial, we recommend to rigidly propagate the GTV and manually check for errors.

The CTV is often defined as an expansion of the GTV. The accuracy of automatic propagation of such a CTV is highly dependent on the properties of the underlying deformable registration and algorithm and the type of GTV regression. As the CTV in this case overlaps with normal tissue that drives (in part) the deformable registration, the relation between the propagated CTV delineation and the underlying microscopic disease distribution is likely to be compromised. We therefore advise to also rigidly propagate the CTV outside a clinical trial. In case a smaller GTV is accepted in the adaptive protocol, the CTV should be carefully evaluated taking into account the initial microscopic disease distribution, the type of tumor regression and the response of the CTV to therapy. Note that when the CTV is defined by organ boundaries such as for prostate or cervix cancer radiotherapy, contour propagation using deformable registration is less controversial.

Similar to the CTV, the PTV contour also overlaps with normal tissue. The deformation of the normal tissue at the PTV contour has little or no correlation with the required PTV margin. We therefore recommend to rigidly propagate the PTV or re-expand from the propagated CTV.

Dose Accumulation as Background Dose

As described above, deformable registration for contour propagation of OAR is uncontroversial; if it looks good it is good. The underlying deformation model does not need to be anatomically correct as long as it accurately maps the organ boundaries. For dose accumulation[94], on the other hand, anatomically correct deformation models establishing tissue-to-tissue correspondence are crucial. Visual verification of deformable registration is therefore challenging in regions of homogeneous intensity and alternative strategies are required to validate deformable registration for dose accumulation.[79,95] Moreover, due to the higher complexity of deformable registration for dose accumulation the resulting accumulated dose should be handled with care. In other words, the uncertainties in the accumulated dose should be quantified and taken into account when incorporating accumulated doses into plan adaptations. Similarly, other uncertainties not captured in the images underlying dose accumulation (Table 1), should also be taken into account to evaluate the accumulated dose distribution.

Dose accumulation in Regressing Tumors

Volume changes over the course of therapy represent an especially challenging case for deformable image registration and dose accumulation. When the volume changes, tissue to tissue correspondence is no longer possible as tissue present in one scan is no longer present in the other scan. A plausible aim for a deformable registration algorithm in such a scenario is to map a voxel in the scan of the reduced volume to the corresponding expanded volume in the other scan containing the remaining tissue combined with tissue that has disappeared. As a consequence, however, when transforming scans and daily doses back to the planning CT, mass and energy are not conserved. While corrections can be applied to enforce mass and energy in such transformations[96] yielding "physically"

more correct representations, it is debatable if such corrections are also biologically more relevant.

Adapting to Dose Constraints/NTCP Models Derived From Planned Dose

During treatment plan optimization, various dose constraints and objective are used to guide the optimization algorithm to a desirable solution and to evaluate acceptability of the resulting plan. Subsequently, such a plan is delivered in the presence of geometric uncertainties and anatomical changes such that the planned dose is not equal to the delivered dose. Although adaptive radiotherapy has the potential to minimize this difference, it is important to realize that most dose constraints are based on associations between treatment outcomes and the planned dose instead of the delivered dose and stem from studies not using adaptive strategies. For example, the planned OAR maximum dose close to the PTV is likely to be an overestimation of the delivered maximum dose in fractionated treatments due to day-to-day variations,[97] while the planned mean parotid dose is often lower than the delivered dose due to weight loss and parotid shrinkage.[7] Consequently, these dose constraints cannot straightforwardly be used to evaluate acceptability of delivered dose or select patients for adaptive replanning. Similarly, in (online) adaptive replanning where differences between planned and delivered dose will be reduced compared to standard radiotherapy, the use of standard dose constraints should also be handled with care. It is therefore important that dose constraints and underlying normal tissue complication probability models are updated using delivered dose[98] to effectively use such adaptive strategies.

Remaining Challenges

Following the introduction of adaptive radiotherapy by Yan et al,[24] ART has been an active field of research. As a result, various adaptive protocols have been clinically implemented in specialized centers.[34,46,56,66,99] Large-scale clinical adoption, however, is still more a dream than a reality. To realize the full potential of adaptive radiotherapy, various challenges remain to be solved.

Imaging

Although offline adaptive protocols can be driven by the imaging systems also used for treatment simulation, in-room imaging systems provide a substantial logistic advantage. In-room volumetric imaging systems are often already being used for image guided patient alignment thus proving 3D anatomical visualization without the need to for additional imaging sessions. For online adaptive protocols, in-room imaging equipment becomes essential as scans in treatment position are required just prior to treatment. Linac integrated cone beam CT (CBC)[100] is the most widely used in-room imaging system. The image quality of linac integrated CBCT, however, is reduced compared to fan beam CT due to increased levels of scattered X-rays associated with the cone beam geometry, lower quality detector systems, and slow revolution acquisitions. Consequently, CBCT's HU accuracy and soft-tissue contrast are reduced, challenging both dose calculation accuracy and image segmentation on CBCT scans.[75,101] Methods to improve CBCT based dose calculation accuracy include HU calibration curves derived from phantoms or patients, bulk density corrections, uniformity corrections and deformable registration to propagate HUs from the planning CT to the CBCT.[102] Dose calculations accuracy varies between 8% to less than 1%. Methods to further improve CBCT image quality include hardware and software scatter mitigation,[103-106] ghosting correction,[107] respiratory correlated (4D) CBCT[108] and advanced reconstruction algorithms.[109,110] Although CBCT image quality has improved considerably over the last decade, it remains inferior to diagnostic CT. Additional efforts are thus required to achieve an image quality on par with diagnostic CT. This is especially true in the thoracic and upper abdominal region where respiratory and cardiac motion as well as peristalsis induce considerable motion artifacts.

A novel alternative to in-room CBCT is in-room MR such as the MRIdian (ViewRay Inc, Cleveland, OH) and Unity (Elekta Oncology AB, Stockholm, Sweden). MRI is well known for its superior soft tissue contrast over (CB) CT enabling advanced adaptive protocols.[111] Moreover, MRI is a more versatile imaging modality that allows a flexible tradeoff between contrast-to-noise, temporal and spatial resolution, field-of-view, and does not deposit any radiation dose to the patient. On the other hand, the image acquisition time of MRI is typically longer than for CBCT. Therefore, accelerated acquisition schemes and fast reconstructions are warranted to limit treatment time slots.[112,113] Additionally, current systems lack the ability to acquire 4D MRI's to visualize the anatomy over the breathing cycle,[114,115,116] Finally, MRI lacks electron density information required to perform dose calculation and treatment plan optimization. While bulk density overrides achieve reasonable dosimetric accuracy further developments in more advanced conversions of MRI scans to electron densities[117] would have the potential to fully replace CT in the pretreatment and adaptive workflows.

Automation

A major obstacle for large scale use of ART is the high work load. Many adaptive protocols require the acquisition of additional scans that need to be segmented and additional treatment plans need to be optimized. Using traditional workflows, this requires a lot of manual labor. Consequently, ART is often limited to a few patients with large anatomical changes. Automation is therefore a key element to expand the number of patients that could benefit from ART.

Autosegmentation

Automatic segmentation and automatic treatment plan optimization are techniques being developed to automate the treatment planning process for both conventional and adaptive workflows. Automatic segmentation [118] aims to

automatically delineate OAR and\or target volumes. Atlas based segmentation[119] is a popular approach for OAR segmentation where a set of validated OAR delineations of previously treated patients (the atlas) is propagated to a new scan using inter-patient deformable registration. Various algorithms have been proposed to combine the propagated contours into the new segmentation. Such approaches typically provide clinicians with a good starting point for review and adjustment.[120] Moreover they are less suitable for segmentation of the target volumes due to the large inter-patient variability in shape and position of gross tumor volumes. An alternative approach is to propagate the planning contours from the planning scan to the daily scan using deformable registration. Novel approaches based on deep neural convolutional networks (CNN) provide more accurate and faster auto-segmentation.[121]

Despite continuous improvements in segmentation accuracy, current clinical practice in online MRI guidance still requires manual intervention and involves radiation oncologists available at the treatment machine.[67,122] Further improvement in robust auto-segmentation is therefore warranted. For adaptive radiotherapy, improved performance might be possible by tailoring the segmentation models to the patient using the planning CT and one or more follow-up scans from previous fractions.[123] On the other hand, the quality of automatic segmentations should be evaluated in the context of inter-observer variability and thus extensive manual contour adjustments might have limited clinical relevance. Note that auto-segmentation algorithms will typically delineate the visible tumor boundaries, also in case of tumor regression thereby ignoring possible remaining microscopic disease as described above.

Automatic Planning

Although IMRT and VMAT are optimized using an inverse treatment planning algorithm minimizing a set of objectives and constraints, the initial result of such an algorithm typically requires extensive time consuming tweaking before an acceptable plan is obtained. Automatic treatment planning aims to reduce the time for treatment plan optimization, reduce plan variability and improve plan quality. Three different classes can be distinguished for automatic planning.[124] First, knowledge based planning where either a model or atlas capturing prior knowledge is utilized to predict an achievable dose distribution. Second, protocol-based automatic iterative optimization where the manual tweaking after the initial inverse optimization is performed by another algorithm following a predefined protocol of prioritization. Thirdly, an a-priory multi-criteria optimization generating a single Pareto-optimal plan based on priorities between objectives. Currently available auto-planning strategies require minimal manual interactions, but overall planning time still exceeds 30 min,[125] making them highly suited for offline ART but too slow for online ART. Novel knowledge based approaches using deep convolutional neural network to predict the 3D dose-distribution might significantly speedup the overall planning time.[126] An alternative approach for online plan adaptation is to use the final objective of the initial plan to re-optimize the plan on the new anatomy.[122] While such an approach might produce high quality plans without further "tweaking" in case the anatomical changes are small, it is unclear if such an approach is valid in case of larger anatomical changes. Note that the automated treatment planning approaches described above optimize the plan based on a single scan and corresponding delineations. To realize the full potential of adaptive radiotherapy, the accumulated dose and a prediction of future anatomical variations should also be taken into account.[4]

Approval and QA

Even when automatic segmentation and treatment planning produce robust and reliable delineations and treatment plans, two important issues remain. Firstly approval of delineations and treatment plans are typically performed by the treating physician and formally captures the treatment intent of the physician. Consequently, frequent adaptation and especially online ART requires considerable time investment from clinician for approval making large scale implementation challenging. Interestingly, in the context of adaptive radiotherapy, the delineations and plans are often adjusted in order to realize the dose distributions of the initial plan in the continuously-changing patient. Consequently, such adaptations do not alter the physician's treatment intent. In order to allow for large scale adaptive replanning, the treatment plan and treatment intend should be disentangled. Dosimetric tolerances relative to the initial plan and superiority of the adapted plan over the initial plan in the new anatomy could be ingredients of decision support systems for plan approval.

A second obstacle to large scale clinical implementation of adaptive radiotherapy is plan QA. Pretreatment patient specific QA of treatment plans already generates a high work load on the clinical physics group of many radiotherapy departments. Advanced adaptive protocols, where multiple treatment plans per patient are generated, makes such a QA approach unfeasible. Even more, for online plan adaptations, pre-treatment QA is impossible. Consequently, alternatives for patient-specific QA need to be developed and adopted. Various approaches have been investigated and implemented in clinical practice such as (1) dose recalculation using an independent dose calculation algorithm,[44] (2) an independent verification of the delivered plan using treatment plan files and delivery log files,[127,128] (3) an entrance fluence detector system mounted at the linac collimator between the MLC and the patient[129] and (4) an portal dosimetry algorithm based on electronic portal imaging device.[130]

Concluding Remarks

The concept of adaptive radiotherapy was introduced 22 year ago[131] as a sophisticated offline setup correction protocol. Since then, volumetric imaging in the treatment room, (deformable) image registration software, inverse treatment planning and insight into anatomical changes

have grown tremendously. Simultaneously, the concept of adaptive radiotherapy has evolved and a range of approaches have been clinically implemented for different types of changes and disease sites. Although various challenges still remain to be solved to realize the full potential of adaptive radiotherapy, more simple approaches have already been shown to be feasible in multicenter trials. With recent advances in image processing and machine learning, adaptive radiotherapy might be ready for prime time in the years to come.

Conflict of Interest Statement

J.-J. Sonke reports research grants from Elekta Oncology Systems AB and license fees from Elekta Oncology Systems AB for CBCT guidance software.

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