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CLINICAL CASE STUDY OPEN ACCESS

The first reported case of a patient with small cell lung cancer treated with fan beam computed tomography-guided online adaptive radiotherapy

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Abstract – Adaptive radiotherapy (ART) allows control of dosimetric impact of patient anatomical and functional variations over the treatment course, to minimize normal tissue exposure and maximize dose delivery to tumor. We present the first reported case of fan beam computed tomography (FBCT)-guided online ART for the treatment of small cell lung cancer (SCLC). A 62-year-old woman was diagnosed with histologically proven limited-stage SCLC. During definitive radiochemotherapy (50 Gy in daily fractions of 2.5 Gy), the tumor shrinkage resulted in an unexpected dose escalation to organs at risk (OAR). To correct the dose change, she received an online ART treatment session in our center with four-dimensional FBCT before the 12th fraction was delivered. The application of online ART, including imaging, recontouring and replanning, was feasible as the total treatment time was <25 min. Further research is warranted to verify the benefit of online ART in individualized treatment.

Key words: Online adaptive radiotherapy, Small cell lung cancer, Fan beam computed tomography, Organs at risk.

Background

Small cell lung cancer (SCLC) is a high-grade malignant epithelial tumor that represents about 15% of all lung cancers. SCLC is sensitive to chemotherapy and the standard regimen is cisplatin–etoposide, which has not changed for the past three decades [1]. Thoracic radiotherapy (TRT) with concomitant chemotherapy is recommended in the management of limited-stage SCLC [2]. When twice-daily radiotherapy cannot be delivered for patient-specific or practical reasons, which is only used in 42% of European centers due to practical reasons, once-daily radiotherapy is a reasonable alternative [3, 4].

Our previous work indicated that post-chemotherapy tumor volume and pre-chemotherapy involved nodal regions could be included in limited-stage SCLC [5, 6]. The margin to cover 95% of the microscopic disease extension was 10.2 mm in patients without neoadjuvant chemotherapy, while only 1.4 mm in patients after neoadjuvant chemotherapy [6]. It indicated that the tumor infiltration of SCLC was slight after chemotherapy. Adjusting gross tumor volume (GTV) of primary tumor based on treatment response may be feasible, as the clinical target volume (CTV) with a margin of 5–10 mm from the GTV is sufficient to encompass microscopic tumor extension.

Adaptive radiation therapy (ART) was first introduced in the late 1990s. It was a closed-loop radiation treatment process to monitor and incorporate treatment variations to modify the treatment plan [7]. At present, ART is an advanced treatment approach in which the administered radiation dose is monitored during the entire treatment process for clinical acceptability and any necessary adjustments are made to the treatment plan with the aim of improving clinical outcomes [8]. It could address patient-specific treatment variations, including changes in target/OAR location, patient morphology, weight loss and tumor response, to minimize dose to normal tissue and maximize dose to target [8, 9].

Online ART, which can adjust plan immediately before a treatment fraction, is a rapidly developing field that requires highly efficient workflow and specialized, integrated technologies for dose assessment, replanning, and quality assurance [10]. It is believed that the baseline variation in the lung is well-suited to online ART [11–14]. A phase I trial for

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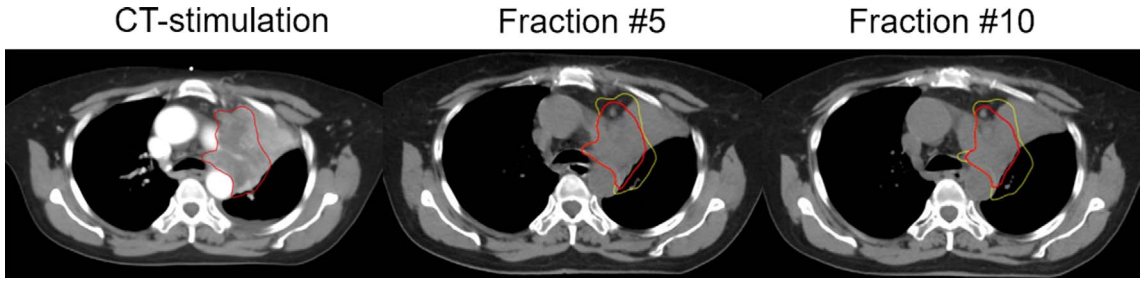


Figure 1. Comparison of gross tumor volume on CT-sim, fraction #5 and fraction #10. GTV contoured in red; GTV copied from CT-sim by rigid registration contoured in yellow. Abbreviations: CT-sim = computed tomography simulation; GTV = gross tumor volume.

ultra-central lung cancer showed that online ART may increase planning target volume (PTV) dose coverage and/or better spare organs at risk (OARs), which was well tolerated and offered excellent local control with no identified acute severe toxicity [15]. However, these results were achieved based on magnetic resonance imaging (MRI)-guidance, and the median on-table treatment time was 69 min. Herein we report a less time-consuming online ART that was guided by fan beam computed tomography (FBCT) images, including a description of the workflow and comparative dosimetric analyses.

Case introduction

A 62-year-old woman presented to the outpatient clinic owing to cough and sputum for more than 1 year and sputum with blood for 3 months. A computed tomography (CT) chest of the local hospital showed a left upper lobe pulmonary mass with left upper lobe atelectasis, and left hilar and mediastinal lymph nodes were likely to be metastatic. Then the biopsy through bronchoscopy revealed that the central pulmonary mass was SCLC. The patient was diagnosed with limited stage (T3N2M0 Stage III) SCLC and recommended to receive induction chemotherapy followed by TRT with concurrent chemotherapy.

Chemotherapy and radiotherapy

The chemotherapy regimen was etoposide (100 mg/m^2 on days 1–3) and cisplatin (25 mg/m^2 on days 1–3), repeated every 3 weeks. TRT was administered concurrently with the second cycle of chemotherapy. A total dose of 50 Gy in 2.5 Gy daily with 20 fractions was prescribed, for delivery using a CT-integrated linac, uRT-linac 506c (United Imaging Healthcare, UIH, Shanghai, China).

Definition of target volume for radiotherapy

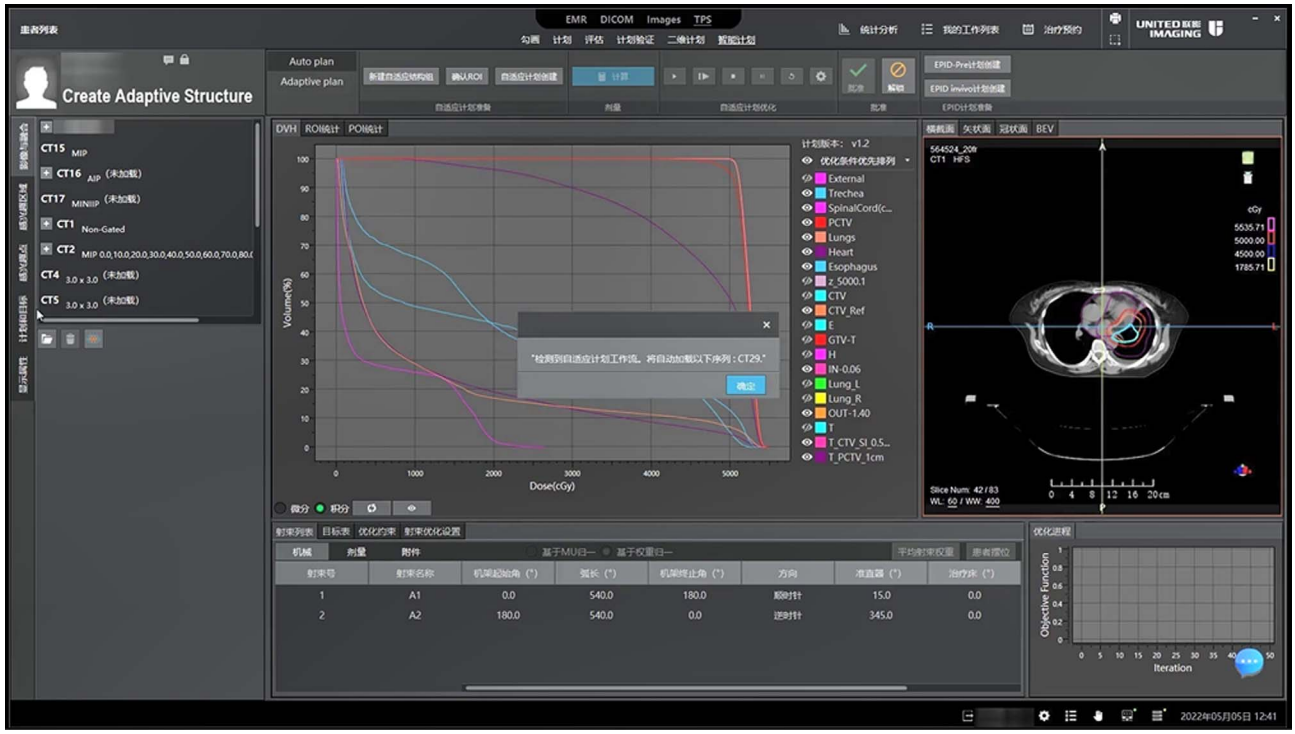
The patient was positioned in a custom-made vacuum bag with both arms up. A computed tomography simulation (CT-sim) and a contrast-enhanced 4-dimensional (4D) CT-sim were performed per our institutional protocol using a 5-mm slice thickness. The GTV included the postchemotherapy primary tumor (GTV-T) and positive prechemotherapy lymph nodes (GTV-N) [6]. The clinical target volume-tumor (CTV-T) included the GTV-T with a margin of 0.6 cm. The lymph node regions originally involved before induction chemotherapy were included in the radiation fields as CTV-N. CTV (including CTV-T and CTV-N) were edited according to anatomy. PTV is expanded from CTV with an isotropic margin of 0.6 cm.

Online adaptive radiotherapy

During the treatment, we expected to observe the tumor regression and/or lung re-expansion of atelectasis using FBCT or 4D FBCT at least once a week. The tumor shrank gradually (Figure 1) and we decided to conduct online ART in the third week of treatment before the 12th fraction was delivered.

The online ART only consumed 22 min. Video 1 showed the critical part of the whole process. Online ART starts from 4D FBCT acquisition, a 4D FBCT was scanned and the average intensity projection (AIP) images were rigidly registered to simulation CT images by matching anatomic structures such as vertebrae, fissures, vessels, and bronchus. Then the ART workflow was launched and regions of interest (ROIs) were created. The target volumes (GTV-T and CTV) were rigidly transferred while OARs were auto-segmented. After manually revising GTV-T and CTV based on maximum intensity projection (MIP), PTV was expanded from CTV with an isotropic margin of 0.6 cm. OARs were checked and edited if necessary.

The adaptive plan was created in Fluence Map Optimization with two arcs and using Monte Carlo dose calculation algorithm. The radiation energy was 6 MV. This step usually lasts 3 min. The adaptive optimization algorithm used dose distribution and clinical goals of the initial plan as inputs. In the clinical goal sheet, users set a wish list with priorities to represent their requirements for planning target's prescription dose coverage and dosimetric criteria of OARs, details were in Table 1. During optimization, the algorithm aims to generate a very similar plan to the initial treatment plan which is mainly reflected in three aspects of 3D dose distribution, that is, a similar dose falloff's level for certain OARs and a similar prescription dose conformity and dose volume histogram (DVH) curve for planning targets. To achieve these goals, firstly, dose-volume histograms (DVHs) of the clinical concerned OARs are predicted by extracting the dose falloff features of these OARs on the reference plan. The optimization objective functions of OARs are created based on the predicted DVHs.



Video 1. The critical process of online adaptive radiotherapy. https://vcm.edpsciences.org/10.1051/vcm/2023003#V1.

Table 1. Goal sheet of adaptive plan.

The ROIs	ROIs Property	Clinical Goal		Priority
PCTV	PTV	The Prescription Dose	50 Gy	2
		The Min Dose	≥50.50 Gy	1
		The Max Dose	≤54 Gy	1
SpinalCord	Organ	The Max Dose	≤45 Gy	1
SpinalCord03 mm	Organ	The Maximum Dose	≤50 Gy	1
Esophagus		The Max Dose	≤63 Gy	2
		The Mean Dose	≤30 Gy	2
Lungs	Organ	The volume at dose	V20 Gy ≤ 30%	1
	Organ	The volume at dose	V30 Gy ≤ 20%	1
	Organ	The volume at dose	V5 Gy ≤ 60%	1
Heart	Organ	The Mean Dose	≤20 Gy	2

Secondly, the targets' dosimetry parameters of the reference plan, including conformity index, dose at 2% and 98% volume and minimum and maximum dose are calculated so that the targets' optimization objective functions of the adapted plan can be created according to these parameters. Considering the situation where the highest priority OAR presents a larger conflict with the planning target in adapted plan than the reference plan, meanwhile, the predicted OAR DVH fails to satisfy the highest priority goal, the algorithm will focus more attention to reducing this OAR dose than other OARs in order to satisfy this OAR's clinical evaluation criteria. Furthermore, to assure the plan quality, various optimization strategies, including OAR dose reducing method, dose conformity optimization and hot spot removal strategy, etc., are implemented in the algorithm.

After the plan optimization was completed, oncologists and physicists evaluated the plan through the clinical goal sheets, DVH, and 3D dose distribution, etc. Once the plan was approved, the treatment beam was scheduled and transferred to treatment delivery administrator (TDA). Before the RT treatment, FBCT was collected and rigidly matched to the planning CT to check the patient/tumor location, which was done prior to each treatment fraction.

As for quality assurance (QA) of the ART plan, it was done through the independent calculation on ArcherQA prior to the TRT treatment, as Figure 2 shows. DVH comparison and Gamma Pass Rate are analyzed. Meanwhile, the uRT-Linac 506c system provides an online EPID-based in vivo dosimetry solution, which could be used as a complementary monitoring tool during the TRT treatment.

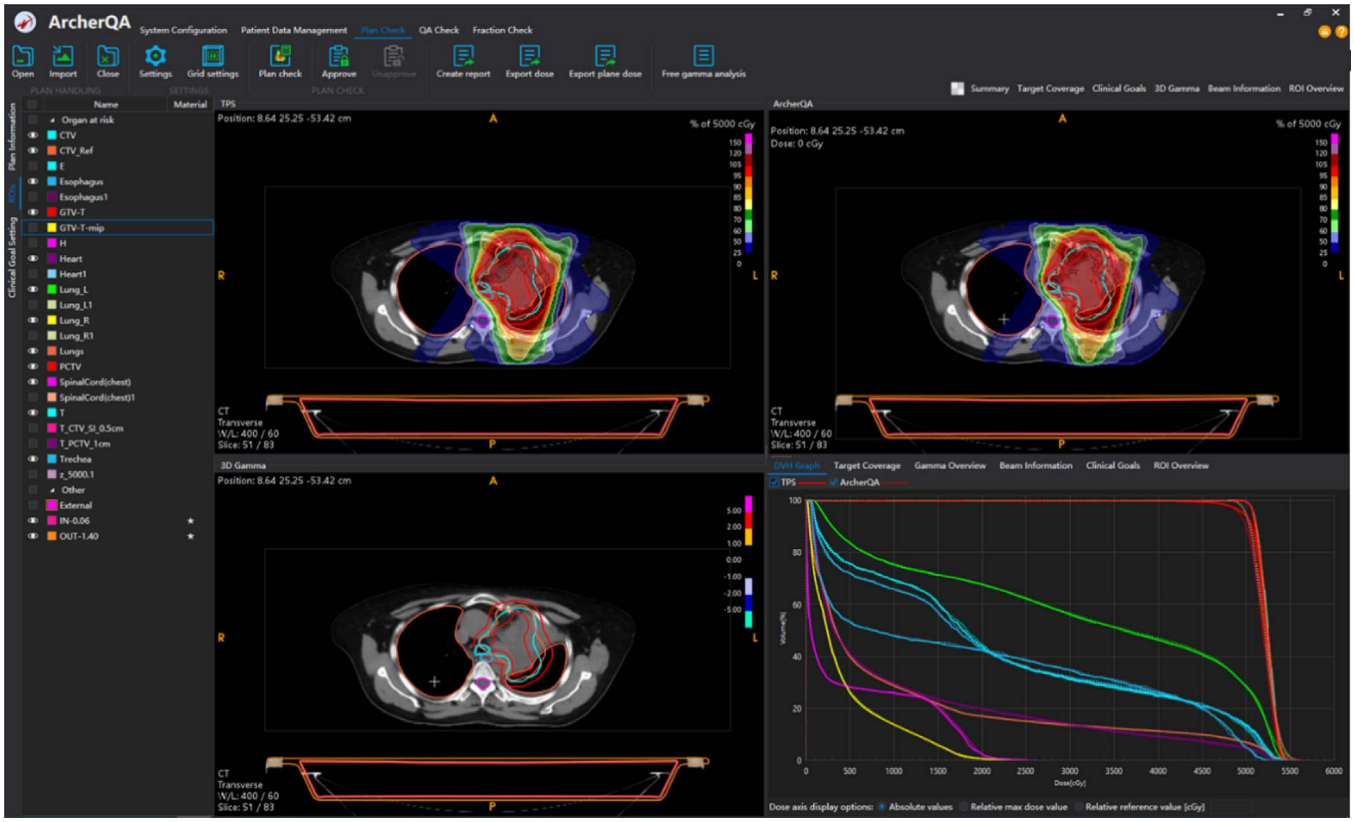


Figure 2. Independent dose calculation of adaptive radiotherapy plans prior to radiotherapy.

Dosimetric constraint comparison

The comparison of the initial plan (P_I) and adaptive plan (P_A) was in Table 2 and Video 2. In order to display the advantage of ART, we provided the results of recalculating the initial plan on the images of FBCT when online ART without modification (P_{FBCT}). It was noted that online ART could maintain the coverage of target volume but decrease the values of OARs. A minimum coverage of 95% was kept to the PTV. GTV-T D95 was 5126.56 cGy in the P_A, 5070.64 cGy in the P_{FBCT}, and 5092.84 cGy in the P_I, respectively. The Dmean was reduced in both the ipsilateral (2690.78 cGy in the P_A vs. 3085.92 cGy in the P_{FBCT} vs. 3166.81 cGy in the P_I) and contralateral Lungs (332.26 cGy in the P_A vs. 396.74 cGy in the P_{FBCT} vs. 423.17 cGy in the P_I).

Discussion

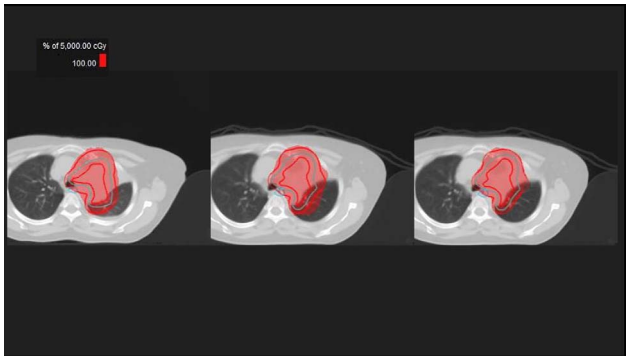
Herein we describe the first reported use of FBCT-guided online ART (FBCT-ART) for the treatment of a patient with small cell lung cancer. It showed the feasibility of online ART for lung cancer as the total treatment time was < 25 minutes. The advantage of online ART was offering dosimetric gains by maintaining target coverage and reducing doses to OARs. More research is warranted to verify the disease control and reduced complications of online ART in individualized treatment.

ART requires four underlying key technologies: imaging, assessment, replanning, and quality assurance [11]. Patient selection for adaptation is based on changes in tumor volume or physiologic changes to OARs, which often require high-quality imaging to detect. For the currently available ART workflows that integrate either kV cone beam computed tomography (CBCT) [16] or MRI [17], a pseudo CT for dose calculation must be generated. The pseudo CT is generated by deforming CT simulation to daily CBCT or MRI, then a water-air-bone density assignment may be required for MRI-based ART workflow. Therefore, dose calculation accuracy is depending on deformable image registration uncertainty which must be carefully quantified. Although a synthetic CT necessary for dose calculation can be obtained from CBCT or MRI images with deep learning [18, 19], the feasibility of CBCT-only or MRI-only treatment planning is still under exploration [20, 21]. In this regard, diagnostic-quality FBCT is a better image modality for adaptive radiotherapy in current practice due to its superior CT-to-density accuracy. In addition, it is essential to acquire quality images in a short time. Therefore, a key benefit of FBCT-based ART workflow is that FBCT soft-tissue contrast is better than CBCT, and the imaging time is shorter than both CBCT and MRI. Moreover, 4D CT is required for moving targets during radiotherapy planning and delivery. The acquisition and reconstruction can be used to accurately monitor tumor trajectory shape. To the best of our knowledge, there is no commercially available online 4D FBCT solution in the radiotherapy field except the uRT-linac 506c platform, which combined the diagnostic-quality FBCT with a C-arm linac [22]. It integrates the multiple radiotherapy steps into one scheme, including simulation, auto-segmentation,

Table 2. Dosimetric constraint results.

ROIs	Constraints	P_I	P_{FBCT}	P_A
Lung	Mean $\leq$ 1700 cGy (cGy)	1090.45	1140.62	984.66
	V20 $\leq$ 25% (%)	16.99	18.34	17.30
	V30 $\leq$ 20% (%)	13.70	15.36	12.50
	V5 $\leq$ 60% (%)	40.29	39.97	37.13
Ipsilateral lung	Mean (cGy)	3166.81	3085.92	2690.78
	V20 (%)	67.79	64.66	60.98
	V30 (%)	56.33	55.53	45.18
	V5 (%)	83.87	79.65	78.28
Contralateral lung	Mean (cGy)	423.17	396.74	332.26
	V20 (%)	0.66	0.63	0.60
	V30 (%)	–	–	–
	V5 (%)	26.28	24.80	21.39
Spinal cord	Dmax $\leq$ 4000 cGy (cGy)	2641.34	2884.09	2745.21
Heart	Dmean $\leq$ 2000 cGy (cGy)	1069.7	943.85	878.72
	V30 (%)	13.30	10.99	9.61
	V40 (%)	8.71	6.93	6.25
	V50 $\leq$ 25% (%)	4.39	3.29	2.86
Esophagus	Dmean $\leq$ 3000 cGy (cGy)	1959.12	1957.15	1885.68
	Dmax $\leq$ 5500 cGy (cGy)	5289.04	5309.33	5231.02
	V40 $\leq$ 30% (%)	26.54	28.29	26.15
PTV V50	$\geq$95% (%)	95.18	96.53	95.18
PTV D95	$\geq$5000 cGy (cGy)	5005.23	5032.31	5005.30
CTV V50	N/A (%)	99.92	99.50	99.99
CTV D95	N/A (cGy)	5102.25	5076.69	5130.27
GTV-T V50	N/A (%)	99.96	99.62	99.99
GTV-T D95	N/A (cGy)	5092.84	5070.64	5126.56

Abbreviations: ROIs = regions of interest; P_I = initial plan; P_{FBCT} = recalculating initial plan on the images of fan beam computed tomography when online adaptive radiotherapy; P_A = adaptive plan.



Video 2. The target volume coverage of different plans. The right side was the dose distribution of the initial plan. The middle was of recalculating the initial plan on the images of fan beam computed tomography when online adaptive radiotherapy. The left side was of the adaptive plan. https://vcm.edpsciences.org/10.1051/vcm/2023003#V2.

auto-planning, 4D image guidance, beam delivery, and in vivo patient-specific QA. The "All-in-One" strategy performs a new radiotherapy treatment seamlessly, reducing the timescale from days to minutes and offering the possibility of clinical practice of online ART [23].

Another key component of online adaptation is the assessment of the need to adapt. There is no uniform consensus about how to select patients for plan adaptation. For example, adaptive planning could be triggered when the target volume or dose to an OAR has changed exceeding a prespecified threshold [9]. Image guidance can be used to identify significant mediastinal shifts or GTV changes that raise the need for adaptive replanning [24, 25]. A retrospective study showed that 20.6% of 281 lung cancer patients underwent replanning, and the timing of replanning was 26% (15 cases) in the first, 43% (25 cases) in the second and 31% (18 cases) in the final third of the treatment course, respectively. The prevalent reason for replanning was changes in GTV of primary tumor, which occurring in 43/58 (74.1%) of cases. This was followed by anatomical changes, including pleural fluid accumulation, atelectasis or pneumothorax alteration, observed in 20/58 (35.4%) of cases. Of note, some cases could have overlap changes [24]. Although developing a model for pre-determining changes in target volume or OARs would facilitate selecting patient for ART, there is no consensus model and more work is needed before this technique is ready for routine clinical applications. The timing and frequency of adaptation should balance objectively the clinical value added to the patient with considerations of the finite resources of the clinic. Some studies support the 40–45 Gy range because they observed 20 fractions [26–28] or Week 3/4 [29–31] as an optimal time for adaptation. A few other studies either preferred a slightly earlier range such as after 15 fractions [32] or depended on weekly scans if feasible [33]. However, ART of small cell lung cancer still lacks relevant evidence. The results above seem to favor adaption slightly

beyond or around the midpoint of treatment, as this allows for the detection of anatomic and dosimetric changes over a longer period. Moreover, such adaptations may have an impact on outcomes and toxicity. Our patient received online ART after 11 fractions, consistent with the researches.

Before the replanning, a new image needs to be acquired first, followed by image registration and contour propagation. The accuracy of contouring would be confirmed and may be revised manually for any deviation. The manual editing of these is the most time-consuming step, and also is the step most prone to error [34, 35]. Auto-segmentation based on deep learning of OARs and even targets may be used to improve efficiency [36, 37]. A simplified workflow is recommended for online ART, in which the attending physicist re-optimizes the plan when significant changes occur in the contours and relative electron densities. As the patient must stay on-table in the treatment position during online ART, patient-specific quality assurance with measurements before treatment, such as delivery of the plan onto a phantom, is not practical. In fact, if integrating the treatment planning system and treatment device, combined with independent dose calculation software and online EPID-based in vivo monitoring technique, the accuracy of treatment plan delivery would be well assured during the online ART process. The fundamental concerns for a safe, robust online ART replan are the high-quality imaging before treatment, recontouring sufficient to capture the new positions of the target and/or OARs, and accuracy of the relative electron density [11]. Hence, a comprehensive quality assurance program for online ART would benefit most from a well-trained, well-prepared team, as well as automation of checks (via either built-in or standalone software) for potential errors in contouring and plan parameters [38, 39]. Besides, the algorithm of adaptive optimization in our case mimics the style of the original plan to some extent because the dose distribution of the original plan is referenced when inferring the dosimetric parameter. This improves the quality and efficiency of treatment planning. For instance, even without setting a maximum dose clinical goal, the algorithm is able to control the global maximum dose of the adaptive plan to the same level as the original plan.

There are many challenges in online ART. One is how to calculate dose accumulation to ascertain the actual total delivered dose, accounting for changes in anatomy and dosimetry, which may be reflected with in vivo dose monitoring. Second, the critical processes need full human interventions and require the presence of dedicated staff, including radiation oncologists and medical physicists, delaying the completion of other tasks and increasing resource cost [40]. Third, determining how and when to adapt with more quantitative, automated or assisted approaches is essential to decrease variability and make sure ART is applied consistently and correctly as it expands beyond high-volume centers. Finally, evidence of the efficacy of online ART is crucial to help guide more widespread deployment and justify the additional resources and tools required for the technique. A phase II study of functional ART has been conducted in non-small cell lung cancer [41] and a phase III randomized clinical trial (RTOG-1106) to compare offline ART to standard radiotherapy is ongoing. In summary, the trials of online ART for lung cancer are limited, and more studies are warranted.

Conflict of interest

The authors declare that they have no conflict of interest.

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