Benefits of adaptive radiation therapy in lung cancer as a function of replanning frequency

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Purpose: To quantify the potential benefit associated with daily replanning in lung cancer in terms of normal tissue dose sparing and to characterize the tradeoff between adaptive benefit and replanning frequency.

Methods: A set of synthetic images and contours, derived from weekly active breathing control images of 12 patients who underwent radiation therapy treatment for nonsmall cell lung cancer, is generated for each fraction of treatment using principal component analysis in a way that preserves temporal anatomical trends (e.g., tumor regression). Daily synthetic images and contours are used to simulate four different treatment scenarios: (1) a “no-adapt” scenario that simulates delivery of an initial plan throughout treatment, (2) a “midadapt” scenario that implements a single replan for fraction 18, (3) a “weekly adapt” scenario that simulates weekly adaptations, and (4) a “full-adapt” scenario that simulates daily replanning. An initial intensity modulated radiation therapy plan is created for each patient and replanning is carried out in an automated fashion by reoptimizing beam apertures and weights. Dose is calculated on each image and accumulated to the first in the series using deformable mappings utilized in synthetic image creation for comparison between simulated treatments.

Results: Target coverage was maintained and cord tolerance was not exceeded for any of the adaptive simulations. Average reductions in mean lung dose (MLD) and volume of lung receiving 20 Gy or more ($V_{20\text{lung}}$) were 65 ± 49 cGy ($p = 0.000\,01$) and $1.1\% \pm 1.2\%$ ($p = 0.0006$), respectively, for all patients. The largest reduction in MLD for a single patient was 162 cGy, which allowed an isotoxic escalation of the target dose of 1668 cGy. Average reductions in cord max dose, mean esophageal dose (MED), dose received by 66% of the heart ($D_{66\text{heart}}$), and dose received by 33% of the heart ($D_{33\text{heart}}$), were 158 ± 280 , 117 ± 121 , 37 ± 77 , and 99 ± 120 cGy, respectively. Average incremental reductions in MLD for the midadapt, weekly adapt, and full-adapt treatments were 38, 18, and 8 cGy, respectively. Incremental reductions in MED for the same treatments were 57, 37, and 23 cGy. Reductions in MLD and MED for the full-adapt treatment were correlated with the absolute decrease in the planning target volume ($r = 0.34$ and $r = 0.26$).

Conclusions: Adaptive radiation therapy for lung cancer yields clinically relevant reductions in normal tissue doses for frequencies of adaptation ranging from a single replan up to daily replanning. Increased frequencies of adaptation result in additional benefit while magnitude of benefit decreases. © 2016 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4943564>]

Key words: non-small-cell lung cancer, adaptive radiation therapy, tumor regression

1. INTRODUCTION

Lung cancer is one of the leading causes of death for both men and women with approximately 570 000 deaths reported for the year 2009 in the United States.¹ For the year 2013, the American Cancer Society estimated approximately 580 000 cancer related deaths and projected nearly 230 000 of those to be associated with lung cancer, making it the number one cause of cancer-related death.² Radiotherapy is a mainstay of treatment and is the preferred modality for approximately 40%

of newly diagnosed patients;³ however, prognosis is poor for those receiving radiation therapy with 5 yr survival around 17% as reported by the National Cancer Institute.⁴

Local control and survival have been shown to improve with increased doses,^{5,6} but for many patients, the deliverable dose is limited by associated normal tissue toxicity. Thus, strategies that limit normal tissue exposure while allowing isotoxic escalation of the prescription dose are desirable.

Replanning to accommodate interfraction variation in lung cancer (i.e., regression of the gross tumor volume)

to reduce treatment margins and allow for dose escalation has been investigated by various authors.^{7–10} These works implement various replanning schedules ranging from single to weekly adaptations and demonstrate a patient-specific benefit for adaptive plans in the context of tumor regression. While a variety of schedules have been implemented by the respective authors, systematic comparisons between schedules of the varying adaptive frequency have not been performed; furthermore, the nature of tradeoff between the replanning frequency and adaptive benefit is not understood. A final limitation of current studies is that they implement at most weekly adaptation, thus the benefit associated with daily replanning remains unclear.

The purpose of this work is to quantify the benefit associated with various frequencies of adaptation, up to daily replanning, for a cohort of lung cancer patients and to characterize the tradeoff between the adaptive benefit and replanning frequency.

2. METHODS

Four treatment schedules that implement different frequencies of replanning are simulated for a group of lung cancer patients. Simulations are based on a set of synthetic images and contours that are deformed instances of the first in a sequence of weekly images, and are generated using principal component analysis (PCA). Daily synthetic images are used for simulated replanning and daily dose calculation after which the dose is accumulated back to the first image for comparison of simulated schedules.

2.A. Synthetic datasets

Synthetic datasets for each fraction of treatment are derived from an existing set of weekly images. Deformable registrations are performed between the first and all subsequent images resulting in a set of mappings that effectively track variation. Displacement vector fields (DVF) that contain translations in the x , y , and z directions are reshaped into a single column vector, are temporally ordered, and concatenated into a joint variation matrix with homologous points residing along rows of the matrix. After mean-correcting the matrix by subtracting the row means from each row, the matrix is decomposed into a set of basis vectors and weighting coefficients using PCA. Each group of coefficients associated with a given basis vector, and corresponding to weekly time points, is plotted against time and a linear fit is performed. Using kernel density estimation, fit residuals are utilized to produce a probability density function (PDF) representing variation around the fit. Synthetic weighting coefficients are then sampled for each basis vector at intermediate time-points by evaluating the linear fit of coefficients and adding a random portion sampled from the associated PDF. Sampling in this fashion preserves temporal trends in the data (e.g., tumor regression) and resulting coefficients are utilized to create synthetic DVFs associated with desired time-points. A pseudoinverse DVF is generated as described by Yan *et al.*¹¹

TABLE I. Patient characteristics of 12 nonsmall-cell lung cancer patients used to generate a set of synthetic datasets. LUL = left upper lobe; LLL = left lower lobe; RUL = right upper lobe; RLL = right lower lobe; RML = right middle lobe.

Patient	Stage	Patient characteristics		
		Location	Nodes	Tumor volume (cm ³)
1	IIIA	LUL	Y	24
3	IIIB	Bilateral	Y	100
4	IIB	LLL	N	65
5	IIIB	RUL	Y	1
6	IIIA	RLL	N	242
8	IIB	RUL	N	11
9	IIIA	RUL	Y	40
14	IIIA	RML	Y	34
17	IIIA	RUL	Y	216
18	IIIB	RUL	N	58
20	NA	LLL	Y	47
21	NA	LUL	N	86

and is used to deform the first image in the series along with associated contours.

Synthetic datasets generated in this work are based on an existing set of patient data corresponding to 12 nonsmall-cell lung cancer (NSCLC) patients undergoing external beam radiation therapy for stage II and III disease; patient characteristics are summarized in Table I. For each patient, 4–6 weekly helical CTs were obtained under an active breathing control (ABC) protocol to minimize respiratory motion, and structures of interest were delineated by a qualified physician including: gross tumor volume (GTV), lungs, spinal cord, heart, and esophagus. Registrations between weekly images utilized in the PCA analysis were performed using the Demons algorithm as implemented in the Pinnacle treatment planning system (Philips Oncology, Fitchburg, WI).

PCA analysis and synthetic data generation resulted in a set of self-consistent images, contours, and mappings, corresponding to each fraction in a typical 35 fraction schedule. For patients with delineated nodal volumes, two sets of simulations were carried out, the first of which excluded nodal targets and the second of which included them; simulations that included nodal volumes are referenced by appending an “N” to the patient identifier. For the single patient that presented with bilateral tumors, treatments are derived based on each tumor separately. This process resulted in 20 different sets of target contours based on 12 sequences of synthetic images for use in treatment simulations.

2.B. Planning

Intensity modulated radiation therapy (IMRT) plans are developed for each patient and target based on a synthetic image corresponding to the first fraction. Planning assumed breath-hold and image guidance throughout the treatment to limit geometric uncertainty associated with respiratory motion and patient setup. A margin of 5 mm was implemented to account for subclinical disease and planning target volume (PTV) margins of 7 mm in the superior–inferior direction, and

5 mm in the axial plane, were utilized as recommended in radiation therapy oncology group (RTOG) protocol 0839 for plans that implement breath-hold and image guidance.

After construction of target volumes, 5–8 coplanar beams were arranged around the patient in a manner as to avoid directly traversing risk structures when possible. Nominal beam energy was set to 6 MV and beams were prescribed to a dose of 63 Gy (1.8 Gy/fraction).

A simplified set of IMRT objectives based on RTOG 0839 is utilized in plan optimization that focuses on target coverage and dose conformality as opposed to implementing individual objectives for each risk structure. A 2 cm thick “rind” region of interest (ROI) beginning 2 mm from the surface of the PTV was utilized to suppress dose to surrounding risk structures and guide the optimization to a conformal solution. For adaptive plans, a new rind ROI was generated based on the propagated clinical target volume (CTV) for use in replanning optimizations. Plans were deemed acceptable if they met criteria associated with PTV coverage and if cord tolerance was not exceeded. Specifically, minimum dose to any volume associated with the PTV of at least 0.03 cm³ in magnitude (PTV min dose) was not to fall below 95% of the prescription dose, 95% of the PTV dose ($D_{95\text{PTV}}$) was to be greater than or equal to the prescription, and the max dose to any volume of 0.03 cm³ associated with the spinal cord (cord max dose) was not to exceed 50.5 Gy. In cases where spinal cord tolerances were exceeded, an additional constraint was added to the set of objectives and an additional optimization was carried out. Additional criteria were considered in plan evaluation but were not considered prohibitive, therefore were allowed to vary within clinical judgment; a summary of normal tissue planning criteria utilized in this work is given in Table II.

2.C. Treatment simulation

Treatment simulations for each of the four adaptation schedules and patients are carried out in an automated fashion using a research version of the Pinnacle treatment planning system (TPS). Simulated treatments include: (1) a “no-adapt” treatment for which the initial plan is delivered throughout the treatment course; (2) a “midadapt” treatment that implements replanning a single time for fraction 18; (3) a “weekly adapt” treatment that implements replanning for fractions 6, 11, 16, 21, 26, and 31; and (4) a “full-adapt” treatment that implements daily replanning for each fraction.

TABLE II. Plan criteria associated with risk structures.

Normal tissue plan criteria		
ROI	Metric	Value
Cord	Max dose	5050 cGy ^a
Lungs	Mean dose	2000 cGy
Lungs	V20	37%
Esophagus	Mean dose	4000 cGy
Heart	Max dose to 1/3 of volume	6000 cGy
Heart	Max dose to 2/3 of volume	4500 cGy

^aPlans not meeting this criterion were not deemed acceptable.

Initial beam angles are held constant throughout treatment and replanning is carried out for adaptive fractions by reoptimizing beam apertures and monitor units (MU) using the same set of objectives and weights implemented in the initial plan; the latter is important to ensure that benefit is due to anatomical variability and not to a reappropriation of objective weights. For nonadaptive fractions, the most recent plan (i.e., configuration of beam apertures and MUs) is transferred to the corresponding fraction image, and the dose is recalculated on the same. In all cases, the beam isocenter is set to the centroid of the propagated CTV simulating a soft-tissue image-guided setup.

After simulation, dose is accumulated from each fraction to the first image in the series using the pseudoinverse of the same DVF utilized in synthetic image creation.

2.D. Adaptive benefit

Benefit in this study is primarily quantified in terms of reductions in planning metrics associated with dose to lungs though changes are also reported for the cord, esophagus, and heart. Comparisons are made between full-adapt and no-adapt treatments along with incremental comparisons of each of the three adaptive treatments to the treatment implementing the next lowest amount of replans, e.g., the full-adapt treatment is compared to the weekly adapt, and the weekly adapt simulation is compared to the midadapt treatment. To ensure that perceived benefits do not come at the expense of plan acceptability criteria, coverage of the PTV, and spinal cord tolerances, are first evaluated for all simulated treatments.

Isotoxic dose escalation afforded by achieved reductions are estimated by scaling dose distributions for the full-adapt treatment until the mean lung dose (MLD) matches that of the no-adapt plan. Differences between the full-adapt cumulative target dose and scaled full-adapt cumulative target dose are reported.

2.E. Statistical analysis

Paired *t*-tests are calculated for all intertreatment dose-metric comparisons. As a conservative measure to control for the familywise error rate associated with multiple comparisons, a Bonferroni correction is utilized. Briefly, when carrying out multiple comparisons, the probability of committing a type I error increases with the amount of comparisons. The Bonferroni correction entails using a statistical significance of α/n for each test where *n* is the number of comparisons.

3. RESULTS

3.A. Plan acceptance

Plan acceptance criteria associated with target coverage and spinal cord tolerance for the initial plan were maintained for all patients and simulations. The cumulative dose to 95% of the initial PTV measured on the primary image ($D_{95\text{PTV}}$) was greater than or equal to the prescription dose

TABLE III. Absolute changes in full-adapt normal-tissue dose metrics compared to the no-adapt simulation. Average changes are listed below along with p -values resulting from paired t -tests comparing full-adapt and no-adapt metrics. Averages for the no-adapt simulation are listed in parentheses.

Patient changes in normal tissue doses for full-adapt treatment						
	Cord max (cGy)	Mean lung dose (cGy)	Lung V20 (% vol)	Mean esophagus dose (cGy)	Heart D66 (cGy)	Heart D33 (cGy)
PT1	40	-48	-1.39	-415	-2	-3
PT1N	132	-20	-0.61	-111	1	-1
PT3L	259	-69	-1.12	-106	-3	-54
PT3LN	-560	-6	-0.15	-68	-5	-151
PT3R	-188	-106	-2.01	-128	-9	-128
PT3RN	-77	-117	-2.29	-55	-16	-320
PT4	-243	-37	0.69	-72	-43	-148
PT5	119	14	0.27	-2	0	0
PT6	-325	-43	-0.44	-144	-337	-280
PT8	-656	-162	-2.76	-186	-17	-49
PT9	-250	-115	-2.96	-2	-2	-22
PT9N	-231	-80	-0.7	66	1	12
PT14	-187	-92	-1.96	-159	-104	-170
PT14N	-91	-37	-0.7	-15	0	38
PT17	-8	-54	1.06	-294	-27	-80
PT17N	-656	-100	-1.72	-253	-14	-54
PT18	65	8	0	26	15	69
PT20	311	10	0.05	1	-7	-7
PT20N	-363	-64	-2.43	-231	-39	-104
PT21	104	-106	-2.22	-47	-87	-367
Mean change	-158	-65	-1.1	-117	-37	-99
(Mean no-adapt)	(4202)	(1350)	(23)	(2106)	(504)	(1174)
p	0.04	0.000 01	0.0006	0.0005	0.05	0.002

of 63 Gy for all simulations, with percent changes from the no-adapt simulation equal to $0.4\% \pm 1.4\%$, $0.4\% \pm 1.0\%$, and $0.4\% \pm 1.0\%$ for the full-adapt, weekly adapt, and midadapt treatments, respectively. Mean PTV min dose was 62 ± 3 Gy for the no-adapt simulations and was 63 ± 2 Gy for each of the adaptive treatments. Spinal cord tolerance of 50.5 Gy was initially exceeded for four patients using the simplified objective scheme but was brought within the range after adding an additional optimizer constraint for these patients to directly limit the cord dose.

Differences between no-adapt and full-adapt normal-tissue dose metrics are listed for all patients in Table III. A maximum decrease in MLD of -162 cGy was observed with an average decrease of -65 cGy over the patient population. V20 showed little variation between no-adapt and full-adapt simulations ranging between -2.96% and 1.06% with a mean decrease of -1.1%. Average change in mean esophageal dose (MED) was -117 cGy with a maximum decrease of -415 cGy, and average decreases of -37 and -99 cGy were observed for heart D66 and D33, respectively. Differences between reported metrics for full-adapt and no-adapt simulations were statistically significant using the Bonferroni criterion ($p < 0.008$) for MLD, lung V20, MED, and heart D33.

Benefit associated with replanning at different frequencies is illustrated for each normal tissue metric in Fig. 1. Comparisons of adaptive simulations to next treatments of lower replanning frequency (i.e., full-adapt to weekly adapt,

weekly adapt to midadapt, and midadapt to no-adapt) are listed in Table IV. Statistically significant differences between all adaptive schedules and the no-adapt simulation were observed for MLD and lung V20.

The relationship between absolute decreases in PTV volume and decreases in both MLD and MED are illustrated in Fig. 2; Pearson correlation coefficients were 0.34 and 0.26 for each comparison, respectively.

Isotoxic escalation of dose resulted in average increases in dose to 95% of the CTV ($D_{95\text{CTV}}$) of 294 (0–1304) cGy, 381 (10–1593) cGy, and 441 (31–1668) cGy for the midadapt, weekly adapt, and full-adapt simulations, respectively.

4. DISCUSSION

In this work, we utilized a set of daily synthetic lung images and contours that exhibited temporal anatomical trends (e.g., tumor regression) to simulate different adaptive schedules with the objective of quantifying the benefit of a full-adapt treatment in lung cancer and to characterize the relationship between adaptive benefit and replanning frequency.

Synthetic images and contours were not required to exactly reproduce the images from which they were derived; rather, our intent was to produce a clinically relevant dataset to carry out the study with inherent consistency between contours, images, dose, and DVFs. As an adaptive benefit is expected to depend on regression trends of the gross tumor, this was

FIG. 1. Distributions of changes in normal-tissue dose metrics compared to the no-adapt simulation for midadapt, weekly adapt, and full-adapt treatments. Increases in planning frequency resulted in further reductions of dose for the majority of structures.

used as the primary criteria for clinical relevancy. The mean decrease in gross tumor volume for the synthetic images in this study was 21.1% and ranged from 0% to 76%. Woodford *et al.* reported a similar range of 12%–87% but a higher average decrease of 38% for their patient population.⁸ While the average amount of regression in the synthetic dataset may be smaller than that observed in other studies, the range of regression is representative of that observed clinically.

Because images and contours for a given time-point are generated from the same DVF, images, contours, and

mappings are self consistent. This mitigated some issues regarding geometrical accuracy of dose mapping; however, the problem of mapping dose backward in time in the presence of cell loss (e.g., tumor regression) has not been resolved.

One issue of importance relates to tumor regression dynamics; specifically, how surrounding tissue moves in relation to the regressing volume. For tumor volumes that infiltrate tissue, as opposed to displacing surrounding structure, mapping the visible GTV border between two time points may be inaccurate. In this scenario, when mapping dose back

TABLE IV. Incremental differences between dose metric averages for adaptive schedules and treatments of next lowest replanning frequency (e.g., full-adapt and weekly adapt). Associated *p*-values resulting from paired *t*-tests listed to the right of each comparison.

	Average change in normal tissue dose					
	Mid – no	<i>p</i>	Weekly – mid	<i>p</i>	Full – weekly	<i>p</i>
Cord max	–52 cGy	0.3	–104 cGy	0.01	–1 cGy	0.9
Mean lung dose	–38 cGy	0.0001	–18 cGy	0.002	–8 cGy	0.03
Lung V20	–0.68%	0.004	–0.37%	0.006	–0.09%	0.4
Mean esophagus dose	–57 cGy	0.03	–37 cGy	0.02	–23 cGy	0.01
Heart D66	–7 cGy	0.09	–25 cGy	0.1	–5 cGy	0.2
Heart D33	–49 cGy	0.09	–45 cGy	0.03	–5 cGy	0.4

to the planning image, high dose regions surrounding the regressed volume may be mapped inaccurately to surrounding lung and over-estimate the dose in that region. This represents a limitation of this study where the typical convention of mapping dose back to the planning image was utilized and may under-estimate the potential benefit of adaptive strategies. While some issues remain regarding dose mapping, dose accumulations here are consistent (i.e., they use the same mapping) and adaptive frequencies are relatively compared.

A limited set of objectives that focused explicitly on conforming dose to target was utilized in all optimizations. While this represents a simplification of clinical practice, adaptive benefit is expected to be driven by continual conformality of dose to regressing target volumes.

Daily adaptation to regressing tumor volumes yielded statistically significant reductions in dose for all reported averages of normal-tissue metrics considered in this work; however, reductions were not realized for all patients, reinforcing the notion that benefit associated with adaptation is ultimately patient dependent. For the three patients (PT5, PT18, and PT20) exhibiting no reduction in MLD as a result of daily adaptation, two had PTVs that did not decrease in volume over the course of treatment; the third exhibited an overall decrease in PTV with an initial pattern of regression followed by a period of increasing volume around fraction 22.

Using an isotoxic criteria based on MLD, average allowable dose escalation was 441 cGy for the full-adapt plan, without exceeding cord tolerances, resulting from an average decrease in MLD of 5%; a maximum escalation of 17 Gy was achieved for a single patient. In a study consisting of 12 patients that implemented replanning twice at weeks 3 and 5, Guckenberger *et al.* reported an average escalation of 7 Gy based on a reduction in MLD of approximately 8%.⁹ In another study which adapted at weeks 2 and 4 conducted by Weiss *et al.*, an average increase of 13.4 Gy with a maximum of 23.4 Gy was achieved.¹⁰ These values are larger than those reported here for daily adaptation; differences may be attributed to volumes used to estimate escalation, i.e., in this work, dose was escalated to the CTV as opposed to primary tumor. Furthermore, average primary tumor regression for the synthetic dataset was smaller than those other researchers have observed clinically as previously noted.

Incremental reductions in all average dose metrics were observed with each increase in replanning frequency (Table IV); however, the magnitude of each reduction decreased with each step. For MLD, 60% of the average total reduction that resulted from the full-adapt plan was realized after a single midtreatment adaptation, and 88% was realized using weekly adaptation. For MED, 50% of the benefit was achieved with a single midtreatment adaptation,

FIG. 2. Correlation of absolute change in PTV volume with changes in both mean lung dose (a) and mean esophageal dose (b). Each point represents the change in MLD or MED between no-adapt and full-adapt simulations plotted against the change in PTV volume from the 1st to 35th fraction for a single patient. Decreases in PTV volume were moderately correlated with reductions in both metrics; Pearson correlation coefficients (*r*) listed in upper left of each plot.

FIG. 3. Percent of potential benefit (i.e., allowable dose to target) as a function of replanning frequency. On average, 65% of benefit was achieved with a single midtreatment adaptation, and 85% was realized after weekly adaptation.

and 80% was realized after weekly adaptation. Average increases in allowable target dose as a function of replanning frequency are summarized in Fig. 3. Approximately 65% of the potential dose escalation was achievable with a single midtreatment adaptation, and about 85% was achievable with weekly adaptation. The last 15% of the reported average benefit is associated with a six-fold increase in workload over weekly replanning which itself represents a large increase in cost over a single adaptation. Considerations of this sort suggest that the workload associated with daily adaptation outweighs additional benefit, and weekly adaptation would be most favorable for the majority of patients. However, as the workload associated with planning decreases through the development of automatic methods, daily replanning may be justified.

In addition to the workload, adaptive planning requires imaging for which the patient may incur additional radiation dose. Assuming a CT study of the thorax to carry out each replan, and an average effective dose of 8 mSv/scan,¹² full-adapt, weekly adapt, and midadapt schedules would result in 272, 48, and 8 mSv, respectively. As the benefit decreases with each increase in planning frequency, reductions in dose may eventually be offset by increases associated with imaging.

Due to the sampling method employed in the generation of synthetic datasets, trends of variation were devoid of large acute change which represents an important limitation of the study. In this work, we simulated replanning at regular intervals; however, such a method is ultimately naïve and acute variation may warrant a more tailored approach.

Though correlation was modest, reductions in both MLD and MED were related to the absolute change in PTV ($r_{\text{MLD}} = 0.34$ and $r_{\text{MED}} = 0.26$). Additional correlations of adaptive benefit were investigated including nodal status and size of the initial PTV, however, no relationship was observed. Ultimately, the small sample size prevented a systematic evaluation of benefit versus patient characteristics; however, the methods employed in this work could be used to carry out such investigations. Enumerating and articulating patient

characteristics related to adaptive benefit will be the work of future studies.

The purpose of this study was to quantify the potential benefit associated with daily replanning in lung cancer in terms of normal tissue dose sparing, and to characterize the tradeoff between adaptive benefit and replanning frequency to aid clinicians in assessing the value of a given adaptive regimen for regularly regressing volumes. Our findings suggest that the majority of the benefit is obtained with a single midtreatment adaptation.

5. CONCLUSION

Daily adaptation in lung cancer radiotherapy produced significant reductions in normal-tissue dose metrics which allowed clinically relevant increases in target dose using an isotoxic MLD criteria. Normal-tissue dose sparing was likewise observed for a single midtreatment adaptation and weekly replanning when compared to a no-adapt simulation. Incremental reductions were realized for MLD and MED with each increase in replanning frequency while the extent of each reduction decreased.

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