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Scientific Article

Unanticipated Radiation Replanning for Stage III Non-small Cell Lung Cancer

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Purpose: The purpose of this study was to identify factors associated with unanticipated radiation therapy (RT) replanning in stage III non-small cell lung cancer (NSCLC).
Methods and Materials: Patients from a single institution with newly diagnosed stage III NSCLC treated with radical RT from January 1, 2016, to December 31, 2019, were retrospectively analyzed. The frequency and reasons for replanning were determined. Logistic regression analysis was used to identify factors associated with replanning.
Results: Of 144 patients included in this study, 11% (n = 16) required replanning after the start of RT. The reason for replanning in these 16 patients was changes in the target detected by cone beam computed tomography (shift in 10 patients, shrinkage in 5 patients, and growth in 1 patient). Larger planning target volume (primary and nodal) was statistically predictive of replanning (odds ratio, 2.5; 95% CI, 1.2-5.4; P = .02). The actuarial median overall survival was 33.3 months (95% CI, 10.3-43.9) for the 16 patients who were replanned and 36.3 months (95% CI, 27.4-66.5) for the remaining 128 patients (P = .96). The median time to local recurrence was 25.0 months (95% CI, 10.3-41.3) for those patients who underwent replanning, which was similar to those patients who did not undergo replanning (19.5 months; 95% CI, 11.8-23.2; P = .28).
Conclusions: In this study, 11% of patients treated with radical RT for NSCLC required replanning due to changes in the target detected by cone beam computed tomography. A larger planning target volume predicts a higher likelihood of requiring adaptive RT. Overall survival and local control were similar between patients who were replanned compared with those who were not replanned.

Introduction

For stage III non-small cell lung cancer (NSCLC), radical lung radiation therapy (RT) is typically planned using intensity modulated RT or volumetric modulated arc therapy. The goals of radical lung cancer RT are to encompass the tumor with conformal dose and reduce normal tissue toxicity. Image-guided techniques (such as the use of cone beam computed tomography [CBCT]) are also required to ensure that the delivered radiation adequately covers the tumor and minimizes dose to normal structures. Anatomic changes during lung RT (such as tumor growth, shrinkage, or shifts) may result in incomplete tumor irradiation and/or toxicity to normal tissues. Although online daily adaptive RT (ART) for lung cancer treatments are commercially available, these daily adaptive platforms for lung cancer are not widely used at present.

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For many radiation departments who do not routinely use online daily adaptive radiation for lung cancer, unanticipated replanning may be required in lung cancer RT, resulting in clinical workflow burden. The time needed to recontour and the additional quality assurance checks associated with lung cancer RT replanning could result in treatment delays. Image guidance using CBCT identifies the potential benefit for ART due to volume shifts, tumor shrinkage, or tumor growth.[1-3] In situations in which the tumor volumes shrink on RT but remain in the planning target volume (PTV), uncertainty regarding whether replanning results in decreased toxicity and/or improved tumor control has led to variability in clinical practice.[3]

In this study, we sought to identify the incidence of unanticipated replanning and the factors associated with unanticipated replanning in patients with stage III NSCLC receiving radical radiation. Clinical outcomes (overall survival [OS] and tumor control) were also examined between patients who were replanned versus those who were not replanned.

Methods and Materials

Patients with newly diagnosed stage III NSCLC treated with radical RT (from January 1, 2016, to December 31, 2019) were retrospectively analyzed. Radical RT was defined as a planned RT dose of ≥60 Gy in 30 daily fractions over 6 weeks or its radiobiological equivalent.

Radiation planning overview

All patients were simulated in the supine position with 4-dimensional (4D) CT planning (1.5 mm slice thickness). Patients were positioned on a wing board and neck rest, usually with arms raised. Immobilization masks (with arms down) were used if nodal volumes extended above the clavicles. Intravenous contrast for CT simulation was used at the discretion of the treating radiation oncologist. Staging positron emission tomography scans and CT data were used to identify gross tumor volumes (GTVs; primary and nodal).

GTVs, primary and nodal, on inspiration, expiration, and maximum intensity projection CT planning images were contoured and combined to generate internal target volumes, primary and nodal. A uniform expansion of 7 mm was added to internal target volumes to generate the PTV, primary and nodal. Our center specific contouring protocol does not include a clinical target volume (CTV).

All patients were planned with intensity modulated RT or volumetric modulated arc therapy planning. Daily CBCT scans were used for treatment verification. Simulation CT images were matched to daily CBCT images based on bony anatomy and analyzed for target coverage by radiation therapists. The daily CBCT assessment by radiation therapists involve matching to bone (spine). The primary tumor and nodal volumes should be within PTV. If there is a concern regarding the primary tumor/nodal volumes or organs at risk (spinal canal, esophagus, trachea/bronchi, brachial plexus) not aligning on CBCT to the simulation images, the radiation oncologist is called to assess the CBCT.

When the CBCT could not be matched to the simulation CT images adequately (eg, due to lung reinflation, tumor shrinkage, tumor growth, shift of the target, or mismatch of the bony or airway anatomy), the treating radiation oncologist was called to consider replanning.

During this study period, our center did not have access to online ART replanning. Patients who required replanning were brought to resimulation. Target volumes and normal tissue contours were recontoured on the resimulation scans and the new contours were subjected to replanning. Whether patients continued the original RT plans until the new resimulation plan was ready or whether there was a treatment gap between the original RT plan and the new plan was at the discretion of the treating radiation oncologist.

Statistical analysis

Descriptive statistics were performed, including the frequency of RT replanning and reasons for replanning. Logistic regression analysis was used to identify predictive factors associated with replanning.[4] Variables significant on univariate modeling, with a P value <.05, were selected for backward stepwise regression. The final model includes the significant predictive factor(s) with $P < .05$.

The factors used to determine whether there was an association with replanning were age; sex; histology; epidermal growth factor receptor; anaplastic lymphoma kinase; programmed death ligand 1status; presence or absence of concurrent chemotherapy; stage (IIIa, IIIb, or IIIc, American Joint Committee on Cancer seventh edition); maximum unidimensional measurement of the primary, nodes, or both (superior/inferior [SI], anterior/posterior [AP], right/left [LR]); and PTV (primary, nodes or both).

OS in months was defined as the time from diagnosis to death or to the last follow-up. The median OS with 95% confidence intervals (CIs) was determined for those patients who were replanned compared with those patients who were not replanned. Median time to local recurrence and to regional recurrence with 95% CIs were determined for those patients who were replanned compared with those patients who were not replanned.

This study received institutional research ethics approval.

Results

Demographics

One-hundred forty-four patients meeting study criteria were analyzed. Thirty-nine percent of participants were

female, and 61% were male. The median age was 68 years. The majority (76%) received concurrent chemotherapy. The most common concurrent chemotherapy regimen was cisplatin and etoposide (65% of patients), followed by carboplatin and paclitaxel (15%), cisplatin and pemetrexed (10%), cisplatin and vinorelbine (4%), carboplatin and pemetrexed (4%), carboplatin and etoposide (1%), and cisplatin and gemcitabine (1%). The mean duration of follow-up from the time of diagnosis was 25.7 months. Table 1 summarizes the characteristics of patients analyzed.

The median prescription dose was 66 Gy in 33 fractions (range, 60-66 Gy). The median and interquartile range (IQR) of the SI, RL, and AP maximum dimensions of the PTV (primary and nodes) were 125 mm (IQR, 102-151), 122 mm (IQR, 102-143), and 105 mm (IQR, 87-122), respectively. The median and IQR for the combined PTV (primary and nodes) was 357.7 cm^3 (IQR, 244.3-498.6).

Replanning

Out of 144 patient, 11% (n = 16) required replanning after the start of RT. The reasons for replanning were based on the radiation oncologist's interpretation of the CBCT. In 10 patients, the radiation oncologist noted a shift of the target without appreciable significant target volume change. Of these 10 patients, 1 patient with supraclavicular nodal involvement required resimulation with a new mask and pretreatment lorazepam to help with radiation treatment tolerance and improved CBCT match. Another patient's target shifted due to an enlarging pleural effusion. An additional patient developed pneumonia/consolidation associated with fever that shifted the target, and 1 patient had partial re-expansion of lung, which shifted the target. The remaining 6 patients had a shift in the target without a documented/explicable cause.

Another 5 patients needed replanning due to target shrinkage, and 1 patient had target growth on visual inspection of the CBCT.

The majority of patients (n = 9) had 1 replan, 6 patients had 2 replans, and 1 patient had 3 replans during the course of RT. Tumor changes detected by CBCT that led to replanning occurred as early as the second fraction and as late as the 25th fraction. The following time intervals were determined for the 16 patients from the initial plan to the first replan. The median time interval from the time the radiation oncologist decided to resimulate the patient to the date of resimulation was 1 day (range, 0-5 days). The median time interval from the time of resimulation to the start of the first replanned treatment was 5 days (range, 0-11 days). Seven patients continued the preceding plan until the new replan was ready. For 9 patients, the radiation treatment course was held until the new replan was ready. In this latter group, the median radiation treatment delay was 6 days (range, 3-13 days).

Table 1 Patient characteristics

Characteristic	Value	Percentage
Age (y)		
Median	68	
Interquartile range	61-75	
Sex		
Female	56	38.9
Male	88	61.1
Histology		
Adenocarcinoma	87	60.4
Non-small cell carcinoma NOS	9	6.3
Squamous	48	33.3
EGFR (for adenocarcinoma or NOS histology)		
Negative	60	62.5
Positive	23	24.0
Unknown	13	13.5
ALK		
Negative	67	69.8
Positive	6	6.2
Unknown	23	24.0
PDL1		
<1%	25	17.4
1%-49%	26	18.0
>50%	42	29.2
Not done/unknown	51	35.4
Stage		
IIIa	83	57.6
IIIb	59	41.0
IIIc	2	1.4
Concurrent chemotherapy		
No	33	22.9
Yes	110	76.4
Unknown	1	0.7
Chemotherapy before radiation		
No	138	95.8
Yes	6	4.2
Adjuvant systemic therapy		
No	59	41.0
Yes	75	52.1
Unknown	10	6.9

Abbreviations: ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; NOS = not otherwise specified; PDL1 = programmed death ligand 1.

Table 2 Factors associated with replanning

Univariate analysis **Covariate**	**OR**	**95% CI**	***P* value**	**R^2**
Age (y)	0.96	0.92-1.01	.09	2.00
Sex (female vs male)	1.11	0.43-2.76	.83	0.03
Histology (overall effect)			.70	0.49
Non-small cell carcinoma NOS vs adenocarcinoma	0.78	0.04-4.85	.69	
Squamous vs adenocarcinoma	1.44	0.55-3.71	.46	
EGFR (positive vs negative)	0.23	0.01-1.30	.17	2.88
ALK (positive vs negative)	1.26	0.06-8.97	.84	0.05
PDL1 (overall effect)			.19	3.76
1%-49% vs <1%	0.96	0.11-8.53	.47	
≥50% vs <1%	3.14	0.72-21.84	.07	
Concurrent chemotherapy (yes vs no)	3.24	0.87-21.04	.13	2.07
Stage IIIb/IIIc vs stage IIIa	1.00	0.41-2.34	.99	<0.01
SI maximum extent: PTV primary and nodes	1.17	1.03-1.35	.02	4.40
RL maximum extent: PTV primary and nodes	1.17	0.97-1.44	.11	2.25
AP maximum extent: PTV primary and nodes	1.05	0.89-1.24	.56	0.28
SI maximum extent: PTV primary	1.00	0.73-1.37	.97	0.01
RL maximum extent: PTV primary	0.89	0.61-1.26	.53	2.29
AP maximum extent: PTV primary	1.21	0.83-1.96	.35	5.45
SI maximum extent: PTV nodes	0.37	0.02-1.16	.23	26.22
RL maximum extent: PTV nodes	0.81	0.24-2.31	.69	2.05
AP maximum extent: PTV nodes	0.30	0.01-1.43	.28	24.91
Volumes: PTV primary (log)	1.52	0.99-2.41	.06	2.50
Volumes: PTV nodes (log)	1.86	0.95-3.91	.08	2.51
Volumes: combined PTV (log)	2.48	1.21-5.38	.02	4.18
Backward stepwise regression* **Final model**	**OR**	**95% CI**	***P* value**	**R^2**
Volumes: combined PTV (log)	2.48	1.21-5.38	.02	4.18%

Abbreviations: AP = anterior posterior; CI = confidence interval; OR = odds ratio; PTV = planning target volume; RL = right left; SI = superior inferior.

* Using the backward stepwise regression, SI maximum extent (PTV primary and nodes) had a nonsignificant *P* value of .44 and was excluded from the final model.

Using backward stepwise regression (Table 2), only larger PTV (primary and nodal) remained in the final model and was statistically predictive of replanning (hazard ratio, 2.5; 95% CI, 1.2-5.4; $P = .02$).

Clinical outcomes

The mean duration of follow-up from the time of diagnosis was 25.7 months. The actuarial median survival was 33.3 months (95% CI, 10.3-43.9) in the 16 patients who were replanned and 36.3 months (95% CI, 27.4-66.5) in the remaining 128 patients ($P = .96$).

Among the 16 replanned patients, 6 patients had local recurrence. The median time to local recurrence was 25.0 months (95% CI, 10.3-41.3) for these 6 patients. Among the 128 remaining patients, 31 patients had local recurrence. The median time to local recurrence for these 31 patients was 19.5 months (95% CI, 11.8-23.2).

Among the 16 replanned patients, 8 patients had a regional recurrence. The median time to regional recurrence was 16.9 months (95% CI, 3.5-41.3) for these 8 patients. Among the remaining 128 patients, 30 patients had regional recurrence. The median time to regional recurrence was 18.2 months (95% CI, 11.8-23.2) for these 30 patients.

Discussion

We report an 11% rate of unanticipated replanning in patients with stage III NSCLC treated with radical intent RT. Replanning was initiated for target shift, target shrinkage, or target growth based on CBCT. These patients all underwent offline ART planning using 4D CT resimulation. This process results in resource burden and unanticipated clinical workflow disruptions.

A planning study of 12 patients with NSCLC reported by Dial et al[2] examined 4 possible radiation treatment scenarios. The first scenario was no adaptation, the second was radiation adaptation starting at fraction 18 using a single replan, the third was weekly adaptation, and the fourth was daily replanning. Target coverage was maintained, and cord tolerance was not exceeded in any of the 4 radiation treatment scenarios. The authors reported significant reductions in normal tissue (lung, esophagus, cord, heart) with all adaptation scenarios compared with no adaptation. The authors noted that while the increased frequency of adaptation was associated with greater reduction in dose to the normal tissues, the magnitude of the benefit decreased. Dial et al[2] reported on only 12 patients with different frequency of planning adaptation, which included no adaptation. This suggests that the 12 patients in the Dial study had targets which remained in the PTV without adaptation, and this represents a different group of patients compared with 16 patients in the present study who required adaptation due to CBCT mismatch.

In this present study, the majority of patients (n = 9) had 1 replan, 6 patients had 2 replans, and 1 patient had 3 replans during the course of RT. Dosimetric analysis of the first replan revealed that half of the patients in this study had a reduction in PTV coverage (V95%), and half had an increase in PTV coverage (V95%) with the first replan. All replan PTV (V95%), primary and nodes, ranged from 93.2% to 99.9%. While 75% of the patients in this study had a reduction in heart maximum dose, and 68.8% of patients had a reduction in Lung V20, a higher percentage of patients (56.3%) had an increase in esophagus maximum dose. As such, predicting target coverage and normal tissue doses with replanning is difficult as target shifts, growth, and shrinkage affect the geometry of the target in relation to the organs at risk. Even though some organ-at-risk doses were higher in the replans, the doses to organs at risk were still deemed to be safe by the treating radiation oncologist.

Harsolia et al[3] reported a planning study in 8 patients. Four plans were generated for each patient: 3-dimensional (3D) conformal, 4D union, 4D offline ART with single correction, and 4D online ART with daily correction. The 3D conformal margin for PTV was defined as CTV + 0.5 cm + tumor motion. The PTV margin for 4D union was CTV + 0.5 cm. The PTV margin for 4D offline adaption ART (single correction) and 4D online ART (daily correction) was CTV + the patient-specific margin. Compared with the 3D plans, the mean relative decreases in PTV volumes were 15%, 39%, and 44% for the 4D union, 4D offline ART, and 4D online ART plans. The study also reported reduction in V20 and mean lung doses favoring 4D online ART with daily correction.

Based on visual interpretation of the CBCT, replans were initiated for target shift in 10 patients, target shrinkage in 5 patients, and target growth in 1 patient. When detailed dosimetric comparisons were made, half the replans were associated with a reduction in PTV (V95%), and half were associated with an increase in PTV (V95%). For these 16 replans, PTV (V95%) ranged from 93.2% to 99.9%. The majority of the replanned patients had a reduction in Lung V20 and in the maximum dose to the heart. Although the Harsolia et al[3] report was based on only 8 patients, further improvements in PTV coverage and lung sparing may be achieved using daily online ART.

In this present study, a larger PTV (primary and nodes) predicted for a higher probability of replanning (odds ratio, 2.5; 95% CI, 1.2-5.4; $P = .02$). The patients in this study did not undergo daily online ART. It remains unclear whether daily online ART may be associated with improvement in PTV coverage and organ-at-risk sparing such as lungs, particularly for patients with a larger PTV.

Deformable image registration is a promising approach[5,6-8] that mitigates the limitations of CBCT in dose calculation due to the inferior image quality and inaccurate Hounsfield units.[9,10] A study by Yuan et al[11] reported dose calculation comparisons between replanning CT simulation images and virtual planning CT images in patients with lung cancer. Daily CBCTs were performed and replanning CTs were acquired after 20 Gy for all patients. A simulated CBCT was then generated by deforming the CBCT to the replanning CT acquired on the same day. The virtual planning CT was then created by deforming the initial planning CT to the simulated CBCT. The authors compared dose calculations on the replanning CT to the virtual planning CT; results showed a mean dose difference smaller than 1.5% for most metrics, and most differences were in the range of ±5% for target and organ-at-risk doses. The authors concluded that virtual CT images could be used to provide a reasonable estimate of the "dose of the day" for lung ART. These promising results support the potential use of virtual CT derived from CBCT in adaptive planning.

Dosimetric advantages after replanning in lung cancer radiation oncology are well highlighted in literature.[5,12,13] However, there is a paucity of data indicating whether replanning translates to improved clinical outcomes, leading to variability in practice.[1] In a review of 281 patients (with the majority of patients having stage III NSCLC), 20.6% of patients had offline CT replanning.[13] The 2-year local control in that study was 60.7%, and median OS was 19.7 months.[13] However, survival and local control were not analyzed for those who were replanned compared with those who were not replanned.

In this study, the median OS and median times to local and regional recurrence were similar between the replanned patients and those who did not require replanning, although the numbers of replanned patients were small in our study. Factors predictive of replanning during a treatment course are not well defined in literature. In this study, larger PTV predicted a higher probability of RT replanning.

Limitations of this study include the retrospective retrieval of study data. There was a risk of selection bias and missing data. Replanning decisions were made at the discretion of treating radiation oncologist, only subject to an alert by radiation therapists based on their CBCT assessment. It is possible that tumor shift, shrinkage, or growth may not have been alerted to the treating radiation oncologist. The study findings were also limited to a single institution with 144 patients included. The analysis would be strengthened with increased power from multicenter contribution.

Commercially available systems that include artificial intelligence for automatic segmentation of target and normal tissue contours with treatment plan reoptimization will streamline the process for daily online ART for lung cancer. Future studies will help determine whether daily online ART translates to improved patient outcomes such as tumor control and toxicity.

Conclusion

Unanticipated replanning occurred in 11% of our patients who started radical RT for stage III NSCLC. Larger PTV of the primary and nodal targets predicted for a higher odds ratio, necessitating replanning. Optimal replanning techniques are needed to enable efficient clinically relevant replanning protocols for widespread adoption into routine clinical practice.

Disclosures

Alexander V. Louie has received honoraria from AstraZeneca for speaker's fees and advisory board participation. Ian Poon is on the advisory board for Sanofi Aventis and AstraZeneca. The rest of the authors have no conflicts of interest to disclose.

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