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Scientific Article

Adaptive Lung Radiation Therapy in the Era of Immunotherapy: A Single-Center Retrospective Study

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Purpose: Treatment for locally advanced non-small cell lung cancer consists of concurrent chemoradiation followed by immunotherapy. Though this combination has been shown to have a benefit in both progression-free survival and overall survival, treatment is often limited by the development of pneumonitis. One way to mitigate toxicity is through adaptive radiation therapy, which does not currently have a standardized implementation in clinical practice.

Methods and Materials: A single-center retrospective review of patients with locally advanced stage III or oligometastatic stage IV non-small cell lung cancer who were treated with chemoradiation with concurrent or subsequent immunotherapy from 2015 to 2020 was performed. Patients were stratified based on having 1 or more offline adapted plan. The aim of this study was to evaluate the association between dose-volume histogram values and common toxicities experienced during this treatment, including pneumonitis and esophagitis.

Results: Twenty-five patients were included in the final analysis: 10 with adapted plans (AP), and 15 with nonadapted plans (NAP). Mean age at onset was 74 years. The most common histology was adenocarcinoma (N = 13). Five patients experienced pneumonitis: 2 in AP and 3 in NAP. Mann-Whitney *U* test of gross tumor volume sizes between AP (346.2 ± 269.7 cm^3) and NAP (153.1 ± 99.6 cm^3) was significant ($P = .019$). Multiple linear regression analysis with adjustment for covariates of pneumonitis versus plan adaptation ($P = .106$) and esophagitis versus plan adaptation ($P = .59$) did not demonstrate a significant difference in toxicity between the adapted and nonadaptive patients.

Conclusions: Despite similar toxicities in both groups, the gross tumor volume size in the AP was more than double compared with NAP, suggesting that adaptive techniques provide a method for patients with larger target volumes to be treated without an observed difference in pneumonitis rates. These results suggest adaptive radiation therapy may have a role in mitigating toxicity experience from chemoradiation and immunotherapy and warrants further investigation.

Introduction

Lung cancer represents the leading cause of cancer mortality, accounting for almost one-quarter of all cancer deaths.[1] Non-small cell lung cancer (NSCLC) accounts for around 85% of lung cancer cases, and approximately 20% to 25% of all patients with NSCLC present with locally advanced disease.[2,3] Currently, the standard-of-care

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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treatment for these patients with a good performance status is chemoradiation followed by durvalumab, a humanized monoclonal antibody-blocking programmed death ligand checkpoint inhibitor immunotherapy, which increases both progression-free and overall survival. The most frequent adverse event leading to discontinuation of immunotherapy is the development of pneumonitis, which is a toxicity independently associated with radiation and immunotherapy.[4-6]

Adaptive radiation therapy (ART) is a technique used to address anatomic or physiological changes that occur during radiation treatment by modification of the treatment plan.[7] In lung cancer, there is evidence to suggest that even after the first fraction of radiation, lung tumors shrink, thereby changing the dosimetric quality metrics used to plan the radiation.[8-10] The offline ART process uses integrated imaging techniques to allow physicians to resimulate and replan a patient's treatment to minimize radiation dose to surrounding structures and healthy lung tissue while still maintaining adequate coverage of the tumor. ART may improve locoregional control and reduce toxicity in patients with NSCLC; however, little is known regarding how the addition of adjuvant immunotherapy affects the toxicity profile of pneumonitis and other radiation-induced side effects.[11,12]

Antonia et al demonstrated, as part of the PACIFIC trial, that in patients with stage III NSCLC who received durvalumab after chemoradiation, any grade pneumonitis or radiation pneumonitis was observed at a rate of 33.9%, with grade 3 and 4 pneumonitis observed at a rate of 3.4%.[5] In the NICOLAS study, which assessed the safety and efficacy of concurrently adding nivolumab to standard definitive chemoradiation demonstrated a grade 3 or higher pneumonitis rate of 11.7%, 4 of the 9 cases were attributed with a probable relation to radiation therapy.[13] Jabbour et al showed, in a phase 1 study of pembrolizumab given concurrently with chemoradiation in patients with stage III NSCLC, a rate of 33% of grade 2 or higher pneumonitis, with grade 2 pneumonitis occurring both within and outside of the radiation fields.[14] Von Reibnitz et al demonstrated a rate of 8% of grade 2 or greater esophagitis in patients with lung cancer and melanoma treated with radiation therapy and immunotherapy.[15] Although these studies investigate toxicities related to radiation therapy and immunotherapy, none have evaluated the toxicity consequences for the combination of ART and immunotherapy. This study aims to retrospectively analyze the differences in toxicity between patients with NSCLC treated with immunotherapy with and without ART.

Methods and Materials

Study population

After obtaining institutional review board approval, a single-center retrospective chart review of electronic medical records to identify patients with lung cancer based on International Classification of Diseases code typing from January 1, 2015 to June 1, 2020 was performed. Patients were then screened for the following criteria: (1) stage III or stage IV oligometastatic NSCLC and (2) primary treatment chemoradiation and concurrent or adjuvant immunotherapy. A total of 49 patients fit the initial inclusion criteria. Patients were excluded if they progressed after chemoradiation but before receiving immunotherapy or were lost to follow-up. A total of 25 patients (n = 15 nonadaptive) met the final inclusion and exclusion criteria; 1 adaptive patient was excluded from the esophagitis analysis due to undergoing transhiatal esophagectomy before radiation therapy. Computed tomography (CT) simulation was performed per department lung protocol with both 3- and 4-dimensional CT protocols depending on the urgency of treatment or the respiratory pattern of the patient. The radiation treatment planning including details regarding simulation, immobilization, target volumes, and dose constraints were consistent with our institution's standardized approach for patients with lung cancer.[16] Contouring was performed in Eclipse (Varian Medical Systems, Palo Alto, CA), the tumor was delineated by the physician, and lung tissue was determined by the clinical segmentation wizard and reviewed by the physician. Treatment planning was performed in Eclipse using the Anisotropic Analytical Algorithm (version 11.0-15.6) with 6 MV, 10 MV, or 15 MV treatment energies depending on the patient habitus. Offline plan adaptation was performed at the discretion of the treating physician with a maximum of 2 adaptations per patient (n = 3, received 2 plan adaptations). Daily cone beam CTs were monitored by the physician, and when there was an observed change of approximately 20% in primary tumor volume, the physician would adapt the plan. Image registration was performed rigidly within Eclipse with an emphasis of matching to the target volume. Plan summation was also performed within Eclipse using rigid registration between the CT simulation planning studies.

Data collection

Baseline demographics were collected for the eligible patients including age at onset of chemoradiation, biologic sex, race, ethnicity, smoking history, histology, staging (American Joint Committee on Cancer, seventh edition), tumor-node-metastasis staging, Eastern Cooperative Oncology Group performance status, location of primary tumor, and International Classification of Diseases diagnosis. Treatment details were extracted from Eclipse version 11 and included prescribed dose, modality of radiation, treatment volumes, dose-volume histogram (DVH) values, and chemotherapy and immunotherapy regimen. Patients were evaluated for the presence of adapted plans. If the patient had an adapted plan, a rigid fusion between the original and adapted plan was performed in Aria version 11. DVH values were queried from the plans using an Eclipse API (ESAPI)

script within Eclipse from the initial plan and the plan sum. The values from the treated plan sum were used for final statistical evaluation. DVH values collected include gross tumor volume (GTV); internal target volume; clinical target volume; planning target volume; $V5_{Lung}$; $V10_{Lung}$; $V20_{Lung}$; $V30_{Lung}$; mean, minimum, and maximum lung doses, $V5_{Heart}$, $V30_{Heart}$, 40_{Heart}, $V45_{Heart}$, $V50_{Heart}$, mean, minimum and maximum heart doses; $V5_{Esophagus}$; $V50_{Esophagus}$; and mean minimum and maximum esophageal doses. Lung volumes were collected as total lung, right lung, and left lung. Plan sums included doses from the initial treatment plans and the adapted plans, with fractionation matching the clinical treatment. Treatment-related toxicity data including grading and frequency were collected for esophagitis and pneumonitis. The Common Terminology Criteria for Adverse Events version 5 was used to assess the grade and frequency among these patients. The highest grade of each toxicity was taken from each patient. The median follow-up time from the completion of radiation therapy was 14.5 months (range, 0.4-50.9 months).

Statistical analysis

Descriptive statistics were used to summarize the patient characteristics, treatment details, toxicity data, treatment volumes, and DVH values. Multiple linear regression analysis was performed to evaluate associations of the toxicities (pneumonitis and esophagitis) between the adapted and nonadapted patients adjusting for covariates. Due to the number of covariates (ie, patient characteristics, DVH values, and target values) compared with the small study sample size, bivariate associations determined with linear regression were used to determine which covariates to include in the multiple linear regression analysis. The Mann-Whitney *U* test was performed to assess differences between the adaptive and nonadaptive tumor volumes, patient characteristics, and DVH values. Statistical analyses were performed in Microsoft Excel and SPSS Statistics for Windows, version 28.

Ethical statement

This study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review board of Rutgers Biomedical and Health Sciences (No. Pro20170001559), and individual consent for this retrospective analysis was waived.

Results

Baseline patient characteristic and treatment details

Baseline patient characteristics are summarized in Table 1. The median age for all patients was 74 years (range, 51-83). Fifty-two percent of patients were women (n = 13), and the majority had a prior smoking history (n = 23, 92%). Fifty-two percent of patients presented with adenocarcinoma (n = 13), 36% presented with squamous cell carcinoma (n = 9), and 12% presented with poorly differentiated carcinoma that was treated as NSCLC. Most patients presented with stage IIIB disease (n = 15, 60%), and the remaining patients presented with stage IIB (n = 1, 4%) and stage IIIA (n = 9, 36%).

Treatment details are outlined in Table 2. A total of 10 patients had adapted plans. The remaining 15 patients served as the control group. Figure 1 demonstrates an example of an adapted plan. Ninety percent of patients had a prescribed dose of 6000 cGy (n = 23), and 96% of patients received standard photon radiation. One patient in the control group received proton radiation at a prescribed dose of 5940 cGy. All patients received concurrent chemotherapy, with the most common regimen being carboplatin and paclitaxel (n = 18, 72%). Most patients received immunotherapy with pembrolizumab (n = 15, 60%), with fewer patients receiving combination adjuvant ipilimumab and nivolumab (n = 5, 20%), single agent nivolumab (n = 3, 12%), and durvalumab (n = 2, 8%). A total of 7 patients received immunotherapy in the form of pembrolizumab concurrent with the radiation therapy.

Patient toxicity patterns are presented in Table 3. Seventy-nine percent of patients experienced grade 1 or higher esophagitis (n = 19/24, as 1 patient was excluded for esophagitis analyses), an acute toxicity, and 20% of patients experienced grade 1 or higher pneumonitis (n = 5), a subacute toxicity. Of the 19 patients who experienced esophagitis, 7 patients were in the adapted group, and 12 patients were in the control group. The highest grade of both groups for esophagitis was grade 2. Of the 5 patients who experienced pneumonitis, 2 patients were in the adapted group, and 3 patients were in the control group. The highest grade of pneumonitis experienced by any patient was grade 3; this patient was in the adapted group.

Mean DVH and target values are presented in Table 4. Mann-Whitney *U* test was performed for the GTV of adapted and nonadaptive patients with $P = .019$, suggesting a significant difference between the GTV sizes of adapted (346.2 ± 269.7 cm^3) and nonadapted (153.1 ± 99.6 cm^3) patients. There were no statistically significant differences in toxicities between the 2 groups. Results for a subset of the bivariate analysis are summarized in Table 5. Multiple regression analysis was performed for esophagitis versus plan adaptation ($P = .59$), which did not show a difference in toxicity between patients when adjusting for covariates (body mass index, age, esophageal maximum dose) (Table 6). Multiple regression analysis of pneumonitis versus plan adaptation ($P = .106$) did not demonstrate a significant difference in toxicity between

Table 1 Baseline demographics

Demographic	Total, no. (%)	Adapted, no. (%)	Control, no. (%)
Biologic sex			
Male	12 (48)	4 (40)	6 (40)
Female	13 (52)	6 (60)	9 (60)
Race			
Asian	2 (8)	0 (0)	2 (13)
Black or African American	4 (16)	1 (10)	3 (20)
White	16 (64)	8 (80)	8 (53)
Unidentified	3 (12)	1 (10)	2 (13)
Ethnicity			
Hispanic or Latino	3 (12)	1 (10)	2 (13)
Nonhispanic or Latino	22 (88)	9 (90)	13 (87)
Smoking history			
No	3 (12)	1 (10)	2 (13)
Yes	22 (88)	9 (90)	13 (87)
Histology			
Adenocarcinoma	13 (52)	3 (30)	10 (67)
Squamous	9 (36)	5 (50)	4 (27)
Poorly differentiated carcinoma	3 (12)	2 (20)	1 (7)
Stage (AJCC 7th)			
IIB	1 (4)	0 (0)	1 (7)
IIIA	9 (36)	1 (10)	8 (53)
IIIB	15 (60)	9 (90)	6 (40)
T stage			
T1	4 (16)	2 (20)	2 (13)
T2	6 (24)	1 (10)	5 (33)
T3	9 (36)	2 (20)	7 (47)
T4	6 (24)	5 (50)	1 (7)
Location of primary tumor			
Left lower lobe	1 (4)	1 (10)	0 (0)
Left upper lobe	8 (32)	1 (10)	7 (47)
Right lower lobe	4 (16)	1 (10)	3 (20)
Right upper lobe	12 (48)	7 (70)	5 (33)
Baseline ECOG performance status			
0	7 (28)	4 (40)	3 (20)
1	17 (68)	5 (50)	12 (80)
2	1 (4)	1 (10)	0 (0)
Body mass index (median, range)*	27.08 (26.93-44.19)	28.20 (18.85-44.19)	26.93 (22.71-44.54)
Age (median, range)*	74 (51-83)	72.5 (51.83)	76 (58-82)

Abbreviations: AJCC = American Joint Committee on Cancer; ECOG = Eastern Cooperative Oncology Group; T stage = tumor stage.
*No statistical difference, $P < .05$.

Table 2 Treatment details

Treatment	Total, no. (%)	Adapted, no. (%)	Control, no. (%)
Radiation technique			
3D-CRT	5 (20)	0 (0)	5 (33)
IMRT	20 (80)	10 (100)	10 (67)
Radiation modality			
Photon	24 (96)	10 (100)	14 (93)
Proton	1 (4)	0 (0)	1 (7)
Prescribed dose (cGy)			
5760	1 (4)	0 (0)	1 (7)
5940	1 (4)	1 (10)	0 (0)
6000	23 (92)	9 (90)	14 (93)
Concurrent chemotherapy regimen			
Abraxane	1 (4)	0 (0)	1 (7)
Abraxane and carboplatin	2 (8)	1 (10)	1 (7)
Pemetrexed and cisplatin	2 (8)	2 (20)	0 (0)
Pemetrexed and carboplatin	1 (4)	0 (0)	1 (7)
Paclitaxel and carboplatin	18 (72)	6 (60)	12 (80)
Etoposide and cisplatin	1 (4)	1 (10)	0 (0)
Immunotherapy agent			
Pembrolizumab	15 (60)	6 (60)	9 (60)
Ipilimumab and nivolumab	5 (20)	1 (10)	2 (13)
Nivolumab	3 (12)	3 (30)	2 (13)
Durvalumab	2 (8)	0 (0)	2 (13)

Abbreviations: 3D-CRT = 3-dimensional conformal radiation therapy; IMRT = intensity modulated radiation therapy.

the adapted and nonadaptive patients when adjusting for covariates (left lung V20 Gy, right lung max dose, body mass index, age) (Table 7). There was no significant association between toxicity and the other DVH values sampled.

Discussion

To our knowledge, this retrospective study is the first to evaluate the utilization of offline adaptive radiation planning in patients with NSCLC treated with chemoradiation

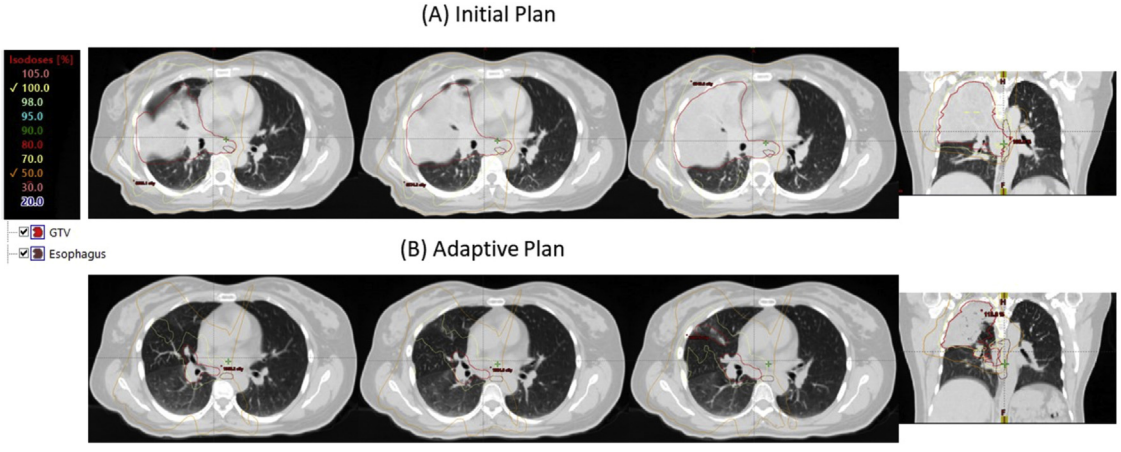

Figure 1 The change in target size and prescription dose coverage in (A) the initial plan and (B) the adapted plan in proximity to the esophagus.

Table 3 Toxicities

Toxicity	Number of patients	
	Adapted, no. (%)	Control, no. (%)
Esophagitis		
Grade 1	3 (30)	5 (33)
Grade 2	4 (40)	7 (47)
Pneumonitis		
Grade 1	1 (10)	1 (6)
Grade 2	0	2 (13)
Grade 3	1 (10)	0

and immunotherapy. However, there are currently 32 active clinical trials exploring lung cancer and both online and offline ART. The primary objective was to describe the occurrence of pneumonitis and esophagitis and compare DVH values of patients treated with ART or with conventional radiation therapy. The results showed that despite a GTV size of more than double in the adaptive group, a difference in pneumonitis rates was not observed between the adapted and nonadaptive groups when accounting for covariates. The results were unexpected given the positive association between larger tumor definition and volumes and the development of radiation pneumonitis.[17] The utilization of adaptive planning may have mitigated toxicity that would have otherwise been observed. Differences in GTV size have previously confounded predictive algorithms for radiation pneumonitis in patients with lung cancer.[18]

Radiation pneumonitis has been extensively studied in the setting of chemoradiation and, more recently, in combination with immunotherapy. In radiation alone or in conjunction with chemotherapy, values such as V5, V20, V30, mean lung dose, and planning target volume are considered risk factors for the development of radiation pneumonitis.[19-22] However, we included 7 patients who received chemoradiation with concurrent immunotherapy, and based off data from KEYNOTE-799, the suggestion is that the effects of concurrent administration on radiation pneumonitis are additive.[6] The PACIFIC phase 3 randomized control trial was pivotal in demonstrating improved

Table 4 Subset of target and dose-volume histogram values

Target and DVH Metrics	Adapted (n = 10) Mean ± SD	Control (n = 15) Mean ± SD
GTV (cm^3)	346.2 ± 269.7*	153.0 ± 99.6*
Bilateral lung volume (cm^3)	2885.1 ± 881.9	3563.1 ± 1299.4
Bilateral lung V5 Gy (%)	56.0 ± 9.2	57.0 ± 8.9
Bilateral lung V10 Gy (%)	42.3 ± 8.7	43.7 ± 6.0
Bilateral lung V20 Gy (%)	27.5 ± 6.1	29.5 ± 3.0
Bilateral lung min (cGy)	31.9 ± 23.4	30.9 ± 16.1
Bilateral lung mean (cGy)	1576.5 ± 242.3	1727.2 ± 186.7
Bilateral lung max (cGy)	6474.1 ± 180.1	6853.7 ± 291.4
Left lung volume (cm^3)	1362.5 ± 521.1	1647.1 ± 588.3
Left lung V20 Gy (%)†	23.0 ± 31.9	22.94 ± 25.5
Left lung max (cGy)	5946.3 ± 2042.1	5636.7 ± 1752.6
Right lung volume (cm^3)	1593.1 ± 691.2	1917.8 ± 735.6
Right lung V20 Gy (%)	41.12 ± 23.5	33.9 ± 21.8
Right lung max (cGy)†	6438.4 ± 214.1	6697.0 ± 415.9
Esophagus volume (cm^3)	43.1 ± 13.6	38.2 ± 13.8
Esophagus V35 Gy (%)	45.2 ± 12.0	27.5 ± 13.5
Esophagus V50 Gy (%)	29.1 ± 13.3	22.1 ± 12.3
Esophagus min (cGy)	108.1 ± 145.2	45.6 ± 34.9
Esophagus mean (cGy)	2989.9 ± 657.1	2051.8 ± 666.4
Esophagus max (cGy)†	6338.0 ± 204.0	6068.1 ± 1056.6

Abbreviations: GTV = gross tumor volume; SD = standard deviation.
*Statistical significance detected with Mann-Whitney *U* test, $P = .019$.
†Covariates used in multiple regression analysis.
All values underwent bivariate analysis to determine covariates for multiple regression.

Table 5 Subset of the variables used for bivariate analysis

	Radiation pneumonitis		Esophagitis	
Target and DVH Parameters	Pearson correlation	Sig. (2-tailed)	Pearson correlation	Sig. (2-tailed)
PTV	−0.081	0.681	−0.285	0.176
ITV	−0.147	0.536	−0.058	0.831
GTV	−0.105	0.593	−0.15	0.484
CTV	−0.212	0.308	−0.201	0.357
Bilat lungs	0.043	0.83	−0.052	0.814
Bilat lungs V5	0.092	0.649	0.035	0.873
Bilat lungs V10	0.069	0.733	0.162	0.46
Bilat lungs V20	0.079	0.694	0.211	0.333
Bilat lungs V30	0.06	0.767	0.167	0.446
Bilat lungs min	0.047	0.816	−0.117	0.594
Bilat lungs mean	0.081	0.687	0.215	0.325
Bilat lungs max	−0.271	0.171	−0.225	0.302
Left lung vol	−0.185	0.356	0.077	0.728
Left lung V5	0.298	0.132	−0.015	0.946
Left lung V10	0.323	0.1	0.027	0.901
Left lung V20*	0.417	0.048	0.008	0.97
Left lung V30	0.346	0.077	−0.003	0.99
Left lung min	−0.106	0.599	−0.058	0.793
Left lung mean	0.326	0.097	0.021	0.926
Left lung max	0.241	0.226	−0.028	0.9
Right lung vol	0.176	0.38	−0.1	0.649
Right lung V5	−0.186	0.352	0.028	0.898
Right lung V10	−0.221	0.267	0.035	0.875
Right lung V20	−0.263	0.185	−0.02	0.928
Right lung V30	−0.299	0.129	−0.018	0.934
Right lung min	0.123	0.542	0.164	0.455
Right lung mean	−0.281	0.156	−0.026	0.905
Right lung max*	−0.47	0.013	−0.25	0.25
Eso vol			−0.151	0.48
Eso V35			0.274	0.195
Eso V50			0.256	0.227
Eso min			−0.05	0.818
Eso mean			0.288	0.173
Eso max*			0.38	0.067

Abbreviation: Bilat = bilateral; CTV = clinical target volume; Eso = esophagus; GTV = gross tumor volume; ITV = internal target volume; max = maximum; min = minimum; PTV = planned target volume; sig = significant; vol = volume.
*Covariates used for multiple linear regression analysis.

progression-free survival and overall survival in patients with locally advanced NSCLC treated with definitive chemoradiation using consolidative radiation therapy, serving as the standard of care.[4,5,23] Thereafter, increasing efforts have been made to establish risk factors for developing radiation pneumonitis after immunotherapy. Most studies have been retrospective in nature and are inconsistent with the data previously reported in radiation pneumonitis and with similar studies conducted. For example, Jang et al demonstrated prognostic significance of mean lung dose,

Table 6 Multiple linear regression analysis of toxicities (esophagitis)

Multiple Linear Regression Parameters	Coefficient	Standard error	*P* value	Lower 95%	Upper 95%
Intercept	3.440	2.189	.133	−1.142	8.022
Adaptation	0.157	0.285	.588	−0.440	0.754
BMI	−0.368	0.242	.144	−0.874	0.138
Age onset of chemo/RT	−0.047	0.018	.019	−0.086	−0.009
Esophagus max (cGy)	0.000319	0.000166	.0694	−2.79E-05	6.66E-04

Abbreviations: BMI = body mass index; RT = radiation therapy.
Esophagitis regression statistics: $R^2 = 0.42$. Dependent variable: esophagitis. Predictors: (constant), adaptation, BMI, age onset of chemo/RT, esophagus max.

Table 7 Multiple linear regression analysis of toxicities (pneumonitis)

Multiple Linear Regression Parameters	Coefficient	Standard error	*P* value	Lower 95%	Upper 95%
Intercept	6.771	3.242	.0504	−0.0143	13.56
Adaptation	0.125	0.328	.707	−0.562	0.812
Left lung V20 (%)	0.0079	0.006	.203	−0.005	0.020
Right lung max (cGy)	−0.001	0.000	.072	0.002	0.000
Age onset of chemo/RT	0.009	0.0203	.648	−0.033	0.052
BMI	−0.447	0.271	.115	−1.01	0.12

Abbreviations: BMI = body mass index; RT = radiation therapy.
Pneumonitis regression statistics: $R^2 = 0.359$. Dependent variable: pneumonitis. Predictors: (constant), adaptation, BMI, age onset of chemo/RT, left lung V20, right lung max.

V20, V30, and V40 in the development of radiation pneumonitis in a cohort of 51 of 106 patients who received immunotherapy after chemotherapy.[24] This is in contrast to the results of Inoue et al, which found no statistical significance in V20 and the development of pneumonitis in a similar patient cohort—similar to our study—but such results are limited by a fairly small sample size (n = 30).[25,26] More recently, V40 and pulmonary fibrosis scoring were found to be predictive of grade 2 or higher radiation pneumonitis, potentially providing a new set of predictive factors given the evolving treatment regimen for patients with locally advanced NSCLC.[27]

There were several limitations in the current study. The retrospective nature of this study in combination with the small sample size exudes caution in drawing definitive conclusions. Additionally, treatment technique was not addressed by this study. Although the majority of patients did receive intensity modulated radiation therapy, 5 patients in the nonadapted study arm received 3-dimensional conformal radiation therapy. The DVH parameters evaluated as part of this study should take into account the conformal nature of the different treatment techniques; however, this difference may influence toxicities. Another source of bias of this study comes from the decision to adapt a patient's plan. This was determined qualitatively by the physician based on daily cone beam CT. Additionally, the contoured lung tissue was delineated by the Eclipse lung segmentation algorithm. Although this algorithm is CT Hounsfield Unit–based and excludes the GTV, it is not a true Boolean subtraction of the normal lung tissue and the GTV. Review of the changes in the lung-GTV contour prior and post adaptation are beyond the scope of this study due to the limited number of adapted patients but will be included in future studies. Further, given the addition of immunotherapy primarily occurred within the study's timeframe, there was a limited number of patients participating in a similar regimen at our institution. Patients were those typically on clinical trials, and patient selection may have been dictated by a trial protocol and/or physician preference. Lastly, some patients were still receiving immunotherapy at the time of data collection, so longer follow-up may have revealed the presence of additional toxicities not captured in this study.

Conclusion

The results suggest that ART has a role in mitigating toxicity experienced from chemoradiation and immunotherapy and warrants further investigation. Future directions include a phase 2 trial that is currently ongoing (NCT04751747), which will prospectively investigate the role of ART on mitigating toxicity in patients with locally advanced NSCLC receiving chemoradiation and immunotherapy.

Disclosures

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