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Cardiac and Pulmonary Dosimetric Parameters in Lung Cancer Patients Undergoing Post-Operative Radiation Therapy in the Real-World Setting

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minority of these patients were felt to have recurrence, leading to a poor PPV for RECIST criteria in this setting. Further work is needed to develop validated criteria for designation of recurrence after lung SABR.

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2838

Observation of Acute Toxicity Events in Lung Cancer Patients Treated Concurrently with a Tyrosine Kinase Inhibitor

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Purpose/Objective(s): Available tyrosine kinase inhibitors (TKI) for patients with non-small-cell lung cancer (NSCLC) have long half-lives. If thoracic radiation is given, it can be impractical to hold the TKI long enough for a washout. We set out to determine whether patients taking a TKI are at elevated risk for acute esophageal, pulmonary, or cardiac toxicity following thoracic radiation.

Materials/Methods: We performed a single-institution retrospective study of patients who had lung radiation from March 2011 to December 2021. Concurrent TKI use was defined as drug use within 3 months before or after radiation. Patients completed palliative or definitive thoracic radiation courses (including SBRT) for any primary lung cancer. Radiation doses and dosimetric parameters (esophagus mean and V30, heart mean and V25, lung mean and V20) were converted to biologically effective doses (BED_{10}) using an a/b ratio of 10 Gy. CTCAE acute toxicity outcomes were determined within 12 months of completion of radiation and compared using chi-square tests, Fisher's exact tests, and multivariate logistic regressions.

Results: A total of 105 patients receiving lung radiation were identified with median follow up of 12 months (range 0.6−114 months). Histologies included adenocarcinoma (51.4%), squamous cell carcinoma (23.8%), other NSCLC (15.2%), and SCLC (9.5%). 33 patients (31.4%) had metastatic disease at the time of radiation treatment. Median dose was 72 BED_{10} Gy (range 15.7 to 151.2 BED_{10} Gy). A total of 14.3% (n=15/105) of patients received concurrent TKI. The rate of grade 2-3 acute esophagitis was 20.0% (18/90) and 53.3% (8/15) for patients receiving radiotherapy without and with concurrent TKI, respectively ($p = 0.006$). There were no grade 4-5 esophagitis events. When controlling for mean esophageal dose and concurrent chemotherapy, concurrent TKI use was found to be an independent predictor for grade 2-3 esophagitis (OR = 6.91, 95% CI = 1.99 − 26.03, $p = 0.003$). Acute esophagitis was most frequently seen with osimertinib (4/7 = 57.1%), lorlatinib (2/2 = 100.0%), and crizotinib (2/3 = 67.7%). The rate of grade 2-3 pneumonitis was 5.6% (5/90) and 15.3% (2/13) without and with concurrent TKI, respectively ($p = 0.261$). On multivariate analysis, TKI use was not associated with pneumonitis. There were no acute grade 4-5 pneumonitis events or grade 2-5 cardiac toxicities.

Conclusion: This study raises the hypothesis that acute esophageal toxicity may be higher after radiation for patients receiving many of the most common TKIs. Thoracic radiation plays a crucial role in the management of NSCLC, and as the use of TKIs expands, it is critical to quickly identify potential complications associated with concurrent thoracic radiation.

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2839

Cardiac and Pulmonary Dosimetric Parameters in Lung Cancer Patients Undergoing Post-Operative Radiation Therapy in the Real-World Setting

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Purpose/Objective(s): The recently published Lung ART trial reported increased rates of cardiac and pulmonary toxicity in the post-operative radiation therapy arm. It remains unknown whether the dosimetric parameters reported in Lung ART are representative of real-world practice. The purpose of this study is to examine heart and lung dose exposure in patients receiving post-operative radiation therapy for non-small cell lung cancer (NSCLC) across a statewide consortium.

Materials/Methods: From 2012 to 2020, 377 patients at 27 academic and community centers within the Michigan Radiation Oncology Quality Consortium (MROQC) underwent surgical resection followed by post-operative radiation therapy for non-metastatic NSCLC. Demographic and dosimetric data were prospectively collected for these patients. Rates of 3D-CRT and IMRT use were analyzed. Mean heart dose (MHD), heart V5, heart V35, mean lung dose (MLD), lung V20, target volume and minimum dose to 95% PTV were calculated for these patients and the reported dosimetric parameters were stratified by treatment modality.

Results: 51% of patients in this cohort had N2 disease at the time of surgery, 18% had a positive margin. 65.8% of patients were treated with IMRT compared to 32.1% treated with 3D-CRT. Average MHD for all patients was 10.3 Gy, mean Heart V5 was 40.3% and mean heart V35 was 12.6%. Average MLD was 11.2 Gy and mean lung V20 was 18.9%. These dosimetric parameters did not significantly differ based on treatment modality, with MHD and MLD 9.9 Gy and 10.1 Gy, respectively, for patients treated with 3D-CRT compared to 10.6 Gy and 11.8 Gy for patients treated with IMRT.

Conclusion: Cardiac and lung dosimetric parameters for patients receiving post-operative radiation therapy for NSCLC are similar to the dosimetric characteristics reported in Lung ART. The mean heart and mean lung doses observed are slightly lower (MHD 10.3 Gy, MLD 11.2 Gy) compared to Lung ART (MHD 13 Gy, MLD 13 Gy), possibly owing to increased use of IMRT. These data support application of Lung ART's findings outside of the clinical trial setting.

Abstract 2839 − Table 1

Radiotherapy Parameter	Lung ART	MROQC
Mean Heart Dose [Gy]	13	10.3
Heart V35Gy [%]	15	12.6
Mean Lung Dose [Gy]	13	11.2
Lung V20Gy [%]	23	18.9

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Systems; Michigan Radiation Oncology Quality Consortium, AAPM. M. Grubb: None. M.M. Dominello: None. B. Movsas: None. L.L. Kestin: Michigan Healthcare Professionals, GenesisCare USA. J.A. Hayman: None. P.A. Paximadis: None. M. Schipper: Consultant; Innovative Analytics. S. Jolly: Advisory Board; AstraZeneca, Varian.

2840

Modeling Survival Outcomes of Immune Checkpoint Inhibitors on Locally Advanced Non-Small Cell Lung Cancer Following Concurrent Chemoradiotherapy

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Purpose/Objective(s): Immune checkpoint inhibitors (ICI) have shown significant improvement in overall survival in locally advanced non-small cell lung cancer (LA-NSCLC), when combined with concurrent chemoradiotherapy (cCRT). The best schedule of cCRT ICI combination is still uncertain. We aim to develop a novel prediction survival model and investigate dose-relationship following cCRT and ICI combinations for LA-NSCLC.

Materials/Methods: ICI and cCRT studies between 2010 and 2021 were collated. ICI were intended to be delivered to 12 months. We modelled the 2-year overall survival ($OS_{2\text{-}yr}$) through sigmoidal TCP and NTCP, where EQD_2 of tumor control were modified to quantify immune-related survival gain as dose effects via adding an immune related term "*I*" − potentially dependent on the ICI doses and duration. Models were fitted using maximum likelihood estimation with 100 times bootstrapping, comparing fits via Akaike Information Criteria and likelihood ratio test. Dose-responses of $OS_{2\text{-}yr}$ were plotted for 60 − 74Gy cCRT given in 6 weeks and standard 2Gy-per-fraction (F).

Results: The data comprised 1001 NSCLC patients from 6 trials. All treated with 2Gy F cCRT, 60 − 66Gy in 30 − 33 fractions. ICI were PD-1/PD-L1 inhibitors 17 doses (range: 13 − 22). 301 patients had cCRT only, 592 patients had ICI sequentially, 108 patients concurrently with cCRT. $OS_{2\text{-}yr}$ was 48% (range: 41% − 55%) using cCRT, 67% (range: 44% − 87%) using cCRT ICI. In the generalized model, *I* was 0.37Gy/ICI-dose (95% CI: 0.12 − infinite), indicating that ICI augmented equivalent 5.6Gy or 7.4Gy EQD_2 dose escalation per 15 or 20 ICI doses respectively. The fitting efficacy improved significantly after incorporating ICI ($p = 1.5*10^{-5}$). The best modelling $OS_{2\text{-}yr}$ for cCRT was 63% (95% CI: 53% − 75%) for stage IIIA and 54% (33% − 69%) for stage IIIB/C; while it raised to 75% (66% − 86%) for stage IIIA and 67% (51% − 79%) for stage IIIB/C using cCRT ICI. Once ICI were added, best $OS_{2\text{-}yr}$ occurred using radiation dose of 60Gy, and dose-escalation did not improve further outcomes. (table)

Conclusion: The model suggests that ICI increase the $OS_{2\text{-}yr}$ by ∼12% for stage IIIA and ∼13% for stage IIIB/C following the cCRT treatment of LA-NSCLC at 60Gy biological dose regardless of fractionation.

Abstract 2840 − Table 1

Biological Dose	Radiation Schedules	Treatment	Predicted $OS_{2\text{-}yr}$	
			IIIA (95% CI)	IIIB/C (95% CI)
60Gy	2Gy/F	cCRT	63 (53 - 75)	54 (33 - 69)
		cCRT + ICI	75 (66 - 86)	67 (51 - 79)
	6 wk	cCRT	63 (53 - 75)	54 (33 - 69)
		cCRT + ICI	75 (66 - 86)	67 (51 - 79)
64Gy	2Gy/F	cCRT	61 (51 - 73)	50 (29 - 62)
		cCRT + ICI	72 (59 - 83)	62 (47 - 73)
	6 wk	cCRT	68 (56 - 78)	59 (42 - 71)
		cCRT + ICI	73 (57 - 84)	63 (47 - 78)
70Gy	2Gy/F	cCRT	62 (52 - 73)	48 (30 - 61)
		cCRT + ICI	69 (53 - 81)	55 (42 - 67)
	6 wk	cCRT	66 (51 - 81)	51 (35 - 68)
		cCRT + ICI	68 (52 - 85)	52 (35 - 75)
74Gy	2Gy/F	cCRT	59 (48 - 73)	44 (25 - 58)
		cCRT + ICI	66 (52 - 80)	49 (35 - 63)
	6 wk	cCRT	63 (45 - 79)	43 (21 - 64)
		cCRT + ICI	63 (45 - 81)	43 (21 - 65)

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2841

GRECO-1: Phase 1/2 Study of Stereotactic Body Radiation Therapy (SBRT) with or without Rucosopasem (GC4711) for Early Stage, Peripheral or Centrally Located Non-Small Cell Lung Cancer (NSCLC)

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Purpose/Objective(s): The number of patients diagnosed with early-stage non-small cell lung cancer (NSCLC) has been increasing with screening programs and more frequent thoracic imaging. SBRT is an alternative for patients who are not candidates for surgery. SBRT for larger and/or centrally located tumors may have reduced efficacy and lead to higher-grade toxicity (Timmerman 2006; Dunlap 2010). Rucosopasem (GC4711) is one of a class of investigational selective dismutase mimetics that rapidly and specifically produces hydrogen peroxide from superoxide (Riley 2006). In preclinical models including NSCLC, the addition of a dismutase mimetic to SBRT regimens demonstrated mechanism-related anticancer synergy with SBRT while protecting normal tissues from radiation damage (Sishc 2021). The purpose of this trial is to test the hypothesis that rucosopasem may improve tumor control without increasing pulmonary toxicity after SBRT.

Materials/Methods: This phase 1/2 trial is designed to test the safety of rucosopasem and its potential to improve tumor control and reduce lung injury due to SBRT for cT1c-3N0M0 peripheral or centrally located (within 2 cm of the proximal bronchial tree) NSCLC. An open-label, phase 1 run-in cohort of 5 patients received rucosopasem 100 mg as a 15-minute IV infusion within a 180-minute window prior to each of 5 SBRT fractions of 10−12 Gy delivered on sequential weekdays. A placebo-controlled phase 2 cohort of approximately 66 patients randomized to either rucosopasem or placebo concurrent with SBRT follows and is ongoing. The primary endpoint for phase 1 is dose-limiting toxicities during treatment or within 30 days post-SBRT, and for phase 2, in-field tumor response. Reduction from baseline in diffusion capacity of lung for carbon monoxide (DLCO) at 6 months (Stone 2015) is a secondary endpoint for phase 2. Progression-free and overall survival, locoregional control, and distant metastasis rate will be followed over 24 months. Additional secondary endpoints include clinical (CTCAE 5.0) and radiological pneumonitis, measured at the same

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