JAMA Oncology | Brief Report

Assessment of a Contralateral Esophagus–Sparing Technique in Locally Advanced Lung Cancer Treated With High-Dose Chemoradiation
A Phase 1 Nonrandomized Clinical Trial

Sophia C. Kamran, MD; Beow Y. Yeap, ScD; Christine A. Ulysse, MS; Catherine Cronin, BS; Cynthia L. Bowes, MSN, MS; Brittany Durgin, BSN; Justin F. Gainor, MD, PhD; Melin J. Khandekar, MD, PhD; Joanna Y. Tansky, MD; Florence K. Keane, MD; Christine C. Olsen, MD; Henning Willers, MD

IMPORTANCE Severe acute esophagitis occurs in up to 20% of patients with locally advanced lung cancer treated with chemoradiation therapy to at least 60 Gy once daily and represents a dose-limiting toxic event associated with poor outcomes.

OBJECTIVE To assess whether formalized sparing of the contralateral esophagus (CE) is associated with reduced risk of severe acute esophagitis.

DESIGN, SETTING, AND PARTICIPANTS This single-center phase 1 nonrandomized clinical trial assessing an empirical CE-sparing technique enrolled patients from July 2015 to January 2019. In total, 27 patients with locally advanced non–small cell lung carcinoma (with or without solitary brain metastasis) or limited-stage small cell lung carcinoma with gross tumor within 1 cm of the esophagus were eligible.

INTERVENTIONS Intensity-modulated radiation therapy to 70 Gy at 2 Gy/fraction concurrent with standard chemotherapy with or without adjuvant durvalumab. The esophageal wall contralateral to gross tumor was contoured as an avoidance structure to guide a steep dose falloff gradient. Target coverage was prioritized over CE sparing, and 99% of internal and planning target volumes had to be covered by 70 Gy and at least 63 Gy, respectively.

MAIN OUTCOMES AND MEASURES The primary end point was the rate of at least grade 3 acute esophagitis as assessed by Common Terminology Criteria for Adverse Events, version 4.

RESULTS Of 27 patients enrolled, 25 completed chemoradiation therapy. Nineteen patients had non–small cell lung carcinoma, and 6 had small cell lung carcinoma. The median age at diagnosis was 67 years (range, 51-81 years), and 15 patients (60%) were men. Thirteen patients (52%) had stage IIIA cancer, 10 (40%) had stage IIIB cancer, and 2 (8%) had stage IV cancer. The median CE maximum dose was 66 Gy (range, 44-71 Gy); the median volume of CE receiving at least 55 Gy was 1.4 cm^3 (range, 0-5.3 cm^3), and the median volume of CE receiving at least 45 Gy was 2.7 cm^3 (range, 0-9.2 cm^3). The median combined percentage of lung receiving at least 20 Gy was 25% (range, 11%-37%). The median follow-up was 33.3 months (range, 11.1-52.2 months). Among the 20 patients who had treatment breaks of 0 to 3 days and were thus evaluable for the primary end point, the rate of at least grade 3 esophagitis was 0%. Other toxic events observed among all 25 patients included 7 (28%) with grade 2 esophagitis, 3 (12%) with at least grade 2 pneumonitis (including 1 with grade 5), and 2 (8%) with at least grade 3 cardiac toxic event (including 1 with grade 5). There was no isolated local tumor failure. The 2-year progression-free survival rate was 57% (95% CI, 33%-75%), and the 2-year overall survival rate was 67% (95% CI, 45%-82%).

CONCLUSIONS AND RELEVANCE This phase 1 nonrandomized clinical trial found that the CE-sparing technique was associated with reduced risk of esophagitis among patients treated uniformly with chemoradiation therapy (to 70 Gy), with no grade 3 or higher esophagitis despite tumor within 1 cm of the esophagus. This technique may be translated into clinical practice.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02394548

JAMA Oncol. 2021;7(6):910-914. doi:10.1001/jamaoncol.2021.0281
Published online April 8, 2021.

Supplemental content

Author Affiliations: Department of Radiation Oncology, Massachusetts General Hospital, Boston (Kamran, Cronin, Bowes, Durgin, Khandekar, Tansky, Keane, Olsen, Willers); Department of Medicine, Massachusetts General Hospital, Boston (Yeap, Ulysse, Gainor); Department of Radiation Oncology, Newton-Wellesley Hospital, Newton, Massachusetts (Tansky, Keane, Olsen).

Corresponding Author: Henning Willers, MD, Department of Radiation Oncology, Massachusetts General Hospital, 55 Fruit St, Cox 3, Boston, MA 02114 (hwillers@mgh.harvard.edu).

The standard treatment of locally advanced non-small cell lung cancer (NSCLC) and limited-stage (LS) small cell lung cancer (SCLC) is concurrent chemoradiation therapy (CRT).[1,2] Because of the high rates of local tumor failure with standard radiation therapy, treatment intensification has been explored. In NSCLC, dose escalation to 74 Gy is associated with severe esophagitis (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥3) in 17.4% of patients.[3] In LS-SCLC, current regimens result in severe esophagitis rates of almost 20%.[2] Severe esophagitis is a serious dose-limiting toxic event requiring hospital admission, feeding tube, or total parenteral nutrition, which may lead to treatment interruptions and poor outcomes.[4]

Intensity-modulated radiation therapy (IMRT), including volumetric-modulated arc therapy, increases dose conformality and provides greater sparing of normal tissues than traditional 3-dimensional conformal radiation. However, grade 3 esophagitis remains a problem.[5-7] The mean esophageal radia-

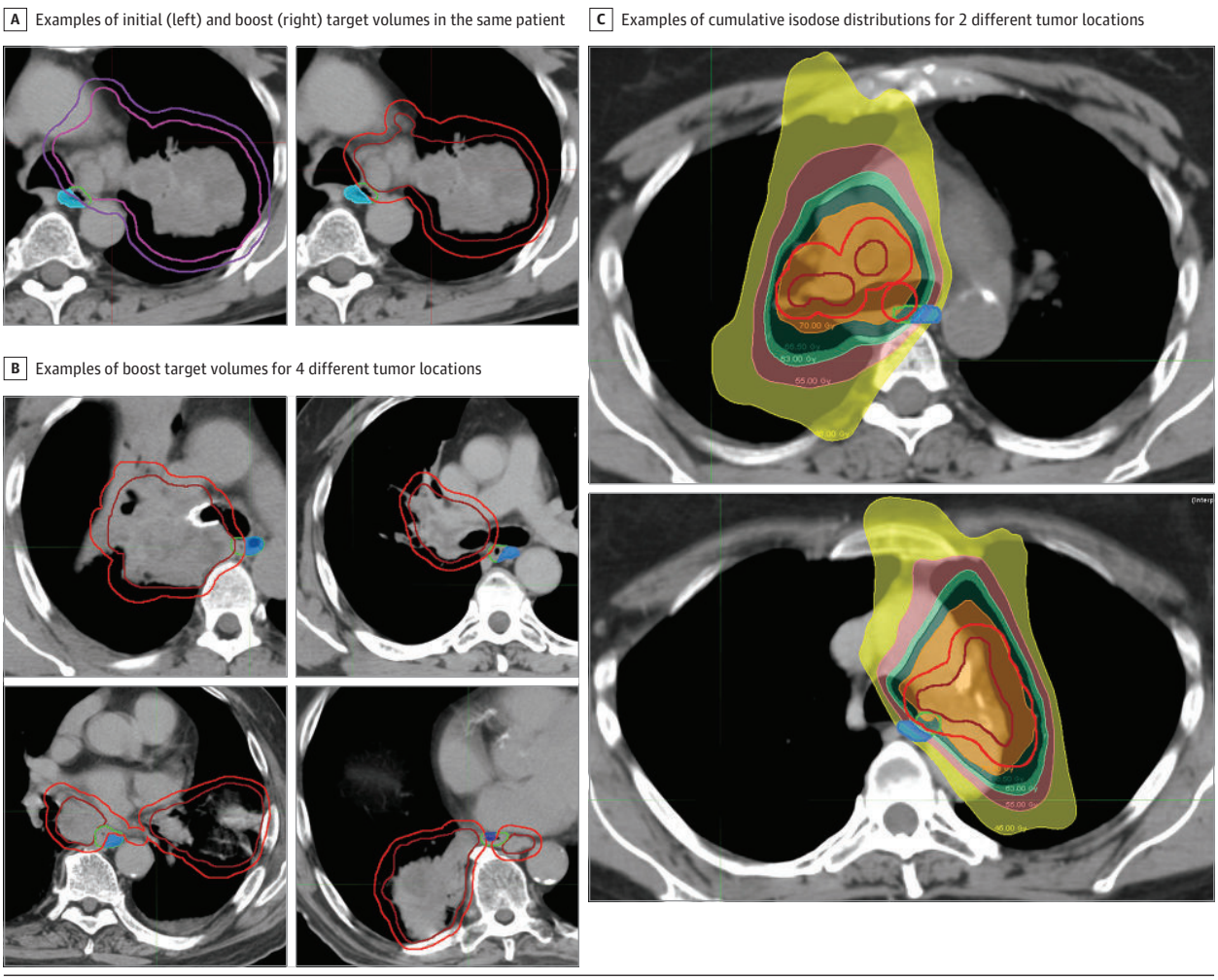
Key Points

Question How can modern radiation techniques reduce the risk of severe esophagitis (Common Terminology Criteria for Adverse Events grade 3 or higher) in the treatment of locally advanced lung cancers?

Findings In this phase 1 nonrandomized clinical trial, esophagitis rates were examined among 25 participants with locally advanced non–small cell or small cell lung carcinoma treated with intensity-modulated radiation therapy and concurrent chemotherapy using a novel contralateral esophagus–sparing technique. Despite the delivery of high-dose radiation to 70 Gy and the requirement for gross tumor within 1 cm of the esophagus, no participant developed grade 3 or higher esophagitis.

Meaning The use of this contralateral esophagus–sparing technique was associated with a reduced risk of severe esophagitis among patients with locally advanced lung cancer receiving high-dose intensity-modulated radiation therapy and may be translated into clinical practice.

Figure. Axial Computed Tomographic Images Illustrating the Contralateral Esophageal–Sparing Technique



A, Contralateral esophagus (shaded blue), esophagus (green), and target contouring. Left, clinical target volume (pink) and associated planning target volume (purple) treated to 44 Gy. Right, boost internal target volume (red) and associated planning target volume (dark red) treated to 26 Gy. B, Four additional cases with different anatomical tumor locations. C, Two participants with isodose distributions for internal target volume treated to 70 Gy (orange) and planning target volume treated to a minimum of 63 Gy (light green).

Table 1. Patient, Tumor, and Treatment Characteristics for 25 Eligible Participants

Characteristic	No. (%)
Age at diagnosis, median (range), y	67 (51-81)
Sex	
Male	15 (60)
Female	10 (40)
Clinical AJCC stage (7th edition)	
IIIA	13 (52)
IIIB	10 (40)
IV (solitary brain metastasis)	2 (8)
Histologic results	
NSCLC	19 (76)
SCLC	6 (24)
ITV size, cm^3	
Mean	96
Median	70
Range	8-385
Chemotherapy received	
Cisplatin plus etoposide	7 (28)
Cisplatin plus pemetrexed	7 (28)
Carboplatin plus paclitaxel	9 (36)
Carboplatin plus pemetrexed	1 (4)
Carboplatin plus etoposide	1 (4)
Total dose of radiation received, Gy	
70	24 (96)
68	1 (4)

Abbreviations: AJCC, American Joint Committee on Cancer; ITV, internal treatment volume; NSCLC, non–small cell lung carcinoma; SCLC, small cell lung carcinoma.

tion dose has been evaluated for limiting esophagitis, but it remains unclear how to optimize IMRT for esophageal sparing.[8]

We have empirically derived a technique to spare the esophageal wall contralateral to gross disease.[9] This technique involves contouring the contralateral esophagus (CE) as an avoidance structure to guide a steep dose falloff gradient across the esophagus. In our experience of using this CE-sparing technique (CEST) for CRT of locally advanced thoracic malignant neoplasms, no patient experienced grade 3 or higher esophagitis, and only 20% had grade 2 esophagitis despite a high median dose of 70.2 Gy (range, 63.0-72.2 Gy).[9] We subsequently designed this phase 1 nonrandomized clinical trial to prospectively examine the frequency of esophagitis in patients with locally advanced lung cancer treated with CRT using CEST. A moderate-dose escalation to 70 Gy was chosen to address the high rates of local failure associated with 60 Gy[3,10] and in keeping with protocols such as Radiation Therapy Oncology Group (RTOG) 1308 (NCT01993810).[11]

Methods

Patient Selection

Patients 18 years of age or older with histologically confirmed locally advanced NSCLC (with or without solitary brain metastasis) or LS-SCLC with gross primary or nodal tumor within 1 cm of the esophagus were eligible (study protocol in Supplement 1). The single-center phase 1 study protocol was approved by the institutional review board of the Dana-Farber/Harvard Cancer Center, Boston, Massachusetts. All patients provided written informed consent that was obtained in a manner consistent with the Declaration of Helsinki.[12] No one received compensation or was offered any incentive for participating in this study.

Study Design and Treatment

Participants received standard-of-care CRT to 70 Gy at 2 Gy/fraction with or without adjuvant durvalumab for NSCLC. Radiation was planned with IMRT or volumetric-modulated arc therapy (RayStation; RaySearch Laboratories) using custom immobilization, 4-dimensional CT planning, and daily image guidance. A shrinking-field technique was used with a boost to the internal target volume after 44 Gy (eMethods and eTable 1 in Supplement 2). The CE was contoured as a distinct avoidance structure for promoting a steep dose falloff across the esophagus (**Figure**; eFigure 1 in Supplement 2). Target coverage was prioritized over CE sparing, and 99% of the internal target volume and of the planning target volume were required to be covered by 100% and 90% of prescription dose, respectively. Participants received concurrent chemotherapy per their treating medical oncologist. To be analyzable for the primary end point, participants were required to have received concurrently 5 or more cycles of weekly combined carboplatin plus paclitaxel or 2 or more cycles of platinum and pemetrexed or etoposide and to have had 3 or fewer days of unplanned treatment interruption unrelated to esophagitis. We followed the Transparent Reporting of Evaluations With Nonrandomized Designs (TREND) reporting guideline.

Statistical Analysis

See the eMethods in Supplement 2 for clinical outcome assessments and failure definitions. Overall survival and progression-free survival rates were estimated using the Kaplan-Meier method with 95% CIs based on the log-log transformation. The primary objective was to describe the rate of grade 3 or higher esophagitis assessed using CTCAE, version 4.0. Secondary end points included the rate of esophagitis using RTOG criteria (eTable 2 in Supplement 2), general toxic events assessed using CTCAE, and 2-year clinical outcomes. We hypothesized that CEST would limit the risk of grade 3 or higher esophagitis to 5% or less of patients. A sample size of 20 participants was chosen to ensure that if no more than 1 participant was observed with grade 3 or higher esophagitis, the 1-sided upper limit of the 90% CI would not exceed 20%. All analyses were conducted from July to October 2020 using R, version 4.0.1 (R Foundation for Statistical Computing).

Results

Patient Characteristics

Between July 2015 and January 2019, 27 participants were enrolled in the trial (eFigure 2 in Supplement 2). Two participants were removed. Patient and treatment characteristics are

Table 2. Nonhematologic Toxic Events[a]

Toxic event	No. (%) [95% CI] of patients			
	Grade 2	Grade 3	Grade 4	Grade 5
CTCAE v 4.0 (primary end point) (20 patients)				
Esophagitis	5 (25) [11-47]	0 (0) [0-16]	0	0
RTOG (secondary end point) (25 patients)				
Esophagitis	6 (24) [12-43]	0 (0) [0-13]	0	0
CTCAE v 4.0 (secondary end points) (25 patients)				
Esophagitis	7 (28) [14-48]	0 (0) [0-13]	0	0
Dysphagia	2 (8)	0	0	0
Dyspepsia	4 (16)	0	0	0
Pneumonitis	2 (8)	0	0	1 (4)
Hypoxia	0	1 (4)	0	0
Pneumonia	1 (4)	0	0	0
Hoarseness	1 (4)	0	0	0
Dyspnea	4 (16)	1 (4)	0	0
Nausea	1 (4)	0	0	0
Fatigue	6 (24)	0	0	0
Dermatitis	5 (20)	0	0	0
Heart failure	0	0	0	1 (4)
Atrial fibrillation	2 (8)	0	0	0
Ventricular tachycardia	0	1 (4)	0	0

Abbreviations: CTCAE v 4.0, Common Terminology Criteria for Adverse Events, version 4.0; RTOG, Radiation Therapy Oncology Group.

[a] Toxic events grade 2 or higher possibly, likely, or definitely associated with high-dose radiation therapy.

given in **Table 1**. The median age at diagnosis was 67 years (range, 51-81 years), and 15 patients (60%) were men. Nineteen participants had NSCLC, and 6 participants had SCLC. Two participants had solitary brain metastases, and all others had stage IIIA cancer (13 participants [52%]) or stage IIIB cancer (10 participants [40%]). The total dose was 70 Gy for 24 participants (96%). The median CE maximum dose was 66 Gy (range, 44-71 Gy); the median volume of CE receiving at least 55 Gy was 1.4 cm^3 (range, 0-5.3 cm^3), and the median volume of CE receiving at least 45 Gy was 2.7 cm^3 (range, 0-9.2 cm^3). The median combined percentage of lung receiving at least 20 Gy was 25% (range, 11%-37%).

Toxic Events

The rate of grade 3 or higher esophagitis was 0% (95% CI, 0%-16%) among 20 patients eligible for the primary end point analysis (**Table 2**). Five participants were ineligible for primary end point analysis owing to unplanned treatment breaks of more than 3 days unrelated to esophagitis (eFigure 2 in Supplement 2). Grade 2 esophagitis was detected in 24% to 28% of patients depending on the scoring criteria and number of participants analyzed. Other common toxic events included cardiopulmonary events, fatigue, and dermatitis (Table 2). Among 25 patients, the rate of grade 2 or higher pneumonitis was 12% (3 patients), and the rate of grade 3 or higher cardiac toxic events was 8% (2 patients). There were 2 grade 5 events—1 participant had fatal pneumonitis, and 1 participant who had preexisting congestive heart failure died of it shortly after radiation therapy. Hematologic toxic events are given in eTable 3 in Supplement 2.

Clinical End Points

The median follow-up was 33.3 months (range, 11.1-52.2 months) among surviving patients. There was no isolated local tumor failure. The 2-year progression-free survival rate was 57% (95% CI, 33%-75%), and the 2-year overall survival rate was 67% (95% CI, 45%-82%) (eFigure 3 in Supplement 2).

Discussion

Severe esophagitis is a dose-limiting toxic event that complicates intensification of treatments in locally advanced NSCLC and LS-SCLC.[2,4] We prospectively tested a simple method to avoid exposing the entire esophagus cross section to high doses.[9] We observed no grade 3 esophagitis and grade 2 events in 24% to 28% of participants despite all participants having gross tumor adjacent to the esophagus and 96% receiving the full 70 Gy. To explain how CE sparing may reduce the risk of severe esophagitis, we consider that the esophagus may be regarded as an organ with functional subunits arranged in a serial fashion such that high-dose irradiation of the entire cross section of the esophagus may result in whole-organ dysfunction.[9,13] Our data suggest that near-normal esophageal function may be maintained by preserving the function of approximately half of the esophageal cross section (ie, by converting the esophagus from a serial organ to a parallel organ) (eFigure 4 in Supplement 2). Mucosa may respond to radiation injury with accelerated repopulation during a course of several weeks of radiation.[13] Esophageal mucosal regenera-

tion cannot compensate for high-dose, full-circumference irradiation but may be able to do so if parts of the adjacent mucosa are exposed to a lower dose.

Limitations

There are limitations to this study. Because this is a single-institution trial with a small sample size conducted at a tertiary academic center, the results may not be representative of a broader patient population. We used multicriteria optimization, which may optimize CE sparing but is not available everywhere.[14] The mean internal target volume was somewhat smaller than that in other series (Table 1), which may have impacted esophagitis.[7] However, we included only patients with tumor within 1 cm of the esophagus, which is expected to increase esophagitis rates. Finally, we did not observe any isolated local tumor failures at a median follow-up of close to 3 years, suggesting that the steep dose gradients resulting from the CE avoidance structure did not compromise target coverage; however, this should be validated in larger series.

Conclusions

In this phase 1 trial, CEST was associated with reduced risk of esophagitis among patients treated uniformly with chemoradiation therapy (to 70 Gy), with no grade 3 or higher esophagitis despite tumor within 1 cm of the esophagus. The method requires validation by other institutions and may be included in prospective trials evaluating the escalation of radiation dose or other treatment intensifications. CEST may be translated into clinical practice where it can support current guidelines for esophagus sparing.[15]

ARTICLE INFORMATION

Accepted for Publication: December 3, 2021.

Published Online: April 8, 2021. doi:10.1001/jamaoncol.2021.0281

Author Contributions: Drs Olsen and Willers are co–senior authors. Drs Willers and Kamran had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Kamran, Yeap, Olsen, Willers.
Acquisition, analysis, or interpretation of data: Kamran, Yeap, Ulysse, Cronin, Bowes, Durgin, Gainor, Khandekar, Tansky, Keane, Willers.
Drafting of the manuscript: Kamran, Yeap, Keane, Olsen, Willers.
Critical revision of the manuscript for important intellectual content: Kamran, Yeap, Ulysse, Cronin, Bowes, Durgin, Gainor, Khandekar, Tansky, Keane.
Statistical analysis: Kamran, Yeap, Ulysse.
Obtained funding: Olsen.
Administrative, technical, or material support: Kamran, Cronin, Keane.
Supervision: Gainor, Keane, Olsen, Willers.

Conflict of Interest Disclosures: Dr Kamran reported having an immediate family member who is an employee of Sanofi Genzyme. Dr Gainor reported receiving personal fees from Agios, Alexo, Amgen, Array, Ariad/Takeda, AstraZeneca, Blueprint, Bristol Myers Squibb, EMD Serono, Genentech/Roche, Gilead, Incyte, Loxo/Lilly, Merck & Co, Moderna, Novartis, Oncorus, Pfizer, and Regeneron; receiving research support from Ariad/Takeda, Genentech/Roche, and Novartis; receiving institutional research support from Adaptimmune, Alexo Array, Biopharma, Blueprint, Bristol Myers Squibb, Jounce, Merck & Co, Moderna, Novartis, and Tesaro; and having an immediate family member as an employee of Ironwood Pharmaceuticals with equity outside the submitted work. Dr Keane reported receiving personal fees from AstraZeneca, OncLive, and UpToDate. No other disclosures were reported.

Funding/Support: The study was supported by the PAN-MASS Challenge and by the Federal Share of program income earned by Massachusetts General Hospital (C06 CA059267).

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 3.

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