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Original Article

Factors associated with acute esophagitis during radiation therapy for lung cancer

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ABSTRACT

Introduction: Limiting acute esophagitis remains a clinical challenge during the treatment of locally advanced non-small cell lung cancer (NSCLC).
Methods: Demographic, dosimetric, and acute toxicity data were prospectively collected for patients undergoing definitive radiation therapy +/- chemotherapy for stage II-III NSCLC from 2012 to 2022 across a statewide consortium. Logistic regression models were used to characterize the risk of grade 2 + and 3 + esophagitis as a function of dosimetric and clinical covariates. Multivariate regression models were fitted to predict the 50 % risk of grade 2 esophagitis and 3 % risk of grade 3 esophagitis.
Results: Of 1760 patients, 84.2 % had stage III disease and 85.3 % received concurrent chemotherapy. 79.2 % of patients had an ECOG performance status ≤ 1. Overall rates of acute grade 2 + and 3 + esophagitis were 48.4 % and 2.2 %, respectively. On multivariate analyses, performance status, mean esophageal dose (MED) and minimum dose to the 2 cc of esophagus receiving the highest dose (D2cc) were significantly associated with grade 2 + and 3 + esophagitis. Concurrent chemotherapy was associated with grade 2 + but not grade 3 + esophagitis. For all patients, MED of 29 Gy and D2cc of 61 Gy corresponded to a 3 % risk of acute grade 3 + esophagitis. For patients receiving chemotherapy, MED of 22 Gy and D2cc of 50 Gy corresponded to a 50 % risk of acute grade 2 + esophagitis.
Conclusions: Performance status, concurrent chemotherapy, MED and D2cc are associated with acute esophagitis during definitive treatment of NSCLC. Models that quantitatively account for these factors can be useful in individualizing radiation plans.

Introduction

Radiation therapy (RT) with concurrent chemotherapy and adjuvant immunotherapy is the current standard of care for locally advanced non-small cell lung cancer (NSCLC). As radiation techniques have improved, the rates of grade 3 or higher esophagitis have decreased. For instance, on RTOG 9410, 23 % of patients in the treatment arm receiving daily RT with concurrent chemotherapy experienced grade 3 + esophagitis [1], compared to 7 % on the 60 Gy arm of RTOG 0617 [2]. While the rates of esophagitis have improved over time, identifying predictors of esophagitis remains clinically important as severe esophagitis can have significant ramifications for quality of life including hospitalization,

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feeding tube placement and narcotic pain medication requirement. These sequalae may result in treatment breaks, which can adversely affect tumor control [3,4].

For these reasons, significant effort has been devoted to determining clinical and dosimetric predictors of acute esophagitis during radiation therapy for lung cancer. Prior work has identified age [5,6], race [7], poor performance status [6], low body mass index (BMI) [6,8], nodal stage [5,6], and pre-existing dysphagia [9] as potential clinical predictors of acute esophagitis during radiation therapy. Additionally, a Cochrane review in 2010 identified receipt of concurrent chemotherapy during radiation as a significant predictor of acute esophagitis [10]. Regarding dosimetric predictors of esophagitis, early work identified maximum extent of circumferential treatment [9], proportion of esophagus receiving > 50–60 Gy [9,11], and maximum point dose to the esophagus [12] as predictors of acute esophagitis. In 2010, the Quantitative Analysis of Normal Tissue Effects (QUANTEC) analysis summarized the available literature and recommended a mean esophagus dose (MED) < 34 Gy for limiting the rate of grade 3 esophagitis to 5–20 %, as well as suggesting additional volumetric constraints for limiting the rate of grade 2 esophagitis to less than 30 %[13]. More contemporary studies have identified V60Gy [14], gEUD of 59.3 Gy, and minimum dose to the 2 cc of esophagus receiving the highest dose (D2cc) of 68 Gy [15] as important potential predictors of grade 3 + esophagitis.

In recent years, advancements in both treatment delivery and statistical modeling have provided the groundwork for more sophisticated analyses aimed at refining the ability to predict the probability of acute esophagitis in individual patients, including the use of radiomics and dosiomics models [16], multivariate logistic [17] and machine learning techniques [18] and models accounting for novel clinical predictors such as pre-treatment cytokine levels [19]. Here, we performed an updated analysis of prospectively collected data incorporating patient-specific factors including performance status, smoking status, body mass index, and presence of medical comorbidities, in addition to dosimetric variables to further refine our ability to predict esophagitis in patients treated with contemporary techniques.

Methods

This analysis included patients undergoing definitive radiation therapy with or without concurrent chemotherapy for stage II-III non-small cell lung cancer from 2012 to 2022 at any site within the Michigan Radiation Oncology Quality Consortium (MROQC). MROQC is a consortium of 27 academic and community radiation oncology practices within the state of Michigan that prospectively collect demographic and dosimetric data for patients undergoing radiotherapy for lung cancer, among other malignancies, with the goal of leveraging this information to improve treatment quality and optimize treatment practices.

Patient-level demographic and medical history were collected, including age, race, body-mass index (BMI), number and type of medical comorbidities, smoking status, performance status, and presence or absence of concurrent chemotherapy. Presence or absence of acute esophagitis during treatment was assessed using standard Common Terminology Criteria for Adverse Events (CTCAE) criteria, reported as the maximum grade experienced by each patient during their treatment course. Dosimetric data were prospectively collected from individual patient dose-volume histograms, including nearest distance of PTV to esophagus, Volume in cubic centimeters of esophagus receiving at least 10 Gy (V10Gy[cc]), V20Gy[cc], V30Gy[cc], V40Gy[cc], V50Gy[cc], and V60Gy[cc], mean esophagus dose, D2cc and gEUD. The gEUD was calculated as described previously [15] with a = 10.4, estimated using maximum likelihood of esophagitis. Contouring for critical organs-at-risk has been standardized throughout our consortium and includes contouring of the entire length of the esophagus. Treatment planning was performed per the expertise of the individual member institutions and included both 3-dimensional conformal radiation therapy (3D-CRT) and intensity modulated radiation therapy (IMRT).

Logistic regression models were used to characterize the risk of grade ≥ 2 and grade ≥ 3 esophagitis as a function of dose and clinical covariates. We performed univariate analyses first for grade ≥ 2 and grade ≥ 3 esophagitis using age, race, presence of concurrent chemotherapy, BMI, smoking status, disease stage, performance status, number of medical comorbidities, if PTV is within 2 cm of esophagus, and the dosimetric parameters V10Gy-V60Gy [cc], mean esophagus dose, D2cc and gEUD. Parameters were estimated using maximum likelihood. Multivariate models were fitted using a stepwise method based on P-value threshold 0.05. Model predictive performance was evaluated using nonparametric estimates of area under the curve (AUC) for the receiver operating characteristic curve (ROC). Calibration plots were generated to ensure model goodness-of-fit (supplement).

We used the fitted multivariate regression models to predict the 50 % risk of grade 2 esophagitis or a 3 % risk of grade 3 esophagitis at each dose value. The risks were calculated for each risk factor combination and median age (68). Leave-one-out cross validation was used to estimate the AUC for the multivariable models to account for the optimistic bias when building models and assessing model performance on the same data. The cross validation included both variable selection and parameter estimation. All statistical analyses were performed using SAS version 9.4.

Results

1760 patients with a median age of 68 underwent definitive radiation therapy for NSCLC from 2012 to 2022 and are included in this analysis. Most patients (84 %) had stage III disease. Ninety-seven percent of patients received conventional fractionation to a median dose of 60 Gy. Most patients (79 %) were treated with IMRT, and most (85 %) received concurrent chemotherapy. Most patients (73 %) had an ECOG performance status of 0 or 1. Almost all patients (95 %) had a planning target volume within 2 cm of the esophagus. Forty-six percent of patients experienced grade II esophagitis during treatment, while only 2.2 % experienced grade 3 esophagitis (Table 1).

On univariate analysis, receipt of concurrent chemotherapy, active current smoking status, disease stage (III vs. II) and ECOG performance status (2 + vs. 0–1) were associated with increased risk of grade 2 + esophagitis. Disease stage (III vs. II) and ECOG performance status (2 + vs. 0–1) were associated with development of grade 3 + esophagitis (Table 2). Increasing age was associated with decreased risk of both grade 2 + and grade 3 + esophagitis. No significant associations were observed between extent of comorbid disease or specific comorbidities and the development of grade 2 or grade 3 esophagitis. All dosimetric variables examined (Table 2) were associated with both grade 2 + and grade 3 + esophagitis.

On multivariate analysis, receipt of concurrent chemotherapy, ECOG performance status, mean esophagus dose, and D2cc all were significantly associated with grade 2 + esophagitis (Table 2). ECOG performance status was associated with grade 3 + esophagitis in separate multivariate models accounting for mean esophageal dose and D2cc (Table 2). Age was associated with decreased risk of both grade 2 + and grade 3 + esophagitis in all models. Multivariable models were cross validated as described in the methods section. Training AUC estimates for models #1, #2, and #3, were 0.71 [95 % CI 0.68–0.74)], 0.74 [95 % CI 0.65–0.83] and 0.76 [95 % CI 0.67–0.84], respectively, and were 0.70 [95 % CI 0.68–0.73], 0.70 [95 % CI 0.61–0.80] and 0.73 [95 % CI 0.64–0.82] with cross-validation. Calibration plots showed reasonable calibration for each of the multivariable models across the range of predicted risk.

Using patient-level characteristics associated with esophagitis on multivariate analysis, including receipt of chemotherapy and performance status, we next evaluated the interplay between D2cc and mean esophagus dose in determining risk of esophagitis (Fig. 1). The threshold doses associated with a 50 % risk of grade 2 esophagitis are shown in Fig. 1A. Patients receiving chemotherapy experienced grade 2

Table 1
Patient demographic and disease characteristics.

Variable	All patients undergoing radiation therapy (N = 1760)
Age (median, years [IQR])	68 [62,75]
Sex	
Female	802 (45.6 %)
Male	958 (54.4 %)
Race	
Black	259 (14.7 %)
White	1424 (80.9 %)
Other	77 (4.4 %)
BMI	
Underweight (<18.5)	93 (5.3 %)
Normal (18.5–25)	595 (33.8 %)
Overweight (25–30)	556 (31.6 %)
Obese (30 +)	494 (28.1 %)
Missing	22 (1.3 %)
Number of Medical Comorbidities	
0	241 (13.7 %)
1	444 (25.2 %)
2	488 (27.7 %)
3+	587 (33.4 %)
Smoker	
Former or Never	1082 (61.5 %)
Current	678 (38.5 %)
Stage	
II	279 (15.9 %)
III	1481 (84.2 %)
Radiation Dose (median, Gy, [IQR])	60 [60,66]
Number of Fractions (median, [IQR])	30 [30,33]
Radiation Treatment Technique	
IMRT	1393 (79.1 %)
3D-CRT	345 (19.6 %)
Unknown	22 (1.3 %)
Concurrent Chemotherapy	
Yes	1502 (85.3 %)
No	258 (14.7 %)
ECOG	
0/1	1283 (72.9 %)
2+	444 (25.2 %)
Missing	33 (1.9 %)
PTV within 2 cm of esophagus	
Yes	1673 (95.1 %)
No	87 (4.9 %)
Maximum Esophagitis during RT	
0	357 (20.3 %)
1	552 (31.4 %)
2	813 (46.2 %)
3	38 (2.2 %)

esophagitis at lower doses than those not receiving chemotherapy. Additionally, patients with ECOG performance status 2 + experience grade 2 esophagitis at lower doses than those with performance status of ECOG 0–1, irrespective of chemotherapy administration. A similar analysis was performed to determine the threshold doses conferring a 5 % risk of grade 3 esophagitis (Fig. 1B). Since receipt of chemotherapy was not associated with grade 3 esophagitis on univariate analysis it was not included in this analysis. Patients with ECOG performance status 2 + experienced grade 3 esophagitis at lower doses than patients with performance status 0–1.

Although modeling based on multiple dose parameters is highly informative, it is difficult to incorporate into routine practice. For this reason, we evaluated the individual relationship between performance status, mean esophagus dose, and D2cc with a 3 % risk threshold for grade 3 esophagitis and 50 % risk threshold for grade 2 esophagitis (Fig. 2). For patients with ECOG performance status 0–1, a mean esophagus dose of 35 Gy was associated with a 3 % risk threshold for grade 3 esophagitis, compared to 26 Gy for patients with an ECOG performance status of 2 (Fig. 2A). Similarly, for patients with worse

Table 2
Univariate and Multivariate analyses for clinical and dosimetric variables associated with grade 2 + and grade 3 + esophagitis.

Univariate Analyses Variables	Grade 2 Esophagitis OR [95 % CI]	P-value	Grade 3 Esophagitis OR [95 % CI]	P-value
Age	0.97 [0.96–0.98]	0<.0001	0.95 [0.92–0.98]	0.004
Concurrent chemo (yes vs. no)	2.08 [1.58–2.77]	0<.0001	1.08 [0.45–3.19]	0.874
BMI	1.01 [1.00–1.02]	0.200	0.98 [0.93–1.03]	0.562
Current smoker (yes vs. former/no)	1.29 [1.05–1.57]	0.013	1.33 [0.67–2.60]	0.41
Stage (3 vs 2)	2.32 [1.76–3.08]	0<.0001	6.59 [1.41–117.48]	0.011
ECOG (2 + vs. 0/1)	1.56 [1.25–1.96]	0<.0001	2.05 [1.00–4.06]	0.049
Number of Comorbidities	0.97 [0.91–1.04]	0.399	0.88 [0.67–1.11]	0.287
1 vs 0	1.09 [0.79–1.50]	0.606	2.43 [0.89–8.53]	0.020
2 vs 0	0.92 [0.67–1.26]		0.63 [0.17–2.57]	
3 + vs 0	0.95 [0.70–1.29]		0.95 [0.30–3.52]	
HTN	0.93 [0.76–1.13]	0.452	0.82 [0.42–1.63]	0.560
DM	1.01 [0.81–1.28]	0.903	0.56 [0.19–1.33]	0.199
Lupus	5.22 [0.84–1.00]	0.080	9.42 [0.48–60.49]	0.112
Cerebrovascular	0.68 [0.47–0.99]	0.042	0.35 [0.02–1.66]	0.228
COPD	0.99 [0.82–1.21]	0.958	1.27 [0.65–2.54]	0.489
CHF	0.79 [0.52–1.18]	0.254	0.92 [0.15–3.10]	0.912
PVD	1.15 [0.81–1.64]	0.442	0.33 [0.02–1.53]	0.186
Volumetric variables (cc)				
V10	1.02 [1.01–1.03]	0<.0001	1.04 [1.01–1.07]	0.004
V20	1.04 [1.02–1.05]	0<.0001	1.05 [1.02–1.08]	0.001
V30	1.05 [1.04–1.07]	0<.0001	1.07 [1.04–1.10]	0<.0001
V40	1.07 [1.05–1.08]	0<.0001	1.09 [1.05–1.12]	0<.0001
V50	1.08 [1.06–1.09]	0<.0001	1.09 [1.06–1.13]	0<.0001
V60	1.09 [1.07–1.12]	0<.0001	1.12 [1.07–1.16]	0<.0001
Mean dose	1.06 [1.05–1.08]	0<.0001	1.07 [1.04–1.10]	0<.0001
D2cc	1.06 [1.04–1.05]	0<.0001	1.1 [1.05–1.16]	0<.0001
gEUD	1.05 [1.04–1.06]	0<.0001	1.09 [1.04–1.15]	0<.0001
Multivariate Analyses				
Model #1 (Nominal AUC 0.71 [95 % CI 0.68–0.74], cross-validated AUC 0.70 [95 % CI 0.68–0.73])				
Variables	**Grade 2 Esophagitis OR [95 % CI]**	**P-value**	**Grade 3 Esophagitis OR [95 % CI]**	**P-value**
Age	0.97 [0.62–0.99]	0<.0001	N/A	N/A
Concurrent Chemotherapy	2.21 [1.57–3.10]	0<.0001	N/A	N/A
ECOG (2 + vs. 0/1)	1.60 [1.24–2.06]	0.0003	N/A	N/A
Mean Esophageal Dose	1.03 [1.01–1.04]	0.0004	N/A	N/A
D2cc	1.03 [1.02–1.04]	<0.0001	N/A	N/A

(*continued on next page*)

Table 2 (*continued*)

Univariate Analyses Variables	Grade 2 Esophagitis OR [95 % CI]	P-value	Grade 3 Esophagitis OR [95 % CI]	P-value
Model #2 (Nominal AUC 0.74 [95 % CI 0.65–0.83], cross-validated AUC 0.70 [95 % CI 0.61–0.80])				
Age	N/A	N/A	0.95 [0.91–0.99]	0.010
ECOG (2 + vs. 0/1)	N/A	N/A	2.36 [1.13–4.92]	0.022
Mean Esophageal Dose	N/A	N/A	1.05 [1.02–1.08]	0.002
Model #3 (Nominal AUC 0.76 [95 % CI 0.67–0.84], cross-validated AUC 0.73 [95 % CI 0.64–0.82])				
Age	N/A	N/A	0.95 [0.92–0.98]	0.012
ECOG (2 + vs. 0/1)	N/A	N/A	2.61 [1.26–5.39]	0.010
D2cc	N/A	N/A	1.07 [1.03–1.12]	0.002

performance status, D2cc of 56 Gy conferred a 3 % risk of grade 3 esophagitis, compared to a D2cc of 66 Gy for patients with better performance status (Fig. 2B).

For patients receiving chemotherapy, the mean esophageal dose corresponding to a 50 % risk of grade 2 + esophagitis was 22 Gy for patients with good performance status, compared to 14 Gy for patients with an ECOG performance status of 2+ (Fig. 2C). Higher doses were required to meet the same 50 % risk threshold in patients not receiving chemo, with a mean esophageal dose of 35 Gy for patients ECOG ≤ 1 and 27 Gy for patients ECOG 2 + . Threshold D2cc doses corresponding with a 50 % risk of grade 2 + esophagitis followed a similar pattern, ranging from 40 Gy in patients with poor performance status receiving chemotherapy to 70 Gy in patients with an ECOG performance status ≤ 1 receiving radiation monotherapy (Fig. 2D). For patients with good performance status who were also receiving concurrent chemotherapy, the D2cc corresponding with a 50 % risk of grade 2 + esophagitis was 54 Gy, which was similar to patients with poorer performance status being treated with radiation monotherapy (56 Gy).

When all patients receiving chemotherapy are analyzed irrespective of performance status the mean esophageal dose and D2cc corresponding to a 50 % risk of grade 2 + esophagitis are 22 Gy and 50 Gy, respectively. Similarly, the mean esophageal dose and D2cc corresponding to a 3 % risk of grade 3 toxicity in all patients receiving treatment irrespective of performance status or receipt of chemotherapy are 29 Gy and 61 Gy, respectively (Fig. 3).

Discussion

In this prospective, multi-center update of rates and predictors of acute esophagitis within a state-wide Radiation Oncology consortium, we observed low overall rates of acute grade 3 + esophagitis despite persistently high rates of grade 2 + esophagitis, in accordance with our previous findings [15]. On univariate analyses, performance status and all analyzed dosimetric variables were associated with grade 3 + esophagitis, while receipt of chemotherapy was only associated with grade 2+, not grade 3 + esophagitis. Improved knowledge of the impact of performance status and receipt of chemotherapy on esophagitis risk may be useful in tailoring dose constraints to the individual patient during radiation planning.

Contemporary estimates of the rate of acute esophagitis indicate roughly 50–55 % of patients experience grade 2 + esophagitis, while estimates of grade 3 + esophagitis range from 1.7 %-18 %[14,15,19]. For example, a 2013 individual patient data *meta*-analysis of 1082 patients treated to a mean dose of 65 Gy between 1993 and 2011 demonstrated that 50 % of patients experienced grade 2 + esophagitis, while 18 % of patients experienced grade 3 + esophagitis. Multivariable analysis revealed the volume of esophagus receiving ≥ 60 Gy as the best predictor of esophagitis in these patients [14]. As treatment techniques have evolved, the rate of grade 3 + esophagitis has declined significantly, though rates of grade 2 + esophagitis have remained stable. For example, our prior work evaluating predictors of esophagitis across our statewide consortium revealed 54.2 % of patients experienced grade 2 + esophagitis, while only 1.7 % of patients experienced grade 3+, with a gEUD of 59.3 Gy and D2cc of 68 Gy corresponding to a 5 % risk of grade 3 esophagitis [15]. While the reduction in overall rate of grade 3 esophagitis observed in this prior study is likely attributable at least in-part to the increased adoption of IMRT [20,21], it is interesting to note that the rate of grade 2 + esophagitis remained unchanged compared to historical rates.

In the current update of our prior state-wide study, rates of grade 2 + esophagitis improved modestly compared to our prior report (48.4 % vs. 54.2 %), while the rate of grade 3 + esophagitis remained similar (2.2 % vs. 1.7 %). With the added benefit of increased statistical power from greater patient accrual, we sought to improve the ability to tailor esophagitis risk to the individual patient by accounting for patient-specific factors such as age, race, BMI, number and type of medical comorbidities, smoking status, performance status, and presence or

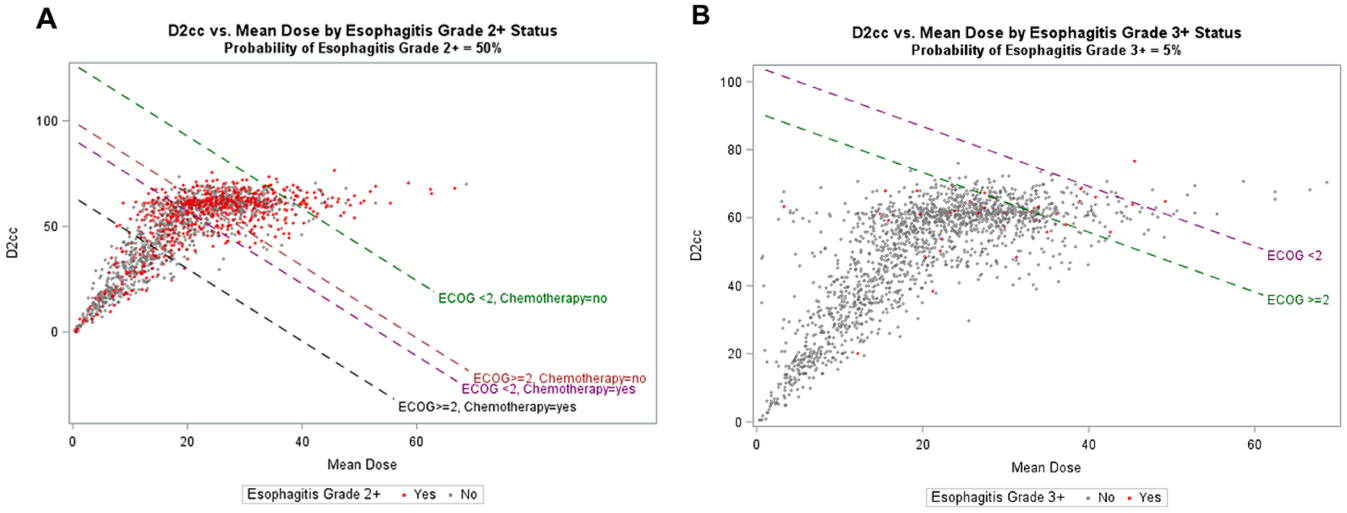

Fig. 1. Graphical representation of relationship of mean esophageal dose and D2cc. Dotted lines represent 50 % risk threshold for grade 2 + esophagitis (A) and 5 % risk threshold for grade 3 + esophagitis (B).

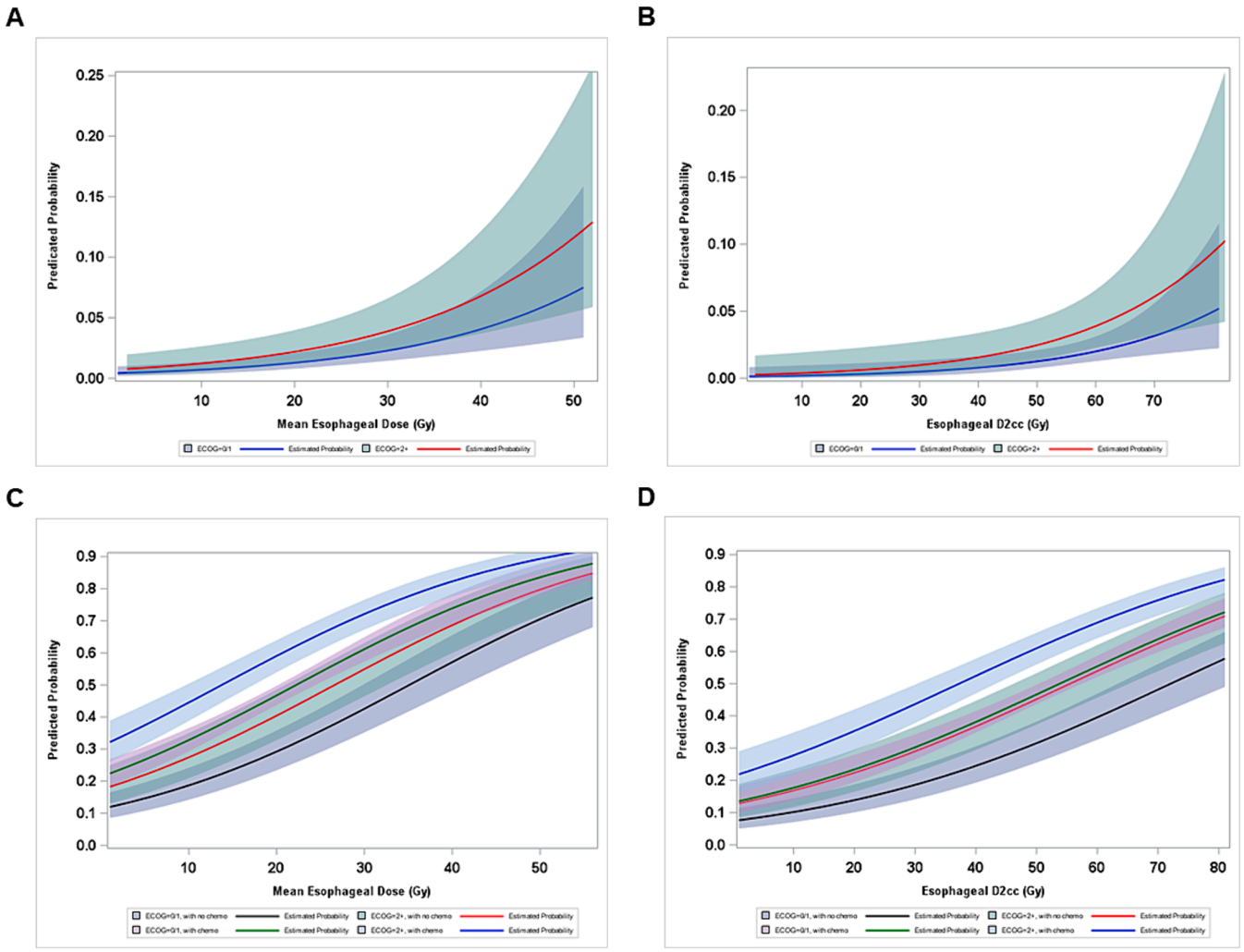

Fig. 2. Predicted probability of grade 3 + esophagitis stratified by ECOG status 0/1 (blue) vs. 2+ (red) and analyzed by mean esophageal dose (A) and D2cc (B), and probability of grade 2 + esophagitis stratified by ECOG status 0/1 with (green) or without (black)concurrent chemotherapy vs. ECOG 2 + with (blue) or without (red) concurrent chemotherapy as a function of mean esophageal dose (C) and D2cc (D). Shaded regions indicate 95 % confidence intervals. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

absence of concurrent chemotherapy in addition to standard dosimetric parameters. Interestingly, no association was observed between risk of esophagitis and BMI, number of comorbidities, individual cardiac, pulmonary and vascular comorbidities, or smoking status. On univariate analysis, performance status, disease stage, and all volumetric variables assessed correlated with increased risk of grade 2 + and 3 + esophagitis, while receipt of chemotherapy was only associated with grade 2 + esophagitis.

Using these models, we attempted to quantify the combination of mean dose and D2cc that correlate to a 50 % risk of grade 2 + esophagitis or a 3 % risk of grade 3 + esophagitis to determine the relative change in dose thresholds for these risks when accounting for performance status and/or receipt of chemotherapy. As expected, the patients at highest risk of esophagitis are those with poor performance status who are receiving concurrent chemotherapy, while those with good performance status or those receiving radiation alone tended to have higher dose thresholds for the development of clinically meaningful esophagitis. These observed differences can provide important insight when considering relative dose tradeoffs during treatment planning.

For clinical practicality we next sought to simplify this analysis by examining the relationship between mean esophageal dose and D2cc with the probability of development of grade 2 + esophagitis in all patients receiving chemotherapy and grade 3 + esophagitis in all patients, irrespective of performance status. The doses that correspond to a 50 % risk of grade 2 + esophagitis in all patients receiving chemotherapy are a mean esophagus dose of 22 Gy and a D2cc of 50 Gy. Similarly, the doses corresponding to a 3 % risk of grade 3 + toxicity in all patients undergoing RT irrespective of concurrent chemotherapy or performance status are a mean esophageal dose < 29 Gy and D2cc < 61 Gy. These doses are slightly lower than historically published constraints and warrant consideration for use in treatment planning when achievable without sacrificing tumor coverage.

One limitation to this study is the reliance on clinician-reported outcomes, which prior work from our group and others has demonstrated only correlate modestly with patient-reported outcomes [22,23]. Despite this limitation, clinician reported adverse events are still highly informative and are routinely used in clinical practice. Another limitation of this study is the potential heterogeneity of treatment, such as treatment modality (3D-conventional radiation therapy vs. intensity modulated radiation therapy (IMRT)) or variability in contouring practices amongst treating physicians. To account for the latter, all volumetric variables are reported in cubic centimeters (cc) as opposed to percentage of the contoured organ. Finally, although this dataset captures the presence or absence of concurrent chemotherapy, it lacks information regarding the specific chemotherapy regimens used. We have recently begun prospectively collecting these data for inclusion in future

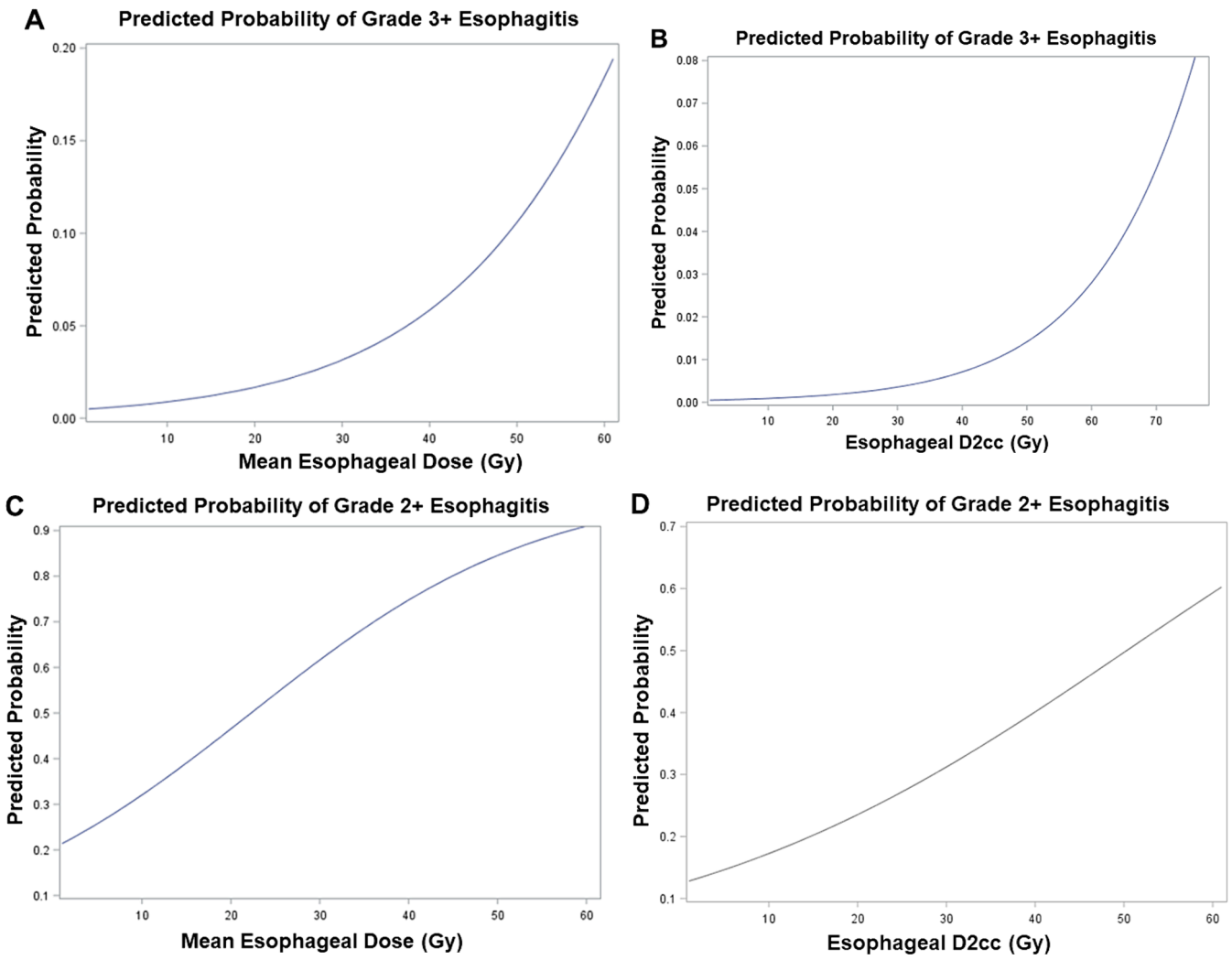

Fig. 3. Predicted probability of 3 + esophagitis as a function of mean esophageal dose (A) and D2cc (B) for all patients and predicted probability of grade 2 + esophagitis as a function of mean esophageal dose (C) and D2cc (D) for all patients receiving concurrent chemotherapy.

analyses.

Myriad ongoing efforts are underway to improve normal tissue toxicity in non-small cell lung cancer, including refining treatment planning to reduce exposure of organs-at-risk (OARs) [24,25], improving knowledge of normal tissue toxicities by treating physicians [26], defining predictors of normal tissue toxicity such as pneumonitis [27] or esophagitis [19], and using proton therapy to reduce exposure of thoracic OARs [28]. These efforts have been implemented with varying degrees of success. For example, the use of proton therapy was investigated in a recent clinical trial which randomized patients with stage II-IIIB disease or stage IV disease with a single brain metastasis to receive IMRT or passive-scattering proton therapy (PSPT). Despite improved dosimetric exposure of lung to low doses, the co-primary endpoints of grade 3 + radiation pneumonitis and local failure were unchanged between the treatment arms [28]. Interestingly, a post-hoc analysis of patients treated on this trial examining rates of radiation esophagitis revealed an increased rate of grade 2 esophagitis on proton arm, with similar rates of grade 3 + esophagitis between IMRT and PSPT. This precipitated an interesting exploration into spatial differences in sensitivity, suggesting that the upper and middle thoracic esophagus may have greater contribution to the development of clinically-apparent esophagitis than the cervical or lower thoracic esophagus [29]. More research is needed to further explore whether tailoring dose exposure based on esophageal subsite can mitigate toxicity.

In conclusion, rates of grade 3 + esophagitis have substantially improved over time with the widespread adoption of advanced treatment planning techniques, while the rate of grade 2 + esophagitis remains largely unchanged. The threshold dose predicting fixed rates of esophagitis correlates with performance status for grade 2 + and grade 3 + esophagitis and with receipt of chemotherapy for grade 2 + esophagitis. Taking these factors into account may be helpful consideration when tailoring treatment planning to the individual patient.

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Data sharing statement

We are not authorized to share MROQC data. The data is individually owned by the member institutions of MROQC.

CRediT authorship contribution statement

Daniel J. Herr: Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Huiying Yin:** Writing – review & editing, Methodology, Formal analysis. **Derek Bergsma:** Writing – review & editing, Investigation. **Aleksandar F. Dragovic:** Writing – review & editing, Investigation. **Martha Matuszak:** Writing – review & editing, Conceptualization. **Margaret Grubb:** Writing – review & editing, Investigation. **Michael Dominello:** Writing – review & editing, Investigation. **Benjamin Movsas:** Writing – review & editing. **Larry L. Kestin:** Writing – review & editing. **Thomas Boike:** Writing – review & editing. **Amit Bhatt:** Writing – review & editing. **James A. Hayman:** Writing – review & editing. **Shruti Jolly:** Writing – review & editing, Conceptualization. **Matthew Schipper:** Writing – review & editing, Formal analysis. **Peter Paximadis:** Writing – review & editing, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2024.110349.

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