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Association of Target Volume Margins with Locoregional Control and Acute Toxicities for Non-Small Cell Lung Cancer Treated with Concurrent Chemoradiation Therapy:

Target Volume Margins for NSCLC

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Abstract

Purpose: To investigate the association between target volume margins and clinical outcomes for patients with inoperable non-small cell lung cancer (NSCLC) treated with concurrent chemoradiation therapy.

Methods/Materials: We reviewed records of 82 patients with inoperable NSCLC treated from 2009–2016 with concurrent chemoradiation. All patients received positron emission tomography-based treatment planning, 4-dimensional computed tomography simulation to define an internal target volume, and daily cone beam computed tomography. We quantified variations in target volume margins with a margin deviation index (MDI), calculated as the percentage change in equivalent uniform dose between the original planning target volume (PTV) and a standard reference PTV 10mm beyond the original gross tumor volume (GTV), consistent with the minimum margins mandated by recent NSCLC trials. Greater MDIs equated to smaller effective target volume margins. We dichotomized patients by the upper tercile MDI value (5.8%). Endpoints included time to locoregional progression and time to grade 3 radiation esophagitis (RE3) or radiation pneumonitis (RP3), modelled with the Fine-Gray method.

Results: Median follow-up was 37.8 months (range, 5.9–58.1 months). Larger MDIs correlated with smaller clinical target volume (CTV)+PTV margins, larger GTVs, later treatment year, and intensity-modulated radiation therapy use. The risk of locoregional progression did not differ for

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MDI 5.8% versus <5.8% (aHR 0.88, $P=.76$), while the risk of RE3 or RP3 was decreased for MDI 5.8% (aHR 0.27, $P=.027$). Patients with MDI 5.8% were treated with smaller CTV+PTV margins (median, 5.6mm versus 8mm, $P<.0001$) and a marginally lower volume of esophagus receiving 50 Gy (median, 31.1% versus 35.3%, $P=.069$).

Conclusions: Smaller margins were used for larger tumors, yet were not associated with an increase in locoregional failures. Additional studies could clarify whether smaller margins, when used alongside modern radiotherapy techniques, decrease treatment-related toxicity for inoperable NSCLC.

Introduction

Traditionally, clinicians based the clinical target volume (CTV) margin for locally advanced non-small cell lung cancer (NSCLC) on early pathologic series suggesting most microscopic disease falls within 5–9mm of the gross tumor volume (GTV) (1–3). Additionally, clinicians formed the planning target volume (PTV) margin based on institutional standards and motion management techniques employed. As a result, CTV and PTV margins remain generally variable and inadequately studied in the modern era with consistent use of position emission tomography/computed tomography (PET/CT)-based treatment planning, 4-dimensional computed tomography (4DCT) simulation to define an internal target volume (ITV), and daily image-guided radiation therapy (IGRT). Each of these technologic advancements enhance tumor targeting, potentially decreasing the required margins (4). Likewise, the addition of concurrent chemotherapy should target microscopic disease, potentially enabling smaller CTV expansions.

It remains unclear to what extent clinicians can reduce standard target volume margins during concurrent chemoradiation therapy (CRT) utilizing newer treatment technologies. Recent prospective trials for locally advanced NSCLC typically required both CTV and PTV margins of at least 5mm. For example, RTOG 0617 required a CTV margin of 5–10mm, and a PTV margin as large as 15mm in the superior-inferior dimensions and 10mm in the axial plane in the absence of motion management techniques such as 4DCT simulation, breath-hold, or gating (5). In the setting of 4DCT simulation and daily IGRT, RTOG 0617 allowed a PTV margin of 5mm. Because concurrent chemotherapy increases the risk of grade 3 esophagitis almost 5-fold (6), it appears warranted to test whether even smaller target volume margins can decrease doses to organs at risk and subsequent toxicity without affecting locoregional control.

Few studies evaluated the effect of target volume margins on clinical outcomes for inoperable NSCLC (7–9). We hypothesized that smaller margins would not compromise locoregional control and would associate with fewer acute toxicities in the setting of concurrent CRT with PET/CT-based treatment planning, 4DCT simulation, and daily CBCT.

Methods and Materials

Patients

We retrospectively reviewed a cohort of 96 patients with histologically confirmed, inoperable Stage II-III or Stage IV oligometastatic NSCLC who were treated with definitive

concurrent CRT from October 2009 to November 2016 and received PET/CT-based radiation therapy (RT) planning, 4DCT simulation and daily CBCT. To ensure treatment homogeneity, we excluded patients who received consolidation immunotherapy (n=10). We also excluded patients whose RT plans contained incomplete information (n=4). This left 82 patients for inclusion.

Treatment

During RT planning, the GTV included the primary tumor and clinically positive lymph nodes identified on the planning CT or PET/CT fusion. Real time fluoroscopy with abdominal compression was used before delineation of an ITV on the 4DCT, which was typically expanded 3–5mm volumetrically to form the CTV, and an additional 3–5mm volumetrically to form the PTV. For the minority of patients, the ITV was created after the CTV expansion. Generally, smaller CTV and PTV margins were used for larger GTVs and to meet normal tissue dose constraints, more frequently in later years as clinicians became more comfortable with the accuracy of daily CBCT. RT was delivered with 3-dimensional conformal radiotherapy (3DCRT), intensity-modulated radiation therapy (IMRT) or a mix of 3DCRT and IMRT to a typical dose of 60–66 Gy in 1.8 or 2 Gy per fraction. IMRT was used for patients presenting with bilateral mediastinal lymph node involvement or for the boost/off-cord component. At least 95% of the PTV was covered by 95% of the prescription dose for all except 5 patients, for whom 90–95% of the PTV was covered. Patients were treated with photon beams of 6- or 15-MV energies, and treatment plans were generated using the Eclipse treatment planning (Varian Medical Systems, Palo Alto, CA) analytic anisotropic algorithm with tissue inhomogeneity corrections. Concurrent chemotherapy usually consisted of either carboplatin/paclitaxel or cisplatin/etoposide.

Follow-up

Patients typically followed up with the radiation and medical oncologists every 1–3 months for the first year post-CRT, every 3–6 months for the following two years, and every 6–12 months thereafter. Follow-up CT scans were usually obtained 6–8 weeks after completion of CRT, and then every 3–4 months for the first year, every 6 months for the following two years, and yearly thereafter.

Quantifying variations in margins

To quantify variations in target volume margins, we calculated a margin deviation index (MDI) based on the methods of Jin *et al.* (8). For each RT plan, we generated a standard reference PTV by expanding the original GTV with a uniform 10mm margin. We chose a 10mm expansion because our institution typically used a maximum CTV+PTV margin of 10mm, consistent with the minimum margins mandated by RTOG 0617. We reviewed and edited the standard reference PTV as necessary to ensure it did not cross outside the thorax or toward the spinal cord any more than the original PTV.

We calculated equivalent uniform dose (EUD) to the original PTV and standard reference PTV from the original treatment plan dose distributions, using an in-house developed API script imported into the Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA). We presumed the EUD formula tissue specific parameter to equal –10, and the

alpha/beta ratio of the tumor to equal 10. We defined MDI as the percentage change in EUD between the original PTV and the standard reference PTV. We also determined the original CTV+PTV margin (in millimeters) used in clinical treatment by retrospectively analyzing contoured structures from RT plans. We assumed that CTV+PTV margins were uniform, which they typically were except in uncommon situations (e.g., PTV margin restricted in one direction to spare the skin or spinal cord). For any patient who received multiple different treatment plans (e.g., because of an off-cord component) with potentially different PTVs, CTV margins, or PTV margins, we calculated the total EUD to the original PTV and standard reference PTV by summing individual EUDs across different plans. In these cases, the overall CTV+PTV margin was weighted by the number of fractions of each individual plan.

We expected MDI to be more accurate than the CTV+PTV millimeter margin in quantifying variations in effective target volume margins because two treatment plans with the same geometric CTV+PTV margin might have different ITV expansions, proportions of the original PTV receiving the prescription dose, dose distributions inside the original PTV and margins, and/or degrees of dose-falloff outside of the original PTV. MDI should account for each of these factors. Conceptually, a larger MDI equates to a smaller effective target volume margin.

Statistical analysis and study endpoints

We first assessed associations between baseline characteristics and MDI. For categorical variables, we compared the median MDI of each group with the Wilcoxon rank-sum test or Kruskal-Wallis test. For metric variables, we used Spearman rank correlation tests. We used these tests because MDI was not normally distributed.

For subsequent analyses, we stratified patients into two groups: those with MDI $\geq 5.8\%$ (upper tercile value) and those with MDI $< 5.8\%$. We chose to dichotomize MDI because the relative, but not exact, MDI value is of clinical relevance. We chose the upper tercile value because: (1) The distribution of MDI was skewed strongly to the right (Fig. 1a), suggesting only a small portion of patients had large MDIs; and (2) We felt that an MDI $\geq 5.8\%$ represented a relatively tight target volume margin. We compared baseline characteristics between the two groups using the Chi square or Fisher exact test for categorical variables, and an independent two sample *t*-test or Wilcoxon-rank sum test for metric variables.

The primary endpoint was time to locoregional progression, defined according to Machtay *et al.* (10). Secondary endpoints included time to distant metastasis, time to grade 3 radiation esophagitis (RE3) or grade 3 radiation pneumonitis (RP3) (combined endpoint; graded according to CTCAEv4.03), and time to RE3. We measured all endpoints from the start of RT to the event of interest or last known follow-up. We used the cumulative incidence method to assess these endpoints. Gray's test compared cumulative incidence functions between MDI strata. We considered death in the absence of the event of interest as a competing event. We then used the Fine-Gray method to assess for associations between covariates and time to locoregional progression, time to RE3 or RP3, and time to RE3. Covariates included MDI (dichotomized by the upper tercile value), age, gender, T stage, N stage, histology, treatment year, GTV, and IMRT. We also tested volume of esophagus

receiving 50 Gy (V50) for associations with time to RE3, chosen on the basis of a meta-analysis that found high-dose metrics to the esophagus were the strongest predictors of RE3 (11). We considered clinically relevant covariates with the lowest P values in the univariate setting for inclusion in the multivariate models. We did not construct multivariate models for time to RE3 as there were too few events. We reported subdistribution hazard ratios (HR) along with 95% confidence intervals (CI). Hypothesis tests were 2-sided. We considered $P < 0.05$ as statistically significant, and $P < 0.10$ as a trend toward significance. We performed all analyses using SAS version 9.4 (Cary, NC).

Results

Figure 1 shows the distributions of MDI and CTV+PTV margins. The median MDI was 2.1% (range, -4.0–55.7%), with MDI 5.8% for the upper tercile ($n=27$). The median CTV+PTV margin was 8mm (range, 0–15mm). Expectedly, greater MDIs strongly correlated with smaller CTV+PTV margins (Spearman's $\rho = -0.74$, $P < .0001$).

Table 1 describes baseline characteristics other than CTV+PTV margins, and their associations with MDI. Larger MDIs associated with larger GTVs, treatment during/after 2013, and IMRT use. When dichotomized by MDI 5.8% versus <5.8%, there were no additional differences in baseline characteristics (Table S1). Patients with MDI 5.8% had marginally larger GTVs (median, 226.2 cm³ versus 108.9 cm³, $P = .052$) yet similar PTVs (median, 506.3 cm³ versus 500.5 cm³, $P = .95$), perhaps because CTV+PTV margins were significantly smaller (median, 5.6mm versus 8mm, $P < .0001$).

Association between margins and disease progression

Median follow-up was 38.6 months (range, 9.6–52.8 months) for those with MDI 5.8%, and 34.5 months (range, 5.9–58.1 months) for those with MDI <5.8%. Locoregional progression occurred in 30 patients (36.6%) and distant metastasis in 45 patients (54.9%).

The cumulative incidence (2-year rate, 34% versus 41%, $P = .61$) and risk (aHR 0.88, 95% CI 0.40–1.93, $P = .76$) of locoregional progression did not differ for MDI 5.8% versus <5.8% (Fig. 2; Table 2). The hazard for MDI 5.8% was similar (aHR 0.88, $P = 0.75$) in a multivariate model with IMRT and treatment year. MDI 5.8% also did not associate with an increased risk of distant metastasis.

Figure 3 compares margin distributions between those who did and did not experience locoregional progression. Among those who experienced locoregional progression (Table S2), median MDI was 0.66%, median CTV+PTV margin was 8mm, and both were strongly correlated (Spearman's $\rho = -0.79$, $P < .0001$). Locoregional progression occurred in 7/23 (30.4%) of those with CTV+PTV margins 6mm and in 10/19 (52.6%) of those with CTV+PTV margins 10mm.

Association between margins and acute toxicities

RE3 or RP3 during or after RT occurred in 20 patients (24.4%). Thirteen patients (15.9%) developed only RE3, six patients (7.3%) developed only RP3, and one patient (1.2%) developed both.

The cumulative incidence (1-year rate, 11% versus 31%, $P=.043$) and risk (aHR 0.27, 95% CI 0.082–0.86, $P=.027$) of RE3 or RP3 was lower for MDI 5.8% versus <5.8% (Table 3). Treatment year, GTV and IMRT did not affect the risk of RE3 or RP3. The 1-year cumulative incidence of only RE3 was also lower for MDI 5.8% versus <5.8%, and the corresponding hazard trended toward significance. Esophagus V50, which increased the risk of RE3, was marginally lower for MDI 5.8% versus <5.8% (median, 31.1% versus 35.3%, $P=.069$), whereas lung V20, mean lung dose and mean heart dose did not differ (Table S3).

Discussion

Among patients with inoperable NSCLC treated with modern RT techniques and concurrent chemotherapy, smaller target volume margins were not associated with an increased risk of locoregional progression. Our results also provide preliminary evidence that smaller margins may result in a favorable toxicity profile. These findings are noteworthy given that patients treated with smaller margins had larger GTVs.

The risk of locoregional progression did not differ with tight target volume margins, defined as MDI 5.8%, for a few possible reasons. First, all patients received modern RT techniques, which likely improved tumor localization and decreased target uncertainty. PET/CT-based treatment planning enhances the ability to differentiate between tumor and atelectasis, can increase the sensitivity for nodal metastases, and may decrease inter-observer variation in GTV delineation (12, 13). 4DCT simulation, by allowing for customization of margins based on respiration-induced target motion, decreases intra-fraction uncertainty (14). Daily CBCT decreases day-to-day set-up uncertainty and may enable a decrease in set-up margins (14, 15). Second, marginal recurrences potentially occur less commonly than in-field recurrences for inoperable NSCLC. Rajpara *et al.* and Jouglar *et al.* found that only 18% and 30% of locoregional failures, respectively, had a marginal component, and 0% and 9% were isolated marginal failures (16, 17). In these two studies, 73% and 79% of locoregional failures, respectively, were in-field. Thus, intrinsic resistance to therapy and/or insufficient radiation dose, rather than inadequate margin coverage, may account for the majority of locoregional failures.

Furthermore, patients with MDI 5.8% experienced decreased RE3 or RP3, and a trend toward decreased RE3. Efforts to minimize these toxicities are particularly important because the maximum grade of esophagitis predicted for worse overall survival in RTOG 0617 (5). One potential explanation for the reduced toxicity is that patients with MDI 5.8% received treatment with smaller CTV+PTV margins (median, 5.6mm versus 8mm) and somewhat lower esophagus V50. Importantly, a higher esophagus V50 increased the risk of RE3. Therefore, we suggest that smaller margins may facilitate the sparing of normal tissue to potentially reduce toxicity. A reduction in target volume margins bares effects similar to the transition from elective nodal irradiation to involved-field RT, a shift which resulted in fewer toxicities while not affecting nodal recurrence rates (18, 19). Because we considered toxicities as secondary endpoints and found borderline significant P values, we consider our data hypothesis-generating.

Our study shows a few limitations. First, the relatively small sample size limits our ability to report a negative result, namely that smaller margins did not affect locoregional control. However, patients were treated homogeneously and the aHR for locoregional progression was below 1 for MDI 5.8% versus MDI <5.8%, imparting additional confidence in our findings. We do not intend to conclude that target volume margins are not important in the treatment of NSCLC, but rather to encourage future prospective trials to consider applying smaller margins than traditionally used. Second, later treatment year and IMRT were associated with greater MDIs, which might confound our results. However, we tested both treatment year and IMRT in multivariate models for locoregional progression, and found no association between either factor and acute toxicities. Moreover, patients with larger MDIs had larger GTVs, which arguably strengthens our findings since larger GTVs typically increase the risk of local failure (20). Still, there may be additional confounders that were unaccounted for.

Preliminary data presented by Jin *et al.* showed that in RTOG 0617, larger MDIs (defined identically as in our study) surprisingly resulted in a trend toward improved local progression free survival (8). Only 11% of patients had an MDI >3%, reflecting the relatively large and consistent margins used compared to our cohort. Also, not all patients received PET/CT scans, 4DCT simulation and daily IGRT. In their retrospective series of 105 patients, Liang *et al.* found that omission of a 6–8mm CTV margin resulted in smaller PTVs, similar rates of local recurrence, and decreased grade 3–4 radiation pneumonitis (7). Because 4DCT simulation was not used, ITV margins ranged from 3–15mm. Kilburn *et al.* also reviewed their single-institution experience in omitting a CTV in the setting of modern radiotherapy techniques, and found that only 2/110 patients (1.8%) experienced locoregional failure in the region of the CTV omission (9). Our study provides novel insight as we used an MDI to more accurately quantify variations in margins, and we only included patients receiving concurrent chemotherapy, PET/CT-based RT planning, 4DCT simulation, and daily CBCT.

Recent trials for locally advanced NSCLC (RTOG 0617, 1306, 1308, and 1106) required a CTV margin of at least 5mm and PTV margin of at least 5mm, even in the setting of 4DCT simulation and daily IGRT. By contrast, in our cohort the median CTV+PTV margin was 8mm among all patients and 5.6mm among patients with MDI 5.8%. Future studies could clarify whether smaller margins can be safely used to better spare organs at risk and decrease toxicity. Smaller margins may particularly benefit dose-escalation efforts, which were likely hampered by normal tissue toxicity (5). In addition, smaller margins may facilitate the integration of immunotherapy with CRT, as overlapping toxicities such as pneumonitis are felt to be of concern (21).

We acknowledge that each patient is unique which necessitates customization of each treatment plan, including the margins and PTV coverage. Nevertheless, this study suggests that smaller target volume margins, when used in conjunction with modern radiotherapy techniques and concurrent chemotherapy, did not increase the risk of locoregional progression and were associated with a favorable toxicity profile. Our findings remain hypothesis-generating and warrant further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1:

(A) Distribution of margin deviation index (MDI). Median MDI was 2.1% (range, -4.0–55.7%), and upper tercile MDI was 5.8%. (B) Distribution of clinical target volume (CTV) +planning target volume (PTV) margin. Median value was 8mm (range, 0–15mm). (C) MDI and CTV+PTV margin were strongly correlated (Spearman's $\rho = -0.74$, $P < .0001$).

Fig. 2:
Cumulative incidence of locoregional progression, stratified by upper tercile margin deviation index (5.8%).

Fig. 3:
 (A) Margin deviation index (MDI) and (B) clinical target volume (CTV)+planning target volume (PTV) margin among those who did (n=30) and did not (n=52) experience locoregional progression. Follow-up was similar between groups (median, 34.5 versus 37.8 months, respectively, $P=0.84$)

Table 1.

Baseline characteristics and associations with margin deviation index

Characteristic	n (%)	Association with MDI		
		Median MDI (%)	Spearman's ρ	P value
Age (years)			−0.069	.54
Median	64.5			
Range	40–83			
Gender				.14
Male	48 (59)	1.2		
Female	34 (41)	4.1		
ECOG PS				.97
0	48 (59)	2.4		
1	34 (41)	2.0		
Clinical Stage				.84
IIA-IIIB	12 (15)	1.7		
IIIA-IIIB	61 (74)	2.6		
IV (oligometastatic)	9 (11)	0.9		
T stage				.45
x, 1–3	56 (68)	1.5		
4	26 (32)	2.6		
N stage				.30
0–2	54 (66)	2.1		
3	28 (34)	2.0		
Histology				.69
Adenocarcinoma	40 (49)	1.4		
Non-adenocarcinoma	42 (51)	2.3		
Treatment Year				.021
2009–2012	28 (34)	0		
2013–2016	54 (66)	3.0		
Prescribed Dose (Gy)			−0.15	.18
Median	60			
IQR	60–63			
Range	52–70.2			
GTV (cm ³)			0.39	.0003
Median	150.8			
Range	17.9–803.5			
PTV (cm ³)			0.065	.56
Median	503.4			
Range	84–1445			
RT Technique				.0033
IMRT only	30 (37)	5.0		
3DCRT or 3DCRT/IMRT	52 (63)	0.7		

Characteristic	n (%)	Association with MDI		
		Median MDI (%)	Spearman's ρ	P value
Concurrent chemo agents				.38
Carboplatin + paclitaxel	56 (68)	2.9		
Cisplatin + etoposide	11 (13)	0.7		
Other	15 (18)	0.9		

Abbreviations: MDI = margin deviation index; SD = standard deviation; ECOG PS = Eastern Cooperative Oncology Group performance status; IQR = interquartile range; GTV = gross tumor volume; PTV = planning target volume; RT = radiation therapy; IMRT = intensity-modulated radiation therapy; 3DCRT = 3-dimensional conformal radiotherapy; chemo = chemotherapy

Table 2

Association between margin deviation index and disease progression

3-year cumulative incidence			Univariate analysis		Multivariate analysis	
%	P-value	HR (95% CI)	P-value	aHR (95% CI)	P-value	
Locoregional progression						
MDI 5.8% (vs <5.8%)	34 vs 41	.61	0.82 (0.38–1.78)	.62	0.88 (0.40–1.93)	.76
Age (y)			1.001 (0.957–1.048)	.96		
Sex (male vs female)			0.67 (0.33–1.36)	.27		
T stage (T4 vs all else)			1.49 (0.71–3.10)	.29	1.49 (0.70–3.17)	.31
N stage (N3 vs all else)			1.18 (0.57–2.46)	.66		
Histology (ACA vs non-ACA)			0.96 (0.48–1.95)	.92		
Treatment year (2013 vs <2013)			0.46 (0.22–0.93)	.031	0.46 (0.23–0.95)	.035
GTV (cm ³)			0.999 (0.997–1.001)	.50		
IMRT (IMRT only vs all else)			0.84 (0.40–1.75)	.63		
Distant metastasis						
MDI 5.8% (vs <5.8%)	58 vs 57	.87	0.95 (0.53–1.72)	.87		

Abbreviations: ACA = adenocarcinoma; aHR = adjusted subdistribution hazard ratio; CI = confidence interval; GTV = gross tumor volume; HR = subdistribution hazard ratio; IMRT = intensity-modulated radiation therapy; MDI = margin deviation index

Table 3

Association between margin deviation index and grade 3 esophagitis/pneumonitis

1-year cumulative incidence			Univariate analysis		Multivariate analysis	
	%	P-value	HR (95% CI)	P-value	aHR (95% CI)	P-value
Grade 3 esophagitis or pneumonitis						
MDT 5.8% (vs <5.8%)	11 vs 31	.043	0.31 (0.094–1.01)	.052	0.27 (0.082–0.86)	.027
Age (y)			0.999 (0.96–1.04)	.95		
Sex (male vs female)			1.35 (0.54–3.36)	.52		
T stage (T4 vs all else)			3.03 (1.27–7.23)	.013	3.43 (1.43–8.24)	.0058
N stage (N3 vs all else)			1.34 (0.56–3.24)	.52		
Histology (ACA vs non-ACA)			0.78 (0.33–1.88)	.59		
Treatment year (2013 vs <2013)			0.78 (0.33–1.88)	.59		
GTV (cm ³)			1.000 (0.998–1.002)	.80		
IMRT (IMRT only vs all else)			0.93 (0.38–2.32)	.88		
Grade 3 esophagitis						
MDI 5.8% (vs <5.8%)	4 vs 24	.025	0.14 (0.019–1.05)	.055		
Esophagus V50 (%)			1.028 (1.007–1.049)	.0088		
Age (years)			0.998 (0.95–1.05)	.95		
Sex (male vs female)			1.28 (0.43–3.79)	.66		
T stage (T4 vs all else)			3.10 (1.09–8.84)	.034		
N stage (N3 vs all else)			1.50 (0.53–4.24)	.45		
Histology (ACA vs non-ACA)			1.03 (0.37–2.90)	.96		
Treatment year (2013 vs <2013)			0.96 (0.33–2.80)	.96		
GTV (cm ³)			1.000 (0.998–1.002)	.91		
IMRT (IMRT only vs all else)			0.69 (0.22–2.22)	.54		

Abbreviations: ACA = adenocarcinoma; aHR = adjusted subdistribution hazard ratio; CI = confidence interval; GTV = gross tumor volume; UR = subdistribution hazard ratio; IMRT = intensity-modulated radiation therapy; MDI = margin deviation index; V50 = volume receiving 50 Gy