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Objectively Quantifying Radiation Esophagitis with Novel CT-based Metrics

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Abstract

Purpose—To study radiation-induced esophageal expansion as an objective measure of radiation esophagitis in patients with non-small-cell lung cancer (NSCLC) treated with IMRT.

Methods and Materials—Eighty-five patients had weekly intra-treatment CT imaging and esophagitis scoring according to Common Toxicity Criteria for Adverse Events 4.0, (24 Grade0, 45 Grade2, and 16 Grade3). Nineteen esophageal expansion metrics based on mean, maximum, spatial length, and volume of expansion were calculated as voxel-based relative volume change, using the Jacobian determinant from deformable image registration between the planning and weekly CTs. An anatomic variability correction method was validated and applied to these metrics to reduce uncertainty. An analysis of expansion metrics and radiation esophagitis grade was conducted using normal tissue complication probability (NTCP) from univariate logistic regression and Spearman rank for grade 2 and grade 3 esophagitis endpoints, as well as the timing of expansion and esophagitis grade. Metrics' performance in classifying esophagitis was tested with Receiver Operating Characteristic (ROC) analysis.

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We examined radiation-induced esophageal expansion as an objective and continuous CT-based measure of radiation esophagitis. A method to reduce esophageal expansion calculation uncertainty from anatomic variability was tested and applied to these metrics. We found esophageal expansion is highly correlated to radiation esophagitis grade, and discovered several candidate metric values for use as endpoints in toxicity prediction modeling. In addition, the anatomic variability correction method provides a more accurate quantification of esophageal expansion.

Results—Expansion increased with esophagitis grade. Thirteen of nineteen expansion metrics had ROC area under the curve (AUC) values >0.80 for both grade 2 and grade 3 esophagitis endpoints, with the highest performance from maximum axial expansion (MaxExp1) and esophageal length with axial expansion 30% (LenExp30%) with AUCs of 0.93 and 0.91 for grade2, 0.90 and 0.90 for grade3 esophagitis, respectively.

Conclusions—Esophageal expansion may be a suitable objective measure of esophagitis, particularly maximum axial esophageal expansion and esophageal length with axial expansion 30%, with 2.1 Jacobian Value and 98.6mm as the metric value for 50% probability of grade3 esophagitis. The uncertainty in esophageal Jacobian calculations can be reduced with anatomic correction methods.

Introduction

Radiation esophagitis is one of the most common and debilitating normal tissue toxicities associated with radiation therapy for non-small cell lung cancer (NSCLC).¹ In addition to being a quality-of-life concern, severe esophagitis may lead treatment interruption; on-time completion of radiation therapy for NSCLC is the most important factor for optimal treatment outcome.² Esophagitis associated with radiation therapy for NSCLC prevents dose escalation, reducing tumor control.

Esophagitis severity is assessed using subjective grading scales based on symptomatic presentation and medical intervention. One example is Common Terminology Criteria for Adverse Events (CTCAE).³ This scale assigns a whole number grade ranging from 0 (no toxicity) to 5 (patient death), which has inter-physician variability in assigning scores and patient subjectivity in reporting symptoms. The patient's specific dietary consumption is also not considered. In addition, the grades represent nominal data, with no definitive numerical meaning between grades. A continuous measure of severity would be advantageous over current esophagitis scoring methods.

Esophageal swelling is a component of inflammatory response to radiation injury, which has not yet been thoroughly studied as a quantification of esophagitis. Several previous studies have shown that an esophageal swelling response is associated with esophagitis. However, these were preliminary studies that did not establish the relationship between the quantitative swelling response and esophagitis severity.⁴⁻⁶ The goal of the current study was to investigate the development and evaluation of a novel method using CT imaging to objectively quantify radiation esophagitis.

Methods and Materials

Patient Population

Eighty-five patients were selected from a prospective clinical trial of radiation therapy for stage III NSCLC at University of Texas-MD Anderson Cancer Center, treated with intensity-modulated radiation therapy and concurrent chemotherapy (paclitaxel and carboplatin), with tumor prescription doses of 60 (n=4), 66 (n=28), or 74 (n=53) Gy in 2-Gy fractions over 6-8 weeks. Patients had weekly 4DCT imaging and esophagitis scoring according to Common Terminology Criteria for Adverse Events version (CTCAE) 4.0. The

grading scale can be summarized as: grade0, no esophagitis; grade1, asymptomatic with only clinical or diagnostic observations; grade2, symptomatic with altered eating/swallowing and oral supplements; grade3, severely altered eating/swallowing with tube feeding, total peritoneal nutrition, or hospitalization; grade4, life-threatening consequences; and grade5 is death.³ Standard clinical practice for esophagitis symptom management is: liquid narcotic medication, topical anesthetics, and antacid medication for grade2, and IV fluids with possible feeding tube for grade3. The distribution of maximum esophagitis grades during treatment was: 24 were grade0, 45 were grade2, and 16 were grade3. There were no grade1 patients in this study, as asymptomatic diagnostic assessment of esophagitis was not conducted. We selected 85 of 97 possible patients from this clinical trial for the present study, excluding 3 patients due to image quality and 9 for having not having 4DCT imaging. Our study was approved by the University of Texas-MD Anderson Cancer Center Institutional Review Board and we complied with HIPAA regulations.

CT scans were acquired on General Electric Lightspeed Discovery ST or Lightspeed RT16 (GE Healthcare, Waukesha, WI) or Philips Brilliance 64 (Philips Healthcare, Bothell, WA) CT scanners operated at 120 kV. Voxel dimensions were 0.98×0.98×2.50 mm in the right-left direction, anterior-posterior, and superior-inferior direction, respectively, with a 512×512 pixel area. Treatment planning for all patients whose data were used in our study was conducted using the Pinnacle treatment planning system (Phillips Healthcare), including segmentation. Esophageal contours were segmented in Pinnacle version9.8 in the axial plane, from the cricoid cartilage to the gastroesophageal junction.

Computational Framework and Jacobian Map Algorithm

The computational framework used to calculate esophageal expansion on the treatment plan for any treatment week can be summarized in 3 steps: segmentation, deformable image registration, and Jacobian map algorithm. Esophagus contours were delineated on the planning image. Next, deformable registration was performed between the plan and weekly CT images to obtain deformation vector fields, and propagate segmentation to weekly CT images. Finally, the algorithm uses the deformation vector fields, planning, and weekly contours to calculate the local esophageal volume change with correction due to anatomical variability as an average of slices of the esophagus along the cranio-caudal axis.

A demons algorithm⁷ was used to perform deformable image registration from the planning CT to the weekly CT image set; this algorithm was validated for thoracic patients.⁸ Let $\mathbf{du} = (dx, dy, dz)$ denote the deformation vector pointing from voxel $\mathbf{u} = (x, y, z)$ in the planning image to the weekly CT image voxel $\mathbf{u}' = (x', y', z')$. The voxel mapping from the plan to the weekly image becomes:

$$\mathbf{u}'(x', y', z') = \mathbf{u}(x, y, z) + \mathbf{du}(dx, dy, dz) \quad (1)$$

The Jacobian Map is calculated by taking the determinant of the Jacobian of this transformation, using $\mathbf{du}$ for every voxel in the esophagus. The Jacobian represents the local voxel-volume change, and thus voxel esophageal expansion, from the plan to the weekly

imageset.^{9,10} A voxel Jacobian map of 1.0, >1.0, and <1.0, represents no volume change, relative expansion, and relative shrinkage, respectively.

For each of the 85 patients, after deforming the planning exhale phase all the other plan phases, and all weekly 4DCT phases, the deformation vector fields were used to calculate the corresponding Jacobians. The Jacobians were then averaged at each axial slice of the esophagus and esophageal expansion metrics were calculated.

Anatomic Volume Variability and Anatomic Variability Correction Methods

Physiological effects that skew esophageal volume calculations are numerous, including motility of the esophagus, dilation, swallowing during CT acquisition, and esophageal air. The presence of air in the esophagus is particularly challenging. Because deformable image registration uses CT number as a measure of image similarity, any 2 images in which esophageal air is present in one image but not the other have a high chance to cause deformable registration error in this region, propagating into the Jacobian calculation.

To reduce errors caused by air content, an “air content correction factor” can be calculated for each axial slice as the relative ratio of tissue in the esophagus on the planning image to that in the weekly image:

$$JM_{air \text{ corrected}} = JM_{detected} * \psi, \text{ where } \psi = \frac{\text{relative amount of weekly treatment esophageal tissue}}{\text{relative amount of plan esophageal tissue}} \quad (2)$$

The quantity $JM_{air \text{ corrected}}$ is the axial-averaged Jacobians corrected for air content in both planning and weekly images, and $JM_{detected}$ is the originally calculated Jacobian. The quantity ψ is the air content correction factor, computed at each axial slice of the esophagus.

Miscalculations of local volume change caused by intra-scan transient effects are minimized in 2 ways. The first method corrects transient effects on the plan image by deforming the exhale phase to all phases of the planning image and then computing an axial-Jacobian-averaged from all the phase deformations, which yields the “plan normalization correction factor”:

$$JM_{plan \text{ norm corrected}} = \frac{\langle JM_{detected} \rangle}{\Phi}, \text{ where } \Phi = \langle JM_{plan \text{ exhale phase to plan phases}} \rangle \quad (3)$$

The mean axial-averaged Jacobian from the exhale phase to the planning phase deformations is the plan normalization correction factor, denoted Φ . Dividing the Jacobian of the planning exhale phase to all weekly phases, denoted $\langle JM_{detected} \rangle$, by Φ yields the Jacobian corrected for transient effects $JM_{plan \text{ norm corrected}}$.

The second method reduces contributions to volume change from non-treatment-related sources on the weekly CT. Similar to the first correction, we utilize all phases of the weekly images to create a mean axial-averaged Jacobian. The mean of the plan exhale phase Jacobian to all weekly phases averaged at each axial segment of the esophagus, applying both anatomic variability correction factors, becomes:

$$JM_{Final} = \langle JM_{Corrected} \rangle = \frac{\langle JM_{detected} \rangle}{\Phi} * \psi \quad (4)$$

where $\langle JM_{Corrected} \rangle$ is the weekly 4DCT phased-averaged axial Jacobian with all correction factors applied, resulting in JM_{Final} , which is the weekly Jacobian used to derive all metrics of esophageal expansion for the given treatment week.

To test our correction method and quantify uncertainties, the Jacobian from planning to first treatment week is used to measure inter-CT scan variability without radiation-response, because insufficient time or dose has been delivered to induce esophageal expansion. The effect of anatomic variability correction is quantified by 2 metrics, with and without anatomic corrections. The first metric is the absolute difference between the axial Jacobians and a value of 1.0. Jacobian calculation without any radiation-induced expansion should show values close to 1.0. The second metric is the full-width half-maximum (FWHM) of the distribution of axial Jacobian values for all phases of the first week; accurate deformations have normal distributions of Jacobians centered near 1.0, with small FWHM values.

Esophageal Expansion Metrics

Various metrics were created to quantify esophageal swelling, described as:

- Mean axial esophageal expansion (MeanExp)
- Maximum axial esophageal expansion (MaxExp) of 1, 3, 5, or 7 axial slices of the esophagus centered at the single slice of maximum expansion and averaged (MaxExp3 stands for 3-slice averaged max expansion)
- Esophageal length with axial expansion given percentage (LenExp), ranging from 20% to 100% in 10% increments (LenExp20% stands for 20% expansion)
- Percentile of esophageal expansion (PerExp), ranging from sixtieth to ninetieth in increments of 10, as well as ninety-fifth percentile (PerExp60 for sixtieth percentile of expansion)

These quantifications allowed us to examine expansion using the average (MeanExp), maximum (MaxExp), spatial-length dependence (LenExp), and volume dependence of the expansion (PerExp). The MaxExp3-MaxExp7 metrics are meant to overcome uncertainties in quantifying MaxExp1 (which measures only a single axial response point). LenExp represents the physical esophageal length that increases in volume at least a given percentage. PerExp represents the expansion value for which the given percentile of all other expansion values are below. An axial comparison of esophagi before and during treatment is shown in Figure 1. The temporal relationship between expansion and esophagitis grade was also investigated by comparing the timing of maximal expansion and esophagitis grade.

Statistical Analysis

An analysis was conducted to determine any relationship between the expansion metrics and radiation esophagitis severity. The treatment week with maximal expansion was compared to the patient's maximum esophagitis grade during treatment. Normal tissue complication probability (NTCP) from univariate logistic regression and Spearman rank correlation

coefficients were calculated for expansion metrics with grade2 and grade3 esophagitis endpoints, with the metric value with 50% probability of grade2 and grade3 esophagitis calculated for each expansion metric. P-values were calculated using the likelihood ratio chi-square test. The Benjamini-Hochberg false discovery rate procedure was applied to all p-values. Receiver operating characteristic (ROC) analysis was used to quantify the performance of each expansion metric in classifying esophagitis. For all analyses, $p < 0.05$ after application of the Benjamini-Hochberg procedure was considered statistically significant. All statistical analyses were carried out in Matlab (Mathworks, Natick, MA).

Results

Anatomic Volume Variability

Of the 85 patients in this study, treatment week1 images were not available for 10 patients; data from these patients were excluded from the anatomic correction analysis.

The top panel in Figure 2 shows the axial Jacobian profile along the esophagus for the planning exhale phase deformed to the planning image for one patient. The volume variability of each phase-Jacobian can be observed on the planning image, and variability was reduced by taking the mean Jacobian of all phases from each axial location (dashed black line). The mean axial Jacobian was close to 1.0 for all points along the esophageal-length, representing an accurate calculation. A similar trend was observed with the Jacobian profiles for treatment week1.

The middle panel in Figure 2 shows the relative air content in plan and week 1 exhale images for the same patient. A large difference in air content occurred around slice 25, causing Jacobian miscalculation at the corresponding slice, shown in the bottom panel of Figure 2 (solid black line). By applying the anatomic corrections, we obtained a more accurate Jacobian value (solid blue line, bottom panel).

Figure 3a,b show the plan to week1 Jacobian distributions with and without anatomic variability correction for one patient. The distribution had a long asymmetric tail to small Jacobians before correction and a more symmetric distribution with smaller FWHM values and a peak centered closer to 1.0 after correction.

Figure 3c is a boxplot showing the distribution of FWHM values for the plan to week1 Jacobian distributions before and after anatomic correction was applied. Applying the anatomic correction reduced the FWHM values of the Jacobian distributions by 10.3% ($\pm 5.6\%$), average percent-difference with standard deviation in brackets. For all axial slices, the mean absolute percent-differences between the Jacobians and a value of 1.0 ranged from 13.3% ($\pm 5.4\%$) to 9.2% ($\pm 5.6\%$) after the anatomic correction was applied.

Expansion Metrics and Esophagitis Severity

Expansion metric distributions were grouped according to esophagitis grade (Figure 4a-c). This analysis illustrated a strong relationship between increased expansion values and increased esophagitis grades; the relationship was most pronounced for the MaxExp metrics.

For most metrics, a gap was evident between the highest value for grade0 and the lowest value for grade3 esophagitis.

Table 1 summarizes the statistical relationships between expansion metrics and esophagitis grade. All expansion metrics were very highly significantly ($p < 0.001$) associated with esophagitis grade2 and 3 according to logistic regression. Spearman rank analysis showed most metrics to have correlation coefficients in the range of 0.50-0.67.

While area under the curve (AUC) values from ROC analysis indicated metric performance varied slightly around the binary cutoff for grade2 or grade3, all MaxExp, PerExp95, LenExp30%, and LenExp40% metrics performed strong with $AUC > 0.88$ for both esophagitis endpoints, indicating these metrics' ability to classify esophagitis (Table 1).

The timing of maximum expansion and esophagitis grade showed a strong temporal correlation, as both esophagitis endpoints occurred on average around the same treatment fraction as the maximum expansion (Figure 3d). In addition, 8 patients had breaks in treatment due to esophagitis symptoms, with an average reduction of 14.3% in maximum expansion.

Discussion

To the best of our knowledge, this study was the first to propose an alternative measure of radiation esophagitis using objective, continuous biomarkers. In addition, we developed a method to reduce uncertainty in Jacobian calculations caused by esophageal anatomic variability. This study's findings can be summarized as: first, the localized esophageal volume change, from planning to any weekly-treatment time point, can be calculated using the Jacobian; second, this correction methodology improves Jacobian calculation accuracy; third, the expansion metrics examined were significantly correlated to radiation esophagitis, with maximum esophagitis occurring near week of maximum expansion.

Although transient effects can lead to erroneous Jacobian calculations, we found our correction methodology reduced these uncertainties. Using our correction methodology, we were able to reduce uncertainty by 10.0%, with air content producing the most error. Air in the esophagus is common, making censoring patients or sections of the esophagus with air not feasible.¹¹ Esophageal air content was observed in 70.0% of the patients. Without the air content correction, 15 of the 61 patients with grade2/grade3 max esophagitis would have MaxExp1 change by at least 10.0%. By utilizing the air content correction, we can obtain a more accurate Jacobian calculation in air-containing esophageal regions.

We quantified esophageal expansion to measure esophagitis severity in a novel way. Berkovich et al observed expansion of the esophageal wall in many forms of esophagitis, including radiation esophagitis.⁵ However, this was presented as clinical observation, not a thorough radiation-response analysis. In addition, that study did not assess esophagitis severity. Previously, we have examined the relationship between esophagitis grade and the ratio of esophageal cross-sectional areas of weekly to planning CT images during treatment and found that this ratio increased with grade, and the ratio increases occurred in regions receiving the highest radiation doses.⁶ On the basis of this work, we improved our analysis

by using a 3-dimensional measure of expansion at the voxel level. We developed localized measures of expansion and identified the highest correlated metrics to esophagitis grade. Furthermore, the timing relationship of maximum expansion and esophagitis grade was investigated. In addition, we corrected for anatomic variation to reduce the associated uncertainties.

Of the various esophageal expansion metrics we tested, most performed well and were highly correlated to esophagitis grade, as shown in Table 1. The highest performing metrics were maximum axial expansion (MaxExp1) and esophageal length 30% axial expansion (LenExp30%). The maximum axial expansion metrics seem intuitive as measures of high-grade esophagitis, if the functional subunit of the esophagus is considered a cross-sectional segment, and the organ is serial. We also combined MaxExp1 and LenExp30% into a multivariate logistic model for both endpoints and computed AUC. We observed improvement for the grade3 endpoint, with AUC=0.93 for grade2 and AUC=0.91 for grade3.

The timing of maximum expansion is correlated to esophagitis grade. On average, patients with maximum grade2 esophagitis had maximum expansion occur at the same treatment fraction (Figure 3d). In addition, 15 of the 16 grade3 max patients had expansion occur before grade3 esophagitis. Whether expansion precedes grade3 symptoms is not currently discernible as expansion and esophagitis scores are quantified weekly. The relationship with grade2 esophagitis had more variance, but both this could be a product of subjectivity within grade2 assessment.

Our study had some limitations. First, a local error in deformable registration causes miscalculation of the Jacobian. We reduced the potential impact of this miscalculation by implementing our correction methodology. In addition, there is no direct method to validate anatomic uncertainty late in treatment, and we assumed that the plan-to-week 1 variance is representative of variance later in treatment. Nevertheless, patients with grade0 esophagitis did not show any appreciable radiation-response, and even in extreme cases these patients exhibit little esophageal expansion, as shown in Figure 4. For every patient, expansion is a localized effect, with the expanding region only existing within the irradiated esophagus. Although dose-response may be considered a paradigm of radiation therapy, the goal of the current work was to show that esophageal expansion can quantify esophagitis, and dose was not a focus in our study. How dose induces esophageal expansion will be presented soon in a future study. We also did not conduct pre-treatment esophageal contrast studies, which allows for identification of pre-existing thickening of the esophageal wall. In addition, chemotherapy does increase occurrence of high-grade esophagitis. How chemotherapy contributes to expansion is not thoroughly investigated. However, every patient in this study had the same course on concurrent chemotherapy, and no appreciable expansion was observed outside the irradiated esophagus.

Quantifying esophagitis with expansion is an attractive method of quantifying esophagitis severity. The continuous nature of the expansion metrics may allow esophagitis severity to be described in mathematical rather than qualitative terms. The spatial localization of expansion allows geometric dose-response information, allowing for a deeper understanding

of radiation injury in the esophagus, which was previously unavailable. Because esophagitis is an endpoint in most thoracic radiation therapy trials, expansion may potentially provide an objective measure for comparison of treatment modalities, as well as *in-vivo* measures of radioprotector effectiveness.

This provides new options for toxicity prediction modeling. The binary endpoint of logistic regression can be chosen with flexibility. As shown in Figure 3, most expansion metrics had a gap between the minimal metric value for grade3 esophagitis and the maximal metric value for grade0. This gap as well as the expansion values of 50% probability of complication (Table 1) represents candidates for dichotomy. NTCP modeling is common practice to predict radiation esophagitis at treatment planning.¹²⁻¹⁶ In previous studies, variation in outcome reporting and differing grading scales presented challenges for obtaining effective NTCP models.^{15,17,18} Review studies by Werner-Wasik et al and Rose et al showed that although many NTCP-based studies have been performed with collectively thousands of patients, no common model can predict esophagitis with high accuracy in external data sets.^{15,16} The continuous nature of expansion metrics may improve prediction model performance. In addition, modeling techniques other than logistic regression may be studied.

Conclusions

Esophageal expansion may be a suitable measure of esophagitis, particularly the metrics maximum axial esophageal expansion and axial length with at least 30% expansion, with metric values of 50% complication probability for grade 3 esophagitis of 2.12 Jacobian Value and 98.63mm, respectively. Expansion metrics may be useful to quantify response associated with new treatment techniques and clinical trials. The uncertainty in esophageal Jacobian calculations can be reduced by using anatomic correction methods.

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Figure 1.

Example of axial expansion of esophagus as relative change from planning (a,c) to treatment week 6 (b,d). Top patient (a,b) has maximum grade 0 esophagitis and no change in esophagus volume. Bottom patient (c,d) has maximum grade 3 esophagitis and considerable expansion.

Figure 2.

(Top) Axial averaged Jacobian map for all phases and mean Jacobian (black dashed line) of all phases for the planning 4DCT image set for one patient. T00 represents the inspiration phase and T50 the exhale phase. (Middle) Relative axial cross-sectional area of air content for the planning (solid black line) and week 1 (dashed red line) T50 phases for one patient. (Bottom) Axial averaged Jacobian map of the week 1 T50 phase, uncorrected (black line) and with full anatomic correction (blue line), for one patient.

Figure 3.

(a) Histogram showing the distribution of planning to week 1 Jacobian values for one patient, without anatomic corrections. Red line represents a normal fit. (b) Histogram showing the distribution of planning to week 1 Jacobian values for one patient, with all anatomic corrections applied. Red line represents a normal fit. (c) Boxplot of the planning to week 1 Jacobian full width half maximum (FWHM) values without and with anatomic corrections. (d) Boxplot of fraction of maximum expansion (MaxExp1) minus the fraction of maximum esophagitis grade, with a dotted line at zero.

Figure 4.

(a-c) Boxplots of the esophageal expansion metrics grouped according to esophagitis grade (yellow is grade 0, white is grade 2, and gray is grade 3). The box edges represent the 75% (top edge) and 25% (bottom edge) quartile values, the middle line represents the median value, the whiskers represent the range of values, and the circles represent outliers. (d) Plot of the NTCP function for grade 2 (blue), and grade 3 (red) complication thresholds with individual patient result above (1.0) and below (0.0) the given threshold (blue +, grade 2; red o, grade 3). Expansion metrics are defined in the Methods and Materials section.

Table 1

Logistic regression analysis of the relationship between expansion metrics and esophagitis grade (n = 85).

Expansion metric *	Grade 2				Grade 3			
	p	AUC [†]	Spearman rank	50% Complication Value	p	AUC [†]	Spearman rank	50% Complication Value
MeanExp	5.39E-08	0.855	0.553	1.191	3.87E-07	0.880	0.515	1.511
MaxExp [‡]	<i>1.51E-11</i>	<i>0.928</i>	<i>0.668</i>	<i>1.445</i>	<i>2.70E-07</i>	<i>0.899</i>	<i>0.540</i>	<i>2.123</i>
PeakExp3	1.72E-11	0.921	0.657	1.208	2.70E-07	0.893	0.532	1.880
PeakExp5	2.44E-11	0.915	0.648	1.139	2.70E-07	0.899	0.540	2.145
PeakExp7	5.98E-11	0.910	0.639	1.371	2.70E-07	0.900	0.542	2.039
LenExp20%	2.08E-08	0.866	0.572	26.911	4.85E-06	0.860	0.488	127.848
LenExp30%	<i>5.98E-11</i>	<i>0.909</i>	<i>0.642</i>	<i>12.625</i>	<i>3.87E-07</i>	<i>0.901</i>	<i>0.546</i>	<i>98.625</i>
LenExp40%	4.10E-10	0.900	0.639	2.536	6.41E-07	0.899	0.553	80.554
LenExp50%	1.26E-09	0.851	0.579	0.708	6.41E-07	0.894	0.564	64.979
LenExp60%	1.56E-07	0.762	0.487	0.393	3.87E-07	0.889	0.606	49.769
LenExp70%	8.41E-07	0.738	0.448	0.500	5.21E-06	0.831	0.530	40.571
LenExp80%	1.93E-05	0.689	0.382	0.000	5.38E-05	0.784	0.492	31.333
LenExp90%	1.48E-03	0.588	0.170	0.000	5.41E-05	0.783	0.475	23.571
LenExp100%	3.16E-03	0.598	0.254	0.000	1.14E-04	0.723	0.499	16.685
PerExp60	6.72E-07	0.815	0.491	1.133	1.29E-06	0.834	0.453	1.456
PerExp70	4.66E-08	0.842	0.533	1.112	2.88E-07	0.894	0.534	1.764
PerExp80	6.53E-09	0.864	0.568	1.083	2.70E-07	0.907	0.551	1.774
PerExp90	4.10E-10	0.885	0.601	1.246	2.70E-07	0.902	0.545	1.910
PerExp95	1.32E-10	0.902	0.627	1.252	2.70E-07	0.908	0.552	1.915

* Expansion metrics are defined in the Methods and Materials section.

[†] Area under the curve.[‡] Italic text indicates highest performing metrics for both grade 2 and grade 3 esophagitis endpoints.