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Multimodal Imaging of Pathologic Response to Chemoradiation in Esophageal Cancer

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Abstract

Purpose—To examine the value of early changes in quantitative diffusion-weighted imaging (DWI) and ¹⁸F-deoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) for discriminating complete pathologic response (pCR) to chemoradiation (CRT) in esophageal cancer.

Methods—Twenty esophageal cancer patients treated with chemoradiation followed by surgery were prospectively enrolled. Patients underwent MRI and FDG-PET/CT scans at baseline (BL), interim (IM, 2 weeks after CRT start), and first follow-up (FU). Based on pathologic findings at surgery, patients were categorized into tumor regression groups (TRG1, TRG2, and TRG3+). Distributions of summary statistics in apparent diffusion coefficient (ADC) and FDG-PET at BL and relative change at IM and FU scans were compared between pCR/TRG1 and non-pCR/TRG2+ groups and across readers. Receiver operating characteristics (ROCs) were evaluated for summary measures to characterize discrimination of pCR from non-pCR.

Results—Relative changes in tumor volume ADC (ADC) mean, 25th and 10th percentiles were able to completely discriminate (AUC=1, p<0.0011) between pCR and non-pCR (thresholds = 27.7%, 29.2%, and 32.1%, respectively) and were found to have high inter-reader reliability (95% limits of agreement of 1.001, 0.944 and 0.940, respectively). Relative change in total lesion glycolysis (TLG) from BL to IM was significantly different among pCR and non-pCR groups (p=0.0117) and yielded AUC of 0.947 (95% CI: 0.8505–1.043). An optimal threshold of 59% decrease in TLG provided optimal sensitivity (specificity) of 1.000 (0.867). Changes in ADC summary measures were negatively correlated with that of TLG (Spearman, -0.495, p=0.027).

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Conclusion—Quantitative volume ADC and TLG during treatment may serve as early imaging biomarkers for discriminating pathologic response to chemoradiation in esophageal cancer. Validation of this data in larger prospective multicenter studies is essential.

Keywords

Esophageal cancer; diffusion weighted imaging; apparent diffusion coefficient; positron emission tomography; pathologic response; chemoradiation; early response biomarker

Introduction

Selection of appropriate patients for a wait-and-see approach after chemoradiation (CRT) for esophageal cancer is predicated on identifying biomarkers of early treatment response, enabling identification of patients most likely to have a pathologic complete response (pCR) and derive the least benefit from additional surgery (1–4). Conventional imaging and assessment are not reliable in gauging treatment response during CRT (5,6). Therefore, with current imaging and assessment techniques alone, typically consisting of baseline and serial follow-up imaging (CT or PET) with endoscopy (7), treatment de-escalation or escalation based on tumor response is still unjustified.

Diffusion-weighted imaging (DWI) is a functional MRI technique that enables detection of Brownian motion of water protons in tissues and a quantitative measure of tissue microenvironment (8,9). DWI is a promising imaging modality to assess treatment response in rectal (10–14) and esophageal cancer (15). The apparent diffusion coefficient (ADC) can be calculated from DWI series of different b-values to remove underlying T2-dependence of signals. Additionally, quantitative ^{18}F -deoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) is indicative of changes in tumor metabolism and could be complementary in discriminating treatment response (11,14,16–18).

The primary objective of this study was to evaluate the discriminatory value of early DWI and FDG-PET/CT for pathologic response during neoadjuvant CRT in patients with esophageal cancer.

Materials and Methods

Patients and Treatment

Patients were enrolled on a single institution, institutional review board-approved prospective study after providing written informed consent. Only potentially resectable esophageal cancer patients were enrolled, and all were treated with neoadjuvant CRT and surgery. Chemotherapy typically consisted of 5-fluorouracil and docetaxel. Radiation dose was 50.4Gray in 1.8Gy daily fractions to the planning target volume. Details regarding simulation and treatment planning are presented in Supplementary Methods.

Imaging and Pathologic Assessment

MRI and FDG-PET/CT scans were acquired at baseline (BL), two weeks after start of CRT (interim, IM), and 4–6 weeks after treatment (FU). Patients were categorized into three

tumor regression groups (TRGs) based on pathological findings at surgery: TRG1 if 0% viable tumor cells/pCR in the primary tumor and lymph nodes, TRG2 if >0% but < 10% viable tumor cells, or TRG3+ if >10% viable tumor cells (19).

Tumor delineation methods, DWI and FDG-PET/CT protocols are delineated in Supplementary Methods. From contoured tumor volumes, a total of 11 ADC summary measures were calculated: Min, Max, Mean, standard deviation, skewness, kurtosis, 10th, 25th, 50th (median), 75th, and 90th percentiles.

To investigate the inter-reader reliability of measurements, DWI studies were contoured in randomized order using both volume and slice contouring techniques by five separate readers.

Statistical Analysis

Distributions of summary measures at BL and relative change at IM and FU scans were compared between pCR (TRG1) and non-pCR (TRG2+) using Mann-Whitney (MW) test. For ADC summary measures, inter-feature dependence was assessed using Spearman-rank correlation. Receiver operating characteristics (ROCs) were evaluated for top summary measures for discrimination of pCR from non-pCR. Detailed statistical methods are presented in Supplementary Methods.

Results

Table 1 depicts detailed patient and tumor characteristics. All 20 patients enrolled were male and 17(85%) had distal adenocarcinomas. There were no significant differences in clinical baseline characteristics between pCR and non-pCR outcomes. After chemoradiation, 5(25%) patients had pCR/TRG1, 9(45%) TRG2, and 6(30%) TRG3+.

Changes in ADC parameters from BL to IM scans, but not from BL to FU scans discriminated pCR from non-pCR. Assessment of changes in ADC parameters (ADC) with treatment identified more than 5 summary measures as discriminant of pCR (Table 2). Volume ADC mean was the most significant discriminant measure ($p = 0.0011$, Fig 2a). On ROC analysis, the relative change of volume ADC mean from BL to IM yielded AUC=1 in classifying patients as pCR and non-pCR with a threshold of 28%. In contrast, ADC summary measures from BL (Table 3) to FU scans were not significantly different between pCR and non-pCR groups.

Furthermore, measurements of relative changes (BL to IM) of volume ADC summary measures were highly reproducible among readers (Supplementary Table 2). Minimum AUC for discriminating pCR vs. non-pCR across the five readers using ADC 25th percentile, ADC mean, and ADC 10th percentile measures was 0.987, 0.973 and 0.960. However, the ADC mean from the slice contouring method yielded AUCs <0.900 for all readers.

Considering relative changes in PET parameters from BL to IM scans, patients with pCR had significantly greater decreases in TLG ($p=0.0138$) than TRG2+ (Table 4). Change in TLG at the IM scan yielded AUC of 0.947 (95% CI: 0.8505 to 1.043). Youden's optimal sensitivity (specificity) were 1.000 (0.867) for change in TLG at the IM scan (Fig 2b).

Changes in SUV_{max} , SUV_{mean} from BL to IM and changes in SUV_{max} , SUV_{mean} , TLG, and MTV from BL to FU were not associated with pathologic response. Change in TLG was negatively correlated with early change in volume ADC mean (Spearman, -0.495 , $p=0.027$).

Discussion

This prospective study evaluated the discriminative value of early changes on DWI and FDG-PET/CT in differentiating pathologic response in esophageal patients treated with chemoradiation followed by surgery. The change in ADC (mean ADC, 10th or 25th percentile, etc) after the first two weeks of CRT, which is not currently part of standard imaging evaluation, was highly discriminant of pCR at the time of surgery. A change in mean ADC of ≥ 28 discriminated pCR with a sensitivity and NPV of 100%. On FDG-PET/CT, early change in TLG was also associated with pCR, and a 59% decrease in TLG discriminated pCR with optimal sensitivity (specificity) of 1.000 (0.867). This study provides encouraging results for the potential value of interim multimodal imaging in early discrimination of patients likely to have a pCR to neoadjuvant therapy.

Our results are consistent with findings from a previous study exploring the role of DWI in discriminating pathologic response (15). Van Rossum et al. found that in 20 patients undergoing CRT before surgery, a change in median tumor ADC of $\sim 29\%$ discriminated residual cancer with a sensitivity (specificity) of 100% (75%) (15). The threshold change in mean tumor ADC identified in that study was similar despite differences in scanner platforms (3.0 vs. 1.5T, GE vs. Philips). Li et al. investigated the discriminatory value of baseline and follow-up ADC for pathologic response, finding that the follow-up ADC and change in ADC from baseline to follow-up were significantly higher in responders (20). In comparison, our study did not find that baseline or follow-up ADC values were associated with pCR. Li et al. used ADC parameters from a 2D region of interest on a single axial slice whereas we delineated a 3D volume of interest, which could explain the difference in findings.

Furthermore, we sought to optimize the method by which ADC measurements are performed. We compared slice to volume delineation methods and found that change in ADC mean based on single-slice contours was not discriminant of pCR with the same sensitivity/specificity as volumetric delineation. In addition, inter-reader agreement on 2D slice contours was inferior to that of volume-based contours.

With respect to FDG-PET/CT imaging, we identified early change in TLG, a proxy measure for overall tumor burden, as significantly discriminant of pCR in contrast to a prior study which did not identify any discriminators of pCR on interim PET (21).

A limitation of this study is the small sample size, thus, the results of this study are hypothesis generating. The optimal threshold value of change in ADC and TLG in discriminating pCR may need further refinement. Secondly, a minority of PET/CT scans were performed at an outside institution, which may have introduced variability in scan technique. Thirdly, all the patients enrolled were men, which potentially limits the generalizability of the study.

In conclusion, quantitative ADC changes from DWI and TLG changes from FDG-PET/CT from baseline to interim scans may enable discrimination of complete pathologic response to chemoradiation in esophageal cancer. Multimodal imaging to validate these approaches in a larger cohort is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Early quantitative change in tumor apparent diffusion coefficients from diffusion-weighted MR imaging discriminates complete pathologic response from nonresponse after chemoradiation in esophageal cancer. Early change in total lesion glycolysis by FDG-PET/CT also discriminates pathologic response from nonresponse after chemoradiation in esophageal cancer. Early prediction of pathologic response to chemoradiation in esophageal cancer is feasible using quantitative ADC and FDG-PET/CT and could enable patient selection for treatment de-escalation.

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Figure 1. Images and parameter maps across imaging modalities on the same axial slice of tumor: diffusion images b200 (a) and b0 (b), ADC map (c), CT (d), FDG-PET (e), and T2 weighted (f).

Figure 2.

Comparison of biomarker distributions between pCR and non-pCR for (a) ADC mean and (b) TLG. In the dot plots, 95% confidence intervals are shown as well as solid horizontal bars indicating average biomarker value for each response group. Dotted lines show cutoffs optimized by Youden's index. Below each plot is an ROC curve showing the classification performance of its respective biomarker.

Table 1

Patient Population Characteristics

Characteristic	N (%)
<i>Gender</i>	
Male	20 (100.0)
Female	0 (0.0)
<i>Age (years)</i>	
	62.1+/-8.0 *
<i>Histological Tumor Type</i>	
Adenocarcinoma	17 (85.0)
Squamous cell carcinoma	3 (15.0)
<i>Histological Tumor grade</i>	
Well Differentiated	0 (0.0)
Moderately Differentiated	9 (55.0)
Poorly Differentiated	11 (45.0)
<i>Clinical Stage</i>	
IIa	1 (5.0)
IIb	5 (25.0)
IIIa	12 (60.0)
IIIb	2 (10.0)
<i>Tumor Location</i>	
Proximal third	0 (0.0)
Middle third	1 (5.0)
Distal third	17 (85.0)
Gastro-esophageal junction	2 (10.0)
<i>Histopathologic T-stage</i>	
ypT0	5 (25.0)
ypT1a	2 (10.0)
ypT1b	2 (10.0)
ypT2	3 (15.0)
ypT3	8 (40.0)
<i>Histopathologic N-stage</i>	
ypN0	14 (70.0)
ypN1	4 (20.0)
ypN2	2 (10.0)
ypN3	0 (0.0)
<i>Histopathologic Tumor Regression Grade</i>	
TRG 1	5 (25.0)
TRG 2	9 (19.0)

Characteristic	N (%)
TRG 3–5	6 (30.0)

* For patient age, the format is mean $\pm$ standard deviation.

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Table 2

Comparing Relative Changes @ IM of ADC Summary Measures between pCR and nonpCR using Mann-Whitney Test

Feature	Bonferroni Adjusted p-value	Histopathologic Response	Relative % Change (Mean +/- STD)	AUC
ADC Mean	0.011	pCR/TRG1 non-pCR/TRG2+	37.73 +/- 8.77 9.41 +/- 7.53	1.000
ADC 25 th Percentile	0.011	pCR/TRG1 non-pCR/TRG2+	47.12 +/- 11.18 10.37 +/- 8.43	1.000
ADC 10 th Percentile	0.011	pCR/TRG1 non-pCR/TRG2+	53.23 +/- 20.46 10.17 +/- 12.50	1.000
ADC Median	0.015	pCR/TRG1 non-pCR/TRG2+	39.63 +/- 9.20 10.65 +/- 7.42	0.987
ADC 75 th Percentile	0.021	pCR/TRG1 non-pCR/TRG2+	35.73 +/- 12.11 9.45 +/- 8.26	0.973

Table 3

Comparing Baseline ADC Summary Measures between pCR and non-pCR using Mann-Whitney Test

Summary Measure	Bonferroni Adjusted p-value	Histopathologic Response	ADC in $\times 10^{-3}$ mm ² /s	AUC
Volume ADC Mean	0.180	pCR/TRG1	2.22 +/- 0.17	0.867
		non-pCR/TRG2+	2.62 +/- 0.34	
Volume ADC 25 th Percentile	0.227	pCR/TRG1	1.82 +/- 0.15	0.853
		non-pCR/TRG2+	2.23 +/- 0.34	
Volume ADC Median	0.287	pCR/TRG1	2.18 +/- 0.16	0.840
		non-pCR/TRG2+	2.59 +/- 0.38	
Volume ADC 75 th Percentile	0.357	pCR/TRG1	2.57 +/- 0.21	0.827
		non-pCR/TRG2+	3.00 +/- 0.38	

Comparing Relative Changes @IM of FDG-PET Parameter Summary Measures between pCR and non-pCR using Mann-Whitney Test

Table 4

% Change Interim		%Change Post-treatment					
Feature	Bonferroni Adjusted p-value	Response	Relative % Change (Mean +/- STD)	Feature	Bonferroni Adjusted p-value	Response	Relative % Change (Mean +/- STD)
TLG	0.0138	pCR	-67.19 +/- 6.81	TLG	0.512	pCR	-73.88 +/- 13.52
		non-pCR	-7.59 +/- 56.37			non-pCR	-40.81 +/- 40.32
MTV	0.198	pCR	-42.18 +/- 14.95	MTV	0.6	pCR	-45.44 +/- 13.47
		non-pCR	17.42 +/- 76.93			non-pCR	-13.98 +/- 45.77
SUV _{mean}	0.424	pCR	-39.64 +/- 21.35	SUV _{mean}	0.704	pCR	-53.65 +/- 14.92
		non-pCR	-14.78 +/- 36.20			non-pCR	-30.52 +/- 39.36
SUV _{max}	0.508	pCR	-45.70 +/- 19.67	SUV _{max}	1.00	pCR	-60.18 +/- 14.88
		non-pCR	-17.17 +/- 42.11			non-pCR	-38.89 +/- 45.93