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The use of molecular imaging to predict clinical outcome in patients with rectal cancer after pre-operative chemotherapy and radiation

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Abstract

Purpose—To correlate changes in ^{18}FDG-PET uptake with response and disease-free survival (DFS) with combined modality neoadjuvant therapy in patients with locally advanced rectal cancer.

Methods—Charts were reviewed for consecutive patients with uT3-4Nx or uTxN1 rectal adenocarcinoma who underwent pre-operative chemoradiation (CRT) at Fox Chase Cancer Center (FCCC) and Robert H. Lurie Comprehensive Cancer Center of Northwestern University with ^{18}FDG-PET scanning before and after combined-modality neoadjuvant CRT. The maximum Standardized Uptake Value (SUV) was measured from the tumor before and 3-4 weeks after completion of CRT preoperatively. Logistic regression was used to analyze the association of pre-treatment SUV, post-treatment SUV, and % SUV decrease on pathologic complete response (pCR), and a Cox model was fitted to analyze DFS.

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Results—Fifty-three patients, (FCCC n=41, RLCCC n=12), underwent pre and post chemoradiation PET scans between September 2000 and June 2006. The pCR rate was 31%. Univariate analysis revealed that % SUV decrease showed a marginally trend in predicting pCR, p=0.08. In the multivariable analysis, post-treatment SUV was shown a predictor of pCR, p=0.07, but the test did not reach statistical significance. None of the investigated variables were predictive of DFS.

Conclusions—A trend was observed for % SUV decrease and post-treatment SUV predicting pCR in patients with rectal cancer treated with pre-operative CRT. Further prospective study with a larger sample size is warranted to better characterize the role of ^{18} FDG-PET for response prediction in patients with rectal cancer.

Keywords

18-FDG PET scan; Rectal cancer; Pre-operative chemoradiation

Introduction

Prevention of treatment related toxicity and/or improved outcomes could result if tumor response or adverse effects could be predicted early in a treatment course. Incorporation of 2-deoxy-2-[18F]fluoro-D-glucose (18-FDG) positron emission tomography (PET) scans in the management of patients with cancer has increased with the introduction of this modality into clinical practice. We previously reported our experience incorporating 18-FDG PET scans in the assessment of patients with rectal cancer receiving pre-operative chemoradiation.(1) Decreased metabolic activity was found comparing pre- and post-chemoradiation PET scans, but post-treatment standardized uptake value (SUV) and % SUV decrease did not predict pathologic complete response. This early study, like others, suffered from small patient numbers.

The specific aim of the current study was to determine if post-chemoradiation PET scans could predict pathologic complete response or disease-free survival in patients with adenocarcinoma of the rectum receiving pre-operative chemotherapy in a combined cohort of patients from 2 NCI-designated comprehensive cancer centers. We hypothesized that PET scans could predict pathologic complete response in patients with adenocarcinoma of the rectum treated with pre-operative chemoradiation.

Material and Methods

Patients with ultrasound (u)-staged T3-T4 Nx or uTxN1 adenocarcinoma of the rectum referred to Fox Chase Cancer Center (FCCC) (Philadelphia, PA) or the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (RLCCC) (Chicago, IL) for pre-operative chemo-radiation underwent 18-FDG PET scans before and after neoadjuvant treatment prior to total mesorectal exicision (TME) of the rectal cancer. The SUV_{max} was measured at the time of the pre-operative scan and 3-4 weeks post chemoradiation before surgery. T staging of the primary rectal tumor was determined by a combination of CT scanning and endoscopic rectal ultrasound.

Fox Chase Cancer Center PET scanning equipment and procedures have been previously reported.(1,2) All images in FCCC are corrected for body weight, dose administered, and radioactive decay and displayed on a Xeleris workstation (GE Medical Systems, Waukesha, WI) with standardized uptake value (SUV) in scale of 0 to 5 for optimal display. The values above 5 will be bright display in the images, and display window can be adjusted for viewing as needed. RLCCC PET scanning procedures consisted of blood glucose levels determined in all patients prior to injection of the radiopharmaceutical. Patients were then injected

intravenously with 15mCi of 18-FDG with imaging initiated one hour following injection, using a Siemens ECAT Exact 47 tomograph operating in 2D acquisition mode. Each 16cm bed position was imaged for 10 minutes, three minutes for transmission data and seven minutes for emission data. Total imaging time was approximately one hour. Image interpretation consisted of visual inspection of attenuation corrected transaxial, sagittal, and coronal projections as well as cine display of maximum intensity projection (MIP) images. Maximum standardized uptake values (SUV's) were computed from three dimensional volumes of interest encompassing the primary lesion. There are no significant technical differences in PET/CT image acquisition and the methodology to calculate SUV between the two centers.

Radiation Therapy

Patients were treated with multiple high-energy photon fields in the prone position. The pre-treatment 18-FDG PET scan was fused with the treatment planning CT scan for improved delineation of the Gross Tumor Volume (GTV) for the boost volume. Patients initially received 45 Gy in 1.8 Gy fractions over 5 weeks to the pelvis with a boost dose to the GTV with a 3 cm margin for an additional 5.4-9 Gy for a total dose of 50.4-54 Gy. Some of the patients treated at FCCC were treated on an in-house clinical trial with intensity-modulated radiation therapy receiving 1.8 Gy to the pelvis and 2.2 Gy to the GTV concomitantly with capecitabine.

Chemotherapy

Chemotherapy regimens included 5-fluorouracil (5-Fu) by protracted venous infusion (PVI), 225 mg/m^2/day, capecitabine 825 mg/m^2/day, and 5-Fu (PVI 450mg/m^2/day) and Mitomycin-C (18mg during the first week). Patients could receive adjuvant chemotherapy after surgery at the discretion of the treating medical oncologist.

Statistical Analysis

Logistic regression was used to find significant predictors of residual disease.(3) Variables included in the model were T stage, overall stage, RT dose, days from RT to surgery, pre and post treatment SUV and % SUV decrease. A Cox proportional hazard model was used to analyze disease free survival.(4) The Wilcoxon test was used to determine association of pathologic T stage and post-treatment SUV and % SUV decrease.(5) Site of treatment, FCCC or RLCCC, was included as a covariate in the multivariable analysis to control for the possible data difference across the two sites.

This research was reviewed and approved by the FCCC and RLCCC Institutional Review Boards.

Results

Sixty patients with adenocarcinoma of the rectum underwent pre-operative chemoradiation prior to surgery. Seven patients were removed from the study due to the sparse distributions of certain clinical characteristics due to outliers in the investigated variables. The analysis was performed with the patients in the study but the results were the same and to provide a more homogenous group, the outliers were excluded from the analysis. Therefore, fifty-three patients comprise the study population for this analysis. Table 1 lists the patient characteristics by site of treatment. Patients treated at RLCCC had lower stage cancers compared to FCCC, p=0.006. Although median RT dose was not different between the two sites, the mean RT dose was higher for patients treated at FCCC, 51.9 Gy (stddev=2.3) compared to 49.9 Gy (stddev=1.6), p=0.008. Patients treated at FCCC had a higher pre-op SUV, 10.1 (stddev=6.6), compared to 8 (stddev=2.4) at RLCCC, p=0.06. Patients treated at FCCC had a shorter time interval between the end of RT until the post-chemoradiation PET scan, 27 days (stddev=11), compared to patients treated at RLCCC, 32 days (stddev=10) p=0.02. Conversely, patients treated at

RLCCC had a longer time from the end of RT until surgery, 74 (stddev=10) vs. 53 days (stddev=19), p<0.0001.

Patient characteristics as a function of residual tumor are listed in Table 2. Pathologic complete response was defined as ypT0N0. A trend exists for a greater % SUV decrease in patients having a pathologic complete response (pCR) compared to patients without a pCR, p=0.08.

Table 3 lists post-treatment SUV and %SUV decrease by pathologic T stage. Between group comparisons are difficult because of the small numbers within each group but a pattern of higher post-treatment SUV (p=0.24) and lower %SUV decrease (p=0.37) emerges for the higher stage tumors. As in comparison, there is no apparent technical difference in the methodology to calculate SUV between the two centers by two major manufactures of PET/CT scanner. Therefore the results are compatible to be in the same group for analysis, no adverse effects are noted to impact the results.

Although PET scans are 95% sensitive in determining when lymph nodes do not contain tumor, the test is not specific (17%) with 10 patients having lymph nodes found to contain tumor at the time of surgery with a post-chemoradiation PET scan interpreted as negative. A greater, but not statistically significant %SUV decrease was noted in the primary tumor, however, in pN0 disease, −61%, compared to pN1 or pN2 disease, −48% and −44% respectively.

The median follow-up of all patients was 31 months (range: 6-70). The median follow-up for alive patients is 35 months (range: 6-70) while median follow-up for dead patients is 12 months (range: 7-58). Forty-seven patients were without evidence of recurrence (NED) at the time of the last follow-up with 6 patients developing metastatic disease. Two patients have not undergone surgery at the time of the writing of this manuscript. One patient with a low lying tumor refused an abdominoperineal resection and underwent further chemotherapy. She has had endoscopic evaluations as well as negative biopsies on two occasions. She has been classified NED. The other patient with advanced Parkinson's disease was diagnosed with a well differentiated papillary thyroid cancer as a result of the post-treatment PET scan and underwent thyroidectomy. He refused surgery and is without evidence disease at the time of the last follow-up.

A trend existed for %SUV decrease to be predictive of pCR on univariate analysis, p=0.08 (Table 2), and post-treatment SUV to be predictive of pCR on multivariate analysis, p=0.07 (Table 5). None of the clinical or PET scan variables were able to predict for disease-free survival (Table 6). Days RT to surgery was not correlated with residual tumor (P=0.17, Wilcoxon test), nor with % suv decrease (P=0.88, Spearman correlation). Days from the end of RT to PET were also not predictive.

Table 4 shows post-treatment SUV and % SUV decrease by pathologic stage. A non-significant trend in mean post-treatment SUV exists between p0 (complete pathologic response) and stages pIIIB, p=0.08.

Discussion

The literature is mixed on the ability of 18-FDG PET to predict response to neoadjuvant treatment in patients with rectal cancer. The majority of studies have reported post-treatment SUV to be lower than pre-treatment scans but post-treatment SUV was not found to correlate with pCR. Calvo et al evaluated the ability of 18-FDG PET to detect tumor changes induced by pre-operative chemoradiation.(6) A SUVmax value ≥ 6 after surgery allowed a discrimination of 3-year survival but the degree of rectal cancer response, microscopic versus macroscopic, was not associated with SUVmax differences. Wieder et al., using 11-C-methyl-L-methionine, also noted a response in PET scans to chemoradiation but the degree of response

was not correlated with histopathologic change.(7) Oku, et al. did not find a statistically significant difference between groups with presence or absence of microscopic residual disease after treatment with chemoradiation in pre-treatment, post-treatment or a ratio of pre to post-treatment SUV.(8) Amthauer et al. also reported a statistically significant different in SUV between responder and non-responders but did not report a correlation between SUV and pCR.(9) Denecke et al also reported a significant difference in mean SUV reduction between responder and non-responders but did not evaluate pCR.(10) This may be in part to only a relatively low 5% pCR rate. Guillem et al. reported a correlation between PET response and pathologic response but did not report pCR rates.(11,12) Capirici et al reported a 35% pCR rate for 81 patients undergoing pre-operative chemoradiation, with 18-FDG PET correctly predicting pCR in 22 of 28 patients experiencing a pCR.(13) The high pCR rate may be in part to the longer time interval, 8-9 weeks, between the end of treatment and surgery.

Time interval between the end of radiation and surgery and time interval from the end of RT to post-treatment PET scan are two variables not previously investigated which could affect the ability of PET scans to predict pCR. Longer time interval between the end of treatment and surgery has been shown to increase pCR. Moore et al showed a trend to increased pCR and down-staging with increased time in between the completion of treatment and surgery.(14) None of the studied variables were associated with disease-free survival in univariate or multi-variable analysis.

A noninvasive method of determining the presence of residual disease after pre-operative chemoradiation could lead to patient selection for minimally invasive surgical approaches. Habr-Gama reported on 265 patients treated with pre-operative chemoradiation, 71 of whom had a complete clinical response to chemoradiation and were observed without going to immediate surgery.(15) Endorectal recurrence occurred in 2 patients, both of whom were successfully salvaged. In addition, the American College of Surgeons Oncology Group (ACOSOG) is currently investigating pre-operative chemoradiation and limited surgery in patients with uT2N0 tumors (Trial Z6041). Patients have the tumor tattooed prior to therapy and undergo chemoradiation and local excision. They are observed if the final pathology at the time of local excision is ≤ pT2 and go onto radical resection if the tumor is pT3. The use of % SUV reduction in the evaluation of treatment response could be incorporated into future trials evaluating limited surgical resection after pre-operative chemoradiation.

18-FDG PET scans were not successful, however, in determining malignant lymphadenopathy after pre-operative chemoradiation. The specificity was very low, 17%, in determining N+ disease. The % SUV decrease was <50% in patients with positive lymph nodes, pathologic stage III, compared to >50% SUV decrease in patients without involvement of lymph nodes. In an update of their original study, Capirci et al concluded identification of a subgroup of patients having a good response to chemoradiation could lead to a conservative surgical approach.(16) They, however did not mention the ability of PET scans to identify malignant lymphadenopathy. Cascini et al also did not mention the ability of PET scans to identify malignant lymphadenopathy found in 9 of 13 patients.(17)

This is the first study evaluating the ability of post-treatment SUV and %SUV decrease to predict pCR in patients with adenocarcinoma of the rectum receiving pre-operative chemoradiation and correlating these parameters with pT and overall stage. This study also identified the weakness of PET scans in detecting malignant lymphadenopathy after pre-operative chemoradiotherapy. This study, however, is limited by being a retrospective study open to all treatment related biases wtih relatively small numbers, as all of these studies have been, but a trend emerged for post-treatment SUV to predict pCR. The usefulness of 18-FDG PET in the management of patients with adenocarcinoma of the rectum needs to be evaluated in future trials and these data can be used to make sample size calculations for an adequately

powered follow-up study. The data we present can be used to inform the design of an adequately powered follow-up study, to help define the usefulness of 18-FDG PET in the management of patients with adenocarcinoma of the rectum. To test a significant difference with a 80% power in mean post-op SUV or % SUV decrease between the residual tumor groups, we need 60 patients per group, that is to say, we need enroll 45 more non-residual tumor patients and 25 more residual tumor patients.

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Table 1

Patient Characteristics by Site of Treatment

	FCCC	RLCCC	Pvalue*
Patients	41	12	
Ultrasound T-stage			
T3	37	12	0.33
T4	3	0	
Overall Stage			
IIA	9	7	0.15
IIB	2	0	
IIIA	1	0	
IIIB	25	5	
IIIC	4	0	
Chemotherapy			<0.0001
5-Fu 220 mg/m^2	1	0	
5-Fu 225 mg/m^2	29	10	
5-Fu 1000mg/m^2	1	0	
Capecitabine 825 mg/m^2	10	0	
5-Fu and Mitomycin C	0	2	
Median RT dose	50.4 Gy (45-55)	50.4 Gy (45-50.4 Gy)	0.0044
Median Pre-op SUV	10.1 (3.6-37)	8 (3.1-11.4)	0.06
Median Post-CRT	3.5 (.5-10)	3.9 (.7-7.5)	0.85
%SUV Decrease	−65% (0- −95%)	−54% (−17-76%)	0.16
Days RT-PET	27 (4-50)	32 (27-58)	0.02
Days RT-Surgery	53 (25-133)	74 (54-91)	<0.0001
pCR	11/40 (28%)	5/12 (42%)	0.35

FCCC-Fox Chase Cancer Center, RLCCC-Robert Lurie Comprehensive Cancer Center, 5-Fu- 5-Fluorouraci, CRT- Chemoradiation, pCR- Pathologic Complete Response; RT-Radiation;

*Wilcoxon test for continuous variables, and Chi-square test for discrete variables

Table 2

Residual Tumor status by Clinical Characteristics

	Residual	**Tumor**	**Pvalue***
	No	**Yes**	
Ultrasound T-Stage			0.88
T3	14	34	
T4	1	2	
Overall Stage			0.77
IIA	5	11	
IIB	1	1	
IIIA	0	1	
IIIB	9	20	
IIIC	1	3	
Mean Pre-op SUV	10.8 (5.6)**	10.7 (6.4)	0.71
Mean Post-CRT SUV	3.2 (1.5)	4.2 (2.3)	0.18
%SUV Decrease	−67% (18.8)	−55% (24.4)	0.08
Days RT-Surgery	65 (22)	57 (18)	0.17
RT Dose	51.05 Gy (1.5)	51.65 Gy (2.6)	0.16
Days RT-Pet	29 (11)	29 (12)	0.87

CRT-Chemoradiation

*Wilcoxon test for continuous variables, and Chi-square test for discrete variables

**()-Standard deviation

Pre-op- Preoperative; RT-Radiation;

Table 3

Post-treatment SUV and %SUV Decrease by pT

	Mean Post-treatment SUV	Mean % SUV Decrease
pT0 (n=16)	3.2 (1.5)	−67% (18.8)
pT1 (n=6)	3.2 (2.5)	−57% (26.5)
pT2 (n=12)	4.0 (1.6)	−57% (23.1)
pT3 (n=18)	4.7 (2.6)	−54% (25.9)

()-Standard deviation

Table 4

Post-treatment SUV and %SUV Decrease by pathologic stage

	Mean Post-Treatment SUV	Mean %SUV Decrease
p0 (n=16)	3.2 (1.5)	−67% (18.8)
pI (n=15)	3.8 (2.0)	−58% (22.2)
pIIA (n=11)	3.9 (1.9)	−59% (22.9)
pIIIA (n=3)	3.7 (1.7)	−48% (33.6)
pIIIB (n=6)	6.2 (3.4)	−44% (32.5)
pIIIC (n=1)	4.4	−49.4%

()-Standard deviation

Table 5

Multivariable analysis (MVA) of residual tumor status*

Variable	Odds ratios	95% CI	p**
Post tx SUV (cont.)	1.4	0.97-2.2	0.07
Endo stage T3 vs T4	1.8	0.13-25.9	0.7
Stage II vs III	1.3	0.2-6.6	0.8
RT dose (cont.)	1.0	1.0-1.004	0.5
Days from RT to surg (cont.)	0.97	0.93-1.01	0.1
Days from RT to PET (cont.)	1.0	0.96-1.1	0.4

* Probability modeled: residual tumor status=Yes

** logistic regression

cont.-continuous variable; Post-tx-Post-treatment; Endo-Endoscopic; RT-Radiation; surg-Surgery;

Table 6

Multivariable analysis (MVA) of disease free survival

Variable	Hazard ratios	95% CI	P*
Post tx SUV (cont.)	1.1	0.8-1.6	0.5
Endo stage T3 vs T4	-	-	-
Stage II vs III	2.5	0.4-17.2	0.3
RT dose (cont.)	1.0	1.0-1.005	0.4
Days from RT to surg (cont.)	1.0	0.96-1.06	0.7
Days from RT to PET (cont.)	0.96	0.86-1.07	0.4
Pre tx SUV (cont.)	1.0	0.9-1.1	0.9
Endo stage T3 vs T4	-	-	-
Stage II vs III	2.9	0.4-18.5	0.3
RT dose (cont.)	1.0	1.0-1.005	0.4
Days from RT to surg (cont.)	1.0	0.96-1.06	0.8
Days from RT to PET (cont.)	0.95	0.86-1.05	0.4
% SUV decrease (cont.)	1.0	0.98-1.04	0.5
Endo stage T3 vs T4	-	-	-
Stage II vs III	2.6	0.4-17.4	0.3
RT dose (cont.)	1.0	1.0-1.005	0.4
Days from RT to surg (cont.)	1.0	1.0-1.06	0.7
Days from RT to PET (cont.)	1.0	0.86-1.06	0.4

*Cox proportional hazard model.

Cont.-continuous variable; Endo-Endoscopic; Surg-surgery; Pre-Tx-Pre-treatment; Post-tx-Post-treatment; RT-Radiation;