Original Article

Early prediction of residual disease after neoadjuvant chemoradiotherapy and cetuximab for locally advanced esophageal cancer using ^{18}F-FDG PET-CT imaging: a prospective cohort study

Baruch Brenner[1,2], Yulia Kundel[1], Zoya Cohen[3]^, Hadar Brand[1], Noa Gordon[1], Aaron Sulkes[1,2], Sara Morgenstern[4], Nikolai Menasherov[5], Hanoch Kashtan[2,6], David Groshar[2,7], Liran Domachevsky[2,7,8#], Hanna Bernstine[2,7#]

[1]Institute of Oncology, Davidoff Cancer Center, Beilinson Hospital, Rabin Medical Center, Petach Tiqva, Israel; [2]Sackler Faculty of Medicine, Tel-Aviv University, Ramat Aviv, Tel-Aviv, Israel; [3]Felsenstein Medical Research Center, Beilinson Hospital, Rabin Medical Center, Petach Tiqva, Israel; [4]Institute of Pathology, Beilinson Hospital, Rabin Medical Center, Petach Tiqva, Israel; [5]Department of Surgery A, Beilinson Hospital, Rabin Medical Center, Petach Tiqva, Israel; [6]Departments of Surgery A and B, Beilinson Hospital, Rabin Medical Center, Petach Tiqva, Israel; [7]Department of Nuclear Medicine, Rabin Medical Center, Beilinson Hospital, Petach Tiqva, Israel; [8]Department of Nuclear Medicine, The Chaim Sheba Medical Center, Tel Hashomer, Israel

Contributions: (I) Conception and design: B Brenner; (II) Administrative support: B Brenner, H Brand; (III) Provision of study materials or patients: B Brenner, Y Kundel; N Gordon, S Morgenstern, N Menasherov, H Kashtan, D Groshar, L Domachevsky; (IV) Collection and assembly of data: B Brenner, Y Kundel; N Gordon, S Morgenstern, N Menasherov, H Kashtan, D Groshar, L Domachevsky, H Brand; (V) Data analysis and interpretation: Z Cohen, H Brand, N Gordon; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this manuscript as senior authors.

Correspondence to: Baruch Brenner. Beilinson Hospital, Rabin Medical Center, Jabotinsky St. 39, Petach Tiqva 49100, Israel. Email: brennerb@clalit.org.il.

Background: Previous studies in locally advanced esophageal cancer (LAEC) suggested that a change in the tumor's metabolic response, i.e., decrease of its interim ^{18}F-FDG uptake compared with baseline, may predict histopathological response. We evaluated the possible predictive correlation between various PET-CT and histopathological parameters following a neoadjuvant biological-containing chemoradiotherapy (CRT) regimen.

Methods: Patients with resectable LAEC received neoadjuvant cisplatin/5-fluorouracil-based CRT and cetuximab following one cycle of induction chemotherapy and cetuximab. Changes in maximum and mean standardized uptake values (ΔSUV-max and ΔSUV-mean, respectively) and metabolic tumor volume (ΔMTV), measured by PET-CT at baseline and 2 weeks after the onset of treatment, were compared with histopathological findings at surgery. Histopathological response was defined by tumor regression grade (TRG), pathological complete response (pCR) and microscopic or macroscopic residual disease (RD).

Results: Of 18 patients, 13 (72%) with adenocarcinoma (AC) and 5 (28%) with squamous cell carcinoma (SCC), were included. None of the changes in the parameters of PET was associated with pCR; only ΔSUV-mean was associated with TRG in the AC cohort. In contrast, both ΔSUV-mean% and ΔSUV-max% were significantly associated with RD, both in the whole cohort and in the AC cohort. Changes in FDG-uptake predicted RD2 at surgery: only patients with less than 13% decrease in SUV-mean% or less than 29% decrease in SUV-max% had RD2, while all patients with RD0 or RD1 had greater reductions [100% specificity and 100% positive predictive value (PPV)].

Conclusions: Changes in ΔSUV-max and ΔSUV-mean after two weeks of onset of cetuximab-based neoadjuvant chemotherapy for LAEC may predict macroscopic RD but not TRG or pCR at surgery.

^ ORCID: 0000-0002-1284-3035.

Keywords: Locally advanced esophageal cancer (LAEC); induction chemotherapy; neoadjuvant chemoradiotherapy; PET-CT; prediction of response; cetuximab

Submitted Apr 11, 2022. Accepted for publication Sep 14, 2022.
doi: 10.21037/jgo-22-352
View this article at: https://dx.doi.org/10.21037/jgo-22-352

Introduction

The sixth cause of cancer-related death in the world is esophageal cancer (EC) (1). Despite extensive research and global attempts to develop new treatment strategies, the overall 5-year survival rates remain poor and stand at only ~10% (2).

The standard approach for locally advanced esophageal cancer (LAEC) is preoperative (neoadjuvant) chemoradiotherapy (nCRT) with subsequent surgery. Chemotherapy usually includes a platinum compound and either 5-fluorouracil (5-FU) or a taxane (3-7).

Histopathological response is generally used for evaluation of treatment efficacy, serving as a surrogate for patients' long-term outcome; however, it can be assessed only upon surgery, when the neoadjuvant treatment has already been completed. Therefore, efforts are made to develop methods for its prediction as early as possible that will allow discriminating between responders and non-responders. Such tools may enable clinicians to switch the neoadjuvant regimen or advance patients to surgery by shortening the preoperative treatment.

18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)-computerized tomography (CT) scan done early in the process of treatment is one of the promising strategies for the prediction of histopathological response. Indeed, several studies have attempted to predict histopathological response in LAEC based upon changes in ^{18}F-FDG-PET values between baseline and either intra- or post-nCRT, utilizing the potentially high sensitivity and specificity of this modality. However, these studies vary greatly in the specific PET-CT parameters tested, cut-off values, histological response criteria, tumor histology (SCC or AC), and nCRT regimen used, with or without an induction phase (8-14). Consequently, the results remain controversial and require additional investigations, especially with new experimental nCRT regimens. These novel regimens integrate multiple targeted drugs, including biological agents such as cetuximab and panitumumab, the anti-epidermal growth factor receptor (EGFR) monoclonal antibodies, and the immune checkpoint inhibitors nivolumab and pembrolizumab (15). We have recently reported the prospective phase I/II trial results on the cetuximab addition to standard nCRT for LAEC (16). Of 64 patients included in the study, 55 underwent surgery, with a pathological complete response (pCR) rate of 33%. At a later stage of the study, we included also an investigational early ^{18}F-FDG-PET-CT, performed two weeks after the initiation of induction chemotherapy and cetuximab, in order to examine whether a change in this PET-CT from baseline can indeed predict histopathological response at surgery. The aims of this investigation were to confirm previous results, to evaluate the optimal PET-CT and histopathological parameters to be used, and most importantly, to test whether the predictive role of early PET-CT in this setup holds true also in the era of biological therapies. We present the following article in accordance with the STARD reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-352/rc).

Methods

Study design

As described above, this prospective cohort investigation was a sub-study of the main therapeutic clinical trial, which we have previously reported (16). This sub-study included only those patients enrolled once the main study's protocol was amended to include also interim PET-CT analysis.

Patients

Eligible patients had untreated, potentially resectable histologically confirmed locally advanced [$T_{2-3}N_{0-1}M_{0-1a}$ according to the 1997 American Joint Committee on Cancer criteria (AJCC) 7th edition (17)] AC or SCC of the middle or distal esophagus or gastro-esophageal junction (GEJ). The disease extent was evaluated by physical examination, esophagogastroendoscopy, endoscopic ultrasound (EUS) and PET-CT scan. Patients had to

have intact hematological, renal and liver functions and an Eastern Cooperative Oncology Group (ECOG) performance status 0–1. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Institutional review board of Rabin Medical Center approved the study (No. 3907) and all patients signed the informed consent.

Treatment protocol

Treatment involved an induction phase and nCRT with subsequent surgery as described elsewhere (16). Briefly, the induction phase lasted 4 weeks and consisted of one chemotherapy cycle [cisplatin 100 mg/m^2 IV, day 1 and 5-FU 1,000 mg/m^2/d as a continuous infusion (CI), days 1–5] and 4 weekly cetuximab injections (400 mg/m^2 followed by 3 injections of 250 mg/m^2 each); nCRT consisted of cisplatin 75 mg/m^2 IV, days 1 and 29, 5-FU 1,000 mg/m^2/d CI, days 1–4 and 29–32 of radiotherapy, weekly cetuximab 250 mg/m^2, and simultaneous radiotherapy (1.8 Gy/d in 5 weekly fractions, for a total of 50.4 Gy dose in 28 fractions). Surgery was scheduled 6–8 weeks after nCRT.

^{18}FDG-PET/CT protocol, imaging, and analysis

Patients underwent whole-body ^{18}FDG-PET/CT as described previously (18) at baseline (within 28 days prior to treatment) and two weeks after the initiation of induction chemotherapy (timing of this second PET-CT had 24-hour margins, i.e., scans were performed 13–15 days after treatment onset). The second PET-CT scans were all performed at Rabin Medical Center (RMC). All patients fasted for a minimum of 4 hours before injection of ^{18}F-FDG. Preceding injection the blood glucose levels were confirmed to be below 200 mg/dL. Patients were required to ingest oral contrast fluid (300 mg Telebrix with 1,000 cc of water). Images were acquired 60 minutes later with an integrated PET/CT scanner (Discovery ST; GE Medical Systems, Milwaukee, Wis). Iodine contrast medium (Ultravist 300) was administered intravenously during CT scan to all patients except for those with a history of iodine allergy or impaired renal function, or patient refusal. Immediately after CT, PET was performed. The acquisition time for emission scans was 3–4 minutes per bed position with a one-section overlap. CT data was used for correction of attenuation. We used a standard iterative algorithm for images reconstruction. Image analysis was done visually and semi-quantitatively. Maximum standardized uptake value (SUV-max), mean standardized uptake value (SUV-mean) and metabolic tumor volume (MTV) were calculated for the target lesions at baseline and after two weeks of induction therapy. Difference between the two time points was depicted as the percentage of SUV-max reduction (ΔSUV-max), SUV-mean reduction (ΔSUV-mean) and MTV reduction (ΔMTV). An expert nuclear-medicine radiologist (HB) evaluated the PET/CT scans, blinded to any clinical information.

Surgery

Patients were restaged with gastroscopy, PET-CT and EUS before surgery. Surgery was planned 6–8 weeks after the end of nCRT. The kind of surgery was decided by the surgeon.

Histopathological evaluation of tumor response

A single expert pathologist (SM) who was blinded to the corresponding PET/CT results analyzed all surgical samples at the Institute of Pathology of RMC. Three parameters of response were examined: pathological complete response (pCR, binary parameter, yes/no); residual disease after surgery (RD; 0, no RD; 1, microscopic RD; and 2, macroscopic RD); and tumor regression grade (TRG) scored according to the College of American Pathologists system [modified Ryan scheme for tumor regression score (19)], as follows: 0—complete response, no viable cancer cells; 1—near complete response, single cells or rare small groups of cancer cells; 2—partial response, residual cancer with evident tumor regression, but more than single cells or rare small groups of cancer cells; and 3—poor or no response, extensive residual cancer with no evident tumor regression.

Statistical analysis

We utilized the Mann-Whitney test to discriminate between patients with pCR and those without and between responders and non-responders per TRG and RD regarding the change of SUV-max, SUV-mean and MTV values between baseline and two weeks PET-CTs. We used receiver operating characteristic (ROC) analysis to find a cutoff for the tests. Analyses were done two-sided at a 5% level of significance. As we planned to correlate changes in the SUV with a more extensive histological response, we assumed that a cutoff of >40% reduction in SUV-max may be able

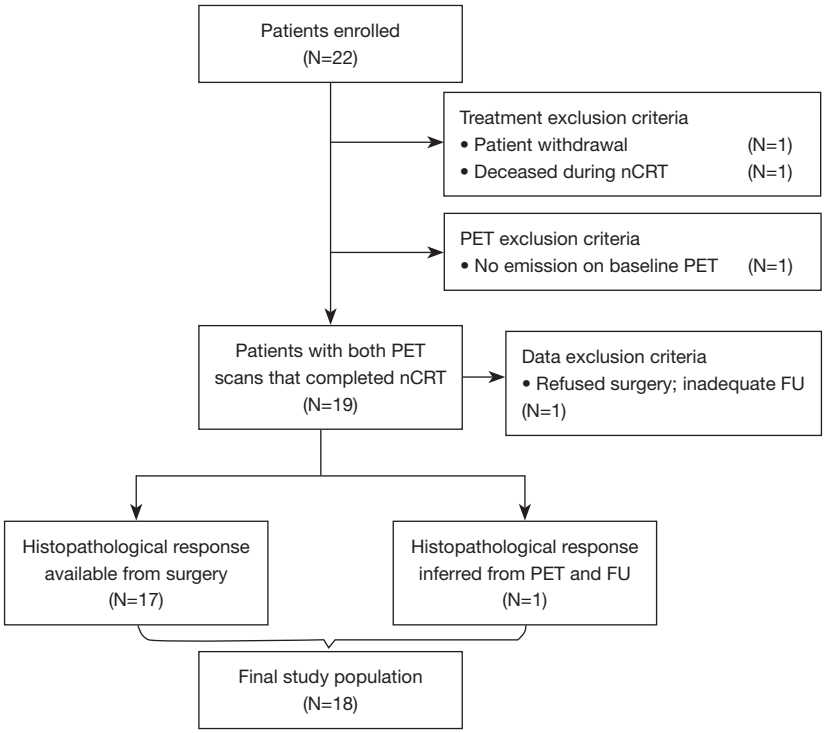


Figure 1 Patients enrollment chart. PET, positron emission tomography; nCRT, (neoadjuvant) chemoradiotherapy; FU, follow up.

Table 1 Patient and tumor characteristics at presentation (N=18)

Characteristic	Number	Valid %
Age, median [range] (years)	66 [52–76]	–
Gender (M/F)	13/5	72/28
Location (middle/lower/GEJ)	3/5/10	17/28/55
Histology (AC/SCC)	13/5	72/28
Grade (I/II/III)	3/10/5	17/55/28
T stage (T_1/T_2/T_3)	0/1/17	0/6/94
N stage (N_0/N_1)	6/12	33/67
M status (M_0/M_{1a})	17/1	94/6

M/F, male/female; GEJ, gastro-esophageal junction; AC, adenocarcinoma; SCC, squamous cell carcinoma; T, tumor; N, nodes; M, metastasis.

to differentiate responders from non-responders. Based on this assumption the minimal size of the sample required to achieve a 95% power level would be at least 16 patients. The data were analyzed by IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, United States).

Results

Patients

The prospective phase I/II trial, accruing 64 patients, was conducted at RMC, Beilinson Hospital, Israel, between October, 2012 and March, 2016. Of the 22 patients accrued to its PET-CT section reported here, 18 were evaluable. We excluded four patients from the analysis: 2 patients did not complete nCRT, 1 patient had a negative baseline PET-CT and 1 patient refused surgery and his PET-CT and follow up did not allow accurate response evaluation. Of the 18 evaluable patients, one patient did not undergo surgery and his response to nCRT was evaluated only clinically, by PET-CT, endoscopy and long-term follow up (*Figure 1*).

Characteristics of patients and tumors at presentation are summarized in *Table 1*. Patients (72% males; median age 66) had relatively advanced disease: 94% had T_3 tumors, 67% had nodal involvement (N_1); 1 patient (6%) had M_{1a} disease. AC was present in 72% of cases and SCC in 28%. Most tumors were located in the GEJ (55%) or the distal esophagus (28%).

Table 2 Treatment details and results (N=18)

Treatment/results[a]	Number	Valid %
Radiotherapy dose (Gy)		
Median	50.4	
Patients receiving 50.4 Gy	18	100
Chemotherapy/biotherapy	18	100
Interval between nCRT and surgery (days)[b], median [range]	68 [46–154]	–
Surgery	17	94
R0[b]	17	100
Pathological TNM stage[b]		
0	5	29
I	5	29
II	3	18
III	1	6
IV	3	18
TRG		
0	6	35
1	6	35
2	5	30
RD[a]		
0	5	28
1	6	33
2	7	39
pCR[a]		
Yes	5	28
No	13	72

[a], all patients; [b], operated patients (N=17). nCRT, neoadjuvant chemoradiation; R0, complete surgical resection; TNM, tumor, nodes, metastasis; TRG, tumor regression grade; RD, residual disease; pCR, pathological complete response.

Treatment

Treatment details and results are described in *Table 2*. All patients received the induction phase as planned, 11 patients got full planned nCRT and 7 patients were given reduced doses of cisplatin and/or 5-FU in cycles 2 and/or 3, due to toxicity in the previous one. All patients received all planned doses of cetuximab.

Following nCRT, 17 patients underwent surgery within a median of 68 days (range, 46–154 days) from the completion of treatment. One patient was operated at another hospital and histopathological data lack TRG. Following treatment, 5 of 17 operated patients (29%) had complete disappearance of their primary tumor (pT0), 11 (65%) had no lymph node involvement (pN0), and 4 (24%) achieved pCR; all available specimens had TRG 0–2, grades that represent a histopathological response. Four operated patients (24%) had no residual disease (RD0), 6 (35%) achieved microscopic RD (RD1) and the remaining 7 (41%) had macroscopic (RD2) disease. Complete (R0) resection was achieved in all operated patients. One patient refused surgery; he had complete regression of disease in the esophagus and the regional lymph nodes at the post-nCRT PET-CT, had no evidence of disease at 3 years of follow up, and was therefore considered to have achieved pCR, RD0 and TRG0.

PET-CT evaluation

Table 3 presents data on individual patients' metabolic and histopathological responses. The values of median SUV-max at baseline and at the second scan were 8.3 (range, 3.5–18.2) and 5.2 (range, 0–7.9), respectively. The corresponding values of median SUV-mean were 4 (range, 2–10.9) and 3.3 (range, 0–4.7), respectively. Reduction in uptake of FDG was observed in 15 (83%) of the 18 patients, with maximum decrease of 100% in both SUV-mean and SUV-max. In 3 patients (17%), SUV-max and SUV-mean values increased, with a maximum increase of 106% and 100% from baseline, respectively. Representative PET-CT analysis is shown in *Figure 2*.

Association between metabolic and histopathological response

To evaluate the association between histopathological response and changes in metabolic values after two weeks of induction chemotherapy, we defined groups of patients according to various histopathological parameters (RD, TRG or pCR) and compared ΔSUV-max, ΔSUV-mean and ΔMTV values between them, in the whole group and in the AC cohort (*Table 4*). The SCC cohort was not analyzed separately because of the small number of patients. A statistically significant difference was found in ΔSUV-

Table 3 Individual patients' metabolic and histopathological responses

Patient number	PET parameters								Response		
	SUV-max baseline	SUV-max week 2	SUV-mean baseline	SUV-mean week 2	ΔSUV-max	ΔSUV-mean	ΔSUV-max %	ΔSUV-mean %	TRG	pCR	RD
1	11.8	5.1	6.7	3.4	–6.7	–3.3	–0.57	–0.49	1	No	1
2	9.3	4.6	5.1	2.9	–4.7	–2.2	–0.51	–0.43	2	No	2
3	3.7	5.7	2.4	4.1	2	1.7	0.54	0.71	2	No	2
4	6.5	5.1	3.6	3.4	–1.4	–0.2	–0.22	–0.06	2	No	2
5	10.7	5.3	6.1	3.2	–5.4	–2.9	–0.50	–0.48	2	No	2
6	18.2	6.2	10.9	3.6	–12	–7.3	–0.66	–0.67	0	Yes	0
7	3.5	7.2	2	4	3.7	2	1.06	1.00	1	No	2
8	7.3	4	4.1	2.4	–3.3	–1.7	–0.45	–0.41	0	Yes	0
9	10.2	4.7	6	2.8	–5.5	–3.2	–0.54	–0.53	1	No	1
10	4.9	0	2.6	0	–4.9	–2.6	–1.00	–1.00	1	No	1
11	7	7.1	3.8	4.2	0.1	0.4	0.01	0.11	NA	No	2
12	12.9	6.80	7.7	4.1	–6.1	–3.6	–0.47	–0.47	1	No	1
13	5.2	0	2.9	0	–5.2	–2.9	–1.00	–1.00	0	Yes	0
14	5.3	0	3	0	–5.3	–3	–1.00	–1.00	1	No	1
15	11.2	7.9	7.5	4.7	–3.3	–2.8	–0.29	–0.37	0	No	1
16	4.4	0	2.6	0	–4.4	–2.6	–1.00	–1.00	2	No	2
17	15.6	6.2	3.9	3.4	–9.4	–0.5	–0.6	–0.13	0	Yes	0
18	15.3	5.7	9.5	3.2	–9.6	–6.3	–063	–0.66	0	Yes	0

PET, positron emission tomography; SUV-max, maximum standardized uptake value; SUV-mean, mean standardized uptake value; TRG, tumor regression grade; pCR, pathological complete response; RD, residual disease; NA, not available.

mean% between patients with no RD (RD0) or microscopic RD (RD1) and those with macroscopic RD (RD2): median –53% *vs.* –6%, P=0.044, in the whole cohort, and median –60% *vs.* –6%, P=0.035, in the AC cohort. ΔSUV-max% also differed between RD groups: median –60% (RD0,1) *vs.* –22% (RD2), P=0.035, in the whole cohort and –61.5% (RD0,1) *vs.* –22% (RD2), P=0.051, in the AC cohort (*Figure 3*).

It should be noted that all five SCC patients achieved RD0 or RD1. Aside of RD, none of the changes in PET parameters were associated with the two other histopathological endpoints, i.e., TRG or pCR, in the whole cohort, while in the AC cohort, ΔSUV-mean was associated with TRG: median –3.2 (TRG0,1) *vs.* –2.2 (TRG2), P=0.048; however, the percentage of change in SUV-mean (ΔSUV-mean%) did not show significant correlation with TRG (*Table 4*).

As can be expected from the above, the distribution of SUV-mean and SUV-max absolute values at baseline and after 2 weeks of treatment demonstrates minimal changes in the RD2 subgroup. On the other hand, the RD0,1 subgroup displayed significant (P<0.05 for all comparisons) reduction in both metabolic parameters in the whole cohort and in the AC cohort (*Figure 4*).

Prediction of response

ROC analysis was used for the determination of the cut-off values of ΔSUV-mean% and ΔSUV-max% that would accurately predict RD2. The area under the curve was 0.79 (95% CI: 0.53–1.04) for ΔSUV-mean% and 0.8 (95% CI: 0.55–1.05) for ΔSUV-max%.

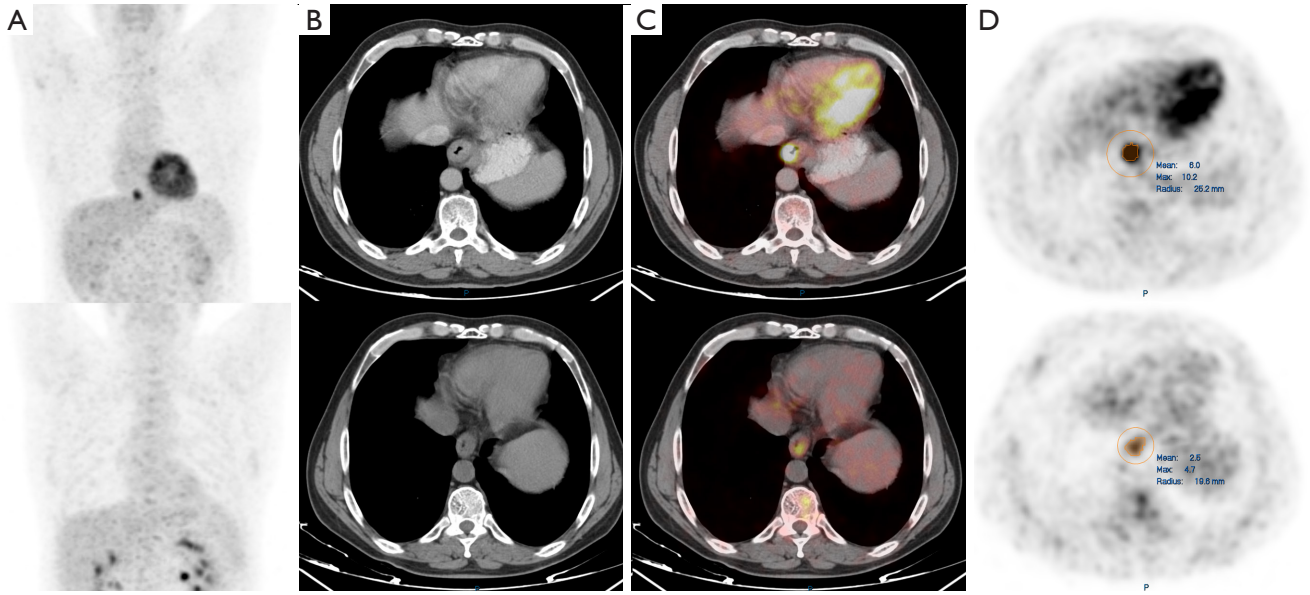


Figure 2 A 64-year-old man with biopsy-proven esophageal cancer. Upper row: (A) PET maximum-intensity-projection image shows abnormal uptake in the distal esophagus. (B) Axial CT image tumor in distal esophagus. (C) Fused PET/CT image shows abnormal increased uptake of ^{18}F-FDG in distal esophagus. (D) Axial PET images showing the volume of interest around the tumor with SUVmax of 10.2. PET, positron emission tomography; CT, computerized tomography; ^{18}F-FDG, 18-fluorodeoxyglucose; SUV-max, maximum standardized uptake value.

According to this analysis, a 13% decrease or more in SUV-mean% predicted all the patients in the whole cohort with RD0 or RD1, while a reduction in ΔSUV-mean% of less than 13% predicted only patients with RD2. This cut off provides an accuracy of 83%, 100% positive predictive value (PPV) and 79% negative predictive value (NPV), a sensitivity of 57% (95% CI: 18–90%), with 100% (95% CI: 59–100%) specificity, in the whole cohort. Similar prediction values were achieved with a 29% cutoff for ΔSUV-max% (*Figure 5A*).

In the AC cohort, the area under the curve for the ROC analysis was 0.86 (95% CI: 0.62–1.1) for ΔSUV-mean% and 0.83 (95% CI: 0.58–1.08) for ΔSUV-max%. A reduction in ΔSUV-mean% of 47% or more predicted all the patients with RD0 or RD1, while a reduction in ΔSUV-mean% of less than 47% will predict only patients with RD2. This cut-off provides an accuracy of 85%, 100% PPV and 75% NPV, a sensitivity of 71% (95% CI: 29–96%), with 100% (95% CI: 54–100%) specificity. Similarly, a cut-off of 47% for ΔSUV-max% provided 77% accuracy, 67% PPV and 67% NPV, a sensitivity of 57% (95% CI: 18–90%) with 100% (95% CI: 54–100%) specificity (*Figure 5B*).

Other histopathological parameters were not analyzed in a similar way since no significant correlations were found between them and any metabolic response parameters.

Discussion

Our results in patients with LAEC, combining a biological agent with standard neoadjuvant chemotherapy, demonstrate that the decrease in metabolic uptake between baseline and interim (after 2 weeks of treatment) PET-CT scans can predict RD at surgery, both in the whole cohort, including SCC and AC histologies, and in the AC cohort; the decrease in both SUV-mean and SUV-max values could discriminate patients with RD0-1 from those with RD2. Moreover, the prediction of RD was associated with high specificity (100%) and PPV (100%). In contrast, neither TRG nor pCR correlated with changes in metabolic uptake in the whole cohort. Thus, in our study RD was found to be the best predictable histopathological parameter that correlates with changes in metabolic uptake.

To date, 14 studies have attempted to predict histopathological response in LAEC based upon changes in early metabolic parameters, mostly (in 11 studies) 2 weeks after the onset of treatment. However, none

Table 4 Correlation between histopathological responses and change in metabolic parameters in the whole and AC cohorts

Histopathologic parameter (group 1, group 2)	Metabolic parameter	Whole cohort (N=18)					AC cohort (N=13)				
		Group 1		Group 2		P	Group 1		Group 2		P
		N	Median	N	Median		N	Median	N	Median	
pCR (yes, no); similar to RD (0, 1+2)	ΔSUVmax	5	−9.4	13	−4.7	0.059	2	−8.6	11	−4.7	0.307
	ΔSUVmean	5	−2.9	13	−2.6	0.336	2	−5.1	11	−2.6	0.230
	ΔMTV	5	−4.7	11	−5.4	0.913	2	0.15	10	−3.9	0.364
	ΔSUVmax%	5	−63	13	−50	0.173	2	−83	11	−50	0.154
	ΔSUVmean%	5	−66	13	−47	0.443	2	−83.5	11	−47	0.154
	ΔMTV%	5	−60	11	−64	0.743	2	−24.5	10	−55	0.909
TRG (0, 1+2)	ΔSUVmax	6	−7.3	11	−4.9	0.256	2	−8.6	10	−5	0.364
	ΔSUVmean	6	−2.8	11	−2.6	0.462	2	−5.1	10	−2.7	0.273
	ΔMTV	5	−4.7	10	−3.9	1	2	0.15	9	−2.4	0.436
	ΔSUVmax%	6	−61.5	11	−51	0.525	2	−83	10	−50.5	0.182
	ΔSUVmean%	6	−53.7	11	−48	0.848	2	−83	10	−47.5	0.182
	ΔMTV%	5	−60	10	−55	0.853	2	−24.5	9	−46	0.909
TRG (0+1, 2)	ΔSUVmax	12	−5.4	5	−4.4	0.104	7	−5.5	5	−4.4	0.106
	ΔSUVmean	12	−2.9	5	−2.2	0.104	7	−3.2	5	−2.2	0.047
	ΔMTV	11	−4.7	4	−3.9	1	7	−0.4	4	−3.9	0.412
	ΔSUVmax%	12	−58.5	5	−50	0.328	7	−57	5	−50	0.432
	ΔSUVmean%	12	−51	5	−43	0.383	7	−53	5	−43	0.343
	ΔMTV%	11	−60	4	−60.5	0.571	7	−10	4	−60.5	0.412

SUV-max, maximum standardized uptake value; SUV-mean, mean standardized uptake value; MTV, metabolic tumor volume; pCR, pathological complete response; TRG, tumor regression grade; RD, residual disease; AC, adenocarcinoma.

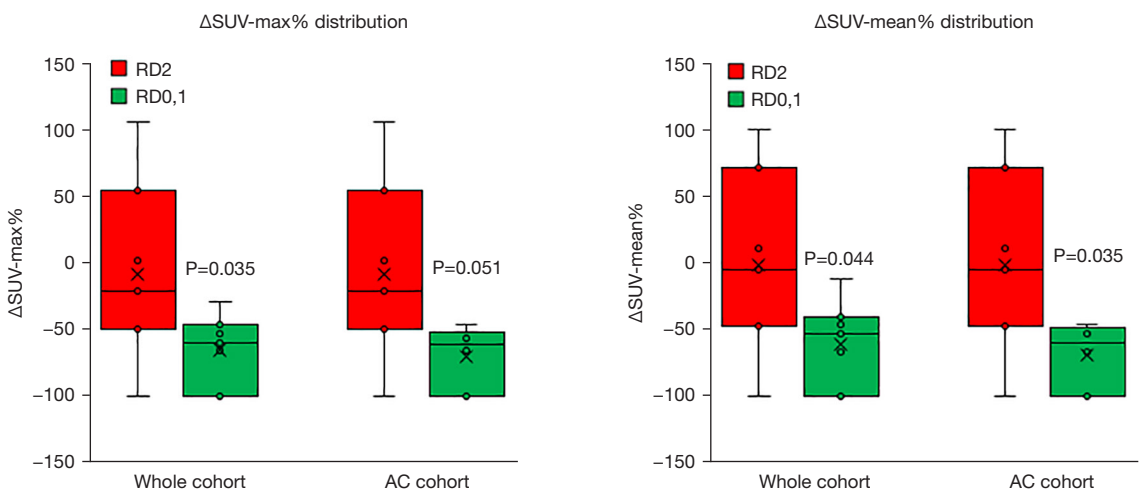


Figure 3 Distribution of ΔSUV-max% and ΔSUV-mean% values in RD0,1 and RD2 groups. Histopathological response was evaluated by presence or absence of no or microscopic RD (RD0,1) versus macroscopic RD (RD2); P values represent the significance of the difference between RD2 and RD0,1. SUV-max, maximum standardized uptake value; SUV-mean, mean standardized uptake value; RD, residual disease.

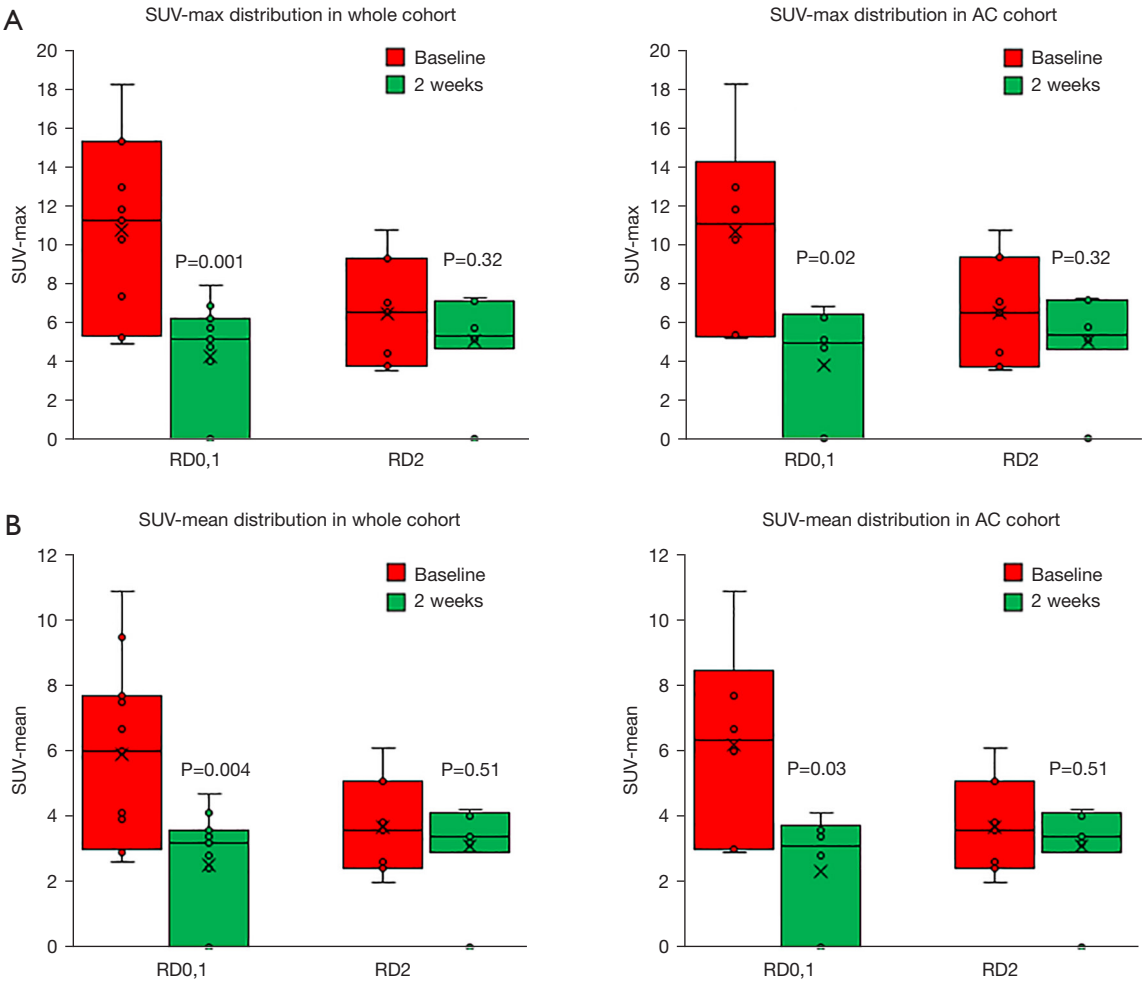
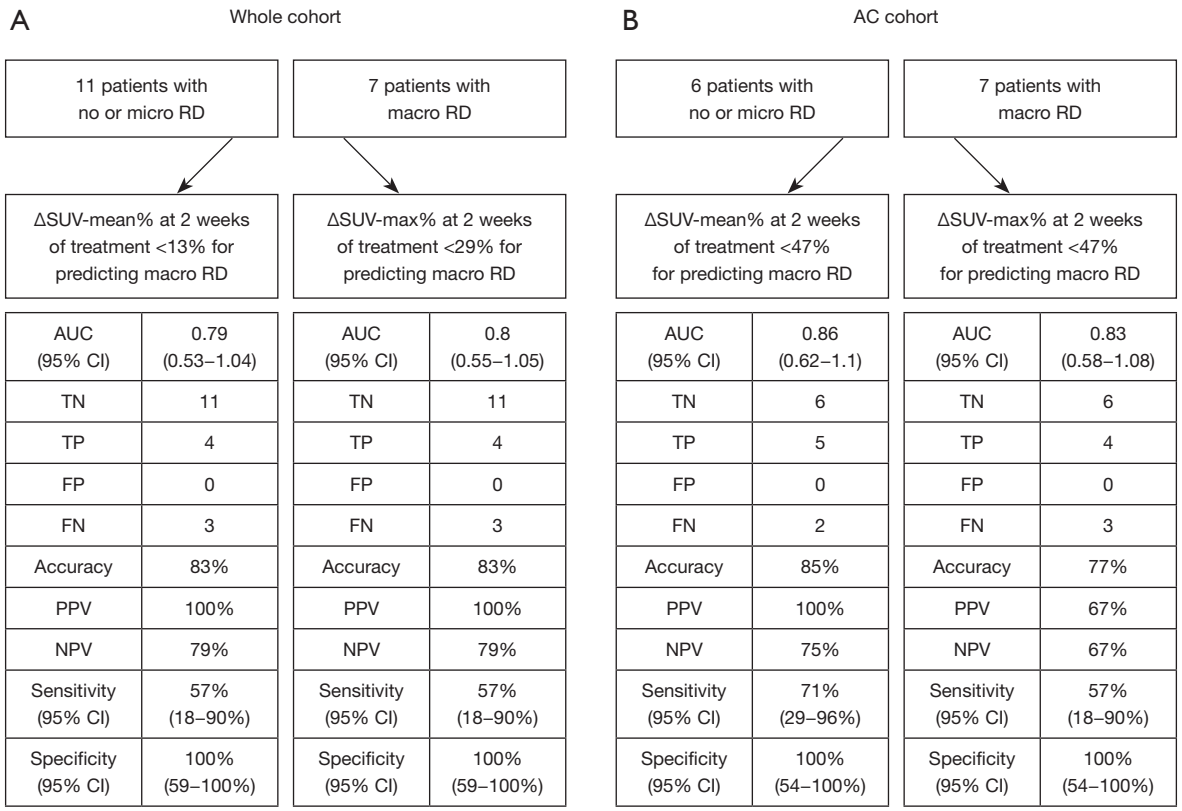


Figure 4 Distribution of SUV-max (A) and SUV-mean (B) absolute values at baseline and after 2 weeks of treatment in RD0,1 and RD2 groups. Histopathological response was evaluated by presence or absence of no or microscopic RD (RD0,1) versus macroscopic RD (RD2). P values represent the significance of change between baseline and 2 weeks values. SUV-max, maximum standardized uptake value; RD, residual disease; AC, adenocarcinoma; SUV-mean, mean standardized uptake value.

compared different histopathological parameters to find the most suitable one, and none evaluated the status of RD (9,11,13,20-30) (*Table 5*). Moreover, differences in analyzed metabolic parameters, histopathological end-points, treatment regimens and cut-off values make any comparison nearly impossible. However, 9 of these studies suggested that changes in early metabolic response, usually SUV-max and SUV-mean, may correlate with histopathological findings, usually pCR or TRG (9,11,21,23,25-29). Here we show that RD, tested for the first time, is probably the most suitable histopathological end-point for such predictions, and that changes in SUV-max and SUV-mean are perhaps the most reliable metabolic predictive parameters.

Being RD the best correlate with early metabolic changes during nCRT, if true, still does not necessarily establish its clinical significance as a robust predictive factor for the subsequent course of the disease. Indeed, most studies evaluated the correlation between early metabolic response to histopathological parameters that are considered reliable surrogates to patients' clinical outcome (*Table 2*), like TRG and pCR (31-34). However, some studies have shown that in LAEC, histopathological response to nCRT, measured by residual carcinoma at surgery, is also predictive for overall survival (OS) (35,36). Moreover, Koshy *et al.* have shown that following nCRT, the presence of gross RD was a negative predictor for OS and cause-specific survival



AUC (95% CI)	0.79 (0.53–1.04)
TN	11
TP	4
FP	0
FN	3
Accuracy	83%
PPV	100%
NPV	79%
Sensitivity (95% CI)	57% (18–90%)
Specificity (95% CI)	100% (59–100%)

AUC (95% CI)	0.8 (0.55–1.05)
TN	11
TP	4
FP	0
FN	3
Accuracy	83%
PPV	100%
NPV	79%
Sensitivity (95% CI)	57% (18–90%)
Specificity (95% CI)	100% (59–100%)

AUC (95% CI)	0.86 (0.62–1.1)
TN	6
TP	5
FP	0
FN	2
Accuracy	85%
PPV	100%
NPV	75%
Sensitivity (95% CI)	71% (29–96%)
Specificity (95% CI)	100% (54–100%)

AUC (95% CI)	0.83 (0.58–1.08)
TN	6
TP	4
FP	0
FN	3
Accuracy	77%
PPV	67%
NPV	67%
Sensitivity (95% CI)	57% (18–90%)
Specificity (95% CI)	100% (54–100%)

Figure 5 Prediction of RD at surgery using early metabolic response in the whole cohort (A) and in the AC cohort (B). RD, residual disease; SUV, standardized uptake value; AUC, area under the curve; AC, adenocarcinoma; TN, true negative; TP, true positive; FP, false positive; FN, false negative; PPV, positive predictive value; NPV, negative predictive value.

(CSS) (36). Their analysis also revealed that patients with microscopic RD had similar outcomes to patients who achieved pCR. This observation supports our decision to divide the patients into RD0,1 *vs.* RD2 subgroups.

As mentioned above, early prediction of histopathological response may enable to switch the neoadjuvant treatment to a more effective one or save time to surgery. According to the results of this prospective evaluation of different PET and histopathological parameters, cutoffs of 13% in ΔSUV-mean and 29% in ΔSUV-max can recognize more than 50% of patients with RD2, those who are potential candidates to intensified treatment and who will definitely need surgery, while accurately leaving all patients with RD0-1 out of range. Our small cohort size did not allow us to analyze the SCC cohort separately; however, the different cut-off values obtained for the AC cohort and for the whole cohort, suggests that such separation in further studies may provide more accurate results.

The major limitation of our research is its small sample size, being a sub-study within a larger clinical trial. This weakness is further emphasized by the two distinct subpopulations within the study group, i.e., patients with AC and SCC tumor histologies. Its main strength, however, is the detailed comparison of various metabolic parameters and histopathological endpoints, each analyzed separately in most of the studies done in this field so far. Moreover, this is the first study to evaluate RD in this setting.

This study is the first to assess the predictive power of early metabolic response in nCRT protocols incorporating biological agents, the anti-EGFR monoclonal antibody cetuximab in this case. The essentially different anti-neoplastic mechanism of action of biological agents, anti-EGFR targeted or others, raise the possibility for a dissimilar effect on the underlying biological process, i.e., "metabolic shut-down", leading to an early metabolic response. Our results suggest that the correlation between

Table 5 Studies on early prediction of pathological response at surgery by interim versus baseline ^{18}F-FDG-PET/CT

Author [P/R] (year) Country	N	Histology	2nd PET (weeks)	PET criteria for metabolic response	Histopathological end-point	Sensitivity	Specificity	PPV	NVP	Conclusions and additional parameters
Neoadjuvant chemoradiotherapy										
Hammoudi (9) [R] [2019] France	42	SCC and AC	2	ΔSUV-max >70%	TRG1-3 (no, scattered or few viable tumor cells)	NA	NA	NA	NA	P=0.023, significant correlation
Xi (11) [R] [2017] USA	134	AC	After induction chemotherapy before concurrent CRT	2nd SUV-max ≤3	pCR	NA	NA	NA	NA	P=0.003, significant correlation
Tandberg (13) [P] [2018] USA	26	AC	After 32.4 Gy out of 45–50.4 Gy	Absolute and relative SUV-max, SUV-mean, MTV (manual, 2.5 and 40%), TLG (manual, 2.5 and 40%)	TRG0-1 (no, single cells or rare small groups)	NA	NA	NA	NA	Low to moderate accuracy of all PET features in prediction of response; intra-treatment MTV and TLG were most discriminatory in response prediction
Malik (20) [P] [2010] Ireland	37	AC	2	ΔSUV-max ≥26.4%	<10% viable tumor cells	62.5%	71.4%	62.5%	71.4%	No correlation
van Heijl (21) [P] [2011] Netherlands	100	SCC and AC	2	ΔSUV-max >0%	<10% viable tumor cells	91%	50%	76%	75%	Significant correlation, but low accuracy to justify clinical use
Elimova (22) [P] [2015] USA	31	SCC and AC	2	ΔSUV-max; ΔTLG	pCR	NA	NA	NA	NA	None of PET parameters is predictive of pCR
Fang (23) [P] [2018]* USA	20	SCC and AC	2	ΔTLG >59%; ΔSUV-max; ΔSUV-mean	pCR	100%	87%	NA	NA	TLG may serve as early imaging biomarker for pCR: SUV-max and ΔSUV-mean did not correlate with pCR
Wieder (28) [P] [2004] Germany	38	SCC	2	ΔSUV-mean >30% (ROI)	<10% viable tumor cells	93%	88%	93%	88%	P=0.0055; ΔSUV-mean significantly correlated with histopathological response
Ilson (29) [R] [2012] USA	55	SCC and AC	After induction chemotherapy before concurrent CRT	ΔSUV-mean >35% (ROI)	pCR	NA	NA	NA	NA	P=0.009; ΔSUV-mean significantly correlated with histopathological response
Westerterp (30) [P] [2006] Netherlands	17	SCC and AC	2	$\Delta SUV_{BSA\text{-}glu}$ >31% (VOI)	<10% viable tumor cells	75%	75%	75%	75%	

Table 5 (*continued*)

Table 5 (*continued*)

Author [P/R] (year) Country	N	Histology	2nd PET (weeks)	PET criteria for metabolic response	Histopathological end-point	Sensitivity	Specificity	PPV	NVP	Conclusions and additional parameters
Neoadjuvant chemotherapy										
Harustiak (24) [P] [2018] Czech Republic	90	AC	2	ΔTLG ≥66%; ΔSUL-max ≥35%	TRG 1–3 (≤50% of viable tumor cells)	59%; 52%	63%; 48%	41%; 30%	78%; 70%	Early FDG-PET/CT does not predict histopathological response
Wieder (25) [P] [2007] Germany	24	AC	2	ΔSUV-mean >33% (ROI)	TRG1 (<10% viable tumor cells)	100%	63%	NA	NA	ΔSUV-mean significantly correlated with histopathological response
Ott (26) [P] [2006] Germany	65	AC	2	ΔSUV-mean >35% (ROI)	TRG1 (<10% viable tumor cells)	NA	NA	NA	NA	P=0.01; ΔSUV-mean significantly correlated with histopathological response
Weber (27) [P] [2001] Germany	15	AC	2	ΔSUV-mean >35% (ROI)	TRG1-2 (no or few scattered cells)	89%	75%	53%	95%	P=0.01; ΔSUV-mean significantly correlated with histopathological response
Neoadjuvant chemoradiotherapy and biological treatment										
Current study [P]	18	SCC and AC; AC	2	ΔSUV-mean <13%; ΔSUV-mean <47%	RD	50%; 63%	100%; 100%	100%; 100%	73%; 67%	Early change in PET-CT can predict macro RD at surgery

*, sensitivity, specificity, PPV and NPV were calculated for the ^{18}F-FDG PET parameter with the highest discriminatory ability (ΔTLG). When the cutoff is not specified, the study compared the relevant PET parameter between responders and non-responders to address the difference. [R], Retrospective study; [P], Prospective study; NA, not available; SUV, standardized uptake value; SUV-max, maximum SUV; SUV-mean, mean SUV; SUL, SUV normalized to lean body mass; $SUV_{BSA-glu}$, SUV normalized to body surface area and plasma glucose concentration; TLG, total lesion glycolysis; ROI, region of interest; VOI, volume of interest; pCR, pathological complete response; TRG, tumor regression grade; RD, residual disease; AC, adenocarcinoma; SCC, squamous cell carcinoma; MTV, metabolic tumor volume; PPV, positive predictive value; NPV, negative predictive value.

early metabolic response and subsequent histopathological treatment effect still holds in the "biological era", at least with anti-EGFR agents.

In conclusion, our study shows, for the first time, that the magnitude of the decrease in ΔSUV-max and ΔSUV-mean as early as two weeks after the onset of induction chemotherapy combined with cetuximab for LAEC is highly predictive for the presence or absence of macroscopic RD at surgery, a surrogate for patient outcome. Additional studies, in larger cohorts, are required to confirm these findings and define precise cutoff values of ΔSUV-max and ΔSUV-mean for SCC and AC patients. If validated, this strategy may provide a very early indication on the benefit of nCRT in this setting and may allow better selection of patients for intensified regimens and for surgery.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-352/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-352/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-352/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional review board of Rabin Medical Center (No. 3907) and informed consent was taken from all the patients.

References

1. Mattiuzzi C, Lippi G. Current Cancer Epidemiology. J Epidemiol Glob Health 2019;9:217-22.
2. Rice TW, Rusch VW, Apperson-Hansen C, et al. Worldwide esophageal cancer collaboration. Dis Esophagus 2009;22:1-8.
3. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011;29:1715-21.
4. Ruhstaller T, Widmer L, Schuller JC, et al. Multicenter phase II trial of preoperative induction chemotherapy followed by chemoradiation with docetaxel and cisplatin for locally advanced esophageal carcinoma (SAKK 75/02). Ann Oncol 2009;20:1522-8.
5. Moehler M, Gockel I, Roessler HP, et al. Prospective, open, multi-centre phase I/II trial to assess safety and efficacy of neoadjuvant radiochemotherapy with docetaxel and oxaliplatin in patients with adenocarcinoma of the oesophagogastric junction. BMC Cancer 2013;13:75.
6. Haisley KR, Hart KD, Nabavizadeh N, et al. Neoadjuvant chemoradiotherapy with concurrent cisplatin/5-fluorouracil is associated with increased pathologic complete response and improved survival compared to carboplatin/paclitaxel in patients with locally advanced esophageal cancer. Dis Esophagus 2017;30:1-7.
7. Shapiro J, van Lanschot JJB, Hulshof MCCM, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol 2015;16:1090-8.
8. Cong L, Wang S, Gao T, et al. The predictive value of 18F-FDG PET for pathological response of primary tumor in patients with esophageal cancer during or after neoadjuvant chemoradiotherapy: a meta-analysis. Jpn J Clin Oncol 2016;46:1118-26.
9. Hammoudi N, Hennequin C, Vercellino L, et al. Early metabolic response to chemoradiotherapy by interim FDG PET/CT is associated with better overall survival and histological response in esophageal cancers. Dig Liver Dis 2019;51:887-93.

10. van Rossum PS, Fried DV, Zhang L, et al. The Incremental Value of Subjective and Quantitative Assessment of 18F-FDG PET for the Prediction of Pathologic Complete Response to Preoperative Chemoradiotherapy in Esophageal Cancer. J Nucl Med 2016;57:691-700.
11. Xi M, Liao Z, Hofstetter WL, et al. 18F-FDG PET Response After Induction Chemotherapy Can Predict Who Will Benefit from Subsequent Esophagectomy After Chemoradiotherapy for Esophageal Adenocarcinoma. J Nucl Med 2017;58:1756-63.
12. Beukinga RJ, Hulshoff JB, Mul VEM, et al. Prediction of Response to Neoadjuvant Chemotherapy and Radiation Therapy with Baseline and Restaging 18F-FDG PET Imaging Biomarkers in Patients with Esophageal Cancer. Radiology 2018;287:983-92.
13. Tandberg DJ, Cui Y, Rushing CN, et al. Intratreatment Response Assessment With 18F-FDG PET: Correlation of Semiquantitative PET Features With Pathologic Response of Esophageal Cancer to Neoadjuvant Chemoradiotherapy. Int J Radiat Oncol Biol Phys 2018;102:1002-7.
14. Odawara S, Kitajima K, Katsuura T, et al. Tumor response to neoadjuvant chemotherapy in patients with esophageal cancer assessed with CT and FDG-PET/CT - RECIST 1.1 vs. PERCIST 1.0. Eur J Radiol 2018;101:65-71.
15. Barsouk A, Rawla P, Hadjinicolaou AV, et al. Targeted Therapies and Immunotherapies in the Treatment of Esophageal Cancers. Med Sci (Basel) 2019;7:100.
16. Brenner B, Purim O, Gordon N, et al. The addition of cetuximab to preoperative chemoradiotherapy for locally advanced esophageal squamous cell carcinoma is associated with high rate of long term survival: Mature results from a prospective phase Ib/II trial. Radiother Oncol 2019;134:74-80.
17. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17:1471-4.
18. Domachevsky L, Kashtan H, Brenner B, et al. Baseline 18F-FDG PET/CT as predictor of the pathological response to neoadjuvant therapy in esophageal cancer: A retrospective study. Medicine (Baltimore) 2018;97:e13412.
19. Pai RK, Pai RK. Pathologic assessment of gastrointestinal tract and pancreatic carcinoma after neoadjuvant therapy. Mod Pathol 2018;31:4-23.
20. Malik V, Lucey JA, Duffy GJ, et al. Early repeated 18F-FDG PET scans during neoadjuvant chemoradiation fail to predict histopathologic response or survival benefit in adenocarcinoma of the esophagus. J Nucl Med 2010;51:1863-9.
21. van Heijl M, Omloo JM, van Berge Henegouwen MI, et al. Fluorodeoxyglucose positron emission tomography for evaluating early response during neoadjuvant chemoradiotherapy in patients with potentially curable esophageal cancer. Ann Surg 2011;253:56-63.
22. Elimova E, Wang X, Etchebehere E, et al. 18-fluorodeoxy-glucose positron emission computed tomography as predictive of response after chemoradiation in oesophageal cancer patients. Eur J Cancer 2015;51:2545-52.
23. Fang P, Musall BC, Son JB, et al. Multimodal Imaging of Pathologic Response to Chemoradiation in Esophageal Cancer. Int J Radiat Oncol Biol Phys 2018;102:996-1001.
24. Harustiak T, Zemanova M, Fencl P, et al. [18 F] Fluorodeoxyglucose PET/CT and prediction of histopathological response to neoadjuvant chemotherapy for adenocarcinoma of the oesophagus and oesophagogastric junction. Br J Surg 2018;105:419-28.
25. Wieder HA, Ott K, Lordick F, et al. Prediction of tumor response by FDG-PET: comparison of the accuracy of single and sequential studies in patients with adenocarcinomas of the esophagogastric junction. Eur J Nucl Med Mol Imaging 2007;34:1925-32.
26. Ott K, Weber WA, Lordick F, et al. Metabolic imaging predicts response, survival, and recurrence in adenocarcinomas of the esophagogastric junction. J Clin Oncol 2006;24:4692-8.
27. Weber WA, Ott K, Becker K, et al. Prediction of response to preoperative chemotherapy in adenocarcinomas of the esophagogastric junction by metabolic imaging. J Clin Oncol 2001;19:3058-65.
28. Wieder HA, Brücher BL, Zimmermann F, et al. Time course of tumor metabolic activity during chemoradiotherapy of esophageal squamous cell carcinoma and response to treatment. J Clin Oncol 2004;22:900-8.
29. Ilson DH, Minsky BD, Ku GY, et al. Phase 2 trial of induction and concurrent chemoradiotherapy with weekly irinotecan and cisplatin followed by surgery for esophageal cancer. Cancer 2012;118:2820-7.
30. Westerterp M, Omloo JM, Sloof GW, et al. Monitoring of response to pre-operative chemoradiation in combination with hyperthermia in oesophageal cancer by FDG-PET. Int J Hyperthermia 2006;22:149-60.
31. Baksh K, Prithviraj G, Kim Y, et al. Correlation Between Standardized Uptake Value in Preneoadjuvant and Postneoadjuvant Chemoradiotherapy and Tumor Regression Grade in Patients With Locally Advanced

Esophageal Cancer. Am J Clin Oncol 2018;41:254-8.
32. Takeda FR, Tustumi F, de Almeida Obregon C, et al. Prognostic Value of Tumor Regression Grade Based on Ryan Score in Squamous Cell Carcinoma and Adenocarcinoma of Esophagus. Ann Surg Oncol 2020;27:1241-7.
33. Francoual J, Lebreton G, Bazille C, et al. Is pathological complete response after a trimodality therapy, a predictive factor of long-term survival in locally-advanced esophageal cancer? Results of a retrospective monocentric study. J Visc Surg 2018;155:365-74.
34. Hammoud ZT, Kesler KA, Ferguson MK, et al. Survival outcomes of resected patients who demonstrate a pathologic complete response after neoadjuvant chemoradiation therapy for locally advanced esophageal cancer. Dis Esophagus 2006;19:69-72.
35. Chirieac LR, Swisher SG, Ajani JA, et al. Posttherapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemoradiation. Cancer 2005;103:1347-55.
36. Koshy M, Greenwald BD, Hausner P, et al. Outcomes after trimodality therapy for esophageal cancer: the impact of histology on failure patterns. Am J Clin Oncol 2011;34:259-64.

Cite this article as: Brenner B, Kundel Y, Cohen Z, Brand H, Gordon N, Sulkes A, Morgenstern S, Menasherov N, Kashtan H, Groshar D, Domachevsky L, Bernstine H. Early prediction of residual disease after neoadjuvant chemoradiotherapy and cetuximab for locally advanced esophageal cancer using ^{18}F-FDG PET-CT imaging: a prospective cohort study. J Gastrointest Oncol 2022;13(6):2721-2735. doi: 10.21037/jgo-22-352

