Predicting Pathologic Response of Esophageal Cancer to Neoadjuvant Chemotherapy: The Implications of Metabolic Nodal Response for Personalized Therapy

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Only a minority of esophageal cancers demonstrates a pathologic tumor response (pTR) to neoadjuvant chemotherapy (NAC). ^{18}F-FDG PET/CT is often used for restaging after NAC and to assess response. Increasingly, it is used during therapy to identify unresponsive tumors and predict pTR, using avidity of the primary tumor alone. However, definitions of such metabolic tumor response (mTR) vary. We aimed to comprehensively reevaluate metabolic response assessment using accepted parameters, as well as novel concepts of metabolic nodal stage (mN) and metabolic nodal response (mNR). **Methods:** This was a single-center retrospective U.K. cohort study. All patients with esophageal cancer staged before NAC with PET/CT and after with CT or PET/CT and undergoing resection from 2006 to 2014 were identified. pTR was defined as Mandard tumor regression grade 1–3; imaging parameters included metrics of tumor avidity ($SUV_{max/mean/peak}$), composites of avidity and volume (including metabolic tumor volume), nodal SUV_{max}, and our new concepts of mN stage and mNR. **Results:** Eighty-two (27.2%) of 301 patients demonstrated pTR. No pre-NAC PET parameters predicted pTR. In 220 patients restaged by PET/CT, the optimal tumor ΔSUV_{max} threshold was a 77.8% reduction. This was as sensitive as the current PERCIST 30% reduction, but more specific with a higher negative predictive value ($P < 0.001$). ΔSUV_{max} and Δlength independently predicted pTR, and composite avidity/spatial metrics outperformed avidity alone. Although both mTR and mNR were associated with pTR, in 82 patients with ^{18}F-FDG–avid nodes before NAC we observed mNR in 10 (12.2%) not demonstrating mTR. **Conclusion:** Current definitions of metabolic response are suboptimal and too simplistic. Composite avidity/volume measures improve prediction. mNR may further improve response assessment, by specifically assessing metastatic tumor subpopulations, likely responsible for disease relapse, and should be urgently assessed when considering aborting therapy on the basis of mTR alone.

Key Words: esophageal cancer; neoadjuvant therapy; positron-emission tomography; precision oncology

In the United States and Europe, the mainstay of curative treatment of esophageal cancer is neoadjuvant chemotherapy (NAC) or chemoradiotherapy (NACR) followed by surgery (*1,2*). Both confer important survival benefits (*3*); however, up to 60% of tumors show either minimal or no pathologic response (pTR) to NAC (*4,5*), and a similarly poor response is seen in 30%–40% after NACR (*6*). For these patients such, in retrospect, futile therapy delays surgery, potentially allowing disease progression and a worse prognosis (*7*). The ability to predict pTR at the outset would therefore be invaluable, as it would allow personalized therapy, with neoadjuvant therapy being omitted or changed to alternative therapy in those patients unlikely to benefit.

The evidence for the predictive value of baseline molecular markers and PET is insufficiently robust to justify major treatment changes (*8,9*). Interval assessment of response during therapy is, therefore, the next best option for personalizing therapy. Interval tumor metabolic response (mTR) on PET predicts pTR, albeit imperfectly. A 35% reduction in SUV_{max} is most commonly used during therapy (*10,11*) and formed the basis of the landmark MUNICON trial, wherein NAC was continued after a single cycle only in patients with a reduction in SUV_{max} greater than 35% (*12*); the alternative PERCIST recommend a 30% reduction after NAC to define mTR (*13*). However, these thresholds may not be optimal: PERCIST is neither tumor- nor context-specific, whereas the MUNICON threshold was derived from just 40 patients; furthermore, SUV_{max} provides no spatial information. More fundamentally, both assess only the primary tumor; the high rates of disease recurrence seen even in patients with pathologically responsive primary tumors suggests important unidentified factors, perhaps involving nodal or distant micrometastases—a recent report described tumor downstaging after NAC (a reduction from pretreatment clinical to posttreatment pathologic stage) to be strongly associated with survival (*14*).

With this in mind, we recently explored the novel concepts of ^{18}F-FDG–avid nodal stage (mN stage) and metabolic nodal response (mNR) and demonstrated major clinical implications for identifying disease progression during NAC, independent of primary tumor stage and response (*15*).

In this study, we aimed to reexamine comprehensively the utility of PET/CT in predicting pTR to NAC. First, we assessed the

predictive ability of clinical, pathologic, and imaging factors available before NAC. Second, we aimed to define and compare optimal thresholds of mTR after NAC and assess, for the first time, to our knowledge, the novel concept of mNR. Third, we aimed to generate and validate predictive models that might have clinical utility.

MATERIALS AND METHODS

Patients and Staging Protocol

All patients who underwent potentially curative surgical resection of esophageal/gastroesophageal junctional cancer and were staged initially with CT and ^{18}F-FDG PET/CT were identified from a departmental database (May 2006 to November 2014) (16). This included all cell types. The study was approved by the institutional clinical governance department, and the need for written informed consent was waived. Patients were also staged with endoscopic ultrasound and laparoscopy for tumors extending below the diaphragm as previously described (16). Examinations were reported by a consultant upper gastrointestinal radiologist/gastroenterologist using the contemporary American Joint Committee on Cancer TNM staging manual (sixth (17) or seventh edition (18)).

NAC

NAC was considered for all patients with disease more advanced than T1N0. Patients with esophageal and gastroesophageal junction (GEJ) Siewert 1/2 tumors (19) received either cisplatin and 5-fluorouracil (5-FU; 2 cycles; $n = 182$) (20); oxaliplatin and 5-FU (2 cycles; $n = 46$) (21); epirubicin, cisplatin, and 5-FU (ECF; 3 cycles; $n = 7$); epirubicin, cisplatin, and capecitabine (ECX; 3 or 4 cycles; $n = 22$) (22); epirubicin, oxaliplatin, and capecitabine (EOX; 3 cycles; $n = 3$); cisplatin and etoposide (2 cycles; $n = 1$); or oxaliplatin and capecitabine (2 cycles; $n = 1$). Patients with type 3 GEJ tumors received ECX/EOX/ECF (3 cycles). Some patients (distal esophageal/GEJ) received 3 cycles of ECX pre- and postoperatively with ($n = 7$) or without bevacizumab ($n = 20$) (23), or 3 cycles of ECF pre- and postoperatively ($n = 12$) (24).

Restaging CT and PET/CT

Patients were restaged 4–6 wk after NAC using CT before 2008 and PET/CT afterward (although a small minority underwent CT because of clinical trial protocols) as previously described (16). ^{18}F-FDG PET/CT was performed using 1 of 2 scanners. Before November 3, 2009, scans were obtained on a Discovery STE (GE Healthcare) 60 min after injection of 400 MBq of ^{18}F-FDG. Images were reconstructed using a time-of-flight ordered-subset expectation maximization reconstruction algorithm (2 iterations, 20 subsets; field of view, 50 cm; matrix, 128; voxel size, $3.9 \times 3.9 \times 3.3$ mm; 2D). After November 3, 2009, scans were obtained on a Discovery 690 (GE Healthcare) 90 min after injection of ^{18}F-FDG (4 MBq/kg). Images were reconstructed using a time-of-flight ordered-subset expectation maximization reconstruction algorithm (2 iterations, 24 subsets; gaussian filter, 6.4 mm; field of view, 50 cm; matrix, 256; voxel size, $1.95 \times 1.95 \times 3.3$ mm; 3D). Examinations were independently reported by 2 dedicated PET/CT radiologists.

Operations

Surgery was typically performed within 2 wk of the restaging scan. A minimum 2-field lymphadenectomy was performed as standard.

Data and Variables

Patient variables included age, sex, and American Society of Anesthesiologists grade (25); pretreatment tumor variables were cell type, grade (26), anatomic site, T (seventh edition), N stage (sixth edition because data were insufficient for conversion to the seventh),

and whether the tumor was impassable at esophagogastroduodenoscopy. PET/CT variables are described below. NAC variables comprised a dual- or triple-agent regimen (due to large number of regimens and small patient groups) and time (d) from staging to restaging scan and scan to surgery to adjust for delays and number of cycles given. pTR was defined as Mandard Tumor Regression Grade (TRG) of 3 or less, after dedicated review by a consultant cellular pathologist (27). The Mandard TRG was used in preference to alternative TRGs, being the most frequently used TRG for esophageal cancer (28), with optimal prediction of survival (29,30).

PET/CT Variables

Variables comprised primary tumor ^{18}F-FDG avidity (SUV_{max} and length [cm]), mN stage, mNR, and SUV_{max} of the most ^{18}F-FDG–avid node. The development of mN stage and mNR have been described previously (15). mN stage (nodes visible discretely from the tumor, within a standard lymphadenectomy territory, with $SUV_{max} > 2.5$ or background mediastinal blood pool) comprised mN0 (0 avid nodes), mN1 (1–2 nodes), and mN2 (>2 nodes). mNR comprised complete metabolic response or partial metabolic response (reduction in mN or $SUV_{max} \geq 30\%$), stable metabolic disease (stable mN or reduction/progression $SUV_{max} < 30\%$), or progressive metabolic disease (progression of mN or $SUV_{max} \geq 30\%$).

For examinations using the second PET/CT scanner, additional variables were generated by 2 authors: metabolic tumor volume (MTV), SUV_{mean}, SUV_{peak}, and tumor glycolytic volume (TGV) mean and max ($TGV_{max/mean}$). MTV was measured using a fixed-threshold technique ($SUV \geq 4$). TGV_{mean} was calculated manually as the product of MTV and SUV_{mean}. TGV_{max} was calculated as the product of MTV and SUV_{max}. mTR was quantified using absolute changes ($\Delta\%$) and thresholds defined previously (PERCIST and MUNICON criteria; SUV_{max}) (13); additionally, new thresholds were generated by receiver-operator characteristics.

Statistical Analysis

Analysis was performed using R software (version 3.0.2) (31). Correction for multiple comparisons was performed using the Bonferroni method (32) or false-discovery rate using FDRtoolv1.2.12 (33). For regression, continuous variable distribution was assessed using density plots and transformed (age^2; $logSUV_{max/mean/peak}$ and time to restaging/surgery). Multivariate analysis included all variables (including PET/CT scanner) after exclusion of perfect separators. Receiver-operator-characteristic optimal thresholds were calculated and compared with pROC (34) (95% confidence intervals using 200 iterations of 0.632 bootstrapping). Sensitivities and specificities were compared using the McNemar test (DTComPair version 1.0.3) (35).

Model Development, Tuning, Validation, and Performance

Three techniques were used as previously described (16): logistic regression (backward stepwise binary logistic), decision-tree analysis (recursive partitioning using loss matrices), and artificial neural networks (feed forward back-propagation multilayer perceptron). Models were tuned, generated, and validated internally (0.632 bootstrapping) using a development group (patients staged/restaged using the more recent scanner) and validated independently (patients staged/restaged using the earlier scanner; validation group). We partitioned patients in this way to minimize any potential bias, to ascertain immediate clinical utility, and also to assess generalizability to a different scanner system.

RESULTS

Three hundred two patients underwent resection after NAC. TRG was available for 301 (Tables 1–3). pTR was evident in 82 patients

TABLE 1
Baseline Patient Characteristics

Characteristic	Overall ($n = 301$)	Pathologic response ($n = 82$)	No pathologic response ($n = 219$)	P ($\alpha = 4.55 \times 10^{-3}$ pre-NAC, $\alpha = 2.63 \times 10^{-3}$ post-NAC)
Median age (y)	64.0 (IQR, 58.0–70.0; range, 36.0–80.0)	62.5 (IQR, 57.3–69.0; range, 36.0–79.0)	64.0 (IQR, 58.0–70.0; range, 38.0–80.0)	0.369*
Sex				0.764†
Male	228 (75.7%)	61 (74.4%)	167 (76.3%)	
Female	73 (24.3%)	21 (25.6%)	52 (23.7%)	
Cell type				0.979†
Adenocarcinoma	249 (82.7%)	68 (82.9%)	181 (82.6%)	
Squamous cell carcinoma	44 (14.6%)	13 (15.9%)	31 (14.2%)	
Adenosquamous	5 (1.66%)	1 (1.22%)	4 (1.83%)	
Small cell carcinoma	1 (0.33%)	0 (0.00%)	1 (0.46%)	
Anaplastic	2 (0.66%)	0 (0.00%)	2 (0.91%)	
Grade of differentiation				0.338†
Well	28 (9.30%)	5 (6.10%)	23 (10.5%)	
Moderate	128 (42.5%)	35 (42.7%)	93 (42.0%)	
Poor	140 (46.5%)	42 (51.2%)	98 (44.7%)	
Undifferentiated	5 (1.66%)	0 (0.00%)	5 (2.28%)	
Tumor site				0.033†
Mid 1/3	18 (5.98%)	9 (11.0%)	11 (5.02%)	
Distal 1/3	52 (17.3%)	11 (13.4%)	41 (18.7%)	
GEJ 1	72 (23.9%)	23 (28.0%)	49 (22.4%)	
GEJ 2	107 (35.5%)	20 (24.4%)	85 (38.8%)	
GEJ 3	51 (16.9%)	19 (23.2%)	32 (14.6%)	
Multifocal	1 (0.33%)	0 (0.00%)	1 (0.46%)	
Surgical approach				0.003*
LTE	200 (66.4%)	12 (14.6%)	156 (71.3%)	
ILE	46 (15.3%)	44 (53.7%)	34 (15.5%)	
3 stage	10 (3.32%)	5 (6.10%)	5 (2.28%)	
THE	1 (0.33%)	1 (1.22%)	0 (0.00%)	
ETG	44 (14.6%)	20 (24.4%)	24 (11.0%)	

*Mann–Whitney test.
†Fisher exact test.
IQR = interquartile range.

(27.2%): TRG 1 in 14 (4.65%), TRG 2 in 13 (4.32%), TRG 3 in 55 (18.3%), TRG 4 in 152 (50.5%), and TRG 5 in 67 (22.3%).

Predicting Pathologic Response Before NAC

Although there were nominally significant associations between tumor anatomic location and response, on multivariate regression, the only variable that predicted pTR was the use of a triple-agent NAC regimen: odds ratio (OR), 5.98 (95% confidence interval, 2.44–14.7; $P = 8.94 \times 10^{-5}$; Table 4).

Predicting Pathologic Response After NAC Using Absolute PET Variables

A more ^{18}F-FDG–avid primary tumor after NAC, as quantified by all metrics, was negatively associated with pTR: $\log SUV_{max}$ OR, 3.84×10^{-4} (1.17×10^{-5} to 2.00×10^{-3}; $P = 9.89 \times 10^{-6}$; Table 5; Supplemental Table 1 [supplemental materials are available at http://jnm.snmjournals.org]).

Predicting Pathologic Response Using Metabolic Tumor Response

mTR predicted pTR (Tables 3 and 6; Supplemental Table 2). This was true both for ΔSUV_{max} and for Δlength, independently on regression: $\log\Delta SUV_{max}$ OR for each percentage reduction, 1.03 (1.01–1.06), $P = 3.24 \times 10^{-3}$; Δlength OR, 1.02 (1.00–1.03); $P = 0.019$. Interestingly, whereas a PERCIST $\geq$ 30% reduction was associated with pTR, the MUNICON $\geq$ 35% threshold was not, once adjusted for Δlength. All additional metrics of mTR were associated with pTR.

TABLE 2
Pre-NAC Staging Results

Parameter	Overall (n = 301)	Pathologic response (n = 82)	No pathologic response (n = 219)	P (α = 4.55 × 10⁻³ pre-NAC, α = 2.63 × 10⁻³ post-NAC)
T stage				0.114*
1	7 (2.33%)	2 (2.43%)	5 (2.28%)	
2	46 (15.3%)	19 (23.2%)	27 (12.3%)	
3	231 (76.7%)	56 (68.3%)	175 (79.9%)	
4a	17 (7.76%)	5 (6.10%)	12 (35.48%)	
4b	0 (0.00%)	0 (0.00%)	0 (0.00%)	
N stage				0.090*
0	88 (29.3%)	58 (26.5%)	30 (36.6%)	
1	213 (70.7%)	161 (73.5%)	52 (63.4%)	
Initial PET/CT				0.011*
^{18}F-FDG–avid	290 (96.7%)	75 (91.5%)	215 (98.2%)	
^{18}F-FDG–negative	11 (3.65%)	7 (8.54%)	4 (1.83%)	
Initial PET/CT scanner				0.897*
1	142 (47.7%)	38 (46.3%)	104 (47.5%)	
2	159 (52.3%)	44 (55.7%)	115 (52.5%)	
NA	0 (0.00%)			
Restaging PET/CT scanner				0.739*
1	62 (20.6%)	16 (19.5%)	46 (21.0%)	
2	158 (52.5%)	46 (56.1%)	112 (51.19%)	
CT	81 (26.9%)	20 (24.4%)	61 (27.9%)	
mN stage				0.371*
0 (0 nodes)	209 (69.4%)	54 (65.9%)	155 (70.8%)	
1 (1–2 avid nodes)	54 (17.9%)	14 (17.1%)	40 (18.3%)	
2 (>2 avid nodes)	38 (12.6%)	14 (17.1%)	24 (11.0%)	
NA	0 (0.00%)			
Impassable at EGD?				0.633*
No	278 (92.4%)	77 (93.9%)	201 (92.8%)	
Yes	23 (7.60%)	5 (6.10%)	18 (8.20%)	

*Fisher exact test.
NA = not applicable; EGD = esophagogastroduodenoscopy.

Predicting Pathologic Response Using mNR

mNR was associated with pTR using the Fisher exact test (Table 3) but not on multivariate regression (Table 6). Notably, mNR and pTR were discordant in 42 of 220 (19.1%) patients (Table 7). In 41 cases, there was a nodal complete metabolic response or partial metabolic response without pTR, representing 51.2% of the 82 patients with ^{18}F-FDG–avid nodes before NAC (Table 7).

mTR and mNR were also compared (Table 7) and were found to be discordant in 13 (5.90%) cases overall, representing 15.9% of patients with ^{18}F-FDG–avid nodes before NAC. Typically, discordance arose due to a mNR in the absence of mTR (10 cases; 4.6% and 12.2%, respectively).

Defining Optimal Metabolic Response Thresholds

The accuracy of each continuous (nonthreshold) metric of mTR in predicting pTR is shown in Supplemental Table 3: all were moderately discriminant (80.2%–84.4%), with no statistically significant differences.

The optimal thresholds for each metric of mTR were determined (Supplemental Table 3), for discrimination, sensitivity, and specificity. The optimal ΔSUV_{max} for sensitivity was a 27.4%–30.6% reduction, identical to PERCIST (30%) and similar to the MUNICON threshold (35%). However, specificity was minimal: 33.0% (23.8–42.6) and 41.8% (32.0–52.2), respectively. By contrast, the optimal ΔSUV_{max} threshold for balancing sensitivity (73.6% [58.6–82.7]) and specificity (84.5% [78.7–89.1]) was dramatically different: a 77.8% reduction. Rounded down to a more pragmatic 75.0%, sensitivity was identical, whereas specificity reduced slightly to 84.0%.

The ability of each mTR metric to predict pTR is shown in Supplemental Tables 4–6. Overall, a ΔSUV_{max} of 77.8% was significantly more discriminant, with a higher negative predictive value than the PERCIST (30%) and MUNICON (35%) thresholds. The same was true for ΔMTV, ΔTGV_{max}, and ΔTGV_{mean}. The highest

TABLE 3
Surgical Approach and Response to Chemotherapy

Parameter	Overall ($n = 301$)	Pathologic response ($n = 82$)	No pathologic response ($n = 219$)	P ($\alpha = 4.55 \times 10^{-3}$ pre-NAC, $\alpha = 2.63 \times 10^{-3}$ post-NAC)
Response to chemotherapy				
Regimen				2.69×10^{-5}*
Dual	230 (76.4%)	48 (58.5%)	182 (83.1%)	
Triple	71 (23.6%)	34 (41.5%)	37 (16.9%)	
Median days to restaging scan	82.0 (IQR, 71.0–93.0)	88.5 (IQR, 71.3–106.8; range, 43.0–167)	82.0 (IQR, 71.0–91.0; range, 40.0–165)	0.036*
Median days from scan to surgery	24.0 (17.0–33.0)	23.0 (IQR, 18.3–31.8; range, 5.0–52.0)	23.0 (IQR, 15.0–33; range, 4.0–72.0)	0.283*
pTR		NA	NA	NA
No	82 (27.2%)			
Yes	219 (72.8%)			
mTR				5.38×10^{-13}*
Nonavid	7 (2.33%)	5 (8.06%)	2 (1.27%)	
CMR	48 (15.9%)	33 (53.3%)	15 (9.49%)	
PMR	108 (35.9%)	20 (32.4%)	88 (55.7%)	
SMD	43 (14.3%)	4 (1.33%)	39 (24.7%)	
PMD	14 (4.65%)	0 (0.00%)	14 (8.86%)	
NA	81 (26.9%)	20 (NA)	61 (NA)	
mNR				1.23×10^{-4}*
No avid nodes	138 (45.8%)	39 (62.9%)	99 (62.6%)	
CMR	50 (16.6%)	21 (33.9%)	29 (18.4%)	
PMR/SMD/PMD	32 (10.6%)	2 (3.22%)	30 (19.0%)	
NA	81 (26.9%)	20 (NA)	61 (NA)	

*Fisher exact test.

LTE = left thoracoabdominal esophagectomy; ILE = Ivor-Lewis esophagectomy; THE = transhiatal esophagectomy; ETG = extended total gastrectomy; IQR = interquartile range; pTR = pathologic tumor response; mTR = metabolic tumor response; CMR = complete metabolic response; PMR = partial metabolic response; SMD = stable metabolic disease; PMD = progressive metabolic disease; NA = not applicable.

sensitivities were seen with PERCIST (sensitivity, 100%), MUNICON (97.1%), ΔMTV (97.1%), ΔTGV$_{max}$ (97.1%), and ΔTGV$_{mean}$ (94.3%); these were significantly more sensitive than Δlength (<4.68×10^{-3}; false-discovery rate = 0.046) but not a ΔSUV$_{max}$ of 77.8%. The most specific were a ΔSUV$_{max}$ of 77.8% (81.7% specific) and Δlength of 53.1% (82.7%) ($P < 4.11 \times 10^{-4}$).

Performance of Predictive Models

Models were generated (Supplemental Table 7) using metrics of mTR/mNR. The most successful was a logistic regression model comprising Δlength + ΔSUV$_{max}$; this was highly sensitive (91.4%), moderately specific (71.4%) and discriminant (0.814), and this sensitivity persisted during internal and independent validation (although with relatively poor specificity and discrimination). However, ultimately none of the composite models outperformed individual mTR thresholds (Supplemental Tables 4–7).

DISCUSSION

In this study of 301 patients treated with NAC and surgery—the largest to date in esophageal cancer—we found no baseline clinical, tumor, or PET variables associated with pTR. This is perhaps unsurprising, reflecting the daunting complexity involved. Chemoresistance is usually multifactorial and constitutes a spectrum of sensitivity, which depends on numerous macroscopic, microscopic, and molecular factors modulating chemotoxicity (36,37). Intratumoral heterogeneity further complicates chemoresistance, with several subclones, potentially demonstrating differential response and baseline characteristics, in addition to heterogeneity between tumor and nodal metastases. In contrast, after NAC, several PET variables, including absolute tumor metrics and those assessing either mTR or mNR, were strongly associated with pTR on multivariate analysis, and several clinically relevant implications were identified.

First, the identification of a significantly better ΔSUV$_{max}$ threshold (77.8% reduction) than the generic PERCIST threshold (30%) suggests that the latter should be raised considerably for esophageal cancer to improve stratification of mTR (perhaps to a more pragmatic 75%). This threshold was nominally significantly better than the MUNICON threshold (35%), but as this threshold was originally derived during therapy rather than after therapy (as in our study), the significance of this is uncertain and we are unable to draw further conclusions.

TABLE 4
Baseline Factors Associated with Pathologic Response to NAC: Univariate and Multivariate Regression

Factor	Univariate OR (95% CI)	P	Multivariate OR (95% CI)	P
		Response		
Median age (y)	1.00 (1.00–1.00)	0.536	1.00 (1.00–1.00)	0.949
Sex				
Female	Ref	Ref	Ref	Ref
Male	0.90 (0.50–1.62)	0.722	0.94 (0.45–1.95)	0.859
Cell type				
Adenocarcinoma	Ref	Ref	Ref	Ref
Squamous cell carcinoma	1.14 (0.56–2.32)	0.716	0.87 (0.31–2.45)	0.792
Grade				
Well	Ref	Ref	Ref	Ref
Moderate	1.77 (0.62–5.02)	0.284	1.07 (0.33–3.49)	0.906
Poor	1.99 (0.71–5.58)	0.194	1.53 (0.47–4.97)	0.477
Site				
Mid 1/3	Ref	Ref	Ref	Ref
Distal 1/3	0.30 (0.10–0.91)	0.034	0.21 (0.05–0.79)	0.021
GEJ 1	0.51 (0.18–1.54)	0.200	0.34 (0.09–1.26)	0.106
GEJ 2	0.28 (0.10–0.78)	0.015	0.17 (0.04–0.69)	0.013
GEJ 3	0.68 (0.23–1.98)	0.480	0.15 (0.03–0.64)	0.020
T stage				
1	Ref	Ref	Ref	Ref
2	1.76 (0.31–10.0)	0.525	2.33 (0.34–16.0)	0.390
3	0.83 (0.16–4.42)	0.830	0.98 (0.15–6.27)	0.986
4a	1.05 (0.15–7.27)	0.967	1.13 (0.13–10.0)	0.916
N stage				
0	Ref	Ref	Ref	Ref
1	0.64 (0.37–1.10)	0.105	0.60 (0.13–1.16)	0.129
Passable at EGD?				
Yes	Ref	Ref	Ref	Ref
No	0.63 (0.20–1.93)	0.416	0.50 (0.13–1.95)	0.317
Chemotherapy				
Regimen				
Dual	Ref	Ref	Ref	Ref
Triple	3.48 (1.97–6.14)	1.76×10^{-5}	5.98 (2.44–14.7)	8.94×10^{-5}
Log time to restaging	63.9 (4.24–964)	2.66×10^{-3}	10.8 (0.42–280)	0.152
Log time to surgery	0.93 (0.31–2.79)	0.896	1.12 (0.29–4.33)	0.873
PET/CT variables				
PET scanner				
1	Ref	Ref	Ref	Ref
2	1.07 (0.64–1.79)	(0.796)	0.69 (0.36–1.32)	0.267
mN stage				
0	Ref	Ref	Ref	Ref
1	0.94 (0.46–1.89)	0.857	1.42 (0.60–3.34)	0.426
2	1.67 (0.80–3.48)	0.720	1.72 (0.67–4.45)	0.261
Log SUV_{max}	0.43 (0.16–1.11)	0.081	0.54 (0.15–1.92)	0.343
Log ^{18}F-FDG–avid length	0.90 (0.81–1.01)	0.070	0.89 (0.77–1.04)	0.145
Subset of patients*				
SUV_{mean}	1.47 (0.09–23.4)	0.784	1.56 (0.04–65.8)	0.814
SUV_{peak}	2.53 (0.41–15.8)	0.320	1.85 (0.50–6.77)	0.356
MTV	1.55 (0.79–3.04)	0.203	1.70 (0.66–4.39)	0.276
TGV_{max}	1.53 (0.84–2.76)	0.163	1.72 (0.74–3.99)	0.230
TGV_{mean}	1.45 (0.86–2.44)	0.164	1.64 (0.78–3.42)	0.189

*This subset of patients was staged using second PET/CT scanner (n = 155).
CI = confidence interval; Ref = reference; NA = not applicable; EGD = esophagogastroduodenoscopy.
Data in parentheses are IQRs.

Factor	Response			
	Univariate OR (95% CI)	P	Multivariate OR (95% CI)	P
Chemotherapy				
Regimen				
Dual	Ref	Ref	Ref	Ref
Triple	4.30 (2.16–8.55)	3.23×10^{-5}	17.6 (4.39–70.1)	5.00×10^{-5}
Log time to restaging	25.1 (1.10–574)	0.044	0.32 (0.00–69.2)	0.678
Log time to surgery	2.28 (0.57–9.07)	0.241	0.52 (0.06–4.82)	0.567
PET/CT variables				
PET scanner				
1	Ref	Ref	Ref	Ref
2	1.09 (0.58–2.07)	0.782	0.10 (0.02–0.55)	0.008
Restaging PET scanner				
1	Ref	Ref	Ref	Ref
2	1.30 (0.66–2.57)	0.446	5.24 (0.95–28.9)	0.057
Restaging mN stage				
0 (0 avid nodes)	Ref	Ref	Ref	Ref
1 (1–2 avid nodes)	0.16 (0.02–1.28)	0.084	1.07 (0.07–16.8)	0.959
2 (>2 avid nodes)	0.16 (0.02–1.28)	0.084	2.39 (0.18–31.6)	0.509
Restaging log SUV_{max}	2.37×10^{-3} (4.21×10^{-4} to 0.01)	6.93×10^{-12}	3.84×10^{-4} (1.17×10^{-5} to 0.02)	9.89×10^{-6}
Restaging log avid length	0.61 (0.51–0.73)	3.80×10^{-8}	1.01 (0.76–1.34)	0.951
Restaging log MTL	0.03 (0.01–0.10)	3.88×10^{-10}	0.02 (4.03×10^{-3} to 0.06)	6.19×10^{-9}
Subset of patients with ^{18}F-FDG–avid nodes ($n = 30$)				
Log nodal SUV_{max}	8.71 (0.01–5787)	0.514	NA	NA
Subset of patients staged using second PET/CT scanner ($n = 155$)				
Log SUV_{mean}	1.58×10^{-4} (7.51×10^{-6} to 3.23×10^{-3})	1.78×10^{-4}	1.13×10^{-7} (8.55×10^{-12} to 1.46×10^{-3})	9.32×10^{-5}
SUV_{peak}	5.05×10^{-3} (1.81×10^{-4} to 0.14)	1.85×10^{-3}	0.57 (0.39–0.84)	3.90×10^{-3}
Log MTV	0.28 (0.18–0.44)	0.203	0.09 (0.03–0.28)	2.03×10^{-5}
Log TGV_{max}	0.32 (0.21–0.48)	3.91×10^{-8}	0.11 (0.04–0.31)	2.72×10^{-5}
Log TGV_{mean}	0.30 (0.19–0.46)	3.27×10^{-8}	0.10 (0.03–0.29)	2.29×10^{-5}

CI = confidence interval; Ref = reference; MTL = metabolic tumor length; NA = not applicable.

Second, rather than considering avidity in isolation, we found evidence that incorporating spatial data improved prediction: Δlength at a most basic level, or ideally a composite metric such as ΔMTV or ΔTGV$_{max/mean}$. These outperformed the existing recommended PERCIST threshold of a 30% SUV$_{max}$ reduction. They were comparably sensitive, but more specific ($P < 4.11 \times 10^{-4}$) and discriminant ($P < 9.38 \times 10^{-5}$), and were supported by internal (bootstrapping) validation. This suggests that composite metrics may have greater predictive ability in clinical trials than ΔSUV$_{max}$ alone (such as in the MUNICON trial 35% threshold). In particular, their superior specificity and high negative predictive value (98.5%–100%) might identify more nonresponders suitable for cessation of therapy. These findings are in keeping with those of recent smaller studies in chemoradiotherapy; in 20 patients using support vectors and logistic regression, Zhang et al. found mTR quantified using spatial avidity metrics outperformed avidity alone in predicting pTR (38); whereas in 37 patients Jayachandran et al. found MTV to outperform SUV$_{max}$ (39).

Third, to our knowledge, this is the first study to assess the novel concept of mNR in association with pTR. We found that the primary tumor and nodal disease often demonstrated a

TABLE 6
Metabolic Response and Other Factors Associated with Pathologic Response to NAC: Univariate and Multivariate Regression (Patients Staged and Restaged Using Same PET Scanner), Adjusted for Baseline Variables

Factor	Univariate OR (95% CI)	P	Multivariate OR (95% CI)	P
Chemotherapy				
Regimen				
Dual	Ref	Ref	Ref	Ref
Triple	4.30 (2.16–8.55)	3.23×10^{-5}	20.3 (4.50–91.4)	8.84×10^{-5}
Log time to restaging	69.1 (1.86–2571)	0.022	0.22 (0.00–172)	0.658
Log time to surgery	1.75 (0.41–7.44)	0.452	0.70 (0.06–8.36)	0.781
PET/CT variables				
Initial/restaging PET scanner				
1	Ref	Ref	Ref	Ref
2	0.87 (0.40–1.88)	0.718	0.71 (0.21–2.38)	0.580
nMR				
Negative	Ref	Ref	Ref	Ref
CMR	1.93 (0.93–4.01)	0.076	2.01 (0.54–7.51)	0.300
PMR	0.45 (0.05–3.87)	0.465	11.2 (0.64–197.3)	0.098
SMD	0.27 (0.03–2.18)	0.219	1.15 (0.09–14.4)	0.911
PMD	NA (NA)	NA	NA (NA)	NA
Reduction $logSUV_{max}$ (%)	1.04 (1.02–1.05)	6.65×10^{-8}	1.03 (1.01–1.06)	3.24×10^{-3}
Reduction avid length (%)	1.03 (1.02–1.04)	9.37×10^{-8}	1.02 (1.00–1.03)	0.019
Additional metrics in all patients ($n = 202$)				
Reduction MTL (%)	1.05 (1.03–1.07)	2.86×10^{-6}	1.11 (1.05–1.16)	1.16×10^{-5}
PERCIST (30.0%)				
CMR	Ref	Ref	Ref	Ref
PMR	0.10 (0.04–0.22)	2.24×10^{-8}	0.08 (0.02–0.32)	3.53×10^{-5}
SMD/PMD	0.04 (0.01–0.14)	2.18×10^{-7}	0.06 (0.01–0.49)	8.46×10^{-4}
MUNICON (35.0%)				
No response	Ref	Ref	Ref	Ref
Response	5.21 (2.08–13.0)	4.22×10^{-5}	1.63 (0.41–6.45)	0.484
Subset of patients staged using second PET/CT scanner ($n = 155$)				
Reduction SUV_{mean} (%)	1.03 (1.02–1.04)	2.25×10^{-8}	1.05 (1.02–1.09)	1.90×10^{-3}
Reduction SUV_{peak} (%)	1.09 (1.03–1.15)	1.91×10^{-5}	1.04 (1.02–1.05)	2.20×10^{-3}
Reduction MTV (%)	1.44 (1.09–1.92)	2.70×10^{-5}	1.16 (1.07–1.25)	0.011
Reduction TGV_{max} (%)	1.30 (1.12–1.52)	5.82×10^{-3}	2.31 (1.27–4.20)	2.72×10^{-5}
Reduction TGV_{mean} (%)	1.23 (1.10–1.37)	3.91×10^{-8}	1.87 (1.20–2.90)	2.29×10^{-5}

CI = confidence interval; Ref = reference; mNR = metabolic nodal response; MTL = metabolic tumor length; CMR = complete metabolic response; PMR = partial metabolic response; SMD = stable metabolic disease; PMD = progressive metabolic disease; NA = not applicable.

discordant response to NAC, with mNR seen in the absence of mTR or pTR. With the use of mTR alone (as in the MUNICON trial), this subgroup of patients would be classed as nonresponders and NAC aborted; our findings suggest that in such patients their nodal metastases may in fact be responding to treatment. Nodal metastases by definition contain an aggressive subpopulation of cancer clones originating from the primary tumor, which then evolve differently at a genetic and phenotypic level (40). A crucial such phenotype is chemosensitivity. Although clearly mNR is likely an imperfect surrogate of pathologic nodal response, no systems for assessing nodal response are in use. Our findings are important, as they offer a vital insight into assessing response in the tumor subclones with proven metastatic behavior, likely to be responsible for local and distant disease relapse.

TABLE 7
Comparison of Tumor and Nodal Metabolic Response

Tumor response	mNR				
	NA	CMR	PMR	SMD	PMD
Pathologic response					
pTR	39 (17.7%)	21 (9.55%)	1 (0.45%)	1 (0.45%)	0 (0.00%
No pTR	99 (45.0%)	29 (13.2%)	12 (5.45%)	13 (5.91%)	5 (22.7%)
Metabolic response					
NA	6 (2.73%)	1 (0.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
CMR	32 (14.5%)	14 (1.82%)	1 (0.45%)	1 (0.45%)	0 (0.00%)
PMR	68 (30.9%)	29 (13.2%)1	8 (3.64%)	2 (0.91%)	0 (0.00%)
SMD	22 (9.09%)	5 (2.27%)	4 (1.82%)	10 (4.55%)	3 (1.36%)
PMD	10 (4.55%)	1 (0.45%)	0 (0.00%)	1 (0.45%)	2 (0.91%)

NA = not applicable; CMR = complete metabolic response; PMR = partial metabolic response; SMD = stable metabolic disease; PMD = progressive metabolic disease.

This study has several limitations. Although the current gold standard technique for disease response assessment is direct histopathologic examination, this remains imperfect. We used the Mandard classification, which originally described the response of esophageal squamous cell carcinoma to cisplatin-based NACR (27). The Mandard TRG has subsequently been validated for esophageal adenocarcinoma (41) although several other classifications have been described (42); all, however, remain relatively subjective and are tempered by potential interobserver variability and intratumoral sampling bias (43). Ultimately, the Mandard TRG is most frequently used and provides the basis for optimal prediction of survival (28,30). An additional limitation of this study is its retrospective design over a long time period, which although necessary to generate a sufficient cohort resulted in a change of PET/CT scanner, and the availability of additional metrics for the more recent scanner alone. In addition, we included a range of cell types, rather than restricting our analysis. We sought to mitigate these limitations with dedicated review of TRG by a single expert pathologist, by adjusting analyses for cell type and the scanner used and by restricting model development to the more recent representative scanner with subsequent validation in the earlier group, to minimize any bias. We also performed a post hoc analysis comparing metrics between scanners, demonstrating no significant differences in either metabolic response of the primary or nodal tumor ($P = 0.109$ [Mann–Whitney] and 0.068 [Fisher exact test]). We believe this to be the largest study performed for esophageal cancer and believe that our results are robust—whether they can be extrapolated to NACR is not clear, but we believe these results warrant urgent assessment. In addition, assessment of several textural response parameters, including entropy and run-length matrices, which although not routinely used in clinical practice have recently been shown to be associated with pTR after NACR (44), and their inclusion in conjunction with volume have been suggested to improve prognostication (45). Such metrics may therefore provide complementary predictive data.

CONCLUSION

We found that the current definitions used for metabolic response assessment after NAC, based solely on ΔSUV_{max}, are both suboptimal and too simplistic and that using composite measures of ^{18}F-FDG avidity and volume could significantly improve the predictive ability of PET. The assessment of nodal response, which is often discordant with the primary tumor response, should be urgently studied, as it may offer the potential to further improve response assessment, specifically within tumor populations with proven metastatic behavior.

DISCLOSURE

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