Review Article

Personalized therapy based on image for esophageal or gastroesophageal junction adenocarcinoma

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Abstract: Preoperative therapy is the gold standard for esophageal or gastroesophageal junction adenocarcinoma. Positron emission tomography (PET) is not only essential for tumor staging, but changes in glucose consumption correspond with response to therapy and correlated with prognosis. Therefore, with further refinement, PET parameter can serve as a tool for personalized therapy. For instance, the Munich trials suggested the possibility of PET-response guided therapy for esophageal adenocarcinoma (EAC) patients, however there are limitations. New PET parameters such as total lesion glycolysis (TLG) or magnetic resonance imaging (MRI) may provide better response prediction. Furthermore, PET parameters combined with genomic profiling might enhance better treatment selection, prediction, and prognostication. Here, we summarized the current state of understanding and future possibilities.

Keywords: Gastroesophageal junction adenocarcinoma; esophageal adenocarcinoma (EAC); positron emission tomography-computed tomography (PET-CT); magnetic resonance imaging (MRI); personalized therapy

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Introduction

Esophageal cancer (EC) is the 8th most common of all cancers in the world (456,000 cases) and the 6th most common cause of cancer death (400,000 deaths) (1). Esophageal adenocarcinoma (EAC), one of the two common EC histologic types, has become quite prevalent in the western world (2). Despite the development of multimodality therapies, the prognosis of EAC patients remains dismal (3,4).

To date, preoperative chemotherapy or chemoradiation followed by esophagectomy is considered a standard option in cases where surgery is possible (5). After preoperative chemoradiation, ~25% patients achieve pathological complete response (pCR) (6). Patients who have pCR often experience a longer overall survival compared to those that achieve < pCR (7,8). Importantly, patients who are destined to have pCR may be able to avoid the esophagectomy (9). Therefore, predicting the response to preoperative therapy can be useful in the clinic and may allow novel algorithms.

Computed tomography (CT), positron emission tomography (PET)-CT and upper endoscopy with endoscopic ultrasound (EUS) have been the standard for staging of localized EC. In addition, these have been used for restaging after preoperative therapy (10).

Predicting preoperative chemotherapy response by PET-CT

Several studies have assessed the value of PET-CT to predict response and prognosticate after preoperative chemotherapy (*Table 1*). Weber *et al.* reported that standardized uptake value (SUV) reduction of clinical responders was significantly

Table 1 Previous study showing the relationship between SUV reduction after preoperative chemotherapy and histological response in EC

Study	Year	Tumor type	SUV reduction cut-off (%)	Definition of histological response	Pathological response rate	P value
Weber *et al*. (11)	2001	N=40, AC 100%	35	TRG 1, 2	PET-responder: 8/15; non-PET-responder: 1/22	0.01
Ott *et al*. (12)	2006	N=65, AC 100%	35	Less than 10% residual tumor cells	PET-responder: 8/18; non-PET-responder: 2/38	0.01
Wieder *et al*. (13)	2007	N=24, AC 100%	33	Less than 10% residual tumor cells	PET-responder: 8/18; non-PET-responder: 0/6	–
Lordick *et al*. (MUNICON) (14)	2007	N=110, AC 83%	35	Less than 10% residual tumor cells	PET-responder: 29/50; non-PET-responder: 0/54	0.001
Kauppi *et al*. (15)	2012	N=66, AC 100%	67	Less than 10% residual tumor cells	Sensitivity: 79%; specificity: 75%	–
Port *et al*. (16)	2007	N=62, AC 82%	50	Less than 10% residual tumor cells	PET-responder: 9/37; non-PET-responder: 1/25	–
Findlay *et al*. (17)	2017	N=301, AC 83%	77.8	TRG 1, 2, 3	Sensitivity: 74%; specificity: 84%	–

EC, esophageal cancer; AC, adenocarcinoma; SUV, standardized uptake value; TRG, tumor regression grade (18); PET, positron emission tomography.

higher than that of non-responders (11). Subsequent studies confirmed these observations and suggested that that SUV reduction could be correlated with the degree of pathological response (12,13,15,16). MUNICON1 phase II trial prospectively evaluated whether PET is useful for predicting histopathological response and survival (14). When 35% SUVmax reduction was defined as PET-responder, major histological responses (less than 10% residual tumor) were detected in 29 of 50 PET-responders, but none in PET-non-responders. But, SUV changes could not predict pCR. The median overall survival was significantly longer for PET-responders than for PET-non-responders [hazard ratio (HR): 2.13; 95% confidence interval (CI): 1.14–3.99; P=0.015] (14). A large retrospective single institution study of 301 patients observed a relationship between SUVmax reduction and pathological response (17). As pathologic response was defined by the Mandard tumor regression grades (TRGs) 1–3 (19), SUV changes could identify pathologic response [odds ratio (OR) for each percentage reduction: 1.03; 95% CI: 1.01–1.06; P=0.003] (17). Thus, metabolic response could be correlated with pathological response. However, there is not standard cut-off value for metabolic response. PERCIST recommends 30% reduction as cut-off value, but this was applied other tumor types and not EAC (20). In EAC setting, 35% SUVmax reduction seem to be most commonly defined as metabolic responder as MUNICON trial (14).

Predicting preoperative chemoradiation response by PET-CT

One drawback of this area of research is that most studies have small cohorts, they are retrospective, and conducted at single institution. Therefore, varying results have been reported (*Table 2*). Unlike preoperative chemotherapy, pCR can be highly anticipated after preoperative chemoradiation (9). A prospective cohort study with 138 EC patients (EAC 75%) showed that when complete metabolic response (cMR) was defined as maximal value of SUVmax of <4, only 27% patients who had cMR achieved pCR after chemoradiation (27). Elliot *et al.* also reported similar result. In 100 EAC patients, when cMR defined as SUVmax of <4 after preoperative chemoradiation, 46 patients (46%) achieved cMR, but 37 patients (80%) had residual EAC in the resected specimen (24). These studies confirm the limitation of SUV after chemoradiation to predict pCR.

Our group reported on consecutive 151 EAC patients and noted that SUVmax changes after chemoradiation was marginally associated with pCR (univariate OR: 1.01, P=0.06; multivariate OR: 1.03, P=0.07) (22). Kukar *et al.* reported in 77 patients and noted that less than 45% SUV decrease was a risk factor for residual disease (25). Another study with 53 EAC patients reported that a decrease of >23.5% SUV resulted in the sensitivity and specificity for

Table 2 Previous study showing the relationship between SUV reduction after preoperative chemoradiation and pathological response in EC

Study	Year	Tumor type	Results
Vallbohmer *et al*. (21)	2009	N=119, AC 45%	Post SUV and SUV reduction were not associate with major histological response (less than 10% residual tumor cells)
Javeri *et al*. (22)	2009	N=151, AC 100%	The percentage SUV decrease correlated marginally with pCR (univariate OR: 1.01, P=0.06; multivariate OR: 1.03, P=0.07)
Piessen *et al*. (23)	2013	N=60, AC 48%	Post SUV and SUV change were not associate with major histological response (less than 10% residual tumor cells) (P=0.71, P=0.31)
Elliott *et al*. (24)	2014	N=100, AC 100%	20% of patients who had post SUV <4 achieved pCR; SUV change was not associate with pCR (P=0.87)
Baksh *et al*. (18)	2015	N=187, AC N/A	Rate of SUV change showed a significant correlation with TRG (r=0.178, P=0.017)
Kukar *et al*. (25)	2015	N=77, AC 100%	The mean pre-SUV (14.5 *vs.* 11.2; P=0.05), and % SUV change (0.6 *vs.* 0.4; P=0.02) were significantly higher in patients with pCR than non-pCR
Kim *et al*. (26)	2016	N=52, AC N/A	>23.5% SUV reduction predicted pCR with the sensitivity 100 % and specificity 52.6%
Heneghan *et al*. (27)	2016	N=138, AC 75%	27% of patients who had Post SUV <4 achieved pCR; % SUV reduction correlated with pCR (OR: 1.03; P=0.013)

AC, adenocarcinoma; SUV, standardized uptake value; pCR, pathological complete response; OR, odds ratio; TRG, tumor regression grade (18); PET, positron emission tomography.

pCR prediction were 100% and 53%, respectively (26). Baksh *et al.* retrospectively reported SUV changes in 187 EC patients who had preoperative chemoradiation and noted a significant correlation with TRG (18). However, Piessen *et al.*, Vallbohmer *et al.*, and Myslivecek *et al.* reported the no benefit of PET-CT parameter after chemoradiation to identify histological responders (21,23,28).

Taken together, PET-CT parameter has a limitation in predicting pCR or histological response after preoperative chemoradiation. This limitation is considered due to inflammatory changes caused by chemoradiation. Inflammation and ulceration can increase SUV uptake (29,30). Further refinements are needed for better correlations.

Volumetry PET parameter

SUVmax represents maximum metabolic activity at one point in the tumor bed. Therefore alternative parameters have been proposed to assess heterogeneity by computed volumetric analyses, such as tumor volume, tumor shape, total glycolytic volume, and spatial patterns (texture features) (31-33). TLG is calculated by the product of average of SUV and metabolic tumor volume (MTV) (34). Therefore, TLG can represent more accurate whole tumor metabolic activity than SUVmax. We reported a prospective phase II trial to assess the SUVmax or TLG could predict pCR, but noted that TLG was prognostic but none of the PET variables was predictive of pCR (35). However, this study was very small. A larger but retrospective study from our institution assessed whether baseline and post-chemoradiation PET changes including texture analysis can improve prediction of pCR in 217 EAC patients (36). Especially TLG improved prediction of pCR, but was not sufficient for clinical implementation (36). Hatt *et al.* reported in 50 patients who underwent chemoradiation (EAC: 28%) and noted that initial SUV parameter was similar between clinical responders and no-responders, while TLG parameter was significantly less in patients with clinical CR (37). And pretreatment TLG of <58 predicted clinical CR with 75% sensitivity and 92% specificity, which was more valuable than SUV (37). Furthermore, Roedl *et al.* reported that a decrease of TLG by >78% had better predictive values (91% sensitivity and 93% specificity) than SUV did (38). However, another study with 79 patients who underwent preoperative chemoradiation could not demonstrate the correlation between TLG after treatment and pCR (39). A study of 50 EC patients with preoperative chemotherapy reported that a certain TLG change (>40% reduction) was an independent prognosticator in

multivariable analysis (multivariate HR: 3.89; 95% CI: 1.46–10.3; P=0.006), but SUV change was not independent prognosticator (40). Further studies are expected.

PET guided treatment

If PET-parameters could identify exquisitely treatment sensitive tumors, we could avoid surgery in some patients. Conversely for patients with resistant tumor, we could avoid toxic and ineffective therapies. Therefore, PET-guided treatment algorithm in EAC has been evaluated. The Municon I trial is the first phase II trial which assessed the PET-response guided treatment algorithm for EAC patients (14). PET responders (>35% SUV reduction) after one cycle chemotherapy continued the same chemotherapy then had surgery, but non-responder stopped chemotherapy and had surgery. The prognosis of responders was better than that for non-responders. In Municon II trial, non-responder received additional chemoradiation, but still the non-responders had poor prognosis compared to responders (41). This suggests that empirically changing therapy cannot overcome primary resistance and in depth analyses are needed to derive benefits.

A Phase II trial evaluating induction chemotherapy followed by concurrent chemoradiation in EC showed that PET responder for induction chemotherapy (>35% SUV reduction) had higher frequency of pCR and favorable prognosis (42). Ongoing CALGB 80803 study has evaluated the strategy of changing concurrent chemotherapy with chemoradiation based on PET response to induction chemotherapy (43). A total of 257 EAC patients assigned to the FOLFOX or Carbo/Taxol group, and then PET non-responder were crossed over to alternative regimen. pCR rate of PET responder was 26% and that of PET non-responder was 18%, but this is not significant. This study design is not ideal to figure out if pCR can be improved by changing concurrent chemotherapy. In the ideal design, one would continue would have two non responding cohorts: one cohort will receive the same chemotherapy with radiation and the other cohort will receive the alternate chemotherapy.

Ancillary analysis of the CROSS trial reported whether the early assessment could predict response for preoperative chemoradiation (44). PET-CT was performed before treatment and 14 days after the start of treatment. The median SUV reduction of histopathologic responders (less than 10% residual tumor) was significantly higher than that of non-responders; 30.9% for histopathologic responders and 1.7% for non-responders (P=0.001). This confirms previous reports. However, when 0% SUV reduction was used as cutoff value, PET identified histopathologic response with 91% sensitivity and 50% specificity. This low specificity indicates difficulty of predicting non-responder by early PET evaluation (44).

Magnetic resonance imaging (MRI)

Diffusion-weighted MRI (DW-MRI) has been evaluated for prediction of treatment response in various cancers (45-47). The apparent diffusion coefficient (ADC) is calculated by diffusion or microstructural density (48). Because diffusion within tumor is interrupted by cellular membranes or macromolecular structures, presence or residual tumor cell can be detected as ADC decrease, conversely treatment response can be detected as ADC increase (49). So far, three studies evaluate the benefit of DW-MRI for predicting preoperative treatment (50-52). A prospective study found that change in ADC during preoperative chemoradiation was associated with pCR (50). One study reported similar result that change in ADC was associated with TRG (52), but another study did not (51). These studies were small, therefore a multi-center study assessing the value of MRI and PET-CT for predicting of preoperative treatment response (NCT02125448).

Discussion

Approximately 25% patients achieve a pCR after preoperative chemoradiation (6). If pCR could be predicted before surgery, one could consider an esophageal preservation strategy. Our group reported that clinical CR defined as negative endoscopic biopsies and PET with physiologic uptake led to favorable OS, but did not predict pCR (53,54). Therefore, we recommend that all operable EAC patients proceed to surgery. To date, the proposed Surgery-as-Needed Approach in Esophageal Cancer (SANO) trial is ongoing, evaluating whether clinical CR at 2-point evaluation (PET and EUS) after preoperative chemoradiation could predict pCR (55). New PET parameter including texture analysis or MRI might provide better pCR prediction.

Identifying who might achieve pCR after chemoradiation is important, but PET parameters are currently unable. Early PET changes can potentially play a role (14,41).

Recently, whole genome analyses of EAC are shedding light on subtypes that exist (56-60). Several gene expression

analyses are exploring predictive biomarkers including glucose transporters-1 and hexokinase (61-64).

Conclusions

This review describes the current state of understanding and future possibilities of images for predicting preoperative therapy response and for guiding personalized therapy in EAC patients. New PET parameters such as TLG or MRI may provide better response prediction. Furthermore, PET parameters combined with genomic profiling might enhance better treatment selection, prediction, and prognostication.

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Footnote

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