

Review

Predicting the Response of Neoadjuvant Therapy for Patients with Esophageal Carcinoma: an In-depth Literature Review

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Abstract

Currently, the most promising strategy to improve the prognosis of advanced esophageal cancer is neoadjuvant chemoradiation (CRT) followed by surgery. However, patients who achieved pathological complete response can experience more survival benefit. Therefore, it is critical to identify the responders early in the course of treatment. Published data demonstrate that clinic-histopathological factors, molecular biomarkers, and functional imaging are predictive of neoadjuvant therapy. The existing biomarkers, including epidermal growth factor receptors, angiogenic factors, transcription factors, tumor suppressor genes, cell cycle regulators, nucleotide excision repair pathway, cytokines, and chemotherapy associated genes, need to be validated and novel biomarkers warrant further exploration. Positron emission tomography (PET) is useful for differentiating the responders of neoadjuvant CRT. The most valuable parameters and the time point of performing PET in the course of treatment remains to be elucidated. Furthermore, predictive models incorporating the multiple categories of factors need to be established with a large, prospective, and homogeneous patient cohort in the future. Standardization of staging, biomarker detection method, and image acquisition protocol will be critical for the generalization of this model. Prospective, multi-center controlled trials, which stratified patients according to these predictive factors, will help guide individualized treatment strategies for patients with esophageal cancer.

Key words: esophageal cancer, neoadjuvant therapy, response, positron emission tomography, biomarkers

Introduction

According to the International Agency for Research on Cancer, there were an estimated 482,000 incident cases of esophageal cancer (EC) with high mortality (84%) around the world in 2008 [1]. EC often infiltrates neighboring organs and easily metastasizes to lymph nodes, and as a result, the prognosis of locally advanced patients is extremely poor, with a 5-year survival of 15-34% [2]. One possible way to

further improve the prognosis of EC is multimodal comprehensive treatment. More recently, preoperative chemoradiotherapy (CRT) has gained popularity with physicians, as its tolerance is better than postoperative CRT, permits downstaging and higher resectability in the subsequent surgery, and may eradicate occult distant disease. Several randomized clinical trials have testified a significant survival ben-

efit for neoadjuvant CRT in patients with squamous-cell carcinoma or adenocarcinoma of the esophagus [2-4]. Sjoquist et al. [5] recently conducted a meta-analysis, which included 24 clinical trials and 4188 patients with resectable esophageal carcinoma. The results showed that neoadjuvant CRT provided an 8.7% absolute survival benefit at 2 years after surgery alone and 5.1% survival benefit after neoadjuvant chemotherapy. Unfortunately, not all esophageal cancer patients benefit from neoadjuvant CRT. A proportion of patients show minor or no response to CRT and are merely exposed to its toxicity. Furthermore, neoadjuvant treatment produces a pathological complete response, and outcomes are better [6]. One retrospective study from Stahl et al. [7] showed that the overall survival was significantly hampered in patients with residual tumor in their resected specimen compared with patients who showed a pathological complete tumor remission (overall survival rate at 3 years 25.2% versus 65.6%; hazard ratio [HR] = 3.50; 95% confidence interval [CI] 1.91-6.44; $p < 0.0001$).

The treatment of tumors has currently stepped into an individualized era. It is vital to select patients who will experience survival benefit from receiving neoadjuvant CRT before treatment. Furthermore, several studies have reported that surgery can be omitted in patients that achieved pathological complete response (pCR) after neoadjuvant CRT [8, 9]. In this article, we summarize the recent literature with respect to the predictive factors of neoadjuvant CRT response and provide a review the progress of the field and future challenges to be expected.

Clinical and histopathological factors

Predictive biomarkers and functional imaging have become a hot technique for the individualized treatment of cancer. However, traditional clinical factors, such as tumor stage, patient age, and performance status, are still used to select the best therapy for a particular patient. Szumilo et al. [10] initially found that tumor invasion depth was the only clinical factor significantly correlated with response to preoperative chemotherapy for thoracic esophageal squamous cell carcinoma (ESCC). Huang et al. [11] and Hamai et al. [12] identified that age, baseline hemoglobin level, smoking habit, and tumor length were important pCR predictors in ESCC. In patients with esophageal adenocarcinoma, Patel et al. [13] found that signet ring cell histology on pretreatment biopsy predicts a decreased likelihood of pCR and survival. Additionally, prediction model or nomogram has greatly increased in the past several years. Schneider et al. [14] created a regression classification based on two parameters (histomorphologic tumor

regression and postoperative pathological node stage) to predict the complete resections following neoadjuvant CRT for EC patients. Additionally, Ajani et al. [15] established a nomogram to predict the pCR of this protocol. The following parameters were incorporated into this model: post-chemoradiation positron emission tomography (PET) standardized unit value (SUV), post-chemoradiation biopsy, sex, histologic tumor grade, and baseline endoscopic ultrasonography tumor stage. The area under the receiver-operating characteristic curve was 0.72 (95% CI: 0.662-0.787). This model needs to be prospectively validated before it can be used in clinical practice.

Serum C-reactive protein (CRP) as an inflammatory factor has also been evaluated in the treatment response prediction of EC patients. Fujiwara et al. [16] was the first to demonstrate that serum CRP levels during CRT were closely associated with the pathological response, particularly in patients with elevated CRP prior to CRT, a decrease in CRP within normal ranges 2-3 weeks following CRT initiation predicted a favorable pathological response with the highest accuracy.

Biomarkers

A large spectrum of biomarkers at the level of alterations of genomic DNA, gene expression of messenger RNA (mRNA), micro-RNA (miRNA), and protein expression have been identified and analyzed to predict the response of neoadjuvant therapy.

Cisplatin (CDDP) and 5-fluorouracil (5-FU) based neoadjuvant chemotherapy have been widely used in clinical practice. The excision repair cross-complementing 1 (*ERCC1*) gene codes for a nucleotide excision repair protein involved in the repair of radiation- and chemotherapy-induced DNA damage. Warnecke et al. [17] and Metzger et al. [18] testified that *ERCC1* mRNA expression and *ERCC1* (rs11615) gene polymorphisms correlated with treatment response to CDDP-based chemotherapy. Furthermore, RNA expression levels of 5-FU metabolism-associated genes, thymidylate synthase (TS), dihydropyrimidine dehydrogenase (DPD), thymidine phosphorylase (TP), methylenetetrahydrofolate reductase (MTHFR), as well as of CDDP and taxane-related genes glutathione S-transferase (*GSTP-1*), Caldesmon, and multi-drug resistance gene (*MRP1*) have been testified to be predictors of response to neoadjuvant therapy [19-22].

MiRNAs are small noncoding RNAs, which are involved in the regulation of gene expression by inhibiting messenger RNA translation [23]. A few studies have investigated its predictive role for therapeutic response. Odenthal et al. [24] conducted a comprehensive miRNA profiling in 16 specimens

with pre-neoadjuvant and post-neoadjuvant therapy, and the selected miRNAs were verified in 80 EC patients. The results showed that miR-192 and miR-194 in pre-therapeutic biopsies are considered indicators of major histopathologic regression. Moreover, *in vitro* assays showed that miR-296 and miR-200c expression correlated with chemotherapy resistance [25, 26]. Furthermore, miR-148a has been reported to improve response to chemotherapy in sensitive and resistant esophageal carcinoma cells [27].

Long non-coding RNAs (LncRNAs) are a new class of non-protein-coding RNAs, which are longer

than 200 bases [28]. Tong et al. [29] initially explored the relationship between LncRNA LOC285194 and the response to neoadjuvant CRT in ESCC and showed that the decreased expression of LOC285194 indicated CRT resistance and poor prognosis. Other biomarkers, such as epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), proliferating cell nuclear antigen (PCNA), p53 status, p21 status, Bcl-2, Ki-67, transcription factor nuclear factor kB (NF-kB), and Rad51 have been shown to correlate with response to neoadjuvant therapy in EC [30-39] (Table 1).

Table 1. Studies demonstrating the potential of molecular biomarkers to predict histopathological response to neoadjuvant therapy in esophageal cancer.

Study	Cancer	Neoadjuvant treatment	Sample size	Method	specimen	predictive factor	Type of cellular pathway/factor
Hickey et al.(1994) [31]	SCC	CRT	14	IHC	Pretreatment biopsy	EGFR or PCNA negative indicates response to CRT	Growth factor receptors Cell proliferation
Sarbia et al. (1998) [32]	SCC	CRT	38	IHC	Pretreatment biopsy	P53 negative and week Bcl-2 related X protein expression are positive predictors	Tumour suppressor Genes and apoptosis
Nakashima et al.(2000) [33]	SCC	chemotherapy	30	IHC	Pretreatment biopsy	P53 negative and P21 positive indicates response to chemo	Tumour suppressor Genes and Cell cycle regulators
Kitamura et al. (2000) [34]	EC	CRT	95	IHC	Biopsy tissue	P53 negative and Ki-67 antigen positive indicates response to CRT	Tumour suppressor Genes and cell proliferation
Miyazono et al.(2004) [35]	SCC: 63.9% AC: 36.1%	CRT	36	qRT-PCR assay	Pretreatment biopsy	c-erB-2 mRNA expression is a negative marker of response prediction	DNA damage repairing
Warnecke et al.(2004) [17]	SCC:63.9% AC: 36.1%	CRT	36	qRT-PCR	Pretreatment biopsy	ERCC1 mRNA expression level correlated with minor response to cisplatin based neo-CRT	Nucleotide excision repair pathway
Izzo et al. (2006) [36]	SCC:2% AC:98%	CRT	43	IHC	Pre-and post-treatment biopsy	NF-kB promotes CRT resistance	Transcription factors
Tong et al. (2014) [29]	SCC	CRT	142	qRT-PCR	Pretreatment biopsy	Decreased lncRNA LOC285194 suggested CRT resistance	Regulate the expression of proliferation-associated genes
Ajani et al. (2014) [39]	SCC:4.19% AC:95.81%	CRT	167	IHC	Pretreatment biopsy	High expression of ALDH-1suggested CRT resistance	Cancer stem cell (CSC) markers which capable of repopulation of resistant
Warnecke et al. (2010) [20]	EC	CRT	41	Low-density array RT-PCR	Pretreatment biopsy	DPD indicates major response	Chemotherapy associated genes
Metzger et al. (2012) [18]	AC	CRT	217	qRT-PCR	Paraffin-embedded tissues from resection	ERCC1 (rs11615) gene polymorphisms	Nucleotide excision repair pathway
Cheng et al. (2014) [30]	SCC	CRT	79	PLA ELISA	Serum before and <1 month after CCRT	Low VEGF-A levels indicates response to neo-CRT	Giogenetic factors
Odenthal et al. (2012) [24]	SCC:48% AC: 52%	CRT	88	miRNA profiling and RT-PCR	Pre-and post-treatment biopsy	miR-192 and miR-194 are considered as indicators of major response	miR-192: 5-FU metabolism; miR-194 targets the suppressor of cytokine signaling 2
Hofler et al. (2006) [19]	AC	chemotherapy	38	RT-PCR	Pretreatment biopsy	<i>MTHFR</i> <i>Caldesmon</i> <i>MRP1</i> and <i>MDR1</i>	Chemotherapy associated genes
Theisen et al. (2008) [21]	AC	chemotherapy	32	RT-PCR	Pretreatment biopsy	Low expression of TS, ERCC1 and GSTP-1 mRNA indicates good response	Chemotherapy associated genes
Nakanoko et al. (2014) [37]	SCC	CRT	39	IHC	Pretreatment biopsy	Rad51-negative indicates pCR	Homologous recombination
Brabender et al. (2012) [22]	SCC:10 AC:19	CRT	29	RT-PCR	blood	High expression of TS RNA indicates minor response	Chemotherapy associated genes

Zhou et al. (2011) [38]	SCC	CRT or chemo-therapy	230	RT-PCR	Pretreatment biopsy	TGF- β 1-509C/T polymorphisms were associated with response to pre-CRT	Transforming growth factor
Makuuchi et al.[41]	SCC	CRT	37	serum profile	serum	Increased sIL6R correlated with poor response to pre-CRT.	Host immune

Abbreviations: CRT, chemoradiotherapy; EGFR, epidermal growth factor receptor; PCNA: proliferating cell nuclear antigen; ERCC1, excision crosscomplementing gene 1; c-erbB-2, human epidermal growth factor receptor-2; VEGF, vascular endothelial growth factor; lncRNA, long noncoding RNA; IHC, immunohistochemistry; ALDH-1: aldehyde dehydrogenase-1; sIL6R: serum soluble interleukin-6 receptor; DPD: Dihydropyrimidine dehydrogenase; MRP1 and *MDR1*, multidrugresistance protein 1; MTHFR, methylenetetrahydrofolate reductase; TS, thymidylate synthase.; GSTP-1, glutathione S-transferase; NF-kB, nuclear factor-kB; TGF- β 1, transforming growth factor- β 1; pCR, pathological complete response; qRT-PCR, quantitative real-time polymerase chain reaction; ESCC, esophageal squamous cell carcinoma; EAC: esophageal adenocarcinoma caicinoma; CRT: chemoradiotherapy;

The above mentioned biomarkers were examined using a biopsy specimen. Noninvasive molecular markers may be more applicable and promotable in the clinic. Cheng et al. [30] adopted the proximity ligation assay (PLA) followed by enzyme-linked immunosorbent assay (ELISA) to identify serum biomarkers that predict treatment response of neoadjuvant CRT in 79 ESCC patients. Both methods testified that low pretreatment serum vascular endothelial growth factor-A (VEGF-A) significantly correlated with pCR. However, the predictive value of transforming growth factor (TGF)- β 1 was not validated by ELISA. Brabender et al. [22] also revealed that TS and DPD RNA expression in the peripheral blood of EC patients could be highly specific predictors to identify a subset of patients who do not benefit from neoadjuvant chemoradiotherapy.

It has been reported that chemoradiotherapy induces cancer cell death through tumor antigen-specific T cell response [40]. Thus, host immune status might influence the efficacy of chemoradiotherapy. Makuuchi et al. [41] conducted serum profiling of 84 cytokines in ESCC patients who received neoadjuvant CRT plus surgery and revealed that increased serum soluble interleukin-6 receptor was correlated with a poor response to preoperative therapy.

Whole genome gene expression array

It is recognized that multiple gene alterations are involved in the development and progression of EC [42]. Markers originating from different molecular levels, such as gene expression, mRNA expression, protein expression, epigenetic modification, and mutation, have always been validated independently in separate studies. Given that tumor cells interact at different levels in the organism, which interferes with angiogenesis, DNA repair and apoptosis, cell cycle control pathways, or cell-to-cell communication pathways, analysis of one pathway alone cannot cope with the complexity of the interacting tumor cells. Whole genome microarray technology allows for high-throughput identification of gene expression profiles in cancers [43]. This approach had already been used to identify genes that could serve as bi-

omarkers of neoadjuvant CRT response prediction. Table 2 summarizes the whole genome profile-related studies regarding the neoadjuvant CRT response prediction.

Luthra et al. [44] initially identified a combination of three differentially expressed genes (*PERP*, *S100A2*, and *SPRR3*) that allowed for the discrimination between pCR and <pCR with sensitivity and specificity of 85% after profiling pretreatment cancer biopsies from 19 EC patients that received neoadjuvant CRT. Duong et al. [45] performed cDNA microarrays of 46 pretreatment endoscopic biopsy samples and identified a 32-gene classifier that can be used to predict the response to CRT in ESCC. Motoori et al. [46] performed gene expression profiling on pretreatment samples of ESCC patients who received chemotherapy, and constructed a diagnostic system with 199 most informative genes that showed 82% accuracy. Schauer et al. [47] proved that the Ephrin B3 receptor, a differentially expressed gene via microarray, is related to the neoadjuvant chemotherapy response. Metzger et al. [48] identified two novel markers, *CUL2* and *STK11* using human genome microarrays, for response prediction in EC. Mahar et al. [49] established a five gene based model that predicted the response to neoadjuvant CRT with 95% accuracy in 74% of EC patients. Wen et al. [50] also performed gene expression profiling on pretreatment biopsies from 28 ESCCs who received neoadjuvant CRT in a phase III clinical trial and developed a prediction model based on three genes (*MMP*, *LIMCH1*, *Clorf226*) with 81% accuracy in the validation cohort (Table 2).

When interpreting these findings, attention must be paid to several points. First, most markers presented within this review were mainly generated by focusing on relatively small cohorts within retrospective analyses. The results are mostly preliminary and require further validation. For popularization and application of these biomarkers, large prospective trials are warranted. Second, the methods of analysis should be standardized and simplified further. Methods applied in research have to be adapted to be clinically applicable. Third, the pretreatment staging of the disease must be accurate. The staging is an

important prognostic factor for EC, which affects statistical analysis. Finally, the CRT or chemotherapy response must be evaluated pathologically. Conventional imaging modalities (endoscopy, endoscopic ultrasonography, computed tomography, and magnetic resonance imaging) cannot reliably differentiate between viable tumor and inflammatory reactions, edema, and scar tissue [51, 52].

Functional imaging data

Positron-emission-tomography with the glucose analog fluorodeoxyglucose (FDG-PET) is a functional imaging modality that can detect changes in tissue metabolism. Current evidence has shown that tumor metabolic activity has been proven to correlate with histopathologic response in EC [53]. However, PET-based parameters to stratify prognosis in the literature has varied from different studies, including pre-radiation standard unit value (SUV), post-radiation SUV, a percentage decrease of SUV, PET-tumor length, and PET-tumor volume based parameters.

The pretreatment PET evaluation is quite important in developing a strategy to identify the value of therapy in its early stage. Kato et al. [54] showed that pretreatment SUV is a reliable predictor of response to definitive CRT in ESCC. Javeri et al. [55] also demonstrated that an initial SUV higher than the median (10.1) was associated with a better pathologic response.

More attention has been paid to the dynamic changes of SUV and the timing of post-radiation FDG-PET imaging. Several studies testified that the decrease of SUV post-neoadjuvant therapy or pre-operatively can be useful for predicting pathologic response [58-61]. However, Swisher et al. [56] found that post-CRT SUV was predictive of pathologic response with a relatively low specificity. This high false positive rate may be due to the inflammatory changes following radiotherapy, which leads to falsely elevated SUV values because of the presence of metabolically active leukocytes and macrophages. Therefore, the timing of rechecking FDG-PET in the course of therapy may be critical because the false positive rate appears to decrease with time [57]. To address this question, Wieder et al. [58] studied the time course of changes in tumor FDG-uptake in patients with ESCC patients treated with preoperative therapy. The results showed that metabolic changes within the first 2 weeks of therapy are slightly better predictors compared with later changes. This observation is most likely related to the complex proinflammatory and anti-inflammatory effects of radiation, which are strongly dependent on time and dose. The authors conceived that the cytotoxic effects of

radiotherapy on radiosensitive cells, such as lymphocytes, limit the intensity of inflammatory reactions in the tumor tissue during and early after completion of therapy. Additionally, in consideration of the application of SUV in clinical practice, relative changes are better predictors of CRT response than absolute SUVs, as absolute SUVs are much more sensitive to differences in data acquisition, image reconstruction, and data analysis than relative changes [59].

Except for the SUV value, other PET image-derived parameters, such as tumor longitudinal length (TL) and volume (TV) and total lesion glycolysis (TLG = TV × SUV mean), had also been evaluated in the therapy response prediction. Hatt et al. [62] investigated the predictive value of baseline FDG-PET image-derived parameters regarding therapy response in EC patients. For study purposes, the tumor was automatically delineated on the baseline PET image using an adaptive threshold and the automatic fuzzy locally adaptive Bayesian (FLAB) methodologies to attract the TL, TV, SUV, and the derived TLG values. The results showed that commonly used parameters, such as SUVs, were not significant predictive factors of the response; parameters related to tumor functional spatial extent (TL, TV, TLG) could significantly differentiate histological response with sensitivity above 75% and specificity above 85%, regardless of the functional volume delineation strategy. However, these results cannot be repeated by Blom et al. [63], who revealed that baseline MTV and TLG were not found to be predictors of response to neoadjuvant therapy in EC patients, although a trend towards a correlation between response to CRT and smaller MTV was observed. This discrepancy may be related to the limited accuracy and reproducibility of the available tumor delineation methods, small sample size, and different response evaluation criteria in both studies.

More recently, the spatial-temporal FDG-PET has gained popularity with physicians, which offers more information, including intensity features, texture features (spatial patterns), geometry features, and geometry-intensity features (total glycolytic volume), compared to the conventional PET measures with SUV [64]. Zhang et al. [65] initially built a predictive model using multiple, comprehensive tumor response measures, including conventional FDG-PET measures, clinical parameters, and demographics, and spatial-temporal FDG-PET features. This model achieved very high accuracy (100% sensitivity and 100% specificity) for prediction of pathologic tumor response to CRT in 20 patients with EC. This model needs to be validated with a large and prospective patient cohort.

Table 2. Studies regarding the potential biomarkers of neoadjuvant-CRT response prediction using whole-genome gene expression array in esophageal cancer.

Investigator	cancer	Neoadjuvant treatment	No. of patients	method	specimen	predictive factor
Metzger et al. (2010) [48]	SCC:61% AC: 39%	CRT	66	whole-genome gene-expression array and qRT-PCR	Pretreatment biopsy	Downregulation of <i>CUL2</i> and <i>STK11</i> mRNA expression indicates minor response
Motoori et al. (2010) [46]	ESCC training cohort:25 validation cohort :10	CRT	35	whole-genome gene-expression array and qRT-PCR	Pretreatment biopsy	A diagnostic system was established with 199 genes and showed 82% of accuracy
Luthra et al. (2005) [44]	AC: 16/19 SCC:2/19 ASCC: 1/19	CRT	19	oligonucleotide microarrays and qPCR	Pretreatment biopsy	Using a combination marker approach, levels of PERP, S100A2, and SPRR3 allowed discrimination of pCR with high sensitivity and specificity (85%).
Duong et al. (2007) [45]	AC: 25/46 SCC:21/46	CRT	46	cDNA microarrays	Pretreatment biopsy	A 32-gene classifier was produced in which 10 of 21 <pCRs could be accurately identified for ESCC
Maher et al. (2009) [49]	EC training cohort:13 validation cohort :27	CRT	40	genome expression microarrays and qRT-PCR	Pretreatment biopsy	Five-genes based model predicted the response with 95% accuracy in the validation cohort
Wen et al. (2014) [50]	ESCC training cohort:28 validation cohort :32	CRT	60	genome expression microarrays and qRT-PCR	Pretreatment biopsy	Three-genes(<i>MMP</i> , <i>LIMCH1</i> , <i>Clorf226</i>) based model predicted the response with 81% accuracy in the validation cohort
Schauer et al. (2010) [47]	EAC:47	Chemotherapy	47	genome expression microarrays and IHC	Pretreatment biopsy	Ephrin B3 receptor correlated with high response rate

Abbreviations: PREP: TP53 apoptosis effector; S100A2: S100 calcium binding proteins; SPRR3: small proline-rich protein 3; MMP: matrix metalloproteinase; other abbreviations as in table 1.

In conclusion, conventional FDG-PET image-derived parameters, especially the relative changes of SUV values, have been proven a significant predictor of treatment response. Furthermore, spatial-temporal FDG-PET offers more information about the intensity, texture, geometry, and geometry-intensity features compared with the conventional PET measures with SUVs and will be useful for differentiating the responders to neoadjuvant CRT. Nevertheless, there are significant issues to be resolved with regard to the standardization of PET imaging protocols, image-processing methods and the time point for repeat imaging.

Diffusion-weighted magnetic resonance imaging (DWMRI) is also a functional imaging that is based on the microscopic random translational motion of water molecules in biological tissues. The magnitude of this motion is characterized by its apparent diffusion coefficient (ADC) values. Recently, a few studies have been published to evaluate the efficacy of ADC values in predicting neoadjuvant CRT response. Aoyagi et al. [66] analyzed the pretreatment ADC values of 80 patients with ESCC and found that an ADC value of $1.10 \times 10^{-3} \text{ mm}^2/\text{s}$ can differentiate CRT responders from non-responders (a high ADC group responded better to CRT than did a low ADC group) with a sensitivity, specificity, and accuracy of 73.8%, 86.8% and 80.0%, respectively. Similarly, Imanishi et al. [67] reported that the ADC at the time of 20 Gy and the increased rate of the ADC at the time of 20 Gy were significant predictors of treatment response in locally advanced ESCC.

Computed tomography perfusion (CTP) images can quantify tumor vascularity by measuring the

temporal changes in tissue attenuation following intravenous contrast administration, which has been reported to associate with tumor characterization, survival, and therapy response in EC [68-70]. The tumor blood flow was closely related to tissue oxygen status and tumor microcirculation, which was demonstrated to be an important factor for determining chemoradio-sensitivity. Moreover, CT is the most common modality for evaluating cancer patients. Thus, CTP parameters will provide an important insight into the individualized treatment of EC.

Conclusions

Published data demonstrate that clinic-histopathological factors, molecular biomarkers, and functional imaging are predictive of neoadjuvant therapy. These clinical factors and biomarkers need to be further validated and novel biomarkers warrant additional exploration. FDG-PET image-derived parameters, especially the relative changes of SUV values, have been proven a significant predictor of treatment response. Nevertheless, there are significant issues to be resolved with regard to the standardization of PET imaging protocols, image-processing methods and the time point for repeat imaging. In addition, it is noteworthy that there is currently no comprehensive clinical study that incorporates clinical factors, biomarkers, and functional imaging to identify patients that may benefit from receiving neoadjuvant therapy. Therefore, a predictive model based on these factors needs to be established with a large, prospective, and homogeneous patient cohort in the near future. Standardization of staging, bi-

omarker detection method, and image acquisition protocol will be critical for the generalization of this model. Aside from these outstanding discoveries, prospective, multi-center controlled trials, which stratify patients according to these predictive factors, will help guide individualized treatment strategies for patients with EC.

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Competing Interests

The authors have declared that no competing interest exists.

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