

## Early response evaluation and prediction in neoadjuvant-treated patients with esophageal cancer

Joerg Theisen, Bernd Krause, Christian Peschel, Roland Schmid, Hans Geinitz, Helmut Friess

Joerg Theisen, Helmut Friess, Department of Surgery, Klinikum rechts der Isar, TU Muenchen, 81675 Munich, Germany

Bernd Krause, Department of Nuclear Medicine, Klinikum rechts der Isar, TU Muenchen, 81675 Munich, Germany

Christian Peschel, Department of Oncology, Klinikum rechts der Isar, TU Muenchen, 81675 Munich, Germany

Roland Schmid, Department of Gastroenterology, Klinikum rechts der Isar, TU Muenchen, 81675 Munich, Germany

Hans Geinitz, Department of Radiation Oncology, Klinikum rechts der Isar, TU Muenchen, 81675 Munich, Germany

**Author contributions:** Theisen J and Friess H designed the study, acquired and analyzed the data, drafted the article and approved the final version; Krause B, Peschel C, Schmid R and Geinitz H acquired and analyzed the data, drafted the article and approved the final version.

**Correspondence to:** Joerg Theisen, PhD, Department of Surgery, Klinikum rechts der Isar, TU Muenchen, Ismaninger Str. 22, D-81675 Munich,

Germany. [theisen@chir.med.tu-muenchen.de](mailto:theisen@chir.med.tu-muenchen.de)

Telephone: +49-89-41405134 Fax: +49-98-41404870

Received: October 9, 2009 Revised: November 3, 2009

Accepted: November 10, 2009

Published online: November 30, 2009

### Abstract

Since the introduction of multimodal therapy regimens, the prognosis of esophageal cancer has improved. There is undoubtedly true for patients with surgically resected tumors in the case of a response to neoadjuvant chemotherapy or chemoradiation. Important conclusions can be drawn from this regarding the indication for perioperative therapies, the radicality of surgery, or the surgical indications. Thus, most of the current research in this field is aimed at the early identification of this subset of patients, at the beginning of, or even before, neoadjuvant treatment. Conventional staging tools have failed to predict responses to neoadjuvant therapy. However, molecular imaging methods, e.g. positron emission tomography (PET)-scans, have shown promising results in the early selection of responders and non-responders during the course of neoadjuvant therapy, allowing physicians to alter the treatment plan

accordingly. Even more desirable is the identification of potential responders before the start of neoadjuvant therapy. Preliminary molecular data on biopsy specimens demonstrate the possibility of early response prediction in these patients. We present the current knowledge on response evaluation and prediction in esophageal cancer and draw conclusions for future clinical practice and studies in this review.

© 2009 Baishideng. All rights reserved.

**Key words:** Esophageal cancer; Response prediction; Individualized therapy

**Peer reviewers:** Giuseppe Aprile, MD, Department of Medical Oncology, University Hospital of Udine, Piazzale S Maria della Misericordia, 33100 Udine, Italy; Mehmet Fatih Can, MD, Kent Koop Mh. 11.Cad. Guneyce Merkez Sit. A/10, 06370, Batikent, Ankara, Turkey

Theisen J, Krause B, Peschel C, Schmid R, Geinitz H, Friess H. Early response evaluation and prediction in neoadjuvant-treated patients with esophageal cancer. *World J Gastrointest Surg* 2009; 1(1): 30-37 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v1/i1/30.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v1.i1.30>

### INTRODUCTION

The last decade has seen a change in the therapy of patients with esophageal cancer. For many years, the standard therapy for locally advanced lesions has been surgical resection. However, overall survival for patients with locally advanced tumors after resection remains poor, with a five-year survival rate between 10% and 30%<sup>[1,2]</sup>. Most patients still present with an advanced tumor stage; therefore, multimodal therapy regimens have been introduced, some using neoadjuvant chemotherapy or radiochemotherapy followed by radical resection, whereas others use adjuvant protocols<sup>[3]</sup>. Furthermore, trials have been presented in which surgery was omitted completely. Currently,

there is no evidence-based international agreement on one or the other multimodal approach. The results have been conflicting. Some have demonstrated a benefit for neoadjuvant radiochemotherapy, others for neoadjuvant chemotherapy, and some favour an adjuvant approach. Other published studies did not find any difference in survival for a multimodal concept. There are multiple reasons for these marginal differences and for the controversies in the preferred regimens, such as the heterogeneity of the groups analyzed, mixing squamous cell cancer of the esophagus with esophageal adenocarcinoma or analyzing true esophageal adenocarcinoma (Barrett's cancer) together with carcinomas of the esophago-gastric junction and proximal gastric carcinomas. It is very important to stress that esophageal adenocarcinoma and squamous cell cancer of the esophagus have to be considered as completely different entities and therefore separate analysis is mandatory<sup>[4]</sup>. Additionally several protocols for chemotherapy and radiochemotherapy have been used. However, careful analysis of the published results indicates that there is always a subset of patients benefiting from the multimodal approach<sup>[5]</sup>. These are patients who show a response to the respective neoadjuvant or adjuvant protocol. This is the case for all the different regimens applied. Unfortunately, in most studies the treatment response is not clearly defined. The current gold standard for response assessment is the pathohistological statement of the amount of viable tumor cells within the resected specimen. This gold standard might be an adequate tool for all adjuvant protocols because of the opportunity to tailor postresection therapy accordingly. However, the current trend favors neoadjuvant trials. The Patterns of Care studies in the US showed that neoadjuvant chemoradiation therapy increased from approximately 10% during 1992-1994 to approximately 26% in 1996-1999 for locally advanced esophageal carcinomas<sup>[5]</sup>. A meta-analysis of the survival benefit in the neoadjuvant setting found an increase in survival for neoadjuvant radiochemotherapy in squamous cell cancer of the esophagus and to a lesser extent for adenocarcinoma using chemotherapy alone. Protocols using radiochemotherapy in the neoadjuvant setting in patients with esophageal adenocarcinoma did show a benefit compared to chemotherapy alone<sup>[6]</sup>. For this preoperative approach, the pathohistological assessment of response is available too late to modify any preoperative protocols. Therefore, current research activities aim to identify predictors of response early or even before the neoadjuvant concepts are applied to individualize therapies according to the respective tumor behaviour.

There are several theoretical components available for the prediction of pretherapeutic response. Demographic data, initial staging imaging tools, biopsies, and serum. Pure clinical response evaluation after neoadjuvant therapy for esophageal cancer is highly inaccurate<sup>[7]</sup>. Despite numerous studies in this field, no clear reliable candidate marker predicting response was identified. However, recent studies using new technologies such as gene chips or molecular imaging have shown promising early results towards a response prediction or response evaluation.

**Table 1** Histopathological response classification according to the amount of residual tumor within the tumor bed according to Becker *et al.*<sup>[9]</sup>

Grade	Description	Response
1a	No residual tumor/tumor bed	Responder
1b	< 10% residual tumor/tumor bed	Responder
2	10%-50% residual tumor/tumor bed	Partial responder
3	> 50% residual tumor/tumor bed	Non-responder

## HISTOPATHOLOGICAL RESPONSE

The current gold standard for response prediction is the histopathological assessment of the tumor regression grade as described by Mandard *et al.*<sup>[8]</sup> and slightly modified by Becker *et al.*<sup>[9]</sup> for esophageal and gastric tumors. This regression grading system stratifies response based on the biological effect of radiation or chemotherapy on the amount of remaining viable tumor cells. There are three to five grades based on the ratio of fibrosis to remaining viable tumor content. Complete pathohistological response means that there are no viable residual tumor cells present. Partial response is defined as the presence of tumor cells scattered through the fibrosis, and minimal regression showing residual cancer outgrowing fibrosis. Absence of any regressive changes is considered a no-change situation. For esophageal and gastric tumors, Becker *et al.*<sup>[9]</sup> described a clinically useful four-grade classification based on an estimation of the percentage of vital tumor tissue in relation to the tumor bed (Table 1). Patients with no or < 10% residual tumor cells (tumor regression score 1) are classified as responders. All other tumors (tumor regression score 2: 10%-50% residual tumor cells and tumor regression score 3: > 50% residual tumor cells) were classified as non responders. This tumor response grading system is clearly associated with survival and currently serves as the gold standard for response assessment. However, this prognostic system is not available prior to neoadjuvant therapy and therefore is more useful in the potential adjuvant setting.

To date, a predictor of response based on demographics or conventional imaging information has not emerged. Performance status, primary location or age has not been shown to be associated with pathological response<sup>[10]</sup>.

## APPROACH TO RESPONSE ASSESSMENT

In addition to the availability of components such as serum or biopsies, several methods have been used to predict as early as possible the response to neoadjuvant therapy. In the past, most studies used immunohistochemical methods to assess the response. The approach to the analyzed proteins has been either chemotherapy drugs driven or proteins have been chosen that have been shown to play a role in the behaviour of certain malignancies. However, single potential biomarkers have failed to sufficiently predict response to neoadjuvant therapy. This is not surprising considering the complex interactions between all the gene products expressed by the cells, and the many proteins

involved in numerous cellular functions, such as apoptosis, DNA repair, and the metabolism and detoxification of drugs; all of which contribute to the individual response of a given tumor. Therefore, it is likely that multiple markers are needed to define the sensitivity or resistance of tumors to specific drugs. In recent years, new technologies using microarray gene chips or proteomics have been used for response prediction studies. These technologies enable the analysis of thousands of genes at the same time with a single biopsy specimen at the RNA/DNA or protein level.

Molecular imaging has emerged in recent years as an important technique. Many studies have been published showing a significant correlation of tumor metabolism and pathohistological response. Based on these results, therapy regimens have been successfully changed according to the response behaviour. Unfortunately, this information is not available prior to the therapy. At least two weeks of the neoadjuvant chemo- or radiochemotherapy has to be given before the molecular imaging is able to distinguish between responders and non-responders.

## MOLECULAR RESPONSE PREDICTION IN ESOPHAGEAL SQUAMOUS CELL CANCER

Patients with locally advanced squamous cell cancer of the esophagus are currently treated with either neoadjuvant radiochemotherapy or definitive radiochemotherapy. These regimens differ in the radiation dosages used. In the neoadjuvant setting, approximately 45 Gray are administered followed by esophagectomy with lymphadenectomy. Radiochemotherapy without resection applies approximately 50 to 60 Gray to the tumor region and the corresponding lymph nodes areas.

In a retrospective study of 68 patients with locally advanced esophageal squamous cell cancer who received a multimodal treatment with 5-Fluorouracil (5-FU) based radiochemotherapy, Sarbia and colleagues examined the correlation of the presence of genetic polymorphisms in genes involved in folate metabolism with the response behaviour and outcome<sup>[11]</sup>. The DNA of pretherapeutic biopsies was genotyped for common genetic polymorphisms of MTHFR (5,10-methylenetetrahydrofolate reductase), MTR (Methionine synthase), and TS (thymidylate synthase) tandem repeat polymorphisms. Tumors with an MTR wild-type genotype showed a shorter survival in contrast to tumors with an MTR variant genotype. This correlated with the response behaviour, where tumors with an MTR variant genotype responded more frequently to the neoadjuvant radiochemotherapy. In a subsequent study by Sarbia and colleagues, the expression of proteins involved in DNA repair and/or cell-cycle regulation, including p53 (phosphorylated at Ser15), EGFR (Epidermal Growth Factor Receptor), ATM (ataxia-telangiectasia mutated) protein kinase (phosphorylated at Ser1981), and checkpoint kinase 2 (CHK2) (phosphorylated at Thr68), was correlated with the response to RCTx and with overall survival<sup>[12]</sup>. Tumours that were positive for CHK2

expression more frequently showed clinically determined regression after RCTx than tumours that were negative for CHK2 expression, whereas other parameters did not correlate with tumour regression. Expression of ATM correlated with expression of CHK2 and p53-phospho. In contrast to histopathological response evaluation, none of the molecular parameters under investigation correlated with overall survival.

Other studies aimed to identify genes or proteins involved in resistance to 5-FU or cisplatin, found that 5-FU metabolism pathway genes, such as TS (thymidylate synthase), TP (thymidine phosphorylase), and DPD (dihydropyrimidine dehydrogenase), or genes involved in DNA-repair mechanisms, such as ERCC-1 (excision repair cross complementing), GSTP-1 (Glutathione S-transferase), or nm23-H1, were somewhat predictive for the response behaviour in patients with neoadjuvant radiochemotherapy. These studies were done either by immunohistochemistry or quantitative RT-PCR technologies<sup>[13,14]</sup>.

Metallothionein (MT) is a small protein involved in many patho-physiological processes such as detoxification, cell proliferation, apoptosis, and therapy resistance. Kishi *et al.*<sup>[15]</sup> demonstrated that high expression of this protein is associated with a poor prognosis due to non-response in patients with localized squamous cell cancer of the esophagus who received neoadjuvant radiochemotherapy. However, no such association could be found in another study by Harpole *et al.*<sup>[16]</sup>.

To date, however, none of these studies has shown one independent predictive factor on multivariate analysis.

With regard to molecular markers, the *p53* gene is one of the most widely investigated genes in human cancer. It has been found as a prognostic indicator in many different carcinomas<sup>[17,18]</sup>. It plays a crucial role in repairing DNA of damaged cells, is involved in triggering apoptosis, and might be intrinsically involved in the response to radiochemotherapy. Several studies have examined *p53* expression and the response to radiochemotherapy in esophageal cancer<sup>[19,20]</sup>. In patients with squamous cell cancer of the esophagus, Seitz *et al.*<sup>[21]</sup> used immunohistochemistry to demonstrate a significant association of *p53* overexpression and decreased response rates. Other groups have not found this association<sup>[22]</sup>. It is postulated that this difference might be due to gene deletion, failure of transcription, or a non-stabilizing mutation, all of which might lead to loss of *p53* function<sup>[23]</sup>.

The protein p21 is transcriptionally regulated by p53 by ionising radiation. This can cause cell cycle arrest and apoptosis. p21 is involved in disruption of regulatory networks and might be a good candidate gene for radioresistance prediction. However, as with many other single gene studies, the published results have been controversial. Some studies describe a positive correlation of p21 positivity and response or survival, while others were not able to demonstrate a correlation of p21 expression and response to radiochemotherapy<sup>[24-26]</sup>.

Much research has been done in the past in studying COX-2 (Cyclooxygenase-2) expression and response in esophageal cancer. COX-2 plays an important role in

prostaglandin synthesis and is involved in angiogenesis and tumor growth. Results from cervical cancer demonstrating a predictive potential of COX-2 mRNA expression have been adapted to squamous cell cancer of the esophagus<sup>[27]</sup>. A study by Takatori *et al.*<sup>[28]</sup> of 29 patients with esophageal squamous cell cancer who received neoadjuvant radiochemotherapy, found that high COX-2 mRNA expression in tumor biopsies was significantly associated with a poor response to radiochemotherapy and ultimately with a poor survival in these patients.

Another important aspect associated with molecular response prediction is growth regulation. Several proteins have been studied, such as epidermal growth factor receptor (EGFR), HER-2 (human epidermal growth factor receptor), and different cyclins. The results have been conflicting; for example HER-2 and cyclin D1 expressions have been found to be correlated with response to neoadjuvant radiochemotherapy in patients with squamous cell carcinoma of the esophagus, but failed to be predictive for the overall survival<sup>[29]</sup>. By studying EGFR and proliferating cell nuclear antigen, Hickey *et al.*<sup>[30]</sup> reported an inverse relationship of response and expression in immunostaining of biopsies of patients with esophageal squamous cell cancer.

More convincing evidence was demonstrated by analysing VEGF (vascular endothelial growth factor) in the context of response prediction. VEGF is the major angiogenic factor in pathological angiogenesis. Angiogenesis plays a very important role in the promotion of tumor growth and formation of metastases. In a study by Shimada *et al.*<sup>[31]</sup>, co-expression of p53, TP, and VEGF (analysed by immunohistochemistry) was correlated to the response behaviour and survival in patients with squamous cell cancer of the esophagus. In a multivariate analysis, only VEGF emerged as a predictor of response to the neoadjuvant radiochemotherapy. Its expression was associated with a high incidence on non-responders and significantly worse survival. These results were supported by a study from Gorski and colleagues, who demonstrated that blocking the activity of VEGF enhances the effects of radiochemotherapy on the tumor<sup>[32]</sup>. The mechanisms behind this effect are not fully understood, but angiogenic factors seem to be a valuable clinical target for influencing the response behaviour in neoadjuvant treated squamous cell cancer of the esophagus.

One of the reasons for the conflicting results is the fact that most studies focused on single or few gene expression analyses. Tumor tissue has a very heterogeneous gene profile; therefore, the likelihood of finding a single gene responsible for the regulation of tumor resistance or sensitivity is very low. Recently, the introduction of RNA/DNA or protein microarrays opened the door for a variety of studies of molecular tumor profiling<sup>[33]</sup>. Duong *et al.*<sup>[34]</sup> were able to demonstrate a positive predictive value of 100% and a negative predictive value of 79% in regards to response prediction in 21 patients with squamous cell carcinoma of the esophagus receiving neoadjuvant radiochemotherapy using SVM (support vector machine) modelling and LOOCV (Leave-one-out cross-validation) analyses as a multigene classifier. A 32-gene classifier was

used to predict response to neoadjuvant radiochemotherapy. By further analyzing the specific genes involved in response prediction, most of the sequences were found to be involved in the apoptosis and angiogenesis pathways.

### Serum markers

Several serum markers have been tested to predict response to neoadjuvant radiochemotherapy in patients with esophageal squamous cell cancer, including CEA (carcinoembryonic antigen), VEGF, and CYFRA (cytokeratin fragment) 21-1<sup>[35,36]</sup>. CYFRA was the only marker showing a close correlation between its serum level and response, but it has not been studied in a large prospective clinical trial.

### Molecular imaging

The introduction of molecular imaging, such as FDG-PET (fluoro-deoxy-glucose-positron emission tomography) has changed the field with respect to the previous disappointing results of the conventional image methods in predicting response to neoadjuvant therapies. CT-scan, MRI, or EUS have failed to accurately predict tumor resistance or sensitivity. A recent meta-analysis found FDG-PET to be more accurate than a CT-scan for the measurement of treatment response<sup>[37]</sup>. There was no differentiation possible between inflammation, scars, and remnant carcinoma. FDG-PET is based on the high glucose metabolism of a tumor compared to normal tissue, enabling a good differentiation of tumor areas from non-tumor tissue. Recently, PET-CT-scans have combined the metabolism with anatomic location<sup>[38]</sup>. The relative changes in FDG uptake have been used for early response evaluation in a variety of tumor entities, such as breast<sup>[39]</sup>, lung<sup>[40]</sup>, and colon<sup>[41]</sup> cancer, as well as in Hodgkin's<sup>[42]</sup> and non Hodgkin's lymphoma<sup>[43]</sup>. There have been encouraging results in predicting response in patients with esophageal squamous cell cancer. Most studies performed the PET examination before the neoadjuvant radiochemotherapy and at the end of the preoperative protocol<sup>[44-48]</sup>. The relative decrease in standardized uptake value (SUV) between these two examinations served as a discriminator for response or non-response. The results were then correlated to the histopathological response assessment. By applying this approach, Brücher *et al.*<sup>[48]</sup> were able to demonstrate a correlation between SUV decrease and histopathological response in 24 patients with esophageal squamous cell cancer. This was confirmed by other authors. Some even suggested that the absolute SUV of the initial PET might be sufficient to predict the response behaviour<sup>[45]</sup>. Recently, studies have been published with PET scans performed initially and two weeks into the neoadjuvant radiochemotherapy<sup>[45]</sup>. With the cut-off point at 30% reduction in SUV, a separation of responders from non-responders was possible after only two weeks with a sensitivity of 93%, a specificity of 88%, and an accuracy of 79%. Notably, non-responding patients who stopped the neoadjuvant chemotherapy after two weeks did not show a difference in survival compared to the patients who previously received the entire three months of chemo-

**Table 2** Studies that have assessed the role of a PET scan in the response prediction of patients with neoadjuvant treated squamous cell cancer of the esophagus

Author	n	RCTx	2nd PET	Correlation of PET with histopathological response yes/no
Song <i>et al</i> <sup>[44]</sup> , 2005	32	Cis/Cap/46 Gy	4 wk	Yes
Wieder <i>et al</i> <sup>[45]</sup> , 2004	38	5-FU/40 Gy	During RCTx	Yes
Flamen <i>et al</i> <sup>[46]</sup> , 2002	27	Cis/5-FU/40 Gy	After RCTx	Yes (tumor:liver ratio)
Kato <i>et al</i> <sup>[47]</sup> , 2002	10	5-FU/30 Gy	After RCTx	No
Brücher <i>et al</i> <sup>[48]</sup> , 2001	24	5-FU/30 Gy	After RCTx	Yes

PET: Positron emission tomography; Cis: Cisplatin; Cap: Capectabine; 5-FU: 5-Fluorouracil; Gy: Gray; RCTx: Radiochemotherapy.

therapy. Without any decrease in survival, 2.5 months of chemotherapy could be avoided in these patients. At this time point, therapeutic regimens could be individualized based on the PET results. Performing the 2nd PET-scan after one week of radiochemotherapy failed to predict the pathological response<sup>[49]</sup>. Table 2 shows a summary of the current available results of PET-guided response evaluation on esophageal squamous cell cancer.

## ADENOCARCINOMA OF THE ESOPHAGUS

### Molecular response prediction

In patients with adenocarcinoma of the esophagus, the multimodal concepts differ considerably compared to the treatment regimens in squamous cell cancer. Some groups apply chemotherapy alone; others prefer a combination of radiation and chemotherapy in the multimodal setting. Therefore, it is difficult to compare the results of different studies. Additionally, adenocarcinoma of the esophagus is a much more heterogeneous tissue, with areas of invasive cancer, high-grade intraepithelial neoplasia, and the precursor lesion specialized intestinal metaplasia (Barrett's metaplasia) adjacent to each other. By taking single biopsies there is always a high risk of sampling error.

With regard to molecular response prediction, more work has been published for adenocarcinomas compared to squamous cell cancer of the esophagus. The introduction of quantitative high-throughput RT-PCR technologies, such as TaqMan, greatly increased the likelihood of identifying potential genes, or groups of genes, involved in response prediction. Most of the published studies focused on the analyses of drug targets involved in the metabolism of the most commonly used chemotherapy agents, such as 5-FU and platinum compounds. In a study by Langer *et al*<sup>[50]</sup> the quantitative RNA expression in biopsies of Barrett's carcinomas prior to the neoadjuvant chemotherapy of genes involved in the 5-FU metabolism (TS, TP, DPD, MTHFR, MAP7 (Mitogen-activated protein), and ELF3 (eukaryotic initiation factor) and platinum-related genes, caldesmon, ERCC1, ERCC4, HER-2/neu, GADD45, and MRP1) were determined and compared to the histopathological response assessment of the post-operative specimen. There was a significant correlation between the pretherapeutic expression levels of MTHFR, caldesmon, and MRP1 with the histopathological response. Other groups found an association between TS,

ERRC1, DPD, and GADD45 (growth arrest and DNA damage-inducible gene) and response<sup>[51,52]</sup>.

In the past, p53 has been one of the most studied genes with regard to response prediction in esophageal adenocarcinoma, as well as in squamous cell cancer of the esophagus. Several trials found an inverse correlation between p53-positive tumors identified immunohistochemically and response. The entire apoptosis pathway seems to play a crucial role in the chemosensitivity of neoadjuvant-treated Barrett carcinomas. Genes such as c-erbB-2, p53, p21, ki76, and bcl-2 (B-cell lymphoma) have been shown to be involved in response prediction<sup>[53]</sup>. These results were obtained either by immunohistochemistry or by quantitative RT-PCR methods.

The introduction of microarray technologies opened an entirely new area of response prediction on biopsy material. This has led to a large increase in published studies that have enhanced our understanding of the biology of esophageal adenocarcinoma. Problems still arise from the difficulties in analysing the enormous amounts of data generated by these arrays. Different analytical approaches are currently available, such as unsupervised hierarchical cluster analysis of LOOCV analysis. The first published studies demonstrated promising results in identifying a cluster of 30-100 genes closely related to the response behaviour of these tumors. Furthermore, these gene expression studies identified some very interesting new genes that might serve as targets for new therapeutic approaches<sup>[54,55]</sup>.

More recently, proteomic profiling has become feasible. First studies on cell lines assessing the chemosensitivity of a variety of cell lines, including esophageal cancer cell lines, provided the basis for the prediction of drug response based on protein markers<sup>[56]</sup>. A combination of these technologies might hold great promise for the future with regard to response prediction.

Currently, there is no reliable molecular marker for tumor response to neoadjuvant therapy. Early results are promising. Luthra *et al*<sup>[57]</sup> and Ashida *et al*<sup>[58]</sup> reported hierarchical clustering of gene expression profiles of esophageal carcinoma segregated samples into two major groups that correlated with response and identified genes differentially expressed between long- and short-term survival after neoadjuvant therapy for esophageal cancer. Additionally, Duong and colleagues<sup>[34]</sup> used a 32-gene classifier to predict response. These are all preliminary results, and to date, no clinical recommendations can be drawn from this.

**Table 3** Studies that have assessed the role of a PET scan in the response prediction of patients with neoadjuvant treated Barrett's cancer and cancer of the gastroesophageal junction

Author	n	CTx	2nd PET	Correlation of PET with histopathological response yes/no
Lordick <i>et al.</i> <sup>[60]</sup> , 2007	110	Cis/5-FU	2 wk during CTx	Yes
Ott <i>et al.</i> <sup>[59]</sup> , 2006	65	Cis/5-FU	2 wk during CTx	Yes
Gillham <i>et al.</i> <sup>[49]</sup> , 2006	29	Cis/5-FU	After CTx	No
Levine <i>et al.</i> <sup>[61]</sup> , 2006	52	Cis/5-FU	After CTx	Yes
Swisher <i>et al.</i> <sup>[62]</sup> , 2004	73	Cis/5-FU/50,4 Gy Irin/5-FU/Taxol/50,4 Gy Taxol/Carbo/50,4 Gy	After RCTx	Yes
Brink <i>et al.</i> <sup>[63]</sup> , 2004	13	Cis/5-FU	After CTx	No
Arslan <i>et al.</i> <sup>[64]</sup> , 2002	22	Cis/Taxol/50,4 Gy	After RCTx	Yes
Weber <i>et al.</i> <sup>[65]</sup> , 2001	40	Cis/5-FU	2 wk during CTx	Yes

Cis: Cisplatin; Irin: Irinotecan; Carbo: Carboplatin; 5-FU: 5-Fluorouracil; Gy: Gray; RCTx: Radiochemotherapy; CTx: Chemotherapy.

### Molecular imaging

In Barrett's cancer, the use of PET-scan for the evaluation of response has been widely studied. These studies suggested that changes in FDG uptake in response to therapy correlates with the pathological response and predicts the risk of local recurrence and survival. Unfortunately, there have been no data published exclusively investigating the role of FDG-PET in adenocarcinoma of the esophagus. Therefore, it is difficult to assess the usefulness of PET imaging in predicting response to neoadjuvant chemotherapy in adenocarcinomas of the esophagus. The only good prospective trials were published in 2006 by Ott *et al.*<sup>[59]</sup> followed by Lordick *et al.*<sup>[60]</sup> in 2007. In the initial study on 65 patients with esophageal adenocarcinoma and some carcinoma at the cardia, the authors demonstrated that by taking a SUV decrease greater than 35% as the precondition of response, a prediction was possible during the neoadjuvant therapy after only two weeks. These results were correlated to the pathohistological response assessment on the operative specimen. This study was followed by a prospective trial where, for the first time, the therapy was tailored according to the changes in SUV uptake after two weeks. The responding group continued on chemotherapy followed by resection, whereas the group of patients who did not respond to the neoadjuvant chemotherapy discontinued chemotherapy after two weeks and proceeded directly to surgery. Complete histopathological response was noted in almost 60% of the PET responders in contrast to the PET non-responders, in which no histological response was noted. This first prospective trial confirmed the feasibility of a PET guided treatment plan after only two weeks of neoadjuvant chemotherapy. Other groups have also shown the value of PET scan in response prediction<sup>[61-65]</sup>. Based on these results, two major questions arose: (1) What treatment changes have to be made to the non-responders to increase the number of patients responding to the therapy? (2) Is it really necessary in the responder group to complete the entire cycle of neoadjuvant chemotherapy or is the biological selection after two weeks already sufficient for a prolongation in survival?

Table 3 lists the currently available data for PET guided response prediction in Barrett's cancer.

### CONCLUSION

It is clear that the identification of predictors of response will change the management of patients with locally advanced adenocarcinoma and squamous cell cancer of the esophagus. Molecular imaging has conclusively shown that an early response evaluation is feasible after only two weeks of neoadjuvant therapy. The changes in SUV-uptake of PET scans prior to, and two weeks after, the beginning of the therapy correlated with the final histological response assessment and survival. Prospective trials have been published using this change in SUV uptake to tailor the therapy regimen accordingly.

It would be more desirable to predict the response prior to any kind of therapy. Several attempts have been made to predict response on the molecular level using biopsy material. Unfortunately, there are no single markers available at present that conclusively predict neoadjuvant therapy response. It is more likely that a panel of genes generated by microarray analyses or proteins detected by proteomics will be able to mirror the complex genetic behaviour of a tumor responding to chemotherapy or radiochemotherapy. Promising initial work is accumulating. Based on these data, a more individualized therapy of these patients could be performed with the ultimate goal of allowing as many patients as possible the survival benefit of a response to a neoadjuvant concept.

### REFERENCES

- 1 **Altorki N**, Kent M, Ferrara C, Port J. Three-field lymph node dissection for squamous cell and adenocarcinoma of the esophagus. *Ann Surg* 2002; **236**: 177-183
- 2 **Lerut T**, Coosemans W, De Leyn P, Deneffe G, Topal B, Van de Ven C, Van Raemdonck D. Reflections on three field lymphadenectomy in carcinoma of the esophagus and gastroesophageal junction. *Hepatogastroenterology* 1999; **46**: 717-725
- 3 **Geh JI**, Crellin AM, Glynne-Jones R. Preoperative (neoadjuvant) chemoradiotherapy in oesophageal cancer. *Br J Surg* 2001; **88**: 338-356
- 4 **Siewert JR**, Ott K. Are squamous and adenocarcinomas of the esophagus the same disease? *Semin Radiat Oncol* 2007; **17**: 38-44
- 5 **Suntharalingam M**, Moughan J, Coia LR, Krasna MJ, Kachnic L, Haller DG, Willett CG, John MJ, Minsky BD, Owen JB. The national practice for patients receiving radiation ther-

- py for carcinoma of the esophagus: results of the 1996-1999 Patterns of Care Study. *Int J Radiat Oncol Biol Phys* 2003; **56**: 981-987
- 6 **Gebski V**, Burmeister B, Smithers BM, Foo K, Zalberg J, Simes J. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. *Lancet Oncol* 2007; **8**: 226-234
  - 7 **Adelstein DJ**, Rice TW, Becker M, Larto MA, Kirby TJ, Koka A, Tefft M, Zuccaro G. Use of concurrent chemotherapy, accelerated fractionation radiation, and surgery for patients with esophageal carcinoma. *Cancer* 1997; **80**: 1011-1020
  - 8 **Mandard AM**, Dalibard F, Mandard JC, Marnay J, Henry-Amar M, Petiot JF, Roussel A, Jacob JH, Segol P, Samama G. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinico-pathologic correlations. *Cancer* 1994; **73**: 2680-2686
  - 9 **Becker K**, Mueller JD, Schulmacher C, Ott K, Fink U, Busch R, Böttcher K, Siewert JR, Höfler H. Histomorphology and grading of regression in gastric carcinoma treated with neoadjuvant chemotherapy. *Cancer* 2003; **98**: 1521-1530
  - 10 **Chirieac LR**, Swisher SG, Ajani JA, Komaki RR, Correa AM, Morris JS, Roth JA, Rashid A, Hamilton SR, Wu TT. Post-therapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemoradiation. *Cancer* 2005; **103**: 1347-1355
  - 11 **Sarbia M**, Stahl M, von Weyhern C, Weirich G, Pühringer-Oppermann F. The prognostic significance of genetic polymorphisms (Methylenetetrahydrofolate Reductase C677T, Methionine Synthase A2756G, Thymidilate Synthase tandem repeat polymorphism) in multimodally treated oesophageal squamous cell carcinoma. *Br J Cancer* 2006; **94**: 203-207
  - 12 **Sarbia M**, Ott N, Pühringer-Oppermann F, Brücher BL. The predictive value of molecular markers (p53, EGFR, ATM, CHK2) in multimodally treated squamous cell carcinoma of the oesophagus. *Br J Cancer* 2007; **97**: 1404-1408
  - 13 **Joshi MB**, Shirota Y, Danenberg KD, Conlon DH, Salonga DS, Herndon JE 2nd, Danenberg PV, Harpole DH Jr. High gene expression of TS1, GSTP1, and ERCC1 are risk factors for survival in patients treated with trimodality therapy for esophageal cancer. *Clin Cancer Res* 2005; **11**: 2215-2221
  - 14 **Gillham CM**, Reynolds J, Hollywood D. Predicting the response of localised oesophageal cancer to neo-adjuvant chemoradiation. *World J Surg Oncol* 2007; **5**: 97
  - 15 **Kishi K**, Doki Y, Miyata H, Yano M, Yasuda T, Monden M. Prediction of the response to chemoradiation and prognosis in oesophageal squamous cancer. *Br J Surg* 2002; **89**: 597-603
  - 16 **Harpole DH Jr**, Moore MB, Herndon JE 2nd, Aloia T, D'Amico TA, Sporn T, Parr A, Linoila I, Allegra C. The prognostic value of molecular marker analysis in patients treated with trimodality therapy for esophageal cancer. *Clin Cancer Res* 2001; **7**: 562-569
  - 17 **Quinlan DC**, Davidson AG, Summers CL, Warden HE, Doshi HM. Accumulation of p53 protein correlates with a poor prognosis in human lung cancer. *Cancer Res* 1992; **52**: 4828-4831
  - 18 **Thomas DJ**, Robinson M, King P, Hasan T, Charlton R, Martin J, Carr TW, Neal DE. p53 expression and clinical outcome in prostate cancer. *Br J Urol* 1993; **72**: 778-781
  - 19 **Ribeiro U Jr**, Finkelstein SD, Safatle-Ribeiro AV, Landreneau RJ, Clarke MR, Bakker A, Swalsky PA, Gooding WE, Posner MC. p53 sequence analysis predicts treatment response and outcome of patients with esophageal carcinoma. *Cancer* 1998; **83**: 7-18
  - 20 **Lowe SW**, Ruley HE, Jacks T, Housman DE. p53-dependent apoptosis modulates the cytotoxicity of anticancer agents. *Cell* 1993; **74**: 957-967
  - 21 **Seitz JF**, Perrier H, Monges G, Giovannini M, Gouvernet J. [Multivariate analysis of the prognostic and predictive factors of response to concomitant radiochemotherapy in epidermoid cancers of the esophagus. Value of immunodetection of protein p53] *Gastroenterol Clin Biol* 1995; **19**: 465-474
  - 22 **Lam KY**, Law S, Ma LT, Ong SK, Wong J. Pre-operative chemotherapy for squamous cell carcinoma of the oesophagus: do histological assessment and p53 overexpression predict chemo-responsiveness? *Eur J Cancer* 1997; **33**: 1221-1225
  - 23 **Catalano V**, Baldelli AM, Giordani P, Cascinu S. Molecular markers predictive of response to chemotherapy in gastrointestinal tumors. *Crit Rev Oncol Hematol* 2001; **38**: 93-104
  - 24 **Nakamura T**, Hayashi K, Ota M, Ide H, Takasaki K, Mitsuhashi M. Expression of p21(Waf1/Cip1) predicts response and survival of esophageal cancer patients treated by chemoradiotherapy. *Dis Esophagus* 2004; **17**: 315-321
  - 25 **Nakashima S**, Natsugoe S, Matsumoto M, Kijima F, Takebayashi Y, Okumura H, Shimada M, Nakano S, Kusano C, Baba M, Takao S, Aikou T. Expression of p53 and p21 is useful for the prediction of preoperative chemotherapeutic effects in esophageal carcinoma. *Anticancer Res* 2000; **20**: 1933-1937
  - 26 **Okumura H**, Natsugoe S, Matsumoto M, Mataka Y, Takatori H, Ishigami S, Takao S, Aikou T. The predictive value of p53, p53R2, and p21 for the effect of chemoradiation therapy on oesophageal squamous cell carcinoma. *Br J Cancer* 2005; **92**: 284-289
  - 27 **Kim YB**, Kim GE, Pyo HR, Cho NH, Keum KC, Lee CG, Seong J, Suh CO, Park TK. Differential cyclooxygenase-2 expression in squamous cell carcinoma and adenocarcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys* 2004; **60**: 822-829
  - 28 **Takatori H**, Natsugoe S, Okumura H, Matsumoto M, Uchikado Y, Setoyama T, Sasaki K, Tamotsu K, Owaki T, Ishigami S, Aikou T. Cyclooxygenase-2 expression is related to prognosis in patients with esophageal squamous cell carcinoma. *Eur J Surg Oncol* 2008; **34**: 397-402
  - 29 **Akamatsu M**, Matsumoto T, Oka K, Yamasaki S, Sonoue H, Kajiyama Y, Tsurumaru M, Sasai K. c-erbB-2 oncoprotein expression related to chemoradioresistance in esophageal squamous cell carcinoma. *Int J Radiat Oncol Biol Phys* 2003; **57**: 1323-1327
  - 30 **Hickey K**, Grehan D, Reid IM, O'Briain S, Walsh TN, Hennessy TP. Expression of epidermal growth factor receptor and proliferating cell nuclear antigen predicts response of esophageal squamous cell carcinoma to chemoradiotherapy. *Cancer* 1994; **74**: 1693-1698
  - 31 **Shimada H**, Hoshino T, Okazumi S, Matsubara H, Funami Y, Nabeya Y, Hayashi H, Takeda A, Shiratori T, Uno T, Ito H, Ochiai T. Expression of angiogenic factors predicts response to chemoradiotherapy and prognosis of oesophageal squamous cell carcinoma. *Br J Cancer* 2002; **86**: 552-557
  - 32 **Gorski DH**, Beckett MA, Jaskowiak NT, Calvin DP, Maurceri HJ, Salloum RM, Seetharam S, Koons A, Hari DM, Kufe DW, Weichselbaum RR. Blockage of the vascular endothelial growth factor stress response increases the antitumor effects of ionizing radiation. *Cancer Res* 1999; **59**: 3374-3378
  - 33 **Schmidt U**, Begley CG. Cancer diagnosis and microarrays. *Int J Biochem Cell Biol* 2003; **35**: 119-124
  - 34 **Duong C**, Greenawalt DM, Kowalczyk A, Ciavarella ML, Raskutti G, Murray WK, Phillips WA, Thomas RJ. Pre-treatment gene expression profiles can be used to predict response to neoadjuvant chemoradiotherapy in esophageal cancer. *Ann Surg Oncol* 2007; **14**: 3602-3609
  - 35 **Quillien V**, Raoul JL, Laurent JF, Meunier B, Le Prise E. Comparison of Cyfra 21-1, TPA and SCC tumor markers in esophageal squamous cell carcinoma. *Oncol Rep* 1998; **5**: 1561-1565
  - 36 **Nakamura T**, Ide H, Eguchi R, Hayashi K, Takasaki K, Watanabe S. CYFRA 21-1 as a tumor marker for squamous cell carcinoma of the esophagus. *Dis Esophagus* 1998; **11**: 35-39
  - 37 **Westerterp M**, van Westreenen HL, Reitsma JB, Hoekstra OS, Stoker J, Fockens P, Jager PL, Van Eck-Smit BL, Plukker JT, van Lanschot JJ, Sloof GW. Esophageal cancer: CT, endoscopic US, and FDG PET for assessment of response to neoadjuvant therapy--systematic review. *Radiology* 2005; **236**: 841-851
  - 38 **Bar-Shalom R**, Guralnik L, Tsalic M, Leiderman M, Frenkel A, Gaitini D, Ben-Nun A, Keidar Z, Israel O. The additional

- value of PET/CT over PET in FDG imaging of oesophageal cancer. *Eur J Nucl Med Mol Imaging* 2005; **32**: 918-924
- 39 **Schelling M**, Avril N, Nāhrig J, Kuhn W, Römer W, Sattler D, Werner M, Dose J, Jānicking F, Graeff H, Schwaiger M. Positron emission tomography using [(18)F]Fluorodeoxyglucose for monitoring primary chemotherapy in breast cancer. *J Clin Oncol* 2000; **18**: 1689-1695
- 40 **Thomas DM**, Mitchell PL, Berlangieri SU, Tochon-Danguy H, Knight S, Clarke CP, Scott AM. Positron emission tomography in assessing response to neoadjuvant chemotherapy for non-small-cell lung cancer. *Med J Aust* 1998; **169**: 227
- 41 **Yoshioka T**, Fukuda H, Fujiwara T, Iwata R, Ido T, Murakawa Y, Gamo M, Ishioka C, Kanamaru R. FDG PET evaluation of residual masses and regrowth of abdominal lymph node metastases from colon cancer compared with CT during chemotherapy. *Clin Nucl Med* 1999; **24**: 261-263
- 42 **Hueltschmidt B**, Sautter-Bihl ML, Lang O, Maul FD, Fischer J, Mergenthaler HG, Bihl H. Whole body positron emission tomography in the treatment of Hodgkin disease. *Cancer* 2001; **91**: 302-310
- 43 **Okada J**, Yoshikawa K, Imazeki K, Minoshima S, Uno K, Itami J, Kuyama J, Maruno H, Arimizu N. The use of FDG-PET in the detection and management of malignant lymphoma: correlation of uptake with prognosis. *J Nucl Med* 1991; **32**: 686-691
- 44 **Song SY**, Kim JH, Ryu JS, Lee GH, Kim SB, Park SI, Song HY, Cho KJ, Ahn SD, Lee SW, Shin SS, Choi EK. FDG-PET in the prediction of pathologic response after neoadjuvant chemoradiotherapy in locally advanced, resectable esophageal cancer. *Int J Radiat Oncol Biol Phys* 2005; **63**: 1053-1059
- 45 **Wieder HA**, Brūcher BL, Zimmermann F, Becker K, Lordick F, Beer A, Schwaiger M, Fink U, Siewert JR, Stein HJ, Weber WA. Time course of tumor metabolic activity during chemoradiotherapy of esophageal squamous cell carcinoma and response to treatment. *J Clin Oncol* 2004; **22**: 900-908
- 46 **Flamen P**, Van Cutsem E, Lerut A, Cambier JP, Haustermans K, Bormans G, De Leyn P, Van Raemdonck D, De Wever W, Ectors N, Maes A, Mortelmans L. Positron emission tomography for assessment of the response to induction radiochemotherapy in locally advanced oesophageal cancer. *Ann Oncol* 2002; **13**: 361-368
- 47 **Kato H**, Kuwano H, Nakajima M, Miyazaki T, Yoshikawa M, Masuda N, Fukuchi M, Manda R, Tsukada K, Oriuchi N, Endo K. Usefulness of positron emission tomography for assessing the response of neoadjuvant chemoradiotherapy in patients with esophageal cancer. *Am J Surg* 2002; **184**: 279-283
- 48 **Brūcher BL**, Weber W, Bauer M, Fink U, Avril N, Stein HJ, Werner M, Zimmermann F, Siewert JR, Schwaiger M. Neoadjuvant therapy of esophageal squamous cell carcinoma: response evaluation by positron emission tomography. *Ann Surg* 2001; **233**: 300-309
- 49 **Gillham CM**, Lucey JA, Keogan M, Duffy GJ, Malik V, Raouf AA, O'byrne K, Hollywood D, Muldoon C, Reynolds JV. (18)FDG uptake during induction chemoradiation for oesophageal cancer fails to predict histomorphological tumour response. *Br J Cancer* 2006; **95**: 1174-1179
- 50 **Langer R**, Specht K, Becker K, Ewald P, Bekesch M, Sarbia M, Busch R, Feith M, Stein HJ, Siewert JR, Höfler H. Association of pretherapeutic expression of chemotherapy-related genes with response to neoadjuvant chemotherapy in Barrett carcinoma. *Clin Cancer Res* 2005; **11**: 7462-7469
- 51 **Theisen J**, Danenberg K, Ott K, Becker K, Danenberg P, Stein HJ, Siewert JR. Predictors of response and survival for neoadjuvant treated patients with esophageal adenocarcinoma. *Dis Esophagus* 2008; **21**: 601-606
- 52 **Warnecke-Eberz U**, Metzger R, Miyazono F, Baldus SE, Neiss S, Brabender J, Schaefer H, Doerfler W, Bollschweiler E, Dienes HP, Mueller RP, Danenberg PV, Hoelscher AH, Schneider PM. High specificity of quantitative excision repair cross-complementing 1 messenger RNA expression for prediction of minor histopathological response to neoadjuvant radiochemotherapy in esophageal cancer. *Clin Cancer Res* 2004; **10**: 3794-3799
- 53 **Duhaylongsod FG**, Gottfried MR, Iglehart JD, Vaughn AL, Wolfe WG. The significance of c-erb B-2 and p53 immunoreactivity in patients with adenocarcinoma of the esophagus. *Ann Surg* 1995; **221**: 677-683; discussion 683-684
- 54 **Luthra R**, Luthra MG, Izzo J, Wu TT, Lopez-Alvarez E, Malhotra U, Choi IS, Zhang L, Ajani JA. Biomarkers of response to preoperative chemoradiation in esophageal cancers. *Semin Oncol* 2006; **33**: S2-S5
- 55 **Schauer M**, Janssen KP, Rimkus C, Raggi M, Feith M, Friess H, Theisen J. Microarray based response prediction in esophageal adenocarcinomas. *Clin Can Res* 2009; In press
- 56 **Ma Y**, Ding Z, Qian Y, Shi X, Castranova V, Harner EJ, Guo L. Predicting cancer drug response by proteomic profiling. *Clin Cancer Res* 2006; **12**: 4583-4589
- 57 **Luthra R**, Wu TT, Luthra MG, Izzo J, Lopez-Alvarez E, Zhang L, Bailey J, Lee JH, Bresalier R, Rashid A, Swisher SG, Ajani JA. Gene expression profiling of localized esophageal carcinomas: association with pathologic response to preoperative chemoradiation. *J Clin Oncol* 2006; **24**: 259-267
- 58 **Ashida A**, Boku N, Aoyagi K, Sato H, Tsubosa Y, Minashi K, Muto M, Ohtsu A, Ochiai A, Yoshida T, Yoshida S, Sasaki H. Expression profiling of esophageal squamous cell carcinoma patients treated with definitive chemoradiotherapy: clinical implications. *Int J Oncol* 2006; **28**: 1345-1352
- 59 **Ott K**, Weber WA, Lordick F, Becker K, Busch R, Herrmann K, Wieder H, Fink U, Schwaiger M, Siewert JR. Metabolic imaging predicts response, survival, and recurrence in adenocarcinomas of the esophagogastric junction. *J Clin Oncol* 2006; **24**: 4692-4698
- 60 **Lordick F**, Ott K, Krause BJ, Weber WA, Becker K, Stein HJ, Lorenzen S, Schuster T, Wieder H, Herrmann K, Bredenkamp R, Höfler H, Fink U, Peschel C, Schwaiger M, Siewert JR. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. *Lancet Oncol* 2007; **8**: 797-805
- 61 **Levine EA**, Farmer MR, Clark P, Mishra G, Ho C, Geisinger KR, Melin SA, Lovato J, Oaks T, Blackstock AW. Predictive value of 18-fluoro-deoxy-glucose-positron emission tomography (18F-FDG-PET) in the identification of responders to chemoradiation therapy for the treatment of locally advanced esophageal cancer. *Ann Surg* 2006; **243**: 472-478
- 62 **Swisher SG**, Erasmus J, Maish M, Correa AM, Macapinlac H, Ajani JA, Cox JD, Komaki RR, Hong D, Lee HK, Putnam JB Jr, Rice DC, Smythe WR, Thai L, Vaporciyan AA, Walsh GL, Wu TT, Roth JA. 2-Fluoro-2-deoxy-D-glucose positron emission tomography imaging is predictive of pathologic response and survival after preoperative chemoradiation in patients with esophageal carcinoma. *Cancer* 2004; **101**: 1776-1785
- 63 **Brink I**, Hentschel M, Bley TA, Walch A, Mix M, Kleimaier M, Moser E, Imdahl A. Effects of neoadjuvant radiochemotherapy on 18F-FDG-PET in esophageal carcinoma. *Eur J Surg Oncol* 2004; **30**: 544-550
- 64 **Arslan N**, Miller TR, Dehdashti F, Battafarano RJ, Siegel BA. Evaluation of response to neoadjuvant therapy by quantitative 2-deoxy-2-[18F]fluoro-D-glucose with positron emission tomography in patients with esophageal cancer. *Mol Imaging Biol* 2002; **4**: 301-310
- 65 **Weber WA**, Ott K, Becker K, Dittler HJ, Helmberger H, Avril NE, Meisetschläger G, Busch R, Siewert JR, Schwaiger M, Fink U. Prediction of response to preoperative chemotherapy in adenocarcinomas of the esophagogastric junction by metabolic imaging. *J Clin Oncol* 2001; **19**: 3058-3065

S- Editor Li LF L- Editor Stewart GJ E- Editor Lin YP