Value of Functional Imaging by PET in Esophageal Cancer

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Abstract

In esophageal cancer, functional imaging using PET can provide important additional information beyond standard staging techniques that may eventually lead to therapeutic consequences. The most commonly used tracer is fluorodeoxyglucose (FDG), which has high avidity for both squamous cell cancer and adenocarcinoma of the esophagus. The value of FDG-PET is limited in early esophageal cancer, whereas additional information is provided in 15% to 20% of locally advanced tumors. Neoadjuvant treatment is currently the standard of care in locally advanced esophageal cancer in most countries because randomized studies have shown a significant survival benefit. Because responders and nonresponders have a significantly different prognosis, functional imaging to tailor preoperative treatment would be of interest. Metabolic imaging using FDG-PET is an established method of response evaluation in clinical trials. The value of metabolic response evaluation is known to depend on the histologic subtype and the type of preoperative treatment delivered. An association of FDG-PET–based metabolic response with clinical response and prognosis was shown for absolute standardized uptake value (SUV) or a decrease of SUV levels before, during, and after therapy. However, contradictory findings exist in the literature and prospective validation is missing. Additionally, no consensus exists on time points or cutoff levels for metabolic response evaluation. Furthermore, correct prediction of a posttherapeutic pathologic complete remission is currently not possible using FDG-PET. Of high interest is early response monitoring during preoperative chemoradiotherapy, with potential subsequent therapy modification. This tailored approach still needs validation in prospective multicenter trials. (J Natl Compr Canc Netw 2015;13:239–247)

Functional imaging based on PET in esophageal cancer is mainly engaged to provide additional important information beyond standard staging techniques, such as endoscopy, endoluminal ultrasound, and multidetector CT.

The most frequently used tracer in esophageal cancer is fluorodeoxyglucose (FDG), which has high avidity for both squamous cell cancer (SCC) and adenocarcinoma of the distal esophagus, because signet ring cell cancer in adenocarcinoma is rare.1

Unfortunately, no randomized trials have proven the superiority of a primary staging modality, including PET/CT, over conventional staging techniques. Currently, FDG-PET has a far higher value in the staging of locally advanced esophageal cancer than in the staging of early esophageal cancer.2 However, given certain limitations, the integration of FDG-PET in esophageal cancer staging at various time points theoretically offers several advantages. First, it improves accuracy in the pretherapeutic cTNM staging, especially regarding the M category, because a coding of M1 would lead to a change of therapy. The second advantage occurs during restaging, with the potential exclusion of interval metastases after preoperative therapy. Third, and perhaps scientifically the most interesting aspect of functional imaging in esophageal cancer, is the possibility of predicting response and prognosis before, during, and after preoperative treatment. Finally, therapy can be altered based on the evaluation of the FDG-PET response. However, the clinical benefits of using FDG-PET depend on the tumor entity and the preoperatively applied treatment. Although the application of preoperative or perioperative chemotherapy allows early treatment modification, preoperative chemoradiotherapy should not be interrupted. Therefore, in patients receiving chemoradiotherapy, functional imaging is required before or after the therapy, whereas functional imaging early during chemotherapy could theoretically lead to
treatment changes, such as an alteration of the chemotherapy regimen, a switch to chemoradiotherapy, or immediate resection.

Furthermore, the different histopathologic tumor entities have different clinical requirements. In patients with SCC, preoperative chemoradiotherapy or definitive chemoradiotherapy delivered. In these patients, the correct prediction of a complete response by the primary tumor and lymph node metastases would be of utmost interest to avoid unnecessary surgery. Furthermore, patients with adenocarcinoma treated with chemoradiotherapy who show a durable pathologic complete response (pCR) by the primary tumor and lymph node metastases would theoretically not need surgery, though the complete response rate is considered to be lower than in SCC. In this instance, a correct evaluation using FDG-PET could help. In adenocarcinoma treated with preoperative or perioperative chemotherapy, early evaluation of response and prognosis using FDG-PET–based monitoring seems to be the most attractive approach. Therefore, the following paragraphs focus only on clinically relevant aspects of functional imaging in esophageal cancer.

**Pretherapeutic Staging and Diagnosis of Synchronous Tumor**

The value of functional imaging is the highest for the cM category and lower for cN and cT category (cM>cN>cT), but seems not to be relevant for early esophageal cancer. Currently, the correct cT category is predicted best with endoluminal ultrasound (EUS), even if EUS is judged to be investigator-dependent in some studies. For very early tumor categories, endoscopic resections gain increasingly more importance and even offer correct pretherapeutic pathologic pT categories. The clinical relevance of the correct pN staging according to functional imaging seems to be controversial, strongly depending on the specific inclusion criteria for pretherapeutic therapy concepts that currently vary nationwide. Some current studies show that PET/CT had superior specificity and positive predictive value for local lymph node metastases compared with CT alone in patients who underwent primary resection and those who underwent preoperative treatment, although the correct evaluation of initially positive lymph nodes after preoperative therapy remains histopathologically challenging. According to recent data, the complementary role of EUS to PET/CT should be considered. The most important role of functional imaging is the correct identification of M1 status in locally advanced tumors. cM1 should be histopathologically confirmed as pM1 to excluded false-positive results, if technically possible. Because M1 currently does not obligatorily exclude patients from curative concepts if the metastatic disease is very limited, correct pretherapeutic staging is of utmost importance in making individual therapeutic decisions. Although in former years an additional PET scan changed pretherapeutic staging in more than 20% of patients, the percentage in the recent literature has mostly decreased to below 20% (Table 1), which corresponds to the increasing quality of the other staging modalities, especially multislice CT scanning. Additional information provided by functional imaging often leads to an upstaging, which requires histopathologic confirmation so that patients are not denied curative concepts as a result of false-positive findings (up to 7%).

Often a technical problem is that a non–contrast-enhanced, low-dose CT scan as part of the FDG-PET/CT requires an additional multislice contrast-enhanced CT, which unfortunately refutes the argument of a “one-stop-shop” staging and generates additional costs. To enable the superiority of PET-based staging over less expensive conventional staging, PET/CT with an adequate-quality and high-resolution CT component is needed to address relevant clinical aspects.

Interestingly, a recently published screening of 200 patients with esophageal cancer using PET/CT revealed that 17% had synchronous cancers in other organs, predominantly the stomach and head and neck region. However, this percentage seems to be relatively high.

**Interval Metastases**

Three studies to date have addressed the issue of detecting posttherapeutic interval metastases after preoperative chemoradiotherapy. Interestingly, the probability was 8% in all 3 studies (7/85, 4/50, and 6/76). Even though unequivocally reported, 8% of interval metastases after 5 weeks of chemoradiotherapy and 4 to 6 weeks of posttherapeutic interval seem to be high if a correct pretherapeutic staging was performed. Precise data about the occurrence of interval metastases after preoperative chemotherapy

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in esophageal cancer do not seem to exist in the literature. The unpublished rate of distant metastases, which excludes patients from resection after conventional staging without PET/CT, is 4% (35/885).27

Response Evaluation

Clinically Relevant Problems
PET is applied mostly for scientific reasons at 2 to 6 weeks after treatment initiation.28 As described in more detail in the following sections, most standardized uptake values (SUVs) or cutoffs reported and associated with prognosis or response were never prospectively verified.29 The published studies used varying SUV parameters (maximum or mean) and cutoff definitions and different outcome parameters (eg, clinical or histopathologic response, survival). In this regard, for clinical30–32 and histopathologic33 response evaluation, different scoring systems were used, rendering study results hardly comparable. Furthermore, in routine clinical practice, the therapeutic consequences for metabolically responding and nonresponding patients are not identified, except in very few studies.34,35 This clearly highlights the need for exact definitions of PET parameters and clinical requirements to render functional imaging studies more productive and comparable. These points are discussed in the following paragraphs.

Parameters for Metabolic Response
Clinical response and histopathologic regression are the principal reference parameters for assessing the value of metabolic response. For clinical response evaluation, several competing classifications with prognostic relevance exist. Generally, the acceptance of clinical response assessment in localized esophageal cancer is relatively low in the scientific community, because it is judged to be investigator-dependent, although many large studies prove its prognostic relevance.27,36 One essential advantage of clinical response evaluation using endoscopy and CT is the ease of application during27 and after therapy,38 and not just after resection. Admittedly, there is a clear difference in the value of clinical response after chemoradiotherapy compared with after chemotherapy only. The validity of clinical response seems to be far better after chemotherapy than after chemoradiotherapy, because therapy-induced changes such as inflammation or stenosis are significantly less. The gold standard for response evaluation remains the histopathologic regression score. This score, first described by Mandard et al39 for patients with esophageal carcinoma treated with chemoradiotherapy, depends on the percentage of residual tumor in resection specimens. In Europe, the most often applied score after chemotherapy was developed by Langer et al.40 The definition of response varies, with some centers defining histopathologic response only as a complete histopathologic response,41 and others classifying up to 50% residual tumor as a histopathologic response.42 All groups correlate prognostic pa-
rameters with their respective classification systems. Again, differentiating between chemoradiotherapy and chemotherapy seems to be important, because the pCR rate after chemoradiotherapy is far higher. To avoid ineffective, toxic, and expensive treatments, nonresponding patients should be identified early during treatment. This was the hypothesis of former studies for adenocarcinomas of the esophagogastric junction in which the cutoff was determined 2 weeks after initiation of therapy based on clinical and histopathologic responses. The metabolic response criteria were then prospectively validated and used for therapeutic changes. To increase the value of future studies including metabolic response evaluation, the response criteria and outcome parameters should be precisely defined. A global consensus regarding response criteria would be desirable to make study results comparable.

Different Tumor Types

Although no randomized studies in SCC proved the superiority of a neoadjuvant treatment followed by surgery compared with chemoradiotherapy alone, in adenocarcinoma, resection after preoperative treatment is generally recommended. Algorithms become more complex when considering the integration of response evaluation. In SCC, nonresponders have been observed to have higher complication rates, higher mortality, and a worse prognosis compared with patients undergoing primary resection. Therefore, resection in nonresponding patients is debatable. But others favor resection in nonresponding patients to remove all residual tumor and to prolong time to recurrence or progression and potentially increase survival, at least in some patients. There is an ongoing discussion, especially in view of the high pCR rate observed in the Dutch CROSS study, regarding whether patients experiencing a complete response should be resected at all if accurate identification of a pCR were possible.

Because preoperative therapy can be different in SCC and adenocarcinoma, different time points for response evaluation are relevant. The optimal time point for the metabolic response evaluation after the end of chemoradiotherapy has been controversially discussed. Dutch data suggest waiting 3 months after therapy completion for both SCC and adenocarcinoma. However, in view of the lack of confirmatory data, this cannot be advocated as a standard of care.

Pretherapeutic Metabolic Imaging

Although in former studies no association between initial SUV and later response was confirmed, this has been reported in the most recent studies (Table 2). Some of these recent studies also show an association between initial SUV and survival, but contradictory findings have been reported. The association between initial higher uptake and improved response and prognosis cannot yet be explained biologically. Currently the pretherapeutic SUV has no clinical relevance, but could theoretically help select patients for preoperative treatment. Clear cutoffs are neither defined nor prospectively evaluated, and therefore the value of the initial SUV for later response and prognosis seems to be limited.

Posttherapeutic Metabolic Imaging

A clear association between posttherapeutic SUV and histopathologic response and prognosis was described in a review of 26 studies involving a total of 1544 patients. The overall survival hazard ratio for complete metabolic response versus nonresponse after chemoradiation was 0.51. An earlier meta-analysis including 20 studies showed a pooled sensitivity and specificity for later response of 67% and 68%, respectively. Interestingly, both studies indicated no relevant impact of analyzed subgroups despite the existing heterogeneity of the included studies. Taken together, these results suggest that a complete metabolic response may offer a better prediction of long-term outcome than a surrogate end point, such as histopathologic response. Table 3 includes the more recent studies predicting response and prognosis based on the posttherapeutic SUV. Importantly, depending on the study, absolute SUVs (maximum and mean) and/or changes in SUV were used. More often an association with prognosis than with response was shown. But these SUVs were not prospectively confirmed and may not be used for clinical decision-making, as previously reported in the systematic review of Kwee.

Prediction of a Complete Histopathologic Response

As mentioned previously, the correct prediction of a pCR could prevent patients from undergoing a futile operation possibly associated with complications and long-term decrease in quality of life. Nowadays, no diagnostic tool predicts pCR with adequate accuracy. For functional imaging, 2 principal strategies (Table
Early Metabolic Response Assessment During Chemotherapy

In the authors’ opinion, the most clinically relevant aspect of functional imaging aside from the correct prediction of a pCR is the early response evaluation during therapy. Early response evaluation is of interest especially in patients with adenocarcinoma of the distal esophagus who undergo preoperative or perioperative chemotherapy according to the European ESMO or German S3 guidelines.14,75,76 However, the NCCN Clinical Practice Guidelines in Oncology for Esophageal and Esophagogastric Junction Cancers77 preferentially recommend chemoradiotherapy for adenocarcinoma of the esophagogastric junction, which may be less feasible for patients with a large tumor burden or other comorbidities.

Table 2 Overview of Studies Comparing Initial SUV Before Initiation of Therapy With Treatment Response

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Histology</th>
<th>Therapy</th>
<th>SUV</th>
<th>P Value (Response)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ott et al32</td>
<td>2006</td>
<td>65</td>
<td>AC</td>
<td>CTx/S</td>
<td>Med</td>
<td>.16</td>
</tr>
<tr>
<td>Lordick et al34</td>
<td>2007</td>
<td>110</td>
<td>AC</td>
<td>CTx/S</td>
<td>Med</td>
<td>.008*</td>
</tr>
<tr>
<td>Rizk et al34</td>
<td>2009</td>
<td>189</td>
<td>AC</td>
<td>CRTx/S</td>
<td>Abs</td>
<td>.02*</td>
</tr>
<tr>
<td>Javeri et al61</td>
<td>2009</td>
<td>161</td>
<td>AC</td>
<td>CRTx/S</td>
<td>Med</td>
<td>.16</td>
</tr>
<tr>
<td>Palie et al55</td>
<td>2013</td>
<td>57</td>
<td>SCC</td>
<td>CRTx</td>
<td>Abs</td>
<td>.05*</td>
</tr>
<tr>
<td>Piessen et al58</td>
<td>2013</td>
<td>60</td>
<td>SCC</td>
<td>CRTx</td>
<td>Abs</td>
<td>.14</td>
</tr>
<tr>
<td>Wieder et al69</td>
<td>2004</td>
<td>33</td>
<td>SCC</td>
<td>CRTx/S</td>
<td>Abs</td>
<td>.23</td>
</tr>
<tr>
<td>Swisher et al70</td>
<td>2004</td>
<td>56</td>
<td>AC/SCC</td>
<td>CRTx/S</td>
<td>Abs</td>
<td>.46</td>
</tr>
<tr>
<td>Hong et al71</td>
<td>2005</td>
<td>47</td>
<td>AC/SCC</td>
<td>CRTx/S</td>
<td>Abs</td>
<td>NS</td>
</tr>
<tr>
<td>Levine et al53</td>
<td>2006</td>
<td>64</td>
<td>AC/SCC</td>
<td>CRTx</td>
<td>Abs</td>
<td>.005*</td>
</tr>
<tr>
<td>Jayachandran et al57</td>
<td>2012</td>
<td>37</td>
<td>AC/SCC</td>
<td>CRTx/S</td>
<td>Abs</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 3 Overview of Studies Comparing SUV After Therapy With Treatment Response and Prognosis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Histology</th>
<th>Therapy</th>
<th>Response</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Konski et al87</td>
<td>2007</td>
<td>81</td>
<td>AC/SCC</td>
<td>CRTx</td>
<td>NS</td>
<td>P=.01 (DFS)</td>
</tr>
<tr>
<td>Vallböhmer et al83</td>
<td>2009</td>
<td>119</td>
<td>AC/SCC</td>
<td>CRTx</td>
<td>P=.056</td>
<td>NS</td>
</tr>
<tr>
<td>Schmidt et al84</td>
<td>2009</td>
<td>55</td>
<td>AC/SCC</td>
<td>CRTx</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Jayachandran et al57</td>
<td>2012</td>
<td>37</td>
<td>AC/SCC</td>
<td>CRTx</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Javeri et al61</td>
<td>2009</td>
<td>151</td>
<td>AC</td>
<td>CRTx</td>
<td>P=.06</td>
<td>P=.01</td>
</tr>
<tr>
<td>Smith et al66</td>
<td>2009</td>
<td>21</td>
<td>AC</td>
<td>CRTx</td>
<td>P=.025</td>
<td></td>
</tr>
<tr>
<td>Kauppi et al82</td>
<td>2012</td>
<td>66</td>
<td>AC</td>
<td>CTx</td>
<td>P&lt;.001</td>
<td>P=.027</td>
</tr>
<tr>
<td>Abdelsalam et al65</td>
<td>2010</td>
<td>21</td>
<td>SCC</td>
<td>CRTx</td>
<td>P=.025</td>
<td>P=.038</td>
</tr>
<tr>
<td>Piessen et al58</td>
<td>2013</td>
<td>60</td>
<td>SCC</td>
<td>CRTx</td>
<td>P=.012</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: AC, adenocarcinoma; CRTx, chemoradiotherapy; CTx, chemotherapy; DFS, disease-free survival; NS, not significant; SCC, squamous cell carcinoma; SUV, standard uptake value.

for which metabolic response evaluation is of less interest, although van Heijl et al showed that it can show histopathologic tumor response, but the accuracy in identifying nonresponding patients was too low to lead to clinical consequences.

In 2001, a cutoff decrease of 35% compared with the initial SUV was reported to be associated with clinical and histopathologic response in adenocarcinoma after 2 weeks of chemotherapy. This cutoff was used to correctly identify nonresponding patients and was prospectively validated in an independent patient cohort. Therefore, in the MUNICON I trial, a metabolic response–based therapy modification was included after 2 weeks, wherein metabolic nonresponders discontinued chemotherapy and underwent immediate resection. Comparison with historical survival data showed that metabolic nonresponders did not seem to have an overall survival disadvantage compared with nonresponding patients who completed the chemotherapy regimen over 3 months (median survival of 26 vs 18 months, respectively). To increase response and prognosis in the MUNICON II trial, patients who did not show a metabolic response were switched to chemoradiotherapy after 2 weeks. The histopathologic response rate was shown to significantly increase to 26% in metabolic nonresponders with the integration of chemoradiotherapy, but the progression-free survival (PFS) remained significantly worse compared with that of metabolic responders (1-year PFS, 74% vs 57%; \( P = .035 \)). Through the sequential study design, the cutoff of –35% was validated prospectively in adenocarcinoma of the esophagogastric junction and the feasibility of metabolic response–based therapy modification after only 2 weeks was proven. Currently, the ongoing CALGB 80803 phase II trial has the goal of increasing the pCR through switching the type of chemotherapy in patients showing no response after 6 weeks of an assigned regimen (FOLFOX6 vs carboplatin/paclitaxel) based on PET response evaluation. This change of chemotherapy regimen during chemoradiotherapy is a different approach from that used in the previous MUNICON II trial. The results will show if the PFS can be increased with this approach.

Studies often combine SCC and adenocarcinoma with cutoffs between 0% and –35% at evaluation time points of 2 to 6 weeks after the initiation of therapy. In most studies, the retrospectively evaluated cutoff is associated with later response and/or prognosis (Table 5). If no association was found, often SCCs were included in the studies and chemoradiotherapy was delivered, highlighting the differences in response monitoring for the different tumor entities and treatment modalities.

### Conclusions

Functional imaging using FGD-PET/CT including a diagnostic multislice contrast-enhanced CT scan can allow one-stop-shop tumor staging of esophageal cancer, leading to a higher accuracy of the initial cN

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**Table 4 Overview of Studies Comparing Changes in PET With Complete Histopathologic Response**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Change in PET</th>
<th>Residual Tumor</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swisher et al</td>
<td>2004</td>
<td>103</td>
<td>FDG ↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerfolio et al</td>
<td>2009</td>
<td>86</td>
<td>&lt;64%</td>
<td></td>
<td>75%</td>
</tr>
<tr>
<td>Molena et al</td>
<td>2014</td>
<td>116</td>
<td>&gt;4%</td>
<td></td>
<td>76%</td>
</tr>
<tr>
<td>Swisher et al</td>
<td>2004</td>
<td>73</td>
<td>Neg</td>
<td>12/17</td>
<td></td>
</tr>
<tr>
<td>Erasmus et al</td>
<td>2006</td>
<td>42</td>
<td>Neg</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Kim et al</td>
<td>2007</td>
<td>62</td>
<td>Neg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Port et al</td>
<td>2007</td>
<td>62</td>
<td>Neg</td>
<td>12/23</td>
<td></td>
</tr>
<tr>
<td>Yen et al</td>
<td>2012</td>
<td>118</td>
<td>Neg</td>
<td>13/73</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: FDG, fluorodeoxyglucose; Neg, negative.

*Lower FGD-PET SUV values predict pathologic response.*

and cM staging and providing useful information for clinical practice. Additionally, this modality can help diagnose synchronous cancers and evaluate interval metastases after neoadjuvant treatment.

However, pretherapeutic or posttherapeutic metabolic imaging and early metabolic imaging during neoadjuvant/periprosthetic chemotherapy to estimate and evaluate clinical or histopathologic response is not yet standardized for general use outside of clinical studies. Valid data exist for posttherapeutic metabolic response and its association with histopathologic response and prognosis; however, clear definitions of cutoffs, prospective validations, and a definition of clinical consequences are required to strengthen the importance of functional imaging in the future. A major problem of many studies involving FDG-PET or FDG-PET/CT seems to be the enormous heterogeneity, including both technical aspects and clinical consequences. From the technical viewpoint, no standardization of the SUVs or cutoff values could be achieved.

Importantly, metabolic response monitoring is of high scientific interest and should be further integrated in clinical studies. The feasibility of PET-based therapy modification in adenocarcinoma has already been shown, but multicenter validation is missing. The prediction of pCR after therapy will be of interest to avoid futile surgery in a subgroup of patients, but currently cannot be achieved accurately with PET/CT. Whether pCR might increase over time after the completion of chemoradiotherapy is the subject of an ongoing discussion, and will need to be further evaluated in the coming years. The goals for the future should be to establish generally accepted definitions of cutoffs and response criteria to increase the comparability of studies, and to provide clinical decision algorithms.

### References


PET in Esophageal Cancer


61. Javeri H, Xiao L, Rohren E, et al. The higher the decrease in the standardized uptake value of positron emission tomography after chemoradiation, the better the survival of patients with gastrointestinal adenocarcinoma. Cancer 2009;115:1584–1592.


