New trends for staging and therapy for localized gastroesophageal cancer: the role of PET

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Treatment options for localized gastroesophageal cancers reach from limited resection to multimodality treatment. Accurate clinical assessment, prognostic and predictive information are needed to select the most appropriate treatment approach. Positron emission tomography (PET) in combination with computed tomography (CT) in a hybrid imaging modality PET–CT may refine the staging accuracy and add prognostic information. Moreover, experiences from diverse centers indicate that PET also might improve significantly the assessment of response to preoperative chemotherapy and chemoradiotherapy. This article outlines the current value of PET in the staging and multidisciplinary care of gastroesophageal cancer. At this stage, it remains unclear whether the prognosis of patients can be improved by implementing PET in the management of localized disease. Prospective multicenter studies have to be carried out to validate metabolic cut-off values and to prove the benefit of PET-guided treatment decisions.

introduction

Considerable improvements have been achieved in the therapeutic management of gastroesophageal cancer. With the implementation of more skillful endoscopic ablation techniques for early cancers, the broader use of intensity-modulated radiation therapy, the introduction of more sophisticated resection methods and standardized perioperative care, and last but not least the growing understanding of gastroesophageal cancer biology and the introduction of new and more effective anticancer drugs, the selection of the right approach for every individual patient has become of paramount importance.

New imaging techniques may help to enhance the accuracy of staging and thereby to improve the estimation of the individual prognosis. They may also be of value to predict and assess the response to particular therapeutic steps.

Positron emission tomography (PET) in combination with computed tomography (CT) in a hybrid imaging modality PET–CT offers the unique chance of combining anatomic and functional information of the tumor. Therefore, PET–CT has been widely investigated in oncology in order to evaluate its prognostic and predictive value. Some centers routinely use FDG-PET when assessing gastroesophageal cancers. However, prospective studies are scarce and the work in this field has to continue.

In this article we review the literature of the past years and attempt to define the current role of PET scanning in the management of gastroesophageal cancer. We also delineate future clinical research directions in this field.

PET scan and staging

tracer uptake

The most widely used tracer for PET scanning in oncology is 2-[fluorine-18]fluoro-2-deoxy-D-glucose (FDG). This tracer is a glucose analogue and is avidly taken up and retained by most tumors. Some investigators looked into the sensitivity of FDG-PET to detect clinically diagnosed gastroesophageal cancers. They found that 83%–95% of esophageal cancers behave as FDG avid tumors and therefore can be accurately detected [1, 2]. In contrast, only 60% of gastric cancers are FDG avid. Particularly tumors with non-intestinal-type histology according to Lauren’s classification (diffuse type, mixed type, signet ring cell carcinomas) often lack sufficient FDG uptake and can therefore not be imaged by FDG-PET [3].

Another drawback of FLT is its high accumulation in the liver, which limits its ability to detect liver metastases [5]. In a pilot study we evaluated FLT-PET for the detection of gastric cancer and compared the diagnostic accuracy with that of FDG-PET. The results of this study indicated that imaging gastric cancer with the proliferation marker FLT is feasible. FLT-PET was more sensitive than FDG-PET in tumors frequently presenting without or with low FDG uptake. However, comparison of mean FLT and FDG uptake in tumors with the presence of signet ring cell revealed no statistically significant difference between the two tracers. Another drawback of FLT is its high accumulation in the liver, which limits its ability to detect liver metastases [5]. In a pilot

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study carried out in esophageal cancer, uptake of 18F-FDG was shown to be significantly higher compared with 18F-FLT uptake. 18F-FLT scans showed more false-negative findings but fewer false-positive findings than 18F-FDG scans. There was no correlation of uptake of either 18F-FDG or 18F-FLT with proliferation measured by histopathologic Ki-67 expression [6].

**staging accuracy**

Numerous studies have looked at the sensitivity and specificity of PET scans in refining clinical tumor staging. Due to its physically determined limitations of spatial resolution, PET is not per se a good tool for defining the T category in gastroesophageal cancer, where the definition of the T stage is based on the depth of infiltration of the intestinal wall layers. In contrast, PET adds information with regard to N and M stage. In a systematic review Westreenen et al. [7] showed that the sensitivity and specificity for CT and PET in lymph node staging (N status) is 51% and 84%, respectively, while for detecting distant metastases (M status) the corresponding numbers are 67% and 91%, respectively. In a more recent meta-analysis the authors come to the conclusion that endoscopic ultrasound (EUS), CT and FDG-PET each play a distinctive role in the detection of metastases in esophageal cancer patients. For the detection of regional lymph node metastases, EUS is most sensitive, whereas CT and FDG-PET are more specific tests. For the evaluation of distant metastases, FDG-PET has probably a higher sensitivity than CT. Its combined use could, however, be of clinical value, with FDG-PET detecting possible metastases and CT confirming or excluding their presence and precisely determining the location(s) [8]. An expert panel recently recommended the use of FDG-PET for the detection of distant metastases in esophageal cancer [9].

In view of the limited accuracy of PET one can conclude that PET-based treatment decisions have to be taken with some caution. The chance of a false-negative result on FDG-PET is not negligible; therefore, irradiation volumes and resection fields should not be reduced based on a negative FDG-PET. However, due to the relatively high specificity of FDG-PET, enlarging the irradiated volume or extending a lymphadenectomy based on a positive FDG-PET in a region without suspected lymph nodes on CT and/or EUS should be considered [10]. It would be worthwhile performing a randomized study. In the experimental group radiation fields and surgery are modified according to PET findings; in the control group radiation and surgery are done on the grounds of conventional (non-PET) staging.

Conversely, the specificity of PET is still limited and false-positive findings occur in up to 20% of cases. Therefore, negative treatment decisions can usually not be based on PET results alone. Positive findings in PET that would lead to relevant treatment limitations need to be confirmed by other methods, especially by histopathology. As an example Figure 1 shows the case of a positive PET in the right neck region of a patient presenting with an adenocarcinoma of the esophagogastric junction. In the case of a lymph node metastasis this finding defines a distant metastasis (cM1) and esophagectomy is no longer the therapy of choice because the condition is considered to be incurable. In this particular case histology revealed a lymph node metastasis of a well-differentiated follicular thyroid microcarcinoma and the patient underwent curative resection of two separate malignant diseases.

**PET and prognosis**

Prognosis is linked to tumor stage. An additional question is, whether quantification of the tracer (FDG) uptake gives independent prognostic information.

The standardized uptake value (SUV) is often used in PET imaging for (semi-) quantitative analysis of dynamic data [11]. The SUV is calculated either pixel-wise or over a region of interest (ROI) for each image of a dynamic series at time points $t$ as the ratio of tissue radioactivity concentration (e.g. in MBq/kg = kBq/g) at time $t$, $c(t)$, and injected dose (e.g. in MBq) at the time of injection $(t=0)$ divided by body weight (e.g. in kg).

**Figure 1.** A positive FDG-PET in the right neck region of a patient presenting with an adenocarcinoma of the esophagogastric junction. In the case of a lymph node metastasis this finding defines a distant metastasis (cM1) and esophagectomy is no longer the therapy of choice in such an incurable condition. In this particular case histology revealed a lymph node metastasis of a well-differentiated follicular thyroid microcarcinoma and the patient underwent curative resection of two separate malignant diseases.
PET and treatment response

Both conventional imaging techniques (EUS and CT) and endoscopy are of limited value in assessing response to preoperative treatment in gastroesophageal cancer, especially after chemoradiotherapy. Especially the discrimination of vital tumor tissue after chemoradiotherapy is difficult; however, in experienced centers clinical response evaluation with CT scan and endoscopy has predictive value for prognosis, especially in adenocarcinomas after chemotherapy only. Clinical evaluation of dysphagia scores seems to be meaningless [15] and even post-treatment cytology and biopsies failed to accurately assess response to preoperative treatment, because residual tumor is often located close to the adventitia and not to the mucosa [16, 17].

Recently, PET Response Criteria in Solid Tumors (PERCIST 1.0) have been advocated [18]. The authors argued that anatomic imaging alone using standard World Health Organization (WHO), and Response Criteria in Solid Tumors (RECIST) criteria have limitations, particularly in assessing the activity of newer cancer therapies that stabilize disease, whereas 18F-FDG PET appears particularly valuable in such cases. The proposed PERCIST 1.0 criteria should serve as a starting point for use in clinical trials and in structured quantitative clinical reporting. According to the authors, undoubtedly subsequent revisions and enhancements will be required as validation studies are undertaken in various diseases and treatments.

post-therapeutic response assessment

The value of resection has been called into question, especially in squamous cell cancer of the cervical and intrathoracic esophagus. Knowing the response and prognosis following chemoradiotherapy would be of paramount importance in order to refine the selection of patients who still require surgery.

Numerous studies have investigated post-therapeutic PET scanning in order to define the predictive and prognostic value of the test (Table 1) [19–27]. In summary, most studies show a clear correlation of metabolic response as assessed by FDG-PET on the one hand and response and survival on the other hand. One recent study even indicated a relatively strong concordance of 71% between histopathologic complete response and metabolic complete response [21]. However, cut-off values that indicate a positive correlation with histopathologic complete response have never been validated in prospective studies. Multicenter experiences from prospective studies are lacking. Finally, the positive predictive value of the test (i.e. the ability of PET to predict complete histopathologic response) does not seem to be high enough to base treatment decisions (against surgery) on the currently available data.

pre-therapeutic assessment

In an ideal scenario, we would use one pre-therapeutic PET to complement staging and to predict response to any preoperative treatment (chemotherapy or chemoradiotherapy). Some groups investigated the value of pre-therapeutic FDG tumor uptake and treatment response (Table 2) [22–24, 28–31]. In summary, results are conflicting. While some investigators found a correlation between higher SUVs and response to subsequent chemo(radio)therapy; some others did not. Prospective validation studies confirming specific techniques and cut-offs are lacking.

early metabolic assessment and response prediction

Early metabolic response assessment during neoadjuvant chemotherapy of adenocarcinoma of the esophagogastric junction has been tested; cut-off values have been prospectively

Table 1. Predictive and prognostic value of FDG-PET scanning after completion of preoperative chemoradiotherapy in patients with gastroesophageal cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Tumor</th>
<th>n</th>
<th>Correlation with response</th>
<th>Correlation with prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Javeri</td>
<td>2009</td>
<td>AC</td>
<td>151</td>
<td>P = 0.06</td>
<td>P = 0.01</td>
</tr>
<tr>
<td>Vällböhmmer</td>
<td>2009</td>
<td>AC/SCC</td>
<td>119</td>
<td>P = 0.056</td>
<td>n.s.</td>
</tr>
<tr>
<td>Kim</td>
<td>2007</td>
<td>SCC</td>
<td>62</td>
<td>n.d.</td>
<td>P = 0.033</td>
</tr>
<tr>
<td>Levine</td>
<td>2006</td>
<td>AC/SCC</td>
<td>64</td>
<td>P = 0.004</td>
<td>n.d.</td>
</tr>
<tr>
<td>Wieder</td>
<td>2004</td>
<td>SCC</td>
<td>38</td>
<td>P = 0.011</td>
<td>n.d.</td>
</tr>
<tr>
<td>Swisher</td>
<td>2004</td>
<td>AC/SCC</td>
<td>83</td>
<td>P = 0.03</td>
<td>P = 0.01</td>
</tr>
<tr>
<td>Downey</td>
<td>2003</td>
<td>AC/SCC</td>
<td>39</td>
<td>n.d.</td>
<td>P = 0.088</td>
</tr>
<tr>
<td>Flamen</td>
<td>2002</td>
<td>SCC</td>
<td>36</td>
<td>P = 0.001</td>
<td>P = 0.002</td>
</tr>
<tr>
<td>Brücher</td>
<td>2001</td>
<td>SCC</td>
<td>27</td>
<td>P = 0.001</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

AC: adenocarcinoma; n.d., not determined; n.s., not significant; SCC, squamous cell cancer.
Table 2. Predictive value of FDG-PET scanning before preoperative chemo(radio)therapy in patients with gastroesophageal cancer

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Tumor</th>
<th>n</th>
<th>SUV</th>
<th>Correlation with response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rizk 2009 [28]</td>
<td>AC</td>
<td>189</td>
<td>absolute</td>
<td>P = 0.02</td>
</tr>
<tr>
<td>Javeri 2009 [29]</td>
<td>AC</td>
<td>161</td>
<td>absolute</td>
<td>P = 0.06</td>
</tr>
<tr>
<td>Lordick 2007 [30]</td>
<td>AC</td>
<td>110</td>
<td>median</td>
<td>P = 0.018</td>
</tr>
<tr>
<td>Levine 2006 [31]</td>
<td>AC/SCC</td>
<td>64</td>
<td>absolute</td>
<td>P = 0.005</td>
</tr>
<tr>
<td>Ott 2006 [31]</td>
<td>AC</td>
<td>65</td>
<td>median</td>
<td>P = 0.16</td>
</tr>
<tr>
<td>Swisher 2004 [24]</td>
<td>AC/SCC</td>
<td>56</td>
<td>absolute</td>
<td>P = 0.56</td>
</tr>
<tr>
<td>Wieder 2004 [23]</td>
<td>SCC</td>
<td>33</td>
<td>absolute</td>
<td>P = 0.23</td>
</tr>
</tbody>
</table>

AC, adenocarcinoma; SCC, squamous cell cancer.

validated and have also been used in an interventional clinical study (Figure 2). In consecutive phase II studies the metabolic tumor activity was quantified, defined by the SUV before and during the course of chemotherapy. It was observed that after only 2 weeks of induction chemotherapy significant decreases in the 18F-FDG SUVs occurred. A drop of ≥35% measured after 2 weeks of chemotherapy was revealed as the most accurate cut-off value to predict the clinical and histopathological response found after full-course preoperative chemotherapy with a duration of 12 weeks. Weber and colleagues [32] first established the cut-off decrease in a retrospective study and Ott et al. [31] carried out a prospective validation study of this cut-off. The validated cut-off was brought further into subsequent study concepts. It was further noticed that the metabolic response to induction chemotherapy was an independent and important prognostic factor in cases of locally advanced adenocarcinoma of the oesophagogastric junction [31]. Metabolic changes measured by PET were revealed to be clearly more sensitive in detecting response early in the course of chemotherapy as compared with morphologic changes measured by high-resolution CT [23]. This indicates that PET can be used to tailor treatment according to the chemosensitivity of tumours. This concept has been realized in the MUNICON-1 trial [29] (Figure 3). This trial prospectively confirmed that responders to induction chemotherapy can be identified by early metabolic imaging using FDG-PET. The rate of major histopathologically confirmed remissions was 58%. The continuation of chemotherapy in the responding population also resulted in a favorable outcome: after a follow-up of 28 months the median overall survival was not reached in metabolically responding patients as compared with 26 months in metabolically non-responding patients. In patients with metabolic non-response, chemotherapy could be discontinued at an early stage, thereby saving time, and reducing side-effects and costs. Compared with patients from previous studies and cohorts one can delineate that the outcome of metabolic non-responders was at least not compromised by the early discontinuation of chemotherapy.

Of note, the concept of early response evaluation was successfully studied only in patients receiving chemotherapy without radiation. In patients being treated with chemotherapy plus radiation therapy, metabolic response assessment during treatment failed to predict histomorphologic tumor response [33, 34]. This indicates that cell death induced by radiation therapy may follow other mechanisms than chemotherapy-induced apoptosis. Radiation may induce inflammatory reactions and other phenomena leading to false-positive and false-negative findings. The two studies also show that step-by-step implementation of cut-off values is required when metabolic thresholds for response monitoring are implemented in clinical practice.

Conclusions and future steps

Current data indicate that FDG-PET refines the staging accuracy in localized gastroesophageal cancer, the main indication being the exclusion of distant metastases with a relevant impact on therapy management. Whether PET may serve as a basis for tailoring radiation fields or defining the extent of surgery should be further studied. In the light of the limited sensitivity of PET in detecting locoregional lymph nodes, the risk of reducing treatment radicality must be carefully weighed against the increased morbidity and mortality associated with surgery and large radiation fields in the preoperative setting.

High FDG uptake values may indicate a critical prognosis of patients presenting with localized gastroesophageal cancers. This finding may guide the decision for multimodality treatment. This is even more true as some studies show that patients with high-FDG-avid tumors have a greater response...
and benefit from neoadjuvant chemoradiotherapy. But cut-off values are not clear at this stage and prospective multicenter studies need to be carried out.

Post-therapeutic FDG uptake values have a prognostic impact and correlate with response. However, the limited positive predictive value for complete histopathologic response does not allow for guiding decisions against surgical resection at this stage. But this latter point certainly merits further investigation, especially in patients presenting with cervical and thoracic esophageal squamous cancers, where the operative risks following chemoradiation are particularly high.

The most exciting use of FDG-PET in the management of localized gastroesophageal cancer is the early assessment of metabolic response during neoadjuvant chemotherapy. These findings may allow for modifications of the treatment plan in patients who do not respond to chemotherapy. However, it must be taken into account that all data are derived from single-center studies, many data have been gathered with older generations of PET machines (before the era of combined PET–CT) and therefore the multicenter validation of cut-offs is of paramount importance. The European Organization of Research and Treatment of Cancer (EORTC) is currently planning an international validation trial of the MUNICON findings, using a central imaging platform and central quality assurance of PET and histopathologic response findings [35, 36].

disclosures

The authors declare no conflict of interest.

references

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