The Role of PET in Predicting Response to Chemotherapy in Oesophago-gastric Cancer

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Abstract

Treatment options for oesophago-gastric cancers reach from limited resection to multimodality treatment. An accurate clinical assessment and prognostic information are needed for selecting the most appropriate treatment approach. Positron emission tomography (PET) in combination with computed tomography (CT) in a hybrid imaging modality may ameliorate the staging accuracy and add prognostic information. Experiences from specialised centers indicate that PET also may aid to estimate and predict response to preoperative chemotherapy and chemoradiation. This article recapitulates the value of PET in the staging and multidisciplinary care of oesophago-gastric cancer. At this stage, it remains unclear if the prognosis of patients can be improved by implementing PET in the management of this disease. Prospective multicenter studies should be performed to validate metabolic cut-off values and to proof the benefit of PET-guided treatment decisions. (Acta gastroenterol. belg., **2011**, 74, **530-535**).

Key words : oesophageal cancer, gastric cancer, response, staging, imaging, positron emission tomography.

Introduction

Notable progress has been made in the management of oesophago-gastric cancer. With the implementation of more skilful endoscopic ablation techniques for early cancers, the broader use of intensity modulated radiation therapy, the introduction of more sophisticated resection methods and standardised perioperative care, and the introduction of active anti-tumour drugs we have moved towards a more personalised and stage-specific approach for every patient.

Novel imaging techniques may help to enhance the accuracy of staging and thereby to improve the estimation of the patient's prognosis. They may also be of value to predict and assess the response to particular therapeutic modalities.

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 tumour. PET/CT has been widely investigated in oncology in order to evaluate its prognostic and predictive value. Some centers routinely use PET imaging when assessing oesophago-gastric cancers. However, in some countries, PET is not refunded for this indication as prospective studies are scarce and the prognostic impact of applying this technique has not yet been proven.

This article reviews the literature of the past decade and attempts to define the current role of PET scanning in the management of oesophago-gastric cancer. Future clinical research directions in this field are delineated.

PET and staging

Tracer uptake

The most widely used tracer for PET investigations in oncology is 18F-Fluordeoxyglucose (FDG). This tracer is a glucose analogue and is avidly taken up and retained by most tumours. Some investigators looked after the sensitivity of FDG-PET to detect clinically diagnosed oesophago-gastric cancers. They found that 83-95% oesophageal cancers are FDG avid and therefore can be accurately detected (1,2). In contrast, only 60% of gastric cancers are FDG avid. Especially tumours with non-intestinal type histology (diffuse type, mixed type, signet ring cell carcinomas) often lack a sufficient FDG uptake and cannot be adequately visualized by FDG-PET (3).

Other tracers have also been investigated : 3'-deoxy-3'-(18)F-fluorothymidine (FLT) has been reported as stable tracer which accumulates in proliferating tissues and malignant disease (4). In a pilot study we evaluated FLT-PET for the detection of gastric cancer and compared the diagnostic accuracy to that of FDG-PET. The results of this study indicate that imaging gastric cancer with the proliferation marker FLT is feasible. FLT-PET was shown to be more sensitive than FDG-PET even in tumors presenting without or with a very low FDG-uptake. However, comparison of mean FLT- and FDG-uptake in tumours with presence of signet ring cells revealed no statistically significant difference between both tracers. Another drawback of FLT is its high accumulation in the liver which limits its ability to detect liver metastases (5). In a study undertaken in oesophageal cancer, uptake of 18F-FDG was shown to be significantly higher compared with 18F-FLT uptake. 18F-FLT scans showed more false-negative findings on the one

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hand but fewer false-positive findings than 18F-FDG scans on the other hand. Neither uptake of 18F-FDG nor 18F-FLT did correlate with proliferation measured by Ki-67 expression on histopathology (6).

Staging accuracy

Several studies have looked at the sensitivity and specificity of PET scans in enhancing clinical tumour staging. Due to its physically determined limitations in spatial resolution, PET is per se not a good tool for defining the T category in oesophago-gastric 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 it was shown that the sensitivity and specificity for CT and PET in lymph node staging (N category) is 51% and 84%, respectively. For the detection of distant metastases (M category) the corresponding numbers are 67% and 91%, respectively (7). In a more recent meta-analysis the authors come to the conclusion that EUS, CT, and FDG-PET each play a distinctive role in the detection of metastases in oesophageal cancer. For the detection of regional lymph node metastases, EUS is the most sensitive investigation, while CT and FDG-PET are more specific. For the assessment 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 their location (8). An expert panel recently recommended the use of FDG-PET for the detection of distant metastases in oesophageal 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 FGD-PET is not negligible ; therefore it is recommended that radiation volumes and resection fields should not be downsized based on a negative FDG-PET finding. However, due to the relatively high specificity of FDG-PET enlarging the irradiated volume or extending a resection based on a positive FDG-PET e.g. in a region without suspected lymph node involvement on CT and/or EUS should be considered (10). The following randomised study design would be of great value : 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. Such a study could clearly demonstrate the impact of PET staging on patients' outcome.

On the other hand, the specificity of PET is still limited and false-positive findings are reported in up to 20% of cases. Therefore, negative treatment decisions can usually not be based on PET results alone. Positive findings in PET which would lead to relevant treatment limitations need to be confirmed by other methods, especially by histopathology. Figure 1 gives the example of a positive FDG-PET in the right neck region of a patient presenting with localised adenocarcinoma of the oesophago-gastric junction. In case of a lymph node metastasis this finding defines a distant metastasis (cM1) and oesophagectomy could be omitted because the surgery then is considered not to be curative. In this particular case histology revealed a lymph node metastasis of a thyroid follicular microcarcinoma and the patient underwent curative resection for both diseases.

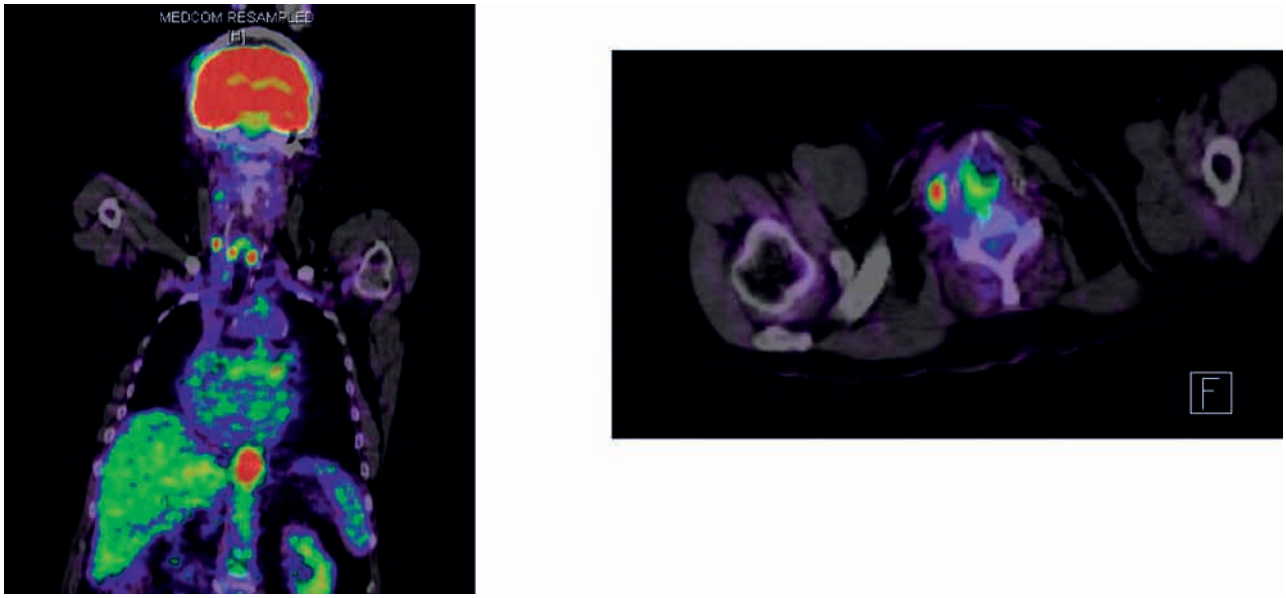


Fig. 1. — shows a positive FDG-PET in the right neck region of a patient presenting with an adenocarcinoma of the oesophago-gastric junction. In case of a lymph node metastasis this defines a distant metastasis (cM1) and oesophagectomy could be omitted. In this particular case histology revealed a lymph node metastasis of a follicular thyroid microcarcinoma and the patient underwent curative resection of two separate malignant diseases.

PET and prognosis

Prognosis is closely linked with tumour stage. An additional question is, if a quantification of the PET-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 pixelwise 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).

$$SUV = \frac{c(t)}{injected\ dose\ (t_0)\ /\ body\ weight}$$

Some authors prefer to use the lean body weight or the body surface area instead of the body weight. Also for c(t) either the maximum or mean value of a ROI is taken (12).

In the newer literature, a change from region of interest-based SUV calculation to volume of interest-based SUV calculation can be observed (13).

Investigators from New York analysed 40 patients with oesophageal cancer who had undergone FDG-PET scanning prior to primary tumour resection without any neoadjuvant treatment. The median SUV in their patients was found to be 4.5. Patients with a higher SUV higher had a significantly worse prognosis than patients with a SUV of less than 4.5 (14). The survival advantage of the SUVmax 4.5 or less group was also seen in clinically early-stage patients (defined as no adenopathy on CT and PET, and by EUS [T1-2 N0]), as well as in patients with pathologically early-stage disease (T1-2 N0). This interesting publication indicates that PET may help to identify patients who are usually no candidates for perioperativen treatment because their tumour stage is considered as "early" based on conventional imaging but who might need neoadjuvant chemotherapy or chemoradiation, because their prognosis is worse than expected. This hypothesis would merit to be tested in a prospective trial. A significant problem is that clear and reproducible cut-off values indicating a poorer prognosis are still lacking and require to be established in multicenter trials with centralised SUV assessment.

PET and treatment response

Both conventional imaging techniques (EUS and CT) and endoscopy are of limited value in assessing response to preoperative treatment in oesophago-gastric cancer, especially after chemoradiation. Particularly, the discrimination of vital tumour tissue after chemoradiation is difficult. 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 tumour is often located at the outward areas of the tumour and not within the accessible luminal parts of it (16,17).

Recently, PET Response Criteria in Solid Tumours (PERCIST 1.0) have been advocated (18). The authors argued that anatomic imaging alone using standard World Health Organization (WHO) criteria, and Response Criteria in Solid Tumours (RECIST) have important limitations, particularly in assessing the activity of newer cancer therapies that stabilise disease rather than shrink it. (18)F-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, subsequent revisions and enhancements are to be expected as validation studies are ongoing in several diseases and during different forms of treatment.

Post-therapeutic response assessment

The value of resection has been called into question in squamous cell cancer of the cervical and intrathoracic oesophagus. Being able to predict the true response and prognosis following chemoradiation would be of major 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). 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 and metabolic complete response (21). However, cut-off values that may indicate a correlation with histopathologic complete response have never been validated in prospective studies. Multicenter experience from prospective studies is lacking. Finally, the positive

Table 1. — **Predictive and prognostic value of FDG-PET scanning following completion of preoperative chemoradiotherapy in patients with oesophago-gastric cancer**

Author	Year	Tumour	n	Correlation with response	Correlation with prognosis
Javeri	2009 (19)	AC	151	P = 0.06	P = 0.01
Vallböhmer	2009 (20)	AC/SCC	119	P = 0.056	n.s.
Kim	2007 (21)	SCC	62	n.d.	P = 0.033
Levine	2006 (22)	AC/SCC	64	P = 0.004	n.d.
Wieder	2004 (32)	SCC	38	P = 0.011	n.d.
Swisher	2004 (23)	AC/SCC	83	P = 0.03	P = 0.01
Downey	2003 (24)	AC/SCC	39	n.d.	P = 0.088
Flamen	2002 (25)	AC/SCC	36	P = 0.001	P = 0.002
Brücher	2001 (26)	SCC	27	P = 0.001	P < 0.001

AC = adenocarcinoma, n = number, n.d. = not determined, n.s. = not significant, SCC = squamous cell cancer.

Table 2. — **Predictive value of FDG-PET scanning prior to preoperative chemo(radio)therapy in patients with oesophago-gastric cancer**

Author	Year	Tumour	n	SUV	Correlation with response
Rizk	2009 (27)	AC	189	absolute	P = 0.02
Javeri	2009 (28)	AC	161	absolute	P = 0.06
Lordick	2007 (29)	AC	110	median	P = 0.018
Levine	2006 (22)	AC/SCC	64	absolute	P = 0.005
Ott	2006 (30)	AC	65	median	P = 0.16
Swisher	2004 (23)	AC/SCC	56	absolute	P = 0.56
Wieder	2004 (32)	SCC	33	absolute	P = 0.23

AC = adenocarcinoma, n = number, SCC = squamous cell cancer, SUV = standard uptake value.

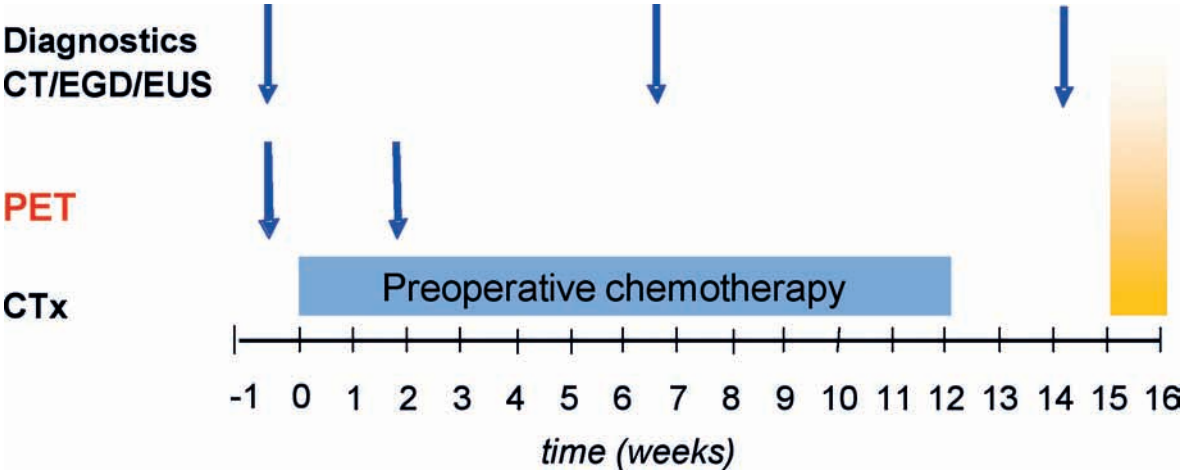
predictive value of the test (i.e. the ability of PET to predict complete histopathologic response) does not seem to be high enough to justify treatment decisions against surgery.

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 chemoradiation). Some investigators examined the value of pre-therapeutic FDG tumour uptake and treatment response (Table 2). In summary, results are conflicting. While some investigators found a correlation between higher SUV's and response to subsequent chemo(radio)therapy, some others did not. Prospective validation studies confirming specific techniques and cut-offs are lacking.

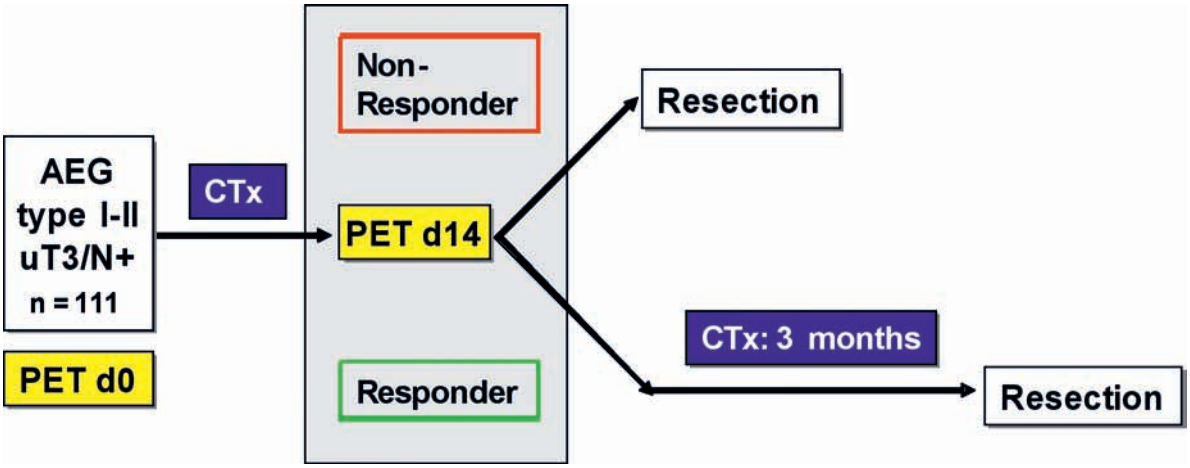
Early metabolic assessment and response prediction

Early metabolic response assessment during neoadjuvant chemotherapy of adenocarcinoma of the oesophago-gastric junction has been studied ; cut-offs have been prospectively validated and have also been used in an interventional clinical study (Fig. 2). In consecutive phase II studies the metabolic tumour activity was quantified, defined by the SUV before and during chemotherapy. It was observed that after only two weeks of induction chemotherapy significant decreases of the 18-FGD standard uptake values (SUV) were measured. A drop of ≥ 35% measured after 2 weeks of chemotherapy revealed to be the most accurate cut-off value to predict the clinical and histopathological response that was found after completion of a preoperative chemotherapy with duration of 12 weeks. Weber and colleagues first established the cut-off decrease in a retrospective study. Ott at al. performed a prospective validation study of this cut-off (30,31). The validated cut-off was brought further into subsequent studies. It was further noticed that the metabolic response to induction chemotherapy was an independent and important prognostic factor in case of locally advanced adenocarcinoma of the oesophago-gastric junction (30). Metabolic changes measured by PET were shown to be much more sensitive in detecting response early in the course of chemotherapy as compared to morphologic changes measured by high resolution CT (32). This suggests that PET can be used to tailor treatment according to the chemoresponsiveness of tumours. This concept has been realised in the MUNICON trial (29) (Fig. 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 in PET responders was 58%. The continuation of chemotherapy in the responding population resulted in a



CT = computed tomography, CTx = chemotherapy, EGD = oesophago-gastro-duodenoscopy, EUS = endoscopic ultrasound, PET = positron emission tomography.

Fig. 2. — Schema of the explorative and validation studies for the early metabolic assessment by PET and response prediction during neoadjuvant chemotherapy of carcinomas of the oesophago-gastric junction (29,30,31).



AEG = adenocarcinoma of the oesophago-gastric junction, CTx chemotherapy, n = number, PET = positron emission tomography.

Fig. 3. — Treatment plan of the MUNICON study (29)

favourable outcome : After a follow-up 28 months the median overall survival was not yet reached in PET responders as compared to 26 months in non-responders. In patients with metabolic non-response, chemotherapy could be discontinued at an early stage, thereby saving time, and reducing side-effects and costs. Compared to patients from previous studies one can delineate that the outcome of metabolic non-responders was at least not compromised by the early discontinuation of preoperative treatment.

Of note, the concept of early response evaluation was successfully studied only in patient receiving chemotherapy without radiation. In patients being treated with chemotherapy plus radiation therapy, metabolic response assessment during treatment failed to predict tumour response (33,34). This indicates that cell death induced by radiation therapy may follow other mechanisms and time lines than chemotherapy-induced apoptosis. Radiation may induce inflammatory reactions and other phenomena leading to false-positive and false-negative features. Therefore, step-by-step implementation of cut-off values is required when metabolic thresholds for response monitoring are implemented into clinical practice.

Conclusions and future steps

Current data indicate that FDG-PET ameliorates the staging accuracy in oesophago-gastric cancer. The main indication is the exclusion of distant metastases which makes a tremendous impact on treatment decisions. Whether PET may serve as a basis for tailoring radiation volumes 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 radical treatment must be carefully weighed against the increased morbidity and mortality associated with surgery and large radiation volumes in the preoperative setting.

High FDG uptake values may indicate a critical prognosis of patients presenting with localised oesophago-gastric cancer. This finding may guide the decision for multimodality treatment. This is even more true, as some studies show that patients with FDG-avid tumours have a better response and benefit more from neoadjuvant chemo(radio)therapy. But cut-off values are not clear at this stage and prospective multicenter studies need to be performed.

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 to taking decisions against surgical resection. But this latter point certainly merits further investigation, especially in patients presenting with cervical and thoracic oesophageal squamous cell cancer, where the operative risk following chemoradiation is very high.

The most exciting use of FDG-PET in the management of oesophago-gastric 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 major 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).

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