Value of Functional Imaging by PET in Esophageal Cancer

Thomas Schmidt, MD, PhD^a; Florian Lordick, MD^b; Ken Herrmann, MD^c; and Katja Ott, MD^d

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 chemotherapy, with potential subsequent therapy modification. This tailored approach still needs validation in prospective multicenter trials. (*J Natl Compr Canc Netw* 2015;13:239–247)

From the ^aDepartment of General, Visceral, and Transplantation Surgery, University of Heidelberg, Heidelberg; ^bUniversity Cancer Center Leipzig, University Hospital Leipzig, Leipzig; ^cDepartment of Nuclear Medicine, University Hospital Würzburg, Würzburg; and ^dDepartment of General, Vascular, and Thoracic Surgery, RoMed Klinikum Rosenheim, Rosenheim, Germany.

Submitted September 23, 2014; accepted for publication December 25, 2014.

The authors have disclosed that they have no financial interests, arrangements, affiliations, or commercial interests with the manufacturers of any products discussed in this article or their competitors.

Correspondence: Katja Ott, MD, Klinik für Allgemein-, Gefäß-, und Thoraxchirurgie, RoMed Klinikum Rosenheim, Pettenkoferstraße 10, D-83022 Rosenheim, Germany. E-mail: Katja.Ott@ro-med.de

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^{3,4} or definitive chemoradiotherapy^{5,6} is 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.⁴ 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.² Currently, the correct cT category is predicted best with endoluminal ultrasound (EUS), even if EUS is judged to be investigator-dependent in some studies.^{7,8} For very early tumor categories, endoscopic resections gain increasingly more importance and even offer correct pretherapeutic pathologic pT categories.⁹ The clinical relevance of the correct pN staging according to functional imaging seems to be controversial, strongly depending on the specific inclusion criteria for preoperative 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 resection¹⁰ and those who underwent preoperative treatment,¹¹ although the correct evaluation of initially positive lymph nodes after preoperative therapy remains histopathologi-

cally challenging. According to recent data, the complementary role of EUS to PET/CT should be considered.¹² 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,^{13,14} 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%^{7,15–22} (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%).¹⁷

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.²³

Interval Metastases

Three studies to date have addressed the issue of detecting posttherapeutic interval metastases after preoperative chemoradiotherapy.^{24–26} 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

Table 1 Overview of Current Studies Analyzing the Additional Diagnostic Value of Functional Imaging in Comparison With Conventional Staging

Author	Year	Change of AJCC Stage	
		(n)	(%)
Pfau et al ⁷	2007	15/56	27
Meyers et al ¹⁶	2007	9/189	5
Salahudeen et al ²⁰	2008	3/25	12
Noble et al ¹⁷	2009	18/191	9
Pifarre-Montaner et al ¹⁸	2009	14/59	24
Walker et al ²¹	2011	17/81	21
Gillies et al ¹⁵	2011	37/200	17
You et al ²²	2013	188/495	24
Purandare et al ¹⁹	2014	25/156	16
Total		326/1452	22.4

Adapted from Ott K, Schmidt T, Lordick F, Herrmann K. Importance of PET in surgery of esophageal cancer [in German]. *Chirurg* 2014;85:505–512; with permission.

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 clinical^{30–32} 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 during³⁷ 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 esophago-gastric 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.^{34,35} 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.^{43–45} 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.⁴⁶ 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.⁴⁷ 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.^{4,48}

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.⁴¹ 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,^{49–52} this has been reported in the most recent studies^{34,53–55} (Table 2). Some of these recent studies also show an association between initial SUV and survival,^{54,56} but contradictory findings have been reported.^{34,51,53,54,57,58} 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.⁵⁹ 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.⁶⁰ 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.^{57,58,61–67} 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.⁶⁰

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

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

Author	Year	n	Histology	Therapy	SUV	P Value (Response)
Ott et al ⁵²	2006	65	AC	CTx/S	Med	.16
Lordick et al ³⁴	2007	110	AC	CTx/S	Med	.008 ^a
Rizk et al ⁵⁴	2009	189	AC	CRTx/S	Abs	.02 ^a
Javeri et al ⁶¹	2009	161	AC	CRTx/S	Med	.16
Palie et al ⁵⁵	2013	57	SCC	CRTx	Abs	.05 ^a
Piessen et al ⁵⁸	2013	60	SCC	CRTx	Abs	.14
Wieder et al ⁴⁹	2004	33	SCC	CRTx/S	Abs	.23
Swisher et al ⁷⁰	2004	56	AC/SCC	CRTx/S	Abs	.46
Hong et al ⁵¹	2005	47	AC/SCC	CRTx/S	Abs	NS
Levine et al ⁵³	2006	64	AC/SCC	CRTx	Abs	.005 ^a
Jayachandran et al ⁵⁷	2012	37	AC/SCC	CRTx/S	Abs	NS

Abbreviations: Abs, absolute; AC, adenocarcinoma; CRTx, chemoradiotherapy; CTx, chemotherapy; Med, median; NS, not significant; S, surgery; SCC, squamous cell carcinoma; SUV, standard uptake value.

^aSignificant P value.

From Ott K, Schmidt T, Lordick F, Herrmann K. Importance of PET in surgery of esophageal cancer [in German]. *Chirurg* 2014;85:505–512; with permission.

4) exist to predict pCR: retrospectively defining cut-off values^{68–70} (accuracies of 75% were reported in 2 studies^{69,70}) and interpreting a posttherapeutic FDG-negative tumor as a subsequent pCR.^{50,71–74} For the latter, the number of included patients is limited, but the percentage of residual tumor in FDG-negative tumors was high, ranging from 17.8% (13/73)⁵⁰ to 70.6% (12/17).⁷¹ This demonstrates that a posttherapeutic FDG-negative tumor is not synonymous with a pCR. Recently, the CROSS study group showed that pCR after neoadjuvant chemotherapy increases with time from completion of chemoradiotherapy.⁴¹ So far no data are available on posttherapeutic evaluation of pCR at a later time point using FDG-PET.

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,

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

Author	Year	n	Histology	Therapy	Response	Prognosis
Konski et al ⁶⁷	2007	81	AC/SCC	CRTx	NS	$P=.01$ (DFS)
Vallböhmer et al ⁶³	2009	119	AC/SCC	CRTx	$P=.056$	NS
Schmidt et al ⁶⁴	2009	55	AC/SCC	CRTx	NS	NS
Jayachandran et al ⁵⁷	2012	37	AC/SCC	CRTx	NS	NS
Javeri et al ⁶¹	2009	151	AC	CRTx	$P=.06$	$P=.01$
Smith et al ⁶⁶	2009	21	AC	CRTx		$P=.025$
Kauppi et al ⁶²	2012	66	AC	CTx	$P<.001$	$P=.027$
Abdelsalam et al ⁶⁵	2010	21	SCC	CRTx	$P=.025$	$P=.038$
Piessen et al ⁵⁸	2013	60	SCC	CRTx	$P=.012$	NS

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

From Ott K, Schmidt T, Lordick F, Herrmann K. Importance of PET in surgery of esophageal cancer [in German]. *Chirurg* 2014;85:505–512; with permission.

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

	Author	Year	n	Change in PET	Residual Tumor	Accuracy
Cutoff	Swisher et al ⁷⁰	2004	103	FDG ↓ ^a		
	Cerfolio et al ⁶⁹	2009	86	<64%		75%
	Molena et al ⁶⁸	2014	116	>4%		76%
FDG-PET–Negative	Swisher et al ⁵⁰	2004	73	Neg	12/17	
	Erasmus et al ⁷⁴	2006	42	Neg	11	
	Kim et al ⁷³	2007	62	Neg		
	Port et al ⁷²	2007	62	Neg	12/23	
	Yen et al ⁷¹	2012	118	Neg	13/73	

Abbreviation: FDG, fluorodeoxyglucose; Neg, negative.

^aLower FGD-PET SUV values predict pathologic response.

From Ott K, Schmidt T, Lordick F, Herrmann K. Importance of PET in surgery of esophageal cancer [in German]. *Chirurg* 2014;85:505–512; with permission.

for which metabolic response evaluation is of less interest, although van Heijl et al⁷⁸ 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.⁷⁹ This cutoff was used to correctly identify nonresponding patients and was prospectively validated in an independent patient cohort.⁵² Therefore, in the MUNICON I trial, a metabolic response–based therapy modification was included after 2 weeks,³⁴ 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).³⁴ 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.³⁵ 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%; $P=.035$).³⁵ Through the sequential study de-

sign, 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%^{34,52,78–81} 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^{34,35,49,55,78–80,82–85} (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

Table 5 Overview of Studies Evaluating Early Response Monitoring by Changes of SUV by PET/CT

Author	Year	n	Histology	Therapy	Time Point	SUV Decrease	P Value ^a	
							(Response)	(Prognosis)
Weber et al ⁷⁹	2001	40	AC	CTx	wk 2	−35%	+	+
Ott et al ⁸⁰	2003	44	AC	CTx	wk 2	−35%	+	+
Ott et al ⁵²	2006	65	AC	CTx	wk 2	−35%	+	+
Lordick et al ³⁴	2007	119	AC	CTx	wk 2	−35%	+	+
Ott et al ⁸⁴	2008	49	AC	CTx	wk 2	−35%	+	+
Malik et al ⁸⁵	2010	37	AC	(c)RTx CTx	wk 2	−26%		−
zum Büschenfelde et al ³⁵	2011	56	AC	CTx CRTx	wk 2	−35%	−	+
Westerterp et al ⁸³	2006	26	SCC/AC	CRTx	wk 2	−31%	+	−
van Heijl et al ⁷⁸	2011	100	SCC/AC	CRTx	wk 2	0%	+	
Ilson et al ⁸¹	2012	55	SCC/AC	CTx CRTx	wk 6	−35%	+	−
Wieder et al ⁴⁹	2004	24	SCC	CRTx	wk 2	−30%	+	+
Wieder et al ⁸²	2007	38	SCC	CRTx	wk 2	−33%	+	+
Palie et al ⁵⁵	2013	57	SCC	CRTx	wk 3	−	−	−

Abbreviations: AC, adenocarcinoma; (c)RTx, chemoradiotherapy or radiotherapy; CRTx, chemoradiotherapy; CTx, chemotherapy; SCC, squamous cell carcinoma; SUV, standard uptake value.

^aStudies evaluated response to treatment and prognosis for overall survival.

From Ott K, Schmidt T, Lordick F, Herrmann K. Importance of PET in surgery of esophageal cancer [in German]. *Chirurg* 2014;85:505–512; with permission.

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/perioperative 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

- Ott K, Weber WA, Fink U, et al. Fluorodeoxyglucose-positron emission tomography in adenocarcinomas of the distal esophagus and cardia. *World J Surg* 2003;27:1035–1039.
- Cuellar SL, Carter BW, Macapinlac HA, et al. Clinical staging of patients with early esophageal adenocarcinoma: does FDG-PET/CT have a role? *J Thorac Oncol* 2014;9:1202–1206.
- Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *Lancet Oncol* 2011;12:681–692.
- van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074–2084.
- Bedenne L, Michel P, Bouché O, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. *J Clin Oncol* 2007;25:1160–1168.

6. Stahl M, Walz MK, Stuschke M, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. *J Clin Oncol* 2009;27:851–856.
7. Pfau PR, Perlman SB, Stanko P, et al. The role and clinical value of EUS in a multimodality esophageal carcinoma staging program with CT and positron emission tomography. *Gastrointest Endosc* 2007;65:377–384.
8. Thosani N, Singh H, Kapadia A, et al. Diagnostic accuracy of EUS in differentiating mucosal versus submucosal invasion of superficial esophageal cancers: a systematic review and meta-analysis. *Gastrointest Endosc* 2012;75:242–253.
9. Pech O, May A, Manner H, et al. Long-term efficacy and safety of endoscopic resection for patients with mucosal adenocarcinoma of the esophagus. *Gastroenterology* 2014;146:652–660.
10. Moon SH, Kim HS, Hyun SH, et al. Prediction of occult lymph node metastasis by metabolic parameters in patients with clinically N0 esophageal squamous cell carcinoma. *J Nucl Med* 2014;55:743–748.
11. Karashima R, Watanabe M, Imamura Y, et al. Advantages of FDG-PET/CT over CT alone in the preoperative assessment of lymph node metastasis in patients with esophageal cancer [published online ahead of print June 28, 2014]. *Surg Today*, in press.
12. Foley KG, Lewis WG, Fielding P, et al. N-staging of oesophageal and junctional carcinoma: is there still a role for EUS in patients staged N0 at PET/CT? *Clin Radiol* 2014;69:959–964.
13. Blank S, Lordick F, Dobritz M, et al. A reliable risk score for stage IV esophagogastric cancer. *Eur J Surg Oncol* 2013;39:823–830.
14. Stahl M, Mariette C, Haustermans K, et al. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;24(Suppl 6):vi51–56.
15. Gillies RS, Middleton MR, Maynard ND, et al. Additional benefit of (1)(8)F-fluorodeoxyglucose integrated positron emission tomography/computed tomography in the staging of oesophageal cancer. *Eur Radiol* 2011;21:274–280.
16. Meyers BF, Downey RJ, Decker PA, et al. The utility of positron emission tomography in staging of potentially operable carcinoma of the thoracic esophagus: results of the American College of Surgeons Oncology Group Z0060 trial. *J Thorac Cardiovasc Surg* 2007;133:738–745.
17. Noble F, Bailey D, Tung K, Byrne JP. Impact of integrated PET/CT in the staging of oesophageal cancer: a UK population-based cohort study. *Clin Radiol* 2009;64:699–705.
18. Pifarre-Montaner P, Fernández-León A, de Juan R, et al. Impact of (18) F-FDG PET/CT on the therapeutic management in the initial staging of the esophageal cancer [in Spanish]. *Rev Esp Med Nucl* 2009;28:101–105.
19. Purandare NC, Pramesh CS, Karimundackal G, et al. Incremental value of 18F-FDG PET/CT in therapeutic decision-making of potentially curable esophageal adenocarcinoma. *Nucl Med Commun* 2014;35:864–869.
20. Salahudeen HM, Balan A, Naik K, et al. Impact of the introduction of integrated PET-CT into the preoperative staging pathway of patients with potentially operable oesophageal carcinoma. *Clin Radiol* 2008;63:765–773.
21. Walker AJ, Spier BJ, Perlman SB, et al. Integrated PET/CT fusion imaging and endoscopic ultrasound in the pre-operative staging and evaluation of esophageal cancer. *Mol Imaging Biol* 2011;13:166–171.
22. You JJ, Wong RK, Darling G, et al. Clinical utility of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in the staging of patients with potentially resectable esophageal cancer. *J Thorac Oncol* 2013;8:1563–1569.
23. Miyazaki T, Sohda M, Higuchi T, et al. Effectiveness of FDG-PET in screening of synchronous cancer of other organs in patients with esophageal cancer. *Anticancer Res* 2014;34:283–287.
24. Blom RL, Schreurs WM, Belgers HJ, et al. The value of post-neoadjuvant therapy PET-CT in the detection of interval metastases in esophageal carcinoma. *Eur J Surg Oncol* 2011;37:774–778.
25. Bruzzi JF, Swisher SG, Truong MT, et al. Detection of interval distant metastases: clinical utility of integrated CT-PET imaging in patients with esophageal carcinoma after neoadjuvant therapy. *Cancer* 2007;109:125–134.
26. Stiekema J, Vermeulen D, Vegt E, et al. Detecting interval metastases and response assessment using 18F-FDG PET/CT after neoadjuvant chemoradiotherapy for esophageal cancer. *Clin Nucl Med* 2014;39:862–867.
27. Schmidt T, Sicic L, Blank S, et al. Prognostic value of histopathological regression in 850 neoadjuvantly treated oesophagogastric adenocarcinomas. *Br J Cancer* 2014;110:1712–1720.
28. Ott K, Schmidt T, Lordick F, Herrmann K. Importance of PET in surgery of esophageal cancer [in German]. *Chirurg* 2014;85:505–512.
29. Zhu W, Xing L, Yue J, et al. Prognostic significance of SUV on PET/CT in patients with localised oesophagogastric junction cancer receiving neoadjuvant chemotherapy/chemoradiation: a systematic review and meta-analysis. *Br J Radiol* 2012;85:e694–701.
30. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma—2nd English edition—response assessment of chemotherapy and radiotherapy for gastric carcinoma: clinical criteria. *Gastric Cancer* 2001;4:1–8.
31. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–247.
32. Heger U, Blank S, Wiecha C, et al. Is preoperative chemotherapy followed by surgery the appropriate treatment for signet ring cell containing adenocarcinomas of the esophagogastric junction and stomach? *Ann Surg Oncol* 2014;21:1739–1748.
33. Karamitopoulou E, Thies S, Zlobec I, et al. Assessment of tumor regression of esophageal adenocarcinomas after neoadjuvant chemotherapy: comparison of 2 commonly used scoring approaches. *Am J Surg Pathol* 2014;38:1551–1556.
34. Lordick F, Ott K, Krause BJ, et al. 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.
35. zum Büschenfelde CM, Herrmann K, Schuster T, et al. (18)F-FDG PET-guided salvage neoadjuvant radiochemotherapy of adenocarcinoma of the esophagogastric junction: the MUNICON II trial. *J Nucl Med* 2011;52:1189–1196.
36. Ott K, Sendler A, Becker K, et al. Neoadjuvant chemotherapy with cisplatin, 5-FU, and leucovorin (PLF) in locally advanced gastric cancer: a prospective phase II study. *Gastric Cancer* 2003;6:159–167.
37. Heger U, Bader F, Lordick F, et al. Interim endoscopy results during neoadjuvant therapy for gastric cancer correlate with histopathological response and prognosis. *Gastric Cancer* 2014;17:478–488.
38. Blank S, Lordick F, Bader F, et al. Post-therapeutic response evaluation by a combination of endoscopy and CT scan in esophagogastric adenocarcinoma after chemotherapy: better than its reputation [published online ahead of print April 11, 2014]. *Gastric Cancer*, in press.
39. Mandard AM, Dalibard F, Mandard JC, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer* 1994;73:2680–2686.
40. Langer R, Ott K, Feith M, et al. Prognostic significance of histopathological tumor regression after neoadjuvant chemotherapy in esophageal adenocarcinomas. *Mod Pathol* 2009;22:1555–1563.
41. Shapiro J, van Hagen P, Lingsma HF, et al. Prolonged time to surgery after neoadjuvant chemoradiotherapy increases histopathological response without affecting survival in patients with esophageal or junctional cancer. *Ann Surg* 2014;260:807–814.
42. Slotta-Huspenina J, Wolff C, Drecoll E, et al. A specific expression profile of heat-shock proteins and glucose-regulated proteins is associated with response to neoadjuvant chemotherapy in oesophageal adenocarcinomas. *Br J Cancer* 2013;109:370–378.
43. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355:11–20.
44. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol* 2011;29:1715–1721.
45. Lutz MP, Zalberg JR, Ducreux M, et al. Highlights of the EORTC St. Gallen International Expert Consensus on the primary therapy of gastric, gastroesophageal and oesophageal cancer - differential treatment strategies for subtypes of early gastroesophageal cancer. *Eur J Cancer* 2012;48:2941–2953.
46. Blank S, Stange A, Sicic L, et al. Preoperative therapy of esophagogastric cancer: the problem of nonresponding patients. *Langenbecks Arch Surg* 2013;398:211–220.
47. Jouve J, Miche P, Mariette C, et al. Outcome of the nonrandomized patients in the FFCD 9102 trial: chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus [abstract]. *J Clin Oncol* 2008;26(Suppl):Abstract 4555.
48. Castoro C, Scarpa M, Cagol M, et al. Complete clinical response after neoadjuvant chemoradiotherapy for squamous cell cancer of the thoracic oesophagus: is surgery always necessary? *J Gastrointest Surg* 2013;17:1375–1381.

PET in Esophageal Cancer

49. Wieder HA, Brücher BL, Zimmermann F, et al. Time course of tumor metabolic activity during chemoradiotherapy of esophageal squamous cell carcinoma and response to treatment. *J Clin Oncol* 2004;22:900–908.
50. Swisher SG, Erasmus J, Maish M, et al. 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.
51. Hong D, Lunagomez S, Kim EE, et al. Value of baseline positron emission tomography for predicting overall survival in patient with nonmetastatic esophageal or gastroesophageal junction carcinoma. *Cancer* 2005;104:1620–1626.
52. Ott K, Weber WA, Lordick F, et al. Metabolic imaging predicts response, survival, and recurrence in adenocarcinomas of the esophagogastric junction. *J Clin Oncol* 2006;24:4692–4698.
53. Levine EA, Farmer MR, Clark P, et al. 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.
54. Rizk NP, Tang L, Adusumilli PS, et al. Predictive value of initial PET-SUVmax in patients with locally advanced esophageal and gastroesophageal junction adenocarcinoma. *J Thorac Oncol* 2009;4:875–879.
55. Palie O, Michel P, Ménard JF, et al. The predictive value of treatment response using FDG PET performed on day 21 of chemoradiotherapy in patients with oesophageal squamous cell carcinoma. A prospective, multicentre study (RTEP3). *Eur J Nucl Med Mol Imaging* 2013;40:1345–1355.
56. Suzuki A, Xiao L, Hayashi Y, et al. Prognostic significance of baseline positron emission tomography and importance of clinical complete response in patients with esophageal or gastroesophageal junction cancer treated with definitive chemoradiotherapy. *Cancer* 2011;117:4823–4833.
57. Jayachandran P, Pai RK, Quon A, et al. Postchemoradiotherapy positron emission tomography predicts pathologic response and survival in patients with esophageal cancer. *Int J Radiat Oncol Biol Phys* 2012;84:471–477.
58. Piessen G, Petyt G, Duhamel A, et al. Ineffectiveness of ¹⁸F-fluorodeoxyglucose positron emission tomography in the evaluation of tumor response after completion of neoadjuvant chemoradiation in esophageal cancer. *Ann Surg* 2013;258:66–76.
59. Schollaert P, Crott R, Bertrand C, et al. A systematic review of the predictive value of (18)FDG-PET in esophageal and esophagogastric junction cancer after neoadjuvant chemoradiation on the survival outcome stratification. *J Gastrointest Surg* 2014;18:894–905.
60. Kwee RM. Prediction of tumor response to neoadjuvant therapy in patients with esophageal cancer with use of 18F FDG PET: a systematic review. *Radiology* 2010;254:707–717.
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 gastroesophageal adenocarcinoma. *Cancer* 2009;115:5184–5192.
62. Kauppi JT, Oksala N, Salo JA, et al. Locally advanced esophageal adenocarcinoma: response to neoadjuvant chemotherapy and survival predicted by ([18F])FDG-PET/CT. *Acta Oncol* 2012;51:636–644.
63. Vallböhmer D, Hölscher AH, Dietlein M, et al. [18F]-Fluorodeoxyglucose-positron emission tomography for the assessment of histopathologic response and prognosis after completion of neoadjuvant chemoradiation in esophageal cancer. *Ann Surg* 2009;250:888–894.
64. Schmidt M, Bollschweiler E, Dietlein M, et al. Mean and maximum standardized uptake values in [18F]FDG-PET for assessment of histopathological response in oesophageal squamous cell carcinoma or adenocarcinoma after radiochemotherapy. *Eur J Nucl Med Mol Imaging* 2009;36:735–744.
65. Abdelsalam M, Bazarbashi S, Abouzied M, et al. Whole body 18F-FDG PET predicts progression free and overall survival in squamous cell carcinoma of the esophagus: results of a prospective trial. *Hematol Oncol Stem Cell Ther* 2010;3:179–184.
66. Smith JW, Moreira J, Abood G, et al. The influence of (18) flourodeoxyglucose positron emission tomography on the management of gastroesophageal junction carcinoma. *Am J Surg* 2009;197:308–312.
67. Konski AA, Cheng JD, Goldberg M, et al. Correlation of molecular response as measured by 18-FDG positron emission tomography with outcome after chemoradiotherapy in patients with esophageal carcinoma. *Int J Radiat Oncol Biol Phys* 2007;69:358–363.
68. Molena D, Sun HH, Badr AS, et al. Clinical tools do not predict pathological complete response in patients with esophageal squamous cell cancer treated with definitive chemoradiotherapy. *Dis Esophagus* 2014;27:355–359.
69. Cerfolio RJ, Bryant AS, Talati AA, et al. Change in maximum standardized uptake value on repeat positron emission tomography after chemoradiotherapy in patients with esophageal cancer identifies complete responders. *J Thorac Cardiovasc Surg* 2009;137:605–609.
70. Swisher SG, Maish M, Erasmus JJ, et al. Utility of PET, CT, and EUS to identify pathologic responders in esophageal cancer. *Ann Thorac Surg* 2004;78:1152–1160.
71. Yen TJ, Chung CS, Wu YW, et al. Comparative study between endoscopic ultrasonography and positron emission tomography-computed tomography in staging patients with esophageal squamous cell carcinoma. *Dis Esophagus* 2012;25:40–47.
72. Port JL, Lee PC, Korst RJ, et al. Positron emission tomographic scanning predicts survival after induction chemotherapy for esophageal carcinoma. *Ann Thorac Surg* 2007;84:393–400; discussion 400.
73. Kim MK, Ryu JS, Kim SB, et al. Value of complete metabolic response by (18)F-fluorodeoxyglucose-positron emission tomography in oesophageal cancer for prediction of pathologic response and survival after preoperative chemoradiotherapy. *Eur J Cancer* 2007;43:1385–1391.
74. Erasmus JJ, Munden RF, Truong MT, et al. Preoperative chemo-radiation-induced ulceration in patients with esophageal cancer: a confounding factor in tumor response assessment in integrated computed tomographic-positron emission tomographic imaging. *J Thorac Oncol* 2006;1:478–486.
75. Moehler M, Balin CT, Ebert M, et al. International comparison of the German evidence-based S3-guidelines on the diagnosis and multimodal treatment of early and locally advanced gastric cancer, including adenocarcinoma of the lower esophagus [published online ahead of print September 7, 2014]. *Gastric Cancer*, in press.
76. Moehler M, Al-Batran SE, Andus T, et al. German S3-guideline “Diagnosis and treatment of esophagogastric cancer” [in German]. *Z Gastroenterol* 2011;49:461–531.
77. Ajani JA, D’Amico TA, Almhanna K, et al. NCCN Clinical Practice Guidelines in Oncology for Esophageal and Esophagogastric Junction Cancers. Version 1, 2015. Available at: NCCN.org. Accessed January 12, 2015.
78. van Heijl M, Omluo JM, van Berge Henegouwen MI, et al. Fluorodeoxyglucose positron emission tomography for evaluating early response during neoadjuvant chemoradiotherapy in patients with potentially curable esophageal cancer. *Ann Surg* 2011;253:56–63.
79. Weber WA, Ott K, Becker K, et al. Prediction of response to preoperative chemotherapy in adenocarcinomas of the esophagogastric junction by metabolic imaging. *J Clin Oncol* 2001;19:3058–3065.
80. Ott K, Fink U, Becker K, et al. Prediction of response to preoperative chemotherapy in gastric carcinoma by metabolic imaging: results of a prospective trial. *J Clin Oncol* 2003;21:4604–4610.
81. Ilson DH, Minsky BD, Ku GY, et al. Phase 2 trial of induction and concurrent chemoradiotherapy with weekly irinotecan and cisplatin followed by surgery for esophageal cancer. *Cancer* 2012;118:2820–2827.
82. Wieder HA, Ott K, Lordick F, et al. Prediction of tumor response by FDG-PET: comparison of the accuracy of single and sequential studies in patients with adenocarcinomas of the esophagogastric junction. *Eur J Nucl Med Mol Imaging* 2007;34:1925–1932.
83. Westertep M, Omluo JM, Sloof GW, et al. Monitoring of response to pre-operative chemoradiation in combination with hyperthermia in oesophageal cancer by FDG-PET. *Int J Hyperthermia* 2006;22:149–160.
84. Ott K, Herrmann K, Lordick F, et al. Early metabolic response evaluation by fluorine-18 fluorodeoxyglucose positron emission tomography allows in vivo testing of chemosensitivity in gastric cancer: long-term results of a prospective study. *Clin Cancer Res* 2008;14:2012–2018.
85. Malik V, Lucey JA, Duffy GJ, et al. Early repeated 18F-FDG PET scans during neoadjuvant chemoradiation fail to predict histopathologic response or survival benefit in adenocarcinoma of the esophagus. *J Nucl Med* 2010;51:1863–1869.