ORIGINAL ARTICLE

The Role of PET and PET-CT Scanning in Assessing Response to Neoadjuvant Therapy in Esophageal Carcinoma

A Systematic Review

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SUMMARY

Background: The response to neoadjuvant (radio-)chemotherapy for esophageal carcinoma is often assessed with the aid of positron-emission tomography (PET), either alone or in combination with computed tomography (PET-CT). In this review, we discuss the diagnostic validity and clinical benefit of these imaging techniques.

Methods: We systematically searched the Medline, Embase, and Cochrane Library databases for randomized controlled trials (RCTs) and controlled clinical trials (CCTs) comparing PET-CT with conventional techniques such as endosonography and CT. We then determined the diagnostic validity of these methods on the basis of information from published systematic reviews, updated with further information from more recent primary studies.

Results: We did not find any RCTs that addressed the question of the patient-relevant benefit of PET-CT. We found 20 studies of diagnostic methods, carried out on a total of 854 patients, of whom 82.2% were male. These studies had a high potential for bias. In two of them, PET-CT was directly compared with endosonography or CT. Estimates of sensitivity and specificity varied widely across studies. 54% of all patients (median value across studies) had no histopathological response to therapy at the end of treatment. Taking a reduction of the standard uptake value (SUV) by at least 35% as a threshold criterion, we found that the median negative predictive value of PET across all studies was 86.5%.

Conclusion: There is no robust evidence for a patient-relevant benefit of PET and PET-CT in patients with esophageal carcinoma. PET could potentially be used to distinguish treatment responders from non-responders after the first cycle of treatment. RCTs with patient-relevant endpoints will be needed in order to determine whether this is useful.

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In Germany, esophageal cancer is responsible for around 3% of all deaths from cancer in men and 1% in women (1). Neoadjuvant chemotherapy (NAC) and radiochemotherapy (NARC) are now important treatment options for cancer of the esophagus and the gastroesophageal junction. The aim of neoadjuvant therapy is to reduce the size of the tumor, in order to allow its complete removal at subsequent surgery (2, 3).

Positron emission tomography (PET), alone or integrated with computed tomography (CT) (PET-CT), is a noninvasive diagnostic technique that could be helpful for early detection of tumor response to neoadjuvant therapy. If lack of response to treatment could be reliably predicted using PET or PET-CT, the neoadjuvant treatment could be discontinued or changed to another treatment, thus allowing unnecessary adverse effects such as fatigue, nausea, and vomiting (4) to be avoided.

The Institute for Quality and Efficiency in Health Care (IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen) was commissioned by the Federal Joint Committee to carry out a systematic assessment of the benefits for patients (i.e., the proven positive effects of a medical intervention on patient-relevant endpoints [5]) of PET-CT and PET in terms of primary staging, treatment response, and diagnosis of recurrence in esophageal cancer (6).

The primary aim of the present review was to examine the benefit for patients of using PET-CT and PET to assess the response of esophageal cancer to NAC and NARC, both early response (after the first few treatment cycles) and late response (after completion of neoadjuvant treatment).

Where there was insufficient evidence to achieve the primary aim, we planned (secondary aim) to assess the diagnostic accuracy of PET-CT and PET in early response (delayed reference test) and late response (imaging and reference test at the same time point).

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FIGURE 1

Assessment of risk of bias in the nine studies in the update search;

*Some values were missing, or there were indications that missing values did not occur randomly bet., between

Inclusion criteria

For our primary aim, RCTs and CCTs with the following features were included:

- Patients with esophageal cancer
 - a) PET or PET-CT compared with a conventional diagnostic test (e.g., CT)
 - b) PET or PET-CT compared to no diagnostic test
- Patient-relevant endpoints (mortality, morbidity, health-related quality of life, and adverse events)
- Full text available (no language limitation).

Various RCT designs are available for this purpose (7–9).

We used the Oxman and Guyatt index (10) to assess the systematic reviews. Eligible systematic reviews had to score at least 5 of 7 possible points. In addition to the previously listed criteria for RCTs, the following criteria were applied for the inclusion of systematic reviews and diagnostic studies:

- Prospective design
- Patient-based analysis
- Number of patients ≥ 10
- Valid reference test (histopathology or clinical follow-up >6 months, or a combination of the two)
- Sufficient data for calculation of 2×2 tables.

If the number of studies that directly compared PET-CT and PET with other diagnostic procedures was too low, we planned also to include studies with a “verification of only positive testers” (VOPT) design. In the VOPT study design, the reference test is carried out only in patients in whom a suspicious lesion was found by one or both of the index tests (11).

Data extraction

The individual steps of the data extraction and risk-of-bias assessment procedures were carried out by one reviewer and checked by another. Disagreements were resolved by consensus. Details regarding the assessment of risk of bias in diagnostic studies are given in Figure 1 and in the final report (6).

Assessment of risk of bias in diagnostic studies

We used a modified version of QUADAS (12) to assess the risk of bias in diagnostic studies identified during the update search. The risk of bias of the diagnostic studies was rated as either “low” or “high” (Figure 1). The risk of bias of studies identified by the systematic reviews was rated according to the ratings provided in those reviews.

Data analysis

Because of the small number of studies that directly compared PET-CT and PET with conventional imaging techniques, prospectively planned bivariate meta-analyses were not carried out. The diagnostic accuracy of the studies included is presented descriptively, divided into early and late responses to treatment. Study results based on less than 70% of the patients originally included are not shown.

Methods

Search strategy and study selection

For our primary aim, we searched Medline (publication dates from 1946 to March 2015) and Embase (publication dates from 1980 to March 2015) for randomized controlled trials (RCTs) and controlled clinical studies (CCTs).

For our secondary aim, we conducted a “review of reviews.” For this, we searched the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment Database for systematic reviews. In addition, in March 2015, we carried out an update search for diagnostic primary studies in Medline and Embase, to cover the period not included in the systematic reviews.

The search strategy was designed by one information specialist and checked by another. It is described in detail in the final report (6).

FIGURE 2

Results of the bibliographic literature search and screening

* Results are given in the final report (6).

RCTs, randomized controlled studies; PET, positron emission tomography; CT, computed tomography; SR, systematic review

The following methodological issues were noted in respect of the studies on early response: two studies—one building on the other (13, 14)—with very homogeneous patient pools and treatment options indicated a reduction by more than 35% of the standard uptake value (SUV) in the tumor region as a cut-off value. This cut-off value was validated by Ott et al. (15).

In other studies on early treatment response, data were presented at the patient level, allowing retrospective evaluation using the cut-off value (>35% SUV reduction) (NAC [16]; NARC [17–20]). On this basis, a histopathological post hoc analysis of treatment response was carried out using the validated cut-off value (>35% SUV reduction). This analysis made it possible

to calculate negative predictive values (NPVs). Assuming that the goal of NAC and NARC is to reduce tumor size and thus allow complete surgical removal of the tumor (R0 resectability), the histology after resection can be regarded as the gold standard for distinguishing between patients who benefit from NAC and NARC and those who do not.

Results

Literature search

The search for primary studies produced 7737 hits (after removal of duplicates). Regarding the primary goal, no relevant RCTs or CCTs were found (Figure 2). Among 1283 bibliographic entries, three high-quality systematic reviews on the diagnostic accuracy

TABLE 1

Results of the included studies

Study	Treatment	Index test	Cut-off for nonresponders	Sensitivity % (95% CI)* ¹	Specificity % (95% CI)* ¹
Early response					
Gillham 2006 (17)	NAC + NARC	PET and integrated PET-CT	Reduction in SUV (R-SUV) >20%	44 (13.7–78.8)	52 (30.6–73.2)
Ilson 2011 (31)	NAC + NARC	PET	(R-SUV) >35%	88.9 (51.8–99.7)	61.4 (45.5–75.6)
Malik 2010 (18)	NARC	PET	R-SUVmax ≥ 26.4%	62.5 (35.5–84.7)	71.4 (47.8–88.6)
Ott 2006 (15)	NAC	PET	R-SUV ≥ 35%	80 (44.4–97.5)	78 (63.6–89.1)
van Heijl 2011 (36) * ^{3,4}	NARC	PET	R-SUV > 30% to ≤ 30%	54.7 (41.7–67.2)	66.7 (49.0–81.4)
Weber 2001 (13)	NAC	PET	n.d.	88 (51.8–99.7)	75 (55.1–89.3)
Westerterp 2006 (19)	NARC	PET	SUV ≥ 31%	— * ²	— * ²
Late response					
Brücher 2001 (24)	NAC + NARC	PET	Reduction in FDG-PET uptake 52%	100 (75.3–100)	55 (23.4–83.3)
Cerfolio 2005 (25)	NARC	PET-CT	R-SUV ≥ 2.5	86.7 (59.7–98.3)	87.9 (71.8–96.6)
	NARC	EUS	n.d.	20 (4.3–48.1)	94 (79.8–99.3)
Flamen 2002 (26)	NARC	PET	Reduction in FDG uptake >80%	71 (41.9–91.6)	82 (59.7–94.8)
Gillies 2012 (29) * ⁵	NAC	PET-CT	R-SUV >42% (median)	68.0 (46.5–85.1)	69.6 (47.1–86.8)
Higuchi 2008 (30)	NAC + NARC	PET	R-SUVmax < 2.5	90.0 (73.5–97.9)i	90.0 (68.3–98.8)
Levine 2006 (27)	NAC + NARC	PET	R-SUV: 4	— * ²	— * ²
Ma 2013 (32) * ⁶	NARC	PET* ⁷	R-SUVmax 75%	86.4* ¹ (65.1–97.1)	86.8* ¹ (71.9–95.6)
Myslivecek 2012 (33)	NARC	PET/CT	R-SUVmax 62.4%	12* ¹ (0.25–31.2)	77.8* ¹ (40.0–97.2)
Piessen 2013 (34) * ⁸	NARC	PET	R-SUV = 5.5	77.8* ¹ (40–97.2)	81.1* ¹ (64.8–92.0)
Roedl 2009 (35) * ⁹	NARC	PET	R-SUV 43%	59 (36.4–79.3)	100 (87.2–100)
		PET/CT	R-SUV 42%	68 (45.1–86.1)	100 (87.2–100)
		PET and/or PET-CT	R-SUVmax 42%	82 (59.7–94.8)	70 (49.8–86.2)
Song 2005 (28)	NARC	PET	R-SUVmax <2.5	27 (6.0–61.0)	95 (76.2–99.9)
Early and late response					
Kroep 2003 (16)	NAC	PET (early response)	R-SUV >40%	100 (39.8–100)	85.7(42.1–99.6)
		PET (late response)	R-SUV >60%	100 (39.8–100)	100 (54.1–100)
		EUS (early response)	n.d.	100 (47.8–100)	100 (54.1–100)
		EUS (late response)		100 (47.8–100)	100 (59.0–100)
		CT (early response)	n.d.	50 (6.8–93.2)	71 (29.0–96.3)
		CT (late response)		50 (6.8–93.2)	71 (29.0–96.3)
Wieder 2004 (20)	NARC (early response)	PET	R-SUV ≥ 30%	— * ²	— * ²
	NARC (late response)		R-SUV ≥ 52%	89 (66.9–98.7)	57 (28.9–82.3)

*¹ IQWiG's calculation

*² Results are not presented because the missing values exceeded 30%.

Cut-off values in footnotes *³ and *⁵ are presented as follows: sensitivity (sens.); specificity (spec.); cut-off explanation

*³ Sens. 90.6%; spec. 50.0%: R-SUVmax <0% to ≤ 0%; sens. 81.3%; spec. 55.6%: R-SUVmax >10% to ≤ 10%; sens. 70.3%; spec. 63.9%: R-SUVmax >20% to ≤ 20%.

*⁴ 100 patients were analyzed. The number of patients included (N) was 108. Characteristics were reported for 145 patients.

*⁵ Sens. 52.0%; spec. 87.0%: no FDG uptake after treatment, sens. 72.0%; spec. 65.2%: SUV >30% R-SUVmax, sens. 70.0%; spec. 72.2%: SUV >50% = median

*⁶ Sens. 73.70%; spec. 78.00%: post-SUVmax(3.0), sens. 81.40%; spec. 80.50%: percentage of PET length

*⁷ PET-CT was described as the index test. Data were only available for PET.

*⁸ Diagnostic accuracy relates to R0 resection.

*⁹ PET: sens. 77%; spec. 85%: 59% (reduction in area); sens. 82%; spec. 89%: 32% (reduction in diameter), sens. 91%; spec. 93%: 56% (index = diameter – SUV),

PET-CT: sens. 68%; spec. 93%: 54% (reduction in area), sens. 91%; spec. 89%: 23% (reduction in diameter); sens. 91%; spec. 93%: 55% (index = diameter – SUV)

n.d., no data; CT, computed tomography; EUS, endosonography; FDG, 2-[18F]fluor-deoxy-D-glucose; CI, confidence interval; NAC, neoadjuvant chemotherapy; NARC, neoadjuvant radiochemotherapy;

PET, positron emission tomography; R-SUV, reduction in SUV; SUV, standardized uptake value; SUVmax, maximum standardized uptake value; post-SUVmax, post-treatment SUVmax

of PET and PET-CT in assessing treatment response in esophageal cancer were identified (21–23).

Screening of the publications underlying the three reviews led to the inclusion of 11 relevant primary studies (13, 15–17, 19, 20, 24–28). The most recent search in these three reviews was carried out by Ngamruengphong et al. (21) in February 2008. Therefore, our search update covered (with a 3-month overlap) the period from December 2007 to March 2015, and yielded another nine relevant diagnostic studies (18, 29–36). No studies with the VOPT design were found. Thus, a total of 20 diagnostic studies were included in the analysis.

Study characteristics

The most important characteristics of the 20 diagnostic studies are shown in the *eTable*. Seven studies investigated early response, 11 studies late response, and 2 studies investigated both early and late response. Fourteen studies investigated PET, five studies investigated integrated PET-CT, and one study investigated both. Direct comparison of PET with other technologies was carried out in one study on early response and two studies on late response. All studies used the tracer F-18-fluoro-2-deoxyglucose (FDG). In most studies, the histopathological evidence of treatment response was classified according to Mandard et al. (37). In total, 854 patients (most with stage T2 or T3 tumors) were analyzed. The mean percentage of men in each study was 82.2% and the mean number of patients participating in each study was 50 (range, 13–145). The studies were published between 2001 and 2013.

Risk of bias

Information about the risk of bias in 11 studies was taken over from the systematic reviews included in the present study (21–23). Ngamruengphong et al. (21) and Rebollo Aquirre et al. (22) used the QUADAS tool to assess risk of bias. Against the QUADAS recommendations, risk of bias was rated on a summary scale. The studies were not classified into those with low and those with high risk of bias.

The main potential source of bias was a lack of information on uninterpretable results. In addition, the patient selection criteria were inadequately described. Finally, several studies showed partial verification bias.

Westerterp et al. (23) used the tool of the Cochrane Methods Working Group on Systematic Reviews. The main source of bias was that the results of the reference tests were not interpreted without knowledge of the results of the index tests. Only the study Kroep et al. (16) was classified as having a low risk of bias.

In our assessment, the risk of bias in all nine studies (18, 29–36) identified in the update search was classified as high (*Figure 1*).

Diagnostic accuracy for early response

Of the nine studies on early response assessment (13, 15–20, 31, 36), only the one by Kroep et al. 2003 (16)

TABLE 2

Calculation of the negative predictive value of PET for prediction of clinical response using a cut-off >35% SUV reduction

Study	No histological response after treatment (%)	NPV % (95% CI)
Gillham 2006 (17)	71	76 (53 to 92)
Ilsen 2011 (31)	33	96 (82 to 100)
Kroep 2003 (16)	60	100 (40 to 100)
Malik 2010 (18)	56	64 (43 to 82)
Ott 2006(15)	82	95 (82 to 99)
Weber 2001 (13)	75	96 (77 to 100)
Westerterp 2005 (23)	52	64 (31 to 89)
Wieder 2004 (20)	34	78 (40 to 97)

PET, positron emission tomography; SUV, standardized uptake value; NPV, negative predictive value; CI, confidence interval

directly compared PET with endosonography (EUS) and CT. On the basis of the data of 10 patients included in the study, the sensitivity and specificity of EUS were highest (both 100%, with differing confidence intervals [CIs]) (*Table 1*). The sensitivity of PET was also high (100%; 95% CI: 39.8 to 100), while the specificity of PET (85.7%; 95% CI: 42.1–99.6) was lower than that of EUS. In this study, CT had the lowest sensitivity and specificity. In seven noncomparative studies, the sensitivity of PET ranged from 44% (with a specificity of 52%) to 100% (with a specificity of 85.7%). Specificity ranged from 52% (with a sensitivity of 44%) to 85.7% (with a sensitivity of 100%) (*Table 1*).

Diagnostic accuracy for late response

Of the 13 studies investigating late response to treatment (16, 20, 24–30, 32–35), two (16, 25) compared PET and PET-CT directly with EUS and CT.

In Kroep 2003 (11 patients), the sensitivity and specificity of PET and EUS were identical (100%, with different CIs), in contrast to the lower sensitivity and specificity of CT (50%; 95% CI: 6.8 to 93.2; 71%; 95% CI: 29.0 to 96.3).

In Cerfolio 2005 (48 patients), the sensitivity of PET-CT (86.7%; 95% CI: 59.7 to 98.3) was clearly higher than that of EUS (20%; 95% CI: 4.3 to 48.1). However, the specificity of EUS (94%; 95% CI: 79.8 to 99.3) was higher than that of PET-CT (87.9%; 95% CI: 71.8 to 96.6).

In the analysis based on 12 noncomparative studies, the sensitivity of PET ranged from 14% (with a specificity of 81%) to 100% (with a specificity of 100%). Specificity ranged from 55% (with a sensitivity of 100%) to 100% (with a sensitivity of 100%).

Post-hoc analysis

On the basis of the individual patient data provided in eight studies, 54% of patients (median value across studies) had no histopathological response to therapy at the end of treatment (*Table 2*). The median NPV of PET in early response was 86.5% for cut-off value of >35% SUV reduction.

Discussion

No RCTs or CCTs were identified that investigated patient-relevant benefit of the use of PET and PET-CT. Few diagnostic studies were identified in which PET and PET-CT were directly compared with conventional imaging techniques.

The diagnostic accuracy for early and late response to treatment varied greatly between studies. Almost all studies were, in addition, very small and had a high risk of bias, so that their findings are subject to considerable uncertainty.

A NPV of 100% for PET and PET-CT would mean, for patients whose tumor has not responded after the first treatment cycles, that the tumor is also unlikely to respond after the entire treatment. In these patients, NAC and NARC could be stopped (or changed) after just a few cycles, thus avoiding unnecessary unwanted effects.

However, a NPV of 100% cannot be statistically proven, and for this reason a lower limit must be set for the confidence interval (e.g., 95%). On the other hand, however, where the NPV is below 100%, there must be some patients in whom it is possible that a relevant tumor reduction would be achieved after the treatment despite negative PET and PET-CT findings. This would mean that a potentially useful treatment would be withheld from these patients if the treatment indication were based on the PET and PET-CT results alone.

In terms of an assessment of the usefulness of PET on the basis of its diagnostic accuracy, the question still remains whether the benefits would outweigh the disadvantages. A predefined cut-off value for the NPV below 100% would be required, beyond which the advantage of diagnosis with PET or PET-CT (more targeted treatment, avoidance of over-treatment) would outweigh its disadvantages (mistakenly not treated). However, we were not able to identify from the literature what this cut-off value might be.]

The MUNICON I and II studies (38, 39) were the first studies of esophageal cancer to show that early response assessment using PET can actually lead to changes in patient management. These studies were not included in the present review, as both lacked a parallel control group (inclusion criterion for aim 1) and treatment was changed on the basis of the PET results (no diagnostic studies; aim 2). In comparison to historical

control groups, however, these studies show a potential for improving patient-relevant endpoints.

The authors of the MUNICON studies planned an international multicenter RCT to investigate early response in patients with esophageal cancer using PET (39, 40). Owing to lack of funding, however, it has not yet been possible to start this study (personal communication). The new legislation in Germany concerning evaluation of the potential of nonmedical treatment ("Erprobungsregelung"; § 137e Social Code [SGB] V) opens up the way for (co-)financing of studies by the Federal Joint Committee and might represent a chance to conduct this important study.

Apart from that, a RCT on PET in early response of esophageal cancer was started in 2009 in Australia (ACTRN12609000665235). No results have been published so far.

Limitations

The limitations of our review are the small number of patients analyzed and the low quality of the studies that were included. A further limitation might be that we conducted a review of reviews, taking over the evaluation of risk of bias from the 11 studies that were included in the 3 systematic reviews. The studies that we analyzed were very heterogeneous. The patients groups investigated were different, and different cut-off values for the PET and PET-CT were used, making it difficult to compare results. Finally, the calculation of NPV referred to a cut-off value validated only for NAC, but we also applied this value to studies on NARC. So far, this cut-off value has been prospectively studied and validated in only two studies (14, 15).

Conclusion

At present, there is no good evidence of any patient-relevant benefit of PET and PET-CT in esophageal cancer. PET has the potential to be able to distinguish between responders and nonresponders after the first few cycles of treatment. For this reason, RCTs investigating patient-relevant endpoints are urgently needed.

KEY MESSAGES

- There is currently no good evidence of a patient-relevant benefit of PET or PET-CT in esophageal cancer.
- Few diagnostic studies were identified that compared PET or PET-CT directly with conventional imaging.
- With regard to the assessment of early and late treatment response, the results of these studies varied widely in their estimates of sensitivity and specificity.
- Almost all the studies were small and had a high risk of bias, meaning that their findings are subject to considerable uncertainty.
- PET has the potential to distinguish between responders and nonresponders during the first few cycles of treatment.

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Conflict of interest statement

The authors declares that no conflict of interest exists.

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[Supplementary material](#)
 eTable:
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Supplementary material to:

The Role of PET and PET-CT Scanning in Assessing Response to Neoadjuvant Therapy in Esophageal Carcinoma

A Systematic Review

by Milly Schöber-Günther, Filip Scheibler, Robert Wolff, Marie Westwood, Brigitta Baumert, and Stefan Lange

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eTABLE

Characteristics of the included studies

Study, year	Number of patients (N)	Sex M/F	Mean age in years (range)	Reference test	Index test(s)	Diagnosis before treatment (number of patients)	Location of the primary tumor (number of patients)
Bruecher 2001 (24)	27 ^{*1}	23/4	52.9 (37.8–61)	Histology/Mandard with modification	PET ECAT 951/R or ECAT EXACT PET scanner (Siemens CTI, Knoxville, TN) Duration of transmission scan: 10–15 minutes ~ 4 million counts per slice	uT2 (2) uT3 (23) uT4 (2)	Cervical (7), intrathoracic (17)
Cerfolio 2005 (25)	48	41/7	68 (48–76)	Histology	PET/CT GE Discovery LS PET/CT scanner; GE, Milwaukee, Wis. Injection (i. v.) of 555 MBq (15 mCi) FDG followed by PET after 1 hour. EUS Radial ultrasound endoscope (GF-UM130; Olympus America, Melville, NY), EUS-FNAs were carried out with adjustable-length 22-G EchoTip needles (Wilson-Cook, Inc., Winston-Salem, NC)	T2 N0 M0, T3 N0 M0 (22), T0–2 N1 M0 (5), T3 N1 M0 (15), any N M0 (2), M1a (3), M1b (1)	n.a.
Flamen 2002 (26)	36	28/8	60 (n.a.)	Histology	PET/CT Siemens 931 or HR+ scanner (SAMI; Knoxville, TN, USA); axial fields 10.1 and 15 cm, spatial resolution 8 and 6 mm, 60 minutes after injection (i. v.) of 6.5 MBq/kg FDG (max. 555 MBq)	n.a.	High (5), mid (12), low (13), gastro- esophageal junction (6)
Gilles 2012 (29)	48	37/11	65 (n.a.)	Histology/Mandard 1–3 (response), 4+5 (no response)	PET/CT GE Discovery STE 16, General Electric Co., 60 minutes after injection (i.v.) of 5 MBq/kg body weight (min. 300 MBq) FDG	AJCC II (22), AJCC III (26)	Mid (6), low (27), gastroesophageal junction (15)
Gillham 2006 (17)	32	n.a.	58 (37–74)	Histology/Mandard TRG 1+2	PET and integrated PET/CT whole-body scan in 2D mode either using the GE-supplied PET Advance Scanner or the Discovery-ST PET/CT scanner; PET 47–78 minutes after injection (i.v.) of 340–450 MBq 18F-FDG	AJCC II (27) AJCC III (5)	Mid (4), low (16), gastroesophageal junction (12)
Higuchi 2008 (30)	50	41/9	n.a. (44–77)	Histology/ >2/3 disappearance of tumor cells	PET HEADTOME/SET 2400 W, Shimadzu Co., Japan, 60 minutes after injection (i.v.) of ca. 370 MBq FDG	AJCC III (24), AJCC IVA (11), AJCC IV B (15)	Cervical (11), high (5), mid (17), low (17)
Ilson 2011 (31)	55 ^{*2}	47/8	n.a. (21–74)	Histology/complete response (+)	PET n.a.	n.a.	High (1), mid (7), low (29), gastro- esophageal junction (18)
Kroep 2003 (16)	13 ^{*3}	12/1	60.6 (50–69)	Histology/Mandard with modification	PET ECAR EXACT HR+ Scanner (CTI/Siemens, Knoxville, TN) axial field 15 cm, injection (i.v.) of 370 or 555 MBq FDG. CT, EUS: n.a.	T3N1M0 (12); T3N1M1 (1)	n.a.
Levine 2006 (27)	64	53/9	60.6 (41.8–83.7)	Histology/no residual tissue available	PET 555–740 MBq FDG, 60 minutes rest, 6–8 mm spatial resolution of peak width at half height	AJCC I (2), AJCC IIA (15), AJCC IIB (10), AJCC III (25), AJCC IVa (8), AJCC IIB (4)	Cervical (4), mid (7), low (24), gastroesophageal junction (29)

Ma 2013 (32)	60	42/18	58 (39–74)	Histology/n.a.	PET FDG (GE, Germany), 350 MBq (range: 259–444)	T2 (17) T3 (27) T4 (16) N0 (56) N1 (4)	High (15) mid (30) low (15)
Malik 2010 (18)	37	31/6	58 (37–73)	Histology/Mandard TRG 1+2	PET Advance Scanner GE Healthcare, USA, ca. 60 minutes after injection of 350–450 MBq FDG	n.a.	n.a.
Mysliveček 2012 (33)	82 ^{*4}	62/11	58.1 (34.0–84.3)	Histology/n.a.	PET/CT Siemens Biograph 16 HI-REZ Scanner injection (i.v.) of 400 MBq FDG	Stage I (3) Stage II (22) Stage III (36) Stage IV (5) Stage IVA (7)	n.a.
Ott 2006 (15)	65 ^{*5}	58/7	58 (n.a.)	Histology/Mandard with modification	PET static emission images of 20 minutes' duration were acquired 40 minutes after injection (i.v.) of 250–370 MBq	Grade I or II (22); grade III or IV (42)	AEG I or AEG II (n.a.)
Piessen 2013 (34)	60	51/9	59.5 (42–74)		PET GE Healthcare scanner. Injection (i.v.) of 370 MBq FDG PET/CT RX HD 16 GE Healthcare, equipped with lutetium-yttrium-orthosilicate crystals	TNM II (13) TNM III (47)	Supracarinal (4), infracarinal (56)
Roedl 2009 (35)	49	37/10	68.9 (n.a.)	Histology/ <10% vital tumor cells	PET/CT Biograph Sensation 16 scanner, Siemens, Erlangen, Germany, 60 minutes after injection (i.v.) of 15 mCi (555 MBq) FDG	T2N0M0 (8), T2N1M0 (8), T3N0M0 (10), T3N1M0 (23)	High (23), mid (22), low (4)
Song 2005 (28)	32	29/3	63 (45–74)	Histology/reduction in tumor volume (<50%)	PET 555 MBq FDG, 60 minutes rest, 7 mm spatial resolution of peak width at half height, 6 minutes scan time (emission)	AJCC II (20), AJCC III (12)	High (1), mid (14), low (17)
van Heijl 2011 (36)	145 ^{*6}	108/37	60 (37–79)	Histology/ <10% vital tumor cells	PET/CT Philips Medical Systems, USA; Gemini TF, ca. 90 minutes after injection (i.v.) of 5 MBq/kg KG FDG, tumor-focused and static scan	T1 (1), T2 (13), T3 (131)	n.a.
Weber 2001 (13)	40 ^{*7}	37/3	55 (25–69)	Histology/Mandard TRG 1+2	PET scan 40 minutes after injection (i.v.) of 250–370 MBq FDG	T3N+ (35), T3N0 (2), T4N+ (3)	AEG I (24), AEG II (16)
Westerterp 2006 (19)	26	24/2	61 (29–73)	Histology/Mandard with modification	PET 250–370 MBq FDG, 5 mm spatial resolution of peak width at half height, 5 minutes acquisition time (emission)	uT1 (1), uT2 (3), uT3 (21), uT4 (1)	n.a.
Wieder 2004 (20)	38 ^{*7}	27/11	60 (46–73)	Histology/Mandard with modification	PET 300–400 MBq FDG, 60 minutes rest, 7 minutes acquisition time (emission)	T2N+ (3), T3N0 (8), T3N+ (29), T3Nx (1)	n.a.

*1 27 patients were included. Data were available for 24 patients.

*2 55 patients were included. Data were available for 53 patients.

*3 13 patients were included. Data were available for 11 patients.

*4 82 patients were included. 39 did not undergo surgery for clinical reasons; results were lacking for 9 patients; diagnostic accuracy based on the data of 34 patients.

*5 65 patients were included. Data were available for 56 patients.

*6 Characteristics of 145 patients were available. The number of patients included (N) was 108. The data of 100 patients were analyzed.

*7 38 patients were included. Data were available for 33 patients.

AEG, adenocarcinoma of the gastroesophageal junction; AJCC, American Joint Committee on Cancer; CT, computed tomography; EUS, endosonography; i.v., intravenous; n.a., not available; FDG, 2-[18F]fluor-deoxy-D-glucose; MBq, megabecquerel;

PET, positron emission tomography; PET-CT, integrated PET and CT in a single imaging device; TRG, tumor regression grade