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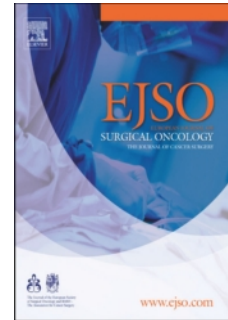
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Title: Positron Emission Tomography for monitoring response to neo-adjuvant therapy in patients with oesophageal and gastro-oesophageal junction carcinoma.

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Statement of Expertise: This group has published on PET work in conjunction with oesophago-gastric cancers. Stuart Suttie has undertaken a period of research, culminating in a higher degree, based on PET imaging (¹⁸FDG and ¹¹C-choline for predicting response to chemotherapy in oesophageal cancer). Andrew Welch is the Director of the John Mallard Scottish PET centre, and has extensive expertise on PET and oesophageal cancer. Kenneth Park, Consultant oesophago-gastric surgeon, published one of the first trials on PET and response prediction in oesophago-gastric tumours and has since lead further research in this field

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Abstract

Aims

The aim of this review is to consolidate our knowledge on an important and rapidly expanding area of expertise. Numerous methods for predicting response (in terms of pathological response and survival) to neo-adjuvant therapy (chemotherapy/chemoradiotherapy) in oesophageal and junctional cancers have been proposed. This review concerns itself only with the use of Positron Emission Tomography for such a purpose. At present there are no standardised criteria amongst PET trials as to what determines a response according to PET; what is the optimal time to perform PET in relation to the timing of neo-adjuvant therapy; what is the ideal method of quantifying PET tracer uptake.

Methods

An electronic search was performed of Pubmed, Ovid and Embase websites to identify studies, in English language, using the search terms: PET; oesophageal; oesophago-gastric; survival; cancer; response; chemotherapy and chemoradiotherapy. The reference lists were searched manually to identify further relevant studies.

Results

Twenty two studies were identified, all using ^{18}F FDG as the tracer, using PET to predict response in terms of pathological response and survival following neoadjuvant therapy (chemotherapy/chemoradiotherapy). PET had a varying degree of success in predicting both pathological response and survival outcomes, with only one study using PET to influence management decisions.

Conclusions

PET seems a promising technique, but large scale conclusions are hindered by small study numbers, lack of criteria as to what constitutes a response and markedly differing PET imaging times. A large randomised trial, concerning a homogeneous group of patients and tumours is required before using PET to influence management.

Introduction

The poor response of tumours (in terms of pathological response and survival), at or around the gastro-oesophageal junction, to neoadjuvant therapy [1-3] suggests the need to predict or identify responders to neoadjuvant therapy at an early stage is paramount.

Several studies looking at neoadjuvant and palliative chemotherapy reported that those patients who responded to treatment had an improved survival outcome [4-9] with neo-adjuvant regimens having a response rate, at best, of 50-60% [1]. Studies clearly demonstrate that those who do not respond to neoadjuvant chemotherapy have a significantly worse prognosis than those who have surgery alone [4, 5, 7]. If outcome is to be maximised in patients likely to derive benefits from neoadjuvant therapy while at the same time ensuring others are not subjected to potentially harmful and ineffectual treatment, an early means of differentiating responders from non responders is required. Therefore we need to identify responders and to do so at the earliest opportunity.

Anatomical imaging techniques are generally used to determine response to treatment on completion of therapy for patients with gastro-oesophageal cancer. The assessment of response based on Computerised Tomography (CT) has relied on various criteria for determining response, including measurement of tumour volume [10], Eastern Cooperative Oncology Group solid tumour response criteria for bi-dimensional measurable disease [11] and a combination of tumour length and wall thickness [12].

One of the larger studies assessing the ability of CT post neo-adjuvant chemoradiotherapy to predict pathological response highlighted that CT findings did not correlate with the pathological findings [11] with CT having a sensitivity of 65% and a specificity of 33% in predicting pathological response, with a poor ability to assess T classification. These findings were reiterated by other studies [10, 13, 14] with Griffith *et al* [10] demonstrating no correlation between tumour volume reduction and pathological response or survival. From these studies it appears that CT is not accurate in identifying loco-regional residual disease or spread. Hence findings at CT alone should not preclude surgery, except perhaps in metastatic disease.

EUS allows for direct visualisation of the tumour as well as evaluation of tumour depth and local nodes (pre treatment) with an accuracy of >85% and 75% respectively [15-17]. EUS is unable to reliably determine tumour depth following neoadjuvant treatment [15, 16, 18-20]. EUS is an invasive procedure with a 20-50% chance of the probe unable to be manoeuvred through the stenotic segment. Furthermore, these studies have assessed response on completion of therapy. A recent systematic review has shown that EUS and CT have poor sensitivity in identifying disease response in oesophageal carcinoma, 50-100% and 33-55% respectively [21]

CT and EUS imaging techniques are often insensitive, relying on changes in tumour bulk which may take considerable time to become apparent. Furthermore, these modalities may have difficulty in distinguishing residual tumour, necrosis, scar tissue and oedema [10, 11, 15, 16, 19, 20].

Pathological criteria for assessing response to treatment have been devised and correlated with outcome, with some degree of success [22, 23]. However, Dunne *et al* [24] utilising the Mandard criteria [23], originally described for assessing pathological response to chemoradiotherapy in squamous cell carcinoma of the oesophagus, reported that pathological response to neoadjuvant chemoradiotherapy in oesophageal adenocarcinomas was not an independent prognostic indicator, a finding reiterated by others [10, 25-28], albeit with differing modes of neoadjuvant therapy, (i.e. chemotherapy alone [10]), differing tumour histological types (combined adenocarcinoma and squamous cell carcinoma [25, 26], or squamous cell carcinoma alone [27, 28]), and with varying therapeutic agents.

Assessment of pathological response requires the resected specimen to be assessed by subjective criteria and is open to sampling errors. Due to the need for the resected specimen, the response according to these criteria is not able to influence treatment at an early stage.

Positron Emission Tomography (PET) images metabolic activity via the distribution of positron emitting tracers that are incorporated into metabolic processes. In practice this translates into the parenteral administration of a metabolically positron-emitting radio-active tracer which is then incorporated into a metabolic pathway. Most of the

common molecules involved in organic processes can be labelled with positron emitting isotopes, meaning different physiologic and biochemical parameters can be evaluated by PET.

Metabolic changes often precede structural changes associated with any given disease. Therefore PET offers the potential to determine response to treatment at an early stage.

Methods

An electronic search was performed of Pubmed, Ovid and Embase websites to identify English language studies using PET to predict response (in terms of pathological response and survival) to neoadjuvant therapy in oesophageal and gastro-oesophageal junctional cancers, using the search terms: PET; oesophageal; oesophago-gastric; cancer; response; survival; chemotherapy and chemoradiotherapy. No other limits were applied. The reference lists of studies were searched manually to identify further studies. The search was conducted by two individuals (SS, KP). Case reports were excluded as were comments, letters and reviews. Manuscripts were chosen on the basis of title, abstract and/or full text. Twenty two studies [3, 29-49], all using ^{18}F FDG as the tracer, using PET to predict response in terms of pathological response and survival following neoadjuvant therapy (chemotherapy/chemoradiotherapy) were identified.

Findings

Twenty two studies have assessed the utility of [^{18}F]2-fluoro-2-deoxy-d-glucose, ^{18}F FDG, PET to identify those patients with oesophageal and junctional cancer who respond to neo-adjuvant therapy (chemotherapy/chemo-radiotherapy), in terms of pathological response and survival [3, 29-49]. The general characteristics of these studies are displayed in table 1, with the specifics of each study detailed in table two. Carbon-11-choline (^{11}C -choline), a PET tracer thought to correlate with cell proliferation, has been used to some success in imaging oesophageal cancers [50, 51]. Although it has not been used to monitor response it may show promise. The 22 studies included, have evaluated both adenocarcinoma and squamous carcinoma alone

and in combination, oesophageal and gastro-oesophageal junctional (GOJ) carcinomas alone and combined, as well as response to neo-adjuvant chemotherapy and chemoradiotherapy, with each study utilising a different therapeutic regimen.

Quantification of Tracer Uptake

Several methods have been used to assess tumour uptake of PET tracers, namely semi-quantitative analysis and kinetic modelling. Methods of semi-quantitative assessment include Standardised Uptake Values (SUV), Tumour to Liver Ratios (TLR) and Tumour to Non Tumour Ratios. SUVs are the most common method of analysis and are recommended by the European Organisation for Research and Treatment of Cancer (EORTC) [52]. Kinetic analysis is more complex than SUV analysis but thought to be more accurate. The majority of studies on gastro-oesophageal cancer have focused on SUV, with a minority assessing tumour to liver ratio and kinetic analysis [34, 39, 44]. In particular, Kroep *et al* found an excellent correlation between SUV and kinetic analysis when monitoring response to therapy [39].

The first study examining the ability of ^{18}F FDG PET to image and monitor response to neo-adjuvant and palliative chemotherapy in gastric and oesophageal cancers, found that patients with the greatest reduction in SUV from the pre treatment value had improved survival outcomes [53].

Predicting Pathological Response

The majority of studies [3, 29-31, 35-49] have based or part based PET responses according to pathological criteria for determining response, either using reported pathological scoring systems [22, 23] or with modifications to these systems. The Mandard criteria [23] breakdown pathological response in to five groups. However, ^{18}F FDG PET studies assessing response to chemoradiotherapy and chemotherapy in both squamous cell carcinomas and adenocarcinomas, suggest that ^{18}F FDG PET is unable to distinguish between each Mandard pathological tumour regression grade [30, 44]. In studies utilising a modified pathological scoring system based on complete response (0% residual tumour), partial response (<10% residual tumour) and no response (>10% residual tumour) or similar, ^{18}F FDG PET was unable to distinguish between complete and partial responders [31, 38, 47]. When the tumour regression

grades and scoring systems are amalgamated into groups indicating either responders or non responders, ^{18}F FDG PET appears successful in distinguishing between them.

One retrospective study evaluated pre treatment ^{18}F FDG PET as a means of predicting pathological response in both adenocarcinoma and squamous cell carcinoma [47], with no correlation between pre treatment SUV and pathological response following chemoradiotherapy, a similar finding to that of Wieder *et al* [49] and Kanski *et al* [38]. However, a study assessing the ability of ^{18}F FDG PET to predict pathological response to neoadjuvant chemoradiotherapy found that a pre treatment SUV >15 was associated with a pathological response [40].

^{18}F FDG PET imaging during the early stages of neoadjuvant treatment has had mixed success in predicting pathological response [35, 39, 41, 48, 49]. Gillham *et al* [35] assessing change in ^{18}F FDG PET uptake following the first of four weeks of chemoradiation for adenocarcinoma and squamous cell carcinoma of the oesophagus and GOJ, found no correlation with pathological response. Wieder *et al* [49] investigating response to chemoradiotherapy, two weeks following commencement of therapy, in squamous cell carcinomas, found that basing a PET response on pathological response using the Receiver Operating Characteristic curve, ROC, PET was able to distinguish responders (reduction in SUV $>30\%$) from non responders (reduction in SUV $<30\%$) with a sensitivity and specificity of 93% and 88% respectively. Kroep *et al* [39], using ^{18}F FDG PET after the second of six cycles of chemotherapy for both adenocarcinoma and squamous cell carcinoma of the oesophagus and GOJ, reported a similar finding, although the ROC identified the threshold SUV value as reduction of more than 40% for pathological responders, with a sensitivity of 100% and a specificity of 86% [39]. The disparity between the results of Kroep *et al* [39] and Wieder *et al* [49] with those of Gillham *et al* [35], may be in part explained by the timing of PET, for radiotherapy is known to result in an initial stunning effect of tumour cells, resulting in decreased ^{18}F FDG uptake irrespective of further cell death [54]. Weber *et al* [48] initially found that using PET for predicting radiological response after the first two weeks of chemotherapy in patients with carcinoma at the GOJ, in terms of 50% reduction in tumour length and thickness on computerised tomography and barium swallow, utilising ROC, a threshold of $\geq 35\%$ reduction in SUV resulted in a 93% and 95%, sensitivity and specificity, for

discriminating responders from non responders. PET responders correlated with pathological responders ($p=0.001$) with an associated improved two year survival outcome for responders ($p=0.01$) [48]. A recent phase II trial by Lordick *et al* [41], assessed the feasibility of using the results from ^{18}F FDG PET imaging to guide neoadjuvant therapy and timing of surgery. Specifically investigating locally advanced GOJ tumours undergoing neoadjuvant chemotherapy, they performed PET imaging before and two weeks after commencing therapy. PET response, based on previous work [48], was taken as $>35\%$ reduction in SUV at two weeks [41]. Patients who showed a metabolic response continued neoadjuvant chemotherapy for 12 weeks whilst those deemed to have no metabolic response underwent no further neoadjuvant therapy and proceeded directly to surgery. Patients deemed to have a metabolic response had a significantly improved overall survival compared to metabolic non-responders ($p=0.015$) [41]. Patients with a combined metabolic and pathological response had a significantly improved overall survival in contrast to those patients with a metabolic response but no pathological response ($p=0.004$) [41]. Interestingly, 21 patients with a metabolic response had no evidence of a pathological response. No patients deemed metabolic non-responders had a pathological response [41].

Studies have compared ^{18}F FDG PET response to pathological response on completion of neoadjuvant therapy [3, 29-31, 34, 36-40, 42-47, 49], with varying degrees of success [31, 34, 39, 47, 49] and failure [3, 29, 30, 36-38, 40, 42-46]. Weider *et al* [49], compared predicting response during and after neoadjuvant chemoradiotherapy for squamous cell carcinoma, with the results during chemotherapy better able to discriminate responders from non responders. Utilising ROC, a threshold of $\geq 30\%$ reduction in SUV resulted in 93% and 88% sensitivity and specificity respectively for predicting pathological response during neoadjuvant treatment, compared with a threshold of $>52\%$ reduction in SUV resulting in a sensitivity and specificity of 89% and 57% respectively on completion of neoadjuvant therapy [49]. In contrast, Kroep *et al* [39], identified that change in SUV following completion of neoadjuvant chemotherapy was better able to predict pathological response (ROC, threshold of $\geq 60\%$ reduction in SUV resulted in 100% sensitivity and specificity) compared with during therapy (ROC, threshold of $\geq 40\%$ reduction in SUV resulted in 100% sensitivity and 86% specificity). The differences between the studies may be in part explained by differing tumour types, tumour locations and neoadjuvant therapy and

timing of the PET during neoadjuvant therapy (see table 1 and 2). Brucher *et al* [31], evaluating response following chemoradiotherapy in squamous cell carcinoma identified a threshold of >52% reduction in SUV between pre and post therapy PET images correlated with pathological response ($p=0.0001$).

Of the studies unable to show a correlation between change in tumour tracer uptake and pathological response on completion of neoadjuvant therapy, a number of possible reasons exist for these results, including use of pathological stage as a surrogate for pathological response [29], not amalgamating different grades of pathological response into either responders or non responders [30, 44], as well as small study numbers [36]. Song *et al* [46] noted that if the initial SUV was ≥ 4 , then pathological response correlated with PET response ($p=0.006$). This may be indicative of ^{18}F FDG uptake relating to tumour blood flow and therefore chemotherapy delivery to the tumour or to tumour proliferation with improved chemoradiotherapy response in tumours with a high proliferation rate. Both Port *et al* [45] and McLoughlin *et al* [43] demonstrated that a complete metabolic response did not equate to a complete pathological response. Smithers *et al* [3] looked at both neoadjuvant chemotherapy and chemoradiotherapy in adenocarcinomas of the oesophagus and GOJ with PET performed three to six weeks post completion of therapy. Irrespective of whether chemotherapy or chemoradiotherapy was given, change in SUV was unable to distinguish pathological responders from non responders, although this may be influenced by the limited number of responders ($n=1$ chemotherapy, $n=6$ chemoradiotherapy). This however reflects realistic response rates to neoadjuvant therapies [3].

Predicting Survival

As well as using pathological response to base PET response on, several studies investigated the use of ^{18}F FDG PET to predict survival following neoadjuvant therapies [31-34, 37, 41, 45, 47-49] with all but one showing significant results [32]. Flamen *et al* [34], basing PET response on the median change in SUV in those patients with a complete pathological response ($T_0N_0M_0$), demonstrated that a reduction in TLR >80% upon completion of neoadjuvant chemoradiotherapy in patients with adenocarcinoma and squamous cell carcinoma of the oesophagus and GOJ, led to median survival of 16.3 months compared to 6.4 months in those with a less than 80%

reduction in TLR ($p=0.005$). Downey *et al* [32] took a different approach to define PET responders on completion of chemoradiotherapy, with a threshold of 60% reduction in SUV used to discriminate responders from non responders. This threshold value was the median change in SUV in all those who had a curative resection. Based on this threshold, responders had an improved two year and disease free survival, albeit non significant ($p=0.088$ and $p=0.055$ respectively) [32]. Wieder *et al* [49] investigating response to chemoradiotherapy, two weeks following commencement of therapy, in squamous cell carcinomas, found PET responders had a significantly improved median survival ($p=0.011$). Furthermore, a high post therapeutic SUV has been correlated with pathological response and survival with a post chemoradiotherapy $SUV \geq 4$ being indicative of a worse survival prognosis compared to those patients with a post treatment $SUV < 4$ ($p=0.001$) [47].

PET-CT

Due to the age of the studies, the majority have utilised PET with separate CT imaging. Combined PET-CT is now the standard, although it may not improve in the identification of metabolic responders it will certainly have a part to play in improving the initial radiological staging, identification of synchronous tumours and identification of interval metastases [21].

Radiotracers

All twenty two studies to date have utilised ^{18}F FDG for monitoring response. ^{11}C -choline has been compared to ^{18}F FDG in terms of staging oesophageal cancer in two studies [50, 51] with contrasting results. Kobori *et al* [51] concluded that ^{11}C -choline was superior in detecting the primary tumour (94% sensitivity) and lymph node metastases in the mediastinum (88% sensitivity, specificity not clarified) compared to ^{18}F FDG (38% and 34% sensitivity respectively) [51]. In contrast, Jager *et al* [50] concluded that ^{18}F FDG was superior at detecting the primary tumour (100% sensitivity, specificity not clarified), regional lymph node metastases (67% sensitivity) and distant metastases (100% sensitivity) compared to ^{11}C -choline (73%, 60% and 75% respectively) [50]. Both studies noted that imaging of the upper abdominal compartment was limited with ^{11}C -choline due to marked uptake within the liver. One possible reason for these differences between the studies is that possibly Kobori *et al* [51] interpreted their images with a high sensitivity at the expense of a low

specificity. Furthermore, Kobori *et al* [51] imaged more proximal, squamous cell carcinomas in comparison to Jager *et al* [50] who imaged adenocarcinoma, squamous cell carcinoma as well as gastro-intestinal stromal tumours of the oesophagus and GOJ.

Conclusions

With the small number of studies, small patient inclusion numbers, marked variation in neoadjuvant treatments between and even within studies, coupled together with the fact there is no consensus as to when to perform PET for predicting/monitoring response, it appears ^{18}F FDG PET is unable distinguish pathological responders from non responders accurately, either during or upon completion of neoadjuvant therapy. However, ^{18}F FDG PET offers promise for predicting survival following neoadjuvant therapies, with only one study utilising ^{18}F FDG PET to alter management with promising results. Although PET may appear to be of limited value in assessing locoregional response, it may identify interval metastases precluding surgical resection. What may be of more importance than identifying responders, is the identification of those who do not respond, thereby allowing alteration of their treatment at the earliest opportunity. However before the application of these techniques to clinical practice there should be evidence based evaluation of the optimal timing of performing the PET imaging, optimal method of quantification and optimal PET tracer to use.

Conflict of Interest

The authors state there is no conflict of interest.

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ACCEPTED MANUSCRIPT

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Table 1: Characteristics of the twenty two neo-adjuvant studies

| Name | Study Type | n | Tumour Site | Tumour Type | Treatment | Treatment Regime |
|---------------|---------------|-----|-------------|-------------|-----------|---|
| Weider 2004 | Prospective | 38 | Oes | SCC | CRT | F + 40Gy |
| Downey 2003 | Prospective | 39 | Oes | A/SCC | CRT | CiP+ 50.4 Gy/CiP alone |
| Weber 2001 | Prospective | 37 | OGJ | A | C | CiLF +/- P |
| Flamen 2002 | Prospective | 36 | Oes/GOJ | A/SCC | CRT | CiF + 40 Gy |
| Brucher 2001 | Prospective | 27 | Oes | SCC | CRT | F + 30 Gy |
| Kato 2002 | Retrospective | 10 | Oes | SCC | CRT | NF + 40 Gy |
| Brink 2004 | Prospective | 20 | Oes | A/SCC | CRT | CiF + 36 Gy |
| Arlsan 2002 | Retrospective | 24 | Oes | A/SCC | CRT | CiF/CiD/FCa + 40.0 – 50.4 Gy |
| Kroep 2003 | Prospective | 13 | Oes/ GOJ | A/SCC | C | GCiGm-csf |
| Swisher 2004 | Retrospective | 83 | Oes | A/SCC | CRT | IDF/CiF/PCa + 50.4 Gy |
| Song 2005 | Prospective | 32 | Oes | SCC | CRT | CiF/CiX + 46Gy |
| Melcher 2004 | Prospective | 23 | Oes | A/SCC | C | CiF |
| Gillham 2006 | Prospective | 32 | Oes/ GOJ | A/SCC | CRT | CiF + 40.05 – 44 Gy |
| Levine 2006 | Prospective | 57 | Oes | A/SCC | CRT | CiF/CaF/PCa/F/MF + 45 – 59 Gy |
| Konski 2007 | Retrospective | 44 | Oes/ GOJ | A/SCC | CRT | CiF/CiFP + 45Gy |
| Kim 2007 | Prospective | 62 | Oes | SCC | CRT | CiF/CiX + 45.6 – 46 Gy |
| Smithers 2008 | Prospective | 22 | Oes/ GOJ | A | C | CiF |
| | | 23 | Oes/ GOJ | A | CRT | CiF + 35Gy |
| Mamede 2007 | Combined | 25 | Oes | A/SCC | CRT | CiI/CiICet/CiF/CiD/CiCam/CiIF/CiCaD + 50.4 Gy |
| McLoughlin | Retrospective | 81 | Oes | A/SCC | CRT | CiF/CaF/F/taxol based + 50.4 Gy |
| Lordick 2007 | Prospective | 119 | OGJ | A | C | CiFFol/OFFol +/- P |
| Duong 2006 | Prospective | 53 | Oes/ GOJ | A/SCC | CRT | CiF + 35 - 50 Gy |
| Port 2007 | Retrospective | 62 | Oes | A/SCC | C | Platinum based (Ca/P commonest regime) |

Oes = oesophageal; GOJ = gastro-oesophageal junction; A = adenocarcinoma; SCC = squamous cell carcinoma; C = chemotherapy; CRT = chemoradiotherapy; F = 5-fluorouracil; Ci = cisplatin; P = paclitaxel; L = leucovorin; N = nedaplatin; D = docetaxel; Ca = carboplatin; G = gemcitabine; Gm-csf = granulocyte macrophage colony stimulating factor; I = irinotecan; X = capecitabine; M = mitomycin C; Cet = cetuximab; Cam = camptosar; Fol = folic acid; O = oxaliplatin

Table 2: Timing, quantification of PET and outcomes of twenty two neo-adjuvant studies

| Name | Quantification | PET Imaging | PET Timing | Response | Response Criteria | Determining Response | PET Response | Outcome |
|--------------|--------------------|----------------|------------------------|-------------------|---|---|---|---|
| Weider 2004 | SUV | During therapy | 2/52 post commencement | Pathological | R <10% viable cancer cells NR >10 viable cancer cells | ROC, Sn 93%, Sp 88% | R=>30% reduction SUV NR=<30% reduction | Median survival R=38 months Median survival NR=18 months (p=0.011) |
| | | Post therapy | Immediate | | | ROC, Sn 89%, Sp 57% | R=>52% reduction SUV NR=<52% reduction SUV | PET during therapy better able to discriminate between R and NR |
| Downey 2003 | SUV | Post therapy | Immediate | PET | Median ΔSUV | Median Δ = 60% | R=>60% reduction SUV NR<60% reduction SUV | R=89% 2yr survival NR=63% 2yr survival (p=0.088) R=67% 2yr DFS NR=38% 2yr DFS (p=0.055) |
| Weber 2001 | SUV | During therapy | 2/52 post commencement | CT/Barium swallow | ≥50% reduction tumour length and thickness | ROC, Sn93%, Sp 95% | R=>35% reduction SUV NR=<35% reduction SUV | R=60% 2yr survival NR=37% 2yr survival (p=0.04) |
| | | | | Pathological | Mandard | R=TRG 1-2 NR=TRG 3-5 | | PET R correlate with Pathological R (p=0.001) |
| Flamen 2002 | TLR | Post therapy | 4/52 | PET | Pathological stage | R=T ₀ N ₀ M ₀ | R=>80% reduction TLR NR=<80% reduction TLR | Median survival R=16.3 months Median survival NR=6.4 months (p=0.005) |
| Brucher 2001 | SUV | Post therapy | 3/52 | Pathological | R <10% viable cancer cells NR >10 viable cancer cells | ROC, Sn 100%, Sp 55% | R=>52% reduction SUV NR=<52% reduction SUV | Median survival R=22.5 months Median survival NR=8.8 months (p=0.0001) |
| Kato 2002 | SUV | Post therapy | 2/52 | Pathological | R <1/3 viable cancer cells NR >1/3 viable cancer cells | Median ΔSUV for pathological R and NR | R=59.8% reduction SUV NR=44.9% reduction SUV | No correlation between ΔSUV and pathology (p=0.39) SUV post therapy able to distinguish R from NR (p=0.01) |
| Brink 2004 | SUV | Post therapy | 2/52 | Pathological | Mandard | | | No correlation between ΔSUV and TRG (1-5) |
| Arslan 2002 | SUV/ΔTumour volume | Post therapy | 4/52 | Pathological | Stage | R=stage T0N0 or microscopic disease NR= all other stages | | ΔTumour volume correlates with pathology (p=0.003) No correlation between ΔSUV and pathology |
| Kroep 2003 | SUV/K | During therapy | 6/52 post commencement | Pathological | R <10% viable cancer cells NR >10 viable cancer cells | ROC, Sn 100%, Sp 86% | R=>40% reduction SUV NR=<40% reduction SUV | Good correlation between K and SUV CT poor correlation with pathological response |
| | | Post therapy | Immediate | | | ROC, Sn 100%, Sp 100% | R=>60% reduction SUV | Correlation between pathological and PET response greatest post therapy |

| Swisher 2004 | SUV | Post therapy | Immediate | Pathological | 0% viable cancer cells, <10% viable cancer cells, >10% viable cancer cells | | | NR= \leq 60% reduction SUV | Post therapy SUV correlates with pathology ($p=0.01$) Post therapy SUV ≥ 4 34% 2yr survival, ≤ 4 60% 2yr survival ($p=0.001$) |
|-----------------|-----------------------------|-----------------------------|--------------------------|--------------|--|---|--|--|--|
| Song 2005 | SUV | Post therapy | 4/52 | Pathological | R=complete pathological response NR=microscopic/gross residual disease | Initial SUV ≥ 4 , Sn=33%, Sp=100% | | R=87.9% reduction SUV NR=68.4% reduction SUV | No correlation between Δ SUV and pathology Correlation between Δ SUV and pathology if pre therapy SUV ≥ 4 ($p=0.006$) |
| Melcher 2004 | SUV/TLR | Post therapy | Immediate | Pathological | Mandard | TRG 1-5 | | | No correlation between Δ SUV and pathology |
| Gillham 2006 | SUV/ Δ Tumour volume | During therapy | 1/52 post induction | Pathological | Mandard | R=TRG 1-2 NR=TRG 3-5 | | | No correlation between Δ SUV or tumour volume and pathology |
| Levine 2006 | SUV | Pre therapy Post therapy | Within 2/52 Immediate | Pathological | Complete response, microscopic residual, partial, stable and progressive disease | R=complete/microscopic NR=partial, stable, progressive | | | SUV >15 associated with pathological response ($p=0.005$) Δ SUV did not correlate with pathological response ($p=0.871$) |
| Konski 2007 | SUV | Pre therapy Post therapy | Within 2/52 4-6/52 | Pathological | Complete response and residual disease | R=complete response NR=residual disease | | | No correlation of pre and post therapy SUV or Δ SUV with pathological response |
| Kim 2007 | SUV | Post therapy | 2-3/52 | Pathological | Complete response and residual disease | R=complete response NR=residual disease | | | Complete metabolic response independent prognostic indicator for disease free ($p=0.006$) and overall survival ($p=0.033$) |
| | | | | PET | CMR and residual FDG uptake (nCMR) | R=CMR NR=nCMR | | | Complete metabolic response Sn 51.2%, Sp 66.7%, accuracy 70.5% in predicting complete pathological response |
| Smithers 2008 | SUV/TLR | Post therapy | 3-6/52 | Pathological | Mandard R=TRG 1-2 NR=TRG 3-5 | Median Δ SUV for pathological R and NR | | C R=84.6% reduction SUV C NR=20.9% reduction SUV | Only 1 chemotherapy responder No correlation between PET response and pathological response ($p=0.09$) |
| | | | | | | | | CRT R=52.1% reduction SUV CRT NR=37% reduction SUV | 6 chemoradiotherapy responders No correlation between PET response and pathological response ($p=0.265$) |
| Mamede 2007 | SUV | Post therapy | 3/52 | Pathological | R= $<$ 10% viable cancer cells NR= \Rightarrow 10% viable cancer cells | ROC, Sn 75%, Sp 58.8% | | R= \Rightarrow 59.4% reduction SUV NR= $<$ 59.4 reduction SUV | PET 64% accuracy in determining pathological response |
| McLoughlin 2008 | Quantitative Assessment | Post therapy | 5-7/52 | Pathological | Complete response, microscopic and | | | | Complete PET response does not indicate complete pathological response |

| | | | | measurable residual disease | | | |
|--------------|-------------------------|----------------|------------------------|-----------------------------|--|------------------------|---|
| Lordick 2007 | SUV | During therapy | 2/52 post commencement | PET | R= \geq 35% reduction SUV NR= \leq 35% reduction SUV | ROC (See Weber 2001) | MR had significantly improved overall survival over nMR ($p=0.015$) MR+HR had significantly improved overall survival over MR+nHR ($p=0.004$) 21 MR had no HR No HR was noted in nMR |
| | | | | Pathological | R= $<$ 10% viable cancer cells NR= \geq 10% viable cancer cells | | |
| Duong 2006 | Quantitative assessment | Post therapy | 4-5/52 | PET | CMR, nCMR | R=CMR NR=nCMR | CMR 78% 2yr survival nCMR 33% 2yr survival ($p=0.001$) |
| Port 2007 | SUV | Post therapy | 2-3/52 | Pathological | R= $<$ 10% viable cancer cells NR= \geq 10% viable cancer cells | ROC, Sn77.8%, Sp 52.9% | PET R= \geq 50% reduction SUV PET NR= $<$ 50% reduction SUV Complete MR does not equate to complete pathological response R median DFS 35.5 months NR median DFS 17.9 months ($p=0.03$) |

R=responder, NR=non-responder, C=chemotherapy, CRT=chemoradiotherapy, CT=computerised tomography, SUV=standardised uptake value, TLR=tumour liver ratio, K=kinetic analysis, x/52=x weeks, ROC=receiver operating characteristic, Sn=sensitivity, Sp=specificity, TRG=tumour regression grade, MR=metabolic responder, nMR=non metabolic responder, HR=pathological responder, nHR=non pathological responder, CMR=complete metabolic responder, nCMR=residual FDG uptake, DFS=disease free survival