PET/CT-Based Response Evaluation in Cancer

a Systematic Review of Design Issues

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PET/CT-based response evaluation in cancer – a systematic review of design issues

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Abstract

Positron emission tomography/computed tomography (PET/CT) has long been discussed as a promising modality for response evaluation in cancer. When designing respective clinical trials, several design issues have to be addressed, especially the number/timing of PET/CT scans, the approach for quantifying metabolic activity, and the final translation of measurements into a rule. It is unclear how well these issues have been tackled in quest of an optimised use of PET/CT in response evaluation. Medline via Ovid and Science Citation Index via Web of Science were systematically searched for articles from 2015 on cancer patients scanned with PET/CT before and during /after treatment. Reports were categorised as being either developmental or evaluative, i.e. focusing on either the establishment or the evaluation of a rule discriminating responders from non-responders. Of 124 included papers, 112 (90%) were accuracy and/or prognostic studies; the remainder were response-curve studies. No randomised controlled trials were found. Most studies were prospective (62%) and from single centres (85%); median number of patients was 38.5 (range 5-354). Most (69%) of the studies employed only one post-baseline scan. Quantification was mainly based on SUVmax (91%), while change over time was most frequently used to combine measurements into a rule (79%). Half of the reports were categorised as developmental, the other half evaluative. Most development studies assessed only one element (35/62, 56%), most frequently the choice of cut-off points (25/62, 40%). In summary, the majority of studies did not address the essential open issues in establishing PET/CT for response evaluation. Reasonably sized multicentre studies are needed to systematically compare the many different options when using PET/CT for response evaluation.

Key words: Cancer, Positron emission tomography, Response evaluation, Study design, SUVmax, Systematic review

Introduction

Response evaluation is a key element in cancer management and testing of new anticancer regimens. Effective cancer therapies are available and are often based on the molecular characteristics of cancer cells. However, our understanding of these mechanisms is too limited to predict which treatment will be most effective. The first choice for a therapy may thus not be optimal, and we need reliable methods for early response assessment in order to optimise cancer management and implement personalised cancer therapy in clinical practice. Positron emission tomography/computed tomography (PET/CT) is applied in many cancers for diagnosis/staging and treatment triage [1-8].

PET/CT is a promising modality for response evaluation due to the unique properties of molecular imaging, including high sensitivity and quantification potential that ensures early detection of disease and disease activity often long before structural tissue changes become detectable by standard imaging. Structural changes can be misleading in time and substance as the presence and degree of active, ongoing disease cannot be depicted, as for example with conventional imaging of bone metastases [9-13]. Moreover, geometric lesion size endorsed by current guidelines does not accurately reflect either tumour aggressiveness or tumour burden. Similarly, change in lesion volume is a suboptimal indicator of treatment success as the nature and activity of residual neoplastic tissue cannot be judged by structural imaging.

The advantages of PET have not yet been fully exploited, and there are no generally accepted guidelines for the use of PET in response evaluation. Most studies still rely on visual assessment of changes and/or inappropriate measures of tumour activity such as the (single voxel) maximum standardised uptake value (SUVmax), the uptake in a spherical 1 cm^3 volume of interest (SUVpeak),

or SULpeak (which is SUVpeak corrected for lean body mass instead of body weight) [14, 15]. More logical approaches of gauging tumour burden and activity based on PET imaging are being elaborated and will hopefully soon reach clinical practice [16-20].

Assessment of the appropriateness of PET parameters is not an objective of this review. It is also noted that various logistic and methodological challenges must be considered in establishing PET/CT as a clinically relevant modality for response evaluation [15, 21]. These include availability and regulatory compliances of PET radiopharmaceuticals, standardisation of imaging and reconstruction protocols, quality control, image processing, and the development and validation of relevant PET outcome measures reflecting tumour burden and cancer activity.

In our quest for an optimised use of PET/CT in response evaluation, we identified central questions to be answered:

- What are the optimal time points of performing PET/CT post-baseline, i.e. during and/or after therapy?
- How should the metabolic activity be quantified?
- How do we transform measured values into a rule to assess response or non-response in the individual patient (absolute values vs. change over time; absolute vs. relative changes, cut-off points)?

Until we know more about the underlying biological processes, these questions can only be answered through a series of empirical clinical studies contributing in a stepwise way: (1) *response-curve studies* mapping first the typical course of metabolic activity during treatment and then comparing the curve courses of responders and non-responders to an external standard to establish a discriminating rule; (2) *rule-performance studies* examining the accuracy and prognostic value of

the established rule; and (3) *randomised controlled trials (RCTs)* demonstrating the clinical usefulness of the rule when applied in cancer management.

We have a clear expectation that these study types should be used when evaluating PET/CT-based response rules, and that such studies should address the central questions mentioned above. It was the aim of this systematic literature review to illuminate the extent to which these expectations are met in the published literature and to suggest how current practice can be improved.

Systematic literature review

The systematic review was undertaken in accordance with the *Preferred Reporting Items for Systematic reviews and Meta-Analysis* (PRISMA) statement [22]. Basic aspects of the review were defined in advance, but due to uncertainty about the methodological scope of the studies to be identified, no detailed review protocol was generated. An ethical review was not required due to the nature of this study.

The *population, intervention, comparison, outcome, and study type* (PICOS) framework [23, 24] was applied to the research question "Which design features characterise clinical studies on response evaluation with PET/CT in cancer?" To this end, the target population consisted of cancer patients who were scanned with PET/CT at least once at baseline and once post-baseline (i.e. during and/or after treatment). Comparators (such as other imaging modalities) were not limited, and the outcome focused on the potential value of PET/CT in response evaluation. Study types were limited to original studies.

The two databases Medline via Ovid and Science Citation Index Expanded via Web of Science were searched on 2 February 2017 for articles in English published in 2015. In the search strategies,

we combined the facets “PET” AND “neoplasms treatment” AND (“response” OR “time of treatment”). For each facet we generally combined keywords, their synonyms, and Medical Subject Headings (MeSH) for the indexed part of MEDLINE. For a full description of the search strategies, see Suppl. Table 1. All search results were collected, merged, and filtered with EndNote X7 (Thomson Reuters, Philadelphia, PA).

Two independent reviewers (KE, OG) screened the list of abstracts that emerged from the search. Potentially relevant articles were chosen for a full-text review. In case of discrepancy between reviewers, the article was included. The selected studies were further investigated by one reviewer (KE) to check that they met the inclusion criteria and were eligible for data extraction. The inclusion criteria were as follows: population of cancer patients; at least one baseline PET/CT and at least one post-baseline PET/CT scan; PET/CT was evaluated with respect to its potential value for response evaluation; original articles and systematic reviews (i.e. case studies, commentaries, editorials, letters, and narrative reviews were excluded); systematic reviews had to include the aspect of response evaluation; in print in 2015; English language.

A data extraction scheme was designed by the project team (KE, OG, WV) after completion of the final list of publications to be included in the study and after a first check of the type of information typically found in such publications. One reviewer extracted the data (KE) and a second reviewer (OG) validated the extracted data from all selected studies and, in cooperation with a third reviewer (WV), extended the data retrieval by adding further variables where deemed appropriate. The data extraction scheme for all included studies covered the items shown in Table 1. For accuracy studies, the following additional items were extracted: *reference standard* (e.g. modality)*, scale of reference standard (continuous vs. categorical vs. binary),* and *time point of PET/CT scan preceding time point of reference standard (yes/no).* For prognostic studies, the following additional items

were extracted: *outcome used* (e.g. overall survival), *non-responder rate*, and *information on second-line therapy given.*

Categorisation of clinical study designs

The studies were categorised according to the following study designs, but hybrid forms were allowed.

Response-curve studies. In a first step, the typical course of the metabolic activity under treatment and its inter-individual variation is investigated by repeated, closely spaced measurements over time, starting at baseline. This can give first insights into the adequate timing of measurements and how to most appropriately quantify metabolic activity and derive rules for response assessment (response vs. non-response). Additionally, options for one-number summaries across the whole time span can be investigated (e.g. a slope to quantify the speed of the decrease in activity) [25]. In a second step, the courses of responders and non-responders are compared using an external reference standard. This standard should be an established criterion for response evaluation that can be applied both within follow-up and at the end of the therapy. Examples are the *Response Evaluation Criteria in Solid Tumors* (RECIST) and *PET Response Evaluation Criteria in Solid Tumors* (PERCIST) [26-33]. Comparing the time courses of responders and non-responders can assist in developing a discriminative rule for responders vs. non-responders.

Rule-performance studies. After the development of a PET/CT-based response evaluation rule (that classifies each patient as either a responder or a non-responder), this rule's performance needs to be assessed. There are two fundamentally different approaches:

1. In an *accuracy study*, the rule is directly compared with the reference standard. The aim is to demonstrate a sufficiently high accuracy (i.e. agreement with the reference standard) to justify a minimal loss counterbalanced by an additional advantage of using PET/CT (e.g. earlier, less invasive, and/or less expensive assessment).
2. In a *prognostic study*, the results of the rule are compared with a long-term patient outcome (e.g. overall or progression-free survival), aiming to demonstrate that responders do have a substantially better survival than non-responders. Alternatively, clinical follow-up of the patients can be used as a (composite) reference standard. A basic limitation of such studies, however, is that non-responders can only be expected to have poor outcome if they are not offered (effective) second-line therapies.

RCTs. The clinical effectiveness of the rule can be demonstrated in an RCT that compares a patient management plan involving a PET/CT-based early response evaluation with the current standard management (which may involve the current standard of early response evaluation or no early response evaluation at all).

The move from studies focusing on the *development* of a response evaluation rule to studies *evaluating* this rule is not as simple as outlined above. When planning accuracy and prognostic studies, we often have only a vague idea of how the rule should look like, but we still have to fix several components of the rule (e.g. timing of response evaluation, relative vs. absolute changes). Therefore, we distinguish in this paper between more dynamic *development studies* that address the question of how to construct the optimal rule, and more static *evaluation studies* that assess a fixed rule. Development studies range from a comparison of fundamentally different approaches (comparing PET/CT with another modality or comparison of two tracers) to fine-tuning aspects such as the choice of a cut-off point for a quantitative parameter. Such development studies are essen-

tial to take into account the many open questions about how to perform a PET/CT-based response evaluation.

Statistical analysis

Variables were displayed descriptively according to data type (continuous variables as median and range; categorical variables as frequencies and percentages). Listings and graphical visualisations were added where appropriate. No inferential statistics were applied. All analyses were done with STATA/MP 15.0 (StataCorp, College Station, Texas 77845 USA).

Findings

Literature search

The literature search resulted in 1280 hits. Removing duplicates reduced this to 904 articles. The screening process led to 148 publications fulfilling the eligibility criteria. The full-text review of these led to exclusion of 24 studies (Suppl. Table 2), and 124 publications were finally used for data extraction and analysis (Figure 1).

Study design types

Sixty-three studies (51%) were prognostic [34-96], 37 (30%) were accuracy studies [97-133], and 12 (10%) were a mix of these [134-145]. Further, 11 studies (9%) were descriptive response-curve

studies [146-156] and one (1%) was a mix of a prognostic and a response-curve study [157] (Figure 2). No RCTs were found.

Basic design features of studies

Nineteen different types of cancer were represented, and 73% of studies included patients with lymphoma, squamous cell carcinoma, breast, lung, colorectal, oesophageal, or rectal cancer (Table 2). The tracer 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) was used most often (90%), followed by 3'-dexoy-3'[^{18}F]fluorothymidine (FLT; 10%; data not shown). Most of the time, FDG was the only tracer applied (85%); only six studies (5%) contrasted FDG with other tracers. Most studies were prospective (62%), single-centre studies (85%), and the median number of patients was 38.5 (range 5-354). The median sample size was largest in prognostic studies (49.5; range 16-354) and smallest in response-curve studies (18.5; range 5-53). In accuracy studies, the median number of patients was 33 (range 5-187). All studies, except one [62], performed one baseline scan only, and 69% and 25% of all studies employed one or two post-baseline scans, respectively. In prognostic studies, up to three post-baseline scans were observed; in response-curve studies, four and nine post-baseline scans were observed [150, 153]. The unit of analysis was equally lesion/site, the patient, or both (one-third each). In all prognostic studies except one [92], the patient was the observational unit; this was the case for 58% of response-curve studies and 29% of accuracy studies.

Approach for quantifying metabolic activity

In 113 of 124 (91%) studies, the primary PET outcome measure used for response evaluation was the SUVmax (Table 3). In one-third of these studies, other PET outcome measures were also evalu-

ated (e.g. SUVpeak, mean SUV (SUVmean), and total lesion glycolysis (TLG) which is the product of SUVmean and the volume of interest). Most studies (79%) used change over time of the PET target parameter(s) as the analytical approach, either alone (75 studies, 60%) or alongside absolute values of the PET target parameter(s) at specific time points (23 studies, 19%). In 21% of all studies, the analytic approach was restricted to using absolute values of the PET target parameter(s), with no change parameters. Of the 75 studies employing change over time, 67 (89%) analysed relative changes (i.e. percentages), and 8 (11%) analysed absolute changes.

Developmental elements

Half of the included reports were categorised as development studies and half as evaluation studies (Table 3). Median sample sizes were similar in development studies (40.5; range 7-282) and evaluation studies (36.5; range 5-354). Of the 62 development studies, 35 (56%) assessed one developmental element, while 21 (34%) and 6 studies (10%) assessed two or three developmental elements. Prognostic studies that analysed one, two, or three developmental elements had similar median sample sizes (around 60) and ranges. The most frequently employed developmental element was the choice of cut-off point (25/62, 40%), followed by the choice of PET target parameter (31%), the modality (25%), and the time points (19%). Accuracy studies most often investigated modality and cut-off points, while prognostic studies most frequently examined cut-off points and PET target parameters (each over 40% of cases).

Accuracy studies

In the 49 accuracy studies, the reference standard was most frequently histopathology (57%), followed by CT (18%), and MRI (10%); Suppl. Table 3. In 59% of accuracy studies, the reference standard comprised more than two response categories, whereas in 41% of studies the patients were classified as “responders” or “non-responders”. In 49% of accuracy studies, PET was used before the reference standard.

Prognostic studies

In the 76 prognostic studies, the most frequently employed endpoints were overall survival (75%), progression-free survival (55%), and recurrence-free survival (21%); Suppl. Table 4. Non-response rates ranged from 0% to 100% (1st quartile 24%, median 38%, 3rd quartile 63%), and in 17 studies (22%) non-responders were offered a second-line therapy or therapy was adapted to the degree/type of disease. In the other 59 studies (78%), a description of second-line therapy was missing, leading us to assume that patients in these studies did not receive second-line therapy.

Discussion

This systematic literature review identified a large amount of clinical research published in 2015 relating to assessment of PET/CT-based response evaluation. The studies covered a wide range of cancer types, with lymphoma, breast cancer, lung cancer, and squamous cell carcinoma as the most frequently addressed types.

Main findings on study design

Nine out of ten studies were accuracy and/or prognostic studies, and only 10% were basic descriptive response-curve studies. No RCTs were found.

The effective use of PET/CT to evaluate response to treatment requires the development of rules for determining response evaluation. This implies decisions about (a) the choice of number and timing of post-baseline PET/CT scans, (b) the quantification of the measured activity using one or more parameters, and (c) how to combine the measured values into a rule. In our study, we observed that:

(a) Two out of three studies employed only one post-baseline time point. Even among the one-quarter of studies (39) with two or more post-baseline time points, only 7 (18%) investigated alternatives related to the choice of time point (data not shown).

(b) SUVmax was by far the most common parameter used for quantifying tracer uptake, and only a few studies considered alternatives.

(c) Half of the studies were static and evaluated only one fixed rule ("evaluation studies"), while the other included developmental elements ("development studies"). The most frequent approach to developing a rule was optimisation of the cut-off point, followed by choice of PET parameter, comparison of PET/CT with other modalities, and time points. Most of the development studies investigated only a single element, and no study addressed more than three elements.

The large number of evaluative studies and the limited focus on developmental elements could be interpreted as a sign that all questions on the optimal construction of response evaluation rules have already been solved. We do not believe that such an interpretation is justified, and our investigation also provides empirical evidence against this. We observed a wide variation in how PET measurements are combined into a rule, with various studies using absolute values at specific

time points, absolute changes, or relative changes. While one-third of all studies were retrospective and thus had no influence on the number of scans performed, about one-half of the prospective studies considered at least two post-baseline time scans, reflecting some awareness of this issue. The limited evidence for considering alternative quantification approaches is surprising, however, in view of the intensive discussion of this topic in recent years [16, 158-167].

Additional methodological issues

Three-quarters of all studies had small to moderate sample sizes (1st quartile 23.5, median 38.5, 3rd quartile 71; data not shown). In accuracy studies, we observed a median study size of 33 (90th percentile 126; data not shown), suggesting that, e.g. an empirical sensitivity of 80% is associated with a confidence interval of 56.6%-96.2% for n=33 (and 67.3%-88.5% for n=126) in the case of equal numbers of responders and non-responders. Clearly, such large intervals do not allow meaningful characterisation of the clinical value of a response evaluation rule.

Although it is essential for the interpretation of the results of a prognostic study whether non-responders received a second-line therapy or not, only a minority of studies reported on this issue.

We observed a wide variation in the applied observational unit (lesion/site, patient, or both). This may partially reflect differences in the type of medical problem considered, but may also reflect a lack of consensus on the most appropriate strategy. In our opinion, we should always aim for analyses at both the lesion/site level and the patient level. Analysis at the lesion/site level has the advantage of a larger sample size, thus enabling a more precise evaluation. Analysis at the patient level mirrors the focus on patient benefit, which may be different from the benefit observed at the lesion/site level.

Our review includes studies on both solid tumours and lymphoma. In the latter the use of FDG PET is much more mature and currently used in clinical practice (Deauville criteria [168, 169]) as well as guiding treatment (e.g. the RAPID trial [170, 171]). Lymphoma studies were more often prognostic studies (16/20, 80%) than studies on solid tumours (60/104, 57.7%); they were more often multicentre studies (8/20, 40% vs. 11/104, 10.6%), employed, on average, more patients (median 61.5, range 27-257 vs. median 34.5, range 5-354), and evaluated response more often at the patient level (18/20, 90% vs. 65/104, 62.5%).

Implications for the design of future studies

The strength of this study is its design as a systematic review, providing a representative picture about the clinical research on evaluating PET/CT-based response evaluation. A limitation is the restriction to one calendar year, which does not allow us to investigate time trends. Moreover, we did not differentiate between conventional chemotherapies and newer therapies, e.g. targeted therapies or immunotherapies, as we sought to give a summary of different study types used and design issues employed and explored. Future studies can overcome both of these limitations by focusing on a single indication over a wider time frame and possibly stratifying the analysis by type of therapy.

Our interpretation of the study results is that there seems to be little recognition or appreciation of the need to understand the typical time course of metabolic activity before, during, and after treatment prior to developing rules for response evaluation. This was documented by the low number of response-curve studies and the few studies employing at least three time points. For theoretical reasons, three is the minimum number of scans required to obtain interpretable results [25]. Using only one post-baseline time point makes an implicit assumption that all patients have a

similar activity course over time and only differ in a quantitative manner. With one baseline and one post-baseline measurement, it is impossible to assess whether the metabolic activity declines further after the last time point under consideration, reaches a plateau at the last time point, or is on the increase after a decline (Figure 3). The ability to differentiate between such patterns is essential in the establishment of clinically useful rules and requires at least two, and preferably more, post-baseline time points.

Future studies should have a greater focus on the issue of number and timing of scans, but they should also address other developmental elements. Having conducted a PET scan in the first place, it is relatively inexpensive to derive additional PET parameters that will enable systematic comparisons to be made. SUVmax and/or SUVpeak or SULpeak should not be the only PET measures analysed; some of the other possibilities (such as SUVmean or TLG) have already been demonstrated as superior [16, 17]. Similarly, it is always possible to compare different ways to combine measurements into a rule, and – given a sufficient sample size – such comparisons can clarify the optimal way to construct such rules. Elements such as cut-off points, definitions of the assignment rule for response/non-response, and combination of PET parameters are easily obtainable, whereas others (time points, modalities, tracers) depend on meticulous planning before the study is conducted.

Accurate quantification of small lesions requires partial volume correction in order to prevent underestimation of tumour tracer uptake on PET/CT [172, 173]. Taking the perspective that a few lesions may not necessarily represent the overall disease activity in a patient (e.g. RECIST, PERCIST), PET-based global measurement of disease can be argued for [174-176]. The latter will, based on partial volume correction, supposedly allow for quantification of global disease activity in both each lesion and the whole body [177].

Finally, PET/CT should not be seen in isolation. Establishing PET/CT as the modality for response evaluation in cancer patients requires proving its clinical superiority to current practice and/or to other modalities, including new approaches such as liquid biopsy. It is unfortunate that after many years of discussion and research on this topic, it was not possible to identify at least one RCT.

Conclusions

This systematic literature review revealed that many studies are not ambitious with regard to providing new and reliable evidence in the field of PET/CT-based response evaluation. Sample sizes are often small, and studies are often retrospective, thus not requiring changes to existing rules. Systematic attempts to compare different choices in constructing rules are rare, and single-centre studies prevail. This limits both sample size and the generalisability of results. We found no study with a randomised design that attempted to demonstrate the potential clinical superiority of a PET/CT-based rule.

Reasonably sized multicentre studies are needed to systematically compare different ways of constructing rules for response evaluation studies, addressing questions such as the necessary number and timing of post-baseline time points, the best way to quantify metabolic activity, and how to combine measurements into a rule.

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Compliance with Ethical Standards

For this type of study formal consent is not required.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Table 1. Variables extracted for all included studies

Variable	Explanation
Study design	Response-curve study, accuracy study, prognostic study, and/or RCT
Cancer type	Medical indication (e.g., lung cancer)
Tracer	PET tracer (e.g. [^{18}F]-fluorodeoxyglucose (FDG))
Prospective or retrospective study	Prospectively planned study according to authors vs. retrospective data collection by means of registries or hospital records
Single- or multicentre study	Number of centres involved in the study
Overall number of patients	Number of included patients in the study
Number of baseline measurements	Number of PET baseline measurements before treatment start
Number of post-baseline scans	Number of PET measurements during and/or after treatment
Timing of post-baseline scans	Timing of the first, second, and third PET measurements during and/or after treatment (weeks)
Unit of analysis	Response evaluation can be performed at the lesion level or/and at the patient level
Quantification approach	Metabolic activity can be quantified by different means, e.g. SUVmax, SUVmean, TLG
Analytical approach	Absolute values at specific time points vs. change over time; absolute vs. relative change over time
Developmental or evaluative study	Developmental study: comparison of different rules or approaches to construct an optimal rule Evaluative study: evaluation of one fixed rule
Developmental elements	Choice of cut-off: comparison of different cut-off values or choice of optimal cut-off based on Receiver-Operating-Curve analysis PET quantification: comparison of different approaches for quantification (e.g. SUVmax, SUVmean) Modalities: comparison of PET/CT with another (imaging) modality for response evaluation (beyond comparison with reference standard) Time points: comparison of different time points of post-baseline scans Definitions: comparison of rules based on absolute values vs. absolute change vs. relative change Combination of parameters: use of multivariable methods to find the best combination of several input parameters (PET/CT-based or from other sources) or to assess the amount of independent information in PET/CT parameters Tracers: comparison of PET tracers

Table 2. Descriptive statistics for all included studies, also stratified by study type

Variable		Study type		
	All included studies	Response-curve	Accuracy	Prognostic
No. studies[a]	124 (100%)	12 (10%)	49 (40%)	76 (61%)
Most frequent cancer types	Lymphoma: 20 (16%) Breast: 18 (15%) Lung: 17 (14%) Squamous cell: 11 (9%) Colorectal: 8 (6.5%) Oesophageal: 8 (6.5%) Rectal: 8 (6.5%)	Renal cell: 2 (17%) Squamous cell: 2 (17%)	Breast: 14 (29%) Rectal: 7 (14%) Squamous cell: 6 (12%)	Lymphomas: 16 (21%) Lung: 15 (20%) Colorectal: 7 (9%) Oesophageal: 7 (9%)
Tracer(s):				
FDG only	105 (85%)	7 (58%)	41 (84%)	68 (89%)
FDG and others	6 (5%)	1 (8%)	2 (4%)	3 (4%)
Others only	13 (10%)	4 (33%)	6 (12%)	5 (7%)
Prospective	77 (62%)	10 (83%)	31 (63%)	46 (61%)
Retrospective	47 (38%)	2 (17%)	18 (37%)	30 (39%)
Single-centre	105 (85%)	10 (83%)	44 (90%)	62 (82%)
Multicentre	19 (15%)	2 (17%)	5 (10%)	14 (18%)
Median no. patients (range)	38.5 (5-354)	18.5 (5-53)	33 (5-187)	49.5 (16-354)
No. baseline measurements	1: 123 (99%) 2: 1 (1%)	1: 12 (100%)	1: 49 (100%)	1: 75 (99%) 2: 1 (1%)
No. post-baseline scans	1: 85 (69%) 2: 31 (25%) 3: 6 (5%) 4: 1 (1%) 9: 1 (1%)	1: 4 (33%) 2: 5 (42%) 3: 1 (8%) 4: 1 (8%) 9: 1 (8%)	1: 40 (82%) 2: 9 (18%)	1: 50 (66%) 2: 21 (28%) 3: 5 (7%)
Time (weeks) from baseline:				
To 1st PET scan	7 (0.14-198)	3 (1-24)	7 (1-198)	7.29 (0.14-40)
To 2nd PET scan	12 (2-59.35)	4.36 (2-59.35)	13.5 (4.43-36)	12 (3-40.5)
To 3rd PET scan	20 (2.86-52)	2.93 (2.86-3)	N/A	36 (20-52)
Unit of analysis:				
Lesion/site	41 (33%)	5 (42%)	35 (71%)	1 (1%)
Patient	40 (32%)	0 (0%)	2 (4%)	40 (53%)
Both	43 (35%)	7 (58%)	12 (25%)	35 (46%)

[a]Shown percentages are row percentages; remaining percentages in table are column percentages. The sum of row percentages exceeds 100% due to hybrid designs (e.g. prognostic and response-curve study [157]).

N/A: not available.

Table 3. Descriptive statistics on developmental and evaluative elements for all included studies, also stratified by study type

Variable	**Study type**			
	All included studies	Response-curve	Accuracy	Prognostic
Quantification approach:				
SUVmax only	76 (61%)	9 (75%)	34 (69%)	41 (54%)
SUVmax and others	37 (30%)	2 (17%)	13 (27%)	26 (34%)
Others than SUVmax	11 (9%)	1 (8%)	2 (4%)	9 (12%)
Analytical approach:				
Values	26 (21%)	4 (33%)	7 (14%)	16 (21%)
Change	75 (60%)	6 (50%)	33 (67%)	45 (59%)
Both	23 (19%)	2 (17%)	9 (18%)	15 (20%)
Type of change approach:				
Absolute	7/75 (9%)	1/6 (17%)	2/33 (6%)	5/45 (11%)
Relative	67/75 (89%)	5/6 (83%)	31/33 (94%)	39/45 (87%)
Both	1/75 (1%)			1/45 (2%)
Developmental study	62 (50%)	3 (25%)	32 (65%)	34 (45%)
Evaluative study	62 (50%)	9 (75%)	17 (35%)	42 (55%)
Median number of patients (range) by type:				
Developmental study	40.5 (7-282)	10 (8-20)	34 (7-187)	58.5 (17-282)
Evaluative study	36.5 (5-354)	22 (5-53)	31 (5-105)	46 (16-354)
Number of developmental elements:				
1	35 (56%)	3 (100%)	20 (63%)	17 (50%)
2	21 (34%)		9 (28%)	14 (41%)
3	6 (10%)		3 (9%)	3 (9%)
Median number of patients (range) by number of developmental elements:				
1	37 (7-257)	10 (8-20)	32 (7-187)	60 (27-257)
2	53 (17-282)		36 (21-181)	58.5 (17-282)
3	59.5 (15-98)		62 (15-68)	57 (34-98)
Developmental elements investigated[a]	Cut-off points: 25/62 (40%) PET parameter: 19/62 (31%) Modalities: 15/62 (25%) Time points: 12/62 (19%) Definitions: 10/62 (16%) Combination of parameters: 8/62 (13%) Tracers: 6/62 (10%)	Tracers: 2/3 (67%) Modalities: 1/3 (33%)	Modalities: 14/32 (44%) Cut-off points: 13/32 (41%) PET parameter: 5/32 (16%) Time points: 5/32 (16%) Definitions: 4/32 (13%) Combination of parameters: 4/32 (13%) Tracers: 2/32 (6%)	Cut-off points: 14/34 (41%) PET parameter: 14/34 (41%) Time points: 8/34 (24%) Combination of parameters: 6/34 (18%) Definitions: 6/34 (18%) Modalities: 4/34 (12%) Tracer: 2/34 (6%)

[a]Multiple counting of studies possible due to employment of several developmental elements in a study.

Figure legends

Figure 1. Flow chart of selection process [22].

Figure 2. Distribution of study types across 124 included studies.

Figure 3. Illustration of the error of "before-and-after" studies using one baseline measurement and one single follow-up determination. If the follow-up point is lower than the baseline point, we tend to accept this as an expression of a declining trend (which potentially might indicate a straight course toward zero illustrated by the dotted blue line). In reality, the follow-up point may represent various, even opposite, courses, of which three potential ones are indicated (dotted green, orange, and purple lines).

Electronic supplementary material

Suppl. Table 1. Full description of search strategies for Medline and Science Citation Index Expanded

Suppl. Table 2. List of excluded studies after full-text screening with reasons (*n*=24)

Suppl. Table 3. Descriptive statistics on additional features in accuracy studies (*n*=49)

Suppl. Table 4. Descriptive statistics on additional features in prognostic studies (*n*=76)

Figure 1

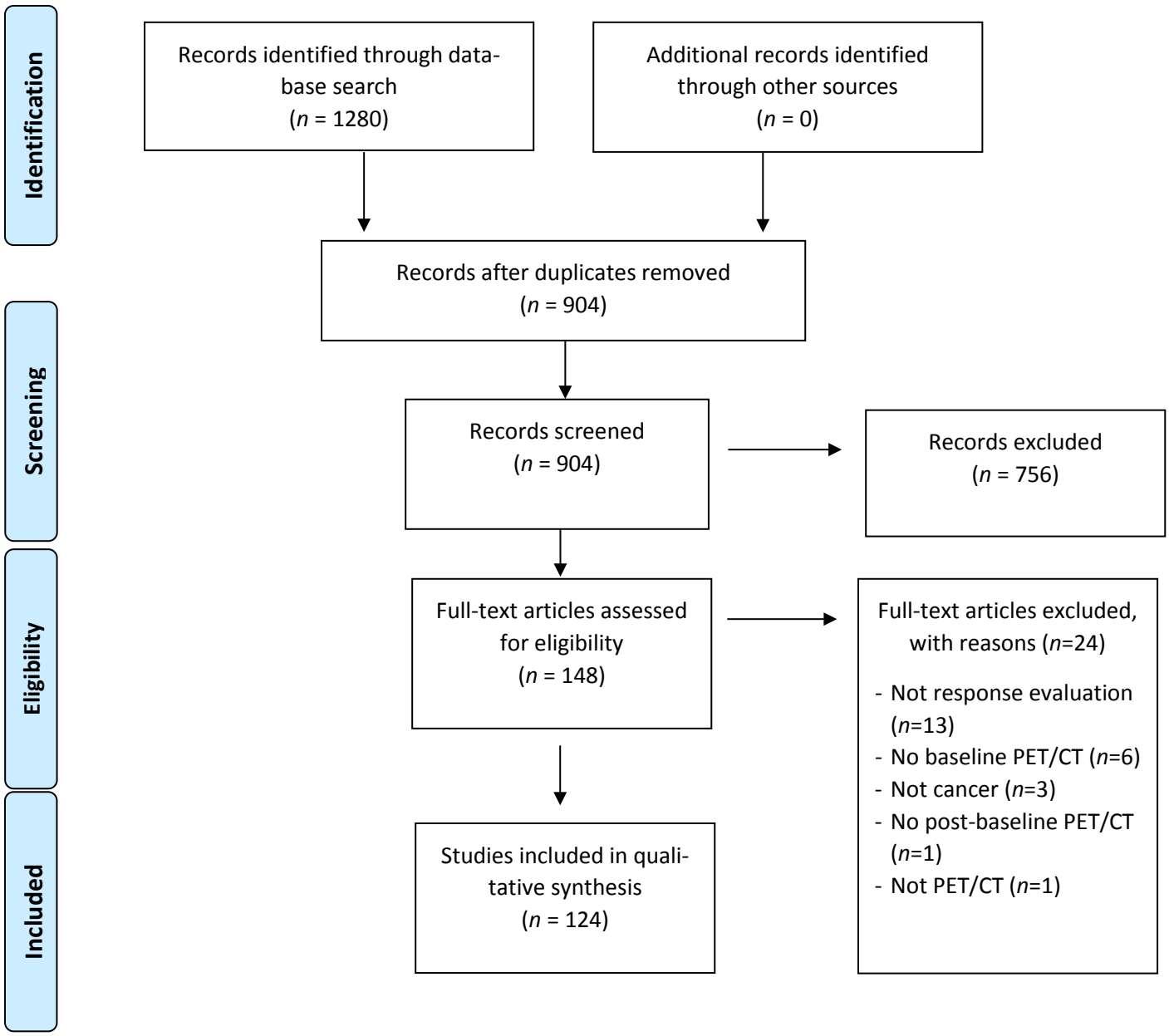

Identification
Screening
Eligibility
Included
Records identified through database search (n = 1280)
Additional records identified through other sources (n = 0)
Records after duplicates removed (n = 904)
Records screened (n = 904)
Records excluded (n = 756)
Full-text articles assessed for eligibility (n = 148)
Full-text articles excluded, with reasons (n=24)
- Not response evaluation (n=13)
- No baseline PET/CT (n=6)
- Not cancer (n=3)
- No post-baseline PET/CT (n=1)
- Not PET/CT (n=1)
Studies included in qualitative synthesis (n = 124)

Figure 2

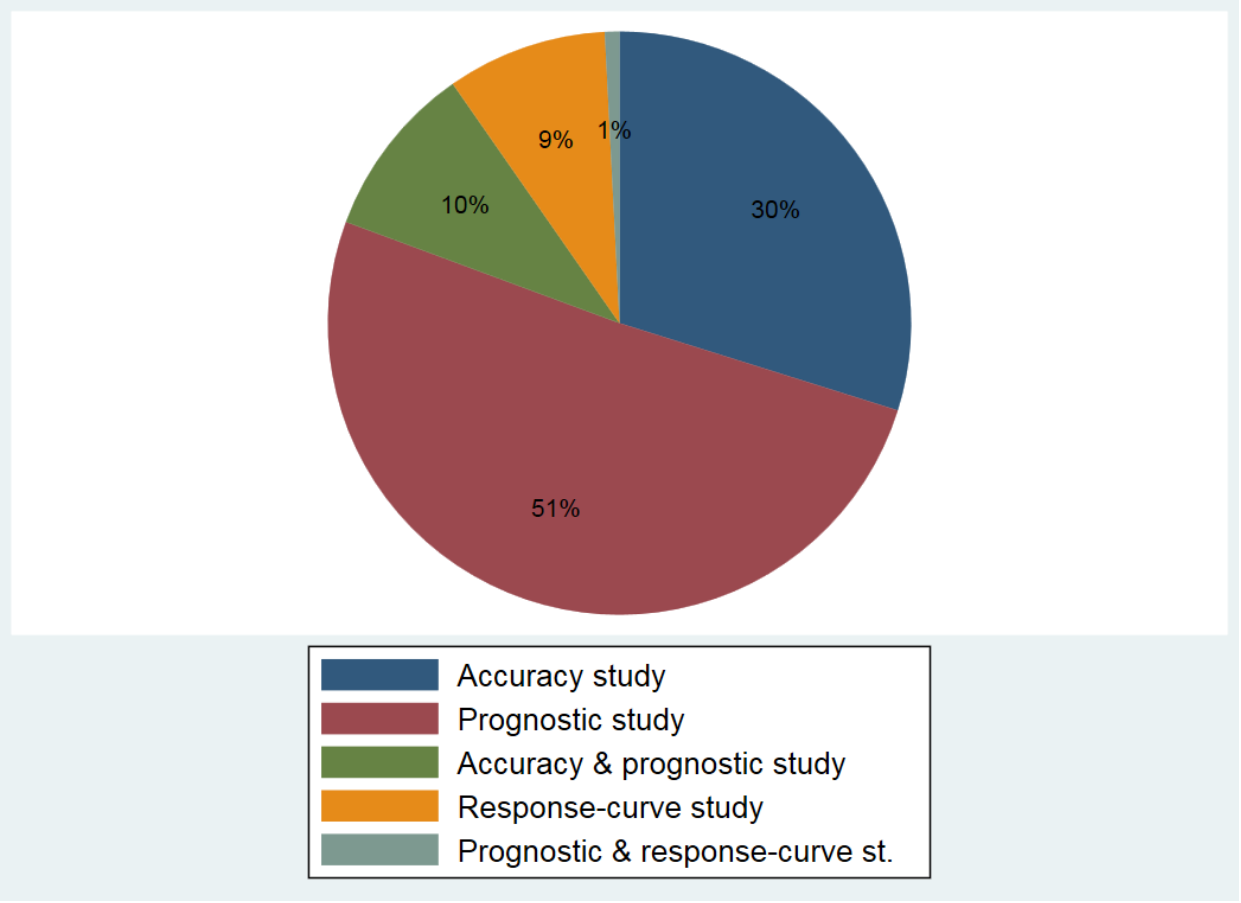
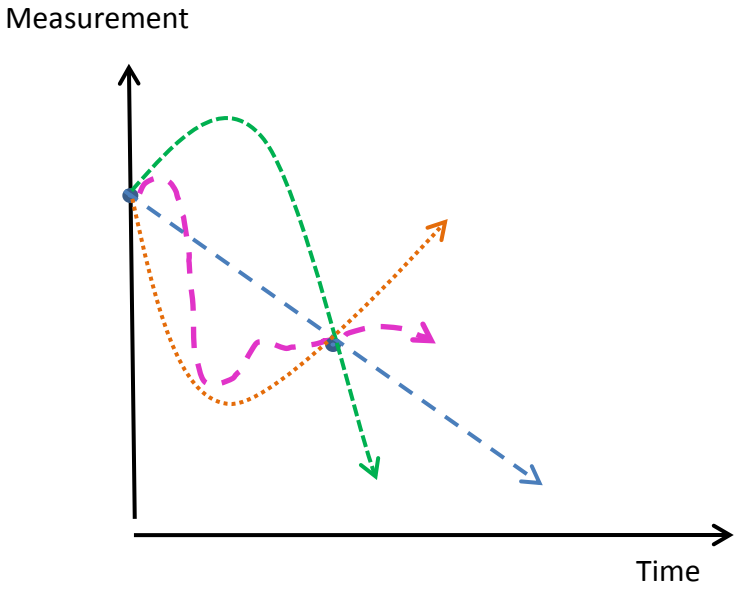

30%
51%
10%
9%
1%
Accuracy study
Prognostic study
Accuracy & prognostic study
Response-curve study
Prognostic & response-curve st.

Figure 3



Electronic supplementary material to:

PET/CT-based response evaluation in cancer – a systematic review of design issues

Molecular Imaging and Biology

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Contents

Suppl. Table 1. Full description of search strategies for Medline and Science Citation Index Expanded

PET Response-Evaluation: Publication year 2015

Search date: 2017-02-02 /Motschall

Database	**Host: Search interface**	**Update Status**	**Results** Restricted to publication year **2015, english**
Medline	Wolters Kluwer: Ovid	1946 to January Week 4 2017	**459**: 442 articles, 17 syst rev, meta-analy
Medline Daily Update		February 01, 2017	
Medline in Process & other non-indexed citations			**121**: 120 articles, 1 syst rev, meta-analy
Medline supplied by publisher			
Science Citation Index (via Web of Knowledge)	Thomson Reuters (now Clarivate Analytics): Web of Science	2017-02-01	**700**: 682 articles 18 sysr rev, meta-analy
Total with duplicates			**1280:** 1244 articles 36 syst rev, meta-analy
Total without duplicates			**904** 880 articles 24 syst rev, meta-analy

Search Strategies: Searcher: Motschall Edith

Via Wolters Kluwer: Search interface Ovid:

1. MEDLINE-databases with MeSH:
- MEDLINE 1946 to January Week 4 2017,
- MEDLINE Daily Update February 01, 2017
Search Date 2017-02-02

#	Searches	Comments

1	Positron-Emission Tomography/	#1 - #13: PET without animals
2	Tomography, Emission-Computed/	
3	Fluorodeoxyglucose F18/	
4	Positron-Emission Tomograph*.ti,ab,kf.	
5	pet scan*.ti,ab,kf.	
6	18?FDG*.ti,ab,kf.	
7	(Fludeoxyglucose adj2 "18").ti,ab,kf.	
8	(18 FDG* adj10 (pet or positron or tomograph* or uptake)).ti,ab,kf.	
9	pet ct.ti,ab,kf.	
10	pet*2ct.ti,ab,kf.	
11	or/1-10	
12	exp animals/ not humans/	
13	11 not 12	
14	(response* or responder* or nonresponder*).ti,ab,kf.	#14 – 16: Response
15	Response Evaluation Criteria in Solid Tumors/	
16	14 or 15	
17	13 and 16	#17: PET and response
18	exp Neoplasms/ dt, pa, rt, th [Drug Therapy, Pathology, Radiotherapy, Therapy]	#18 - #20: PET and response and neoplasms treatment
19	17 and 18	
20	remove duplicates from 19	
21	(post* adj6 (treat* or therap* or chemo* or irradiat* or radi*)).ti,ab,kf.	#21 - #28: Time of treatment
22	(posttherap* or posttreat* or postchemo* or postirradiat* or postradi*).ti,ab,kf.	
23	(after* adj6 (treat* or therap* or chemo* or irradiat* or radi*)).ti,ab,kf.	
24	(during adj6 (treat* or therap* or chemo* or irradiat* or radi*)).ti,ab,kf.	
25	(mid adj6 (treat* or therap* or chemo* or irradiat* or radi*)).ti,ab,kf.	
26	(midtherap* or midtreat* or midchemo* or midirradiat* or midradi*).ti,ab,kf.	
27	(interim adj6 (treat* or therap* or chemo* or irradiat* or radi* or pet or positron* or scan*)).ti,ab,kf.	
28	or/21-27	
29	13 and 18 and 28	#29 - #30: PET and Neoplasms treatment and Time of Treatment
30	remove duplicates from 29	
31	20 or 30	#31 - #35: PET and Neoplasms treatment and
32	"2015".yr.	
33	31 and 32	
34	eng.la.	

35	33 and 34	(Response or Time of treatm) and year 2015, english
36	(case reports or comment or editorial or letter or "review").pt.	#37: excluding publication types of #36
37	35 not 36	
38	((systematic adj3 review) or (systematic adj3 overview) or meta-analy* or metaanaly*).ti.	#38 - #42: PET and Neoplasms treatment and (Response or Time of treatm) and systematic reviews
39	meta-analysis.pt.	
40	38 or 39	
41	35 and 40	
42	41 not 37	
43	37 or 42	**Final result:** PET and Neoplasms treatment and (Response or Time of treatm) and (systematic reviews or articles)

Legend:
/ = MeSH term
Exp = explode Mesh term
* = truncation
.ti,ab,kf. = title, abstract, keyword heading word
.ti. = title
.la. = Language
.pt. = publication type
.yr. = publication year
adj*n* = within n words

2. MEDLINE-databases without MeSH:
MEDLINE In-Process & Other Non-Indexed Citations February 01, 2017
MEDLINE Epub Ahead of Print February 01, 2017
Search Date 2017-02-02

#	Searches	Comments
1	Positron-Emission Tomograph*.ti,ab,kf.	#1 - #9: PET
2	pet scan*.ti,ab,kf.	
3	18?FDG*.ti,ab,kf.	

4	(Fludeoxyglucose adj2 "18").ti,ab,kf.	
5	(Fluorodeoxyglucose adj2 F18).ti,ab,kf.	
6	(18 FDG* adj10 (pet or positron or tomograph* or uptake)).ti,ab,kf.	
7	pet ct.ti,ab,kf.	
8	pet*2ct.ti,ab,kf.	
9	or/1-8	
10	(response* or responder* or nonresponder*).ti,ab,kf.	#10 response
11	9 and 10	#11 PET and response
12	(tumo* or neoplas* or carcino* or cancer* or adenocarcino* or malignan*).ti,ab,kf.	#12 neoplasms
13	11 and 12	#13: PET and response and neoplasms
14	(post* adj6 (treat* or therap* or chemo* or irradiat* or radi*)).ti,ab,kf.	#14 - #21: Time of treatment
15	(posttherap* or posttreat* or postchemo* or postirradiat* or postradi*).ti,ab,kf.	
16	(after* adj6 (treat* or therap* or chemo* or irradiat* or radi*)).ti,ab,kf.	
17	(during adj6 (treat* or therap* or chemo* or irradiat* or radi*)).ti,ab,kf.	
18	(mid adj6 (treat* or therap* or chemo* or irradiat* or radi*)).ti,ab,kf.	
19	(midtherap* or midtreat* or midchemo* or midirradiat* or midradi*).ti,ab,kf.	
20	(interim adj6 (treat* or therap* or chemo* or irradiat* or radi* or pet or positron* or scan*)).ti,ab,kf.	
21	or/14-20	
22	9 and 12 and 21	#22: PET and neoplasms and time of treatment
23	13 or 22	#23 - #27: PET and neoplasms and (response or time of treatment) and year 2015 and englisch
24	"2015".yr.	
25	23 and 24	
26	eng.la.	
27	25 and 26	
28	(animal? or rat or rats or mice or mouse or rabbit? or pig?).ti.	#28 - #29: excluding animals in title
29	27 not 28	
30	(systematic review or meta-analy* or metaanaly*).ti.	#30 - #33: PET and Neoplasms
31	meta-analysis.pt.	
32	30 or 31	

33	29 and 32	and (Response or Time of treatm) and systematic reviews
34	(case reports or comment or editorial or letter or "review").pt. or ((report* adj3 case?) or comment or editorial or letter or review).ti.	#34 - #35: excluding publication types and syst reviews
35	29 not 34 not 33	
36	33 or 35	**#36: Final result:** PET and Neoplasms and (Response or Time of treatm) and (systematic reviews or articles)

Legend:
*, ? = truncation
.ti,ab,kf. = title, abstract, keyword heading word
.ti. = title
.la. = Language
.pt. = publication type
.yr. = publication year
adj*n* = within n words

Web of Science via Thompson Reuters (now Clarivate Analytics):
Science Citation Index Expanded: Timespan=2015
Data last updated: 2017-02-01
Search date 2017-02-02 /searcher Motschall

Search steps from bottom to top:

Set	**Queries in Indexes=SCI-EXPANDED Timespan=2015**	**Comments**
# 33	#32 OR #30	**#33: Final result:** PET and neoplasms and (time of treatment or (response and treatment)) and (articles or syst rev)
# 32	#28 not #30	#31 - #32: PET

	Refined by: DOCUMENT TYPES: (ARTICLE)	and neoplasms and (time of treatment or (response and treatment)) and articles
# 31	#28 not #30	
# 30	#28 and ti=((systematic near/2 review) or metaanaly* or "meta-analy*") **Refined by: DOCUMENT TYPES:** (REVIEW OR ARTICLE)	#29 - #30: PET and neoplasms and (time of treatment or (response and treatment)) and systematic reviews
# 29	#28 and ti=((systematic near/2 review) or metaanaly* or "meta-analy*")	
# 28	(#27) *AND* **LANGUAGE:** (English)	#25 – 28: excluding animals and case reports in title, limit to english
# 27	#24 not #25 not #26	
# 26	ti=((case or cases) near/3 report*)	
# 25	ti=(animal or animals or rat or rats or mouse or mice or rabbit or rabbits or pig or pigs)	
# 24	#23 OR #14	#24: (PET and neoplasms and time of treatment) or (PET and response and neoplasms and treatment)
# 23	#22 AND #11 AND #8	#23: PET and neoplasms and time of treatment
# 22	#21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15	#15 - #22: time of treatment
# 21	ts=(interim near/6 (treat* or therap* or chemo* or irradiat* or radiat* or radio* or pet or positron* or scan*))	
# 20	ts=(after near/6 (treat* or therap* or chemo* or irradiat* or radiat* or radio*))	
# 19	ts=(midtherap* or midtreat* or midchemo* or midirradiat* or midradi*)	
# 18	ts=(mid near/6 (treat* or therap* or chemo* or irradiat* or radiat* or radio* or pet))	
# 17	ts=(posttherap* or posttreat* or postchemo* or postirradiat* or postradi*)	
# 16	ts=(during near/6 (treat* or therap* or chemo* or irradiat* or radiat* or radio*))	
# 15	ts=(post* near/6 (treat* or therap* or chemo* or irradiat* or radiat* or radio*))	
# 14	#13 AND #12	#14: PET and response and neoplasms and treatment
# 13	ts=(treat* or therap* or chemo* or irradiat* or radiat* or radio*)	#13: treatment

# 12	#11 AND #10	#12: PET and response and neoplasms
# 11	ts=(tumo* or neoplas* or carcino* or cancer* or adenocarcino* or malignan*)	#11: neoplasms
# 10	#9 AND #8	#10: PET and response
# 9	ts=(response* or responder* or nonresponder*)	#9: response
# 8	#7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1	#1 - #8: PET
# 7	ts=pet*ct	
# 6	ts="pet ct"	
# 5	ts=("18 FDG*" near/10 (pet or positron or tomograph* or uptake))	
# 4	ts=(Fludeoxyglucose near/2 "18")	
# 3	ts=18*FDG*	
# 2	ts="pet scan*"	
# 1	ts="Positron-Emission Tomograph*"	

Legend:

ts= topic (Title, Abstract, Author Keywords, Keywords Plus®)
* = Truncation
near/n = within n words

Suppl. Table 2. Excluded articles

Article	Reason for exclusion
Boers-Sonderen MJ, Desar IM, Futterer JJ, et al (2015) Biological Effects After Discontinuation of VEGFR Inhibitors in Metastatic Renal Cell Cancer. Anticancer Res 35:5601-5606	No response evaluation
Byrne K, Siva S, Chait L, et al (2015) 15-Year Experience of ^{18}F-FDG PET Imaging in Response Assessment and Restaging After Definitive Treatment of Merkel Cell Carcinoma. J Nucl Med 56:1328-1333	No baseline scan
Calais J, Dubray B, Nkhali L, et al (2015) High FDG uptake areas on pre-radiotherapy PET/CT identify preferential sites of local relapse after chemoradiotherapy for locally advanced oesophageal cancer. Eur J Nucl Med Mol Imaging 42:858-867	No response evaluation (SUVmax threshold identification for target area delineation in RT planning)
Calais J, Thureau S, Dubray B, et al (2015) Areas of high ^{18}F-FDG uptake on preradiotherapy PET/CT identify preferential sites of local relapse after chemoradiotherapy for non-small cell lung cancer. J Nucl Med 56:196-203	No response evaluation (SUVmax threshold identification for target area delineation in RT planning)
Chi MS, Lee CY, Huang SC, et al (2015) Double autophagy modulators reduce 2-deoxyglucose uptake in sarcoma patients. Oncotarget 6:29808-29817	No response evaluation (the study looked at glucose utilization in sarcoma patients)
Cho LP, Kim CK, Viswanathan AN (2015) Pilot study assessing ^{18}F-fluorothymidine PET/CT in cervical and vaginal cancers before and after external beam radiation. Gynecol Oncol Rep 14:34-37	No response evaluation (comparison of FDG and FLT immediately after chemotherapy)
Dercle L, Chisin R, Ammari S, et al (2015) Nonsurgical giant cell tumour of the tendon sheath or of the diffuse type: are MRI or 18F-FDG PET/CT able to provide an accurate prediction of long-term outcome? Eur J Nucl Med Mol Imaging 42:397-408	Not cancer patients
Gungor H, Saleem A, Babar S, et al (2015) Dose-Finding Quantitative 18F-FDG PET Imaging Study with the Oral Pan-AKT Inhibitor GSK2141795 in Patients with Gynecologic Malignancies. J Nucl Med 56:1828-1835	No response evaluation (the study looked at pharmacokinetics)
Hayashi S, Tanaka H, Hoshi H (2015) Imaging characteristics of local recurrences after stereotactic body radiation therapy for stage I non-small cell lung cancer: Evaluation of mass-like fibrosis. Thorac Cancer 6:186-193	No post-baseline scan (follow-up scan only performed in case of suspected relapse of disease; N=20 out of 81)
Huntington SF, Nasta SD, Schuster SJ, Doshi JA, Svoboda J (2015) Utility of interim and end-of-treatment [^{18}F]-fluorodeoxyglucose positron emission tomography-computed tomography in frontline therapy of patients with diffuse large B-cell lymphoma. Leuk Lymphoma 56:2579-2584	No baseline scan
Lee HD, Ahn SG, Lee SA, Lee HM, Jeong J (2015) Prospective evaluation of the feasibility of sentinel lymph node biopsy in breast cancer patients with negative axillary conversion after neoadjuvant chemotherapy. Cancer Research & Treatment 47:26-33	No response evaluation
Ma QJ, Min KY, Wang T, et al (2015) ^{99m}Tc-3PRGD(2) SPECT/CT predicts the outcome of advanced nonsquamous non-small cell lung cancer receiving chemoradiotherapy plus bevacizumab. Ann Nucl Med 29:519-527	Not PET/CT (the study looked at SPECT)
Marcus C, Paidpally V, Antoniou A, Zaheer A, Wahl RL, Subramaniam RM (2015) 18F-FDG PET/CT and lung cancer: value of fourth and subsequent posttherapy follow-up scans for patient management. J Nucl Med 56:204-208	No response evaluation (but patient management; the study looked at the prognostic relevans of 4th and subsequent scan(s))
Moskowitz AJ, Schoder H, Yahalom J, et al (2015) PET-adapted sequential salvage therapy with brentuximab vedotin followed by augmented ifosamide, carboplatin, and etoposide for patients with relapsed and refractory Hodgkin's lymphoma: a non-randomised, open-label, single-centre, phase 2 study. Lancet Oncol 16:284-292	No baseline scan
Nagle SJ, Chong EA, Chekol S, et al (2015) The role of FDG-PET imaging as a prognostic marker of outcome in primary mediastinal B-cell lymphoma.	No baseline scan

Cancer Med 4:7-15	
Ohri N, Duan F, Machtay M, et al (2015) Pretreatment FDG-PET metrics in stage III non-small cell lung cancer: ACRIN 6668/RTOG 0235. J Natl Cancer Inst 107(4)	No response evaluation (pre-treatment scan correlated to outcome)
Pan Y, Brink C, Schytte T, Petersen H, Wu YL, Hansen O (2015) Planned FDG PET-CT Scan in Follow-Up Detects Disease Progression in Patients With Locally Advanced NSCLC Receiving Curative Chemoradiotherapy Earlier Than Standard CT. Medicine (Baltimore) 94:e1863	No baseline scan
Romano A, Parrinello NL, Vetro C, et al (2015) Circulating myeloid-derived suppressor cells correlate with clinical outcome in Hodgkin Lymphoma patients treated up-front with a risk-adapted strategy. Br J Haematol 168:689-700	No baseline scan
Simoncic U, Perlman S, Liu G, Staab MJ, Straus JE, Jeraj R (2015) Comparison of NaF and FDG PET/CT for assessment of treatment response in castration-resistant prostate cancers with osseous metastases. Clin Genitourin Cancer 13:e7-e17	No response evaluation (the study looked at pharmacokinetics)
Siva S, Callahan JW, Kron T, et al (2015) Respiratory-gated (4D) FDG-PET detects tumour and normal lung response after stereotactic radiotherapy for pulmonary metastases. Acta Oncol 54:1105-1112	No response evaluation (correlation of 4D PET and 3D PET as well as normal lung function and dose (dose-response study))
Siva S, Hardcastle N, Kron T, et al (2015) Ventilation/Perfusion Positron Emission Tomography--Based Assessment of Radiation Injury to Lung. Int J Radiat Oncol Biol Phys 93:408-417	Not cancer (ventilation/perfusion PET-based asssessment of lung injuries due to radiation)
van Kruchten M, Glaudemans AW, de Vries EF, Schroder CP, de Vries EG, Hospers GA (2015) Positron emission tomography of tumour [(18)F]fluoroestradiol uptake in patients with acquired hormone-resistant metastatic breast cancer prior to oestradiol therapy. Eur J Nucl Med Mol Imaging 42:1674-1681	No response evaluation (the study looked at FES uptake during treatment)
Wen SW, Everitt SJ, Bedo J, et al (2015) Spleen Volume Variation in Patients with Locally Advanced Non-Small Cell Lung Cancer Receiving Platinum-Based Chemo-Radiotherapy. PLoS ONE 10:e0142608	No response evaluation (the study looked at changes in the size of the spleen during chemotherapy)
Park JH, Lee YK, Kim DH, et al (2015) Usefulness of ^{18}F-fluorodeoxyglucose Positron Emission Tomography-Computed Tomography in Monitoring Adhesive Capsulitis After Breast Cancer Treatment. J Comput Assist Tomogr 39:349-355	Not cancer patients

Suppl. Table 3. Descriptive statistics on additional features in accuracy studies (*n*=49)

Variable	Outcome
Reference standard	Histopathology: *n*=28 (57%)
	CT: *n*=9 (18%)
	MRI: *n*=5 (10%)
	Biomarker: *n*=3 (6%)
	Composite: *n*=3 (6%)
	Endoscopy: *n*=1 (2%)
Scale of reference standard	Categorical: *n*=29 (59%)
	Binary: *n*=20 (41%)
PET used earlier than reference standard	Yes: *n*=24 (49%)
	No: *n*=22 (45%)
	Information missing: *n*=3 (6%)

CT: computed tomography. MRI: magnetic resonance imaging. PET: positron emission tomography.

Suppl. Table 4. Descriptive statistics on additional features in prognostic studies (*n*=76)

Variable	Outcome
Endpoint [a]	Overall survival: *n*=57 (75%) Progression-free survival: *n*=42 (55%) Recurrence-free survival: *n*=16 (21%) Disease-free survival: *n*=5 (7%) Event-free survival: *n*=4 (5%) Distant metastasis: *n*=3 (4%) Local control: *n*=3 (4%) Cancer-specific survival: *n*=2 (3%) Distant metastasis-free survival: *n*=2 (3%) Relapse-free survival: *n*=2 (3%) Disease-control rate: *n*=1 (1%) Local recurrence: *n*=1 (1%) Loco-regional relapse: *n*=1 (1%) Metastasis-free survival: *n*=1 (1%)
Non-response rate (mininum, 10th percentile, 1st quartile, median, 3rd quartile, 90th percentile, maximum)	0%, 12%, 24%, 38%, 63%, 87%, 100%
Information on offered 2nd line therapy	No: *n*=59 (78%) Yes: *n*=17 (22%)

[a]Multiple counting possible due to use of several endpoints in the same study.