Randomized Controlled Trials on PET: A Systematic Review of Topics, Design, and Quality

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Randomized controlled trials (RCTs) add important information to diagnostic accuracy studies in the evaluation of PET and PET/CT. We evaluated how many RCTs on PET existed, which clinical topics they addressed, and what their design and quality were. **Methods:** We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (Clinical Trials) up to August 2010. We also searched in ClinicalTrials.gov and the International Clinical Trials Registry Platform for ongoing RCTs up to March 2011. Titles and abstracts and full texts were screened independently by 2 reviewers. Study characteristics were extracted with standard extraction sheets for ongoing and published RCTs, and risk of bias was assessed for published ones. **Results:** We identified 54 RCTs, 12 of which were published. The main topics in published studies were non–small cell lung cancer and colorectal cancer; only 3 were conducted in nononcologic fields (this trend was similar in ongoing studies, in which the most common topic was Hodgkin disease). The main indications in the oncologic PET studies were staging in published studies and restaging (mostly including an early assessment of treatment response) in ongoing ones. All except 1 of the published studies applied a marker-based strategy design, whereas about 43% (18/42) of ongoing studies use a more efficient design (Enrichment Design or Marker by Treatment Interaction Design). **Conclusion:** A relatively high number of ongoing RCTs of PET in several oncologic fields are expected to produce robust results over the next few years. For nononcologic topics, further high-quality studies are still needed to ascertain the benefit of this technique for patients. As funding is usually difficult in nondrug topics, alternative concepts of funding, which should also involve the manufacturers of diagnostic devices, but also more efficient study designs, should be applied to bridge the evidence gap on PET in the near future.

Key Words: positron-emission tomography; randomized controlled trials; evidence-based medicine; systematic review

Positron emission tomography (PET) or PET/CT is a rapidly evolving technique that enables the imaging of metabolically active tissue, such as many types of cancer (*1*). PET is widely applied because of its expected capacity to detect, describe, and monitor various malignant and benign diseases. Between 2004 and 2008, the annual rates of PET examinations increased by 18% in the United States (*2*). In most European countries, the annual rate of PET examinations is increasing at a similar pace and ranges between 1,000 and 2,000 per 1 million inhabitants (*3*).

According to the principles of evidence-based medicine, evidence from RCTs measuring patient-relevant outcomes (i.e., mortality, morbidity, and quality of life) is required for new diagnostic tests or markers (e.g., for those with higher sensitivity than existing ones) to draw valid conclusions as to their benefit (*4–6*). Studies investigating diagnostic test accuracy alone are unable to prove that patients with the disease of interest who were additionally identified with the new test actually benefit from the detection of the disease (*7,8*). The same applies to test-negative patients additionally identified: here too, it needs to be demonstrated that a reduction in treatment is actually accompanied by an improvement in patient-relevant outcomes. The Grading of Recommendations Assessment, Development and Evaluation working group, therefore, regards test accuracy only as a surrogate for such outcomes (*8*). Thus, the evaluation of a diagnostic intervention is inevitably linked to the evaluation of a therapeutic intervention, and a benefit will be achieved only if both are effective (*9,10*).

In the past, most clinical studies on PET have focused on diagnostic accuracy or changes in management, without bridging the gap to patient-relevant outcomes. There has been some debate in the field of nuclear medicine on whether randomized designs are necessary and possible (*11,12*). It has to be considered that ^{18}F-FDG PET and PET/CT entered clinical practice at the same time as evidence-based medicine and have thus been subjected to closer scrutiny than older technologies. Meanwhile, more RCTs on PET measuring patient-relevant outcomes have been published (*13–15*), and clinical guidelines and funding agencies call for evidence from RCTs to make positive recommendations or reimbursement decisions (*1,5,16*). These developments

indicate that the future use of PET will heavily depend on the availability of evidence from RCTs. Therefore, it seems important to overcome reservations concerning the conduct of such studies and to improve their design.

The aim of the present review was to systematically identify RCTs on PET measuring patient-relevant outcomes in any medical indication to outline both the main fields and any gaps in research and to summarize features of study design and quality. Furthermore, it was to be assessed whether it was feasible to conduct RCTs to demonstrate a patient-relevant benefit of PET.

MATERIALS AND METHODS

Study Inclusion Criteria

We included both published and unpublished studies comparing PET or PET/CT with standard diagnostic technologies or clinical examinations in patients with any medical condition. Eligible studies were those that used a randomized controlled design. We applied no restrictions on language or time of publication or on the type of PET tracer used.

Randomized Designs for Diagnostic Tests or Markers

Three major types of randomized designs for proving the benefit of diagnostic tests and markers are discussed in the methodologic literature (6,17,18). In their seminal paper, Sargent et al. (17) proposed to distinguish among the following 3 different designs: marker-based strategy, enrichment, and marker by treatment interaction.

Marker-Based Strategy Design. In the marker-based strategy design, patients are randomized to a group applying the new marker (or diagnostic technology) and a group not applying it (i.e., relying on the old diagnostic strategy for selecting treatment). Similar to drug studies, the new technology should result in better patient-relevant outcomes than the old one.

Enrichment Design. In the enrichment design, the marker (or diagnostic technology) is used to enrich the sample before randomization. For instance, in the ongoing PETAL (Positron Emission Tomography Guided Therapy of Aggressive Non-Hodgkin's Lymphomas) study (19), only those patients with aggressive non-Hodgkin lymphoma who have a positive PET scan after 2 cycles of the standard therapy R-CHOP (rituximab–cyclophosphamide, doxorubicin, vincristine, and prednisone) are being randomized to receive either a further 6 cycles of R-CHOP or 6 blocks of the more aggressive B-ALL protocol (rituximab, methotrexate, ifosfamide, etoposide, cytarabine, vincristine, cyclophosphamide, doxorubicin, vindesine, and dexamethasone) (19). If studies using this design find a difference in patient-relevant outcomes, a PET-guided therapy plan will have proven to be beneficial. The same technique can be applied to identify test-negative patients in the sample who can then be randomized into 2 different treatment groups (e.g., one with a deescalating treatment strategy, "derichment" design) (20). An enrichment design requires strong arguments against the existence of a marker-by-treatment interaction.

Marker-by-Treatment-Interaction Design. The marker-by-treatment-interaction design is similar to an RCT on a new drug or any kind of intervention. Patients are randomized to receive either the new drug or the conventional treatment (or a placebo). The diagnostic test is performed before the randomization and should ideally be kept masked. This test is then used to prove whether treatment is particularly effective, or not effective at all, for given (ideally prespecified) subgroups (21). To prove the benefit of the diagnostic test, a qualitative or a strong quantitative interaction between the result of the test (or marker) and the effect of the therapy should be demonstrated in the study (Fig. 1).

Search Strategy and Study Selection

We searched for relevant primary studies in MEDLINE (Ovid, 1966 to August 2010), Pubmed (NLM, specific search for nonindexed references), EMBASE (Ovid, 1980 to August 2010), and the Cochrane Central Register of Controlled Trials (Clinical Trials–Wiley, to August 2010). The search strategy in MEDLINE is described in detail in Table 1. To identify further studies, we also searched reference lists in secondary publications (systematic reviews and health technology assessment reports) identified within the framework of a series of reports on PET prepared by our institute in the last 3 y. In addition, we searched ClinicalTrials.gov and the International Clinical Trials Registry Platform search portal for completed and ongoing RCTs up to March 2011.

Assessment of Primary Studies

Two reviewers independently screened titles and abstracts of the retrieved citations to identify potentially eligible primary and secondary publications. The full texts of these articles were obtained and evaluated independently by 2 reviewers. Primary publications were identified, and subsequently the full set of inclusion and exclusion criteria was applied to identify eligible studies. All documents retrieved from nonbibliographic sources were also screened for eligibility or relevant information on studies. Disagreements were resolved by a third reviewer.

Data Extraction

From each included study, information was extracted on study characteristics, including country, period of recruitment, aim, length of follow-up, sample size, diseases, and indication; characteristics of the study participants; and characteristics of the test and control interventions and indication for the use of PET within the treatment plan. From completed and published studies, information on risk-of-bias items was also extracted. Details of the studies were extracted using standardized tables developed and routinely used by our institute.

Information and data from publications were supplemented by publicly available reports from study registries. The consistency was assessed between the data reported in publications and those reported in additional sources such as study registries.

The individual steps of the data extraction and risk-of-bias assessment procedures were always conducted by one person and checked by another; disagreements were resolved by consensus. The risk of bias in individual studies was assessed by determining the adequacy of the following quality criteria: randomization and allocation concealment, masking of patients, investigators and outcome assessors, handling and reporting of study discontinuations, and application of the intention-to-treat (ITT) principle. Studies for which it was likely that correcting for methodologic problems would have altered the main results and conclusions were classified as having a high risk of bias.

RESULTS

The search in bibliographic databases yielded a total of 3,118 references (after exclusion of duplicates), from which
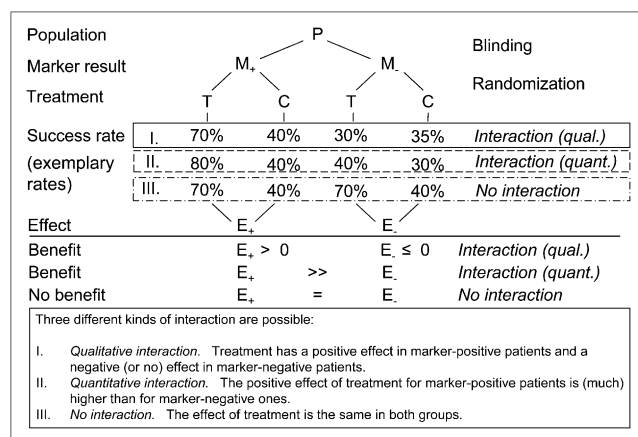
FIGURE 1. Framework for marker-by-treatment-interaction study design. P = population; M_+ = marker-positive; M_- = marker-negative; T = treatment; C = control; E_+ = treatment effect in marker-positive; E_- = treatment effect in marker-negative; qual. = qualitative; quant. = quantitative.

12 eligible completed and published studies (21 publications) were identified (Fig. 2).

In addition, of 200 unique entries in study registries, 42 eligible but ongoing studies and 2 completed studies already detected in the bibliographic search were identified. In total, 54 ongoing or completed RCTs were found.

Description of Completed and Published Studies

Tables 2 and 3 show the main characteristics of the 12 studies considered. The studies included a total of 1,242 patients (range, 6–232), with ages ranging from 30 to 67 y. In the 10 studies providing data on sex, 32.4% of the participants were women.

Most of the included studies investigated PET in non–small cell lung cancer (NSCLC; 5/12 studies), followed by colorectal cancer and coronary heart disease (2 each). Nine studies were conducted in oncology (7 of these in staging, 1 in restaging, and 1 in diagnosing recurrent disease), 2 in coronary heart disease, and 1 in tinnitus. Four studies (25%) applied an integrated PET/CT device. Four were conducted in The Netherlands and 2 in Canada. The other countries (Denmark, Italy, Australia, France, Taiwan, and Germany) accounted for 1 study each. Recruitment for the earliest study started in 1998; recruitment periods ranged from 1 to 5 y. One study was closed earlier because of insufficient recruitment and a change in diagnostic technology. Eleven studies applied a marker-based strategy design (one of which was a crossover design) and one an enrichment design. No study using a marker-by-treatment-interaction design was identified.

Two of the 12 published studies had been registered (13,14). Eleven studies were publicly funded, and 1 study was partly financed by a grant from a company producing PET tracers.

According to the authors' conclusions, the results of 4 of the 12 studies were positive, 7 studies were negative, and 1 showed mixed findings (Table 3) .

Risk of Bias

Half of the studies (6/12) showed a low risk of bias (Table 4). Information on allocation concealment was provided in 6 studies. Masking was incomplete in 3 studies. In 10 studies, a sample size calculation was published, and in 11 an ITT analysis was performed. All studies used predefined patient-relevant outcomes. However, in 1 study the primary outcome in the publication had been changed, compared with the primary outcome defined in the registry (13).

Description of Ongoing or Unpublished Studies

Our search in study registries identified 42 ongoing RCTs (Table 5; we also identified the 2 registered published studies, which are not listed here). Most of them refer to Hodgkin disease (11), followed by NSCLC (7), colorectal cancer (5), cervical cancer (3), and head and neck cancer (3). Only 2 studies are investigating nononcology topics (dementia and major depressive disorder). The restaging of cancer is the most frequent indication (19 studies; 11 of which are investigating early assessment of treatment response), followed by staging (7) and planning of radiotherapy (7). The estimated sample sizes range from 30 to 1,600 (median, 300). More than half of the studies apply a marker-based strategy design (24/42), 9 a marker-by-treatment-interaction design, and 9 an enrichment design. Most of the ongoing studies are being conducted in the United States (8), followed by the United Kingdom and France (6 each), Germany (5), and Canada (4). According to the registry data, 6 of these studies should have been completed in 2011, 5 will be completed in 2012, and 6 in 2013.

DISCUSSION

Our systematic review of RCTs on PET and PET/CT identified 12 published and 42 ongoing studies, indicating an increasing number of RCTs in this field. The main fields of research are NSCLC, Hodgkin disease, and colorectal cancer, with only a few studies conducted in nononcologic fields. Half of the published studies showed a low risk of bias.

The aim of this review was to systematically identify and descriptively evaluate the study design and other characteristics of published and ongoing RCTs on PET. It was not the aim to synthesize the results of these studies. For most of the diseases (and indications within diseases), only 1 published RCT was identified, often with a high risk of bias. At this stage, it seems to be too early to draw general conclusions on the clinical benefit of this technology. It is hoped that the current intense research activities identified in our searches for ongoing trials will continue in the next few years. If at least 2 high-quality RCTs with adequate numbers of patients were available in an indication, it would allow robust recommendations on the use of PET in the clinical setting investigated. This may soon be achieved in some indications. For example, 5 RCTs on the staging of NSCLC have already been published, and our group is currently conducting a metaanalysis of these studies.

TABLE 1
MEDLINE (Ovid) Search Strategy for RCTs
(1950 to August 2010)

No.	Searches	Results
1	positron emission tomography	16,699
2	(pet or petscan* or positron).ab,ti.	47,103
3	((pet* or tracer*) and (deoxy* or de oxy* or fluor* or fdg* or amino*)).ab,ti.	24,966
4	or/1–3	60,174
5	randomized controlled trial.pt.	297,967
6	(randomized or randomised).ab,ti.	270,389
7	or/5–6	405,562
8	and/4,7	1,046

This review has certain limitations. As we searched only bibliographic databases and trial registries, additional RCTs may have been missed. Further studies might have been identified by systematically searching conference proceedings or by additional hand searches. However, we previously searched conference proceedings within the framework of 7 ongoing reports on PET in different indications and were unable to identify any additional studies in these sources.

To manage the vast amount of literature in this field (60,000 hits without the use of a filter), we applied a filter for RCTs in our searches. Our filter was based on the one developed by Wong et al. (22), which was expanded by a search for the word randomized (or randomised) in the title or abstract. The filter by Wong reached a sensitivity of 93%. Our filter should be even more sensitive. Additionally, searches in ClinicalTrials.gov should have identified more relevant papers. We cannot exclude that relevant RCTs might have been missed with this strategy. However, in our institute's ongoing PET reports we have used search strategies without this filter for specific diseases; so far, we have not found an RCT that was missed by applying the filter.
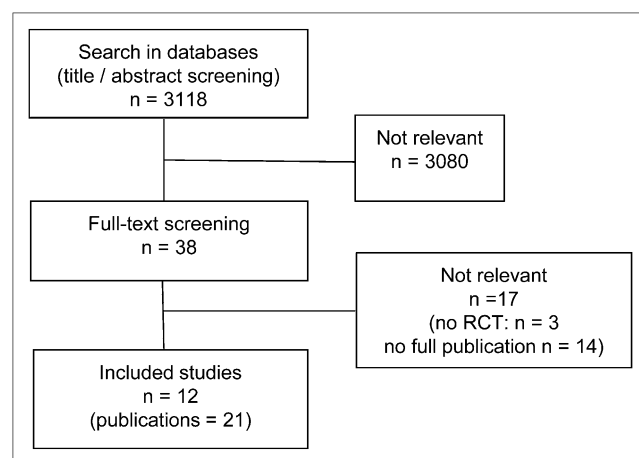

FIGURE 2. Flowchart of study selection (bibliographic search).

Furthermore, the results for ongoing and unpublished studies with a marker-by-treatment-interaction design are somewhat hypothetical. On the basis of registry data, it is difficult to determine whether an interaction is going to be calculated between the PET result and the effect of therapy. Some of the identified studies will probably not calculate such interactions. However, it is also possible that studies applying PET as a predictive marker were not identified, because its use was not documented in the registries.

The results of this review show that the calls in the methodologic literature for RCTs to evaluate the benefit of diagnostic technologies such as PET are not too ambitious and that this type of design is feasible (6,11,16,17). Considering the number of published RCTs on PET, but also the fact that in future approximately 5–7 such RCTs will be published annually, this design could add important information on the patient-relevant benefit of PET to the knowledge on diagnostic and prognostic accuracy.

Depending on the clinical question, disease characteristics (e.g., incidence), and practical and ethical considerations, different RCT designs can be applied (6,17).

Most of the published trials applied a marker-based strategy design and only one an enrichment design. The latter is more efficient, because a smaller number of patients is needed to show a significant difference between the intervention (PET-guided therapy) and the control group (standard therapy). Interestingly, the marker-by-treatment-interaction design has not been identified so far in the published literature on PET. At the moment, we can only speculate on the reasons. For example, this approach might be unfamiliar to researchers in this field, interaction difficulties between different medical professions (e.g., oncologists and radiologists) might exist, or industry might not be interested in evaluating tests that might considerably reduce the number of eligible patients. However, this design seems to be increasingly applied in ongoing trials. It offers a highly valid but at the same time pragmatic solution to the evaluation of diagnostic tests. Because it is at least as valid as the 2 other randomized designs for evaluating the benefit of PET, it might offer an efficient alternative. For example, this design, which has been applied successfully in studies on genetic markers, can be applied as a piggyback strategy within any RCT for new drugs or other treatment interventions. The additional effort required for such a study involves the conduct of the PET examinations, the interpretation of the images, and the statistical analyses. In this context, it should be noted that health care professionals involved in the medical treatment of patients undergoing PET should ideally be masked to the test results. A limitation of the marker-by-treatment-interaction design is that it can be applied only to certain clinical questions. If, for instance, PET is used for radiation planning, the result of the test is necessary for the intervention: in this case, the radiation

TABLE 2
Characteristics of Published Studies I (*n* = 12)

Study	Country	Disease	Indication	No. of patients randomized/ analyzed	Period of recruitment	Mean follow-up (mo)
Beanlands et al. 2007 (PARR-2) (*23,24*)	Canada	Coronary heart disease	Detection of viable myocardium	PET: 218/218	06/2000– 09/2004	12
				CG: 212/212		
Fisher et al. 2009 (*25*)	Denmark	NSCLC	Staging (preoperative)	PET/CT: 98/98	01/2002– 02/2007	27
				CG: 91/91		
Herder et al. 2006 (*26*)	The Netherlands	NSCLC	Staging	PET: 232/232	09/1999– 06/2001	12
				CG: 233/233		
Maziak et al. 2009 (*14*)	Canada	NSCLC	Staging	PET/CT: 170/167	06/2004– 08/2007	CG: 22.5
				CG: 167/162		PET/CT: 21.8
Picardi et al. 2007 (*20*)	Italy	Hodgkin lymphoma	Restaging	No radiation: 80/80	No information	40
				Radiation: 80/80		
Plewnia et al. 2007 (*27*)	Germany	Chronic tinnitus	Localization	Crossover study	No information	<1
				6/6		
Ruers et al. 2009 (*13*)	The Netherlands	Recurrent colorectal cancer	Staging	PET/CT: 75/75	05/2002– 02/2006	36
				CG: 75/75		
Siebelink et al. 2001 (*28*)	The Netherlands	Coronary heart disease	Diagnosis	PET: 49/49	No information	PET: 28
				CG: 54/54		CG: 29
Sobhani et al. 2008 (*29*)	France	Colorectal cancer	Diagnosis of recurrence	PET: 65/65	01/2001– 06/2004	24
				CG: 65/65		
van Tinteren et al. 2002 (PLUS) (*30,31*)	The Netherlands	NSCLC	Staging (primary)	PET: 92/92	01/1998– 01/1999	12
				CG: 96/96		
Tsai et al. 2010 (*32*)	Taiwan	Cervical cancer	Staging (diagnosis lof metastases)	PET: 66/66	01/2002– 04/2006	53
				CG: 65/65		
Viney et al. 2004 (*33*)	Australia	NSCLC	Staging	PET: 91/91	04/1999– 12/2000	12
				CG: 92/92		

CG = control group.

target region found with PET is different from that found with, for example, CT. Because the PET result is part of the intervention, no interaction can be calculated.

Our review shows that it is important to precisely describe the clinical indication for the use of PET, because in most studies it was unclear whether PET was tested as an additional or alternative diagnostic device. In addition, because patients included in the studies were rarely described exactly, the transferability of existing study results seems to be questionable. A detailed description of the test (tracer, time of fasting, stage of disease, and so on) and the algorithm for defining cutoff points, especially if

the PET results are being interpreted qualitatively (e.g., reporting of the number and qualification of radiologists involved and handling of interrater disagreement), are further important points to consider in future studies. Only a few of the published studies reported unclear or equivocal PET or PET/CT results and how they were interpreted.

Our results indicate that ongoing and unpublished studies have on average (~3 times) higher estimated patient numbers than published studies. These adjusted sample sizes, which will have greater statistical power to detect smaller effects, might be a consequence of the nonsignificant results of some

TABLE 3
Characteristics and Results of Published Studies II (*n* = 12)

Study	Mean age PET/CG*	Sex m/w	Intervention	Control group	Study design	Primary outcome	Results*
Beanlands et al. 2007 (PARR-2) (*23,24*)	63/62	PET: 184/34	PET	Standard care	MBSD	Composite cardiovascular outcome†	Negative
		CG: 179/33					
Fisher et al. 2009 (*25*)	63/64	PET: 53/45	PET/CT	CWU	MBSD	Number of futile thoracotomies	Positive
		CG: 49/42					
Herder et al. 2006 (*26*)	63/65	PET: 158/74	PET	CWU	MBSD	Number of tests and procedures to finalize staging and to define operability	Negative
		CG: 155/78					
Maziak et al. 2009 (*14*)	67/66	PET: 83/87	PET/CT	CWU	MBSD	Correct upstaging of cancer, avoiding stage-inappropriate surgery	Positive and negative
		CG: 83/84					
Picardi et al. 2007 (*20*)	30/31‡	Radiation: 45/35	Additional radiotherapy PET-positives only	Additional radiotherapy for all patients	Enrichment	Event-free survival	Negative
		CG: 44/36					
Plewnia et al. 2007 (*27*)	58	PET: 5/1	PET/rTMS	Sham stimulation	MBSD	Reduction of symptoms (tinnitus questionnaire)	Positive
		CG: 5/1					
Ruers et al. 2009 (*13*)	62.6/62.9	PET: 48/27	PET/CT	CT	MBSD	Number of futile laparotomies§	Positive
		CG: 56/19					
Siebelink et al. 2001 (*28*)	62 ± 2/63 ± 1	PET: 40/9	PET	SPECT	MBSD	Cardiac event-free survival	Negative
		CG: 49/5					
Sobhani et al. 2008 (*29*)	58.1/62.0	No information	PET	Conventional follow-up	MBSD	Recurrence after 9 and 15 mo; OS	Negative
van Tinteren et al. 2002 (PLUS) (*30,31*),	66/65	PET: 69/23	PET + CWU	CWU	MBSD	Number of futile thoracotomies	Positive
		CG: 75/21					
Tsai et al. 2010 (*32*)	53.4 ± 11.9	No information	PET-guided radiotherapy	Standard radiotherapy	MBSD	Disease-free-survival and OS at 2 y after treatment	Negative
Viney et al. 2004 (*33*)	66/68	PET:66/25	PET	CWU	MBSD	Number of thoracotomies	Negative
		CG: 68/24					

*Results according to authors' conclusions.

†CCO = Composite cardiovascular outcome at 1 y: cardiac death, myocardial infarction, transplantation, or rehospitalization for unstable angina or heart failure.

‡Median age.

§Primary outcome in study protocol: disease-free survival (9 mo) and economic evaluation (9 mo); primary outcome in publication: number of futile laparotomies.

MBSD = marker-based strategy design; CG = control group; CWU = conventional work-up; rMTS = repetitive transcranial magnetic stimulation; OS = overall survival.

of the published studies. Another explanation could be the noninferiority design of studies investigating the superiority of PET-induced changes in management and concurrent non-inferiority for other patient-relevant outcomes such as mortality; this type of design usually requires a higher number of patients.

TABLE 4
Risk of Bias in Published Studies

Trial	Description of randomization process	Allocation concealment	Masking	Sample size estimation	Analysis method	Dropouts described	Predefined patient-relevant outcome (defined in trial registry)	Risk of bias
Beanlands et al. 2007	Yes	Yes	Partially*	Yes	ITT	Yes	Yes (yes)	Low
Fischer et al. 2009	Yes	No	Unclear	Unclear	ITT	Yes	Yes (unclear)	High
Herder et al. 2006	Yes	Yes	Unclear	Yes†	ITT	Yes	Yes (unclear)	Low
Maziak et al. 2009	Yes	Yes	Unclear	Yes	PP	Yes	Yes (yes)	Low
Picardi et al. 2007	Unclear	Unclear	Unclear	Yes	ITT	Yes	Yes (unclear)	High
Plewnia et al. 2007	Unclear	Unclear	Unclear	Unclear	ITT	No dropouts	Yes (no)	High
Ruers et al. 2009	Yes	Yes	Unclear	Yes	ITT	No dropouts	No (no)‡	High
Siebelink et al. 2010	Yes	Unclear	Partially§	Yes	ITT	No dropouts	Yes (unclear)	Low
Sobhani et al. 2008	Unclear	Unclear	No	Yes	ITT/PP	No dropouts	Yes (unclear)	High
VanTinteren et al. 2002	Yes	Yes	Unclear	Yes	ITT	No dropouts	Yes (yes)	Low
Tsai et al. 2010	Unclear	Unclear	No	Yes	ITT	Early closure‖	Yes (yes)	High
Viney et al. 2004	Yes	Yes	Partially¶	Yes	ITT	Yes	Yes (?)	Low

*Events were reviewed and verified by adjudication committee masked to results of ^{18}F-FDG PET scan.

†In earlier observational study in 2 participating hospitals, at least 3 (mean ± SD, 3.2 ± 1.6) diagnostic procedures in half of patients were performed in addition to bronchoscopy, chest radiography, laboratory, lung function and cardiovascular tests, and thoracotomy. Here, we considered PET up-front strategy clinically useful if a proportion of patients needing at least 3 tests was reduced from 50% to 30%. Furthermore, we anticipated inclusion of 30% of patients with other histologies (e.g., small cell lung cancer, benign lung diseases) in which PET might have a different impact. Therefore, to assess impact in patient sample of interest with sufficient reliability, its size was increased by 30% to total of 465.

‡Primary outcomes in study protocol were defined as disease-free survival (9 mo) and economic evaluation (9 mo). Primary outcome in publication was number of futile laparotomies.

§Radiologists were not masked. Uniformly masked polar map of heart was used to mask treating physicians. Patients' masking was unclear.

‖Because of change of equipment and fact that patients declined randomization, study was closed early.

¶In the case of postsurgical pathology, independent review was undertaken masked to randomization.

Because RCTs are not yet mandatory for the approval of nondrug interventions, funding is usually difficult. Only one of the published RCTs identified was (in part) funded by the manufacturer of the diagnostic device. Alternative concepts of funding, which should also involve the manufacturers, and more efficient study designs should be applied to bridge this evidence gap in the near future.

CONCLUSION

In addition to diagnostic and prognostic accuracy studies, RCTs on PET should be conducted to prove the benefit of this technology in terms of patient-relevant outcomes. Although 12 RCTs have already been published and about 5 will be published per year in the future, more high-quality studies are needed to ascertain the benefit of this technology for patients.

TABLE 5
Characteristics of Ongoing and Unpublished Studies ($n = 42$)

Register ID	Acronym	Medical condition	Indication	Design	Estimated enrolment	Primary outcome	Estimated study completion date (first enrollment)	Country
ACTRN 1260900066 5235	OES2008	Adenocarcinoma of the esophagus or gastroesophageal junction, invasive	Restaging (interim response assessment)	Enrichment	150	Histologic response	(July 2009)	Aus
NCT00146458		Cervical cancer, advanced	Staging	MBSD	200	DFS, OS	December 2007	Taiwan
NCT00895349	PET LACE Trial	Cervical cancer, locally advanced	Staging	MBSD	288	Change in management	October 2017	Can
NCT01075412		Cervical cancer, uterine cervical neoplasms	Radiotherapy planning	MBSD	30	3'-deoxy-3'-18F-fluorothymidine uptake	September 2013	U.S.A.
NCT00823810	RESCORE	Colorectal cancer, advanced	Restaging	MBSD	150	OS	February 2011	Fin
NCT00265356	PETCAM	Colorectal cancer, liver Metastases	Staging	MBSD	404	Change in management	April 2010/2015	Can
ISRCTN97323814	TRAVASTIN-1	Colorectal cancer, metastatic	Stratification	Interaction	25	PFS	(November 2009)	U.K.
NCT00199654		Colorectal cancer, stage II and III	Follow-up	MBSD	376	Time to relapse	(February 2004)	F
NCT00624260	ITEP	Colorectal cancer, stage III and IV	Follow-up	MBSD	240	Decrease of noncurative recurrences	December 2013	F
NCT00329706	MCI-ID	Dementia	Primary diagnosis	MBSD	710	Cognitive function	January 2016	U.S.A.
NCT00367341		Depressive disorder, major	Stratification	Interaction	100	Remission	June 2010	U.S.A.
DRKS00000633	GLIAA-Pilot	GBM, recurrent	Radiotherapy planning	MBSD	30	AA-PET/MRI nonoverlap	(December 2010)	Ger
NCT00500188		GIST	Stratification	Interaction	48	DFS	July 2011	U.S.A.
NCT00784537	HD0801	HD	Restaging (interim response assessment)	Enrichment	300	PFS	December 2014	I
NCT00736320	HD 16	HD	Restaging (interim response assessment)	MBSD	1,100	PFS	November 2013	Ger
NCT00795613	HD0607	HD, advanced	Restaging (interim response assessment)	Enrichment	450	PFS	July 2012/2015	I
NCT00515554	HD18	HD, advanced stages	Restaging (interim response assessment)	Enrichment	1,500	PFS	May 2012	Ger
NCT01092182		HD, Burkitt lymphoma/leukemia (BL)	Stratification	Interaction	73	PFS, EFS and OS	March 2018	U.S.A.
NCT00169598	TEPELY	HD, NHD	Restaging	MBSD	80	Change in management	(February 2002)	F
NCT00433433	EORTC-GELA-IIL	HD, stage I and II	Restaging (interim response assessment)	MBSD	1,600	PFS	(October 2006)	NL

TABLE 5 (Continued)

Register ID	Acronym	Medical condition	Indication	Design	Estimated enrolment	Primary outcome	Estimated study completion date (first enrollment)	Country
NCT00943423	RAPID	HD, stage Ia and IIa	Restaging (interim response assessment)	Enrichment	400	PFS	December 2009	U.K.
ISRCTN99811594	18F-FDG PET	HD, stage Ia to IIa	Restaging	Enrichment	400	PFS	(October 2003)	U.K.
NCT00678327	U.K. NCRI Lymphoma Group	HD, stage II - intravenous	Restaging	MBSD	1,200	PFS	September 2012	U.K.
ACTRN 1260800063932 5	HD0607	HD, stage IIb to IVb	Restaging (interim response assessment)	Enrichment	450	PFS	(June 2008)	I
NCT00554164	PETAL	NHD, aggressive	Restaging (interim response assessment)	Enrichment	696	Time to treatment failure	December 2014	Ger
NCT01285765		NHD, DLBCL with low risk	Restaging (interim response assessment)	Enrichment*	420	PFS	January 2017	F
NCT01287390		HNC	Radiotherapy planning	MBSD	100	Treatment-induced dysphagia	December 2015	Be
NCT00720070		HNC	Restaging	MBSD	560	OS	Aug 2012	U.K.
ISRCTN13735240	PET-NECK	HNC, locally advanced	Staging	MBSD	560	OS	(April 2007)	U.K.
ISRCTN49573946	BOOST	Lung cancer	Staging	MBSD	168	Time to treatment decision	(April 2008)	U.K.
NCT00199615		NSCLC	Follow-up	MBSD	73	DFS	December 2006	F
NCT00697333	PET-Plan	NSCLC, advanced	Radiotherapy planning	MBSD	394	Local PFS	February 2013	Ger
NCT01170923		NSCLC, advanced	Restaging (interim response assessment)	MBSD	100	Response rate	August 2010	South Korea
NCT00840749	STARS	NSCLC, stage I	Radiotherapy planning (CyberKnife; Accuray Inc.)	Interaction	1,030	OS	December 2013	U.S.A.
NCT01024829	BTV Boost	NSCLC, stage II and III	Radiotherapy planning	MBSD	106	Local PFS	August 2013	NL
NCT00533949		NSCLC, stage III	Radiochemotherapy planning	Interaction	500	OS	January 2014	U.S.A.
NCT00136864	PET-START	NSCLC, stage III	Staging	MBSD	400	Upstaging by PET	May 2011	Can
NCT01050426	PERU	Pancreatic cancer, locally advanced	Stratification	Interaction	90	OS	September 2015	U.K.
NCT00313560		Pancreatic cancer, stage I or II	Stratification	Interaction	60	Pharmacodynamics	December 2008	Aus
ACTRN 1260800064139 2		Prostate cancer	Staging and restaging	MBSD	100	Change in management	(December 2008)	Aus
NCT00964275		Thromboembolism, unspecified adult solid tumor	Primary diagnosis	MBSD	310	Number of cancers diagnosed	March 2011	F
NCT01240590		Thyroid cancer, anaplastic	Stratification	Interaction	70	Dose-limiting toxicity	September 2012	U.S.A.

*This study applied noninferiority design.

Aus = Australia; MBSD = marker-based strategy design; DFS = disease-free survival; OS = overall survival; Can = Canada; Fin = Finland; PFS = progression-free survival; U.K. = United Kingdom; F= France; GBM = glioblastoma multiforme; AA = amino-acid; Ger = Germany; GIST = gastrointestinal stromal tumor; HD = Hodgkin disease; I = Italy; EFS = event-free survival; NHD = non-Hodgkin disease; NL = Netherlands; DLBCL = diffuse large B-cells non-Hodgkin lymphoma; HNC = head and neck cancer; Be = Belgium.

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