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**Positron emission  
tomography (PET and  
PET/CT) in malignant  
lymphoma<sup>1</sup>**

**Executive Summary**

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<sup>1</sup> Translation of the executive summary of the final report “Positronenemissionstomographie (PET und PET/CT) bei malignen Lymphomen” (Version 1.0; Status: 31.03.2009). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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# **Positron emission tomography (PET and PET/CT) in malignant lymphoma**

## **Executive summary**

### **Research question**

This investigation had 2 aims

#### *1 Determining the patient-relevant benefit of PET and/or PET/CT*

This was primarily concerned with describing the patient-relevant benefit that doctors and patients can expect from imaging procedures using PET or PET/CT in malignant lymphoma. Its use was considered in the following indications:

- a) Determination of the tumour stage (staging),
- b) Treatment response of lymphoma (residual disease evaluation/restaging), and
- c) Evidence of recurrence in the case of justified suspicion

“Benefit” was understood here to mean changes that have perceptible consequences for the patient, such as the effect on mortality and morbidity, the optimum choice of treatment options available with more or less toxic side effects, the general clinical management of the patient and changes in quality of life.

#### *2 Assessing the diagnostic and prognostic accuracy of PET or PET/CT*

Due to the lack of valid primary trials on determining patient-relevant benefit (first aim), a systematic assessment of the diagnostic and prognostic accuracy of PET or PET/CT was also carried out (second aim). This was primarily concerned with finding out to what extent PET or PET/CT is superior to the standard diagnostic procedure without PET. In other words: Does the use of PET or PET/CT offer an improvement in accurate staging along with the various prognostic consequences, in the accurate recognition of patients with or without residual tumours after treatment is finished, or in the correct diagnosis or correct exclusion of recurrences? In a similar vein, does the use of PET or PET/CT enable more reliable prognostic statements to be made concerning a recurrence than was possible with existing standard diagnostic procedures?

### **Methods**

(Randomized) controlled comparative trials (strategy with vs. without PET) with patient-relevant outcomes (e.g. reduced mortality/morbidity) were used in the benefit assessment,

while systematic reviews and prospective cohort and cross-sectional studies were used for evaluating the test accuracy.

The second research question was addressed by a “review of reviews”. This was supplemented by an additional search for primary trials (2005 to 2008) whose search period overlapped with that of the HTA reports and systematic reviews (update of existing systematic reviews).

## **Results**

A comprehensive systematic search in bibliographic databases and other sources only produced one comparative trial on benefit assessment. HTA registries and websites of international HTA organizations were also systematically searched for the assessment of diagnostic accuracy. The inclusion criteria of the report were met by 11 HTA reports, systematic reviews and meta-analyses with a total of 100 primary trials. The question of staging was addressed by 7 evidence syntheses, the question of therapy response during and after treatment in addition to prognostic statements was addressed by 8 evidence syntheses. None of the evidence syntheses evaluated recurrence recognition. The update search for primary studies did not produce any primary trials for the assessment of recurrence recognition either.

### *Proof of patient-relevant benefit from PET*

The only comparative trial on benefit assessment investigated the “recurrence-free” outcome with and without consolidation radiation therapy in 160 patients with Hodgkin’s disease, residual tissue in the CT after chemotherapy and a negative PET finding. It showed that radiation therapy possessed a treatment advantage. However, due to methodological weaknesses, the low number of patients and few results, the validity of this trial is considerably limited.

### *Diagnostic accuracy of PET for staging*

In the studies included on diagnostic procedures, the evidence syntheses show low numbers of patients and considerable methodological weaknesses in planning and conducting the trials (incorporation bias, follow-up periods too short, etc.), which considerably limit the validity of the results found. Overall, the data were heterogeneous and inconsistent. Owing to the lack of a valid reference standard, the trials on primary staging were additionally impaired in the comparative assessment with conventional diagnostic procedures. Overall, in the combined assessment of staging and restaging, PET showed high diagnostic accuracy, which tended to be superior to that of CT, the most frequently used comparator technology, and to that of gallium scintigraphy on its own. In a few, exclusively retrospective studies, PET/CT provided indications of greater diagnostic accuracy than CT or PET on their own. In view of the inherent methodological problems, no reliable conclusion can be drawn concerning the

advantage of PET and PET/CT compared to conventional staging procedures for initial staging and for restaging.

#### *Diagnostic and prognostic accuracy of interim PET*

The update search identified 6 primary trials of average quality on diagnostic and prognostic accuracy of interim PET. The interim PET demonstrated its ability to differentiate between responders and non-responders after only a few chemotherapy cycles. Discriminatory power was greater with PET than with gallium scintigraphy. Whether a risk-adapted therapy can translate the observed discriminatory power into a therapeutic benefit for patients was not investigated in the trials, but is the subject of several planned and ongoing trials.

#### *Diagnostic and prognostic accuracy of PET for restaging*

With regard to the diagnostic trials on tumour response following therapy, on evaluating the residual tissue in the CT and on prognostic statements, PET appears to be superior to gallium scintigraphy and even more so to CT. However, the same methodological limitations apply as for the other diagnostic trials. The consequences for patient-relevant benefit are currently being investigated in randomized and non-randomized prospective trials, while further prospective trials are at the planning stage. In the foreseeable future, it will be possible to better evaluate the value of PET in lymphoma therapy for different patient groups.

#### *Diagnostic accuracy of PET for identifying recurrences*

In the case of suspected recurrences, no trials could be found on the assessment of PET that matched the inclusion criteria. In one single small trial with partially retrospective data, there were identical results for PET and CT.

### **Conclusions**

The value of PET for routine primary staging has not been resolved by trials up till now. The application of PET for the assessment of therapy response both in interim staging and when used between 2 treatment modalities is the subject of numerous current studies. Interim PET demonstrated its ability to differentiate between responders and non-responders after only a few cycles of chemotherapy. The discriminatory power with PET was greater than with gallium scintigraphy. Whether the observed discriminatory power can be translated into a patient-relevant benefit (reduction in toxicity, improvement in progression-free survival or total survival) using risk-adapted therapy is currently the subject of several randomized trials with various lymphoma entities and disease stages. The role of PET for diagnosing recurrence is unclear due to the absence of relevant trials.

Due to the lack of a valid reference standard, the value of PET compared to conventional imaging procedures can only be defined for all research questions in this report using controlled (ideally randomized) trials which investigate the diagnostic-therapeutic unit as a

research question. In the case of the clinical features of malignant lymphoma, therefore, this imaging procedure should be used either only after an effectiveness test has been done or within the framework of comparative clinical trials. In this respect, special attention should be directed towards children, as the effects of the PET diagnostic procedure have been least investigated in this patient group up till now.

**Keywords:** positron emission tomography, FDG-PET positron emission tomography, malignant lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, systematic review, benefit assessment

The full report (in German) is available on [www.iqwig.de/index.554.html](http://www.iqwig.de/index.554.html)