IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Positron emission tomography (PET) and PET/CT in malignant melanoma[1]

Executive Summary

[1] Translation of the executive summary of the final report "Positronenemissionstomographie (PET) und PET/CT bei malignem Melanom" (Version 1.0; Status: 23.05.2011). 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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Executive summary

Background

Malignant melanoma refers to a malignant tumour that arises from the pigment cells of the skin (melanocytes). Even though malignant melanoma only account for 5% of all skin cancers, they cause the majority of deaths due to skin cancer. Several risk factors play a role in the aetiology of malignant melanoma, such as light type of skin, existence of moles, family disposition, UV radiation and prior sun burns. The course of the disease is mainly determined by the disease stage at first diagnosis. Due to these factors the survival period may be only 4 to 6 months, depending on the location and extent of the disease. In the case of metastasized melanoma, the 5-year survival rate is less than 10%. Through application of positron emission tomography (PET) or PET/computed tomography (CT) it is hoped to achieve correct disease staging (particularly for the detection of metastases), as well as reliable and useful supplementation to necessary examinations.

Research question

This report had 2 goals:

1 Determination of the patient-relevant benefit of PET or PET/CT

The primary goal of this report was to describe the patient-relevant benefit that physicians and patients can expect from imaging techniques with PET or PET/CT in primary staging and diagnosis of recurrences in malignant melanoma. “Benefit” was understood here to mean changes that causally arise from the use of PET or PET/CT and have perceptible consequences for patients.

2 Assessment of the diagnostic and prognostic accuracy of PET or PET/CT

If too few informative primary studies to determine the patient-relevant benefit were identified (first goal), a systematic assessment of the diagnostic and prognostic accuracy of PET or PET/CT was also to be carried out (second goal). In this context it was to be examined to what extent PET or PET/CT were superior to standard diagnostic procedures without PET. In other words, does the use of PET or PET/CT improve primary staging or the correct exclusion of recurrences? It was also to be tested whether, by means of PET or PET/CT, more reliable prognostic conclusions could be drawn within the framework of primary staging or detection of recurrences than is possible with current standard diagnostic procedures.

Methods

(Randomized) controlled trials (RCTs) – strategy with vs. without PET – with patient-relevant outcomes (e.g. reduced mortality / morbidity) were to be considered for the benefit assessment.

A “review of reviews”, i.e. an assessment on the basis of published evidence syntheses, was to be applied for the evaluation of diagnostic and prognostic accuracy. Relevant primary

literature (prospective cohort and cross-sectional studies) was to be additionally identified by our own supplementary searches for the period not covered by the literature search of the most current evidence synthesis.

Within the framework of the supplementary search, a systematic literature search for RCTs and studies on diagnostic and prognostic accuracy was conducted in the following databases: EMBASE, MEDLINE, and the Cochrane Central Register of Controlled Trials (Clinical Trials). In addition, the following databases were screened to identify evidence syntheses: the Cochrane Database of Systematic Reviews (Cochrane Reviews), the Database of Abstracts of Reviews of Effects (Other Reviews), and the Health Technology Assessment Database (Technology Assessments). In addition, documents submitted by the Federal Joint Committee (G-BA) were screened, as were publicly accessible trial registries, documents submitted within the framework of the hearing on the preliminary report plan and on the preliminary report, as well as databases of guideline developers. Moreover, requests were sent to authors and conference proceedings scrutinized. The bibliographic search covered the period up to 11 January 2011. The reference lists of potentially relevant evidence syntheses were also checked.

The literature screening was conducted by 2 reviewers independently of each other. After an assessment of study quality, the results of the individual studies were organized according to research questions and described. In addition, the studies included within the framework of the supplementary search were assessed with regard to their transferability to the German health care context. IQWiG's preliminary benefit assessment, the preliminary report, was published on the Internet and interested persons and parties were invited to submit comments (hearing procedure). All relevant arguments from the comments were considered in the present final report.

Results

The systematic search for published literature yielded no published comparative primary study that would allow a statement on the patient-relevant (additional) benefit of PET or PET/CT in primary staging or in the detection of recurrences of malignant melanoma. Only the second research question on diagnostic accuracy could therefore be answered. No study was found that investigated prognostic accuracy and fulfilled the inclusion criteria of the report.

Indication: Primary staging

For the indication "primary staging" 2 meta-analyses were included that summarized the available studies up to March 2007 (time of the initial literature search) on the diagnostic accuracy of PET in malignant melanoma. Within the framework of the supplementary search a further meta-analysis was included (Xing et al. 2011), which, however, contained no additional information on further primary studies. Therefore no further data were extracted

from this meta-analysis. Furthermore, within the framework of the supplementary search an additional primary study was included in the report.

11 primary studies from the 2 meta-analyses fulfilled the inclusion criteria of the present report. All of these studies investigated PET, none PET/CT. Within the framework of the supplementary search a further 6 studies could be included. 5 of them investigated PET/CT, and one the non-integrated PET.

The authors of the meta-analyses classified 6 of the 11 studies as having a low risk of bias. Of the 6 studies on primary staging included within the framework of the supplementary search, 2 were assessed as showing a low risk of bias.

The sensitivities and specificities of PET or PET/CT for primary staging varied considerably due to the great heterogeneity of research questions and study designs. The stage of disease seems to be a factor explaining this heterogeneity at least partially. It could not be determined with certainty what further factors influence heterogeneity. It is conceivable that such factors may be the different reference and index tests used, the different research questions, the different risks of bias of the studies or the different range of patients investigated. Two studies were found that reported a direct comparison of PET or PET/CT with the comparator technology CT in primary staging (Veit Haibach et al. 2009 and Bastiaannet 2009). In both studies hardly any differences in diagnostic accuracy between PET and CT were shown.

The different research questions and designs of the included studies already described prevented the results of all studies, as well as those of the subgroup analyses, from being related to each other and statistically pooled.

Two subgroup analyses were performed: patients with a melanoma in a lower stage of disease progression (American Joint Committee on Cancer [AJCC] stages I and II) and patients with a melanoma in an advanced stage of disease progression (AJCC stages III and IV). In 4 studies in which patients with AJCC I and II had been investigated, the sensitivity of PET or PET/CT ranged from 0% to 17%; in 2 further studies in this subgroup, the values for sensitivity were 100% and 67% (Rinne et al. 1998 and Klein et al. 2000). In all studies in the subgroup of patients with AJCC I and II, specificity of PET or PET/CT ranged between 77% and 100%.

In all 4 studies investigating patients with AJCC stages III and IV, PET or PET/CT reached a sensitivity of 68% to 87% and a specificity of 92% to 98%.

Overall, an indication of a dependency of the diagnostic accuracy of PET or PET/CT on the tumour stage can be inferred from the results. However, in the interpretation of results, the risk of bias already described (internal validity), as well as heterogeneity (different research questions, reference and index tests, and follow-up periods) need to be considered.

Indication: Diagnosis of recurrences

No evidence synthesis was found for the research question "Diagnosis of recurrences in malignant melanoma". Within the framework of the supplementary search, a prognostic accuracy study that used sensitivity and specificity as an association measure was included.

However, no statements on the diagnostic accuracy of PET in the diagnosis of recurrences could be made on the basis of only 1 study investigating only 30 patients.

Conclusions

The benefit of PET or PET/CT in primary staging and in the diagnosis of recurrences of malignant melanoma is not proven.

The 17 primary studies on diagnostic accuracy included in this report for the research question "primary staging" were all very heterogeneous, some were very small, and many showed methodological flaws. A summarizing statement was not possible due to different ranges of patients, research questions, index tests, reference tests, and follow-up times. In addition, no secure statement could be made concerning the potential superiority of PET/CT versus PET or the comparator technologies, as only 2 studies made a direct comparison and hardly any differences in diagnostic accuracy were found.

Statements on the diagnosis of recurrences could not be made, as only 1 study with a small number of patients fulfilled the inclusion criteria of the present report.

Further studies of high methodological quality are urgently required to be able to reliably assess diagnostic and prognostic quality, and in particular the patient-relevant benefit or harm of PET or PET/CT in primary staging and in the diagnosis of recurrences of malignant melanoma.

Keywords: positron-emission tomography; tomography, X-ray computed; neoplasm staging; neoplasm recurrence, local; systematic review; melanoma

The full report (German version) is published under www.iqwig.de