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Positron emission tomography (PET) and PET/CT in head and neck tumours[1]

Executive Summary

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Executive summary

The Institute for Quality and Efficiency in Health Care (IQWiG) was commissioned by the Federal Joint Committee (G-BA) to assess the benefit of positron emission tomography (PET and PET/computed tomography [CT]) in patients with head and neck tumours.

Research question

The present investigation had 2 goals:

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

The primary goal of this report was to describe the patient-relevant benefit and harm from imaging techniques with PET or PET/CT in patients with head and neck tumours, including those with an unknown primary tumour (i.e. particularly patients with metastatic cervical adenopathy [metastases of the cervical lymph nodes] of unknown origin). The investigated indications for the use of PET or PET/CT were a) determination of the tumour stage ("staging"), b) response of the tumour to treatment ("residual disease evaluation/restaging"), and c) detection of recurrence in the case of justified suspicion. In addition, it was examined whether, in patients with an unknown primary tumour, patient-relevant benefit or harm resulted from diagnosis by means of PET or PET/CT versus conventional diagnostic procedures applied in the search for the tumour and in TNM staging. "Benefit and harm" were understood here to mean changes that have perceptible consequences for the patient, such as the effect on mortality and morbidity, as well as on health-related quality of life.

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

Due to the lack of informative primary studies to determine the patient-relevant benefit (first goal), a systematic assessment of the diagnostic and prognostic accuracy of PET or PET/CT was also carried out (second goal). In this context it was primarily 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 increase a) the number of correct allocations to the corresponding tumour stage with the different prognostic consequences, b) the number of correct assessments of treatment response, or c) the number of correct diagnoses or correct exclusions of recurrences?

Methods

(Randomized) controlled comparative trials (strategy with vs. without PET) with patient-relevant outcomes (e.g. reduced mortality / morbidity) were considered for the benefit assessment. Evidence syntheses or, alternatively, prospective cohort and cross-sectional studies were considered for the assessment of test accuracy.

A "review of reviews" served as a basis for answering the second research question. This was supplemented by an additional search for primary studies; the search period for these studies overlapped with that of the evidence syntheses included (supplementary search).

Results

A comprehensive systematic search in bibliographic databases and other sources yielded only 1 comparative study investigating benefit for inclusion in the benefit assessment. Four evidence syntheses including a total of 69 primary studies fulfilled the inclusion criteria of the report. The question of staging and detection of recurrences was examined in 1 evidence synthesis each; the question of detection of unknown primary tumours was examined in 2 evidence syntheses. No evidence synthesis was found on the question of treatment response. In addition to the evidence syntheses, 30 relevant primary studies were identified.

Proof of a patient-relevant benefit or harm of PET or PET/CT

The only comparative study assessing the benefit of PET or PET/CT in staging investigated 2 diagnostic-therapeutic strategies with and without PET in a direct comparison; however, this study did not detect a difference between groups for the outcome "recurrence-free 2-year survival". Due to the small number of recurrences (6 events in group with PET; 4 in the group without PET) in a population of 102 patients, the study had insufficient power to demonstrate a potential difference between the 2 strategies. On the basis of these study results, a patient-relevant benefit or harm of PET can neither be proven nor refuted.

Diagnostic accuracy of PET or PET/CT for staging

Overall, only 1 evidence synthesis and 10 additional primary studies were included: 5 studies investigated the general question of staging, while the evidence synthesis and 3 further studies investigated the more specific sub-question "staging of lymph node metastases"; 2 studies investigated the sub-question "staging of distant metastases". One study, which also provided details on the staging of distant metastases, supplied information on the sub-question "staging of secondary tumours".

The diagnosis studies included in the evidence synthesis showed substantial methodological flaws: all studies were of low to moderate quality. The main problems were the frequently retrospective design and the unclear or lack of blinding in the assessment of PET or PET/CT.

The quality of the evidence in most of the primary studies additionally identified (except for 2 studies) was very low; this was mainly due to the unclear or lack of blinding in the assessment of the test and reference standard, to unclear patient selection, and in particular to very small patient populations. For the question "staging of the primary tumour", 3 primary studies particularly investigated the detection of bone invasion, for which a test with high specificity is required. The comparator tests CT and single photon emission computed tomography (SPECT) mainly tended towards higher specificity than PET. The test should have high sensitivity for the sub-question "detection of lymph node metastases". In this context, PET

did not perform significantly better than the comparator tests magnetic resonance imaging (MRI) and CT. In the subgroup analysis according to lymph node staging, due to their very low sensitivity the tests had no detection potential in patients with the clinical stage cN0. For the sub-question "detection of distant metastases" the combination PET+CT showed no significant improvement versus PET, whereas in the individual tests PET showed higher sensitivity than CT. However, the results were in part very imprecise. All technologies showed a comparatively high specificity. The partly extremely wide confidence intervals for all questions (in part 1–99 %) with broad overlapping between technologies do not allow reliable conclusions on the superiority of PET or PET/CT compared to conventional technologies.

Diagnostic accuracy of PET or PET/CT in treatment response

The assessment of treatment response after different treatments was investigated in 10 primary studies. The quality of the evidence in all studies was low to very low, except in one study where the quality was moderate. The main problems were very small patient numbers, unclear or lack of blinding in the assessment of the test and the reference standard, and a lack of information on any treatment possibly administered between the PET test and the reference standard (follow-up test). For several comparisons only 1 small study was available; the most common comparison (PET vs. CT) was based on 3 small studies. Neither PET nor CT showed good pooled sensitivity; specificity was very good for PET and inadequate for CT. There was a tendency towards better specificity for PET than for CT. However, in accordance with the small study sizes and methodological flaws, reliable conclusions on the diagnostic accuracy of PET or PET/CT compared to other technologies are not possible.

Diagnostic accuracy of PET or PET/CT in the detection of recurrences

The evidence synthesis on the detection of recurrences in patients with laryngeal carcinoma included only low-quality studies. A particularly common problem was an inadequate reference standard. Overall, PET showed good pooled sensitivity and moderate pooled specificity. Of the 10 primary studies additionally identified, 8, 1, and 1 had a very low, low, and moderate quality of evidence, respectively. For PET the results ranged from clinically very relevant values to clinically irrelevant values; the sensitivity of PET was higher than that of the comparator tests.

In the comparison of the technologies PET versus a combination of CT and/or MRT, PET showed a distinctly higher pooled sensitivity (92% [95% CI: 82–97%]) than the combination of CT and/or MRT (62% [95% CI: 36–82%]); specificity was 72% [95% CI: 56–84%] versus 61% [95% CI: 43–77%]. Only slight overlapping was noted between the confidence intervals of the pooled sensitivities of PET and conventional imaging. For all other comparisons the confidence intervals overlapped and were very wide, so that no conclusion can be drawn as to the superiority of PET or PET/CT versus other technologies.

Diagnostic accuracy of PET or PET/CT in the detection of an unknown primary tumour

One evidence synthesis reported on the diagnostic accuracy of PET, another on that of PET/CT in the detection of primary tumours in patients with metastases of unknown primary origin. Due to substantial methodological flaws the primary studies in both syntheses provided only low-quality evidence. Both evidence syntheses exclusively investigated the diagnostic accuracy of PET and PET/CT without reference to an established comparator test. The detection rate for PET (applied in 433 patients) lay at 43% (median value; range between 8% and 65%). Pooled sensitivity was good (87% [95% CI: 81-92%]); pooled specificity was only moderate (71% [95% CI: 64-78%]). The comparison of PET/CT with PET (3 studies) showed no significant difference. The pooled detection rate of PET/CT lay at 37% (range between 22% and 73%).

The pooled sensitivity (84% [95% CI: 78-88%]) and specificity (84% [95% CI: 78-89%]) for PET/CT from the analysis of 433 patients was classified as good. The small primary study from the supplementary search, which contained substantial methodological flaws and showed insufficient diagnostic accuracy, did not change the assessment of the results of the evidence syntheses. In patients with an unknown primary tumour, both PET and PET/CT can detect additional primary tumours. The time point of application of PET in the course of diagnosis (complete vs. incomplete clarification) influences the prevalence rates (and thus the detection rates) of the tumours not yet identified. In the available studies no difference in diagnostic accuracy could be demonstrated for PET/CT and CT.

Management changes due to PET or PET/CT

Eight of the included primary studies reported on management changes, which are only presented as supplementary information in this report. The percentage of reported management changes ranged from 5% to 100%. Potential reasons for these different frequencies are, among others, different clinical scenarios (e.g. different indications for the PET examination), different definitions of what is meant by a management change, or different types of recorded data (e.g. theoretical vs. actual changes). A management change as such cannot be classified as proof of a benefit of a diagnostic test, as not all management changes necessarily need to be linked to positive effects for patients. For example, in the study by **Yen 2005**, the use of PET resulted in an unnecessary extension of the neck dissection in 3 patients (6%). Such a retrospective evaluation of management changes was often not conducted in the studies and can at best provide indications of the value of management changes.

In order to prove that management changes arising from the results of a diagnostic test actually lead to a benefit for the patient, in most cases comparative intervention studies are required, preferably with a randomized design.

Conclusions

For primary staging, lymph node staging, and the diagnosis of distant metastases, a potential additional benefit of PET or PET/CT in the context of the available test procedures currently used in health care is neither proven by the only study investigating benefit nor by the identified studies on diagnostic accuracy. Even though a large number of test accuracy studies have examined the relevance of PET and PET/CT in primary lymph node staging, a clear improvement versus other diagnostic procedures could be achieved neither for sensitivity nor for specificity.

In the assessment of treatment response, PET showed a tendency in the individual studies towards higher diagnostic accuracy than the other technologies; however the estimated values showed substantial uncertainty. Even the pooling of the 3 studies directly comparing PET with CT allowed no conclusions on the superiority of PET.

PET for the detection of recurrences achieved high sensitivity in the meta-analysis included and thereby detected the majority of patients with a recurrence; however, at the same time the moderate specificity in the meta-analysis led to a high number of false-positive findings with the need for further clarification. It cannot be reliably answered by means of the results whether PET or PET/CT is superior or inferior to conventional diagnostic procedures. With regard to the comparison PET versus combined CT and/or MRT, an advantage of PET seems to exist in the detection of recurrences. It still needs to be examined to what extent an earlier detection of recurrence and possible corresponding treatment have an impact on patient-relevant outcomes (mortality, morbidity and quality of life).

In patients with an unknown primary tumour, PET and PET/CT are of potential relevance if the tumour cannot be located after complete examination with all other diagnostic procedures available. The advantage to be expected cannot be (sufficiently) well quantified in the studies due to the heterogeneous study population and the different stages of clarification in patients (complete vs. incomplete clarification before the use of PET or PET/CT). It currently remains unclear as to whether an examination with PET or PET/CT in the detection of unknown primary tumours is linked to a patient-relevant benefit.

Need for research

In general, there is still a substantial need for improvement in the planning, conduct, and reporting of diagnostic studies. In patients with head and neck tumours, PET/CT can possibly play a role in the diagnosis of recurrences. The same applies to the diagnosis of unknown primary tumours. In this context, comparative studies with the current diagnostic standard are indispensable. Due to the widespread use of PET/CT such studies should be conducted using the combined technology. Only randomized controlled trials can determine whether an existing higher diagnostic accuracy of PET or PET/CT is also linked to a patient-relevant benefit.

Keywords: positron-emission tomography; tomography, X-ray computed; head and neck neoplasms; neoplasms, unknown primary; neoplasm staging; neoplasm recurrence, local; systematic review

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