IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports - Commission No. D06-01I

Positron emission tomography (PET) and PET/CT in ovarian cancer[1]

Executive Summary

[1] Translation of the executive summary of the final report "Positronenemissionstomographie (PET) und PET/CT bei Ovarialkarzinom" (Version 1.0; Status: 27.03.2012). 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.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Positron emission tomography (PET) and PET/CT in ovarian cancer

Contracting agency:
Federal Joint Committee

Commission awarded on:
21.12.2006

Internal Commission No.:
D06-01I

Address of publisher:
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This report was prepared in collaboration with external experts. According to § 139b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received." The Institute received the completed form "Disclosure of conflicts of interest" from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information on conflicts of interest provided by the external experts and external reviewers is presented in Appendix F of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

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External review of the preliminary report:

- Peter Mallmann, Department of Gynaecology and Obstetrics, University of Cologne; Germany

IQWiG thanks the external reviewer for his comments on the preliminary report. However, the external reviewer was not involved in the preparation of the final report. Individual sections and conclusions in the final report therefore do not necessarily reflect his opinion.

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Background

On 21.12 2006, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to search for, present and assess current medical knowledge about positron emission tomography (PET) and the integrated use of PET and computed tomography (PET/CT), in 14 different diseases. This final report concerns the part of the commission regarding ovarian cancer.

Research question

The present report had 2 goals:

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

The primary aim of the report was to describe the patient-relevant benefit that doctors and patients can expect from imaging methods with PET and PET/CT in the primary diagnosis, primary staging, restaging and recurrence diagnosis of ovarian cancer. "Benefit" was understood here to mean the changes that are causally attributed to the use of PET and PET/CT and which have perceptible consequences for the patient.

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

If too few informative trials to determine the patient-relevant benefit (first goal) were identified, a systematic assessment of the diagnostic and prognostic accuracy of PET and PET/CT was also to be carried out (second goal). In this context, the extent to which PET and PET/CT are superior to standard diagnostic procedures without PET was to be examined. In other words, does the use of PET and PET/CT improve primary diagnosis, primary staging, restaging or the detection of recurrences? Similarly, does the use of PET and PET/CT enable more reliable prognostic statements of the named indications than is possible with existing standard diagnostic procedures?

Methods

(Randomized) controlled trials (RCTs) – e.g. strategy with versus without PET – with patient-relevant outcomes (e.g. reduced mortality/morbidity) were to be considered for the benefit assessment within the framework of a systematic review.

Diagnostic and prognostic accuracy were to be evaluated by a "Review of Reviews", i.e. an assessment based on published evidence syntheses. For the time period and research questions not covered by its literature search for the most recent evidence synthesis, the Institute was to undertake supplementary searches to identify additionally relevant primary literature (prospective cohort and cross-sectional studies).

A systematic literature search was performed in the following databases: EMBASE, MEDLINE and the Cochrane Central Register of Controlled Trials (Clinical Trials). An additional search was performed in the following databases 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). The literature search covered the period up to 27.07.2011. In addition, the following sources were screened: documents submitted by the G-BA, publicly available trial registries, documents submitted within the framework of the hearing on the preliminary report plan, as well as databases of guideline developers. In addition, a search was performed in conference proceedings. Reference lists of potentially relevant evidence syntheses were also scrutinized.

The literature screening was performed by 2 reviewers independently of each other. After the assessment of study quality, the results of the individual studies were organized and described according to the research questions. In addition, the studies that had been included as part of the supplementary search, were evaluated for their applicability to the German health care context.

Results

Patient-relevant benefits

The systematic search for published literature did not identify any comparative study that would allow a conclusion to be drawn on the patient-relevant (additional) benefit of PET and PET/CT in ovarian cancer. Likewise, the search in conference proceedings and trial registries produced no evidence of on-going comparative studies.

Diagnostic and prognostic accuracy

The search for diagnostic and prognostic studies was carried out in 2 stages. First, a systematic search was performed for evidence syntheses of high methodological quality that combined the available studies in the respective indications. This search was supplemented by a further investigation to identify primary studies published after the inclusion period of the included evidence syntheses or to complete research questions that were not answered in the included evidence syntheses (supplementary search).

6 evidence syntheses and 9 primary studies fulfilled the inclusion criteria of this report. The evidence syntheses contained 31 primary studies, so the report is based on a total of 40 studies (primary diagnosis [n = 5], primary staging [n = 4], restaging [n = 4], recurrence detection [n = 29]: 2 studies provided data on 2 indications).

Some 11 research questions were examined in the 40 primary studies (see Table 50 of the full report).

The biopsy/histology and/or the follow-up were used as reference tests in all studies. Only the results of included studies that reported a direct comparison of PET or PET/CT with a conventional diagnostic strategy are reported below (exception: PET and PET/CT as “add-on” diagnosis). Comparisons between PET and PET/CT were not identified. None of the included prognosis studies offered a direct comparison.

Recurrence detection

From the 6 evidence syntheses, 26 primary studies fulfilled the inclusion criteria of this report for the indication "detection of recurrence". In addition, the supplementary search identified a further 3 primary studies. Of the 29 primary studies included, 9 showed a low risk of bias.

Recurrence detection on suspicion

Twelve studies carried out no direct comparison of PET and PET/CT with a conventional diagnostic strategy.

In 12 other studies with mixed populations (patients with and without suspected recurrence), PET or PET/CT was compared directly with CT and/or MRI. A bivariate meta-analysis demonstrated a statistically significant different diagnostic accuracy of PET and PET/CT. This difference was essentially based on a higher sensitivity. However, the results of this comparison cannot be interpreted, because it is unclear whether it was undertaken during routine follow-up or due to a definite suspicion. Furthermore, the detailed arrangement of the combination of CT and MRI is not stated.

In 5 studies with mixed patient populations, PET or PET/CT was compared directly with the tumour marker CA-125. Four of these studies were already contained in the direct comparisons with CT and MRI. The bivariate meta-analysis showed no difference in the test accuracy in respect of recurrence detection. It should be borne in mind here that, as a laboratory parameter, CA-125 does not permit the localization of a possible recurrence.

In 4 other studies, PET or PET/CT was investigated as additional diagnostic technique when tumour markers showed an increase and findings from conventional diagnosis were negative or unclear (= "add-on"). Here the sensitivities ranged from 83% (corresponding specificity = 75%) to 100% (corresponding specificity = 50%). Specificities were reached in an interval between 50% (corresponding sensitivity = 100%) and 100% (corresponding sensitivity = 91%).

Recurrence detection without suspicion

Results in routine follow-up were only available from 2 studies, whose results were already contained in the direct comparisons. In one of these studies, PET was compared with CT; in the other PET/CT was compared with CA-125. Both studies were small and the difference between the results was therefore not statistically significant.

Primary diagnosis

For this indication, three primary studies from an included evidence synthesis and 2 more from the supplementary search could be identified.

In 2 of the 5 studies, direct comparisons were carried out. The comparison PET/CT versus CT/MRI was only reported in the paper by Nam 2010. However, no interpretation of the comparison is possible because of the high number of missing values for the CT/MRI. The

two studies produced contradicting results for the comparison PET/CT versus Doppler ultrasound.

Primary staging

Two evidence syntheses for this indication contained a total of 1 primary study relevant for the report. The supplementary search identified one prognosis study that provided no results on direct comparisons and 2 other primary studies that investigated the diagnostic accuracy of PET/CT in primary staging. Only 2 of these studies undertook direct comparisons.

A meta-analysis of the results of these two studies showed no statistically significant higher test accuracy of PET over CT in primary staging.

Restaging

Two primary studies from the 3 evidence syntheses fulfilled the inclusion criteria of this report and the indication of restaging. The comparisons undertaken in these studies between PET and PET/CT (integrated or side by side), CT and CA-125 showed no clear difference in terms of diagnostic accuracy.

A further 2 primary studies were identified in the supplementary search. Neither of these prognosis studies contained comparisons of PET or PET/CT with other diagnostic techniques.

Conclusions

The patient-relevant benefit of PET or PET/CT in ovarian cancer is not proven. Neither ongoing nor completed comparative studies on the patient-relevant benefit of PET or PET/CT in ovarian cancer could be identified. However, such a study is urgently needed, particularly in the indication of recurrence detection.

As regards the second research question of the report – the diagnostic and prognostic accuracy, a total of 40 primary studies could be assessed from 6 included evidence syntheses and the supplementary search.

Too few studies on the indications of primary diagnosis, primary staging and restaging could be identified to allow reliable conclusions to be drawn on the diagnostic and prognostic accuracy of PET or PET/CT.

For the indication “recurrence detection”, 12 of the 29 included studies included a direct comparison of the diagnostic accuracy of PET or PET/CT as replacement for CT and/or MRI. A bivariate meta-analysis showed a statistically significantly higher diagnostic accuracy of the joint pooled PET or PET/CT, which was essentially due to a higher sensitivity. Because the details given in the studies were imprecise, it is not clear whether these results only apply to patients with a definite suspicion, or to those undergoing routine follow-up. The diagnostic accuracy of PET or PET/CT when tumour markers increase and findings from conventional diagnosis are negative or unclear (“add-on”) could not be clarified because the studies

included in this report were few and heterogeneous. However, it is unclear whether an earlier or more accurate diagnosis of a recurrence (still in the asymptomatic stage) actually enables treatment and patient-relevant outcomes to be improved. Furthermore, in the meantime, the usefulness of routine follow-up with tumour markers and primary conventional imaging diagnosis has been questioned (MRC study). Hence it is also a matter of debate whether PET or PET/CT in the context of such a follow-up can lead to improved patient-relevant outcomes, even if its diagnostic accuracy is higher than that of conventional diagnosis.

It is essential that patients are fully told of the possible benefits (due to earlier diagnosis) and harms (earlier start of a side effect-bearing second-line treatment without any prolongation of survival) of PET or PET/CT in recurrence diagnosis, in order that they can make informed decisions.

Keywords: Positron Emission Tomography, Tomography – X-Ray Computed, Diagnosis, Staging, Recurrence, Systematic Review, Ovarian Neoplasms

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