IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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

Executive Summary

[1] Translation of the executive summary of the final report "Positronenemissionstomographie (PET and PET/CT) bei rezidivierendem kolorektalem Karzinom (Version 1.0; Status: 28.08.2012). 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.

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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 G 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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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 assess *positron emission tomography (PET and PET/CT) in recurrent colorectal cancer* (rCRC).

Research question

The primary aim of the report was to describe the patient-relevant benefit that doctors and patients can expect from the imaging techniques PET or PET/CT in the diagnosis and staging of recurrence of colorectal cancer. The indication for use of these methods was focussed on the case of a justified suspicion. "*Benefit*" was understood here to mean the changes that are causally attributed to the use of PET or PET/CT and which have perceptible consequences for the patient.

If too few informative trials to determine the patient-relevant benefit were identified, a systematic assessment of the diagnostic and prognostic accuracy of PET or PET/CT was also to be carried out. In this context, the extent to which PET or PET/CT is superior to standard diagnostic procedures without PET was to be examined. In other words, does the use of PET or PET/CT in patients with a justified suspicion of rCRC improve the diagnosis (confirmation or exclusion) of recurrences and the correct classification of patients to the respective stage of the disease, or does the use of PET or PET/CT enable more reliable prognostic statements with regard to patient-relevant outcomes?

Methods

The patient-relevant benefit was to be assessed by undertaking a systematic review of (randomized) controlled trials (RCTs) with patient-relevant outcomes (e.g. mortality / morbidity).

Diagnostic and prognostic accuracy were to be evaluated by a "Review of Reviews", i.e. an assessment based on published evidence syntheses. The Institute itself was to carry out a supplementary search to identify relevant primary literature (prospective and retrospective cohort and cross-sectional studies) for the period not covered by the most recent comprehensive evidence synthesis with its literature search.

In the context of the benefit assessment, a systematic literature search for RCTs was carried out in the following databases: MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (Clinical Trials). These databases were also used in the supplementary search for studies on diagnostic and prognostic accuracy. A further 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 21.10.2011. In addition, the following sources were screened: documents submitted by the G-BA, publicly accessible trial registries, documents submitted within the framework of the hearing on the preliminary report plan, as well as

databases of guideline developers. Reference lists of potentially relevant evidence syntheses were also scrutinized.

The literature screening was performed by 2 reviewers independently of each other. After assessing the risk of bias, the results of the individual studies were classified according to the research question and then described. If permitted by the data available, the comparative studies on diagnostic accuracy were pooled in a bivariate meta-analysis.

Results

Patient-relevant benefit

The only identified study for assessing the patient-relevant benefit of PET in rCRC was carried out to investigate whether an additional PET investigation for the diagnosis of potentially operable liver metastases has an (added) benefit compared to routine diagnostic methods alone.

As IQWiG discovered after requesting information from the authors, because of ethical concerns, at the beginning of the study the advisory committee had advised against basing the further management of patients (surgery or not) on the PET results. This information was not stated in the publication or in the entry in the clinical trials registry. With the implementation of the advisory committee's vote, the study lost its central purpose, namely to investigate the (added) benefit of PET results in patient management decisions. The results documented in the publication are therefore obviously unsuitable for a benefit assessment of PET and an assessment of the patient-relevant benefit of PET in rCRC is not possible on the basis of this study.

Therefore, the patient-relevant benefit and harm of PET or PET/CT in rCRC cannot be determined due to lack of data.

Diagnostic accuracy

Assessment of the diagnostic accuracy of PET or PET/CT was based on the results of primary studies from 5 evidence syntheses and 13 primary studies (of which 11 had a high risk of bias).

As there were an adequate number of comparative studies, bivariate meta-analyses could be carried out for recurrence diagnosis irrespective of the region and for 3 separately documented regions (detection of local recurrences, of liver metastases, and of distant metastases).

Due to the low number of comparative studies, in the bivariate meta-analysis the diagnostic tests were pooled in respect of technical variants: for these analyses, the diagnostic techniques of PET, PET/CT and PET/contrast-enhanced CT (CE-CT) were considered together and recorded as the PET or PET/CT group. Likewise, as comparator, the diagnostic intervention using CT was combined, where applicable, with the conventional diagnostic intervention (CON) which was not specified further (CT or CON group). The latter consisted

predominantly of CT investigations, but other technologies such as magnetic resonance imaging (MRI) were also used.

Since direct comparisons for CT and/or CON were available and to aid better interpretation of the data, direct comparisons of PET or PET/CT versus MRI or immunoscintigraphy alone were considered separately.

If data on PET/CT as well as on PET/CE-CT were reported in studies for the comparison with CE-CT, then for the sake of an informative comparison, the PET/CE-CT data were used for the analyses.

Detection of recurrences (irrespective of region)

A total of 10 studies with direct comparisons were identified. Of these, 5 studies were found by the evidence syntheses and 5 by the supplementary search.

One study compared PET/CT with CT and/or MRI. For the sake of an informative comparison, these data were not aggregated with the pure CT comparisons. On the basis of the results from 1 study with a high risk of bias, all in all no robust conclusion could be derived for the comparison of PET/CT versus CT and/or MRI.

Two studies compared PET with PET/CE-CT. On the basis of the results from 2 studies with a high risk of bias, overall, no robust conclusion could be derived for the comparison of PET alone versus PET/CT.

Seven studies provided data on the direct comparisons of PET alone or PET/CT versus CT. The Likelihood Ratio Test (LRT) showed a significant difference between PET or PET/CT and CT ($p = 0.0003$). In 6 of 7 studies, the individual study results showed in each case a higher sensitivity as well as a higher specificity for the PET or PET/CT group. In a direct comparison, there was a higher sensitivity with a lower specificity for the PET or PET/CT group compared with the CT group. The observations are reflected in the position of the 95 % confidence regions.

The bivariate meta-analysis calculated the sensitivity and specificity [95 % confidence interval] for PET or PET/CT as 95 % [91; 97] and 85 % [69; 94]. The sensitivity and specificity of CT amounted to 77 % [68; 83] and 67 % [45; 83].

Taken as a whole, the results for the recurrence diagnosis (irrespective of the region) show a higher diagnostic accuracy of both PET and PET/CT compared to a diagnostic intervention using CT. The data indicate that the higher diagnostic accuracy of the former is attributable to a higher sensitivity as well as a higher specificity. These results are based on studies with a predominantly high risk of bias.

Detection of local recurrences

A total of 15 studies with direct comparisons were identified. Of these, 9 were identified by the evidence syntheses and 6 by the supplementary search.

Two studies compared PET or PET/CT with MRI and one study compared PET with immunoscintigraphy. To assist an informative comparison, the data of these 3 studies were not aggregated with the CT or CON comparisons. On the basis of the results from 2 studies – one with a high and one with a low risk of bias – overall no robust conclusion could be derived for the comparison of PET or PET/CT versus MRI. The same applies to the comparison of PET versus immunoscintigraphy.

Two studies (of which one also had data on CT) compared PET with PET/CT (in one study PET + CT [Fusion]). On the basis of the results from 2 studies, overall no robust conclusion could be derived for the comparison of PET versus PET/CT.

Eleven studies provided data on direct comparisons of PET alone or PET/CT versus CT or CON. The LRT showed a significant difference between PET or PET/CT and CT or CON ($p < 0.0001$). Apart from 1 study, the individual study results for the PET or PET/CT group showed in each case a higher sensitivity with comparable or higher specificity. The observations are also reflected in the position of the 95 % confidence regions.

The pooled sensitivity and specificity [95 % confidence interval] of PET or PET/CT amounted to 94 % [90; 97] and 98 % [95; 99]. The sensitivity and specificity of CT or CON amounted to 73 % [66; 78] and 92 % [86; 96].

Taken as a whole, the results for local recurrence diagnosis show a higher diagnostic accuracy of PET or PET/CT compared to a diagnostic intervention using CT or CON (mainly consisting of CT). The data indicate that the higher diagnostic accuracy of PET or PET/CT is chiefly attributable to a higher sensitivity. These results are based on studies with a predominantly high risk of bias.

Detection of liver metastases

A total of 12 studies with direct comparisons were identified. Of these, 8 were identified by the evidence syntheses and 4 by the supplementary search.

All 12 studies provided data on direct comparisons of PET alone or PET/CT versus CT or CON. There were no direct comparisons between PET and PET/CT concerning the detection of liver metastases.

The LRT showed a significant difference between PET or PET/CT and CT or CON ($p = 0.0139$). In 6 of 12 studies, higher values were found for sensitivity and also for specificity for the PET or PET/CT group in comparison with the CT or CON group. In one comparison, there was a higher sensitivity with a comparable specificity for the PET or PET/CT group compared to the CT or CON group. In 2 studies, comparable values for

sensitivity and also for specificity were observed for the PET or PET/CT group compared to the CT or CON group. In 3 comparisons there was a lower sensitivity with higher specificity for the PET or PET/CT group compared to the CT or CON group. The observations are also reflected in the position of the 95 % confidence regions.

The pooled sensitivity and specificity [95 % confidence interval] of PET or PET/CT amounted to 95 % [91; 97] and 99 % [96; 100]. The sensitivity and specificity of CT or CON amounted to 91 % [86; 94] and 92 % [80; 97].

Taken as a whole, both PET and PET/CT have a probably higher diagnostic accuracy for the detection of liver metastases than a diagnostic intervention using CT or CON (consisting mainly of CT). However, it remains unclear whether this is due more to higher sensitivity and/or specificity. The studies on which this comparison is based also showed a high risk of bias.

Detection of distant metastases

A total of 7 studies with direct comparisons were identified. All 7 were identified by 1 evidence synthesis.

All 7 studies provided data on direct comparisons of PET alone versus CON. No direct comparisons of PET and PET/CT for the detection of distant metastases were available.

The LRT showed a significant difference between PET and CON ($p = 0.0011$). In 6 out of 7 direct comparisons, both sensitivity and specificity were higher for the PET group than for the CON group. In a direct comparison, there was a higher sensitivity with a lower specificity for the PET group compared to the CON group. The observations are also reflected in the position of the 95 % confidence regions.

Pooled sensitivity and specificity [95 % confidence interval] of PET amounted to 94 % [88; 97] and 80 % [70; 88]. Sensitivity and specificity of CON amounted to 71 % [56; 83] and 64 % [52; 75].

Taken as a whole, PET alone shows a higher diagnostic accuracy for the detection of distant metastases than a diagnostic intervention using CON (consisting mainly of CT). The data indicate that the higher diagnostic accuracy of PET is attributable to a higher sensitivity as well as a higher specificity. These results are based on studies with a predominantly high risk of bias.

Detection of recurrence in other regions of the body

The supplementary search produced 2 comparative studies on the recurrence diagnosis of other regions of the body, which compared PET/CT with CT in terms of the detection of pulmonary metastases. Overall, on the basis of results from 2 studies with a high risk of bias, no robust conclusion could be derived for the comparison of PET/CT versus CT.

Regarding recurrence diagnosis in other regions of the body, 3 direct comparisons on the detection of extrahepatic metastases were also found. All 3 studies were identified by the supplementary search and compared PET or PET/CT with CT or CON (consisting of CT, ultrasound and coloscopy). Overall, on the basis of results from 3 studies with a high risk of bias, no robust conclusion could be derived for the comparison of PET or PET/CT versus CT or CON.

Staging of recurrences

No studies that had explicitly investigated the *staging of recurrences* (e.g. the correct allocation to TNM[3] stages) were identified.

Prognostic accuracy

No data were available from evidence syntheses concerning the prognostic accuracy of PET in rCRC. The assessment of prognostic accuracy was based on a primary study with data of 91 patients with suspected rCRC and 96 patients in whom rCRC had been diagnosed. The risk of bias of the study was rated as high. Due to the overlapping of therapeutic and diagnostic effects, no superior classification of patients into prognostic groups by PET compared to a conventional diagnostic intervention could be derived from these results.

Conclusions

Due to the lack of data, the patient-relevant benefit and harm of PET or PET/CT in recurrent colorectal cancer cannot be determined.

The expanded research question of the report concerning diagnostic and prognostic accuracy was addressed on the basis of data from 5 included evidence syntheses and 13 primary studies identified by the supplementary search. In the majority of cases, the data were subject to a high risk of bias. The bivariate meta-analyses relating to comparative diagnostic studies from both sources of information showed a higher diagnostic accuracy for the detection of recurrences (irrespective of region), of local recurrences and of distant metastases when PET is considered together with PET/CT compared to a conventional diagnostic intervention. The latter consisted predominantly of CT. As regards the detection of liver metastases, the results of the bivariate meta-analyses showed a probably higher diagnostic accuracy of PET or PET/CT compared to a diagnostic intervention using CT or a not further specified conventional diagnostic intervention. On the basis of the few studies (all with a high risk of bias) concerning the detection of pulmonary or extrahepatic metastases, no robust conclusions about diagnostic accuracy can be derived for these two regions.

From the few identified studies (the majority with a high risk of bias) on direct comparisons of PET or PET/CT versus MRI and immunoscintigraphy, in each case no robust conclusions can be drawn regarding diagnostic accuracy.

[3] Tumour staging according to extent of tumour (T = tumour), lymph nodes (N = lymphatic nodes) and metastasis (M = metastasis)

On the basis of 2 comparative diagnostic studies on recurrence diagnosis (irrespective of region) and 2 on local recurrences, no robust conclusions can be drawn regarding diagnostic accuracy for the comparison of PET versus PET/CT.

In the absence of any studies that explicitly investigated the staging of recurrences, no conclusions can be deduced on the diagnostic accuracy of PET or PET/CT.

Only 1 primary study on the prognostic accuracy of PET or PET/CT could be identified, on the basis of which no conclusions can be drawn.

Despite the fact that higher diagnostic accuracy of PET or PET/CT was nearly always found, no answer can be given to the present question concerning the value of the PET technology with regard to how a higher diagnostic accuracy affects patient-relevant outcomes.

Results of methodologically high-quality (prospective, comparative) studies are needed to enable a reliable assessment of the evidence gap between the diagnostic classification properties and the effects of the related therapeutic consequences for patient-relevant outcomes.

Keywords: positron-emission tomography, tomography – X-ray computed, colorectal neoplasms, rectal neoplasms, recurrence, staging, systematic review

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