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SYSTEMATIC REVIEW

Evidence-based indications for the planning of PET or PET/CT capacities are needed

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Abstract

Purpose To identify evidence-based indications for PET/PET–CT scans in support of facilities planning and to describe a pilot project in which this information was applied for an investment decision in an Austrian region. The study updates a Health Technology Assessment (HTA) report (2015) on oncological indications, extending it to neurological indications and inflammatory disorders.

Methods A systematic literature search to identify HTA reports, evidence-based guidelines, and systematic reviews/meta-analyses (SR/MA) was performed, supplemented by a manual search for professional society recommendations and explicit "not-to-do's". A needs-assessment was conducted in the context of the pilot study on investing in an additional PET–CT scanner in the Austrian region of Carinthia.

Results Overall recommendations for indications as well as non-recommendations for the three areas (oncology, neurology, and inflammatory disorders) were compiled from the 2015 PET–HTA report and expanded for a final total of ten HTA, comprising 234 (positive and negative) recommendations from professional societies and databases, and supplemented by findings from 23 SR/MA. For the investment decision pilot study in Carinthia, 1762 PET scans were analyzed; 77.8% were assigned to the category "recommended evidence-based indications" (54.7%), "not recommended" (1.8%) or "contradictory recommendations" (21.3%). The remaining could not be assigned to any of the three categories.

Conclusions The piloting of PET capacity planning using evidence-based information is a first of its kind in the published literature. On one hand, the high number of PET scans that could not be ascribed to any of the categories identified limits to the instructive power of the study to use evidence-based indication lists as the basis for a needs-assessment investment planning. On the other hand, this study reveals how there is a need to improve indication coding for enhanced capacity planning of medical services. Overall recommendations identified can serve as needs-based and evidence-based decision support for PET/PET–CT service provision.

Keywords Evidence-based planning · Needs-based planning · PET/PET–CT · Oncology · Neurology · Inflammatory disorders · Advanced diagnostics

Introduction

Europe is one of the largest markets for the fast-growing sector of medical devices (MDs) and diagnostic procedures, which encompass a broad and heterogeneous range of technologies. Due to the rising costs associated with introducing of new MDs and procedures into the healthcare system, payers have started to pay more attention to the effectiveness and financial implications of such new technologies. In this context, health technology assessment (HTA) has gained increasing recognition at the European level as a decision support tool [1].

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No other medical technology has been evaluated as frequently by HTA institutions in European countries as "positron emission tomography (PET)", or rather "positron emission tomography/computed tomography (PET/PET–CT)" [2, 3]. In its 2015 assessment report [4] on PET/PET–CT, the Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA) aimed to capture the evidence base on oncological indications for a needs-based planning of PET/PET–CT facilities in Austria. It identified around 160 assessments on PET or PET–CT in a 10-year period (2004–2014), of which the first HTA were already published in 1995. This expresses uncertainty about the value of PET diagnostics in patient care. Notably, despite ongoing and controversial discussions about the patient-relevant benefits of PET/PET–CT, these technologies have rapidly been adopted both in Europe and abroad [2]. Additionally, the majority of those assessments is not accompanied by decisions regarding the reimbursement or planning of PET/PET–CT indications or devices. However, several approaches exist to deal with (to varying degrees) uncertain evidence or contradictory recommendations around reimbursement and capacity planning in Europe and globally [4]. In practice, capacity planning employs a mix of different methods and methodological approaches such as comparative approaches (e.g., benchmarking), analytical (e.g., health care needs-assessment) and/or reactive approaches (e.g., waiting lists). To provide volume forecasts for facility planning and workload vis-à-vis PET/PET–CT, the number of patients with (sub-)indications is important as is the estimated number of patients eligible for therapy monitoring and radiotherapy dose planning. In addition, some special features of PET/PET–CT (e.g., required radionuclides/tracers) have to be taken into account. Yet the planning of capacities based on evidence-based indications is rarely seen—neither in the literature nor in practice.

On the initiative of the German Society for Nuclear Medicine (DGN), the LBI-HTA and the Department of Health Care Management at the Berlin University of Technology collaborated to (1) update the LBI-HTA 2015 report to identify indications recommended by evidence [HTA, systematic reviews/meta-analyses (SR/MA), evidence-based guidelines (EBG)] for PET/PET–CT scans supporting facility planning in Germany and Austria and (2) describe a pilot study which applied those recommendations identified in the evidence review from step (1) to an investment decision in the Austrian region of Carinthia. The subsequent, updated, HTA report extended the scope of the 2015 report by including indications for neurology and inflammatory disorders in addition to oncological indications.

The following article summarizes both the results of the updated PET–HTA report, which has already been published (in German [5]), and the pilot study in Austria testing the practicalities of the recommendations.

Materials and methods

(1) Evidence-based indications and recommendations

Sources of information, search strategy, and study selection

A systematic literature search was carried out in July 2017 to identify HTA reports, SR/MA, and EBG to be included in the study. The databases MEDLINE, EMBASE, PubMed, and Cochrane Library were searched using a search strategy retrieved from a published report by the German Institute for Quality and Efficiency in Health Care (IQWiG), which was then updated and adapted [6]. A 5-year window (2012–2017) for EBG and SR/MA was chosen [7]. HTA for the newly included indications (neurology and inflammatory disorders) were limited to the last 10 years (2007–2017), while the most recent HTA [8–10] included in the PET–HTA report [4] were used for oncological indications, though oncological guidelines already included in the PET–HTA were updated if newer ones were available. Details about the searches are found in the Appendix A of the report [5] and a translated version is found in the Online Resource 1 of this article.

The literature was screened in a two-stage process (First: title/abstract; second: full text) by two researchers of the author group. Inclusion and exclusion criteria were determined based on the criteria from the PET–HTA report 2015 [4] for consistency. English- and German-language HTA, SR/MA, and EBG on the benefits of PET/PET–CT were included, if they discussed (1) patient-relevant benefits; (2) diagnostic accuracy/quality or change in patient management; (3) if they focused on one of the three indications/treatment areas (oncological and neurological indications, or inflammatory diseases); (4) were developed with an evidence-based methodology (e.g., a description of a literature search referenced more than two databases, inclusion/exclusion criteria and quality assessment, and double-check principle); and (5) were freely available. Differences in the assessment of literature were resolved through discussion and consensus building. A detailed overview of the criteria for inclusion and exclusion can be found in the Online Resource 2 of this article.

In addition to the systematic search, a supplementary, comprehensive manual search for evidence-based recommendations on the use of PET/PET–CT was conducted. The selection of databases or websites [e.g., Cancer Care Ontario (CCO) and National Comprehensive Cancer Network (NCCN)] was based on the PET–HTA report 2015 [4] and complemented by relevant sources for the two new indications. The search could not be carried out in a systematic manner due to variation in search interfaces, but the search term PET was a common factor. Up-to-date

recommendations of the following national and supranational societies of nuclear medicine were included: Austrian Society of Nuclear Medicine and Molecular Imaging (ÖGN), German Society for Nuclear Medicine (DGN), Swiss Society for Nuclear Medicine (SGNM), European Association of Nuclear Medicine (EANM), Society of Nuclear Medicine and Molecular Imaging (SNMMI), and Joint Collaboration of EANM and SNMMI. Databases (e.g., Choosing Wisely, NICE Do-not-Do database) that explicitly identify "inappropriate" (not-to-do) services were also included as a source of information. Screening of documents from websites or professional societies was carried out by one person, with the extraction performed using the double-check principle. During the process of updating the HTA report, information sources were again scanned between January and February 2018.

Data extraction

Extraction tables were compiled separately for the three indications, using the double-check principle. In a first summary table, study characteristics were extracted separately, because they differ among HTA (e.g., reported endpoints and number of included studies), SR/MA (e.g., reference standard), and EBG (e.g., funding/sponsoring and strength of the evidence). Evidence derived from HTA and SR/MA was thus presented in the further tables including the evidence base and verbatim conclusions. The recommendations from EBG and websites and databases of national and supranational societies were first extracted in tabular form and assessed along two dimensions: (1) appropriate use criteria and (2) inappropriate use criteria (e.g., suspension of decisions, recommendations based on insufficient evidence, and disinvestment recommendations), including also the corresponding strength of the evidence. Recommendations of a certain level/strength of evidence (see Box 1) were then considered and clustered according to type and content of recommendations for further analysis into their similarities and differences.

Box 1: included professional societies and databases and the level/ strength of evidence taken into account for the recommendations

Level and strength of evidence considered for appropriate use:

- American College of Chest Physicians (ACCP): own grading system (only 1B recommendation available; grade 1B = strong recommendation, moderate quality evidence)
- American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS): evidence hierarchy developed by the AANS/CNS Guidelines Committee (but no recommendation due to insufficient evidence)
- American College of Radiology (ACR): ACR Appropriateness Criteria®: 7–9 = appropriate indications (4–6 = may be appropriate indications was not considered for the table, are available on request)*
- British Society for Hematology (BSH): GRADE was used to evaluate LoE and to assess the strength of recommendation (only A and B recommendations were considered)
- Canadian Association of Radiologists (CAR) Referral Guidelines: GRADE 1 = indicated, ("2 = Specialized Investigation" was not considered for this table, available on request)* & based on A (high-quality diagnostic studies such as studies in which a new test is independently and blindly compared with a reference standard in an appropriate spectrum of patients, etc.), B (lower case evidence in which the reference standard does not appear on all subjects, etc.), or C (studies in which the reference standard was not objective, expert opinion, etc.) were considered
- Cancer Care Ontario (CCO): LoE/GoR not indicated (only literature assigned to the recommendations)
- European Association of Nuclear Medicine (EANM)/ Society of Nuclear Medicine and Molecular Imaging (SNMMI): only Grade A and B considered
- European Federation of Neurological Societies (EFNS): good practice points not considered (lack of evidence but consensus by expert reached) and only recommendations for PET taken
- German Society for Nuclear Medicine (DGN): LoE/ GoR not indicated (only literature assigned to the recommendations)
- International myeloma Working Group (IMWG): LoE/ GoR according to OECBM (only A = Evidence of type I or consistent findings from multiple studies of types II, III, or IV and B = Evidence of II, III, or IV, findings are generally consistent) were considered
- Response Assessment in Neuro-oncology working group/European Association for Neuro-Oncology (RANO/EANO): only 1–3 LoE according to OCEBM included in their study (no information of LoE for the recommendations separately)
- Royal College of Radiologists and Royal College of Physicians (RCR/RCP): no LoE/GoR indicated (only literature assigned to the recommendations)
- Ryken et al.: evidence hierarchy developed by the AANS/CNS Guidelines Committee (level III = Clinical uncertainty (inconclusive or conflicting evidence or opinion)

- SNMMI/Alzheimer's Association (AA): no LoE/GoR indicated (only literature assigned to the recommendations)
- SNMMI + EANM and American College of Nuclear Medicine (ACNM), American College of Preventive Medicine (ACPM), American Society of Clinical Oncology (ASCO), Canadian Association of Nuclear Medicine (CANM), and Society for Pediatric Radiology (SPR): 7–9 = appropriate indications (4–6 = may be appropriate indications which were not considered for this table, available on request)
- National Comprehensive Cancer Network (NCCN): only LoE category 2A was considered (= based on lower level evidence, there is uniform NCCN consensus that the intervention is appropriate; LoE 2B available on request; LoE 1 was not indicated for any of the recommendation)* & only 'preferred' recommendations were considered

Level and strength of evidence considered for inappropriate use:

- ACR: 1–3 = not appropriate (4–6 = may be appropriate indications was not considered for the table, are available on request)*
- Choosing Wisely USA (ChW) and NICE Do-not-Do database: respective recommendations (both without "ratings") were evaluated
- CAR: GRADE 5 = not indicated (GRADE 3 = not indicated initially, 4 = indicated only in specific circumstances were not considered for this table, available on request) based on A, B, and C LoE (see above)*
- European Crohn's and Colitis Organization/European Society of Gastrointestinal and Abdominal Radiology (ECCO/ESGAR): OECBM LoE 1–3 considered
- NCCN guidelines provide no separate category for inappropriate use; all guidelines were searched manually for information on inappropriate use/insufficient evidence
- BSH, CCO, CNS/AANS, EANM/SNMMI, EFNS, IMWG, RANO/EANO, RCR/RCP, Ryken, and SNMMI/AA: see information above on appropriate use

LoE level of evidence, *GoR* grade of recommendation
*Mainly due to the large amount, only those recommendation from ACR, CAR, and NCCN with a certain level of recommendation were taken into account

Synthesis of recommendations

A summary of the recommendations derived from each of the three source types (HTA, EBG, SR/MA) was structured according to their indication. These are presented below. Based on the PET–HTA report 2015 [4], a classification of the recommendations into the categories "Yes", "No", "Restricted Use", and "Unclear" was applied (Table 1). A color system shows the level of contradictories between the evidence sources (HTA, EBG, and SR/MA) regarding the respective recommendations and the strength of evidence. For oncological indications, recommendations from the PET–HTA report 2015 are included as well.

Quality assessment

The quality of the included information sources was appraised by appropriate and validated tools, depending on the respective sources. The quality of HTA was assessed via a double-check approach supported by a checklist from the International Network of Agencies for Health Technology Assessment (INAHTA [11]) of 14 questions answered with "yes", "partly", and "no" (no total score). The AGREE II instrument (German version [12]) was used to assess the quality of EBG. Each guideline was evaluated by three independent reviewers across six domains and a total of 23 items on a seven-point scale. It was determined that reviewers would deviate a maximum of two points in their final evaluations. In the event of a discrepancy of more than two points per item, the questions were discussed and a consensus was

Table 1 Colour coding of recommendations and level of contradictions between the evidence sources for the overall recommendations table

Classification of recommendations	"Yes" (indication to use, PET/PET-CT as primary treatment)				
	"No" (no indication to use, insufficient/inconclusive evidence)				
	"Restricted Use" (only as second-line or continuative method within an indication)				
	"Unclear" (no concrete or contradictory recommendations)				
Level of contradictions between the evidence sources	Consensus of sufficient evidence in favour of PET/PET-CT	Consensus of not sufficient evidence in favour for (against) PET/PET-CT	Divergent statements (HTA vs. EBG vs. SR/MA) or contradictory results	Divergent statements between EBG or contradictory results	Recommendation derived only from one source (HTA or EBG)

reached. The EBG were finally re-evaluated in their entirety resulting in an average score for each guideline. The SR/MA were assessed by two reviewers independently with AMSTAR-2 [13], comprising a questionnaire consisting of 16 yes/no questions. Discrepancies were resolved by consensus. Overall quality was determined primarily by considering the critical questions (defined by the developers of the instrument [13]) and by allocating each SR/MA into one of four suggested categories (high, moderate, low, and critically low) [13]. For more details on the methods used, see the full report and the corresponding Appendix C [5].

(2) Pilot study: evidence-based PET/PET–CT planning

A study was carried out to guide the investment decision for an additional PET–CT scanner in the region of Carinthia in Austria (561,000 inhabitants). First, a needs-assessment based on a data analysis of PET scans was conducted. Diagnoses were coded according to the International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10, 2016 [14]). All PET scans performed from January to September 2017 were retrieved and clustered according to disease diagnosis (e.g., tumour type: C.00; malignant neoplasm of lip) and, if available, to subgroups of indications (e.g., C00.1 external lower lip). The information was then matched to identify recommendations for evidence-based indications or non-indications [see step (1)]. Indications with contradictory recommendations were—due to lack of detailed clinical information—ascribed to the category of dissenting or unclear evidence from HTA and/or guidelines. The categorization as well as the matching with evidence-based indications was performed by two researchers.

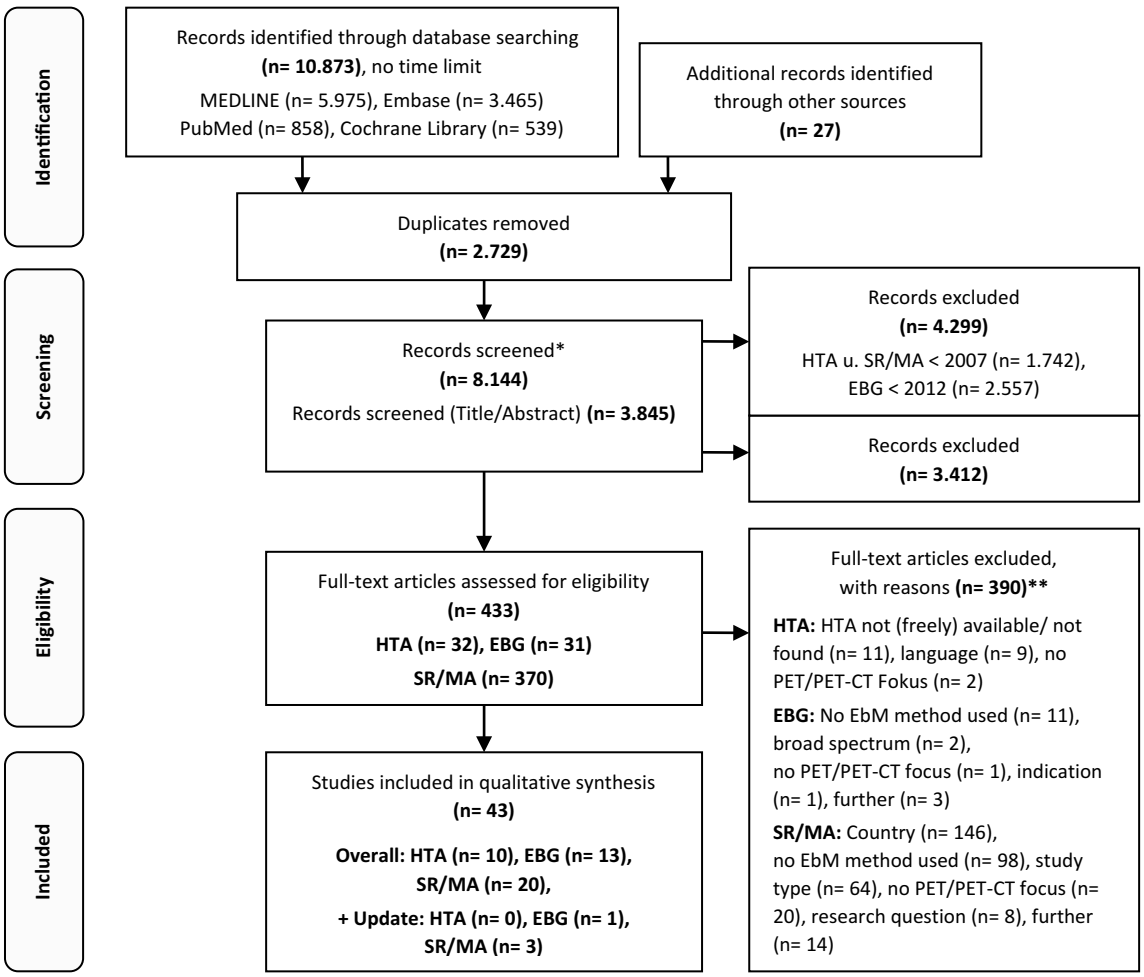

Fig. 1 PRISMA flowchart: study selection process of the systematic search [5]. *Due to the large amount of records identified, a time limit was set up for the title/abstract screening of SR/MA. **Online Appendix D [5] contains a list of excluded articles with reasons

Results

(1) Evidence-based indications and recommendations

Results of the evidence selection process

The systematic search yielded 10,873 references (Fig. 1). After the removal of duplicates (2729 references) and the—ex post—introduction of a time limit (due to an enormous amount of materials), 4299 references were ultimately excluded and 3845 references remained for the two-step screening. Of these, 3412 references were excluded according to the inclusion and exclusion criteria, leaving 433 full texts, 43 of which were finally included (10 HTA reports, 20 SR/MA, and 13 EBG). An overview of the excluded references ($n=390$) with reasons can be found in the Appendix D of the updated HTA report [5]. The screening of the collected alerts of the database searches (update: from July to December 2017) resulted in three more HTA, one EBG, and three SR/MA. As such, a total of 47 references were included.

The updated search results in guideline databases and websites and databases of relevant national and supranational societies regarding recommendations (see tables in report [5]) was compared with the results of the systematic research and the PET–HTA Report 2015, resulting in additional "appropriate use" recommendations from seven professional societies: DGN and the joint collaboration between EANM and SNMMI, RCP/RCR, ACR Appropriateness Criteria®, CAR Referral Guidelines, and two oncology expert networks for guideline development, CCO and NCCN. It also resulted in concrete "not-to-use" recommendations from four societies or databases: ACR, CAR, and the two disinvestment databases Choosing Wisely and NICE Do-not-Do database. Thus, a total of ten HTA, and 234 positive and negative recommendations from professional societies and databases were included, supplemented by the statements from 23 SR/MA.

Evidence on oncological indications

Study characteristics

The PET–HTA report (2015) included 35 HTA assessments on 20 oncological indications. In addition, the report update revealed two novel HTA on bronchial carcinoma from the US Agency for Healthcare Research and Quality (AHRQ) [15] and the HTA-Center for the Västra Götaland Region, Sweden [16] as well as one HTA each on mamma carcinoma, compiled also by AHRQ [15], on penile/testicular carcinoma and on bladder/renal cancer, the latter two compiled by the Scottish Health Technologies Group within Healthcare Improvement Scotland (SHTG/HIS [17–20]). For further oncological indications considered in the PET–HTA report 2015, no more recent HTA was found. Reported endpoints in the included studies used for the HTA reports refer to diagnostic accuracy (mainly tumour grading and change in management).

Recommendations as well as non-recommendations ($n=188$) from professional societies (see Box 1 for abbreviations) were retrieved and extracted from AANS/CNS [21], ACCP [22], BSH [23], CCO [24–26], DGN [27], IMWG [28], and RCR/RCP [29]. Three common guidelines, one from SNMMI/EANM and others (ACNM, ACPM, ASCO, CANM, and SPR) [30], one from RANO/EANO [31], and one from EANM/SNMMI [32], were also considered. One guideline (Ryken et al. [33]) has been elaborated by several universities.

Three guidelines (CCO [24], RCR/RCP [29], SNMMI/EANM/others [30]) provided recommendations for tumours generally as well as for non-oncological indications. Another three guidelines dealt with tumours of the head (DGN [27], Ryken [33], RANO/EANO [31]); two focused on myeloma (BSH [23], IMWG [28]); and one guideline addressed prostate cancer (EANM/SNMMI [32]), anal canal carcinoma (CCO [25]), lung carcinoma (ACCP [22]), paraneoplastic syndrome (PNS) (CCO [26]), and pituitary adenoma (AANS/CNS [21]), respectively. The recommendations of ACR [34], CAR [35] and NCCN [36] as well as the explicit non-recommendations of choosing Wisely [37] and NICE Do-not-Do [38] were also considered.

Moreover, 12 SR/MA for seven oncological sub-indications were included [39–50]; of those, two supplemented an HTA report [49, 50] and all considered diagnostic accuracy as an endpoint, especially for primary diagnosis and staging for pre-treatment/treatment planning. The systematic reviews consisted primarily of retrospective studies.

Quality assessment

The quality of the HTA was overall very good, with only a few questions not evaluated with "yes". The assessment of the quality of the guidelines varied. In domain 1: "scope and purpose" and domain 4: "clarity of presentation", the guidelines received high ratings and there were fewer variations among the guidelines. Domain 3 ("rigour of development"), which considers the accuracy of guideline development, ranged from 11% (DGN [27]) to 93% (ACCP [22]), showing the largest differences among the guidelines. In the overall rating, the ACCP guideline [22] was given a score of 5.67 (max. 7) and also ranked highest among two domains 3 and 4. The RCR/RCP guideline [29] attained last place with a mean score of 2.67.

The quality of the SR/MA in terms of overall qualitative assessment (no overall score) revealed that 10 out of 12 were "critically low". Hence, the SR/MA is used only as supplementary information.

Table 2 PET/PET–CT indications (oncology): overall recommendations

HTA (n)	Notes	EBG (n)	Notes	Additional information from SR/MA
Brain Tumor				
No*	No recommendation, weak evidence	RU*	Contradictory recommendation (glioma)	
		RU (2)[h,l]	D/S (grading tumor, disting. WHO grades, differential diagn. of tumor/glioma)	• Primary diagnosis (brain tumor, glioma): ^{18}FET-PET higher diagnostic performance than FDG PET (Grading: no difference between tracer)
		RU (3)[h,k,l]	*Amino Acid*:D/S (gradingtumor), R/R + TM	
		No (4)[b,e,k,m]	D/S & TP (glioma) Routine use (brain metastases & glioblastoma) Follow-up (specific case described by ACR) R/R + TM (glioma)- insufficient evidence	
		Unclear (2)[k,l]	Contradictory recommendation: TP (glioma): RU (RCP/RCR) vs. RU (RANO/EANO: not grade III/IV glioma)	
Head and NeckCa				
RU*	Some evidence, Re/Staging + Thyroid	RU*	CUP, Thyroid, contradictory for other Ca	
		RU (5)[b,d,e,l,n]	D/S (+ CUP), R/R (local recurrence, metastases) + TP head and neckCa TM (response evaluation) Head and NeckCa R/R (suspected recurrence) thyroid R/R (residual disease) parotidCa (problem solving tool) *^{11}C-Menthione*:D/S (localization) parathyroidCa (difficult cases)	
		No (2)[b,d]	D/S head and neckCa (specific cases described by ACR) Staging (I or IIA/B) thyroidCa	
MammaCa				
No*	Inconclusive evidence	No*	No appropriate use criteria, pot. diagnostic of recurrence	
Yes (1)	*^{18}F-FET:* TM (tumor response) metastatic MammaCa (mainly bone metastases)	Yes (2)[l,n]	TM (treatmentresponse) bone metastases	• D/S: Better diagnostic performance for distant metastasis staging of whole body ^{18}F -FDG-PET/PET-CT compared to conventional imagining
		Yes (3)[b,l,n]	R/R (suspicion of metastatic disease, local recurrence) known breastcancer/dense breast	
		No (5)[b,e,f,o,p]	D/S (specific cases decribed by ACR, e.g. high risk patients) D/S (staging) TM (monitor) advanced breast cancer	
BronchialCa– *Update: Thorax/LungCa*				
RU*	Some evidence Re/Staging	RU*	Different sub-indications, less contradictory	
Yes (1)	*^{18}F-FDG:* Pre-treatment staging of SCLC	Yes (4)[b,d,e,l]	*^{18}F-FDG:* Pre-treatment staging SCLC/NSCLC (curative intent), thymic tumor, pleural malignancy	
Yes (1)	*^{18}F-FDG:* TP (prior to dose planning) SCLC/NSCLC			
		RU (2)[b,d]	D/S pulmonary & thoracic nodule (specific cases described by ACR, CAR)	
		No (3)[b,e,o]	D/S pulmonary nodule (specific cases described by ACR) TM (routine surveillance + follow-up)SCLC/NSCLC TP (routine use outside research setting) SCLC/NSCLC	
		Unclear (4)[a,e,n,o]	Contradictoryrecommendation: R/R SCLC/NSCLC: Yes (SNMMI/ACCP) vs. insufficient evidence (CCO) TM (response evaluation) SClC: Yes (SNMMI) vs. No (NCCN)	
EsophagealCa				
No*	No recommendation due to insufficient evidence	RU*	Just as continuative diagnostics, contradictory	
		Yes (2)[e,l]	Re-/Staging before therapy/treatment	• TM (treatment response): pot. useful
		Unclear (3)[e,l,o]	Contradictory recommendation: R/R (suspected recurrence): RU (RCR/RCP) vs. insufficient evidence (CCO) TM (treatment response): Yes (NCCN) vs. insufficient evidence (CCO)	
GastricCa				
No*	Scarce evidence	No*	No appropriate use criteria	*No HTA/GL/SR/MA identified (Update)*
PancreaticCa				
RU*	Inconclusive evidence, pot.diagnosis	RU*	Contradictory recommendation	
		No (2)[d,e]	Primary diagnosis R/R (re-staging), TP (treatment response), TM (guide clinical management) pancreatic adenocarcinoma–insufficient evidence	
		Unclear (3)[d,e,l]	Contradictoryrecommendation: Staging before curative surgical resection: Yes (CAR, CCO) vs. RU (RCR/RCP)	
LiverCa				
No*	Weak (scarce) evidence	No*	No appropriate use criteria	
		Yes (1)[l]	*^{11}C- Choline, ^{18}F-fluoro-choline, Ga-PSMA, ^{11}C-Acetate:*TP HCC	
		RU (2)[d,l]	D/S, R/R hepato-(pancreatico)-billaryCa D/S liver lesion	
		No (2)[b,o]	D/S (primary diagnosis) HCC D/S liver lesion (specific cases described by ACR) TP (routine use preoperative)–insufficient evidence	
AnalcanalCa				
		No (1)[e]	D/S (routine investigation), R/R & TM analcanalCa–insufficient evidence	

Table 2 (continued)

HTA (n)	Notes	EBG (n)	Notes	Additional information from SR/MA
ColorectalCa				
RU*	Some evidence Staging/Recurrence	RU*	Remote metastases/Re-staging/Therapy monitoring less contradictory	
		RU (4)[d,e,l,n]	D/S (staging) only in selected cases (problem solving tool) Less contradictory R/R (re-staging (recurrence)), TP (therapy planning, monitoring)	• Highly accurate for detection of liver metastases in PT with ColorectalCa, more specific than PET/MRI • Affects changes in PT management
		No (4)[d,e,f,o]	D/S (routine use) TM (routine surveillance)	
BladderCa				
No*	Scarce/inconclusive evidence	No*	No appropriate use criteria	
No (1)	Scarce evidence (D/S, R/R)	No (3)[b,d,o]	D/S bladder/urothelialCa + TM superficial TCC	
		Yes (1)[l]	TP (curative intent) advanced muscle-invasive bladderCa	
RenalCa				
No*	Scarce evidence	No*	No appropriate use criteria	
Unclear (1)	R/R (disease recurrence or metastases) insufficient evidence	RU (1)[l]	D/S (staging) (metastatic) renal (ureteric)Ca	
UtericCa				
No*	Scarce evidence	No*	No appropriate use criteria	
		Yes (2)[d,l]	Re-/staging utericCa (radical intent)	
		RU (2)[b,d]	R/R (recurrence) endometrialCa	
CervicalCa				
RU*	Some evidence Staging/Recurrence	No*	No appropriate use criteria, pot. for locally advanced Ca	
		Yes (2)[d,l]	Re-/staging (radical chemotherapy) locally advanced cervicalCa TP (pelvicexenteration/chemoradiation, curative intent)	
		RU (2)[b,l]	R/R (recurrence) cervicalCa TM (after chemoradiotherapy) locally advancedCa	
		No (2)[b,e]	TM (follow-up) specific cases described by ACR, after chemotherapy	
		Unclear (1)[e]	D/S (staging)—insufficient evidence	
OvarialCa				
No*	Scarce/inconclusive evidence	No*	No appropriate use criteria	
		Yes (1)[b]	R(R (recurrence) loco-regional and distant disease	
		RU (1)[l]	D/S (detection of tumor) rising CA125 level	
		No (2)[b,e]	D/S (diagnosis) D/S (staging), specific cases (high risk) described by ACR R(R (recurrence, re-staging) not considered for surgery TP (PT considered for secondary cytoreduction) – insufficient evidence	
TesticularCa				
No*	Inconclusive evidence	No*	No appropriate use criteria	
No (1)	D/S (staging), R/R (re-staging) – insufficient evidence	RU (3)[d,e,l]	D/S (M staging) R/R (recurrence) TM (treatment response) seminoma	
		No (1)[e]	R/R (routine use) – insufficient evidence TM (treatment response) nonseminoma	
ProstateCa				
No*	Not indicated	No*	No appropriate use criteria	
		RU (2)[h,l]	*^{11}C-Choline, ^{18}F-fluoro-choline, ^{68}Ga-PSMA*: Pre-treatment staging in high-risk PT + recurrence	• *^{11}C-Choline, ^{68}Ga-PSMA:* pre-treatment staging + recurrence (GA-PSMA-favorable) • *^{18}F-FACB:* R/R (pot. tool for recurrence)
		No (2)[b,f]	D/S, TM (specific cases described)	
PenilCa				
No*	Not indicated	No*	No appropriate use criteria	
		Yes (1)[l]	Pre-treatment staging	
No (1)	D/S (staging) R/R (re-staging) PenileCa – insufficient evidence			
Musculosceletal and soft tissue CA (+GIST)				
No*	No final recommendation possible	RU*	Biological aggressiveness before surgery, GIST	
		Yes (2)[l,n]	D/S (staging), TP (pre-amputation) high grade sarcoma R/R (recurrence) sarcoma D/S, TP (pre-treatment staging), R/R (treatment response) GIST	
		RU (2)[b,l]	D/S, R/R musculoskeletal tumor (specific cases described by ACR) D/S metastatic sarcoma suitable for metastasectomy *^{18}F-fluoridebone imaging* : D/S benign malignant bone disease	
		No (1)[b]	D/S soft tissue masses and musculoskeletal tumor (specific cases described by ACR)	
		Unclear (3)[b,l,n]	Contradictory recommendation: D/S osteosarcoma: Yes (RCR/RCP) vs. No (specific case described by American College of Radiologists) TM (treatment response): Yes, sarcoma (SNMMI) vs. Yes, but only for high grad sarcoma RCR/RCP	

Table 2 (continued)

HTA (n)	Notes	EBG (n)	Notes	Additional information from SR/MA
Lymphoma				
RU*	Some evidence Interim-/Re-/Staging/Recurrence	RU*	Different sub-indications	
		Yes (4)[d,e,l,o]	D/S e.g. castelman's disease TM (treatment response)	• PET-based treatment assessment should be considered in the management of PT with follicular lymphoma *(post-chemotherapy response assessment)*
		RU (2)[e,l]	D/S, TP HL/NHL	
		No (4)[b,e,l,p]	TM (monitoring + surveillance) routine use HL/NHL	
		Unclear (4)[d,e,l,n]	Contradictory recommendation: R/R (recurrent disease): RU (CCO, CAR) vs. Yes (RCR/RCO, SNMMI)	
Melanoma				
RU*	Diagnostic accuracy depending on tumor grade	RU*	Staging/Recurrence in higher stages, less contradictory	
		Yes (4)[d,e,l,n]	D/S (staging) high-risk PT (advanced stages) with pot. resectable disease D/S (specific cases described, e.g. merkel -cellCa) R/R (recurrence)	• Staging: better diagnostic accuracy in high-risk PT
		No (3)[e,f,l]	D/S (routine use) primary uveal malignant melanoma D/S (staging) I, IIa, IIb melanoma D/S (diagnosis) sentinel lymph node micrometastatic disease D/S localised primary cutaneous melanom TM (treatment response, routine surveillance) – insufficient evidence	
		Unclear (2)[l,n]	Contradictory recommendation: TM (treatment response): Yes (SNMMI) vs. RU (RCR/RCP)	
Paraneo-plastic syndrom (PNS)				
No*	Scarce evidence	No*	Not described	
		RU (2)[e,l]	D/S (specific cases described)	
Medical indications not reported in LBI-HTA report				
All tumors				
		RU (2)[d,l]	D/S (specific cases described) oligometastatic disease + CUP	
		No (3)[d,f,g]	R/R, routine surveillance + screening healthy individuals TP adenoma	
Myeloma				
		Yes (3)[c,j,l]	D/S, R/R, TM (specific cases described)	
		No (2)[b,l]	D/S (routine use)– insufficient evidence D/S multiple myeloma (specific case decribed)	
Neuroendocrine tumor				
		Yes (1)[l]	D/S, R/R (re-staging), TP paraganglioma	• ^{68}GA-DOTATATE PET more sens. & spec. than ^{68}GA-DOTATOC
		Yes (1)[l]	*^{68}Ga-labelled SSR*: D/S (staging), R/R (recurrence) *^{18}F-FuoroDOPA:* D/S (selected patients)	
		RU (1)[l]	TP (pre-treatmant) adrenocorticalCa	
		No (1)[o]	TM (surveillance)	

Ca carcinoma, *D/S* diagnostic/staging, *^{18}F-FDG* fludeoxyglucose (18F), *^{68}Ga-PSMA* ^{68}Ga-labelled prostate-specific membrane antigen, *GoR* grade of recommendation, *GIST* gastrointestinal stromal tumours, *GL* guidelines, *HTA* health technology assessments, *LoE* level of evidence, *MRI* magnetic resonance imaging, *NHL* non-hodgkin-lymphoma, *NSCLC* non-small cell lung cancer, *PT* patients, *R/R* recurrence/re-staging, *RU* restricted use, *SCLC* small cell lung cancer, *TCC* transitional cell carcinoma, *TM* therapy monitoring, *TP* therapy planning

*Recommendations from PET–HTA report 2015 [4]; color coding of recommendations and level of contradictories between the evidence sources: see Table 1; the number of HTA reports/guidelines is given in brackets; superscript letters indicate the respective guideline: a. ACCP, b. ACR, c. BSH, d. CAR, e. CCO, f. ChW, g. CNS/AANS, h. DGN, i. EANM/SNMMI, j. IMWG, k. RANO/EANO, l. RCP/RCR, m. Ryken, n. SNMMI, o. NCCN, p. NICE Do-not-Do; LoE/GoE for appropriate use/inappropriate use: see Box 1; information given in the table refer to FDG PET and PET–CT, and the use of other tracer are indicated in the table

Overall recommendations

Table 2 provides an overview of the overall recommendations on oncological indications (see also Table 1 for the explanation of colors and categories).

There is a (relative) consensus that there is sufficient evidence for sub-indications in eight indications in favour of PET or PET–CT examinations (in Table 2 highlighted green). The first six were already determined in the 2015 report—(1) bronchial carcinoma (update: mainly pre-treatment, contradictory in re-staging and response control and in therapy monitoring), (2) colon carcinoma, (3) malignant lymphoma, (4) malignant melanoma (update: contradictory for diagnosis of recurrence), (5) mamma carcinoma (treatment response, for diagnosis of recurrence), and (6) head–neck tumours (in 2015 report: CUP, thyroid carcinoma; update: mainly for diagnosis of recurrence)—while two new treatment areas were added by the update: (7) myeloma and (8) neuroendocrine tumours.

There is a (relative) consensus that, in eight other indication areas, there was too little evidence in favour of PET examination (individual decisions possible) (in Table 2 highlighted red): (1) bladder carcinoma, (2) hepatic cancer, (3) cervical carcinoma, (4) gastric cancer, (5) ovarian and (6) uterus carcinoma, (7) prostate cancer, and (8) paraneoplastic neurological syndrome.

Table 3 PET/PET–CT indications (neurology): overall recommendations

HTA (n)	Notes	EBG (n)	Notes	Additional information from SR/MA
Alzheimer's disease dementia and any other form of dementia/Mild cognitive impairment (MCI)				
		No (1)[f]	Routine use *(Amyloid tracer)* Evidence level unclear	• No Routine use (^{11}C-PIB-PET, ^{18}F-FDG PET) • Sensitivity & specificity of the three beta-amyloid radiotracers for quantitative and visual analysis are comparable to those with other imaging or biomarker techniques used to diagnose ADD • No differences in the diagnostic accuracy of the three beta-amyloid radiotracers
		RU (4)[d,e,f,g]	*^{18}F-labelled Amyloid (Florbetaben, Flutemetamol, Florbetapir, NAV4694) and ^{18}F-FDG PET, PET-CT:* D/S: PT with specific characteristics and cases described (different for the tracer*) Less contradictory, but based on weak evidence	
		No (5)[a,c,d,f,g]	*^{18}F-labelled Amyloid (Florbetaben, Flutemetamol, Florbetapir, NAV4694)* and *^{18}F-FDG PET, PET-CT:* D/S: PT with specific characteristics and cases described (different for the tracer*) Less contradictory, but based on weak evidence	
Unclear (1)	*^{18}F-FDG PET, PET-CT*: Diagnostic quality – able to detect temporoparietal changes with high degree of accuracy; marginally superior at identifying midly affected brain regions (compared to SPECT) – no concrete recommendation given			
Epilepsy (seizures)				
No (1)	Pre-surgical evaluation (pot. useful in conjuction with other imaging modalities)	RU (3)[a,b,f]	Pre-surgical evaluation (specific cases described*), setting: spec. epilepsy centres Less contradictory, but evidence level only given by ACR (7)	
		No (2)[a,b]	D/S: specific cases described, e.g. new-onset seizure, neonatal seizures D/S: PT with intractable infantile spasms after inconclusive initial diagnostic – insufficient evidence	

ADD Alzheimer's disease dementia, *11C-PIB* 11C-Pittsburgh compound B radiotracer, *D/S* diagnostic/staging, *FDG* 18F-Fluordesoxyglucose radiotracer, *GL* guidelines, *GoR* grade of recommendation, *HTA* health technology assessment, *LoE* level of evidence, *MA* meta-analysis, *PT* patients, *RU* restricted use, *SR* systematic reviews

*See PET–HTA report 2018 [5] for detailed cases; color coding of recommendations and level of contradictories between the evidence sources: see Table 1; number of HTA reports/guidelines is given in brackets; superscript letters indicate the respective guideline: a. ACR, b. CCO, c. ChW, d. EANM/SNMMI, e. EFNS, f. RCP/RCR, g. SNMMI/AA; LoE/GoE for appropriate use/inappropriate use: see Box 1; information given in the table refer to FDG PET, PET–CT, and the use of other tracer are indicated in the table

For a further set of eight indications, there is contradictory and equivocal evidence and recommendations were developed along with reservations (in Table 2 highlighted yellow or blue): (1) anal canal, (2) brain (especially glioma), (3) testicular, (4) renal, (5) penile carcinoma, (6) esophagus cancer (except re-staging), and (7) pancreatic carcinoma as well as (8) bone and soft-tissue tumour (+ gastrointestinal stromal tumour).

Evidence on neurological indications

Study characteristics

Two HTA reports were identified about neurological indications for the use of PET—one from the Australian Medical Services Advisory Committee (MSAC) [51] looking into Alzheimer's dementia (AD) and one compiled by the Canadian Agency for Drugs and Technologies in Health (CADTH) on epilepsy [52]. Reported endpoints in the included studies of these HTA reports refer mainly to diagnostic accuracy; no study could be identified that investigates diagnostic effectiveness and safety.

Recommendations and non-recommendations ($n = 28$) from professional societies (see Box 1 for abbreviations) were retrieved and extracted from CCO [24, 53], EFNS [54], RCR/RCP [29], SNMMI/AA [55], and a common guideline from EANM/SNMMI [56]. RCR/RCP [29] provides recommendations for several non- and oncological indications. Two further guidelines ([54, 55]) consider Alzheimer's dementia/dementia (ADD) or AD only, while another guideline (EANM/SNMMI [56]) presents general recommendations on brain-related disorders (refer to SNMMI/AA [55]) CCO [24, 53] (two guidelines) which considers epilepsy. In total, three SR/MA were included (for AD) [57–59]. All consider diagnostic accuracy in terms of primary diagnosis as the endpoint. Primarily, prospective studies were included in the SR/MA.

Quality assessment

The quality of the HTA was rated as very good, with only one question not judged as "yes". The assessment of the quality of the guidelines showed that domains 1 ("scope and purpose") and 4 ("clarity of presentation") received very high ratings and are quite consistent. However, in terms of editorial independence, applicability, and accuracy of the guideline development, big differences were observed. In the overall assessment, SNMMI/AA [55] ranks first; RCR/RCP is in last place [29]. All the SR/MA rated "critically low" in the overall quality assessment (no comprehensive score). As such, the SR/MA are to be used as supplementary information for the overall recommendations.

Overall recommendations

For recommendations of neurological indications, evidence identified and presented only two sub-indications: Alzheimer's dementia/dementia and epilepsy (see Table 3 for details).

There is a (relative) agreement that there is not sufficient evidence in favour of a PET/PET–CT for either of these two sub-indications (in Table 3 highlighted red), though professional societies uniformly/consistently name specific cases of AD or specific patient characteristics that speak for/against the use of PET, depending mainly on the respective tracer (amyloid vs. FDG). These recommendations, however, are only based on one source [55, Update: 60] and the authors themselves acknowledge the limitations, stating that, "At the time of this review, experience with clinical amyloid PET imaging [was] limited. Most published studies to date … [were] designed to validate this technology and understand disease mechanisms rather than to evaluate applications in clinical practice. As a result, published data are available primarily from highly selected populations with prototypical findings rather than from patients with comorbidities, complex histories, and atypical features often seen in clinical practice (e7)" [55].

Equivocal evidence (e.g., contradictory between HTA and EBG in Table 3, highlighted yellow or blue) was also found for the application of PET/PET–CT in patients having epilepsy (again, only in certain cases, in specialized epilepsy centres), though there is (some) consensus among the professional societies.

Evidence on inflammatory disorders

Study characteristics

In total, three HTA could be included about inflammatory disorder indications. One focused on infections in general from CADTH [61], dating back to 2008, and two other reports (each consists of a scoping report and an advice statement) from SHTG/HIS (2013) focus on pyrexia of unknown origin and sarcoidosis [62–65]. Reported endpoints in the studies within these HTA reports refer to diagnostic accuracy (mainly for primary diagnosis).

Recommendations and non-recommendations ($n = 18$) from professional societies (see Box 1 for abbreviations) were retrieved and extracted from ECCO/ESGAR [66], a common guideline of EANM/SNMMI [67] and RCR/RCP [29] who gave recommendations for several non-oncological indications. EANM/SNMMI [67] gave general recommendations on inflammatory disorders and ECCO/ESGAR [66] considers inflammatory bowel disease alone. Explicit non-recommendations by Choosing Wisely [37] or NICE Do-not-Do [38] were not identified.

In total, eight SR/MA were included for five indications [68–75]. All but two reviews [68, 69] include a meta-analysis and consider diagnostic accuracy as the primary endpoint.

Quality assessment

The quality of the three HTA was rated "very good", with only a few questions that could not be judged "yes". And the quality of the three guidelines revealed that domain 3 [on the rigour of the guideline development (including evidence clearly assigned to recommendations)] ranges widely, from 16% (RCR/RCP [29]) to 55% (ECCO/ESGAR [66]). Notably, all guidelines were rated 0% with regard to editorial independence (domain 6). The RCR/RCP [29] guideline scored poorest on in all areas compared to the other two. In the overall rating, ECCO/ESGAR [66] ranked first of the guidelines and all SR/MA were rated as "critically low".

Overall recommendations

Table 4 shows the overall recommendations regarding the appropriate or inappropriate use of PET/PET–CT for inflammatory disorder indications. There is (relative) consensus around sufficient evidence in favour of PET or PET–CT for infections of the vertebral column/spondylodiscitis. For the following four sub-indications, however, there is contradictory or inconclusive evidence: periprosthetic joint infection, osteomyelitis, sarcoidosis, and fever of unknown origin.

(2) Pilot study: evidence-based PET/PET–CT planning

In a second step, the recommendations derived from the evidence were applied (matched) to the hospital data on PET scans in one hospital (Carinthia, Austria) to gain an understanding of the PET utilization and capacity needs. Between January and September 2017, 1762 PET scans were conducted at the Clinicum Klagenfurt/Carinthia (KABEG Management: Needs-assessment of PET–CT at the Clinicum Klagenfurt, June 2018, unpublished). Of those, 1370 (77.8%) could be assigned to the three categories (see Tables 1–4) as recommended by evidence-based indications (963, 54.7%), not recommended (311.8%) and contradictory recommendations (376, 21.3%). The other 392 (of 1762, 22.2%) could not be allocated to any of the three treatment areas due to missing information of the diagnostic code or lack of information from recommendations in HTA or clinical guidelines.

A systematic analysis of all 1762 PET scans was not possible for two reasons: first, all ambulatory patients who

Table 4 PET/PET–CT indications (inflammatory indications): overall recommendations

HTA (n)	Notes	EBG (n)	Notes	Additional information from SR/MA
Immune-compromised PT/problematic cases				
		Yes (1)[d]	D/S: site of focal infection	
Infective endocarditis (native valve)				
				• Currently not sufficient for the diagnosis of infective endocarditis because of its low sensitivity
Infective endocarditis related to intravascular devices, pacemakers, catheters or prosthetic valves				
		Unclear (3)[a,b,d]	Post-surgery (after a certain time) vs. insufficient evidence/unclear	• As a promising imaging modality (adjunctive diagnostic tool) in evaluating PT with suspected CIED infection, PVE or IE in general • Should be considered in cases where the diagnosis is uncertain (PVE)
Inflammatory bowel disease				
		Unclear (2)[b,c]	D/S: Poorly specific	
Invasive mould infections				
Yes (1)	Helpful in clinical management			
Limbic encephalitis				
				• Should be integrated with other clinical or imaging investigations (such as MRI)
Lung infections				
		No (1)[a]	Specific case described	
Multiple infection indications				
Unclear (1)	Diganostic quality – no recommendation given			
Musculoskeletal infections – Charcots neuroarthopathy				
Yes (1)	Grading			
Musculoskeletal infections – Chronic extremity/back pain				
		No (1)[a]	D/S: Specific case described	
Musculoskeletal infections – Chronic osteomyelitis of the mandible				
Yes (1)	Follow-up			
Musculoskeletal infections – Infections of vertebral column or spondylodiscitis				
Yes (1)	Diagnostic quality – superior accuracy compared with other imaging methods	Yes (1)[b]	D/S: non-postoperative	• Robust diagnotisc test for suspected spondylodiscitis
Musculoskeletal infections – Joint (peri-)prosthetic infections (e.g. knee or hip implants)				
Yes (1)	Diagnostic quality – superior accuracy compared with other imaging methods	Unclear (2)[a,b]	Contradictory recommendation: Specific cases where it is not recommended vs. unclear (insufficient evidence)	• May not yet been the preferred imaging technique
Musculoskeletal infections – Osteomyelitis of foot (related to diabetes)				
		No (1)[a]	Specific case described	• As potentially useful tools if combined with other imaging methods
Musculoskeletal infections – Osteomyelitis				
Yes (1)	Diagnostic quality – superior accuracy compared with other imaging methods	No (1)[a]	D/S: Specific case described	
PUO				
No (1)	Diagnostic quality – insufficient evidence	RU (2)[b,d]	D/S (primary diagnosis + diagnostic quality)	
Sarcoidosis				
No (1)	Primary diagnosis (routine investigation) – insufficient evidence	RU (2)[b,d]	Specific cases (selected PT, after conv. imaging)	
Vasculitis				
		Yes (2)[b,d]	Specific cases described	
Further indications (no details given): Evaluation of potentially infected liver and kidney cysts in polycystic disease; AIDS-associated opportunistic infections, associated tumors, and Castleman disease; Assessment of metabolic activity in tuberculosis lesions; Diabetic foot infections				
		No[b]	Based on insufficient evidence**	
Further indications (no details given): Metastatic infection & of high-risk PT with bacteremia				
		Yes[b]	Based on insufficient evidence**	

AIDS Acquired Immune Deficiency Syndrome, *AS* anti-granulocyte scintigraphy, *BMS* bone-morrow scintigraphy, *BS* bone scintigraphy, *CIED* cardio-vascular implantable electronic device, *D/S* diagnostic/staging, *FDG* ^{18}F-Fluordesoxyglucose tracer, *GL* guidelines, *GoR* grade of recommendation, *HTA* Health Technology Assessment, *LoE* level of evidence, *LS* leukocyte scintigraphy, *MA* meta-analysis, *MRI* magnetic resonance imaging, *PT* patients, *PUO* Pyrexia of unknown origin, *PVE* prosthetic valve endocarditis, *SR* systematic reviews

*HTA report from 2008; **EANM/SNMMI: "Although there is still insufficient literature for this to be described as an evidence-based indication, we can conclude [major indications], on the basis of a cumulated reported accuracy (> 85%) and expert opinion…" and "Level of evidence available at this time for many of these indications remains insufficient to strongly advise the use of 18 F-FDG imaging as a first-line diagnostic tool."; color coding of recommendations, and level of contradictories between the evidence sources: see Table 1; the number of HTA reports/guidelines is given in brackets; superscript letters indicate the respective guideline: a. ACR, b. ECCO/ESGAR, c. EANM/SNMMI, d. RCP/RCR: LoE/GoE for appropriate use/inappropriate use: see Box 1; information given in the table refer to FDG PET, PET–CT, and the use of other tracer are indicated in the table

underwent a PET scan were coded with a non-specific diagnostic code (such as 'other' investigation), so that the underlying reasons for PET diagnosis could not be identified and, second, no diagnostic code was assigned to in-patients transferred for the PET scan from the other Carinthian hospitals. Of the 963 PET scans that were possible to match to evidence-based recommendations (see Table 5), four ICD-10 tumour categories alone accounted for 79%: C30–C39:

Table 5 PET scans and corresponding ICD-10 category matched to evidence-based recommendations ($n=994$), Clinicum Klagenfurt/Carinthia (KABEG Management: Needs-assessment of PET–CT at the Clinicum Klagenfurt, June 2018, unpublished)

ICD-10 categories	Recommended evidence-based indications ($n=963$), n (%)	Not recommended evidence-based indications ($n=31$), n (%)
C15–C26: malignant neoplasms, digestive organs	28 (3)	6 (19)
C30–C39: malignant neoplasms, respiratory system and intrathoracic organs	273 (28)	–
C43–C44: malignant neoplasms, skin	224 (23)	–
C50–C58: malignant neoplasms, breast, and female genital organs	67 (7)	6 (19)
C60–C63: malignant neoplasms of male genital organs	–	2 (7)
C64–C68: malignant neoplasms, urinary organs	–	10 (32)
C73–C75: malignant neoplasms, endocrine glands, and related structures	36 (4)	3 (10)
C76–C80: malignant neoplasms, secondary and ill-defined	5 (< 1)	1 (3)
C81–C96: malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic and related tissue	177 (18)	–
D00–D09: in situ neoplasms	–	1 (3)
D10–D36: benign neoplasms	52 (5)	2 (7)
D37–D48: neoplasms of uncertain or unknown behaviour	99 (10)	–
G30–G32: other degenerative diseases of the nervous system	2 (< 1)	–

malignant neoplasms, respiratory system, and intrathoracic organs (273, 28%), C43–C44: malignant neoplasms, skin, (224, 23%), C81–C96: malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic and related tissue (177, 18%), and D37–D48: neoplasms of uncertain or unknown behaviour (99, 10%).

The majority (22, 70%) of the 31 PET scans not recommended within evidence-based recommendations (see Table 5) were in the following three ICD-10 indications: C64–C68: Malignant neoplasms, urinary organs (10, 32%), C15–C26: malignant neoplasms digestive organs (6, 19%), and C50–C58: malignant neoplasms, breast and female genital organs, respectively (6, 19%).

Discussion

Summary of findings: (1) evidence-based indications and recommendations

Evidence assessments on PET/PET–CT have been increasingly published over the past two decades in many countries and languages. Taking a 2004–2014 perspective, the PET–HTA 2015 report identified 155 HTA reports to evaluate PET or PET–CT; even with a timeframe of 2008–2014, there were still 82 HTA available. Thirty-five of these were included and extracted for their statements on the use of PET/PET–CT for oncological indications. Five more recent HTA on oncological (sub-)indications were identified during the HTA report update. For the new indications—for neurological and inflammatory disorders—only five HTA could be considered. Recommendations of professional societies (e.g., guidelines) were also updated and explored for the three indications. A total of 234 recommendations were, therefore, included in the updated report. In addition, a total of 23 SR/MA provided supplementary information. Fifteen looked only at oncological indications. Cost-effectiveness of PETs was not an inclusion criterion and was, therefore, not explicitly considered; however, while almost no evidence exists, information was extracted from the reports when there was mention of cost-effectiveness.

In a comparison of HTA results, the tabulated recommendations of professional societies and SR/MA for oncological indications reveal that there is general agreement on "significant" indications (e.g., bronchial carcinoma, and head and neck tumours) for the use of PET/PET–CT. However, there are significant differences in the level of detail of sub-indications and in the approach for when a scan should not be performed. There is also significant variance in the reliance on the access of graded pre-diagnostics.

Between the current study and the 2015 PET–HTA report, several changes in the categorization of oncology indications and in level of contradictory among the evidence sources have occurred (below is an overview; see Tables 1, 2, 3, 4):

– Mamma carcinoma (now recommended for certain sub-indications such as tumour response assessment for metastatic mamma carcinoma (mainly bone metastases), before: not recommended)

- Cervix carcinoma (not recommended, before contradictory)
- Testicular, renal, and penis carcinoma (contradictory, before not recommended)
- New (not included in the PET–HTA report 2015): myeloma (recommended), neuroendocrine tumours not recommended), anal canal cancer (contradictory)

In the case of neurological indications and inflammatory disorders, there is comparatively more discrepancy in the recommendations of professional societies and between the HTA and professional societies. There is a notable, consistent emphasis on the weak and insufficient evidence base. The SR/MA included in our report demonstrate this: all were considered "critically low" in the quality assessment.

Summary of findings: (2) pilot study on evidence-based PET/PET–CT planning

Based on evidence-based recommended and not recommended indications formulated in step (1) of this study, a first-ever pilot of planning PET capacities was conducted and, as such, has no comparator.

A data-driven needs-assessment was initially conducted to provide a basis for an investment decision around the need for an additional PET–CT scanner in Carinthia, Austria. First, diagnoses were coded according to ICD-10 classifications. Then, the 1762 PET scans performed between January and September 2017 were matched to relevant recommendations for evidence-based indications/non-indications, resulting in 77.8% being assigned to either recommended (54.7%), not recommended (1.8%) or contradictory (21.3%) evidence-based indications. 22.2% could not be ascribed due to missing information of the diagnostic code or lack of information from recommendations in HTA or clinical guidelines. Based on the data analysis and an additional assessment of the utilization as well as occupancy rates, it was decided against the investment in a second PET scanner in Carinthia.

Limitations

The main strength of the presented work is the rigorous, systematic approach applied in all steps (e.g., double-check principle and quality assessment), complemented a comprehensive, targeted manual search. Nevertheless, the methodical process has some limitations. The systematic synthesis of available evidence, which mainly relies on already aggregated evidence, may result in a certain loss of detailed information. In addition, the primary outcome of interest in the data extraction was the conclusions as articulated by the respective authors, which are different in terms of formulation and meaning and, therefore, difficult to compare. As a result, a trend can be seen in the statements.

Moreover, the multitude of recommendations from professional organizations necessarily led to a capping of the number of sources, meaning that some were not included and important contextual insight may have been lost. For example, the S3 guidelines from the Association of Scientific Medical Societies e.V. (AWMF) in Germany and the guidelines from the Scottish Intercollegiate Guidelines Network (SIGN) were not included as they do not have a specific PET/PET–CT focus. However, they both provide important recommendations as they consider not only "study evidence", but also detailed aspects of the diagnostic-therapeutic chain and differentiate more comprehensively among tumour entities. That some guidelines were a priori omitted may lead to a potential bias (of the overall picture). Similarly, the heterogeneous quality of the included guidelines may also result in a skewed overall picture of existent recommendations. The summary tables make this transparent by assigning respective recommendations to the corresponding guidelines, referencing, as well, the strength of evidence. Finally, in Tables 2, 3, and 4 of the overall recommendations, a differentiated consideration of tumour entities is lost. Nevertheless, they provide an overall picture that can be useful (see pilot).

Regarding the 22.2% of PET scans in Carinthia, Austria, that could not be assigned to a recommendation in the pilot study, one reason could be the very specific indications found in the evidence or a too detailed coding. In general, while the high number of PET scans that could not be ascribed to any category could be seen as limiting the explanatory/instructive power of the pilot to use evidence-based indication lists as basis for a needs-assessment and investment decisions, it also shows clearly that there is a need for improvement of coding indications within the context of planning of medical services. For the final investment decision, further information on timing and frequency of PET utilization and occupancy rate over full work days and weeks are needed.

Conclusion

Overall, this study has resulted in more detailed information and specifications around PET/PET–CT indications as compared to the 2015 PET–HTA report. This update together with the aggregate list of overall recommendations for indications as well as the explicit non-recommendations from the 2015 PET–HTA report can serve as needs-based and evidence-based decision support for PET/PET–CT service provision in hospitals as evidenced by the pilot study in Austria. A better coding of PET utilization is needed for planning. Furthermore, additional information such as timing, frequency of PET utilization, as well as occupancy rate

over full work days and weeks, is also necessary to guide an investment decision.

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Conflict of interest All authors declare that they have no conflict of interest.

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