Positron Emission Tomography (PET) and PET/CT in Thyroid Cancer: A Systematic Review and Meta-Analysis

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Keywords

Thyroid cancer · Positron emission tomography · Systematic review · Meta-analysis

Abstract

Background: Positron emission tomography (PET) and PET/CT are functional imaging methods that are widely used in diagnostic procedures in oncology. **Objectives:** The objective of this study was to assess the patient-relevant benefit of PET or PET/CT in patients with thyroid cancer based on a literature review and meta-analysis. **Methods:** A systematic review including studies that had been published until December 2013 was performed. To be included, studies had to prospectively investigate patients with thyroid cancer in a clinical setting of staging, restaging, or diagnosing tumour recurrence. **Results:** Out of 3,506 potentially relevant articles, 29 studies were included. No study directly evaluated the benefits of PET. Twenty-eight studies dealt with the diagnostic accuracy of PET or PET/CT, and 1 study evaluated the prognostic value of PET/CT. The authors showed that a positive result of PET/CT in restaging patients with differentiated thyroid cancer yielded a significant decrease in overall survival (hazard ratio, HR 5.01, CI 3.41–6.62). In patients with

suspected recurrence of differentiated thyroid cancer, meta-analysis showed higher sensitivity of PET (89.7%, CI 78–99%) and PET/CT (94.3%, CI 87–97%) compared with conventional imaging (65.4%, CI 32–88%) and comparable results for specificity. Due to the low numbers of studies and patients, meta-analyses on medullary carcinoma did not produce meaningful results. **Conclusion:** The patient-relevant benefits of PET or PET/CT in thyroid cancer could not be evaluated satisfactorily based on the included studies. It remains unclear whether higher diagnostic test accuracy leads to changes in therapeutic strategies and better patient-relevant outcomes.

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Introduction

Thyroid cancer is the most common endocrine cancer, responsible for approximately 1% of all malignant diseases [1]. Since the end of the 1990s, the incidence of thyroid cancers in women has increased to nearly double in

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Germany. Still, malignant thyroid tumours have a comparatively good prognosis. In 2012 in Germany, the 10-year survival rate was 71% for men and 85% for women [2]. Despite these high rates, some patients suffer from metastatic and/or recurrent disease, which makes a precise diagnostic evaluation necessary to determine further treatment options. Because morphological imaging by CT or MRI may give inconclusive information, especially in pre-operated areas, the application of functional imaging may be useful [3]. Positron emission tomography (PET) is such a functional imaging method. Considering the elevated rate of glucose metabolism in malignant tissue, the application of chemically modified glucose molecules such as fluorodeoxyglucose-18F (^{18}F -FDG) may be helpful in visualizing metastatic or recurrent disease. However, according to current European Guidelines, the application of PET or PET/CT using ^{18}F -FDG (FDG PET, FDG PET/CT) should only be considered for patients with differentiated thyroid carcinoma and suspicion of recurrence because of rising thyroglobulin levels and negative whole-body scintigraphy [4]. Other indications for PET or PET/CT in patients with thyroid carcinoma are under discussion. It especially remains unclear whether the application of PET or PET/CT in patients with thyroid cancer affects therapeutic strategies and will have an impact on patient-relevant outcomes. The aim of the following work was the investigation of the patient-relevant benefits and harms of PET or PET/CT in patients with thyroid cancer.

Methods

In 2006, the German Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to investigate the current state of outcomes on PET in 14 oncological entities. The authors of this paper, constituting the project group, were engaged as scientific experts to support the preparation of the report on PET in thyroid cancers. Afterwards, the official commission was retracted for priority reasons. The current paper describes the results of the scientific output of this project. All reporting follows PRISMA standards [5]. All methods were prospectively defined and published as a German-language report plan on the IQWiG website [6].

Literature Search

We conducted a systematic literature search in the databases MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials in February 2010 and in December 2013. An example of the full search strategy is given in online supplementary Table 1 (see www.karger.com/doi/10.1159/000481707 for all online suppl. material). Furthermore, we performed a search for relevant studies in the following study registers and congress proceedings: American Society of Clinical Oncology (ASCO), European Association

Fig. 1. Results of the systematic literature search. Inclusion criteria: E1, patient characteristics; E2, PET and reference test; E3, study design; E4, outcome; E5, single publication; E6, publication with full text.

of Nuclear Medicine (EANM), European Cancer Organisation (ECCO), European Society of Medical Oncology (ESMO), US National Institute of Health, World Health Organization, International Clinical Trials Registry Platform Search Portal, and UK Clinical Research Network Study Portfolio. Two readers independently performed the review process in two steps. All abstracts and subsequently all full texts were screened in order to identify relevant studies. Discrepancies were resolved by consensus.

Inclusion Criteria

Intervention studies and diagnostic accuracy studies were both eligible for the current review. There were no restrictions with regard to type of thyroid cancer (differentiated, medullary, other). Studies had to investigate clinical settings of staging, detection of recurrence, or restaging. However, patients with suspected recurrence had to be iodine-negative. Intervention studies had to have a randomized or non-randomized design with parallel controls and had to compare PET or PET/CT with any other imaging modality (including no imaging or other PET imaging). Outcomes of interest included mortality, morbidity, and health-related quality of life. Diagnostic and prognostic accuracy studies were included if imaging results were verified against either histopathological findings or clinical follow-up (at least 6 months and at most 12 months) reference standards. Studies were required to have a prospective cohort design and were excluded only if they were of clear retrospective design. Again, it was required that studies compared PET or PET/CT with any other imaging modality. Missing data did not exceed 20% of the study population per item.

Table 1. Characteristics of included studies

Histology	Indication	Outcome	Study	Design	Patients, <i>n</i>	M/F	Test	Comparison	Potential bias
Differentiated thyroid carcinoma (<i>n</i> = 22)	Restaging (<i>n</i> = 3)	Prognostic value	Nagamachi, 2011 [10]	N/A	70	22/48	FDG PET/CT	whole-body scintigraphy, MRI	high
		Diagnostic value	Nakajo, 2013 [11]	prospective	20	5/15	FDG, FLT PET/CT	–	high
			Oh, 2011 [12]	N/A	140	30/110	FDG PET/CT	whole-body scintigraphy, SPECT	high
	Recurrence (<i>n</i> = 19)	Diagnostic value	Chen, 2003 [13]	N/A	23	8/15	FDG PET	SPECT	low
			Chung, 1999 [14]	N/A	54	12/42	FDG PET	thyroglobulin level	low
			Dietlein, 1997 [15]	prospective	41 ^a	N/A	FDG PET	–	high
			Frilling, 2001 [16]	prospective	24	8/16	FDG PET	US, CT	low
			Giovanella, 2012 [17]	N/A	46	9/37	FDG PET/CT	–	low
			Giovanella, 2013 [18]	N/A	124	25/99	FDG PET/CT	–	low
			Grünwald, 1997 [19]	N/A	40 ^b	N/A	FDG PET	SPECT	high
			Helal, 2001 [20]	prospective	37	19/18	FDG PET	conventional imaging (chest X-ray, CT, MRI, bone scintigraphy)	high
			Jadvar, 1998 [21]	N/A	10	2/8	FDG PET	conventional imaging (CT, MRI, octreotide scintigraphy, US)	high
			Kim, 2009 [22]	prospective	20	4/16	FDG PET/CT	–	high
			Kingpetch, 2011 [23]	N/A	22	0/22	FDG PET/CT	–	low
			Kunawudhi, 2012 [24]	prospective	30	8/22	FDG PET/CT	–	low
			Mirallí, 2007 [25]	prospective	45	14/31	FDG PET/CT	–	high
			Ozkan, 2013 [26]	N/A	59	15/44	FDG PET/CT	–	low
			Palmedo, 2006 [27]	prospective	40	N/A	FDG PET, PET-CT, PET/CT	CT	high
			Sager, 2013 [28]	N/A	20	7/13	FDG PET/CT	SPECT, MIBI scintigraphy	high
			Vural, 2012 [29]	prospective	105	38/67	FDG PET/CT	–	high
			Weber, 2012 [30]	prospective	18	7/11	FDG PET/CT	–	low
			Yamaga, 2007 [31]	N/A	24	8/16	FDG PET/CT	conventional imaging (CT, MRI, US)	low
Medullary thyroid carcinoma (<i>n</i> = 7)	Recurrence	Diagnostic value	Kauhanen, 2011 [32]	prospective	19	10/9	FDG, FDOPA PET/CT	CT, MRI	high
			Marzola, 2010 [33]	N/A	18	8/10	FDG, FDOPA PET/CT	–	low
			Musholt, 1997 [34]	N/A	10	7/3	FDG PET	CT, MRI	high
			Naswa, 2012 [35]	prospective	52	38/14	FDG, DOTANOC PET/CT	–	high
			Rubello, 2008 [36]	prospective	19	8/11	FDG PET/CT	SPECT, US, CT	high
			Sager, 2013b [37]	N/A	16	2/14	FDG PET/CT	SPECT, octreotide scintigraphy	high
			Skoura, 2012 [38]	prospective	51	15/36	FDG PET/CT	–	high

N/A, not available. ^a Study population *n* = 58, patient characteristics N/A for relevant subpopulation. ^b Study population *n* = 54, patient characteristics N/A for relevant subpopulation.

Methodological Study Quality Assessment

Studies were evaluated concerning their methodological quality. Depending on study outcomes (prognostic vs. diagnostic accuracy), different questionnaires based on the QUADAS criteria were applied [7]. Finally, all studies were classified as having either a high or a low risk of bias.

Statistical Analysis

Only studies that reported results for both sensitivity and specificity were included in the analysis. Furthermore, only patient-level data were used, as lesion-specific analyses in primary studies can hinder data interpretation. For the analysis of conventional imaging only studies with whole-body procedures were included.

A meta-analysis was performed for diagnostic accuracy studies using a generalized random effects model (GLIMMIX procedure in SAS) [8]. The results of the bivariate analysis are presented with summary ROC curves generated with Review Manager [9]. If a calculation of confidence intervals was not feasible because of an insufficient number of studies, the standard error of the mean (SEM) was given. Confidence intervals are given with a coverage probability of 95%.

Results

The systematic literature search revealed 3,506 potentially relevant abstracts. After the primary screening, 373 potentially relevant publications were identified. Finally, 29 studies met the inclusion criteria (Fig. 1). No study directly evaluated the benefits of PET. The study population consisted of patients with differentiated thyroid carcinoma in 22 studies, whereas patients with medullary carcinoma were investigated in 7 studies. In 26 studies, patients were recruited because of suspected recurrence of disease. In the 3 remaining studies, patients were evaluated during restaging. The diagnostic accuracy of PET was investigated in 28 studies, and 1 study reported the prognostic value of PET/CT. Patient and study characteristics of the included studies are given in Table 1.

Differentiated Thyroid Carcinoma: Prognostic and Diagnostic Value in Restaging

The study by Nagamachi et al. [10] was the only publication that dealt with the prognostic value of PET/CT in thyroid cancer. The authors showed that, among several potentially prognostic factors, only a positive PET/CT result (hazard ratio, HR 5.01, CI 3.41–6.62) and an age older than 45 years (HR 4.64, CI 3.89–5.26) have a significant negative impact on overall survival in patients with differentiated thyroid carcinoma in restaging. The 2 remaining studies on restaging patients with differentiated thyroid carcinoma showed a pooled sensitivity and specificity for PET/CT of 77.8% (SEM 13.5) and 95.2% (SEM 4.2) in the bivariate meta-analysis.

Differentiated Thyroid Carcinoma: Diagnostic Value in Recurrence

In 8 studies, patients with differentiated thyroid carcinoma and suspected recurrence were evaluated with FDG PET. The pooled sensitivity and specificity were 89.7% (CI 78.1–98.5%) and 87% (CI 73.5–94.2%) (Fig. 2). The pooled sensitivity of studies evaluating FDG PET/CT ($n = 11$) was better at 94.3% (CI 87.1–97.6%) but showed

Fig. 2. Summary ROC for bivariate meta-analysis of FDG PET in differentiated thyroid carcinoma with suspected recurrence: a, Frilling 2001; b, Chen 2003; c, Chung 1999; d, Jadvar 1998; e, Helal 2001; f, Grünwald 1997; g, Palmedo 2006; h, Dietlein 1997; i, pooled sensitivity and specificity with 95% confidence region (dashed line): sensitivity 0.897 (CI 0.781–0.985), specificity 0.87 (CI 0.735–0.942).

a lower specificity of 78.4% (CI 52.4–92.3%) compared with FDG PET (Fig. 3). The pooled results for studies that included conventional whole-body imaging ($n = 5$) showed a lower sensitivity of 65.4% (CI 32–88.4%) and a similar specificity of 87.9% (CI 43.9–98.5%) for conventional imaging techniques compared with PET results (Fig. 4).

Medullary Thyroid Carcinoma: Diagnostic Value in Recurrence

The pooled sensitivity and specificity of FDG PET/CT of the included studies ($n = 2$) evaluating patients with medullary thyroid carcinoma was 62.8% (SEM 17.1) and 34.2% (SEM 57.3). In the bivariate analysis of the included studies ($n = 2$), conventional imaging showed a similar sensitivity of 67.4% (SEM 9.8) and a higher specificity of 67.1% (SEM 37.2).

Methodological Assessment

Due to the results of the methodological assessment, 18 of 29 studies were deemed potentially highly biased.

Fig. 3. Summary ROC for bivariate meta-analysis of FDG PET/CT in differentiated thyroid carcinoma with suspected recurrence: a, Kim 2009; b, Weber 2012; c, Giovanella 2013; d, Palmedo 2006; e, Giovanella 2012; f, Vural 2012; g, Yamaga 2007; h, Kunawudhi 2012; i, Kingpetch 2011; j, Ozkan 2013; k, Mirallié 2007; I, pooled sensitivity and specificity with 95% confidence region (dashed line): sensitivity 0.943 (CI 0.871–0.976), specificity 0.784 (CI 0.524–0.923).

Fig. 4. Summary ROC for bivariate meta-analysis of conventional imaging in differentiated thyroid carcinoma with suspected recurrence: a, Jadvar 1998; b, Chen 2003; c, Helal 2001; d, Grünwald 1997; e, Palmedo 2006; f, pooled sensitivity and specificity with 95% confidence region (dashed line): sensitivity 0.654 (CI 0.32–0.884), specificity 0.879 (CI 0.439–0.985).

The main limitations of the study methods were the following:

- Unacceptable time interval between index and reference test (mostly between PET or conventional imaging) concerning the evaluation of follow-up information (19/29 studies).
- Given or missing information about PET as part of follow-up imaging and, therefore, as part of the reference test (15/29 studies).
- Missing information about consecutive patient recruitment (19/29 studies).
- Missing information about blindness of evaluation of index and reference test, especially in studies with follow-up periods (29/29 studies).

Discussion

The patient-relevant benefits of PET or PET/CT for patients with thyroid cancer could not be evaluated satisfactorily on the basis of the included studies. None of the

included studies evaluated the effect of PET or PET/CT on therapeutic strategies and, therefore, patient-relevant outcomes in patients with thyroid cancer. Only 1 study showed a significant negative association with overall survival of a positive FDG PET/CT result in restaging patients with differentiated thyroid cancer. However, it remains unclear how this affects treatment decisions and consequent outcomes such as mortality or progression-free survival. During a phase II trial investigating the tyrosine-kinase inhibitor sunitinib in patients with metastatic thyroid cancer, only PET-positive patients were recruited, and further PET studies were used to evaluate the therapeutic response [39]. The authors showed a median time to progression under sunitinib of 12.8 months. Because the study missed a control group, the significance of the progression-free survival intervals remains uncertain. Additionally, in approval studies for other tyrosine-kinase inhibitors, conventional imaging methods such as CT and MRI were used instead of PET [40–42].

A possible procedure to evaluate a patient-relevant benefit of PET or PET/CT in patients with thyroid cancer

could be a randomization of patients with iodine-negative differentiated thyroid cancer. One study group would receive PET/CT imaging and the other conventional imaging such as CT and MRI. Depending on the results of the imaging methods, a decision of therapeutic management could be made and patient-relevant outcomes such as overall survival could be evaluated.

For patients with differentiated thyroid carcinoma and suspicion of tumour recurrence, the meta-analysis showed a higher sensitivity and a similar specificity for FDG PET/CT compared with conventional imaging. However, the differences between diagnostic modalities (PET vs. PET/CT vs. conventional imaging) cannot lead to general conclusions because of overlapping confidence intervals throughout the analysis. This is the first meta-analysis that also addresses the comparison between PET/CT and conventional imaging in thyroid cancer. Haslerud et al. [43] published a recent meta-analysis including patients with recurrent differentiated thyroid cancer. The authors showed a sensitivity and specificity for PET and PET/CT of 79.4% (CI 73.9–84.1%) and 79.4% (CI 71.2–85.4%). The published sensitivity is therefore lower than in our analysis, whereas the specificity is comparable to ours. In contrast to our work, the authors included prospective and retrospective studies that had been published until December 2014. They also pooled the results for both PET and PET/CT studies.

The meta-analysis for patients with medullary thyroid carcinoma showed a similar sensitivity of 62.8% (SEM 17.1) versus 67.4% (SEM 9.8) and a lower specificity of 34.2% (SEM 57.3) versus 67.1 (SEM 37.1) for FDG PET/CT compared with conventional imaging. However, the conclusions from these results are highly restricted because of the few studies with small sample sizes that were eligible for the bivariate analysis. A recently published meta-analysis has pooled sensitivities of PET/CT from studies investigating patients with medullary thyroid carcinoma [44]. The results for the sensitivity of PET/CT of 69% (CI 64–74%) are similar to ours.

A possible shortcoming of our analysis is the inclusion of studies only until December 2013. Since then a few potentially relevant accuracy studies with small sample sizes have been published dealing with the application of PET in differentiated and medullary thyroid carcinoma [45–51]. Two studies prospectively investigated the prognostic role of PET/CT addressing patient-relevant outcomes [52, 53]. However, so far no study has used a comparative and controlled study design in order to investigate the impact of PET/CT on the therapeutic man-

agement of thyroid cancer patients and its potential influence on patient-relevant outcomes.

Conclusion

In conclusion, the patient-relevant benefit of PET or PET/CT in patients with thyroid cancers remains unclear. A systematic evaluation of the application of PET imaging in thyroid cancer in randomized controlled trials is needed in order to assess its value for these patients.

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Disclosure Statement

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

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