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ORIGINAL ARTICLE

Practice-based evidence for the clinical benefit of PET/CT—results of the first oncologic PET/CT registry in Germany

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Abstract

Purpose The purpose of this study was to evaluate the impact of PET/CT on clinical management of cancer patients based on a prospective data registry. The study was developed to inform consultations with public health insurances on PET/CT coverage.

Methods We evaluated a prospective patient cohort having a clinically indicated PET/CT at a single German University Center from April 2013 to August 2016. The registry collected questionnaire data from requesting physicians on intended patient management before and after PET/CT. A total of 4,504 patients with 5,939 PET/CT examinations were enrolled in the registry, resulting in evaluable data from 3,724 patients receiving 4,754 scans. The impact of PET/CT on patient management was assessed across 22 tumor types, for different indications (diagnosis, staging, suspected recurrence) and different categories of management including treatment (curative or palliative) and non-treatment (watchful waiting, additional imaging, invasive tests).

Results The most frequent PET/CT indication was tumor staging (59.7%). Melanoma, lung cancer, lymphoma, neuroendocrine tumor and prostate cancer accounted for 70% of cases. Overall, the use of PET/CT resulted in a 37.1% change of clinical management (95% CI, 35.7–38.5), most frequently (30.6%) from an intended non-treatment strategy before PET/CT to active treatment after PET/CT. The frequency of changes ranged from 28.3% for head and neck cancers up to 46.0% for melanomas. The impact of PET/CT was greatest in reducing demands for additional imaging which decreased from 66.1% before PET/CT to 6.1% after PET/CT. Pre-PET/CT planned invasive tests could be avoided in 72.7% of cases. The treatment goal changed after PET/CT in 21.7% of cases, in twice as many cases from curative to palliative therapy than vice versa.

Conclusions The data of this large prospective registry confirm that physicians often change their intended management on the basis of PET/CT by initiating treatment and reducing additional imaging as well as invasive tests. This applies to various cancer types and indications.

Keywords PET/CT · Benefit assessment · Registry · Patient management

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Introduction

In times of rising healthcare costs not only therapeutic interventions but also diagnostic procedures like PET/CT have to demonstrate their patient-related benefit if they are to be reimbursed by public health insurance [1–3]. Evaluation of diagnostic tests is often restricted to test accuracy only. There is a growing body of evidence in the literature that PET/CT has superior sensitivity and specificity in staging of many cancers compared to other imaging methods [4]. However, improved test performance does not necessarily translate into changes of treatment and better patient outcome. Diagnostic imaging like PET/CT is always embedded in a clinical pathway, and the separation of the specific contribution of the test to patient outcome is challenging [5]. Randomized controlled trials

(RCT) comparing two diagnostic procedures and resulting therapies regarding survival allow to assess the influence of a new test on patient-related outcome directly. This type of direct evidence is almost lacking in the context of PET/CT because diagnostic RCT's are difficult to perform due to constraints by time, recruitment, and resources [6–10]. Literature regarding effectiveness of PET/CT and its influence on clinical decision making is limited and relates to selected tumors like lymphoma, lung, colorectal and head and neck cancers as well as neuroendocrine tumors (NET) [11–18]. Only few studies have a randomized controlled design [19–21]. The missing RCTs and the lack of agreement on how to generate evidence on the benefit of PET/CT have led to considerable differences in adoption and coverage of this technology, with significant reimbursement restrictions in some countries.

Prospective data of the US National Oncologic PET Registry (NOPR) gathered from more than 1,000 PET centers several years ago have shown that PET has a substantial impact on management decisions, with a change of management in 36.5% of patients [22]. Encouraged by these results and to prevent limited patient access to PET/CT we established a prospective oncologic PET/CT registry at a large university hospital in Germany, to collect comprehensive data on the clinical impact of this imaging technology. The regional health insurance companies agreed to provide coverage for the PET/CT studies as part of the registry. The primary endpoint of the study was to assess the impact of PET/CT on referring physicians' intended management in the daily routine across different cancers and clinical indications.

Patients and methods

Registry design and workflow

The prospective and consecutive data base registered all patients with a clinically indicated PET/CT performed for oncological reasons at the PET/CT center of the Tuebingen University Hospital in Germany, during a 3.5-year period from April 2013 to August 2016. The study was reviewed and approved by the University Institutional Review Board. Informed consent regarding the use of data for research was obtained from all patients. Referring physicians from in-house and outpatient care were briefed in advance about the aim of the study, the registry design, and the handling of the standardized pre- and post-PET/CT questionnaires. They were also instructed to strictly follow a predefined catalogue of cancer-related PET/CT indications. Each PET/CT request had to be checked by qualified personal to avoid non-justified (and non-reimbursed) cases where conventional imaging (CT, MRI etc.) would be sufficient to establish the diagnosis. When a PET/CT scan was ordered, the referring physician was asked to complete the standard PET/CT request form including information on cancer type, indication for imaging, prior imaging and therapy, as well as basic clinical data of the patient. A registry-related pre-PET/CT questionnaire also had to be completed which included the specific PET/CT indication (diagnosis, staging, or detection of recurrence), the cancer type by ICD-10 code and the intended management plan if PET/CT was not available (for definitions of management categories see below). After the PET/CT examination, the referring physician had to fill in the post-PET/CT form which records the management plan established with knowledge of the PET/CT report. The questionnaire format was designed by the PET/CT center following the conception of the NOPR [23] and was the same for all cancer types (Supplementary Fig. 1). The PET/CT examinations were performed using standardized protocols including state-of-the-art CT with oral and intravenous contrast (Biograph mCT, Siemens Healthineers, Germany). Depending on cancer type, different PET tracers were applied: [68Ga]-DOTATATE (NET), [68Ga]-PSMA (prostate cancer), [11C]-Choline (prostate cancer), [11C]-Methionine (brain tumors, parathyreoid tumors), [18F]-FET (brain tumors), [18F]-FDG (all others). Examination protocol and reporting of PET/CT results were not influenced by participation in the study.

All patient-related data such as social-demographic and morphometric information (age, sex, health insurance coverage, weight, size, BMI), relevant medical data and the pre- and post-PET/CT questionnaires were collected prospectively and consecutively in paper-based case record forms (CRFs). The CRFs were entered into the Koordobas-database (www.koordobas.de) managed by qualified and approved personel under the guidance of the University Institute of Clinical Epidemiology and applied Biostatistics. Koordobas is a validated web-based database application to support the organization and data management of clinical and epidemiological research projects, studies and registries according to common requirements for conduction of studies (ICH/GCP, FDA). The correctness of the data entry was controlled by double data entry (DDE). Figure 1 illustrates the workflow of the PET/CT registry.

Definition of PET/CT indications

For ordering a PET/CT scan the referring physicians had to follow a predefined catalogue of cancer-related indications. Based on the pre-PET/CT registry questionnaire he had to decide between "diagnosis", "staging" or "detection of recurrence" as specific indication for the PET/CT. "Diagnosis" was defined as differentiation between benign and malignant lesions (e.g. single pulmonary nodule) or searching of the primary tumor site (CUP). "Staging" included primary TNM staging as well as re-staging after therapy or during interval monitoring. For the indication "detection of recurrence" a clinical suspicion was required.

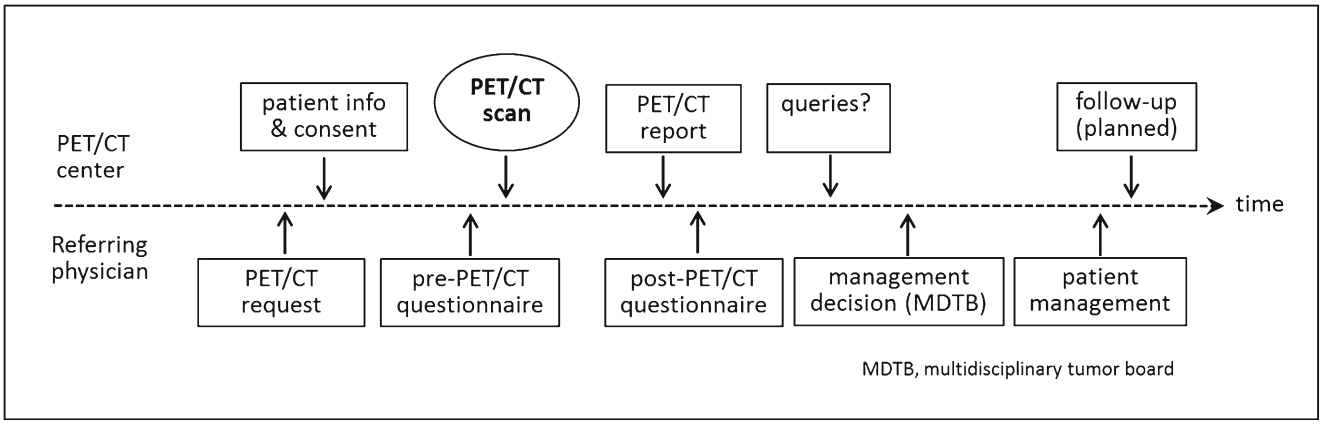

Fig. 1 Workflow PET/CT registry

Categories of management

In the questionnaires (Supplementary Fig. 1), the referring physicians were asked about hypothetical clinical management options if PET/CT was not available (pre-PET/CT questionnaire) and about the final management decision after knowing the PET/CT result (post-PET/CT questionnaire). In this regard they had to choose between the treatment options surgery, radiotherapy or systemic therapy (alone or in combination)—for data analysis summarized in the management category "treatment"—and the non-treatment options, which consisted of watchful waiting, additional testing (imaging or invasive procedures) or best supportive care—summarized in the management category "non-treatment". In case of "treatment" the therapeutic goal was determined as either curative or palliative treatment. In accordance with the NOPR, a change in management after PET/CT was assigned to the following different categories (Fig. 2): (1) a switch from non-treatment to active treatment or vice versa, (2) in case of treatment, a change of therapeutic goal from curative to palliative or vice versa, (3) in case of non-treatment, a change to watchful waiting including best supportive care, or (4) prevention of invasive tests. Management changes were analyzed for the whole study cohort as well as for each cancer type and PET/CT indication, respectively.

Methods of statistical analysis

Survey data was collected and recorded by the PET/CT center of the Department of Radiology. The data was then cleaned and anonymized by the University Institute of Clinical Epidemiology and applied Biostatistics. Double data entry was applied, and in case of discordant data, the questionnaires were checked. Age of patients was described using mean, median, and interquartile range. To investigate management changes, in a first step we classified management plans in categories (details given above and in Fig. 2) and compared these categories before and after PET/CT. The analysis focused on changes concerning treatment/non-treatment and curative/palliative treatment goal. Results are presented using

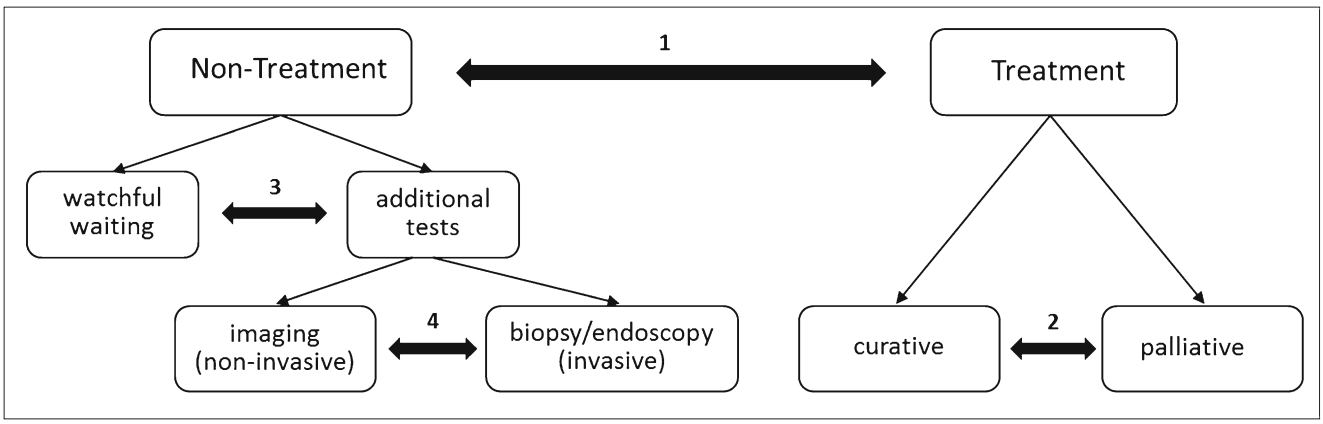

Fig. 2 Categories of management changes after PET/CT: (1) switch between active treatment (all types) and non-treatment strategies (watchful waiting, additional testing like imaging or biopsy, or best supportive care), (2) change between curative and palliative treatment goal, (3) change between watchful waiting and the demand for additional testing, and (4) change between imaging and invasive tests

absolute and percentage frequencies. Sankey graphs [24] are used to visualize the frequency of transitions from the pre-PET/CT to the post-PET/CT management plan, separately for the non-treatment and treatment category. For the main results, two-sided 95% confidence intervals were given. Analysis was performed using software SPSS (release 23) and R (release 3.2.2).

Results

Registry cohort

Figure 3 shows the details of the PET/CT registry cohort. A total of 4,504 oncological patients with 5,939 clinically indicated PET/CT scans were enrolled in the registry between April 2013 and August 2016, potentially eligible for evaluation. Of them, 780 patients with 1,185 PET/CT scans had to be excluded because of missing or incomplete questionnaires ($n = 739$) or no patient consent to the use of their data for research ($n = 41$). Accordingly, 3724 patients with 4,754 PET/CT examinations formed the final study cohort, representing 80.0% of the registered cases.

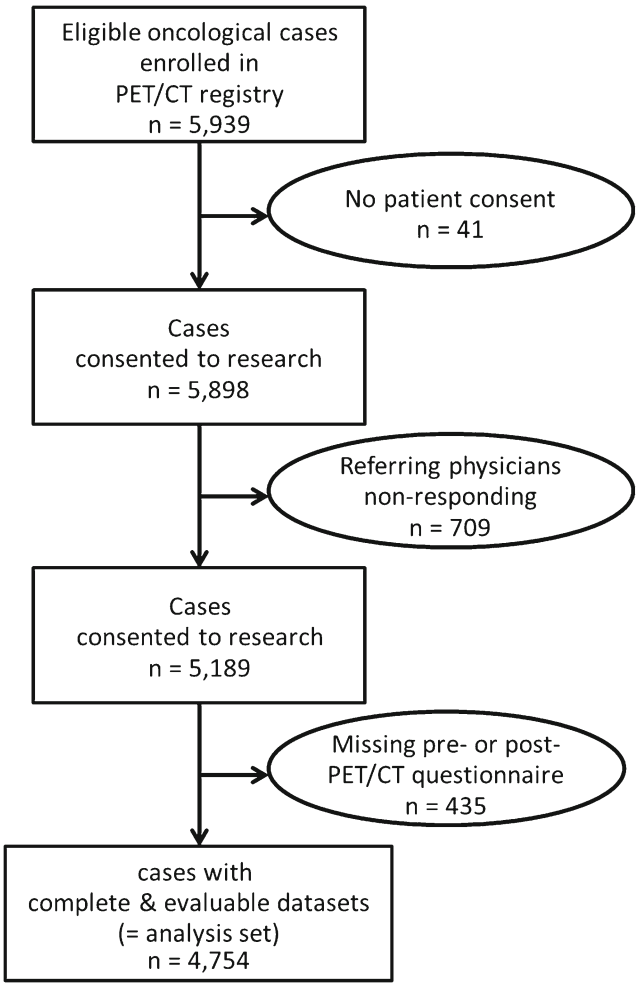

Fig. 3 Details of the PET/CT registry cohort. Numbers represent PET/CT scans

Patient characteristics

The cohort profile is summarized in Table 1. Mean patient age was 61.8 (IQR 54.0–72.9) years, and 65.4% of patients were men. In 17.4% of the patients two or more PET/CT scans were performed. In-house physicians accounted for 68.3% of the referrals. 11.3% of PET/CT scans were performed for diagnosis (suspected primary, cancer of unknown primary, CUP, and paraneoplastic syndrome), 59.7% for staging in known cancer (primary staging and restaging during and after therapy) and 29.0% for suspected recurrence of previously treated cancer. There was a total of 22 different cancer types, including one category, "other", for a set of miscellaneous tumor types with very rare occurrences (<2%). Melanoma, lung and prostate cancer, neuroendocrine tumors (NET) and lymphomas represented 69.1% of cases. When stratifying the indications for PET/CT by cancer type (Table 2) the majority of tumors showed results similar to the whole group for the indication "staging". Higher frequency of the indication "diagnosis" was found in NET (16.9%), brain tumors (27.1%) as well as in CUP (24.0%) and paraneoplastic syndrome (81.2%). In prostate (60%), ovarian (61%) and breast cancers (52%), the indication category "suspected recurrence" was by far the most frequent one.

Impact of PET/CT on management

Table 3 summarizes the impact of PET/CT on intended management, based on the two main categories "treatment" or "non-treatment" and stratified by clinical indication. Considering this classification, physicians changed their intended management on the basis of PET/CT results in 37.1% of all cases (95% CI, 35.7–38.5) ranging from 32.2% (95% CI, 28.3–36.2) in case of indication category "diagnosis" to 38.9% (95%CI, 37.1–40.7) when "staging" was the reason for PET/CT. In 1,456 cases (30.6%) the intended non-treatment strategy before PET/CT was revised to treatment after PET/CT, whereas only 307 cases (6.5%) switched from a pre-PET/CT treatment strategy to a post-PET/CT non-treatment approach (watchful waiting or additional tests). The observed change of intended management differed moderately between the cancer types (Table 4). Changing rates above 40% were shown for melanoma (46%; 95% CI 42.2–49.6), lung cancer (40.4%; 95% CI 37.2–44.5), lymphoma (40.5%; 95% CI 35.9–44.7), and testicular cancer (54.8%; 95% CI 37.3–72.4; however, the latter was represented with few cases only). The largest groups demonstrated changing rates between 20 and 40%, including prostate cancer (34.8%; 95% CI 31.2–38.3), neuroendocrine tumors (33.1%; 95% CI

Table 1 Cohort characteristics (patients, N = 3,724)

Characteristic	Value	Percent (%)
Age (years)		
Mean	61.8	
Median	64.1	
Interquartile range (25–75%)	54.0–72.9	
Sex (*n*)		
Male	2435	65.4
Female	1289	34.6
PET/CT scans (N = 4754) (number of scans)		
Inpatient	3247	68.3
Outpatient	1507	31.7
No. of scans per patient		
One	3078	82.6
Two and more	646	17.4
Total	4754	100.0
Indication for PET/CT[a]		
Diagnosis	537	11.3
Staging	2841	59.8
Suspected recurrence	1376	28.9
Cancer type		
Melanoma	750	15.8
Lung	698	14.7
Prostate	693	14.6
Neuroendocrine	658	13.8
Lymphoma	484	10.2
Colorectal	237	5.0
Esophagus, stomach, intestine	229	4.8
Head and neck	152	3.2
Brain, CNS	107	2.3
Liver, pancreas	85	1.8
Thyroid	82	1.7
CUP syndrome	75	1.6
Breast	73	1.5
Sarcoma, GIST, connective tissue	67	1.4
Gynecological	66	1.4
Ovarian	62	1.3
Anal	42	0.9
Paraneoplastic	32	0.7
Endocrine	31	0.6
Testicular	31	0.6
Urological	14	0.3
Other	86	1.8
Tracer		
[18F]FDG	3287	69.2
[68Ga]DOTATATE	658	13.8
[11C]Choline	351	7.4
[68Ga]PSMA	342	7.2
[11C]Methionine	58	1.2
[18F]FET	58	1.2

CNS central nervous system, *CT* computed tomography, *CUP* cancer of unknown primary, *Dotatate* 1,4,7,10-Tetraazacyclododecane-1,4,7,10-Tetraazacylododecantetraacetate, *FDG* Fluoro-2-deoxy-D-glucose, *FET* Fluoroethyl-L-tyrosine, *GIST* gastrointestinal stroma tumour, *PET* positron emission tomography, *PSMA* prostate specific membrane antigen

[a] PET/CT indications are classified in diagnosis (suspected primary, cancer of unknown primary, CUP and paraneoplastic syndrome), staging (primary staging and restaging after therapy of histologically confirmed cancer), and suspected recurrence of previously treated cancer

Table 2 Indication for PET/CT stratified by cancer type (N = 4754)

Cancer type	Indication for PET/CT No. of scans (%)		
	Diagnosis	Staging	Suspected recurrence
Melanoma	24 (3.2)	503 (67.1)	223 (29.7)
Lung	104 (14.9)	486 (69.6)	108 (15.5)
Prostate	12 (1.7)	265 (38.3)	416 (60.0)
Neuroendocrine	111 (16.9)	438 (66.6)	109 (16.6)
Lymphoma	41 (8.5)	378 (78.1)	65 (13.4)
Colorectal	29 (12.2)	113 (47.7)	95 (40.1)
Esophagus, stomach	26 (11.4)	161 (70.3)	42 (18.3)
Head and neck	20 (13.1)	98 (64.5)	34 (22.4)
Brain, CNS	29 (27.1)	32 (29.9)	46 (43.0)
Liver, pancreas	5 (5.9)	46 (54.1)	34 (40.0)
Thyroid	6 (7.3)	42 (51.2)	34 (41.5)
CUP syndrome	18 (24.0)	53 (70.7)	4 (5.3)
Breast	7 (9.6)	28 (38.4)	38 (52.0)
Sarcoma, GIST	16 (23.9)	37 (55.2)	14 (20.9)
Gynecological	4 (6.1)	32 (48.5)	30 (45.4)
Ovarian	2 (3.2)	22 (35.5)	38 (61.3)
Anal	0 (0)	39 (92.9)	3 (2.1)
Paraneoplastic	26 (81.2)	2 (6.2)	4 (12.6)
Testicular	3 (9.7)	21 (67.7)	7 (22.6)
Endocrine	5 (16.1)	15 (48.4)	11 (35.5)
Urological	2 (14.4)	6 (42.8)	6 (42.8)
Other	47 (54.7)	24 (27.9)	15 (17.4)
Total	537 (11.3)	2841 (59.8)	1376 (28.9)

29.5–36.7), colorectal cancer (38.4%; 95% CI 32.2–44.6), esophageal cancer (30.6%; 95% CI 24.6–36.5), head and neck cancer (28.3%; 95%CI 21.1–35.4), CUP syndrome (33.3%; 95% CI 22.7–44.0), breast tumors (38.4%; 95% CI 27.2–49.5), ovarian cancer (38.7%; 95% CI 26.6–50.8) and sarcomas (35.8%; 95% CI 24.3–47.3). The lowest changing rates below 20% were observed for cervical/endometrial cancer (16.7%; 95% CI 7.7–25.7), anal cancer (19.0%; 95% CI 7.2–25.7) and paraneoplastic syndrome (9.4%; 95% CI 3.2–24.2). Considering only the nine cancer types with at least 100 cases in the cohort, the frequency of management changes ranged from 28.3% in head and neck cancers up to 46.0% in melanomas. The impact of PET/CT was greatest in patients where the pre-PET/CT intended management plan was the request for additional imaging. This was the most common planned strategy if PET/CT was unavailable, accounting for 66.1% of all cases. In Fig. 4 the frequency of transitions from the pre-PET/CT to the post-PET/CT management plan is shown for the sub-cohort of patients with a pre-PET/CT "non-treatment" strategy including watchful waiting and requests of further imaging or invasive tests. Only in 6.1% of cases the post-PET/CT plan was additional imaging, in 60.1% of these cases the strategy was changed to active treatment and in 28.5% revised to watchful waiting. The frequency of these changes differed only slightly between the most common cancer types melanoma, lung cancer, NET, and prostate

Table 3 Impact of PET/CT on intended management (N = 4,754)

Management plan		Indication for PET/CT			Total	95% CI
Pre-PET/CT	Post-PET/CT	Diagnosis	Staging	Recurrence		
No. of scans (%)		537 (11.3)	2841 (59.8)	1376 (28.9)	4754 (100)	
Treatment[a]	Treatment	171 (31.8)	1244 (43.8)	616 (44.8)	2031 (42.7)	41.3–44.1
Nontreatment[b]	Nontreatment	193 (35.9)	492 (17.3)	275 (20.0)	960 (20.2)	19.1–21.3
Nontreatment	Treatment	133 (24.8)	957 (33.7)	366 (26.6)	1456 (30.6)	29.3–31.9
Treatment	Nontreatment	40 (7.4)	148 (5.2)	119 (8.6)	307 (6.5)	5.8–7.2
Overall change in management		173 (32.2%)	1105 (38.9)	485 (35.2)	1763 (37.1)	35.7–38.5

[a] Treatment: surgery, systemic therapy, radiotherapy, radio/chemotherapy, and combinations

[b] Nontreatment: additional tests required (e.g. imaging, biopsy), and watchful waiting

cancer. Furthermore, the percentage of planned invasive procedures decreased from 19.1% pre-PET/CT to 5.2% after PET/CT.

Table 5 shows the impact of PET/CT on management, if the goal of treatment, classified as either curative or palliative, is also considered. For the subgroup of patients with a pre-PET/CT "treatment" strategy, the therapeutic goal changed after PET/CT in 21.7% of cases (95%CI 19.9–23.5) (Fig. 5). This was observed most frequently in patients referred for suspected recurrence (27.3%, 95%CI 23.8–30.8). For the whole group the treatment goal switched twice as often from curative to palliative therapy than vice versa. However, the frequency of changes showed a wide variation across the different cancer types (Table 6). The frequency of changes of treatment goal was lower in neuroendocrine tumors (12.2%, 95% CI 8.4–16.0) and lymphoma (12.3%, 95% CI 6.8–17.8) and went up to 29.1% (95% CI 22.0–36.2) in melanoma and 35.6% (95% CI 21.6–49.5) in gynecological tumors.

When asked about how the oncologic status of patients changed after PET/CT, the referring physicians indicated an upstaging in 32.2% of all cases, equally distributed over the indication groups "staging" and "suspected recurrence". A downstaging was reported in 11.1% of all cases, mainly if "diagnosis" was the reason for the test.

Table 4 Impact of PET/CT on intended management stratified by cancer type (N = 4,754)

Cancer type	No. of scans	Change in management No. of scans (%)			
		Nontreatment to treatment	Treatment to nontreatment	Total change in management	95% CI
Melanoma	750	319 (42.5)	26 (3.5)	345 (46.0)	42.2–49.6
Lung	698	255 (36.5)	30 (4.3)	285 (40.8)	37.2–44.5
Prostate	693	191 (27.6)	50 (7.2)	241 (34.8)	31.2–38.3
Neuroendocrine	658	163 (24.8)	55 (8.4)	218 (33.1)	29.5–36.7
Lymphoma	484	150 (31.0)	45 (9.3)	195 (40.3)	35.9–44.7
Colorectal	237	76 (32.1)	15 (6.3)	91 (38.4)	32.2–44.6
Esophagus, stomach	229	64 (27.9)	6 (2.6)	70 (30.6)	24.6–36.5
Head and neck	152	30 (19.7)	13 (8.6)	43 (28.3)	21.1–35.4
Brain, CNS	107	27 (25.2)	6 (5.6)	33 (30.8)	22.1–39.6
Liver, pancreas	85	26 (30.6)	5 (5.9)	31 (36.5)	26.2–46.7
Thyroid	82	24 (29.3)	5 (6.1)	29 (35.4)	25.0–45.7
CUP syndrome	75	20 (26.7)	5 (6.7)	25 (33.3)	22.7–44.0
Breast	73	23 (31.5)	5 (6.8)	28 (38.4)	27.2–49.5
Sarcoma, GIST	67	21 (31.3)	3 (4.5)	24 (35.8)	24.3–47.3
Gynecological	66	5 (7.6)	6 (9.1)	11 (16.7)	7.7–25.7
Ovarian	62	16 (25.8)	8 (12.9)	24 (38.7)	26.6–50.8
Anal	42	7 (16.7)	1 (2.4)	8 (19.0)	7.2–25.7
Paraneoplastic	32	2 (6.3)	1 (3.1)	3 (9.4)	3.2–24.2
Testicular	31	7 (22.6)	10 (32.3)	17 (54.8)	37.3–72.4
Endocrine	31	6 (19.4)	1 (3.2)	7 (22.6)	7.9–37.3
Urological	14	2 (14.3)	2 (14.3)	4 (28.6)	4.9–52.2
Other	86	22 (25.6)	9 (10.5)	31 (36.0)	25.9–46.1
Total	4754	1456 (30.6)	307 (6.5)	1763 (37.1)	34.6–37.4

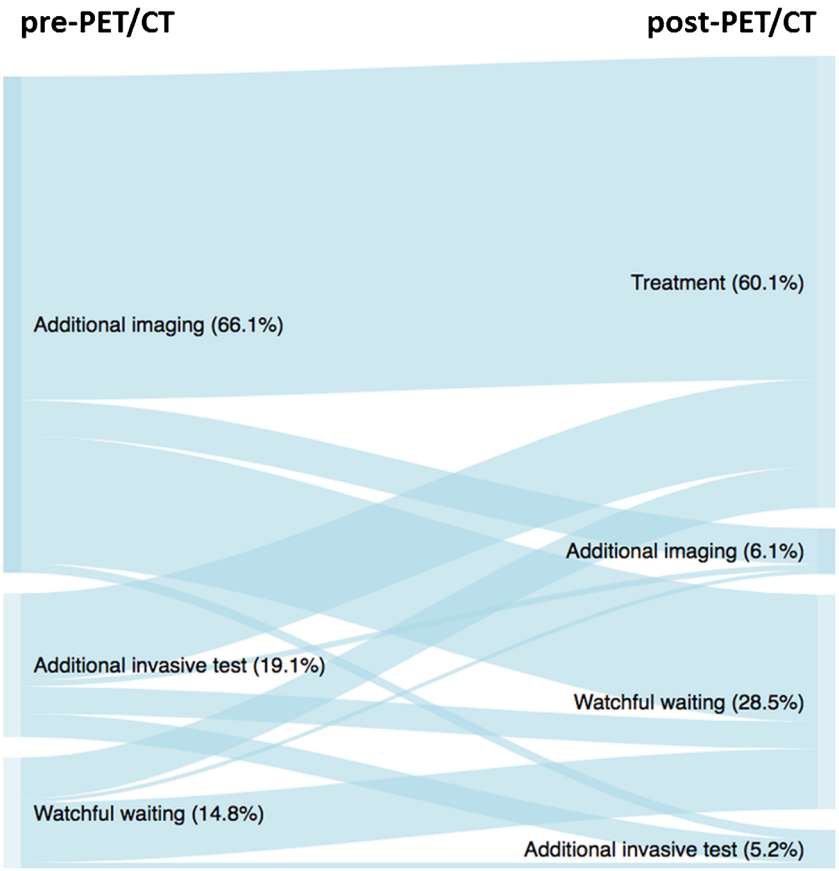

Fig. 4 Sankey diagram represents the relative proportions of management categories pre- and post-PET/CT and the frequency of changes for each category in the subgroup of patients with a pre-PET/CT "non-treatment" strategy ($n = 2281$). The widths of the bands are directly proportional to the number of PET/CT scans

Discussion

PET/CT is widely used in clinical oncology due to its high diagnostic accuracy [4]; however, the number of studies dealing with the evaluation of the clinical benefit of this technology is limited. Single-center studies report management changes after PET/CT from 40 to 70%, primarily in lung, colorectal and head and neck cancer [12, 13, 15, 25], but these studies are influenced by variable patient population and study design. Seeking alternative ways of benefit assessment outside from RCT and helping to inform consultations with health insurances on PET/CT coverage we established a comprehensive prospective data registry including nearly 5,000 PET/CT scans across 22 cancer types and different test indications. The catalogue of PET/CT indications includes most of the internationally established clinical indications for PET/CT. However, the indication list also had to be defined in consultation with the regional public health insurance to secure coverage for PET/CT. In this way it reflects the reimbursement policy in Germany which is heterogeneous and site-specific. The primary goal of the registry was to investigate the clinical impact of PET/CT on patient management (further testing, watching or treatment) in the daily routine for an unselected broad spectrum of tumors.

The main result of our study is a 37.1% overall change in physician's decision making based on PET/CT findings with a switch from a pre-PET/CT "non-treatment" strategy (watchful waiting or additional testing) to post-PET/CT active treatment (surgery, radiotherapy or systemic therapy) being four times more frequent than its opposite. Overall, the impact of PET/CT on clinical management differed only minimally by the test indication "staging" or "suspected recurrence". The slightly lower frequency of changes in patients with the indication "diagnosis" can be explained by the primary target of PET/CT in this group to determine whether a lesion is cancer or not. The impact of PET/CT by cancer type shows moderate variations across the eight most common cancer types, only in melanoma patients the clinical impact of PET/CT differed significantly from that of all other cancer types with observed management changes up to 46.0% of cases. When changes of the therapeutic goal were also considered, differences between the cancer types became more evident. Changes of the treatment goal occurred more frequently in melanoma, lung, prostate and colorectal cancer and less often in lymphoma and neuroendocrine tumors. In general, the shift of therapeutic goal was twice as often from a curative to a palliative strategy, probably due to the delineation of a greater tumor burden or more tumor sites due to the higher sensitivity of PET/CT. If a patient is moved from a curative to a palliative treatment

Table 5 Impact of PET/CT on intended management stratified by treatment goal and indication (N = 4,754)

Treatment goal		Indication for PET/CT No. of scans (%)			Total	95% CI
Pre-PET/CT	Post-PET/CT	Diagnosis	Staging	Recurrence		
Nontreatment	Nontreatment	193 (35.9)	492 (17.3)	275 (20.0)	960 (20.2)	19.1–21.3
	Curative	93 (17.3)	441 (15.5)	171 (12.4)	705 (14.8)	13.8–15.8
	Palliative	40 (7.4)	516 (18.2)	195 (14.2)	751 (15.8)	14.8–16.8
Curative	Nontreatment	35 (6.5)	110 (3.9)	78 (5.7)	223 (4.7)	4.1–5.3
	Curative	113 (21.0)	609 (21.4)	245 (17.8)	967 (20.3)	19.2–21.5
	Palliative	21 (3.9)	168 (5.9)	103 (7.5)	292 (6.1)	5.5–6.8
Palliative	Nontreatment	5 (0.9)	38 (1.3)	41 (3.0)	84 (1.8)	1.4–2.1
	Curative	5 (0.9)	78 (2.7)	65 (4.7)	148 (3.1)	2.6–3.6
	Palliative	32 (6.0)	389 (13.7)	203 (14.8)	624 (13.1)	12.2–14.1
Total No. of scans (%)		537 (11.3)	2841 (59.8)	1376 (28.9)	4754 (100)	

option based on the results of the PET/CT, a substantial benefit in survival cannot be expected; however, the avoidance of unnecessary but stressful (and costly) surgery or radiotherapy will result in an improvement of the quality of life and may have a positive influence on healthcare costs. This scenario is difficult to address by an RCT focusing on therapeutic efficacy [1]. Based on the registry data another clinical benefit of PET/CT was apparent, namely, the replacement of 70% of planned invasive tests by the noninvasive alternative of hybrid imaging, clearly reducing the risk of patient discomfort and test-related morbidity.

Our results are in agreement with the large-scale data of the US-PET registry (NOPR), which demonstrated an overall change in management in 36.5% of cases, with variations between 35 and 40% depending on cancer type [22] and the results of the large Danish study with management changes on the same scale in 36% of cases [26]. Both the results of the NOPR and our data indicate that the impact of PET/CT was

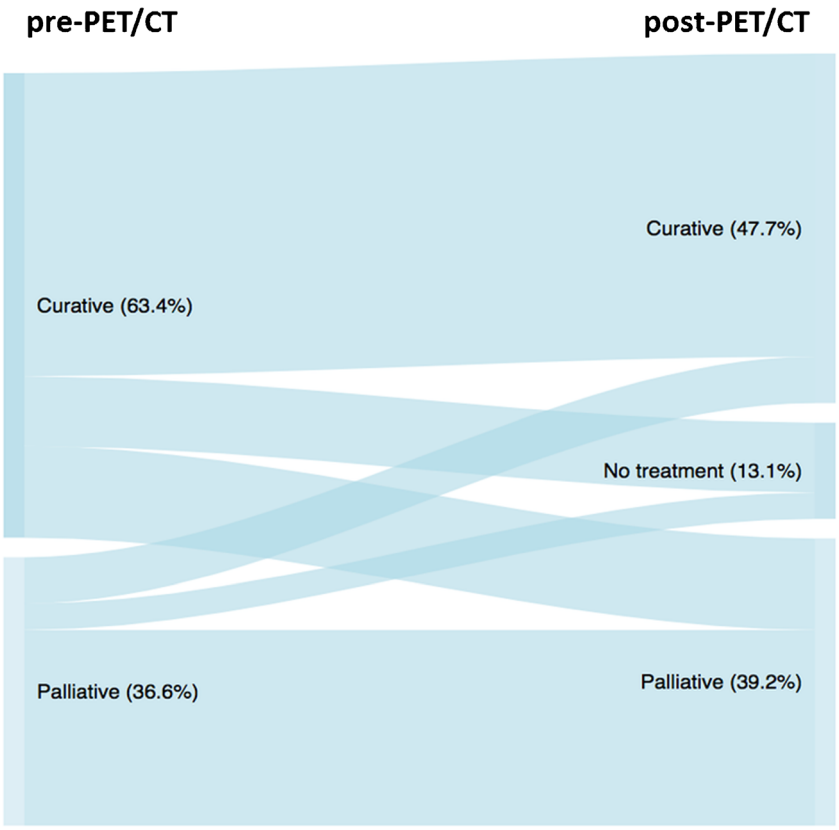

Fig. 5 Sankey diagram represents the relative proportions of curative and palliative treatment goal pre- and post-PET/CT and the frequency of changes for each category in patients with planned treatment (n =, 2338). The widths of the bands are directly proportional to the number of PET/CT scans

Table 6 Impact of PET/CT on intended management stratified by treatment goal and cancer type (N = 2,031)

Cancer type	No. of scans	No change		Change of treatment goal			
		Curative to curative	Palliative to palliative	Curative to palliative	Palliative to curative	Σ Change in treatment goal (%)	95% CI
Prostate	410	165	136	59	50	109 (26.6)	22.3–30.9
Lung	358	162	98	67	31	98 (27.4)	22.8–32.0
Neuroendocrine	286	75	176	18	17	35 (12.2)	8.4–16.0
Melanoma	158	81	31	43	3	46 (29.1)	22.0–36.2
Lymphoma	138	113	8	11	6	17 (12.3)	6.8–17.8
Esophagus, stomach	128	85	18	18	7	25 (19.5)	12.7–26.4
Colorectal	108	38	40	17	13	30 (27.8)	19.3–36.2
Head and neck	99	70	11	14	4	18 (18.2)	10.6–25.8
Gynecological	45	19	10	11	5	16 (35.6)	21.6–49.5
CUP syndrome	40	26	8	6	0	6 (15.0)	3.9–26.1
Thyroid	31	14	10	3	4	7 (22.6)	7.9–37.3
Liver, pancreas	30	9	19	2	0	2 (6.7)	1.9–21.3
Breast	30	6	18	4	2	6 (20.0)	5.7–34.3
Anal	29	29	0	0	0	0 (0.0)	0–11.7
Ovarian	28	9	12	6	1	7 (25.0)	9.0–41.0
Brain, CNS	28	12	10	4	2	6 (21.4)	6.2–36.6
Sarcoma, GIST	27	19	5	3	0	3 (11.1)	3.9–28.1
Endocrine	11	3	7	1	0	1 (9.1)	1.6–37.7
Paraneoplastic	9	5	2	1	1	2 (22.2)	6.3–54.7
Urological	7	3	2	0	2	2 (28.6)	8.2–64.1
Testicular	7	6	0	1	0	1 (14.3)	2,6–51.3
Other	24	18	3	3	0	3 (12.5)	4.3–31.0
Total	2031	967	624	292	148	440 (21.7)	19.9–23.5

greatest in reducing demands for additional imaging and invasive tests. It seems to be obvious that in an early decision process PET/CT helps the physicians to "triage" between curative therapy, palliative treatment or watchful waiting. Fast and early information for decision making and clinical management is in itself a direct benefit for the patient. Furthermore, the study data reveal that PET/CT is an efficient imaging modality providing comprehensive diagnostic information, as no additional imaging was necessary in the majority of cases after PET/CT.

The strengths of our registry—which represents the first PET/CT registry in Germany—are its large data collection and prospective design, the broad spectrum of cancer types, and the high response rate (80%) by our referring physicians. This makes the results more generalizable to the real world practice. An inherent limitation of every registry is its observational design that bears the risk of unrecognized biases [22, 27]. We cannot exclude a sampling bias in our patient population and an overestimation of the benefit of PET/CT because the allocation of patients to PET/CT was not random and we are unable to define what circumstances have led the referring physician in each case to select the PET/CT or an alternative imaging test instead. To minimize these biases we made efforts to restrict PET/CT referrals to established clinical indications and, additionally, to cases where the results of prior standard conventional imaging (CT or MRI) were not sufficient to establish a diagnosis.

There is an ongoing debate regarding the implementation of intermediate outcome criteria such as changes in intended patient management instead of survival as primary endpoint in benefit assessment of an imaging test [1, 6, 7, 28]. As a first step to address this issue we already tested the so-called "linked-evidence-approach" [7, 28] in a different study investigating a patient group with advanced melanoma considered for surgical metastasectomy after conventional (CT) imaging [29]. Registry data of treatment changes stratified by PET/CT results were linked with the follow-up data of the same patient cohort. High survival rates and the avoidance of futile surgery in half of the patients confirmed the positive impact of PET/CT on outcome in this population. We thus expect that similar results will be found for other tumor entities, proving a generic benefit of PET/CT imaging, going beyond management changes.

Conclusion

Data of the first German PET/CT registry confirm that physicians often change their intended management on the basis of PET/CT results. The registry data reflect that clinicians are convinced of the validity of PET/CT results, and they accept PET/CT as a valuable tool in order to provide optimal treatment, often in accordance with established guidelines. The lack of RCTs proving clinical effectiveness of PET/CT does not seem to have an impact on the clinical practice.

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Compliance with ethical standards

Conflict of interest K.N. is on the speakers bureau of Bracco, Bayer and Siemens. The institution has cooperative research grants from Bayer and Siemens. All other authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This study was approved by the Ethics committee of the University of Tuebingen, reference number 064/2013B01.

Informed consent Informed consent was obtained from all individual participants included in the study.

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