First Experiences of Radiation Treatment Planning with PET/CT

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Background: Positron emission tomography/computed tomography (PET/CT) is composed of modern CT and PET technology in one machine enabling examinations of patients in one session in the same position. Its value for modern radiation treatment planning is under investigation.
Methods: In 53 patients with head-and-neck (n = 11), non-small cell lung (n = 16), prostate (n = 14) and other cancers (n = 12), a PET/CT investigation was performed. During the diagnostic examination process an integrated scan under radiation treatment-planning conditions was included. Interpretation and delineation of macroscopic tumor were done in an interdisciplinary approach. Treatment changes occurred after critical interpretation of the PET/CT findings by the responsible radiotherapist. Analysis is descriptive with regard to changes in treatment intention, mode, radiation volumes and doses.
Results: Examinations were well tolerated. CT datasets in treatment position could be used for planning. Delineation of macroscopic tumor led to changes of the planning target volume after PET/CT 15 times, total dose was modified twelve times. PET/CT examinations led to changes of the general treatment mode in 19 cases. Using the separate CT and PET datasets, fusion in the planning software was easily performed in all patients due to the use of the same positioning and immobilization devices in PET/CT.
Conclusion: Despite the low number of patients and an expectable bias of selection, the first results are encouraging to perform more extended and detailed trials of this technology in radiotherapy planning. Whether PET/CT is superior to PET alone is part of ongoing investigations.

Key Words: Radiotherapy · Planning · PET/CT

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Erste Erfahrungen mit der PET/CT im Rahmen der Strahlentherapieplanung

Hintergrund: Die Positronenemissionstomographie/Computertomographie (PET/CT) ist eine Weiterentwicklung der Einzelkomponenten moderner CT- und PET-Technologie in einer kombinierten Hybridmaschine, die eine Untersuchung in einer Sitzung in derselben Position ermöglicht. Die Bedeutung für die moderne Strahlentherapie wird intensiv erforscht.
Methodik: Bei 53 Patienten mit fortgeschrittenen Kopf-Hals- (n = 11), nichtkleinzelligen Bronchial- (n = 16) und Prostatakarzinomen (n = 14) sowie anderen Tumoren (n = 12) wurde eine PET/CT durchgeführt. Während der diagnostischen Untersuchung wurden die Patienten in Bestrahlungsposition gelagert und ein Scan zur Bestrahlungsplanung integriert. Die Interpretation und Einzeichnung makroskopischen Tumors wurden in einem interdisziplinären Ansatz aus erfahrenem Strahlentherapeut, Nuklearmediziner und radiologischem Diagnostiker vollzogen. Änderungen der Behandlung wurden eingeleitet, wenn sich nach kritischer klinischer Abschätzung der PET/CT-Ergebnisse relevante neue Befunde ergaben. Die Analyse ist deskriptiv in Bezug auf Änderungen von Behandlungsmodalität, -intention, Bestrahlungsvolumen und -dosis.
Ergebnisse: Die Untersuchungen mit der PET/CT wurden von den Patienten gut toleriert. Die CT-Datensätze in Behandlungsposition konnten für die Planung verwendet werden. Die Einzeichnung des makroskopischen Tumors führte nach 15 Untersuchungen (26%) zu Änderungen des Planungszielvolumens. Die Gesamtdosis wurde nach zwölf PET/CT-Untersuchungen (21%) modifiziert. PET/CT führte 19-mal (33%) zu Änderungen des generellen Behandlungsmodus. Die separaten CT- und PET-Datensätze der Patienten in derselben Position mit denselben Immobilisierungshilfen konnten zur Fusion in der Planungssoftware einfach genutzt werden.
Schlussfolgerung: Trotz der relativ niedrigen Patientenzahl und eines möglichen Selektionsfehlers sind die ersten Ergebnisse erfolgversprechend, um weitere, ausgedehntere Untersuchungen mit großen Patientenzahlen durchzuführen. Inwieweit die kombinierte PET/CT den Einzelkomponenten mit späterer Fusion überlegen ist, sollte in diesem Zusammenhang evaluiert werden.

Schlüsselwörter: Radiotherapie · Planung · PET/CT

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Introduction

Modern technology influences modern radiotherapy planning processes. The development of improved diagnostic procedures changes common approaches rapidly [19, 25, 27]. Positron emission tomography (PET) has shown impact on the initial staging in different tumor entities [18, 26]. In non-small cell lung cancer (NSCLC), several groups have shown an influence of PET with the tracer ^{18}F-fluorodeoxyglucose (FDG) on radiation treatment-planning volumes or portals [4, 6, 12, 14, 24] as was also observed in head-and-neck cancer (HNC) [6, 20]. In prostate cancer (PC), ^{11}C-choline promises some improvements in the detection of metastases [2, 6].

As a new technical development, PET/CT (CT: computed tomography) as combined scanner using the same positioning of the patient was introduced. The risk of a geographic miss was reduced in comparison to CT alone or PET alone in NSCLC [11]. In HNC, FDG PET used as PET/CT improved the findings of metastatic lymph nodes [8, 22]. In these studies, the combined interpretation of metabolic data of PET and the anatomic resolution of CT led to a different diagnostic result. Its impact on radiotherapy planning is of strong clinical and socioeconomic interest. We describe our first experiences of the integration of PET/CT information and data into the planning process of patients before radiotherapy.

Table 1. Patients' characteristics and examination data. CUP: cancer of unknown primary; CT: computed tomography; FDG: ^{18}F-fluorodeoxyglucose; HNC: head-and-neck cancer; NSCLC: non-small cell lung cancer; PC: prostate cancer; PET: positron emission tomography.

Tabelle 1. Patientencharakteristika und Untersuchungsdaten. CUP: unbekannter Primärtumor; CT: Computertomographie; FDG: ^{18}F-Fluordesoxyglucose; HNC: Kopf-Hals-Karzinom; NSCLC: nichtkleinzelliges Bronchialkarzinom; PC: Prostatakarzinom; PET: Positronenemissionstomographie.

Patients	**n = 53**
Sex	Male n = 45 (84.9%) with 50 examinations Female n = 8 (15.1%) with 8 examinations
PET/CT examinations	**n = 58**
Entities	NSCLC n = 21 (36.2%) PC n = 14 (24.1%) HNC n = 11 (19%), including • nasopharyngeal carcinoma n = 3 • paranasal sinus carcinoma n = 2 CUP n = 4 (6.9%), including • cervical lymph node metastases n = 3 • adenocarcinoma lower limb n = 1 Other n = 8 (13.8%), with n = 1 each of • gastric cancer • breast cancer • rectal cancer • esophageal cancer • carcinosarcoma of corpus uteri • sarcoma • suspicion of lung cancer without histological proof • PC (history of Hodgkin's disease and undifferentiated epithelial cancer)
Tracer	FDG n = 44 (75.9%) Choline n = 14 (24.1%)
Indication for PET/CT	Radiotherapy planning n = 23 (39.7%) Diagnostic n = 31 (53.4%) Follow-up during radiotherapy n = 4 (6.9%)

Methods

Before or during the radiation treatment-planning process in patients with advanced HNC, NSCLC, PC, cancer of unknown primary (CUP) and some single entities, a PET/CT (LSO Hi-REZ Biograph 16, Siemens Medical Solutions, Erlangen, Germany; CTI, Knoxville, TN, USA) examination was performed either as staging procedure exclusively (n = 35/60%) or used as treatment planning CT (n = 23/40 %). Patients with a high risk for extended disease were selected for PET/CT in our own clinical conference.

The diagnostic examination protocol consisted of a low-dose CT scan of the body for attenuation correction of PET (120 kV, 30 mAs), contrast media-supported diagnostic CT scan (120 kV, 110–160 mAs), and PET scan. PET was performed with ^{11}C-choline (PC) or FDG (others). Non-contrast-enhanced CT scans (120 kV, 100 mAs) were used for radiation treatment planning. If these CT scans are not available, the low-dose CT scans can also be used for treatment planning, because measurements have shown similar Hounsfield values. The planning protocol prescribed patients' treatment position, no iodine contrast media, slowest possible CT scanning of the chest (in patients with NSCLC, 40 s), and the usage of typical immobilization devices (e.g., masks for HNC). Patients were oriented supine for all examined tumor entities except one patient with rectal cancer examined in prone position. Arms were located over the head for NSCLC and PC, and at the body for HNC and CUP patients. Datasets used for radiation treatment planning were sent separately to a planning system (Focal, CMS, St. Louis, MO, USA), in which an external image fusion was performed. The software is commercially available and uses a mutual information algorithm. Clinical usefulness of external fusion of PET and CT was controlled with the simultaneously produced dataset by the PET/CT machine. After its control and delineation of macroscopic tumor, CT and contour set was used in routine clinical planning systems Helax-TMS® (MDS Nordion, Kanata, Canada) or Hyperion® (M. Alber, University of Tuebingen, Germany).

Interpretation of the PET and CT data was performed by specialists of the Departments of Nuclear Medicine and Radiologic Diagnostics. Delineation of macroscopic tumor was done in an interdisciplinary approach of these experts with the radiation oncologist. To include the information of PET into the planning process, we started a 50% isocontour, i.e., 50% of the difference of maximum and background standardized uptake value (SUV), and corrected this in case of obviously better-defined anatomic threshold. This additional information was used, if this volume matched with suspicious tissue in an

oncologically typical way of treatment planning. Changes of the treatment were decided after critical clinical interpretation of the PET/CT findings by the responsible radiotherapist considering special findings and clinical risk.

The evaluation of PET/CT examinations included a prospective structured documentation of the examination results with regard to changes in clinical treatment mode, radiation treatment-planning volume and dose because of the PET/CT examination. The decision to perform a PET/CT was individually clinical, e.g., suspicion of metastases or local recurrence, incomplete staging or unknown resection status. SPSS statistical software package (Chicago, IL, USA) was used for calculations. Due to the small number of patients, the analysis is descriptive.

Results

All examinations were well tolerated. Transfer of both CT and PET datasets was possible. Fusion of the separate CT and PET datasets in the treatment-planning system was easily performed in all patients and revealed no observable difference as compared to the initial combined PET/CT set.

Patient and examination characteristics are summarized in Table 1. The therapeutic concept was primary curative (chemo)radiotherapy in 31/58 cases (53%), adjuvant curative (chemo)radiotherapy in 9/58 cases (15%), neoadjuvant curative (chemo)radiotherapy in 10/58 cases (17%), and twice palliative radiotherapy (3.4%) before PET/CT. A primary tumor was suspected in one of four PET/CTs in patients with CUP (primary lung cancer).

Correlation of PET and CT findings was possible in 27 examinations (46%), definitively no correlation was described in seven (12%). Clinically relevant results with changes in any way of treatment were found in 30 PET/CTs (51%) leading to alterations of the principal treatment intention in 19 cases (32%; e.g., palliative instead of curative intention after ten PET/CTs [17%], other modalities after six PET/CTs [10%], Figure 1). Radiation treatment-planning target volume (PTV) was modified after 15 PET/CTs (26%), dose was adapted after twelve PET/CTs (20%), and radiotherapy was omitted because of new findings in seven cases (12%). In 23 PET/CT examinations performed solely for radiation treatment planning, target volume was modified in 44% (Figures 2 and 3), dose was adapted in 35%, and radiotherapy was omitted in 17%. Altogether, PET/CT revealed new results in 43/58 PET/CT examinations (74.1%; Figure 4).

Looking at special tumor entities, the following results were analyzed. In NSCLC, 21 FDG PET/CT examinations were performed, seven for radiation treatment planning, eleven for diagnostic purposes, and four as follow-up during radiotherapy. In 17 PET/CTs (81%), new results were obtained with consecutive treatment changes in ten cases (48%). In PC, 14 examinations with ^{11}C-choline were performed, three times for treatment planning, and eleven times for diagnostic purposes. After twelve PET/CTs (86%), new results were reported with 64% clinical treatment changes. In eleven HNC patients, eight FDG examinations were performed for treatment planning and three for diagnostic purposes revealing 64% new results leading to 55% treatment changes. However, also in the other twelve patients with different tumor entities, twelve FDG PET/CTs led to 42% treatment changes.

Discussion

PET and, therefore, PET/CT seems to show advantages in general oncological decisions, as it demarks formerly unknown

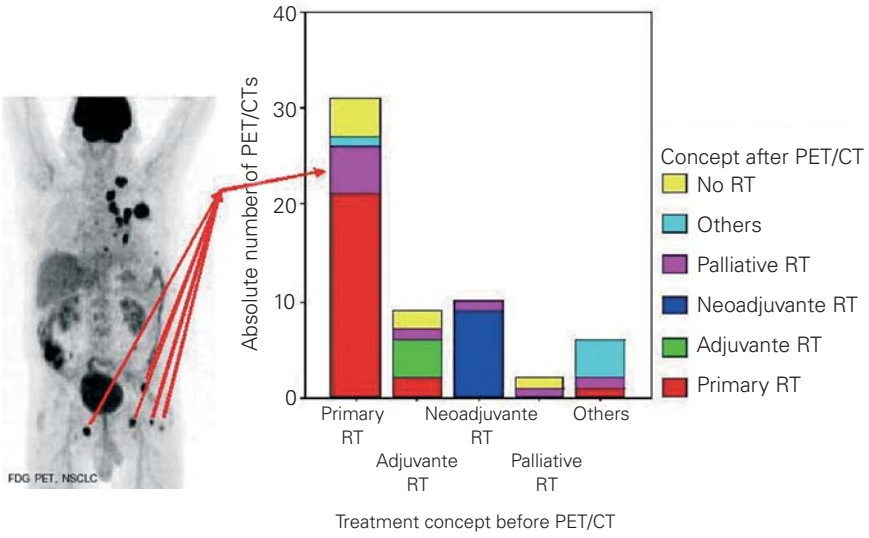


Figure 1. FDG PET/CT in a patient with NSCLC initially considered for curative radiochemotherapy. PET revealed several distant activity spots which were confirmed by CT as being metastases (arrows). CT dataset was used for palliative irradiation of the primary. The graph shows changes of general treatment intention before and after PET/CT: curative definitive (chemo)radiotherapy ("Primary RT"), curative adjuvant (chemo)radiotherapy ("Adjuvant RT"), curative neoadjuvant (chemo)radiotherapy ("Neoadjuvant RT"), palliative radiotherapy ("Palliative RT"), omission of radiotherapy ("No RT").

Abbildung 1. FDG-PET/CT eines Patienten mit NSCLC vor kurativ intendierter Radiochemotherapie. Das PET zeigt multiple Herde erhöhter FDG-Aktivität, die im CT als Metastasen bestätigt wurden (Pfeile). Der CT-Datensatz wurde für die Planung der palliativen Bestrahlung des Primarius verwendet. Die Graphik zeigt Änderungen der generellen Behandlungsintention vor und nach PET/CT: kurative definitive (Chemo-)Radiotherapie („Primary RT"), kurative adjuvante (Chemo-)Radiotherapie („Adjuvant RT"), kurative neoadjuvante (Chemo-)Radiotherapie („Neoadjuvant RT"), palliative Bestrahlung („Palliative RT"), Absetzen der geplanten Bestrahlung („No RT").

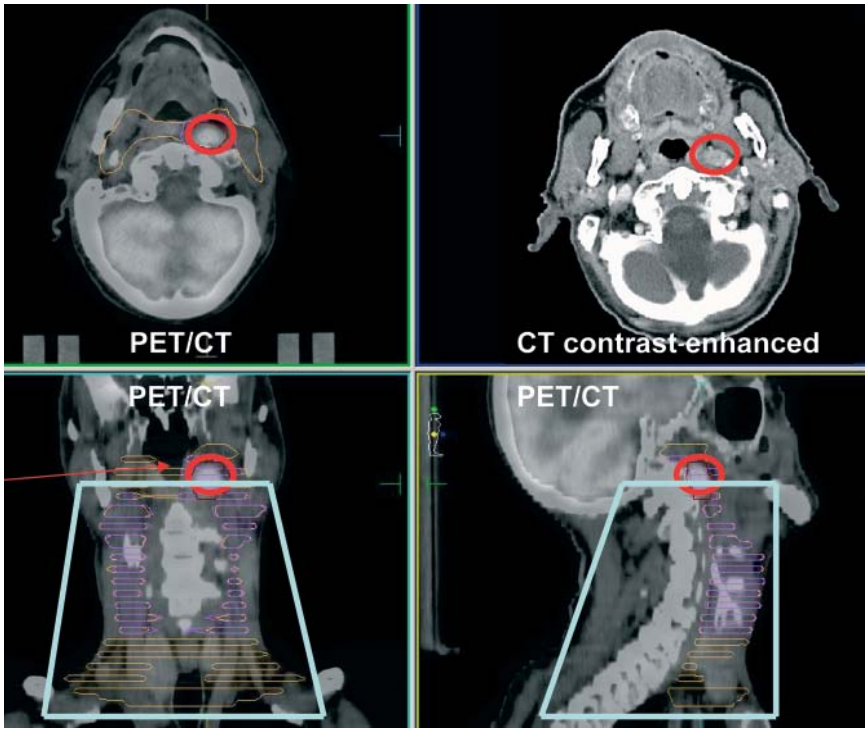
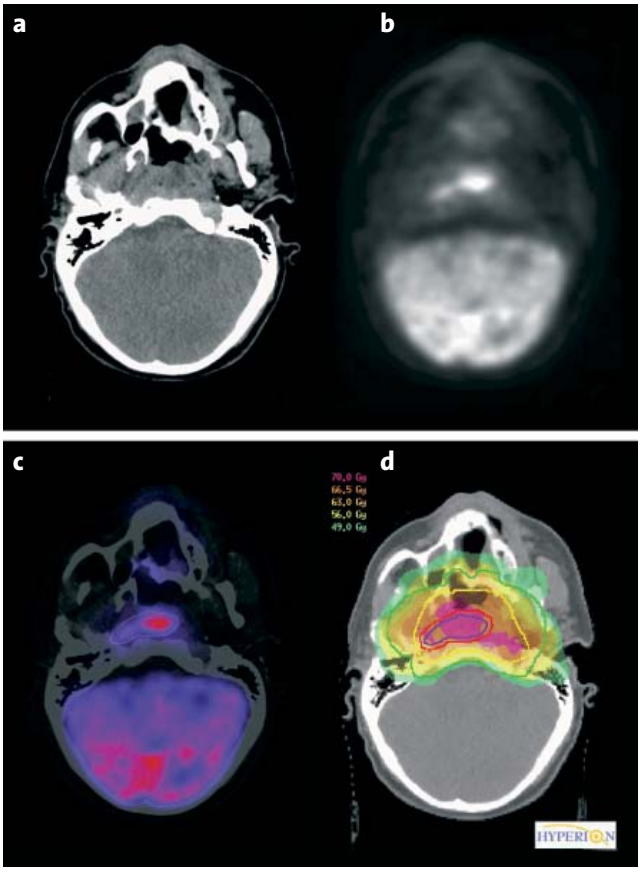


Figure 2. FDG PET/CT in a patient considered for adjuvant radiotherapy. PET showed a solitary FDG activity spot (arrow) which was suspect of macroscopic tumor in CT. Green lines schematically show the initial planned radiation portals. Management was changed to radiochemotherapy with higher total dose, and treatment volume was enlarged cranially (PTV and boost PTV in yellow and purple). Contrast-enhanced CT was performed at a different time as was PET/CT.

Abbildung 2. FDG-PET/CT eines Patienten vor geplanter adjuvanter Radiotherapie. Die PET zeigt einen solitären FDG-Herd (Pfeil), der sich in der diagnostischen CT als verdächtig auf makroskopischen Tumor erwies. Die grünen Linien markieren schematisch die vor PET/CT vorgesehenen Bestrahlungsfelder. Die Behandlung wurde in eine Radiochemotherapie mit höherer Gesamtdosis und modifiziertem Zielvolumen geändert (PTV und Boost in Gelb und Lila). Die kontrastmittelunterstützte CT wurde separat durchgeführt.

metastases [26]. Furthermore, it has an impact on radiation treatment decisions, as it provides additional information about the locoregional tumor extension and may alter treatment volumes and portals or influence the prescribed dose due to the tumor extension [6]. First regarding staging information, FDG PET has shown significant impact [18]. In advanced NSCLC, a substantial proportion of 25 of 101 patients with formerly unknown distant metastases were found by FDG PET, and the diagnostic accuracy of mediastinal lymph nodes was reported as 96% sensitivity and 73% specificity after surgical evaluation [5]. In a meta-analytic comparison of 19 publications with 1,268 patients, CT had a specificity of 76% and a sensitivity of 65% for nodal involvement, whereas FDG PET reached 92% and 88% in 20 studies with 1,292 patients. With 94% sensitivity and 97% specificity (four studies, 336 patients), M-staging with FDG PET is very accurate and changed therapeutic management in 18% of the cases (eight studies, 695 patients). In seven studies with 581 patients, formerly unknown distant metastases of NSCLC were found in 12%, distant metastases were detected with a specificity of 97% and a sensitivity of 94% [7]. Locoregional spread improved prediction from 75% (CT) to 89% (combination of CT and FDG PET), especially mediastinal, in a surgical evaluation [24]. In HNC, FDG PET showed a sensitivity of 87–90% and a specificity of 80–93% for N-staging being superior to CT and MRI [18]. In 36 patients with HNC, co-registered PET and CT images had a histologically confirmed sensitivity of nodal zone involvement of 96% (98.5% specificity) being superior to CT alone (82% sensitivity and 100% specificity) for geographic localization [22]. In patients suffering from metastases of unknown primaries (CUP), the origin tumor was found in 24–53% [18]. Relevant changes of therapeutic management were reported in 18–52% of advanced NSCLC [5, 12, 18, 21]. In patients with CUP, 44–63% had a different therapy after FDG PET [13, 16]. In PC, the tracer 11C-choline promises some improvements in determination of metastases [2]. All these data show an important impact of PET on treatment decisions. Although histological proof is missing and our interpretation of the data is only clinically based, our first results of the reported PET/CT data with changes in the treatment intention underline these reports. Similar findings for general treatment decisions were reported in a trial of 248 patients being submitted to PET alone of whom 40% had new or suspected cancer and 60% were undergoing restaging or had suspected recurrence [9]. Most of these patients suffered from lung cancer, HNC, or lymphoma. Clinical decisions of the responsible physician were evaluated after PET with regard to relevant changes. The authors report a change of the intended treatment in 61% of patients. The therapeutic goal and mode changed in 22 (7%) and 21 cases (8%), respectively.

Radiotherapeutic management was changed after FDG PET in 27% of 202 patients in whom irradiation was planned. These included 55 patients with HNC and 26 with lung cancer, 28 with gynecologic and 18 with gastrointestinal tumors, 24 with malignant lymphoma, and 23 with other cancers. In 9% irradiation was cancelled, 10% changed from curative to palliative intention, in 12% dose and in 6% treatment volume were altered. In the subgroup of HNC, the initial planned radiotherapy was changed in 33% [3]. FDG PET led to changed target volumes in 5/6 HNC patients. Gross tumor volume



Figures 3a to 3d. FDG PET/CT of a patient with spindle cell carcinoma of the epipharynx: a) non-contrast-enhanced planning CT; b) FDG activity, PET alone; c) FDG PET/CT delineates macroscopic tumor; d) IMRT (intensity-modulated radiotherapy) planning based on the delineation in c (see violet line).

Abbildungen 3a bis 3d. FDG-PET/CT eines Patienten mit Spindelzellkarzinom des Nasopharynx: a) natives Planungs-CT; b) FDG-Aktivität, nur PET; c) FDG-PET/CT mit Markierung makroskopischen Tumors; d) IMRT-Planung (intensitätsmodulierte Radiotherapie), basierend auf der Tumordarstellung in c (s. violette Linie).

(GTV) was larger by an average of 15%, lymph node volume was modified in three cases, in one case a pathologic lymph node was not identified on CT [20]. In 9/22 patients with primary HNC, treatment parameters were altered due to additionally detected tumor manifestations, especially in patients with advanced tumor stage [17]. Several studies have shown an important influence of FDG PET on the radiation treatment-planning process in NSCLC [4, 12, 14, 21, 24]. Of 27 patients, PTV was smaller (between 3–21%) in 25 and larger in the remaining two patients due to new lymph node metastases < 1 cm [21].

Besides pure staging information, integration of the locally resolved PET data into the radiation treatment-planning process is done in some different ways. First, the comparison of treatment portals with plane PET scans is the most widely used alternative. Second, integration of the PET dataset into the treatment-planning system is performed. This way needs software solutions working on different strategies as mutual information or landmark-based superpositioning procedures. These landmarks used could be anatomic (e.g., bony structures) or external markers. Similar patient positioning leads to improved fusion results [23]. Integration of PET hard-copy data into a planning system is possible by scanning PET scans into the system but is critically exact and work-intense [15]. The most elegant way seems to produce exact co-registered image information directly. The development of PET/CT as a hardware solution enables this strategy. First clinical experience of the usage of PET/CT in oncology was reported by Lardinois et al. in patients with NSCLC. PET/CT provided additional information in 20 of 49 patients (41%). Tumor staging was significantly more accurate with integrated PET/CT than with CT alone, PET alone, or visual correlation

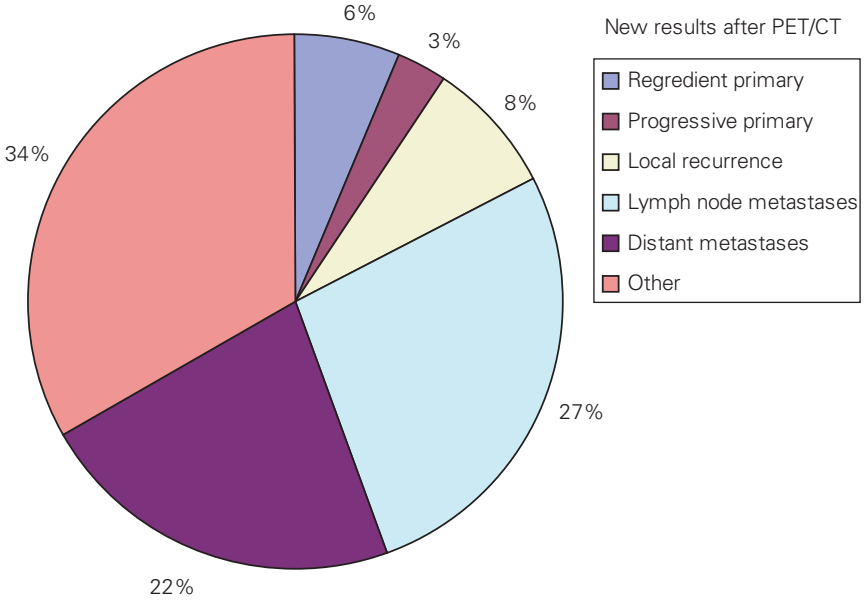


Figure 4. New results after PET/CT, n = 63 (100%), in 43/58 PET/CT examinations, "Other" including seven patients with suspected second tumor.

Abbildung 4. Neue Befunde nach PET/CT, n = 63 (100%), in 43/58 PET/CT-Untersuchungen; „Other" beinhaltet sieben Patienten mit V.a. zweiten Tumor.

of PET and CT. Nodal staging was also significantly more accurate with integrated PET/CT than with PET alone, thus lowering the risk of a geographic miss in NSCLC [11]. In HNC, FDG PET used as PET/CT improved the findings of metastatic lymph nodes. In a series of 21 patients examined at a PET/CT scanner with FDG, PET found all primaries and, in eight patients, additional areas of disease in comparison to CT. The average ratio of the GTV volumes of PET to CT was 3.1 but 0.7 for nodal involvement [8].

The impact of PET data with several tracers is under investigation and promises some advantages for radiation treatment planning. Besides additional information in defining macroscopic tumors, PET might help to find important biological tumor properties or evaluate tumor response to oncologic treatment [6, 10]. An important advantage of our preliminary study is the usage of the combined dataset for treatment planning. After bringing the patient in treatment position, the CT data are sent into the planning program. Working in an interdisciplinary group with a multimodal diagnostic crew leads to a simplified delineation of the GTV. After transferring the structure set into the planning system, the radiotherapeutic procedures of PTV definition and calculation of the treatment plan are performed in a routine matter. Former literature data describe a reduced interobserver variation in GTV delineation [1]. The risk of a geographic miss is lowered by a combined usage of anatomic and metabolic data with improved precision of localization. While creating the patient's matrix during one session of PET/CT, less visiting dates are necessary reducing time and costs. Our first results show an unexpected high impact on therapeutic management especially in patients with advanced NSCLC and HNC even in an adjuvant situation. This and the better comfort of a combined scanning including radiation treatment planning improve the acceptance of this procedure in our patients. Despite the low number of patients these first experiences are very encouraging and will be further examined. The special value of a combined scanner in comparison to separately performed PET and CT examinations at different locations and times has to be evaluated. Getting the data in identical position on a hybrid system as PET/CT improves fusion in the treatment-planning system. An interdisciplinary interpretation of the data accounts for an easier and improved delineation of macroscopic tumor and reduces the risk of a geographic miss.

Conclusion

PET/CT performed in radiation treatment position enables an integration of interdisciplinary evaluation of basic staging information including anatomic as far as metabolic staging information and the treatment-planning procedures for radiotherapy. In the described prospective observational investigation, a high proportion of planning processes as well as treatment decisions were altered by the information of PET/CT. Our first experiences encourage further evaluation of the impact of PET/CT on radiation treatment planning.

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