The Use of FDG-PET to Target Tumors by Radiotherapy

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Fluorodeoxyglucose positron emission tomography (FDG-PET) plays an increasingly important role in radiotherapy, beyond staging and selection of patients. Especially for non-small cell lung cancer, FDG-PET has, in the majority of the patients, led to the safe decrease of radiotherapy volumes, enabling radiation dose escalation and, experimentally, redistribution of radiation doses within the tumor. In limited-disease small cell lung cancer, the role of FDG-PET is emerging. For primary brain tumors, PET based on amino acid tracers is currently the best choice, including high-grade glioma. This is especially true for low-grade gliomas, where most data are available for the use of ^{11}C-MET (methionine) in radiation treatment planning. For esophageal cancer, the main advantage of FDG-PET is the detection of otherwise unrecognized lymph node metastases. In Hodgkin's disease, FDG-PET is essential for involved-node irradiation and leads to decreased irradiation volumes while also decreasing geographic miss. FDG-PET's major role in the treatment of cervical cancer with radiation lies in the detection of para-aortic nodes that can be encompassed in radiation fields. Besides for staging purposes, FDG-PET is not recommended for routine radiotherapy delineation purposes. It should be emphasized that using PET is only safe when adhering to strictly standardized protocols.

Key Words: PET · Radiotherapy · Treatment planning · Target delineation

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Der Einsatz der FDG-PET bei der Behandlung von Tumoren mittels Strahlentherapie

Die Fluordesoxyglucose-Positronenemissionstomographie (FDG-PET) spielt eine zunehmende Bedeutung in der Strahlentherapie, neben der bereits etablierten Bedeutung für Tumorstaging und Patientenselektion. Insbesondere bei nichtkleinzelligen Lungenkarzinomen führt der Einsatz der FDG-PET in der Mehrzahl der Fälle zu einer unbedenklichen Abnahme des Strahlenvolumens, wodurch Dosiseskalationen und auf experimenteller Ebene selbst Dosisumverteilungen der Strahlendosis im Zielvolumen möglich werden. Bei kleinzelligen Lungenkarzinomen nimmt die Bedeutung der FDG-PET ebenfalls zu. Bei primären Hirntumoren stellt die Aminosäure-PET derzeit die beste Wahl dar, auch bei den hochgradigen Gliomen. Für die niedriggradigen Gliome favorisieren die meisten Daten den Einsatz von ^{11}C-MET (Methionin) in der Strahlentherapieplanung. Beim Ösophaguskarzinom liegt der wesentliche Vorteil der FDG-PET in der Detektion von unerkannten Lymphknotenmetastasen. Beim Morbus Hodgkin ist die FDG-PET essentiell für die „involved-field"-Bestrahlung und führt zu einem reduzierten Strahlenvolumen bei gleichzeitig vermindertem Risiko der geographischen Fehlbehandlung. Die bedeutendste Rolle der FDG-PET bei der Behandlung des Zervixkarzinoms liegt in der Detektion von paraaortalen Lymphknoten, die in das Bestrahlungsgebiet mit aufgenommen werden. Zusammenfassend wird die FDG-PET neben dem Einsatz beim primären Tumorstaging derzeit nicht für den Routineeinsatz bei der Einzeichnung des Zielvolumens in der Strahlentherapie empfohlen. Der Einsatz der FDG-PET sollte nur nach streng standardisierten Protokollen erfolgen.

Schlüsselwörter: PET · Strahlentherapie · Bestrahlungsplanung · Zielvolumeneinzeichnung

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Introduction

Radiotherapy is a key treatment modality in the curative treatment of patients with cancer. The probability for radiotherapy to achieve tumor control is dependent on two crucial issues: dose and treatment time on the one hand and precise delivery of that dose on the tumor on the other. The latter seems obvious, but is not trivial at all. Indeed, theoretically, when extremely high radiation doses (e.g., 200 Gy) could be given to the tumor only, thus sparing normal tissues, a virtually 100% probability to achieve local tumor control would emerge, without toxicity. Apart from biological and physical factors, central to achieve, the ultimate therapeutic ratio is adequate delineation of the tumor. An incorrect definition of the gross tumor volume (GTV, i.e., detectable tumor) or clinical target volume (CTV, tumor plus a margin for microscopic extension) is a source of systematic errors, which can lead to undertreatment and reduces the probability of tumor control.

Perfect delineation of the tumor requires – apart from optimal diagnostic accuracy (cancer or not) – also the capability to sharply identify the anatomic borders of the tumor. Indeed, underdosage of parts of the tumor results in a dramatic decrease in tumor control probability. Moreover, many tumors move substantially due to physiological processes such as respiration, cardiac beats, bowel and bladder filling. As the delivery of radiotherapy typically takes 10–15 min, any imaging modality should take this time frame into account. Tracking or gating techniques may tackle some of these problems, but apart from their availability, many technical problems still have to be solved for many tumor locations. Repeated imaging would also deal with volume and shape changes during therapy. All this should be done in radiotherapy position, in order to avoid mismatching, image warping and other image manipulations, which all increase the chance of errors.

A weak point in current tumor delineation protocols is its manual component. Indeed, visual tumor contouring is routinely used in clinical practice. Even with carefully designed protocols, significant inter- and intraobserver variability still occur. Automated tools are therefore needed.

Positron emission tomography (PET) and, certainly, integrated PET-CT (computed tomography) have many potential advantages for radiotherapy planning. They combine anatomic and biological information in an identical patient position as radiotherapy will be delivered, there is no time interval between PET and CT scan, the CT can be used for attenuation correction, and CT densities can be used for radiation dose calculation.

Although not the aim of this article, it should be stressed that, as with any other imaging and therapeutic modality, also PET in radiotherapy should be calibrated thoroughly as well as used in strict clinical protocols. Volume assessment with PET is crucially dependent on technical factors and huge mistakes can only be avoided by sticking to well-established protocols [9].

PET with fluorodeoxyglucose (FDG) as tracer in radiotherapy planning has been investigated in many cancer types, of which non-small cell lung cancer (NSCLC) is the most widely applied in clinical practice. In other tumor types, such as head and neck cancer, neurological tumors, esophageal carcinoma, rectal cancer, lymphoma and cervical carcinoma, radiotherapy planning using FDG-PET has a role to play.

For each of these tumor types, the following questions will be addressed:

(1) Does PET scanning allow accurate tumor delineation? Does PET scanning change GTV, CTV and/or the PTV (planning target volume), both for the primary tumor and the local and regional lymph nodes?
(2) Does PET scanning allow improvement of treatment outcome?

Lung Cancer

Non-Small Cell Lung Cancer (NSCLC)

PET for Defining Tumor Volumes (Figure 1)

Nodal Target Volume

Accurate identification of nodal metastases is crucial for planning curative radiotherapy, particularly as routine elective nodal irradiation is no longer recommended in NSCLC [64]. FDG-PET scan has a higher sensitivity, specificity and accuracy for detection of lymph node involvement and distant metastases in NSCLC than CT scan and, therefore, results in a more accurate staging [75].

In several planning studies, it was shown that PET or PET-CT influences the GTV [50, 51]. The PET volumes were in general smaller than with CT [14, 72]. A prospective clinical trial using selective mediastinal radiotherapy of PET-positive nodes reported isolated nodal failures in only one of 44 patients [15]. These results were subsequently confirmed in another, similar prospective study from the Netherlands Cancer Institute [6], but not in a US retrospective series [68]. The latter may be due to the absence of a clearly defined PET delineation protocol. Although PET-defined mediastinal radiotherapy fields appear to be safe, because of a false-positive rate of approximately 30% and a false-negative rate of about 7%, depending on the patient population, ideally, pathologic confirmation of PET-positive mediastinal nodes should be obtained by mediastinoscopy or endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA).

Target Volume for Primary Tumor

At present, FDG-PET scans offer little additional advantage over CT or MRI (magnetic resonance imaging) scans for staging of the primary tumor because of its lack of precise anatomic localization. The spatial resolution of modern CT scanners (typically about 1 mm) is far superior to that of current PET scanners (6–8 mm), so that the extra gain with fusion is expected not to be large, unless PET scans can reliably address tumor delineation caused by atelectasis or intratumor heterogeneity. However, PET did show a remarkably good correlation with pathology and patient data [61, 67, 70].

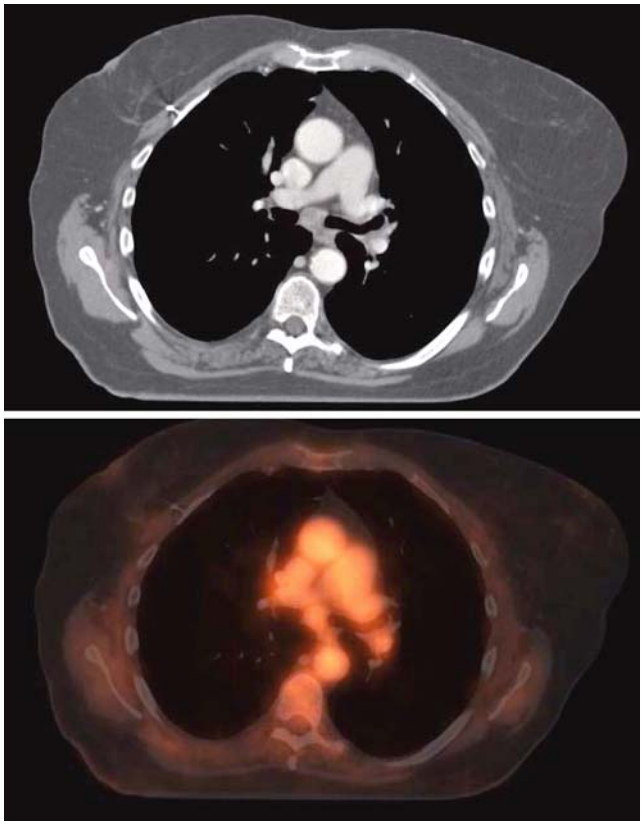

Figure 1. Non-small cell lung cancer. Axial view of ^{18}F-FDG-PET-CT with contrast. CT shows an enlarged node (level 7, diameter of 1.9 cm), while PET shows no FDG uptake in level 7. This finding influences the delineation of the nodal target volume.

Abbildung 1. Nichtkleinzelliges Lungenkarzinom. Axialer Schnitt einer ^{18}F-FDG-PET-CT mit Kontrast. Das CT zeigt einen vergrößerten Lymphknoten (Level 7, Diameter 1,9 cm), während das PET keine FDG-Aufnahme in Level 7 zeigt. Dieser Befund beinflusst die Definition des nodalen Zielvolumens.

Moreover, PET scans reduced the interobserver variability compared to CT alone [45]. Integrated PET-CT scans further improved delineation variability [66]. The next step is to use the PET signal to construct automatic delineation of the tumor and to offer the radiation oncologist a solution that only needs contour editing. This method was on its turn to be less prone to variability than PET-CT [70].

As PET acquisition takes several minutes, tumor motion due to respiration or cardiac action results in PET "GTVs" that incorporate at least some effects of this motion. Respiration-gated PET acquisition techniques have been developed [23, 49] and are, at present, evaluated in clinical studies.

Clinical Target Volume

In view of the relatively poor spatial resolution of PET scans, it does not come as a surprise that at the time of writing, no clear advantages of PET to define the microscopic extensions of the tumor were reported. The development of new methods may change this picture in the future [67].

Do PET Scans Change the Outcome of Patients with NSCLC Treated with Radiotherapy?

PET scans have shown to detect distant metastases in up to 30% of the patients with stage III NSCLC who were M0 with conventional staging [29, 44]. This clearly affects patient outcome, for it spares toxic therapy in individuals who will not benefit from it.

The PET volumes were, in general, smaller than with CT. The incorporation of PET in radiotherapy planning has, as previously shown, the potential to allow radiation dose escalation without increasing side effects, namely because of the reduction of radiation fields [14, 72]. In a phase I/II trial, it was shown that this prerequisite is indeed true [71].

Whether this radiation dose increase will ultimately lead to higher cure rates is a matter of current research.

PET scans may also allow the identification of therapy-resistant areas within the tumor that could be given a higher radiation dose and hence lead to a better outcome [2, 3].

Small Cell Lung Cancer (SCLC)

PET Scan for Radiotherapy of Limited-Disease Small Cell Lung Cancer

Literature is sparse on the role of PET in limited-disease small cell lung cancer (LD-SCLC). Although after CT-based radiotherapy planning, isolated nodal recurrences may be seen in > 10% of the patients, selective nodal irradiation based on PET scans proved to result in only 3% of isolated nodal failures in a prospective study [74].

Conclusions

For NSCLC, FDG-PET allow more thorough staging, thus avoiding unnecessary treatments. In most patients, it reduces radiation treatment volumes because of the avoidance of mediastinal lymph nodes that are PET-negative and hence reduces toxicity with the same radiation dose or enables radiation dose escalation with the same toxicity. Data are also encouraging for SCLC. More research is needed to assess the effect of PET on survival. PET also reduces interobserver variability for delineating tumors and opens perspective for more automated delineation parts in radiotherapy planning, as well as innovative radiation treatment delivery.

Primary Brain Tumors

Compared with other organ systems, FDG-PET imaging of the brain presents unique challenges because of the high background glucose metabolism of normal gray matter structures. Highly metabolically active tissues such as the normal brain can mask detection of adjacent abnormalities and as such are not always helpful for tumor and target delineation. Furthermore, many primary brain tumors, for example, meningioma, show no uptake of FDG and cannot be imaged with FDG-PET. Inter-

pretation of functional PET images can be improved by correlation with anatomic imaging. Co-registration of MRI or CT and FDG-PET images is essential for accurate evaluation of brain tumors. Also, primary brain tumors consist of a group of various pathologies and carry variable prognoses. They have the tendency to recur locally and to undergo malignant degeneration in which case PET can have added value during follow-up.

Low-Grade Glioma

Functional imaging with modern tracers such as ^{11}C-MET (methionine) results in good visualization of low-grade gliomas. Baseline amino acid uptake on ^{18}F-FET-PET in a diffuse versus circumscribed tumor pattern on MRI is a strong predictor for the outcome of patients with low-grade glioma [20]. The combination of PET with conventional imaging techniques (MRI, CT) may lead to synergy in delineating these tumors in the course of radiotherapy planning. Early reports [54] found ^{11}C-MET to be superior to CT in delineating gliomas. Comparing FDG-PET with MRI in 14 patients with predominantly low-grade glioma, PET volumes were larger than, equal to, or smaller than MRI-derived tumor volumes in seven, four, and three patients, respectively [53]. PET was helpful in outlining the GTV in three cases only. Jacobs et al. [30] and Kaschten et al. [37] found ^{11}C-MET superior to ^{18}F-FDG and ^{18}F-FLT (^{18}F-fluoro-3'-deoxy-3'-L-fluorothymidine) respectively, in delineating low-grade glioma. For low-grade glioma, an amino acid tracer is the tracer of first choice in radiotherapy planning.

Pituitary Adenoma

The value of ^{18}F-FDG and ^{11}C-MET in addition to MRI was investigated in a population of 57 patients comprising a variety of tumors including ten pituitary adenomas [41, 42]. PET influenced the target volume in 69% of the target volumes for stereotactic radiosurgery. In recurrent adenoma after surgery, ^{11}C-MET may distinguish between active tumor and fibrosis, which is essential to define an optimal target volume for radiotherapy purposes [8].

High-Grade Glioma (Figure 2)

Studies comparing tumor volumes based on PET (both ^{18}F-FDG and ^{11}C-MET) and other imaging modalities usually show that PET scan volumes are smaller than MRI- and CT-based volumes [24, 27]. In a study of 57 patients treated by radiosurgery for 72 target volumes, an abnormal uptake of FDG or ^{11}C-MET on PET was seen in 86% of the targets, leading to a change in target volume in 69% of these cases compared to MRI delineation [41]. In 36% of these patients, the PET-based volume was fully encompassed with the MRI-based volume, while in 18 cases, PET showed a target volume outside the MRI-based delineation.

Using FDG-PET, in 22 out of 27 patients with glioblastoma, the tumor volumes were at least 25% smaller on FDG-PET than on MRI [69]. Occasionally, there was FDG uptake outside the region with gadolinium enhancement on MRI. Another study confirmed a decrease in mean volumes on FDG-PET as compared to MRI (T1-weighted images with gadolinium) [24].

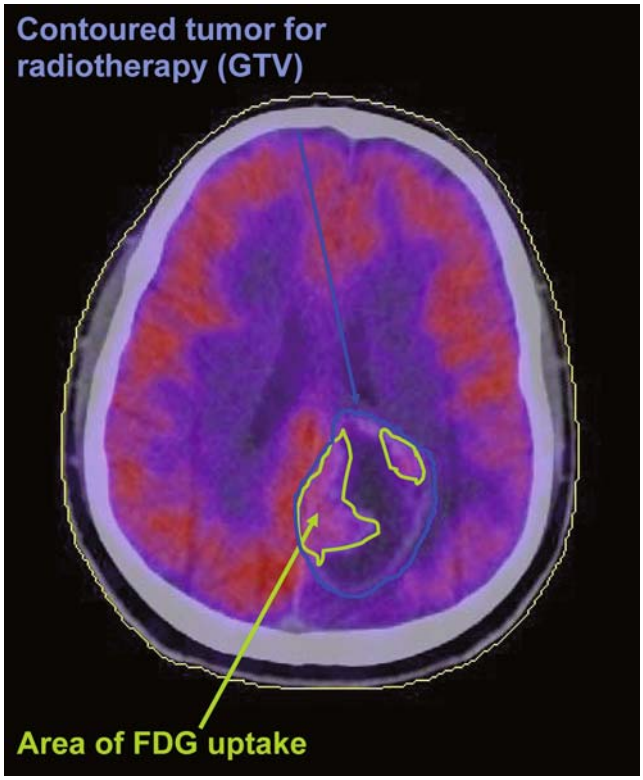

Figure 2. Glioblastoma. Axial view of ^{18}F-FDG-PET-CT with contrast. The area of the postoperative tumor volume for radiotherapy is defined in blue. Yellow areas are those of FDG uptake. Volumes are usually within the contrast-enhanced area of CT and MRI. The normal brain shows high uptake of FDG in general and makes a clear distinction between tumor and normal brain difficult.

Abbildung 2. Glioblastom. Axialer Schnitt einer ^{18}F-FDG-PET-CT mit Kontrast. Das Gebiet des postoperativen Tumorvolumens für die Strahlentherapie ist in Blau wiedergegeben. Das grüngelbe Areal stellt das FDG-Aufnahmegebiet dar. Die Volumina sind üblicherweise innerhalb des kontrastverstärkten Gebiets der CT und MRT lokalisiert. Da das normale Gehirn generell eine hohe FDG-Aufnahme zeigt, sind klare Unterscheidungen zwischen Tumor und normalem Hirngewebe schwierig.

By contrast, an increase in GTV with the use of ^{11}C-MET in 79% of the patients compared to MRI was reported [25]. This was confirmed by another study [47]. A first study comparing patients with recurrent high-grade gliomas reirradiated using ^{11}C-MET-PET-based tumor delineation versus CT/MR images for treatment planning showed an improvement in survival [27]. Whether ^{11}C-MET-PET-defined tumor volumes for radiation treatment planning and, as a consequence, extended radiation fields will have a significant influence on outcome in terms of overall survival, has to be proven in future studies.

Additionally, PET can reduce interobserver variability in delineation of brain tumors. Van Laere et al. compared FDG and ^{11}C-MET-PET for the delineation of brain tumors [73].

The interobserver agreement was 100% for ^{11}C-MET and 73% for FDG-PET. Many high-grade gliomas show intratumor heterogeneity and PET could be used to define tumor regions being at high risk for recurrence. Regions with abnormal tracer uptake (reported for FDG or FET [^{18}F-fluoroethyltyrosine]) are at risk for first tumor progression and could therefore be a target for dose escalation [59, 65, 79]. Areas of FET uptake on FET-PET-CT for radiotherapy planning were being observed up to 20 mm outside the area of gadolinium enhancement on MRI [79].

Meningioma

A small study of ten patients treated with fractionated stereotactic radiotherapy showed a significant increase of the GTV, when ^{11}C-MET-PET was used for tumor delineation [26]. The addition of ^{11}C-MET-PET was beneficial for GTV delineation in all but three out of 32 patients. Radiotherapy planning for skull base meningiomas influenced the GTV, possibly resulting in an increase, as well as in a decrease [5]. ^{68}Ga-DOTATOC-PET delivered additional information concerning tumor extension in all investigated patients planned for fractionated stereotactic radiotherapy of meningiomas [46].

In 73% of the patients, the planning tumor volume was significantly modified, and in one patient, no tumor was exactly identified on CT/MRI but was visible on PET.

Another tracer currently being tested is ^{18}F-tyrosine. This tracer is also taken up by meningiomas with a tumor-to-cortex ratio of 2.53 ± 0.35 [60]. The ^{18}F-tyrosine anomalies completely overlapped with the MR image in 54%, extended beyond the MRI lesion in 38%, and were smaller in 8% of the tumors. Meningiomas of the skull base are clearly visualized using ^{18}F-tyrosine PET, even after radiotherapy.

Conclusions

FDG-PET is mainly used in brain tumors for definition of tumor grading and prognosis as well as differentiation between recurrence and radionecrosis. Tumor delineation for radiotherapy planning was not substantially influenced, as physiologically, the most intense FDG uptake is seen in brain tissue. Therefore, the tracer is not very suitable for the imaging of most intracerebral malignancies.

For low- and high-grade gliomas and meningiomas, ^{11}C-MET or other amino acid tracers such as tyrosine are currently the tracers of first choice in radiotherapy planning. First data have shown a survival advantage for patients with a high-grade glioma, if MET-PET-based radiotherapy planning was used. However, further investigation is needed.

Esophageal Carcinoma

PET for Defining Tumor Volumes

Nodal Target Volume

Nodal staging using FDG-PET is limited by local tumor invasion. Consequently, the accuracy of staging regional node metastases decreases with an accuracy rate of 24–90% for PET compared with 40–73% for CT. The reported sensitivity and specificity of FDG-PET regarding nodal staging was 24–72% and 82–100%, respectively [18, 28, 58]. Generally, FDG-PET has a higher specificity (89% vs. 67%) with a lower sensitivity (33% vs. 81%) for identifying nodal metastases compared with the use of combined CT/EUS-FNA. The lower sensitivity of FDG-PET for detecting local lymph nodes depends on the limited spatial resolution of PET with a difficulty to discriminate the primary tumor from local, peritumoral lymph nodes.

Vrieze et al. assessed lymph node involvement by CT, EUS, and FDG-PET in 30 patients with advanced esophageal carcinoma [78]. In 47% of patients, discordance was noted between lymph nodes detected by FDG-PET and by CT/EUS. The authors suggested that irradiated volumes should not be reduced based on negative FDG-PET results, given the false-negatives noted in this report. However, they also concluded that FDG-PET demonstrated adequate specificity to conclude that FDG-PET-positive disease should be included in the irradiated volume. As these patients received neoadjuvant chemoradiation, no histological confirmation of discordant findings is possible.

Target Volume for Primary Tumor

Konski et al. performed CT and FDG-PET for radiation treatment planning in 25 patients with esophageal carcinoma; 18 of the 25 patients also had EUS for comparison [39]. Mean GTV as determined by CT scan was significantly bigger than that determined by FDG-PET. EUS detected more regional adenopathy than both CT and PET. Moureau-Zabotto et al. performed FDG-PET and CT for simulation purposes in 34 patients with esophageal carcinoma [48]. Five fiducial markers were used to precisely co-register the CT and FDG-PET images for planning purposes. GTV was reduced in 35% and increased in 21% of patients. Leong et al. enrolled 21 esophageal carcinoma patients in a prospective trial to determine effects of PET-CT on delineation of tumor volume for radiotherapy planning [40]. PET-CT detected disease in eight patients that was not detected by CT scan: four of these patients were found to have metastatic disease and four had regional nodal disease. In 16 of 21 patients who proceeded to the radiotherapy planning phase of the trial, 69% had PET-CT-positive disease that would have been excluded, if CT alone had been used for radiation treatment planning.

Do PET Scans Change the Outcome of Patients with Esophageal Cancer Treated with Radiotherapy?

Well-performed FDG-PET improves the selection of patients with esophageal cancer for potentially curative surgery, especially in stages III–IV [76]. This clearly affects patient outcome, since it saves an extra complication and mortality risk in individuals who will not benefit from surgery. The incorporation of PET in radiotherapy planning has, as previously shown, the potential to allow radiation dose escalation with-

out increasing side effects, namely because of the reduction of radiation fields.

Conclusions

A well-performed FDG-PET-CT is important to detect distant metastases and hence to select patients suitable for local therapy. For the nodal target volume, FDG-PET has a higher specificity with a lower sensitivity compared with the use of combined CT/EUS-FNA. FDG-PET results in a smaller GTV in most of the patients analyzed. If validated, the use of FDG-PET might result in a smaller target volume, which would reduce the toxicity or enable radiation dose escalation with the same toxicity.

Rectal Cancer

PET for Defining Tumor Volumes (Figure 3)

Nodal Target Volume

Studies investigating the role of FDG-PET for the initial staging of rectal cancer suggest that PET is useful in the diagnosis of the primary tumor, but it is of limited value for detecting regional lymph node metastases, with a sensitivity of only about 30% [1, 36].

Irradiated volumes should therefore not be reduced based on negative FDG-PET results. However, as the positive predictive value was approximately 90%, FDG-PET-positive disease should be included in the irradiated volume.

Target Volume for Primary Tumor

FDG-PET represents the imaging technique of choice to discriminate between benign or malignant tumors of presacral residual postsurgical masses in rectal cancer patients [19], although infection can lead to false-positive findings. The data on the use of FDG-PET for radiation treatment planning in rectal cancers is limited. Ciernik et al. evaluated the value of PET-CT on radiotherapy planning for patients with tumors at several sites, including carcinoma of the rectum (six patients) and carcinoma of the anus (seven patients) [12]. The GTV increased in three of six patients with rectal primaries,

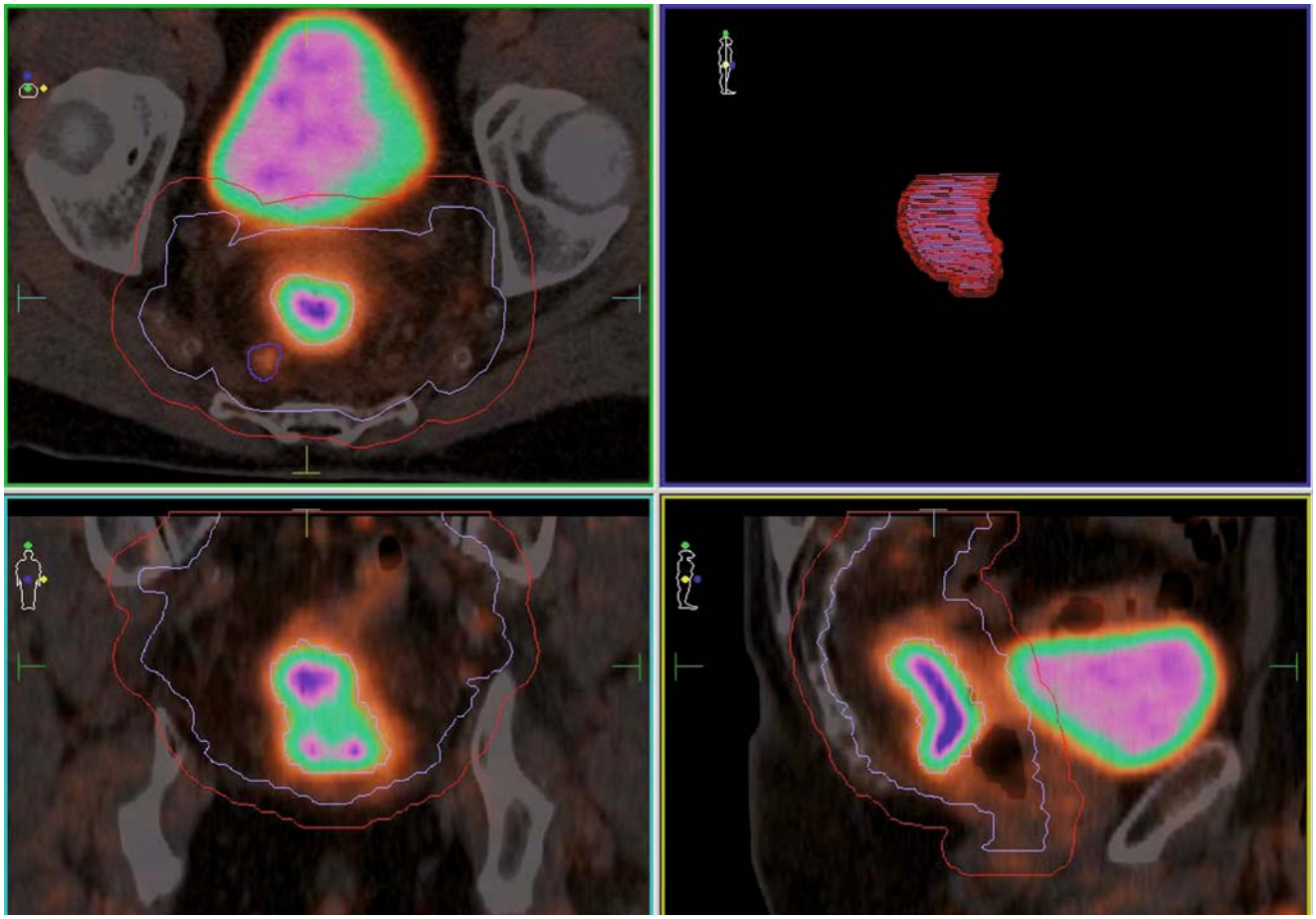

Figure 3. Delineation of the GTV, CTV, and PTV on the basis of an ^{18}F-FDG-PET-CT from a patient with midrectal cancer. GTV is light brown, the enlarged PET-positive mesorectal lymph node blue, the CTV light blue, and the PTV red.

Abbildung 3. Einzeichnung des GTV, CTV und PTV auf Basis einer ^{18}F-FDG-PET-CT eines Patienten mit einem mittleren Rektumkarzinom. Das GTV ist hellbraun, der vergrößerte PET-positive mesorektale Lymphknoten blau, das CTV hellblau und das PTV rot dargestellt.

with a mean GTV increase of 50% and a PTV increase of 20%. Several groups have investigated the impact of PET-CT use on the treatment and the radiotherapy volume definitions [4, 12, 55, 77]. Significant tumor volume changes were observed. However, even if PET can provide additional functional information, its usefulness in the treatment of rectal cancer is still questionable and needs to be evaluated in prospective trials with strict methodology. Its benefit may be of little interest in preoperative three-dimensional conformal radiotherapy, as the total mesorectum included in the CTV will be surgically removed anyway. However, it may become important, when higher doses in relevant biological regions need to be achieved with boost techniques [55].

Several studies have demonstrated the substantial variability among radiation oncologists in defining the target volume using CT images. At the time of writing, it remains unclear as to whether PET-based delineation accurately represents the real macroscopic tumor extension.

Clinical Target Volume

In general, the current treatment regimens for rectal cancer question the additive value for the use of PET-CT in the definition of the CTV, since the total mesorectum included in the CTV will be surgically removed anyway.

Do PET Scans Change the Outcome of Patients with Rectal Cancer Treated with Radiotherapy?

The incorporation of PET in radiotherapy planning has the potential to allow radiation dose escalation without increasing side effects, this because of the reduction of radiation fields. Whether this radiation dose increase will ultimately lead to higher cure rates or less surgical resections with, as a result, less complications is a matter of current research. A more individualized approach based on early treatment response might have the advantage of a response-adjusted radiation treatment with the goal of more complete tumor responses.

This could then help to avoid unnecessary surgical resections, thereby improving outcome and quality of life. Published data indicate that PET-CT has a high predictive value in the therapeutic management of rectal cancer [10, 31–34]. This could be an asset for improving patient care by reducing the effort, cost, and morbidity associated with ineffective treatment in nonresponders. The available studies on preoperative radiochemotherapy indicate that PET-CT is a significant predictor of therapy outcome and correlates better with pathology than morphological imaging modalities. Since PET-CT is able to predict the final outcome, it may be used to guide treatment regimens in the near future, thereby better individualizing treatment while improving the patients' outcome.

Conclusions

Although FDG-PET-CT is of limited value for detecting regional lymph node metastases, its high positive predictive value may change irradiation volumes. In spite of the fact that the current radiotherapy treatment of rectal cancer includes the whole mesorectum, which will be surgically removed anyway, future developments may involve FDG-PET in patient selection suitable for nonsurgical therapy as well as for more sophisticated radiation treatment delivery.

Lymphoma

PET for Defining Tumor Volumes

FDG-PET is superior to CT or MRI for the staging of both non-Hodgkin's and Hodgkin's lymphoma [16]. Early assessment of FDG uptake in the tumor during chemotherapy is highly predictive for subsequent outcome, as is residual FDG avidity after treatment [38, 63, 82]. With the concept of involved-node irradiation in Hodgkin's disease [17, 22, 81], increased interest has emerged to include FDG-PET scan information for defining target volumes [21]. After chemotherapy, the initial FDG-PET helped the delineation of involved-node radiotherapy fields due to the identification of lymph nodes that were undetected on CT in 36% of the patients. Prechemotherapy FDG-PET data were thus essential for correctly implementing the involved-node radiotherapy concept.

Do PET Scans Change the Outcome of Patients with Lymphoma Treated with Radiotherapy?

No trials have been completed thus far that address this question, but in view of the decreased irradiation volumes [81] and, at the same time, the decreased probability of geographic miss [21], it is very likely that the inclusion of FDG-PET information improves the outcome of patients with Hodgkin's disease.

Conclusions

In Hodgkin's disease, FDG-PET is essential for involved-node irradiation and leads to decreased irradiation volumes while also decreasing geographic miss.

Cervical Carcinoma

PET for Defining Tumor Volumes (Figures 4 and 5)

Target Volume for Primary Tumor

The sensitivity of FDG-PET for detecting local disease ranges between 91% and 100%. Due to the limitations in spatial resolution, PET imaging is inaccurate for assessing local tumor extension in adjacent structures such as the parametrium. For this purpose, MRI is the modality of choice [7].

Nodal Target Volume

Due to the small risk of lymphatic spread in early-stage cervical cancer, the sensitivity of PET is low [80]. In locally advanced cervical carcinoma, biological PET criteria have been demonstrated to be superior to morphological MRI criteria for assessing retroperitoneal metastases [11]. In case of spread to the para-aortic nodes, about one third of the patients may still be cured following extended-field radiotherapy. FDG-PET is the most accurate technique for evaluating para-aortic lymph nodes [43]. Identification of gross tumor deposits will change

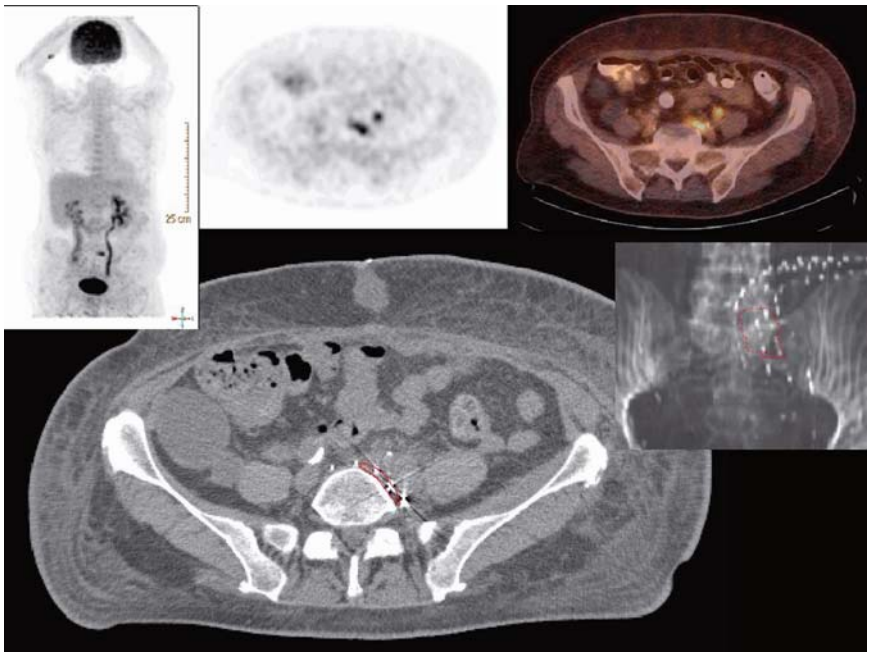

Figure 4. Cervical cancer. Patient presenting with isolated lymphatic recurrence 15 months following initial treatment with chemoradiation. Treatment consisted of gross tumor resection with subsequent high-dose-rate brachytherapy delivered to the tumor bed.

Abbildung 4. Zervixkarzinom. Die Patientin stellte sich 15 Monate nach der initialen Radiochemotherapie mit einem isolierten Lymphknotenrezidiv vor. Die Behandlung bestand aus einer Tumorresektion, gefolgt von einer konsolidierenden High-Dose-Rate-Brachytherapie auf das Tumorbett.

the radiation treatment volume and/or total dose in locally advanced disease.

Do PET Scans Change the Outcome of Patients with Cervical Cancer Treated with Radiotherapy?

At present, no randomized study has been performed to answer this question. However, in view of the detection of otherwise unrecognized nodal disease in the para-aortic region that can be irradiated with curative intent, a significant gain can reasonably be expected.

Although definite conclusions cannot be drawn yet on determining cutoff values for SUV_{max} (standardized uptake value), integration of SUV_{max} in clinical studies as an additional prognostic marker seems warranted. So far, changes in metabolic response observed during treatment did not correlate with survival outcome, whereas posttreatment evaluation seems to be a reliable measure for treatment outcome enabling decision-taking regarding additional salvage treatment.

Conclusions

Currently, FDG-PET is the imaging modality of first choice for assessing lymphatic spread in locally advanced disease. Its role in providing additional prognostic information with impact on primary treatment decision-making needs to be evaluated in prospective clinical trials.

Head and Neck Cancer

PET for Defining Tumor Volumes

An in-depth comparison between FDG-PET, MRI and CT scans with the histology of resection specimen showed that FDG-PET may be the most accurate of the three for the detection of head and neck cancer [52]. Tumor volume determined by FDG-PET tends to be smaller than the volume determined by the other modalities, but most closely approximates the pathologic tumor volume [13]. However, some tumor regions that are apparent on CT or MRI may not be imaged on PET, or the reverse may occur. PET-based delineation of the primary tumor is, at present, not ready for clinical routine [57].

PET for Defining Nodal Volumes

FDG-PET often changes the nodal staging in head and neck cancer [56]. However, many lymph nodes that are enlarged and considered metastatic by standard CT-based criteria are negative on FDG-PET scan [62]. On the other hand, a small proportion of marginally enlarged nodes are positive on FDG-PET scan. However, as the results are largely dependent on the PET segmentation tool used, until proper validation with pathology, FDG-PET cannot be recommended for target volume definition of metastatic lymph nodes in routine radiotherapy.

Do PET Scans Change the Outcome of Patients with Head and Neck Cancer Treated with Radiotherapy?

Besides for staging purposes, such as for carcinoma with unknown primary [35], for purely radiotherapy purposes, FDG-PET has not shown to be beneficial for head and neck cancer patients.

Conclusions

FDG-PET-defined tumor volumes are more closely related to pathology than those determined by CT and MRI, but both over- and underestimation still occur. Besides for staging purposes, FDG-PET is not recommended for routine radiotherapy delineation purposes.

General Conclusions

FDG-PET plays an increasingly important role in radiotherapy, beyond staging and selection of patients. Especially for NSCLC, FDG-PET has led to the safe decrease of radiotherapy volumes, enabling radiation dose escalation and, experimentally, redistribution of radiation doses within the

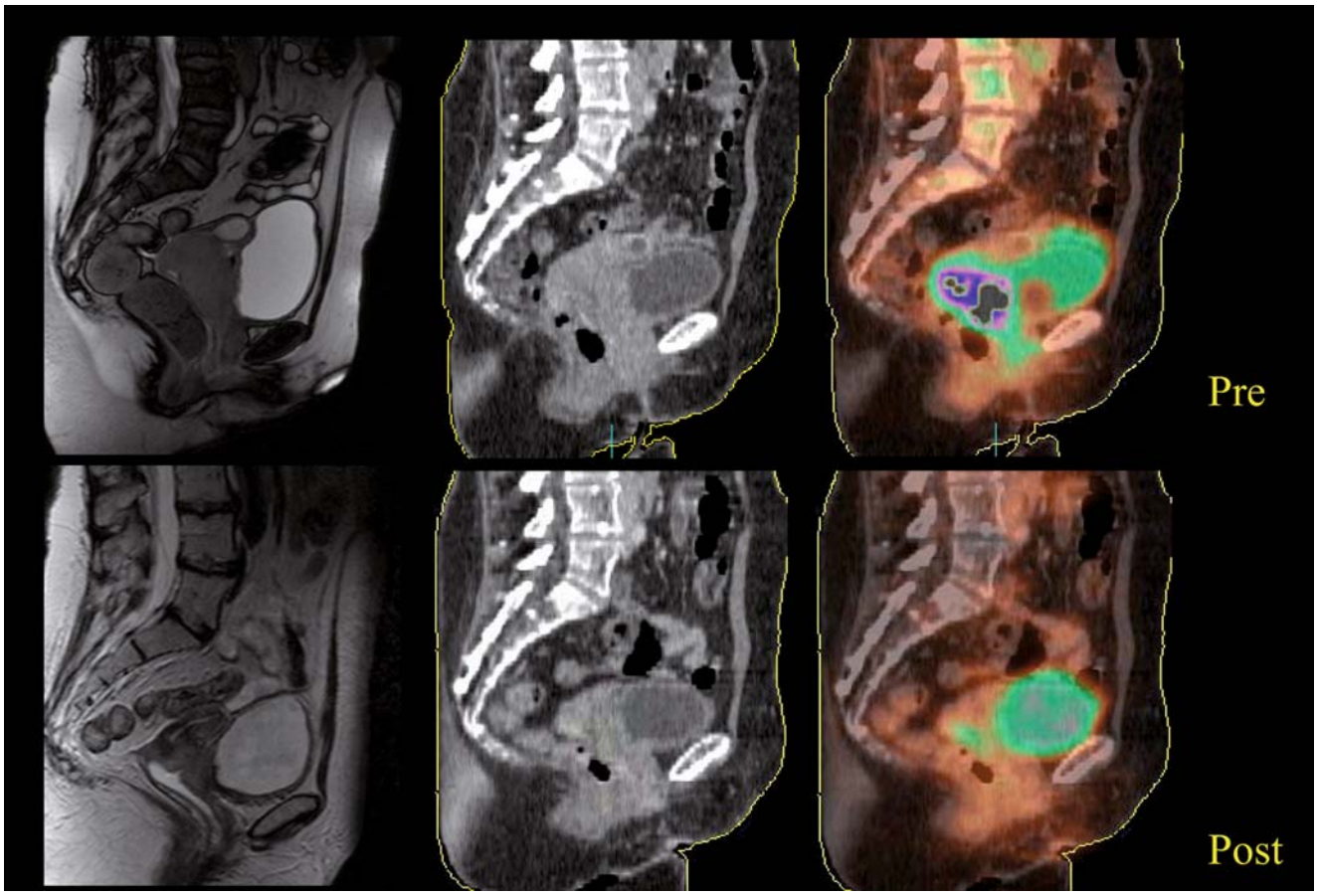

Figure 5. Tumor response in a patient with cervix carcinoma FIGO stage IVA (extension to bladder) following 50 Gy of external-beam radiotherapy plus hyperthermia as determined with MRI, CT, and FDG-PET.

Abbildung 5. MRT-, CT- und FDG-PET-Darstellung der Tumorreduktion bei einer Patientin mit Zervixkarzinom FIGO-Stadium IVA (Ausdehnung bis zur Harnblase) nach 50 Gy externer Strahlentherapie in Kombination mit Hyperthermie.

tumor. In LD-SCLC, the role of FDG-PET is emerging. For low-grade gliomas, ^{11}C-MET is the tracer of first choice in radiotherapy planning. PET for high-grade gliomas is investigational.

For esophageal and rectal cancer, the main advantage of FDG-PET is the detection of otherwise unrecognized lymph node metastases. In Hodgkin's disease, FDG-PET is essential for involved-node irradiation and leads to decreased irradiation volumes while also decreasing geographic miss. FDG-PET's major role in the treatment of cervical cancer with radiation lies in the detection of para-aortic nodes that can be encompassed in radiation fields. Besides for staging purposes, FDG-PET is not recommended for routine radiotherapy delineation purposes.

It should be emphasized that using PET is only safe, when adhering to strictly standardized protocols.

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