Value of PET imaging for radiotherapy planning

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Abstract

This comprehensive review written by experts in their field gives an overview on the current status of incorporating positron emission tomography (PET) into radiation treatment planning. Moreover, it highlights ongoing studies for treatment individualisation and per-treatment tumour response monitoring for various primary tumours. Novel tracers and image analysis methods are discussed. The authors believe this contribution to be of crucial value for experts in the field as well as for policy makers deciding on the reimbursement of this powerful imaging modality.

5

Introduction

Positron emission tomography (PET) has found its way into primary disease staging of numerous solid tumours and of lymphomas. This has mainly been the contribution of [^{18}F]Fluorodeoxyglucose (^{18}F-FDG) PET, a glucose analogue which depicts the altered metabolism of malignant tumours as well as the physiological metabolism of organs and inflammatory processes. Functional ^{18}F-FDG-PET combined with anatomical imaging modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI), has also altered radiation treatment planning and response assessment, in particular in lung cancer, prostate cancer and lymphoma. Moreover, local radiation dose-escalation, termed dose-painting, based on increased metabolism has been applied both in theoretical treatment planning studies as well as in the context of prospective clinical trials. Finally, tracers depicting additional tumour characteristics beyond glucose metabolism have become available and their value is being assessed. For many years, the incremental value of a close interaction between radiation oncologists and nuclear medicine physicians has been highlighted by interdisciplinary studies in various tumour entities. Whereas this review is primarily aimed to provide a concise overview over the current value of PET in radiation oncology, it might also serve as a stimulus for future collaboration in both daily practice and scientific trials to further enhance patient care.

Primary brain tumours

Different from peripheral oncological diseases, which are predominantly imaged with ^{18}F-FDG-PET, non-glucose tracers have shown clear superiority in the workup of tumour lesions in the brain. This is due to their high physiological glucose consumption, leading to a low tumour-to-background contrast and sensitivity for ^{18}F-FDG, as well as to a high glucose uptake of inflammatory cells, which particularly hampers the evaluation of unequivocal lesions after radiotherapy [1-3]. Therefore, amino acid tracers such as ^{18}F-FET, ^{11}C-MET, ^{18}F-FDOPA or ^{18}F-FACBC are recommended for the assessment of gliomas and brain metastases [4, 5], while radiolabelled ligands of the somatostatin receptor type 2 (SSR2; e.g. ^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE, or ^{18}F-SIFATATE) are used for the imaging of meningiomas due to their overexpression of the SSR2 [6].

Radiotherapy planning

Conventional MRI of the brain is the gold standard to delineate tumour extent in primary brain tumours. But yet, due to their infiltrative growth, tumour margins are inadequately assessed by MRI alone and histological studies have proven that amino acid PET may be more sensitive to detect the true tumour extent [7-12]. Therefore, the PET/RANO report [4] proposed that delineation of the so-called "biological tumour volume" (BTV) using amino acid PET might more accurately disclose the true tumour volume and that biologically more active tumour regions may be amenable for dose escalation/selective boosting.

Several trials have shown the value of PET to reduce classical margins for delineation of the clinical target volume (CTV). For example, a recent study reported that a 1.5cm margin on ^{18}F-FET-PET based BTV and MR-based gross tumour volume (GTV) yielded equivalent results according to recurrence

patterns compared to classical 2cm margins while significantly reducing dose exposure to healthy brain parenchyma [13-16].

Concerning the clinical benefit, a small prospective trial suggested that amino acid PET-based re-irradiation may lead to enhanced survival compared to radiotherapy planning based on conventional MRI alone [17]. Currently, a multicentre phase II trial (GLIAA, NOA-10, ARO2013/1) is testing the hypothesis that ^{18}F-FET-PET-based re-irradiation will be superior to radiotherapy solely based on conventional MRI [18].

Also with regard to radiotherapy planning of meningiomas, the MRI-based morphologic GTV delineation may be insufficient to truly address the entire tumour volume. Particularly for the detection of an intra-osseous meningioma infiltration or for the tumour delineation at the skull base, PET using SSR-ligands has been shown to strongly complement anatomical information from MRI and CT [19-21].

Taken together, PET is a highly valuable tool to complement conventional imaging to improve the therapeutic ratio [22].

Treatment response and radiation-induced changes

In contrast to ^{18}F-FDG, which is not valuable for the response prediction to radiotherapy [23, 24], early ^{18}F-FET or ^{11}C-MET-PET changes are predictors for progression-free survival (PFS) and overall survival (OS) [25-29].

After radiotherapy to primary brain tumours or radiosurgery to metastases [6], MRI, similarly to ^{18}F-FDG PET, does not offer reliable specificity to differentiate tumour progression from treatment effects such as pseudo-progression (early event) or radiation necrosis (delayed toxicity) [1-3, 22, 30-32]. Contrarily, amino acid PET studies report a high diagnostic accuracy, which can even be increased by the evaluation of tracer uptake kinetics, at least for ^{18}F-FET [33-35].

Head and neck squamous cell carcinomas (HNSCC)

In recent years, significant improvements in radio(chemo)therapy of head and neck squamous cell carcinomas (HNSCC) have been achieved.

The impact of ^{18}F-FDG-PET on target volume (TV) delineation and dose prescription has been studied extensively. ^{18}F-FDG-PET improves primary tumour delineation, in particular in advanced stages. ^{18}F-FDG-PET based TV is smaller than the volume derived by CT or PET, and thus ^{18}F-FDG-PET has a significant impact on the radiation dose distribution [36-40]. Compared to CT or MRI, ^{18}F-FDG-PET demonstrates a higher level of concordance with local tumour extent as identified on histopathology [38]. Prospective studies were able to show that the use of ^{18}F-FDG-PET leads to a higher degree of conformal radiation dose distribution and to a decreased rate of late side-effects, without compromising effects of the irradiation [41, 42]. Leclerc *et al.* [41] conducted a study in oropharyngeal tumours employing TV delineation based on ^{18}F-FDG-PET, which led to decreased radiation doses to the parotid glands and oral cavity.

^{18}F-FDG-PET cannot reliably localize small superficial tumour deposits of the primary tumour or nodal micrometastases. This underlines the high relevance of clinical assessment in HNSCC as well as the necessity to further improve imaging modalities in the context of radiation treatment planning.

Tracers imaging tumour cell hypoxia in HNSCC, ^{18}F-MISO, ^{18}F-FAZA, ^{18}F-HX4, have been validated against immunohistochemical staining and been applied for patient selection during the course of radiochemotherapy [RCHT; [43-47]]. Several prospective clinical trials have assessed the value of ^{18}F-MISO-PET for patient stratification. A recently published prospective clinical phase II study suggests that radiation dose may be deescalated from 70 Gy to 30 Gy in oropharyngeal cancer patients with no hypoxia on ^{18}F-MISO-PET prior to or with a re-oxygenating tumour during radiation treatment [48]. ^{18}F-FLT-PET, an imaging biomarker of tumour cell proliferation in HNSCC, also holds high prognostic value regarding locoregional control [49-51]. Even though, the tracer has not yet found its way into routine clinical practice, owing to its complex synthesis.

The so-called [68]Ga- or ^{18}F-FAPI-PET is a novel imaging modality of the *Fibroblast Activation Protein* (FAP), which is highly expressed on the fibroblasts of tumour stroma. Syed *et al.* [52] have shown that a high tumour-to-background-ratio of the FAP-ligand along with significant alteration of TV-delineation in HNSCC patients. The value of ^{18}F-FAPI-PET for a variety of tumours is being evaluated in the context of a prospective register (NCT04571086). The value of this novel radiotracer PET for radiotherapy planning is to be assessed in prospective clinical studies with relevant oncological endpoints.

Non-small cell lung cancer (NSCLC)

^{18}F-FDG-PET/CT has been recognized as the key imaging method for staging of (non-)small cell lung cancer [(N)SCLC] and for detection of disease recurrence. High sensitivities and specificities reported for the detection of distant metastases allow for accurate staging and treatment allocation, i.e., local therapy with curative intent or systemic therapy for palliation, and high imaging contrast enables delineation of the primary tumour and lymph nodes for radiation treatment planning for both tumour types [53-55].

According to the present state-of-the-art, an ^{18}F-FDG-PET-CT scan in radiation treatment position should indeed be performed within 3 weeks before start of irradiation, even before chemotherapy is administered [56]. This scan may also be acquired as 4D-PET/CT for motion management, such as for stereotactic body radiotherapy (SBRT). For definition of the GTV containing the primary tumour and metastatic lymph nodes, institutionally standardized visual contouring is the most widespread method and the value of ^{18}F-FDG-PET/MRI subject to ongoing research [55, 57]. Recently, it has been confirmed in an international randomized multicentre-trial, that the CTVs (containing GTV and additional assumed microscopic spread) can safely be reduced when using ^{18}F-FDG-PET for treatment planning in the context of primary RCHT of locally advanced NSCLC [55].

Serial PET scans, combined with CT or MRI, have been investigated in multimodality protocols during induction treatment before radiotherapy or during definitive RCHT aiming at either acquiring

prognostic information or defining individualized treatment adaptation [58-60]. Semi-quantitative metabolic ^{18}F-FDG-PET parameters [i.e. maximum standardised uptake value (SUV$_{max}$), metabolic tumour volume (MTV)] during RCHT have been observed to significantly correlate with overall and progression free survival, and/or local tumour control, even when reassessment is performed early (at 2 or 3 weeks after the start of radiotherapy) [61-67]. Newer approaches using radiomics and artificial intelligence are under investigation, but robust independent features, including 4D-PET imaging, were not of complementary prognostic or predictive value [56, 68, 69].

Beyond ^{18}F-FDG-PET, other PET tracers reflecting tumour characteristics expressed by NSCLC have been investigated. Regions of tumour cell hypoxia, which could be imaged using ^{18}F-HX4, ^{18}F-MISO, ^{18}F-FAZA or ^{62}Cu-ATSM, were found to be smaller than ^{18}F-FDG and to only (partially) overlap with ^{18}F-FDG-PET [70]. Hypoxia markers were found to predict poor outcome in early and advanced stage NSCLC patients and might be helpful to guide dose escalation strategies [71, 72]. ^{18}F-FLT-PET representing tumour cell proliferation has been used to monitor treatment response during RCHT as well as during targeted therapy [73-75].

Oesophageal cancer

Current ESMO and NCCN guidelines recommend staging PET/CT using ^{18}F-FDG to identify otherwise undetected distant metastases in patients suffering from oesophageal cancer (EC) [76, 77]. Specifically, ^{18}F-FDG-PET should be carried out in patients who are candidates for oesophagectomy to detect unknown metastatic spread, which may prevent patients from undergoing futile surgery. With the exception of cases with limited stage disease (i.e., cT1/2 cN0 M0) for which primary resection is indicated, the remaining patients are candidates for combined treatment using RCHT with either neoadjuvant or definitive intent [76, 77]. However, curatively intended high-dose radiotherapy to the thorax could be associated with significant cardiac and pulmonary toxicity. Thus, limiting excessive radiation exposure to healthy tissue is of great importance to current research. The status of PET-based radiotherapy is less clear in EC than in NSCLC, although patients with oesophageal squamous cell carcinoma share several adverse features with lung cancer patients, especially a high rate of cardiovascular comorbidities. In addition, surgical resection of EC is associated with perioperative mortality estimated as high as 10%, without an improvement of OS when compared to definitive RCHT in two phase-III studies [78, 79]. In contrast to this, survival among patients with potentially curable oesophageal or oesophagogastric-junction cancer was improved, when neoadjuvant RCHT was administered [80]. However, parameters, which may be used to predict response to neoadjuvant or definitive RCHT, are urgently warranted for an individually tailored treatment.

Currently, there is no gold standard for delineation of radiation target volumes in EC. Nevertheless, several publications have demonstrated that PET imaging may lead to improvement in the efficacy of radiotherapy of EC. A large Dutch delineation study showed that ^{18}F-FDG-PET influenced the delineated volume in the majority of benchmark cases [81]. Additionally, results from a small prospective clinical trial suggest a significant benefit of additional PET imaging, with 6 out of 20

patients enrolled receiving subsequent modifications to their radiation treatment following ^{18}F-FDG-PET/CT when compared to patients receiving conventional imaging [82]. A recently published delineation proposal of neoadjuvant target volumes in EC is also based on ^{18}F-FDG-PET imaging, optimally acquired in treatment position [83]. Furthermore, preliminary retrospective data suggest that inclusion of PET into treatment planning potentially improves survival compared to conventional imaging [84].

Besides contributing to improved biological tumour delineation, PET parameters are additionally associated with favourable outcomes in neoadjuvant and definitive treatment settings. This holds true for baseline PET-parameters but even more so for interim PET parameters [85-89]. Novel PET-parameters (e.g. standard uptake ratio, SUV) obtained at interim showed very encouraging results in the selection of optimal candidates for organ preservation [90]. Moreover, the use of ^{18}F-FDG-PET/CT for restaging following neoadjuvant RCHT enables detection of distant interval metastases in up to 9% of cases [91, 92]. Recent clinical trials have also indicated that response assessment by PET during chemotherapy can be used to escalate local therapies in non-responders [93]. Collectively, a large meta-analysis found that restaging by ^{18}F-FDG-PET/CT may considerably impact on treatment decision-making [91]. Nevertheless, the clinical benefit of ^{18}F-FDG-PET/CT for assessing response to definitive radiochemotherapy or neoadjuvant treatment before surgery remains controversial. Following German national guidelines, interim PET imaging is not routinely recommended [94]. Therefore, the further validation of the role and promising PET parameters with an emphasis on objective quantitative parameters for response assessment through prospective, multicentre studies is of utmost importance to further optimize personalized treatment approaches.

Rectal cancer

PET in primary staging

Regarding primary tumour staging, MRI is the gold standard and established in all international guidelines. MRI allows a reliable assessment of infiltration depth, mesorectal fascia involvement or infiltration of adjacent organs owing to its excellent soft tissue contrast [95]. In this aspect, MRI is superior to ^{18}F-FDG-PET/CT imaging. Regarding nodal status, no single modality achieves high accuracy for the prediction of lymph node involvement. For MRI staging, morphological features such as shape and signal intensity outperform size [96]. Thus far, no study has compared MRI with ^{18}F-FDG-PET/CT regarding nodal status. There are a number of studies showing partial superiority of ^{18}F-FDG-PET imaging compared with conventional imaging. Kwak *et al.* [97] analysed 473 patients and found a sensitivity of 66% with a specificity of 60% using ^{18}F-FDG-PET/CT. On CT, there was a significantly lower specificity of 29% with slightly higher sensitivity of 87%. Overall, this resulted in a non-significantly different accuracy of 63% for ^{18}F-FDG-PET/CT and of 59% for CT only [97]. No difference was documented for the detection rate of lymph node metastases. In another study, univariate and multivariate analysis demonstrated that quantitative parameters obtained from [18]F-

FDG-PET [metabolic tumour volume (MTV), maximum SUV ($SUVm_{ax}$)] were independent predictors of the presence of lymph node metastases [98].

PET for radiation planning

The 'classic' target volume for locally advanced rectal cancer in the neoadjuvant setting includes the entire mesorectum in addition to the primary tumour, and thus also the rectum up to the level of the promontory. Pelvic lymphatics are included depending on the clinical scenario (S3 guideline Colorectal Carcinoma [99]). Usually, the entire target volume receives a uniform dose, such that a highly precise delineation of the primary tumour is not of clinical relevance. However, clinical trials are currently investigating whether dose escalation to the primary tumour can lead to an increase in complete remission rates and thus allow for an organ-preserving approach in a larger number of patients [100]. Here, a precise definition of the primary tumour is relevant to apply the highest possible dose to the primary tumour while sufficiently sparing normal tissue. Several studies have compared MRI and ^{18}F-FDG-PET-based primary tumour definition. The ^{18}F-FDG-PET-based primary tumour delineation consistently resulted in a smaller tumour volume compared to the MRI-based definition [101, 102]. However, it should be taken into account that, as described above, an excellent correlation with the actual tumour extent has been established for MRI. For ^{18}F-FDG-PET-based primary tumour definition, these data are currently lacking. Furthermore, it should be considered that the rectum shows an extremely variable anatomy and a tumour volume generated based on "offline" image data requires a large safety margin to be irradiated. Overall, the utility of ^{18}F-FDG-PET-CT in target volume definition in rectal cancer seems limited.

PET for response assessment

The prediction of a clinical complete remission is one of the major challenges in establishing organ preservation strategies, as neither endoscopic assessment nor MRI after therapy have shown reliable sensitivity to date [103]. A promising approach is to incorporate early changes in functional, quantifiable imaging data, such as ^{18}F-FDG-PET/CT [104]. In a prospective study comparing quantitative imaging methods with molecular markers in terms of predictive power for complete remission, imaging methods including ^{18}F-FDG-PET/CT were shown to have the highest sensitivity of approximately 80% [105].

Anal cancer

The standard of care of non-metastatic anal cancer is definitive, organ-preserving concurrent RCHT [106, 107]. Due to usually high FDG-avidity of the primary tumour, locoregional lymph node and distant metastases, ^{18}F-FDG-PET/CT may provide useful diagnostic information for RCHT planning [108-113]. Furthermore, PET-derived metabolic biomarkers including pre-treatment SUV_{max} and MTV have shown prognostic significance in terms of OS, PFS and event-free survival (EFS) [108, 114, 115]. ^{18}F-FDG-PET/CT can be helpful in identifying the primary tumour, but both the spatial resolution of PET and physiologic anal uptake limit accurate T-staging [116, 117]. Thus, MRI and transanal endoscopic ultrasound remain the clinical standard for T-staging [118-120]. Although data on the use

of ^{18}F-FDG-PET/MRI are limited, recent data indicate that PET/MR provides a more precise assessment of the local extent of rectal cancers in evaluating cancer length, nodal (N) status, and external sphincter involvement [121]. There is good agreement between ^{18}F-FDG-PET- and MRI-based GTVs [122]. Accurate N-staging is crucial for dose prescription and target volume delineation concerning (elective) lymph node irradiation by consensus contouring guidelines and definition of boost volumes (simultaneously integrated or sequential) for involved lymph node disease [123, 124]. A particular strength of ^{18}F-FDG-PET/CT is the additional detection of small lymph node metastases in unsuspected pelvic and inguinal lymph nodes, and the detection of occult distant metastases.

Several studies focused on the impact of ^{18}F-FDG-PET/CT for radiation treatment planning and target volume definition. Two meta-analyses focused on disease staging with a particular focus on radiation treatment planning: ^{18}F-FDG-PET/CT led to upstaging in 5-38%, and to downstaging in 8-27% of patients; the identification of lymph node metastases lead to treatment plan adaptions in 12.5%-59% of patients [117, 125]. Furthermore, recently published data reported that up to 20-26% of ^{18}F-FDG-PET positive lymph nodes were located outside the target volume of common guidelines for elective lymph node irradiation and would have been missed without the ^{18}F-FDG-PET/CT-derived information [126].

Furthermore, ^{18}F-FDG-PET/CT – performed 12 weeks after completion of RCHT – may be useful to identify patients with insufficient metabolic response of the primary tumour predicting the need for early salvage therapy [127, 128]. A metabolic partial response was predictive for a significantly decreased 2-year PFS compared with metabolic complete response [22-71% versus 95% [128, 129]]. However, as reported in the meta-analysis of Jones *et al.* [125], ^{18}F-FDG-PET/CT performed too early during follow-up occasionally prompted unnecessary resection. Therefore, and since according to current guidelines the final response of anal cancer should be assessed as late as 26 weeks after RCHT, the timing of an ^{18}F-FDG-PET scan during follow up should be late and any consequences should be drawn with caution.

Cervical cancer

External beam RCHT followed by 3D-planned MRI-based brachytherapy maximizes tumour doses for excellent local control rates and is thus the standard of care [130]. Even though, lymph node metastases are the most important prognostic factor in cervical cancer patients, which is not considered in the current FIGO classification. This results in under- and overtreatment of patients and an unacceptably high rate of postoperative RCHT [130, 131]. CT and MRI have demonstrated disappointingly low accuracy rates in primary lymph node staging. Consequently, in some countries ^{18}F-FDG-PET/CT has been increasingly used to overcome the limitations in accurate lymph node staging. Since ^{18}F-FDG-PET/CT suffers from a high rate of false negative readings of up to 20%, ^{18}F-FDG-PET/CT cannot replace laparoscopic staging [132, 133]. Thus, laparoscopic staging is widely applied leading to upstaging in >30% of locally advanced cervical cancer patients and allowing for treatment triage (radical hysterectomy versus definitive RCHT). Recently, the randomized trial Uterus-

11 has shown that laparoscopic staging did not only avoid under- or overtreatment, but had an impact on disease-free survival and cancer-specific survival, respectively, without increased toxicity rates [134]. Laparoscopic staging therefore remains the gold standard for FIGO stage IIB and >IIB patients [134-136].

5 The implications of undertreating patients with false negative paraaortic disease is disastrous, given the fact that the survival rate for patients with histologically positive paraaortic lymph nodes treated with extended-field radiation therapy is as high as 50% [137]. A prospective trial evaluated the use of laparoscopic staging after (false) negative ^{18}F-FDG-PET/CT and showed significantly superior oncological outcomes for patients with lymph node metastases < 5mm vs. > 5mm after surgical

10 staging and RCHT [138]. The shortcoming of the above mentioned Uterus-11 trial [134] is that ^{18}F-FDG-PET/CT was not used in that study. The idea of combining the validation of ^{18}F-FDG-PET/CT and laparoscopic staging has been discussed by the LilACS study group. The study aimed at randomizing patients with ^{18}F-FDG-PET/CT positive pelvic, but negative para-aortic lymph nodes to either laparoscopic lymph node dissection or pelvic RCHT [139]. Unfortunately, the trial was not able to

15 recruit a sufficient number of patients and was subsequently closed. This approach should be the aim of a future multicentre trial.

^{18}F-FDG-PET/CT-based therapy response assessment allows for a reliable prediction of overall survival in patients with locally advanced cervical cancer treated with concomitant RCHT [140]. This should be used within clinical trials to tailor adjuvant treatment, e.g. maintenance treatment with

20 immunotherapy in case of persistent FDG uptake. In the setting of neoadjuvant RCHT, data showed that early changes in metabolic ^{18}F-FDG-PET parameters might allow for differentiation of histopathological response of the primary tumour [141]. However, negative results of two randomized trials have now questioned the role of neoadjuvant chemotherapy at all [142, 143]. ^{18}F-FDG-PET/CT has a high sensitivity and specificity in the detection of distant metastases, which may lead to a

25 change of the treatment intent [curative versus palliative [144]]. However, ^{18}F-FDG-PET uptake depends on the histological subtype being highest in squamous cell carcinoma, whereas e.g. mucinous adenocarcinoma often show only faint ^{18}F-FDG uptake resulting in a limited sensitivity in these subtypes [145].

Regarding restaging of cervical cancer, a recently published meta-analysis showed a pooled sensitivity

30 of 0.97 (0.95-0.99) for ^{18}F-FDG-PET/CT. 57% of the therapeutic approaches were modified due to the results of ^{18}F-FDG-PET/CT [146]. At present, according to national guidelines, in the setting of recurrent cervical cancer, ^{18}F-FDG-PET/CT might be reserved for individual patient cases for tailored treatment [147]. In the follow-up, ^{18}F-FDG-PET/CT remains a helpful tool after RCHT or radical hysterectomy, even in patients with increasing tumour markers and negative MRI findings.

35 In the future, the use of hybrid PET/MRI protocols could contribute to improve imaging of cervical cancer patients, and the use of alternative PET radiopharmaceuticals, *e.g.*, ^{68}Ga-FAPI is under investigation [148].

Prostate cancer

PET in primary staging

Accurate detection of intra- and extraprostatic tumour foci by imaging is of high clinical relevance for radiation treatment planning in patients with primary and recurrent prostate cancer. A large of number studies performed during the last 5 years has shown that PET imaging with radiolabelled small molecule inhibitors of the glutamate carboxypeptidase PSMA (prostate specific membrane antigen) allows for more sensitive and specific detection of prostate cancer lesions than other imaging techniques. Several radiolabelled PSMA inhibitors have been developed but most of the clinical so far has been obtained with the ligand ^{68}Ga-PSMA-11 [149-151]. This radiotracer has recently been approved by the FDA for imaging of primary and recurrent prostate cancer. Several ^{18}F-labelled PSMA inhibitors are being investigated in prospective clinical trials; these tracers can be produced in larger batch sizes and have better physical properties for PET imaging. Furthermore, some of them show less urinary excretion, which facilitates detection of primary tumours and local recurrences. The diagnostic performance of these ^{18}F-labelled tracers is overall probably similar or superior to ^{68}Ga-PSMA-11, but head-to-head comparisons are so far limited [149-152]. Therefore, the results of these various agents are summarized under the name 'PSMA-PET/CT' in the following text.

In the primary setting, PSMA-PET/CT imaging can be applied for initial staging in patients with high-risk profiles [153]. A prospective phase III study (proPSMA) showed that the application of PSMA-PET/CT has relevant impact on patient management since the accuracy for lymph node and bone metastases is higher as compared to conventional imaging [154]. In particular the performance of PSMA-PET/CT often leads to changes in TNM-staging with subsequent alterations in radiation treatment planning. Several retrospective analyses have also addressed this issue. Dewes *et al.* [155] reported on a change in TNM stage in 8 of 15 patients or modifications of CTVs and changes in prescribed dose in 5 and 12 patients, respectively. In another retrospective analysis, PSMA-PET/CT was shown to have a major impact on final radiotherapy planning in approximately one-third of the patients, especially when no elective radiation to the pelvic lymphatic drainage system was initially planned [156]. Recently, another phase III trial has been started which randomizes patients with unfavourable, intermediate, and high risk profiles to a group with and a group without PSMA-PET for definitive radiotherapy planning (NCT04457245).

In addition, in prostate cancer a clear dose-response relationship could be described. The prospective multicentre phase III study 'FLAME' demonstrated that dose escalation to intraprostatic tumour lesions defined by MRI imaging resulted in a significant improvement in recurrence-free survival [157]. However, it can be assumed that the intraprostatic tumour mass determined on the basis of PSMA-PET information can be contoured with a higher sensitivity [158-161]. Zamboglou *et al.* [162] reported on the feasibility of dose escalation to intraprostatic lesions defined by ^{68}Ga-PSMA to 95 Gy in 10 patients. Thus, a multicentre phase II study from Germany is currently investigating focal dose escalation to intraprostatic tumour volumes defined by combined PSMA-PET/CT and MRI imaging (HypoFocal; DRKS00017570). Of note, PET/CT imaging for prostate cancer in Germany almost is now exclusively performed with PSMA-ligands and Choline-derivates have been completely replaced. Phase III studies are already underway to investigate whether the use of PET/CT imaging and the associated

individualization of the therapeutic approach leads to the expected improvement in oncological outcome.

Salvage radiotherapy in recurrent prostate cancer

Before the introduction of PSMA-PET/CT, usually no extensive imaging workup was indicated in low-level biochemical recurrence (increasing PSA out of the undetectable range) after radical prostatectomy (RP) or a persisting PSA after RP before salvage radiotherapy (SRT, start of RT at a PSA-level <0.5 ng/ml) due to the known limited accuracy of conventional staging with CT and bone scintigraphy [163-165]. An exception is MRI with dynamic contrast enhanced MRI (DCE-MRI) which shows excellent results for identifying small areas of local recurrence, however has not been widely used in clinical routine up to now [166, 167]. The situation has changed substantially with PSMA-specific PET radiotracers, which show superior sensitivity and specificity for detecting recurrent prostate cancer compared with conventional imaging and also other compared to other radiotracers such as choline-based substances or fluciclovine [168-170]. PSMA PET-CT appears to be particularly effective at low PSA levels after radical prostatectomy below 0.5 ng/ml when SRT to the prostate bed would typically be initiated and may even detect recurrent disease in 33% to 42% of patients at PSA levels <0.2 ng/ mL [171, 172]. Most studies used ^{68}Ga-labelled PSMA compounds, however, these are more and more replaced by ^{18}F-labelled PSMA tracers, as these can be produced in higher quantities and also mostly have less renal excretion, thus showing superior image quality adjacent to the bladder for identification of local recurrences [173]. Recent reports also suggest that PET/MR might be advantageous in this respect and superior to PET/CT for detection of local recurrences [174, 175].

Through improved characterization of recurrent prostate cancer, PSMA-targeted PET/CT has shown significant impact on management decisions, such as by identifying men with recurrence confined to the prostate or pelvic nodes [176, 177]. At a PSA value of less than 0.5 ng/mL, PSMA PET/CT detects lymph node metastases in approximately 20% of patients [178]. Thus, PSMA PET/CT in the setting of biochemical recurrence with low PSA values changes patient management in nearly 50% of the patients according to a review of 45 studies evaluating the use of PSMA PET/CT in the setting of biochemical recurrence [178].

Of special relevance in this respect is the identification of distant metastases, mostly to the bone, which can even occur in the group with low-level biochemical recurrence (10% at a PSA level <0.5 ng/mL) and in case of oligometastatic disease might be irradiated as well or in more extensive metastatic disease might change the original treatment concept completely [179]. Moreover, adaption of the radiation target volume was noted such as extension of the field to include suspicious lymph nodes or in case of atypically localized recurrences at the border of the standard target volume [180-182]. The success of PSMA-PET/CT has also led to the inclusion in the German S3 guideline for diagnosis and treatment of prostate cancer as an option for imaging in case of low-level biochemical recurrence after RP before SRT [183]. However, it has to be stressed that in case of a negative PSMA-PET result, SRT shall not be delayed as 'blind' prostate SRT remains an effective treatment. Moreover, while one expects PSMA-PET guided SRT with potentially also a dose-escalated simultaneous integrated boost directed to the PSMA-positive local recurrence to have a positive impact on the

course of the disease, e.g., improved success rates concerning PSA-response, the ultimate clinical value and influence on progression survival or even overall survival is not yet known. This will be evaluated in ongoing prospective randomized studies (Clinicaltrials.gov NCT01666808, NCT03762759, NCT03525288) including a phase III study (NCT03582774) in the setting of post-RP biochemical
5   failure, which compare the current standard of care (salvage RT to prostatic fossa) with PSMA/fuciclovine PET-CT-guided SRT.

Malignant lymphoma

^{18}F-FDG-PET has significantly changed the treatment of malignant lymphomas (mL) in recent years. This is especially true for radiation oncology.

10   **PET in the context of staging**

In the case of exclusive radiation, e.g. in follicular lymphoma (FL) or lymphocyte-predominant Hodgkin's lymphoma (HL), ^{18}F-FDG-PET plays a crucial role. Staging must be performed as accurately as possible to ensure, first, that early stage is present and, second, that all affected lymph nodes are included in the target volume. The use of ^{18}F-FDG-PET has led to systematic up-staging in early
15   stages [184-186], at the same time showing improved PFS for early stage FL [187, 188]. Also in the context of combined treatment with chemotherapy followed by consolidative radiotherapy according to the involved site (ISRT) definition, PET helps to define a correct and adequate target volume size [189].

The benefits of PET in the context of target volume definition

20   ^{18}F-FDG-PET has played a critical role in early stage mL radiation treatment planning. CT-morphologically normal lymph nodes can be included in the target volume when positive on ^{18}F-FDG-PET [190-193]. This can reduce recurrences due to geographical misses [191, 194, 195]. Also, in advanced stages, extranodal involvement can be better detected, implementing ^{18}F-FDG-PET in the ILROG guidelines for treatment of mL [196-198]. Whenever ^{18}F-FDG-PET is performed as part of
25   staging, the patient positioning is usually not identical to that for radiation therapy. Thus, ^{18}F-FDG-PET and the planning CT scans need to be fused for the treatment planning purposes. Since spatial discrepancy in the area of affected lymphomas may arise, the ISRT definition is applied, which takes into account a greater uncertainty in positioning [197]. Whenever the ^{18}F-FDG-PET scan is performed in the setting of a treatment planning PET/CT, the imprecision of the CTV definition is very small and
30   consequently, the involved node (INRT) definition can be used [199].

The utility of PET for therapy stratification in the combined modality setting

Based on the Lugano criteria, PET is used as part of the re-staging of mL [200]. Assessment is based on a 5-point scale, the Deauville Score (DS), which evaluates lymphoma activity in comparison with the mediastinum and liver. In various studies, two main treatment stratification approaches have been
35   and are being pursued; (1) whether a negative progression PET can de-escalate therapy, e.g., by omitting radiotherapy or reducing chemotherapy, and (2), whether therapy escalation can be performed by a positive interim PET. Therefore, in particular a DS3 score is sometimes evaluated

differently in escalation and de-escalation studies [201, 202]. The statement of a metabolic complete remission after chemotherapy has prognostically favourable significance for patients with both HL and diffuse large-cell B-NHL (DLBCL). However, local recurrences still occur in some cases when radiotherapy has not been given because of negative PET after chemotherapy. This is particularly confirmed in a number of studies for early stages [201-205]. The data on ^{18}F-FDG-PET-guided radiotherapy in HL is now secure for intermediate and advanced stages. In DLBCL, the results of the pivotal trials are not yet conclusive. However, ^{18}F-FDG-PET-guided radiotherapy indication in the advanced stages seems to be established here as well.

Future prospects

PET/CT, PET/MRI and radiomics in radiotherapy planning

Multimodal ^{18}F-FDG-PET/CT and PET/MRI data have been shown by various studies to improve RT planning in different aspects, such as better patient selection and precision in target delineation [55, 190, 206-212]. Inclusion of PET/CT or PET/MRI data into radiation dose planning requires dedicated acquisition protocols [213-217] to ensure reproducible manual or automatic contouring of tumour regions [207, 218-220].

Furthermore, PET/CT and PET/MRI data can be used for automated high-throughput radiomics analyses [221, 222]. In such studies, standardised quantitative image characteristics are extracted to develop models that support the diagnosis of tumour diseases, the prediction of therapy adaptation, or the prognosis of therapy response, using modern methods of artificial intelligence [223-228]. For applicability in clinical practice, efforts on a standardised and reproducible radiomics workflow are decisive [229-234]. To further improve reliability, imaging characteristics may be combined with molecular and clinical information in a multi-omics approach [235].

New PET tracers

While amino-acid-based PET tracers, somatostatin receptor specific PET tracers and PSMA ligands are already used for radiation therapy planning in gliomas, meningiomas and prostate cancer [see above and [236]], radiotracers showing specific aspects of tumour biology such as proliferative activity and cancer-associated fibroblasts might be of relevance for biological target definition. The most commonly used radiopharmaceutical for imaging cell proliferation is ^{18}F-FLT [237]. Contrary to ^{18}F-FDG, ^{18}F-FLT-PET identifies the proliferating cell compartment within the GTV and could potentially be used to define tumour sub-volumes with high proliferative activity. Escalation of radiation dose within these regions could improve the tumour control probability by diminishing accelerated repopulation [50]. Several investigators evaluated the effectiveness of ^{18}F-FLT-PET for radiotherapy planning in oropharyngeal tumours, oesophageal carcinoma, and NSCLC but it has not found its way into clinical routine [238, 239]. In recent years, more promising is a novel group of tracers targeting the fibroblast activation protein on the so-called cancer-associated fibroblasts (CAFs), such as ^{68}Ga-FAPI [240]. Due to its high tumour to background contrast in many malignancies, which often is superior to that in ^{18}F-FDG, there is also rising interest in the use of FAP-specific PET for radiation treatment planning [241,

242]. Promising first preliminary results in HNSCC with ^{68}Ga-FAPI-PET suggest it might help in accurately assessing the extent of tumour spread prior to treatment start to reduce the area exposed to radiation and thereby reduce toxicities [242]. An optimized radiation therapy planning and reduction of the treatment field is also reported in lung cancer where differentiating tumour from normal tissue is often difficult with ^{18}F-FDG in particular when the lung is affected by inflammatory conditions or chronic obstructive pulmonary disease [243]. However, large prospective trials are necessary to define the future role of ^{68}Ga-FAPI-PET for radiation therapy planning [244].

There has also been significant progress in imaging with radiolabelled antibodies and antibody fragments. Labelling of these proteins with [89]Zr via the chelator DFO is a routine process, which only rarely affects their ligand binding properties. Clinical studies have shown that radiolabelled antibodies allow for imaging of a variety of important targets including, for example, HER2, CA19-9, and PD-L1 [245-247]. Using these antibodies PET imaging may therefore reveal biological changes during radiotherapy, e.g. the up- or down-regulation of PD-L1. Broader clinical use of radiolabelled antibodies is currently limited by the significantly higher radiation dose from the long-lived isotope [89]Zr. However, PET/CT systems with several fold higher sensitivity than existing scanners are currently entering the clinic. These systems allow imaging with radiolabelled antibodies at radiation doses similar to ^{18}F-FDG-PET/CT [248].

PET-based dose painting

Imaging biomarkers measured with hypoxia tracers such as ^{18}F-MISO and ^{18}F-FAZA but also with routing ^{18}F-FDG have been shown to be prognostic for outcome after radiotherapy [43, 46, 206, 249-254]. Consequently, radiation treatment adaptation by means of PET-guided dose escalation or de-escalation to account for individual radiation sensitivities in tumour sub-regions, so-called dose painting, seems attractive and might enable for increased tumour control rates and/or reduced toxicity [48, 249, 255]. Final results from randomized studies are necessary to estimate the full potential of PET-based dose painting RT [48, 249, 256, 257].

Reimbursement

Unfortunately, only few of the presented, internationally accepted indications for PET/CT are currently recognized and reimbursed by German statutory health insurances in the outpatient setting. A more thorough discussion of this delicate issue can be found in [258]. However, the authors of this article are convinced that this technique is a very powerful tool for optimal patient care and therefore hope for future adjustment of reimbursement regulations to allow for excellent patient care in accordance with (international) recommendations and guidelines.

Conclusions

In conclusion, PET/CT is an established tool for radiation therapy of various tumour entities in different clinical scenarios. Large multi-centre, prospective trails are needed to further enhance evidence for improved oncological outcomes due to incorporation of this imaging technique into patient management.

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