Critical Reviews in Oncology / Hematology 140 (2019) 74–79

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Positron emission tomography with computed tomography imaging (PET/CT) for the radiotherapy planning definition of the biological target volume: PART 1

Pierpaolo Alongi[a], Riccardo Laudicella[b], Isacco Desideri[c], Agostino Chiaravalloti[d,e], Paolo Borghetti[f], Natale Quartuccio[g], Michele Fiore[h], Laura Evangelista[i], Lorenza Marino[j], Federico Caobelli[k], Carmelo Tuscano[l], Paola Mapelli[m], Valentina Lancellotta[n], Salvatore Annunziata[o], Maria Ricci[p], Elisa Ciurlia[q], Alba Fiorentino[r,*]

[a] Department of Radiological Sciences, Nuclear Medicine Service, Fondazione Istituto G. Giglio, Cefalu. Italy
[b] Department of Biomedical and Dental Sciences and of Morphofunctional Imaging, University of Messina. Italy
[c] Department of Biomedical, Experimental and Clinical Sciences "Mario Serio", Section of Radiation Oncology, University of Florence, Italy
[d] IRCCS Istituto Neurologico Mediterraneo (INM) Neuromed, Pozzilli, Italy
[e] Department of Biomedicine and Prevention, University of Rome Tor Vergata, Italy
[f] Radiation Oncology Department University and Spedali Civili, Brescia, Italy
[g] Nuclear Medicine Unit, ARNAS Civico Palermo, Palermo, Italy
[h] Radiation Oncology, Campus Bio-Medico University, Rome, Italy
[i] Nuclear Medicine Unit, Veneto Institute of Oncology IOV – IRCCS, Padua, Italy
[j] Radiotherapy Oncology Department, REM, Viagrande, Catania, Italy
[k] Clinic of Radiology and Nuclear Medicine, University Hospital Basel, University of Basel, Basel, Switzerland
[l] Radiotherapy Oncology Department, Azienda Ospedaliera Bianchi-Melacrino-Morelli, Reggio Calabria, Italy
[m] Department of Nuclear Medicine, IRCCS San Raffaele Scientific Institute, Milan, Italy
[n] Radiation Oncology Section, University of Perugia, Italy
[o] Fondazione Policlinico A. Gemelli IRCCS-Università Cattolica Sacro Cuore, Roma, Italy
[p] Department of Radiological, Oncological and Pathological Sciences, Sapienza University of Rome, Rome, Italy
[q] Radiotherapy Oncology Department, Vito Fazzi Hospital, Lecce, Italy
[r] Radiotherapy Oncology Department, General Regional Hospital "F. Miulli", Strada Prov. 127 Km 4, 70021, Acquaviva delle Fonti, Bari, Italy

ARTICLE INFO

Keywords:
Radiotherapy
PET/CT
Target volume
Imaging

ABSTRACT

Aim: Functional and molecular imaging, including positron emission tomography with computed tomography imaging (PET/CT) is increasing for radiotherapy (RT) definition of the target volume. This expert review summarizes existing data of functional imaging modalities and RT management, in terms of target volume delineation, for the following anatomical districts: brain (for primary and secondary tumors), head/neck and lung.

Materials and methods: A collection of available published data was made, by PubMed a search. Only original articles were carefully and critically revised.

Results: For primary and secondary brain tumors, amino acid PET radiotracers could be useful to identify microscopic residual areas and to differ between recurrence and treatment-related alterations in case of re-irradiation. As for head and neck neoplasms may benefit from precise PET/CT-based target delineation, due to the major capability to identify high-risk RT areas. In primary and secondary lung cancer, PET/CT could be useful both to delimit a tumor and collapsed lungs and as a predictive parameter of treatment response.

Conclusion: Taken together, molecular and functional imaging approaches offer a major step to individualize radiotherapeutic care going forward. Nevertheless, several uncertainties remain on the standard method to properly assess the target volume definition including PET information for primary and secondary brain tumors.

DOI of original article: https://doi.org/10.1016/j.critrevonc.2019.03.008
* Corresponding author.
E-mail address: albafiorentino@hotmail.it (A. Fiorentino).

https://doi.org/10.1016/j.critrevonc.2019.01.011
Received 23 November 2018; Received in revised form 11 January 2019; Accepted 21 January 2019
1040-8428/

1. Introduction

Radiotherapy (RT) is a curative treatment modality for tumors, used in up to 60–70% of cancer patients. In the last decades, technical and technological improvements, including intensity-modulated radiotherapy (IMRT) and volumetric arc radiotherapy (VMAT), enable clinicians to reduce normal tissues irradiation, in order to obtain a better dose distribution to the target volume. Further, the accuracy of RT delivery is guaranteed by innovative in-room image-guidance systems (IGRT) (Jelercic and Rajer, 2015). In this scenario, the target delineation is crucial.

The progress in nuclear medicine with the new concept of 'biological imaging', has brought additional knowledge about tumor characteristics including functional, physiological, genotypic and phenotypic data.

The role of [18 F]-fluorodeoxyglucose positron emission tomography with computed tomography imaging (^{18}FDG PET/CT) in the assessment of several types of cancers in term of staging process, evaluation of response to treatment and detection of tumour recurrence and metastases, has been widely demonstrated (Jelercic and Rajer, 2015). Furthermore, the role of PET-CT with FDG or other tracers, as shown in Table 1, has been proposed and studied for the precise definition of RT Target Volume in several cancer patients. The aim of the present analysis is to review the present literature regarding implications of PET/CT for radiotherapy planning, in terms of the definition of RT target volume for the following anatomical districts: brain (for primary and secondary tumors), head/neck and lung. Thus, a collection of available published data was made to emphasize strength and weaknesses.

2. Biological target volume (BTV)

The implementation of PET/CT imaging in routine radiotherapy planning has lead to at least two relevant innovations in the radiation oncology scenario. On first hand, biological data obtained from PET imaging may cause a sensible change in volume definition (e.g. by showing as biologically active metastatic lymph nodes that were not detected upon morphological imaging). Secondly, the metabolic information provided by a PET study can be further utilized to characterize the anatomical gross tumor volume (GTV) by identifying functional sub-volumes leading to the definition of a biological target volume (BTV). The introduction of the BTV paves the way to the concept of "dose painting", where the target volume receives an inhomogeneous dose distribution according to its functional activity. Different dose-painting strategies have been suggested recently: dose escalation and dose redistribution. Dose escalation applies an additional dose to the functional sub-volumes of the target, whereas dose redistribution consists of increasing the dose to the radioresistant areas while reducing the dose to the rest of the target. This approach is attractive because it could theoretically increase the dose to targets considered to require higher doses and, at the same time, could reduce the dose to critical organs (Devic, 2013).

Table 1
Radiopharmaceutical and Physiopathological Process.

Physiopathological Process	Radiopharmaceutical
Glucose transport and metabolism	^{18}F-FDG
Amino acid transport and protein synthesis	11C-leucine
	11C-MET
	123I-alpha-methyltyrosine (123I-IMT)
	11C-tyrosine
	18F-FET
	alpha-[11C]methyltryptophan
	18F-proline
Amino acid transport and dopamine metabolism	^{18}F-FDOPA
Cellular proliferation	18F-fluorothymidine (18F-FLT)
	18F-2-fluoro-5-methyl-1-beta-D-arabinofuranosyluracil (18F-FMAU)
Somatostatin receptor imaging	111In-DTPA-octreotide
	68Ga-DOTANOC
	68Ga-DOTATOC
Lipid metabolism	11C-Choline
	18F-Fluorocholine
Hypoxia	18F-fluoromisonidazole (18F-MISO)
	123I-iodoazomycin arabinoside (123I-IAZA)
	18F-azomycin arabinoside (18F-FAZA)
	64Cu-methylthiosemicarbazone (64Cu-ATSM)

3. Primary and secondary brain cancers

3.1. Nuclear medicine point of view

Cancers brain involvement represents a difficult clinical challenge even due to the neurological toxicities of therapies that, despite the improvement in diagnostic and strategies, are responsible for a significant decline in patients' quality of life and cognitive functions. Regarding the WHO subclassification into multiple specific types and 4 malignancy grades, gliomas represent 31% of all malignant brain and 81% of central nervous system (CNS) tumors diagnosed in the United States, respectively. Globally, brain metastases involve up to 30% of adult patients with cancer, making these tumors an order of magnitude more common than primary brain tumors. Magnetic resonance imaging (MRI) is considered as the state-of-the-art imaging modality in neuro-oncology (Marner et al., 2017). Nonetheless, exploiting PET with amino acid tracers able to evaluate a specific aspect of tumor biology shows enormous potential in terms of disease detection, grading, tumor delineation to guide biopsy and resection, evaluation of treatment response and targeting radiotherapy (Brindle et al., 2017). Several uncertainties still remain on the standard method to properly assess the target volume definition including PET information. In the past, few tracers have been used for brain imaging (Table 2): ^{18}F-FDG, the most common radiopharmaceutical in clinical nuclear oncology, has some intrinsic limitations due to the physiological high glucose metabolism in normal brain tissue (Olivero et al., 1995; Chen, 2007). Nevertheless, an interesting clinical application of brain imaging with ^{18}F-FDG-PET/CT is based on the high FDG avidity of lymphomas that can help in the setting of differential diagnosis of them from metastases and glioblastomas (GBM) (Purandare et al., 2017). Amino acid analog PET tracers are another class of nuclear-medicine radiotracers that represent an excellent tool to assess the physiopathology of brain cancers (Ishiwata et al., 1993), due to the high amino acid selective uptake in tumor tissue (where protein synthesis is increased) and low uptake in normal brain tissue, enabling a higher tumor-to-normal-tissue contrast (Jager et al., 2001). The leading experience with this class of PET tracers for brain tumor imaging has been obtained with ^{11}C-methyl-L-methionine (^{11}C-MET) (Herholz et al., 2012). Otherwise, because of the short half-life of ^{11}C (20 min) and consequent need of an on-site cyclotron, ^{18}F-labeled aromatic amino acid analogs have been developed for tumor imaging: interestingly, tumor uptake of O-(2-^{18}F-fluoroethyl)-L-tyrosine (FET) and 3,4-dihydroxy-6-^{18}F-fluoro-L-phenylalanine (FDOPA) have been reported to be similar to that of ^{11}C-methionine (Weber et al., 2000). The ^{18}F-FDOPA metabolite 3-O-methyl-6-^{18}F-fluoro-L-DOPA has also been investigated for brain tumor imaging with PET: recently, the diagnostic accuracy of ^{18}F-FDOPA in evaluating recurrent low-grade and high-grade gliomas was described to be superior to that of ^{18}F-FDG (Chen et al., 2006). The well-represented uptake of amino-acid tracers in low-grade gliomas is related to the activity of L amino acid transporter type 1 (LAT1) system that is upregulated in brain gliomas, whilst its expression in the physiological blood-brain barrier (BBB) is considerably lower. Since these amino acid tracers are also transported into the normal brain, disruption of the BBB is not a prerequisite for the intratumoral accumulation of MET, FET, or FDOPA, as already been reported (Rapp et al., 2013). The most important features of amino acid brain PET tracers are summarized in Table 2. Sensitivity and specificity for the diagnosis of brain gliomas/gliomas-recurrence for amino-acid PET tracers are briefly represented in Table 3 (Nihashi et al., 2013; Dunet et al., 2012).

3.2. Radiotherapy point of view

Optimizing the tumor volume delineation represents the foremost aim of PET imaging in treatment planning of patients with brain tumors. An accurate contouring process is crucial to minimize toxicity to normal brain tissue and to prevent geographical misses. In patients with malignant brain tumors, gadolinium-enhanced MRI T_1-weighted is the standard imaging technique for gross tumor volume (GTV) definition (Fiorentino et al., 2013). However, in

Table 2
PET Tracers for brain tumors.

Tracer for Brain	Sensitivity (95% CI)	Specificity (95% CI)	Indication	Reference
^{11}C-MET	0.70 (0.50-0.84)	0.93 (0.44–1.0)	Necrosis versus recurrence	(Dunet et al., 2012)
^{11}C-MET	75–95% (range)	87–100% (range)	Diagnosis	(Weber et al., 2000)
^{18}F-FET	0.82 (0.74–0.88)	0.76 (0.44–0.92)	Diagnosis	(Fiorentino et al., 2013)

Table 3
PET Tracers for Head and neck cancer.

Tracer for Head and neck	Sensitivity	Specificity	Indication	Reference
^{18}F-FDG	91%	87%	Pre-treatment detection of regional nodal metastases	(Quartuccio et al., 2016)
^{18}F-FDG	88%	95%	Pre-treatment detection of distant metastases	(Quartuccio et al., 2016)
^{18}F-FDG	91%	89%	Detection of local recurrence after definitive treatment	(Quartuccio et al., 2016)

surgically resected patients with brain tumors, data suggest that the GTV defined by amino acid PET radiotracers differs from the GTV defined by MRI (Grosu et al., 2005; Weber et al., 2009). In this setting, Niyazi et al. showed in their study that PET-based GTVs (median 43.9 cm^3) were larger than the corresponding MRI GTVs (median 34.1 cm^3, $p = 0.028$); the conformity index was different from 1 (0.73 ± 0.03, $p < 0.001$), indicative of major differences between the clinical target volume (CTV) MRI-based from the corresponding PET-based one (Niyazi et al., 2011). Navarria et al., for delineating tumor volume purpose, evaluated the impact of fluid-attenuated-inversion-recovery MRI (FLAIR/MRI) and ^{11}C-MET-PET on 69 high-grade glioma (HGG) patients: CTV-1 (generated by adding a 10 mm margin to FLAIR-MRI area), CTV-2 (generated by adding a 20 mm margin to enhanced T_1MRI) and PET-based CTV were delineated on pre-operative MRI images and ^{11}C-MET-PET, respectively. In all cases, the whole biological target volume (BTV) was included into the CTV-1, while in 35/69 patients (50%) part of BTV, despite the use of larger margins, resulted outside of the CTV-2. In all patients, recurrences were contained by the CTV-1 vol, whilst in 19/38 (50%) partially outside the CTV-2. In all cases, relapse corresponded to the BTV area. The significant conclusion of the group of Navarria was that MET-PET uptake could help identify microscopic residual areas (Navarria et al., 2014).

MRI is also the preferred imaging modality for radiation treatment monitoring beyond that RT planning. Matsuo et al. evaluated the differences, in terms of the extent of tumor growth, between ^{11}C-MET-PET and MRI demonstrated that in the setting of GTV-MRI, GTV-PET volumes were 0.5 mL larger than MRI volumes. Interestingly, for all tumor sizes and characteristics, a 2-mm margin outside the GTV-MRI significantly improved the coverage of the GTV-PET (Matsuo et al., 2009).

Re-irradiation is an important issue in modern brain RT for primary and secondary cancer. The higher specificity of amino acidic PET tracers in the diagnosis of gliomas, as well as in the differentiation between recurrence and treatment-related alterations, in comparison to contrast enhancement T_1-weighted MRI, has been demonstrated in several studies, representing the rationale for their availability into radiation oncology treatment planning (Oehlke et al., 2016).

3.3. Take home message

In both primary and secondary brain tumors, amino acid radiotracers for brain PET identify microscopic residual areas and for re-irradiation to differ between recurrence and treatment-related alterations. However, MRI remains the gold standard to target definition.

4. Head and neck Cancer

4.1. Nuclear medicine point of view

The utility of PET/CT in the definition of the BTV in patients with head and neck squamous cell cancer (HNSCC) has been widely documented in literature and ^{18}F-FDG represents the most common tracer used in this setting (Quartuccio et al., 2016; Fleming et al., 2007; Hoeben et al., 2013, Table 4). ^{18}F-FDG uptake essentially correlates with the expression of GLUT1-transporters and glycolysis, which are increased in tumours with high metabolic activity. Before RT treatment, ^{18}F-FDG PET/CT can provide prognostic information based on metabolic parameters, being helpful in identifying patients who may benefit from additional treatment strategies or dose escalation; in this setting, Mohamed and his group retrospectively evaluated 49 patients affected by HNSCC: in this cohort of patients, they were able to identify in pre-treatment FDG-PET the radio-resistant sub-volumes (the perfect candidate for a dose-escalation strategy) through mapping the spatial location of the tumour recurrence site after IMRT (Picchio et al., 2014; Mohamed et al., 2017). Mazzola et al. analyzed the ^{18}F-FDG PET/CT impact in radiotherapy planning strategy for 60 HNSCC patients, showing that PET/CT findings were able to alter nodal radiation treatment volumes in 10% of the population, including FDG positive neck-nodes in the high-risk RT volumes (Mazzola et al., 2017a; Mirghani et al., 2015). Another important facet to evaluate in patients with head and neck tumours is hypoxia since it is associated with cellular resistance to conventional treatments, higher predisposition to metastases and recurrence (Bhatnagar et al., 2013). Several PET tracers (^{18}F-FMISO, ^{18}F-FAZA, ^{18}F-EF3, ^{18}F-EF5, ^{18}F-HX4,^{18}F-FETNIM and ^{62}Cu-ATSM) have successfully evaluated hypoxia in patients with head/neck tumours (Cammaroto et al., 2016). Positive findings in hypoxia PET imaging may advise dose de-escalation in patients with no hypoxia features before treatment (based on a tumor to muscle ratio of 1.2 when using ^{18}F-FMISO PET/CT) or in patients with resolution of hypoxia in the maintenance of treatment (Lee et al., 2016).

4.2. Radiotherapy point of view

^{8}F-FDG PET/CT prior RT can provide crucial diagnostic and prognostic information based on metabolic parameters and extension of disease, being helpful in identifying patients who may benefit from additional treatment strategies or dose escalation. Significant advantages of pre-treatment ^{18}F-FDG PET/CT are the capability to alter the initial radiotherapy planning in up to one-third of patients and the higher accuracy (and smaller dimensions) of PET-guided GTV delineation compared to GTV derived from CT (Fleming et al., 2007; Ciernik et al., 2003). Even tumor proliferation, as a surrogate of early response to therapy in course of RT treatment, could be monitored by ^{18}F-FLT PET/CT, being applied to adaptive radiotherapy planning (Troost et al., 2010). In this sense, Troost et al. in a small series of ten patients affected by oropharyngeal cancer (OPC) were able to identify early radiation treatment responders: this topic is of high interest due to the de-escalation policy currently being tested in HPV-related OPC Treatment de-escalation in HPV-related OPC is one of the major challenges for the radiation oncologists: in this setting, Lee et al. were able to use in-treatment functional imaging in order to safely de-escalate radiation treatment dose. On the other hand, dose-painting models proposed that higher RT doses should be delivered to hypoxic tumor regions, possibly resulting in improved tumour control (Thorwarth et al., 2007a, b; Toma-Dasu et al., 2012). Finally, considering the potential upgrading of tumor hypoxia, a further role of PET imaging could be in monitoring the extension of hypoxic volume during RT, even as a prognostic indicator (Mortensen et al., 2012). Nonetheless, despite several simulation studies which demonstrated the feasibility and utility of hypoxia

Table 4
PET Tracers for lung cancer.

Tracer for Lung	Sensitivity	Specificity	Indication	Reference
^{18}F-FDG	80%	75%	Primary tumor	(Postmus et al., 2017; Konert et al., 2015)
^{18}F-FDG	72%	90%	Mediastinal lymph nodes	(Postmus et al., 2017; Konert et al., 2015)
^{18}F-FDG	89%	91%	Adrenal metastasis	(Postmus et al., 2017; Konert et al., 2015)

PET-tailored RT plans, there is actually still a lack of clinical trials (Hoeben et al., 2013, Table3).

4.3. Take home message

18 F-FDG PET/CT could be useful for identifying high-risk RT volumes for HN cancer. Other tracers are still under evaluation.

5. Primary and secondary lung cancer

5.1. Nuclear medicine point of view

According to the ESMO guidelines, ^{18}F-FDG PET/CT is recommended in patients with lung cancer for the initial staging of the disease, particularly in presence of enlarged lymph nodes at CT scan and in stage III patients who are eligible for a specific treatment (Postmus et al., 2017, Table 4). Further, according to the ESTRO recommendation, ^{18}F-FDG PET/CT before stereotactic ablative radiotherapy (SABR), is considered as an optional imaging modality for nodal and metastasis staging and for the target volume definition (Guckenberger et al., 2017).

Currently, ^{18}F-FDG PET/CT in lung cancer patients is the most important imaging modality for the target volume delineation after RT treatment and for disease-extent staging (Konert et al., 2015). The 2015 International Atomic Energy Agency (IAEA) consensus recommend that the interval between PET scan staging and the beginning of RT should not exceed 3 weeks, in order to avoid the widespread of disease and thus any treatment delay (Konert et al., 2015). The advantages of ^{18}F-FDG PET/CT in the evaluation of lung cancer patients can be schematically reassumed as 1) the capacity to differentiate between an underlying tumor that caused the lobe/lung collapse and the atelectatic lung; 2) the capability to draw the target volume for RT planning, maintaining the same position both for PET/CT acquisition and for RT; 3) the use of four-dimensional (4D) PET acquisition, allowing a detailed assessment of tumor movement in order to facilitate gated therapy, in which the treatment beam is only turned-on in a particular part of the respiratory cycle (thereby reducing the exposure of normal tissues); 4) the ability to detect the resistant sub-volumes (in course of RT) that could be treated with different RT doses (interim-response PET/CT); 5) the assessment of clinical pneumonitis severity and/or esophagitis, particularly in case of thoracic high-dose RT (Konert et al., 2015; Nestle et al., 1999; Mac Manus et al., 2001; MacManus and Everitt, 2018; Chirindel et al., 2015; Callahan et al., 2014; Sindoni et al., 2016; Jaffray et al., 2002; Nielsen et al., 2009; Jaffray et al., 1999; Sorcini and Tilikidis, 2006; Mac Manus et al., 2011; Guerrero et al., 2007).

5.2. Radiotherapy point of view

Recently, in non-small-cell-lung-carcinoma (NSCLC) patients several clinical studies evaluated the utility of PET-CT for RT planning with particular emphasis to its value for lesion-contouring that has often led to changes of the target volume in terms of shape and size (Bradley et al., 2004). In case of atelectasis areas (common feature in NSCLC), contiguous tumor margins may be indistinguishable making difficult to determine the appropriate target volume for RT: in this setting, FDG-PET is crucial to delimit the border between a tumor and collapsed lung, in order to enable the treatment of small volume lesions (Konert et al., 2015; Fox et al., 2005). Without PET imaging, RT treatment is focused on the whole tumor region and atelectatic lung with the consequently possible damage to large irradiated volumes in lung tissues.

Further, BTV based on PET-CT could have a significant role in the planning of RT treatment as a tool to evaluate tumor response under treatment or to select suitable cases eligible for dose escalation.

There are some criticisms to evaluate when using PET scans to define target volumes for RT, due to possible influences to target margins (Ashamalla et al., 2005; Biehl et al., 2006; Black et al., 2004; Davis et al., 2006): a) the variability of FDG uptake within/between tumors and normal tissues; b) the effects of possible concomitant inflammatory and infectious illness; c) possible artefacts on scans, such as the apparent leaching of signals from FDG avid structures in adjacent low avidity areas; d) the effects of movement. The CT scans are usually acquired simultaneously in a part of the respiratory cycle while the PET information is an average of the absorption acquired in about 30 min through many respirations; PET image is then blurred and expanded by the effect of the movement, unless the acquisition is controlled; e) registration/merger inaccuracies; f) difficulty to standardize the delineation procedure. A very promising work on gating has been done, but it still has to be widely validated and g) inter-observer variability.

New technological advancements such respiratory-gated (4D) system PET/CT has been proposed to reduce motion artefacts, improving tumor detection and (potentially) the delineation volume for RT planning (Guerra et al., 2012). Recently, some preliminary studies demonstrated that (4D) PET/CT is a valid technique to improve quantification, lesion detectability of lung and to define the RT planning of moving lesions (Guerra et al., 2017). Preliminary results of a study by Guerra et al. showed that (4D) PET/CT in lung cancer can affect not only the planning target volume (PTV) but also its shape, as demonstrated by the assessment of gated PTVs outside standard PTV (Guerra et al., 2014). Similarly, Scarsbrook et al showed that approximately 20% of PTV (3D) PET/CT and PTV (4D) PET/CT are not included in PTV (4D) CT, leading to underestimation of the target volume and to potential geometrical misses (Scarsbrook et al., 2017). The use of a gating technique could be thus crucial for better delineate PTV by tailoring the target volume to the lesion motion in lung cancer patients.

Recently, FDG-PET has been used in the setting of oligo-metastatic cancer or in stage I primary lung cancer, where SABR could be indicated (Bradley et al., 2004; Mazzola et al., 2017b). furthermore, FDG PET metabolic quantitative parameters could be considered as predictive of response after SABR for lung oligometastatic patients: in a study of 50 patients with 70 metastases treated with SABR, the complete response from lung metastasis at 6 months was significantly associated with the standardized uptake value maximum (SUVmax) and mean (SUVmean) values of pre-SABR ^{18}FDG-PET/CT (Mazzola et al., 2017b). Finally, PET/CT can improve the tumor control probability as compared to conventional CT planning (van Der Wel et al., 2005). Improving target coverage and reducing target volumes could potentially lead PET/CT-based planning to achieve a greater likelihood of cancer's control through an increased dose to tumors (De Ruysscher et al., 2005) and a lower dose to normal tissues. Several studies have attempted to investigate how different GTV-delineation strategies correlate with the tangible tumor volume in NSCLC surgical samples (Faria et al., 2008): despite all these results, further clinical studies are required to confirm the definitive role of combined PET-CT in RT planning for NSCLC (Macmanus and Hicks, 2008; Hanna et al., 2010).

5.3. Take home message

^{18}F-FDG PET/CT imaging is useful for target definition of primary and secondary lung cancer both to delimitate the border between tumor and collapsed lung and for SABR, to be a predictive tool of treatment response.

6. Conclusion

The present review highlights the utility and the limitation of these modalities (Table 5), including differentiating between tumor and normal

Table 5
Advantages and disadvantages of PET/CT in target volume definition of brain, head and neck and lung cancer.

Advantages	Disadvantages
Brain tumors	
Available for PET as well as for SPECT	Tracer uptake is poorly affected by tumor grade
Negligible uptake in normal brain	
Optimal tumor delineation and contrast	
Correlate with prognosis	
Very high negative predictive value in distinguishing recurrence from necrosis	
Head and neck tumors	
Identify patients who may benefit of dose escalation	lack of evidence from clinical trials
Higher accuracy and smaller dimensions of PET-guided GTV	
adaptive radiotherapy planning	
Reveal primary disease in cases with unknown primary	
Correlate with prognosis	
PET imaging could be in monitoring the extension of hypoxic volume during radiation treatment	
Lung cancers	
the capability to differentiate between atelectatic lung and the underlying tumor that caused the lobe/lung collapse	variability of FDG uptake within/between tumors and normal tissues
Higher accuracy and smaller dimensions of PET-guided GTV	the effects of possible concomitant inflammatory and infectious illness
adaptive radiotherapy planning	Respiratory movements
Correlate with prognosis	
FDG uptake can provide some information about the severity of clinical pneumonitis	

tissue, identify high-risk areas, select the exact high dose for ablative RT, optimize the dose to normal tissue (Verma et al., 2018). RT target definition based on molecular and functional imaging is steadily increasing and represents a large step to “personalize radiotherapy planning” in a “multidisciplinary oncological approach way”.

Compliance with ethical standards

None.

Funding

None.

Conflictof interest

The authors declare that they have no conflict of interest.

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