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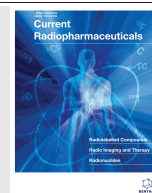
Radiotherapy Planning and Molecular Imaging in Lung Cancer

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Abstract: *Introduction:* In patients suitable for radical chemoradiotherapy for lung cancer, ^{18}F-FDG-PET/CT is a proposed management to improve the accuracy of high dose radiotherapy. However, there is a high rate of locoregional failure in patients with locally advanced non-small cell lung cancer (NSCLC), probably due to the fact that standard dosing may not be effective in all patients. The aim of the present review was to address some criticisms associated with the radiotherapy image-guided in NSCLC.

Materials and Methods: A systematic literature search was conducted. Only published articles that met the following criteria were included: articles, only original papers, radiopharmaceutical ([18F]FDG and any tracer other than [18F]FDG), target, only specific for lung cancer radiotherapy planning, and experimental design (eventually "*in vitro*" studies were excluded). Peer-reviewed indexed journals, regardless of publication status (published, ahead of print, in press, etc.) were included. Reviews, case reports, abstracts, editorials, poster presentations, and publications in languages other than English were excluded. The decision to include or exclude an article was made by consensus and any disagreement was resolved through discussion.

Results: Hundred eligible full-text articles were assessed. Diverse information is now available in the literature about the role of FDG and new alternative radiopharmaceuticals for the planning of radiotherapy in NSCLC. In particular, the role of alternative technologies for the segmentation of FDG uptake is essential, although indeterminate for RT planning. The pros and cons of the available techniques have been extensively reported.

Conclusion: PET/CT has a central place in the planning of radiotherapy for lung cancer and, in particular, for NSCLC assuming a substantial role in the delineation of tumor volume. The development of new radiopharmaceuticals can help overcome the problems related to the disadvantage of FDG to accumulate also in activated inflammatory cells, thus improving tumor characterization and providing new prognostic biomarkers.

1. INTRODUCTION

The goal of the radiotherapy (RT) planning process is to select and delineate target volumes with the best accuracy on the basis of all the available diagnostic information and the knowledge of the physiology of the disease. The recommendation of the International Atomic Energy Agency (IAEA) expert panel, is that an appropriately timed and technically adequate 2-[18F]fluoro-2-deoxy-d-glucose/Positron Emission Tomography-Computer Tomography (^{18}F-FDG-PET/CT) imaging is an essential component in the radiotherapy treatment planning (RTP) process for lung cancer [1]. Each patient considered for radical radiotherapy should have had a staging ^{18}F-FDG-PET/CT for RTP, acquired in treatment position and co-registered with the planning CT [2]. When used without specific adaptations for RTP, ^{18}F-FDG-PET/CT scan can be visually correlated with the RTP CT to identify areas of disease to be included in the treatment volume. Technically the best available option is to acquire an [18]F-

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FDG-PET/CT scan exclusively for the purpose of RTP. This scan may be performed when a staging PET has already been acquired and the patient is deemed suitable for radical radiotherapy. This approach requires two separate PET scans, which has an advantage that it removes any staging or patient selection issues but is expensive and therefore, may not be possible in all health care systems because of financial or logistical limitations. Another valid approach is to acquire a single ^{18}F-FDG-PET/CT scan in a radiotherapy treatment position to serve the dual purposes of staging and target volume delineation (TVD). It is imperative that the time interval between any imaging used for the purpose of radiotherapy target volume delineation and the radiotherapy treatment delivery, should be as short as possible. In NSCLC, several studies have examined the effect of radiotherapy field changes, size and the effect of staging accuracy with different time scales from ^{18}F-FDG-PET/CT scan acquisition [3, 4]. All of them have demonstrated that ^{18}F-FDG-PET/CT scan accuracy decreases over time and that some patients may develop more advanced stage disease before starting treatment, which will affect their chances of long-term survival. Long delays in time to treatment could result in a geographic miss if radiotherapy fields based on prior ^{18}F-FDG-PET/CT scans no longer encompass the entire tumor or all involved lymph node stations. To avoid this issue, it is suggested that radiotherapy treatment should commence no later than 4 weeks after the acquisition of the ^{18}F-FDG-PET/CT scan. The combined procedure consisting of image interpretation, patient staging, treatment selection, and target volume definition requires many different aspects of multidisciplinary clinical expertise [1].

2. OVERVIEW OF RADIOTHERAPY ROLE IN NON-SMALL CELL LUNG CANCER

In 2018, lung cancer was estimated to have the highest number of new cases (11.6% of total cases) and cancer deaths (18.4% of total cancer deaths) in both sexes. Non-Small Cell Lung Cancer (NSCLC) accounts for approximately 85% of all lung cancers [5]. There are subtypes of NSCLC, which originate from different types of lung cells, but they are grouped together as NSCLC because the approach to treatment and prognosis is often similar. About 40% of lung cancers are adenocarcinomas, 25%-30% squamous cell carcinomas and 10%-15% large cell (undifferentiated) carcinomas. When feasible, surgical resection remains the single most consistent and successful option for cure. However, close to 70% of patients with lung cancer already have locally advanced or metastatic disease at the time of diagnosis. Chemotherapy is beneficial for patients with metastatic disease, and concurrent chemo-radiotherapy is indicated for stage III lung cancer when surgery is not recommended. The introduction of angiogenesis, epidermal growth factor receptor inhibitors, and other new anticancer agents is changing the present and future of this disease and will certainly increase the number of lung cancer survivors. Radiotherapy plays a major role in the management of all stages of NSCLC as either definitive, preoperative/postoperative or palliative treatment according to NCCN guidelines, which were used as the main reference for the present chapter [6].

2.1. Early-Stage (I-II) NSCLC

In early-stage NSCLC, surgery is the standard treatment for operable patients [7]. Definitive radiotherapy is recommended in patients who are clinically inoperable or who refuse surgery. Early-stage NSCLC commonly refers to stage I and II, but from a radiation treatment standpoint, patients are differentiated as node-negative or node-positive. Node-negative should be treated with stereotactic body radiotherapy (SBRT), defined as a high dose per fraction delivered in ≤ 5 fractions. SBRT techniques include fixation, ultraprecise treatment planning, RT directed to gross disease alone, and high doses per fraction. SBRT utilizes small margins for positional uncertainty, facilitated by 4-dimensional computed tomography (4DCT), multiple conformal or intensity-modulated beams or arcs and volumetric image-guidance. The dose should be a biologically equivalent tumor dose of ≥ 100 Gy, in order to achieve control rates that are similar to surgery [8]. Severe acute toxicity of SBRT is unusual and less common than in surgery, as shown in a comparison study [9]. Pulmonary complications grade >2 are not common and occurred in 5.4% of patients in a big multi-institutional study [8]. Late toxicities reported in trials include chest wall pain, cough, dyspnea, fatigue and rib fracture [10, 11]. There is an ongoing debate about the role of SBRT in patients who are fit to undergo surgery. Pooled analysis of two randomized trials of operable patients, which closed prematurely due to slow accrual, showed a 16% higher 3-year survival with SBRT compared to surgery (p = 0.037). This was due to the higher rate of perioperative mortality in the surgical group [9]. A propensity score matched analysis revealed that for stage I-II NSCLC, rates of treatment associated mortality and severe toxicity were lower with SBRT for stage I-II NSCLC than with lobectomy performed by minimally-invasive video-assisted thoracoscopic surgery (VATS) [12]. Data from both retrospective [13, 14] and prospective phase II studies of SBRT suggest survival outcomes similar to surgery [15, 16]. The role of SBRT in surgical patients continues to be examined in several studies (STABLE-MATES, SABRTooth, POSTILV and VALOR). In particular, both the SABRTooth and STABLE-MATES trials focus on patients with a high risk of complications from surgical resection.

Furthermore, ultra central lesions, defined as tumors with a planning target volume overlapping the trachea or mainstem bronchi [17], or tumors larger than 5 cm, should be treated with hypofractionated radiotherapy of 6–15 fractions as risks of SBRT are deemed to be too high [18].

Node-positive patients should be treated with definitive chemo-radiotherapy, such as locally-advanced NSCLC (see below), delivering conventional fractionation up to 60-66 Gy [7].

Postoperative radiotherapy is not indicated in radically resected early-stage NSCLC, but can be considered for microscopically (R1) positive margins [19].

2.2. Locally Advanced (Stage III) NSCLC

Stage III NSCLC is a heterogeneous group due to a broad range of local and nodal presentations. Chemotherapy, radiotherapy and surgery are all treatment options that should be

appropriately selected, alone or in combination. Definitive concurrent chemo-radiotherapy is the treatment of choice when surgery is not recommended [20]. 60-66 Gy in 30-33 fractions should be delivered and optimal concomitant chemotherapy should be cisplatinum-based unless contraindicated [7].

Sequential chemo-radiotherapy is a valid alternative for frail patients [21]. Preoperative radiation doses of 45-50 Gy in 25-28 fractions combined with chemotherapy are standard for resectable superior sulcus tumors [22].

Pathologic N2 disease and positive microscopic margins are indications for postoperative radiation that should be delivered to a total dose of 50-54 Gy in 25-30 fractions [23].

2.3. Metastatic (Stage IV) NSCLC

Patients with stage IV NSCLC may benefit from palliative radiation, which can play a role in symptom control of primary tumor or metastasis, including chest pain, bone pain, dyspnea, hemoptysis, cough, neural structures compression [24]. The goal of palliation should be the relief of symptoms, limiting toxicity and maintaining the quality of life. Dose and fractionation should be individualized according to performance status and patient convenience. Possible dose regimens are various: 8 Gy in 1 fraction, 16-18 Gy in 2 fractions, 20 Gy in 5 fractions, 30 Gy in 10 fractions, 45 Gy in 15 fractions [25, 26]. Protracted regimens with higher doses can be considered for patients with good performance status, while shorter schedules are more suitable for patients with a short life expectancy. In oligometastatic and/or oligoprogressive patients, SBRT can have an important role. A recent multi-center phase II trial randomized NSCLC patients with ≤ 3 metastases who did not progress after first line systemic treatment to either local consolidative therapy (surgery, RT or chemo-RT to all metastases, with or without systemic therapy) or to systemic therapy alone[27]. The study was closed early, after that, only 49 patients were enrolled when an interim analysis found the median PFS in the consolidative therapy arm to be 11.9 months compared to 3.9 months in the standard arm. The interest in exploring ablative treatments for the oligometastatic disease will increase following the proposed revision in the 8th Edition of the TNM lung cancer classification system, where the current M1b category is subdivided into a new M1b, comprising a single extra-thoracic metastasis in a single organ, and M1c, encompassing multiple extra-thoracic metastases [28]. Another area of investigation is the use of SABR in the setting of oligo-progression, where the disease that initially responded to systemic treatment subsequently demonstrates limited progression [29]. In patients with stage IV disease who receive molecular targeted therapy for an activating mutation of the EGFR receptor, or an ALKtranslocation, and who subsequently develop progression at limited sites, the use of local ablative therapies is now recommended in the European Society for Medical Oncology (ESMO) guidelines [30].

3. RADIATION THERAPY IN SMALL CELL LUNG CANCER

Small cell lung cancer (SCLC) has high chemo and radiation sensitivity and its standard treatment in patients with limited disease and good performance status is concurrent radio-chemotherapy [31, 32]. Thoracic irradiation up to the dose of 45 Gy with 2 daily fractions of 1.5 Gy is the standard radiation regimen when possible with concomitant chemotherapy [33]. From a practical point of view, once-daily radiotherapy up to 60-66 Gy in conventional fractionation could be considered when delivery of twice-daily radiotherapy is impossible because of logistical problems or patient preference. Hypofractionated RT (i.e., 45 Gy/15 fx) is a viable option in unfit patients. In SCLC (both limited and extended), in cases of response to a chemoradiotherapy treatment, prophylactic radiation therapy of the brain (PCI) is indicated, in order to prevent metastasis. In extensive disease, palliative/antalgic radiation therapy is indicated for brain or bone metastases. Since local recurrence plays a determinant role in the prognosis of extended disease, and occurs in the first year after the end of chemotherapy in 89-93% of patients, thoracic radiation can be taken into consideration as it reduces the incidence of thoracic recurrence in selected cases (with reduced residual disease and with extrathoracic response) [34].

4. ^{18}F-FDG-PET/CT FOR RADIOTHERAPY PLANNING

4.1 ^{18}F-FDG-PET/CT for Radiotherapy Planning in Non-Small Cell Lung Cancer

After the initial diagnosis, accurate staging of NSCLC using CT and ^{18}F-FDG-PET/CT is crucial to determine the appropriate therapy. It has been shown that ^{18}F-FDG-PET/CT has a high sensitivity for the detection of metabolically active malignant disease and can lead to changes in initial staging and treatment plans for NSCLC when used in combination with conventional workup. In particular, in NSCLC, ^{18}F-FDG-PET/CT is recommended as a useful tool in staging and treatment planning [35]. To date, ^{18}F-FDG-PET/CT imaging for the purpose of baseline staging is considered as the standard of care in patients with NSCLC being considered for treatment with radical intent [36] and is recommended for the planning of definitive radiotherapy for both early-stage and locally advanced disease because it can improve TVD [2, 37]. Although PET has been used since the '70s, it is in the last 20 years that clinical studies have examined the impact of using ^{18}F-FDG-PET/CT for TVD [38, 39]. The TVD is a key part of the patient's therapeutic process because it influences precise dose delivery, clinical results and radiotherapy complications (Fig. **1** for the Principles of Outlining Volume in Radiation Oncology). The introduction of [18]FDG-PET/CT has shown to have a significant impact on selecting patients for curative intent or radical radiotherapy [40, 41]. While the CT study provides the anatomical information related to the area to be irradiated and allows the drafting of the treatment plan, the ^{18}F-FDG-PET/CT study provides information on the biological and metabolic characteristics of the disease which, combined with the CT anatomical information, allows better selection and delineation of the target volume. ^{18}F-FDG-PET/CT is superior to CT in the staging of lung cancer. Several staging studies, in fact, have clearly demonstrated the superiority of PET/CT for the identification of the involved mediastinal lymph nodes [42, 43]. PET-based TVD was shown to improve the inclusion of truly involved mediastinal lymph nodes (Fig. **2**) [44, 45]. Lymph nodes that are [18]FDG-PET/CT-positive should be included in Gross Tumor Volume (GTV) even in case of a negative endobronchial or endo-esophageal ultrasound-guided biopsy [37]. Although ^{18}F-FDG-PET/CT imaging is more useful than other imaging modalities for determining the nodal stage of a lung cancer,

PTV: Planning Target
(PTV = CTV + IM: internal margin + SM: set- up margin

CTV: Clinical Target Volume

GTV: Gross Target Volume

ITV: Internal Target Volume

GTV: clinical volume encompassing
imaging-detectable tumor
(macroscopic disease)

CTV: clinical volume encompassing
potential subclinical tumor
(microscopic disease)

ITV: internal margin added to the CTV to compensate for internal
physiologic movement and variations in size, shape, and position
(account for internal motion)

PTV: geometric volume designed to ensure that
the prescription dose is delivered to the CTV
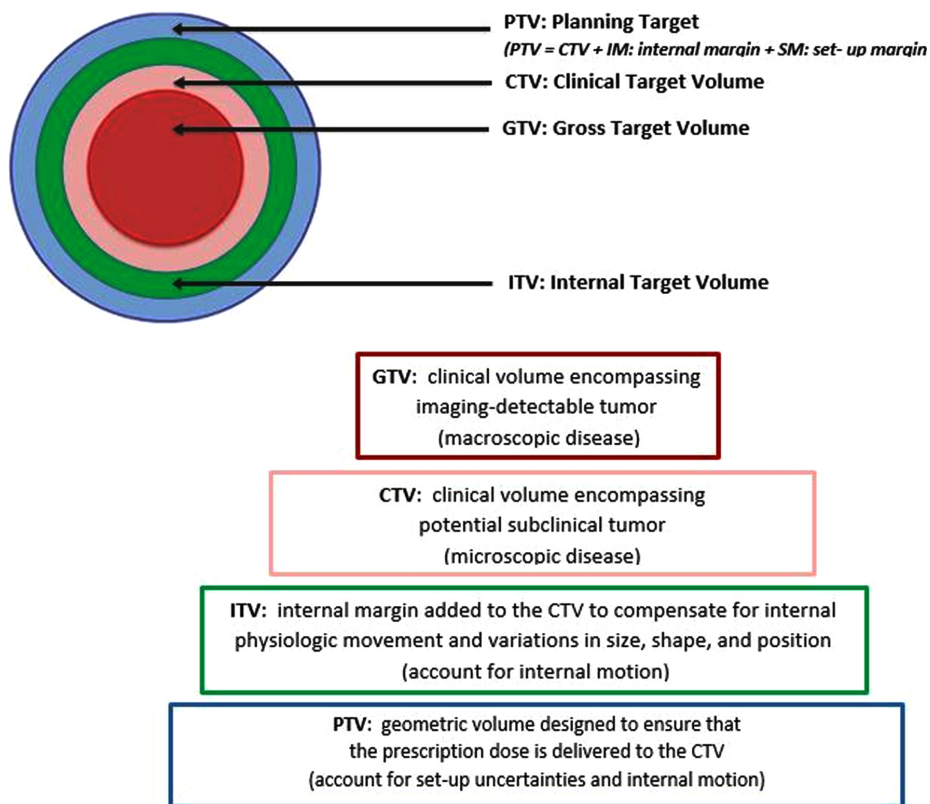(account for set-up uncertainties and internal motion)

Fig. (1). Principles of volume delineation in radiation oncology.
Adapted from:

- International Commission on Radiation Units and Measurements. ICRU report 83 prescribing, recording, and reporting photon-beam intensity-modulated radiation therapy (IMRT)-Journal of the ICRU-vol 10 no 1 2010. Oxford University Press, 2010.
- ICRU. "Report 62." Prescribing, Recording and Reporting Photon Beam Therapy (Supplement to ICRU Report 50) (1999).

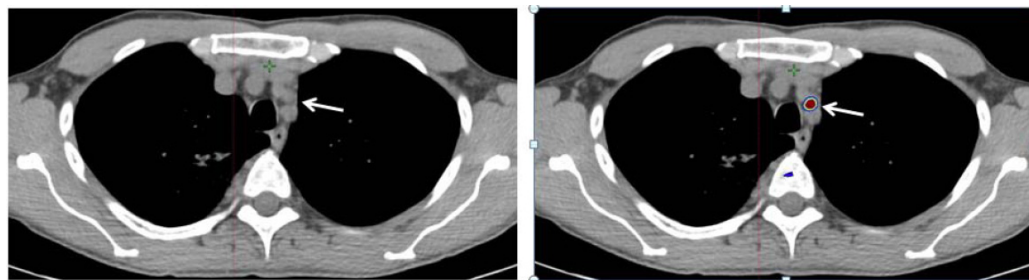(*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Fig. (2). ^{18}F-FDG-PET/CT acquired in the treatment position of a patient with cT3cN3M0 NSCLC undergoing concurrent chemoradiation. CT images (left, arrow) show a small node without suspicious morphology in station 2L. It was not detectable with endobronchial ultrasound bronchoscopy; therefore, no pathologic data was available. However, because of its PET-avidity (right, arrow), it was considered suspicious for metastasis and included in the target volume. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

PET findings should be confirmed when possible by biopsies obtained with mediastinoscopy or endoscopic ultrasonography. Moreover, in patients with atelectasis, it was apparent already from the first studies, that ^{18}F-FDG-PET/CT could help to distinguish between atelectatic and neoplastic areas [46]. Regions of atelectasis, which are sometimes impossible to distinguish from primary tumor on CT images, can easily be identified on ^{18}F-FDG-PET/CT and excluded from GTV (Fig. **3**) [47]. In fact, besides the impact on staging, ^{18}F-

FDG-PET/CT imaging greatly reduces the undesirable impact of inter- and intraobserver variability, in particular in delineating GTV of both primary tumor and lymph nodes [48, 49]. Furthermore, a study compared the accuracy of GTV defined on CT (GTVCT) and on ^{18}F-FDG-PET (GTVPET) with gross tumor based on pathologic examination (GTVpath). Interestingly GTVPET, which was delineated using a fixed threshold (42% of SUV_{max}) was better correlated with the GTVpath than the manually
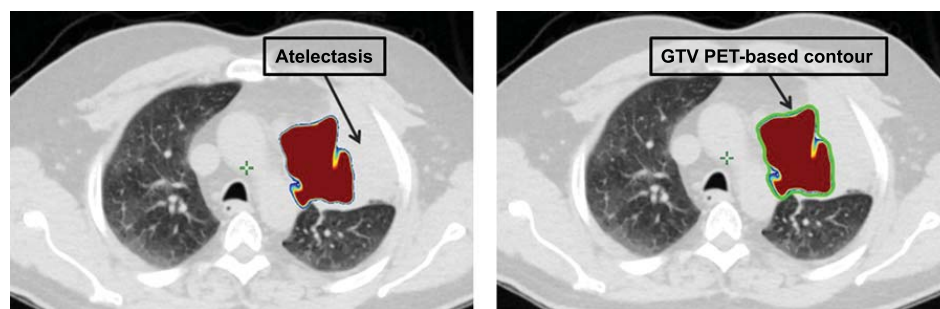
Fig. (3). **¹⁸F-FDG-PET/CT acquired in the treatment position of a patient with cT3N2M0 NSCLC undergoing concurrent chemora-diation.** CT images cannot allow differentiation between tumor and atelectasis when the latter is present; therefore, gross tumor volume (GTV) delineation should be defined by PET avid areas. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

delineated GTVCT [50]. The delineation of the target volume based on ¹⁸F-FDG-PET/CT is, on average, smaller than the non-PET method, thus reducing the dose to normal structures. This could open the possibility of dose escalation [51, 52]. This approach is now widely accepted and applied clinically, even though there are only a few studies with a direct comparison of imaging and pathological samples due to difficulties with correlation and processing of artefacts [53].

4.2 ¹⁸F-FDG-PET/CT for Radiotherapy Planning in Small Cell Lung Cancer (SCLC)

An interesting opportunity in SCLC could be offered by the employment of ¹⁸F-FDG-PET/CT, although, its value in staging and RT planning in SCLC is still to be validated. Bradley *et al.*, showed that in a cohort of 24 patients considered to have limited-stage disease based on conventional staging procedures, F-FDG-PET/CT accurately upstaged 2 of them (8.3%) to extensive-stage SCLC [54]. ¹⁸F-FDG-PET/CT correctly identified tumors in each SCLC lesion (primary or nodal) that was suspected on CT imaging, thus giving a lesion-based sensitivity relative to CT of 100%. Furthermore, PET identified unsuspected regional nodal metastasis in 25% of patients leading to a significant alteration in radiation planning by including the PET-positive/CT-negative nodes within the high-dose region in each of these patients [54]. A planning study by van Loon *et al.*, showed that PET information in a group of 21 patients with limited-stage SCLC changed the radiation treatment plan in 5 patients (24%) compared to CT by increasing or decreasing the number of nodal areas included in the target volume [55]. These studies suggest that ¹⁸F-FDG-PET/CT is more accurate compared to morphological diagnostics tool, in particular in the identification of mediastinal and supraclavicular lymphadenopathies, thus reducing the risk of both "geographical miss" and radiation exposure of normal tissues. However, further prospective studies are required to clarify the potential benefit of incorporating FDG-PET in radiotherapy planning.

4.3. ¹⁸F-FDG-PET/CT and Response to Radiotherapy Assessment

Response assessment after radiotherapy should be based on CT and RECIST criteria because false negative and false positive rates of ¹⁸F-FDG-PET/CT are still relevant among both patients with NSCLC or SCLC [56, 57]. However, most guidelines consider ¹⁸F-FDG-PET/CT useful in differentiating CT scan abnormalities, which may be related to radiation fibrosis, atelectasis, or other conditions [58]. Regarding NSCLC, both retrospective and prospective studies showed a predictive value of early metabolic changes in FDG-uptake during chemo-radiotherapy [59-61]. Mattoli *et al.*, retrospectively investigated the role of early metabolic response after low-dose fractionated radiotherapy concurrent to induction chemotherapy (IC-LDRT). According to PET response criteria in solid tumors (PERCIST), patients with complete/partial metabolic response were classified as early responders and had better PFS and OS compared to patients with stable/progressive disease classified as early non-responders. [59]. Huang *et al.*, conducted a prospective study in which patients had undergone ¹⁸F-FDG-PET/CT after 40 Gy of radiotherapy with concurrent chemotherapy and found that a decrease in metabolic tumor volume (MTV) during treatment correlates with long-term overall survival [61]. In a secondary analysis of the ESPATUTE randomized phase III trial, Pottgen *et al.*, found a prognostic value of percentage of maximum standardized uptake value remaining in the primary tumor after induction chemotherapy (%SUVmax). Interestingly, %SUVmax was predictive for freedom from extracerebral progression but not for local recurrence. Hence investigators concluded that intensification of local therapy according to SUV decreasing may not be of great benefit but might help in more homogeneous prognostic groups stratification. In the group of poor responders, treatment intensification by other systemic options may be offered [60].

5. ¹⁸F-FDG-PET/CT: OPEN PROBLEMS AND DEVELOPMENT IN TECHNOLOGIES AND RADIOPHARMACEUTICALS

5.1 Methods for Target Volume Definition

A large variety of automatic and semi-automatic PET image segmentation techniques have been proposed. A recent report of the American Association of Physicists in Medicine (AAPM) presented a review of the available current algorithms [62].

5.1.1. Methods

A visual tumor contouring is commonly used in clinical practice. A detailed protocol should be followed. Before

starting the visual delineation process, the accuracy of the co-registration must be checked and an adequate diagnostic window must be adjusted for image display, preferably in consultation with the nuclear medicine physician. A rigorous visual contouring protocol using predefined window and colour settings and with assistance from the nuclear medicine physician can give highly reproducible results in NSCLC. Visual planning methodology relies on human experience to recognize various processes that lead to physiological uptake of FDG in the human body. Nevertheless, without a carefully designed contouring protocol, it is likely that significant variations in GTV will occur [63].

Automated or Semi-automated methods: to reduce interobserver variability in FDG-based GTV definition (PET_{GTV}), various automatic or semi-automatic methods have been proposed. These must be used with caution because none can distinguish between FDG-uptake caused by the neoplastic or common physiological or inflammatory process.

SUV-based contouring has commonly been used in attempts to define the edges of tumors for RT planning. To define the PET_{GTV}, many investigators have chosen a threshold, or cut-off value [64]. Some authors employed a percentage of the maximum or peak SUV concentration, whereas others recommend an absolute SUV value [65]. However, SUV measurement can be unreliable and can suffer from problems with accuracy and reproducibility. By itself, an SUV cut-off may be inadequate for RT planning.

The most widely used thresholding approach involves outlining the lesion as the region encompassed by a given fixed percent intensity level relative to the maximum activity in the tumor lesion [66]. Thresholds of 15%–50% of the maximum standardized uptake value (SUV_{max}) have been used for gross tumor volume (GTV) delineation by PET (PET_{GTV}), with 40% being the most commonly used value.

However, there is currently no established agreement on the most reliable approach for clinical PET image auto segmentation. The recommendations published in the AAPM Task Group 211 report were used to develop a software tool to evaluate current algorithms, to estimate the contouring uncertainty and therefore, to increase confidence in selecting an adequate method for a specific application [67].

5.2. Motion Artifacts: 4D PET-CT and Radiotherapy

^{18}F-FDG-PET/CT imaging can be affected by motion artifacts that can cause distortions of the target resulting in inaccurate information regarding size, shape and volume of the tumor. The introduction of 4D PET-CT acquisition in clinical practice has made it possible to reduce the effects of breathing motion, to improve the localization of the tumor, reducing motion smearing and increasing the accuracy in measuring the radiotracer uptake. 4D images can be generated by means of the use of external sensors able to track the breathing cycle of the patient to estimate respiratory motion [68], such as the use of infrared reflective markers placed on patient's chest wall, pressure sensor integrated into an elastic chest belt and real-time spirometry recording and monitoring of temperature changes. A significant advantage of 4D PET-CT could be in the field of radiotherapy, where information about the extent and trajectory of lesion motion is critical for

a more precise dose delivery [69]. Errors in the delineated tumor volume may lead to a geographic missing of the tumor and the risk to give high dose irradiation to healthy tissues. The uncertainty due to the motion necessitates the expansion of the margin around the tumor during radiotherapy planning, to ensure adequate dose coverage (Internal Tumor Volume ITV) (Fig. **4**). The expansions of the margins around the tumor are usually not patient-specific but rather based on clinical experience or published margin guidelines. The goal of 4D PET-CT in radiotherapy treatment planning is to define target volume with precise motion information in order to increase the likelihood of including the target during dose delivery. A comprehensive review of the effectiveness of respiratory-gated PET/CT for radiotherapy planning in patients with lung carcinoma has been recently published [70]. The authors reported that in most studies, there is a decrease in the measured tumor volume when respiratory gating is used, but these differences are not always significant. The heterogeneous methodology used in the published literature prevents an adequate evaluation of the impact of 4D PET/CT in terms of target volume delineation accuracy. The design of randomized multicentre trials to assess the impact of 4D PET/CT on radiotherapy planning of thoracic lesions could provide evidence to support its use in clinical practice. Moreover, the authors also suggest that the possibility to correlate pre-treatment target volumes obtained with 3D and 4D PET/CT with postsurgical histology could be ideal in future multicentre trials. They affirm that this would assist in validating the use of 4D PET/CT in radiotherapy planning, even if technically challenging. The quality of the 4D PET/CT imaging is influenced by the regularity of breathing patterns and by the statistical quality of the PET data. To overcome this issue, specific software have been proposed [71], that are able to apply deformable image registration methods, thus generating a single 3D motion-corrected PET image with good count statistics. As an alternative to conventional hardware-based gating methods, data-driven gating (DDG) approaches have been recently developed and available on the latest generation of PET/CT systems [72]. Specific software involves mathematical modelling of the motion of tissues based on PET acquisition data. This approach requires that motion information is collected mainly from PET-active structures within the body instead of relying on external devices. Software respiratory gating techniques facilitate automated, operator-independent data processing and can also help the motion management of target structures in radiotherapy planning applications [73]. In recent years, there has been a growing interest in the application of texture analysis techniques to PET imaging, with the challenging objectives to identify specific tumor phenotypes, predict treatment resistance and project overall survival [74]. New and more descriptive metrics of tumor heterogeneity based on texture analysis of ^{18}F-FDG PET images are being investigated to further improve lesion characterization and treatment planning in different types of cancer, including 4D PET/CT in lung cancer [75]. The impact of tumor motion on PET-based quantification needs to be more thoroughly studied. The recent advances in respiratory-gated PET/CT are extremely promising for radiotherapy planning of thoracic lesion purposes; nevertheless, multicentre trials are needed to standardize and validate the available techniques.
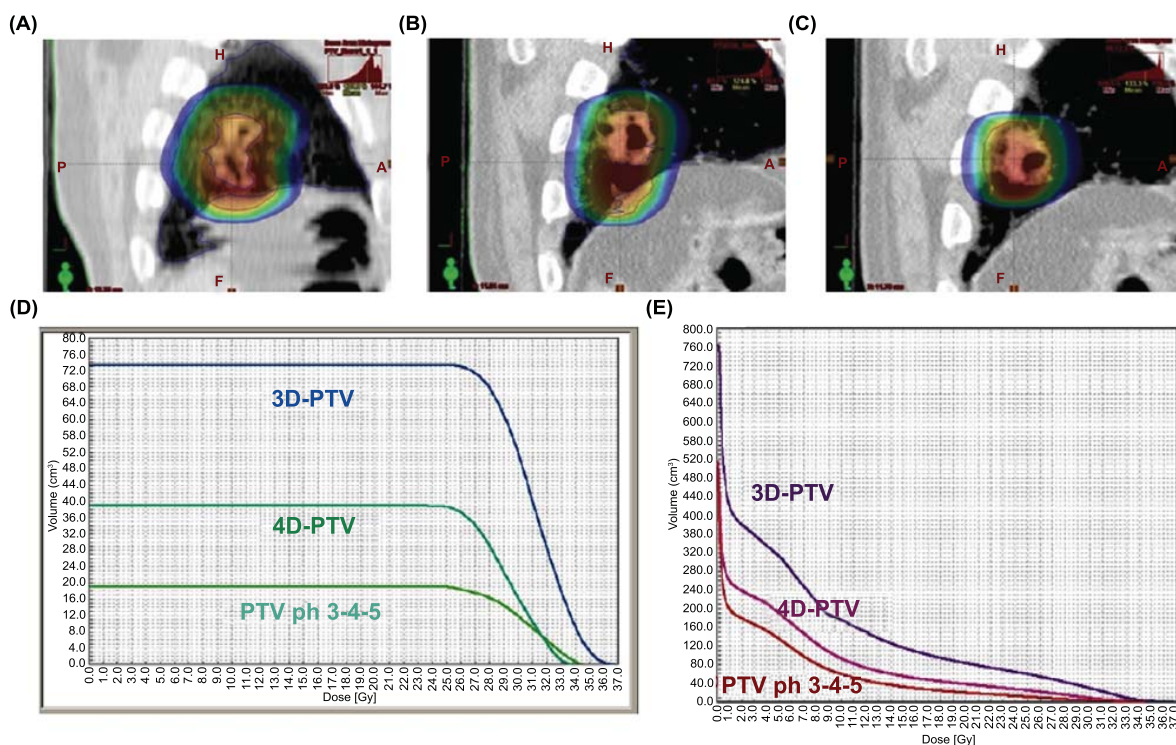
Fig. (4). Patient with lung cancer. (**A**) Planning Tumour Volume defined adding to gross tumour volume, obtained by free-breathing CT, conventional margins to account for mobility and setup error (3D PTV – 73,1 cc), (**B**) Planning Tumour Volume defined adding to ITV, obtained by 4D ^{18}F-FDG PET/CT scan, conventional margins to account for setup error (4D PTV – 38,9 cc), (**C**) Planning Tumour Volume defined adding to ITV, obtained by respiratory phased 3-4-5 of the 4D ^{18}F-FDG PET/CT scan, conventional margins to account for setup error (PTV ph 3-4-5, 19 cc), (**D**) Dose Volume Histogram PTVs, (**E**) Dose Volume Histogram healthy lung. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

5.3. Other PET/CT Tracers for Radiotherapy Planning in Lung Cancer

^{18}F-FDG is the most widely used tracer in the field of oncology for the study of glucose metabolism of neoplastic forms. Although it has undeniable advantages, it nevertheless has the disadvantage to accumulate also in activated inflammatory cells. For this reason, it has been necessary to explore other alternative metabolic tracers able to overcome this cause of false-positive results. Among these tracers, we report, in particular [^{68}Ga]Ga-MAA (MAA=macroaggregated human serum albumin), hypoxia and proliferation tracers.

5.3.1. ^{68}Ga-MAA

Le Roux *et al*., demonstrated the feasibility of PET/CT for functional lung imaging: ventilation imaging obtained using the same synthesis device as Technegas®, substituting ^{99m}Tc with [68]Gallium to produce carbon nanoparticles, and perfusion imaging with ^{68}Ga-MAA. The authors showed a degree-correlation between visually defined ^{68}Ga-V/Q PET/CT functional lung volumes and pulmonary function tests (PFTs), suggesting the possibility to better manage patients with the pulmonary disease [76].

5.3.2. Tumor Hypoxia Tracers

In relation to RT, tumor hypoxia is one of the most important contributors to the phenomenon of radioresistance. It results from an imbalance between oxygen supply and con-

sumption, due to an abnormal structure and function of the microvessels supplying the tumor [77-79]. Ionizing radiation damages neoplastic cells through the action of oxygen free radicals that cause irreversible breaks to their DNA. The direct consequence of the presence of a hypoxic component within a tumor is the production of a lower quantity of free oxygen radicals during the radiation treatment and, consequently, of causing less nuclear damage and less efficacy with the same amount of radiation administered [79, 80]. Hypoxia state induces an up-regulation of the Hypoxia Inducible Factor (HIF) by neoplastic cells, with consequent over-production of the so-called Hypoxia Responsive Elements (HRE's), such as: (1) Vascular Endothelial Growth Factor (VEGF) which promotes angiogenesis, (2) glycolytic enzymes that stimulate anaerobic metabolism to meet their demands leaving an acidic tumor environment after each cycle, (3) erythropoietin hormone (EPO) which promotes tumor cell survival and proliferation, and (4) *BNIP3* (Bcl-2 and 19-kilodalton interacting protein-3) which leads to genomic instability by evading apoptosis. All these factors contribute to multifactorial resistance to chemo-radiotherapy [81-83]. Hypoxia imaging may also provide prognostic information and may be of help to monitor treatment response [84] Hypoxic tracers are fat-soluble agents able to penetrate with a quick reaction through the phospholipidic bilayer of the membranes of normoxic cells, to expand into the surrounding tissues, and even to return to the bloodstream according to their concentration gradient. In hypoxic condi-

tions, the increase in water-soluble nature, limits the passage of hypoxic tracers through the phospholipid double layer, with consequent entrapment within the cell [85]. PET/CT with hypoxic tracers, in fact, has the main advantage of correctly identifying simultaneous areas potentially more resistant to radiotherapy treatment, and to improve loco-regional control and patient survival by increasing the corresponding radiation dose to neoplastic cells [84]. The most modern radiotherapy techniques as Intensity Modulated Radiation Therapy (IMRT,) are able to deliver higher radiation doses to specific hypoxic sub-volumes, sparing normal tissues, and avoiding, as much as possible, radio-induced pneumonitis. Fluorine-18-labeled fluoromisonidazole (^{18}F-FMISO) is a nitroimidazole which undergoes specific reductive metabolism under hypoxic cell conditions and is able to selectively bind to macromolecular cell components. Rasey *et al.*, evaluated the applicability of ^{18}F-FMISO PET to detect hypoxic zones in a series of patients, (21 non-small cell lung cancer patients, 7 head and neck cancer patients, 4 prostate cancer patients, and 5 patients with other malignancies) resulting in an increased uptake of the tracer in 97% of the studied cases [86]. Gagel *et al.*, evaluated ^{18}F-FMISO-PET as an early tumor response monitor. In unresectable locally advanced (stage III-IV) NSCLC patients treated with chemotherapy, re-oxygenation assessed with FMISO early after treatment was associated with tumor response, whereas stable or increasing tumor hypoxia resulted in worse local tumor control. These authors concluded that reduction in ^{18}F-FMISO neoplastic uptake, reflecting re-oxygenation state, correlated with response to treatment, and they also hypothesized that hypoxic volumes (defined as "Biological Target Volume, BTV") could represent areas with a high risk of local recurrence [87]. The relatively high lipophilicity of ^{18}F-FMISO has been demonstrated to be responsible for slow specific accumulation in hypoxic tissues as well as slow clearance from normoxic tissues, resulting in low target-to-background contrast [88, 89]. In conclusion, ^{18}F-FMISO unfavorable biokinetics limits the clinical applications of this tracer. Currently, a new nitroimidazole tracer [fluorine-18-labeled fluoroazomycin arabinoside (^{18}F-FAZA)] has been developed to achieve faster clearance through reduced lipophilicity [90]. This tracer is rapidly cleared from the circulation and normoxic tissues and is excreted mainly via the renal pathway, thereby providing more favourable tumor to background (T/B) ratios in most anatomical regions as compared to ^{18}F-FMISO. Cu-diacetyl-bis(N^4-methylthiosemicarbazone) ([60]Cu-ATSM) is another tracer which undergoes reductive metabolism under hypoxic conditions, forming stable adducts that subsequently bind to macromolecules inside the cell. Due to its higher membrane permeability, as compared to nitroimidazole-based compounds, this tracer is more attractive than the others described. Dehdashti *et al.*, studied [60]Cu-ATSM for the identification of hypoxic areas in 19 patients with stage IA to IV NSCLC receiving radiotherapy, chemotherapy or chemo-radiotherapy (CHRT) [91]. [60]Cu-ATSM PET and ^{18}F-FDG PET were both performed prior to treatment, while the response was assessed by means of follow-up CT scans of the chest 3-months after completion of therapy. In conclusion, although tumor hypoxia is associated with the up-regulation of glucose transporters and subsequent increased ^{18}F-FDG uptake, no direct correlation between tumor FDG uptake and

hypoxic tracer uptake is actually demonstrated. To summarize, hypoxic data obtained by specific PET tracers can play a role in the radiotherapy planning for many reasons, firstly for the development of radiation dose escalation strategies directed to the hypoxic sub-volumes, secondly because distribution of tumor hypoxia has been shown to change during radiation treatment, thirdly since tumor hypoxia seems to be associated with resistance to radiotherapy, the presence of PET-assessed tumor hypoxia could theoretically be used to predict outcome.

5.3.3. Proliferation Tracers

3′-deoxy-3′-[^{18}F]Fluorothymidine (FLT) *Et al*lows non-invasive evaluation of tumor proliferation. FLT uptake depends primarily on phosphorylation mediated by thymidine kinase 1 (TK1) which is up-regulated 10- to 20-fold during "S" phase [92]. Validation studies have demonstrated significant correlations between baseline lung tumor FLT uptake parameters and the proliferation index Ki-67 [93-96]. Using [18F] FLT-PET, it is possible to evaluate the tumor proliferation heterogeneity, which is not possible in biopsy specimens.Trigonis *et al.*, [97] found that in the absence of significant changes in average primary tumor size, RT (5-11 fractions) induced a significant decrease of about 25% in FLT uptake after a week of treatment, as measured by both SUV$_{mean}$ and SUV$_{max}$. These authors showed that SUV$_{mean}$ reproducibility (standard deviation [SD]: 8.9%) in primary tumors was better than SUV$_{max}$ reproducibility (SD: 12.6%) in NSCLC patients. In contrast, metastatic nodes sustained a significant decrease in mean volume associated with a decrease in FLT uptake significantly exceeding that observed in primary tumors. This result was related to genuine differences in biological behavior between primary and metastatic nodal lesions in terms of perfusion, FLT-specific transport and/or phosphorylation in response to treatment. Saga *et al.*, [98] evaluated the clinical value of [^{18}F]FLT-PET imaging prior and 3 months after carbon ion radiotherapy in NSCLC patients. They demonstrated that all NSCLC patients who developed recurrence or who died of lung cancer during follow-up had higher pre-treatment [^{18}F]FLT-PET uptake compared to patients who did not, suggesting the possibility of using [^{18}F]FLT-PET as a tool for patient stratification and risk assessment. Bollinemi *et al.*, [99] concluded that [^{18}F]FLT-PET seems to be a good predictor of early response to systemic-, radio- and concurrent chemo-radiotherapy. The authors suggested that [^{18}F]FLT-PET might be developed into a tool for guiding individualization of treatment strategies as it is able to detect active proliferative tumor sub-volumes and could provide additional information on chemo-radioresistant areas. Everitt *et al.*, [100] evaluated [18F] FLT-PET in NSCLC during immunochemotherapy in a pilot study, suggesting the idea of a dynamically adaptive dose to the molecular imaging changes, and therefore to significantly improve treatment results for individual patients. However, imaging of proliferation and tumor hypoxia is promising, but not yet useful in treatment planning, in particular because of poor availability: more studies are needed to validate its use for this purpose.

CONCLUSION

^{18}F-FDG-PET/CT has a central place in RTP for lung cancer and in particular, for NSCLC assuming a substantial role in the delineation of TV. To be able to deliver higher

radiation doses to the tumor, sparing healthy tissues is a goal to be pursued during RT and for this reason, all possible efforts must be done to overcome the issues. It certainly represents a challenge in fact, to be able to standardize some procedures such as image acquisition, tumor segmentation and so on. The evaluation of the images should be done, possibly in consultation with the nuclear physician in a multidisciplinary approach. Furthermore, considering that respiratory motion during the acquisition may cause smearing, using respiratory motion correction techniques (4D PET/CT) can improve the accuracy. Finally, the development of new radiopharmaceuticals can help overcome the problems related to the disadvantage of [18F]-FDG to accumulate also in activated inflammatory cells, improving tumor characterization and providing new prognostic biomarkers.

LIST OF ABBREVIATIONS

[18F]FDG	=	Fluorodeoxyglucose
[68Ga]Ga-MAA	=	Gallium-68 Macroaggregated Human Serum Albumin
18F-FAZA	=	fluorine-18-labeled fluoroazomycin arabinoside
[18F]-FDG-PET/CT	=	2-[18F]fluoro-2-deoxy-d-glucose/Positron Emission Tomography-Computer Tomography
18F-FMISO	=	Fluorine-18-labeled fluoromisonidazole
4DCT	=	4-dimensional computed tomography
60Cu-ATSM	=	Cu-diacetyl-bis(N4-methylthiosemicarbazone
68Ga-V/Q	=	Gallium-68 Ventilation/Perfusion
AAPM	=	American Association of Physicists in Medicine
ALK	=	Anaplastic Lymphoma Kinase
BNIP3	=	Bcl-2 and 19-kilodalton interacting protein-3
BVT	=	Biological Target Volume
CHRT	=	chemo-radiotherapy
CT	=	Computed Tomography
DDG	=	data-driven gating
EGFR	=	Epidermal Growth Factor Receptor
EPO	=	Erythropoietin hormone
ESMO	=	European Society for Medical Oncology
FLT	=	3′-deoxy-3′-[18F]Fluorothymidine
GTV	=	Gross Tumor Volume
Gy	=	Gray
HIF	=	Hypoxia Inducible Factor
HRE	=	Hypoxia Responsive Elements
IAEA	=	International Atomic Energy Agency
IC-LDRT	=	Low-Dose Fractionated Radiotherapy Concurrent To Induction Chemotherapy
IMRT	=	Intensity Modulated Radiation Therapy
MTV	=	Metabolic Tumor Volume
NCCN	=	National Comprehensive Cancer Network
NSCLC	=	Non-Small Cell Lung Cancer
OS	=	Overall Survival
PCI	=	Prophylactic Cranial Irradiation
PERCIST	=	PET Response Criteria in Solid Tumors
PET/CT	=	Positron Emission Tomography Computed Tomography
PET	=	Positron Emission Tomography
PFS	=	Progression Free Survival
PFTs	=	pulmonary function tests
RECIST	=	Response Evaluation Criteria in Solid Tumors
RT	=	radiotherapy
RTP	=	Radiotherapy Treatment Planning
SBRT	=	Stereotactic Body Radiotherapy
SCLC	=	Small Cell Lung Cancer
SD	=	Standard Deviation
SUV	=	Standardized Uptake Value
T/B	=	Tumor to Background
TK1	=	Thymidine Kinase 1
TNM	=	Tumor-Nodes-Metastasis
TVD	=	Target Volume Delineation
VATS	=	video-Assisted Thoracoscopic Surgery
VEGF	=	Vascular Endothelial Growth Factor

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