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Review

^{18}F-Fdg-PET-guided Planning and Re-Planning (Adaptive) Radiotherapy in Head and Neck Cancer: Current State of Art

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Abstract. *Background/Aim: A review of the literature is proposed as a contribution to current knowledge on technical, physical, and clinical issues about PET-guided planning and re-planning radiotherapy (RT) in head and neck cancer. Materials and Methods: PubMed and Scopus electronic databases were searched for articles including clinical trials. Search terms were "gross tumor volume (GTV) delineation", "head and neck cancer", "radiotherapy", "adaptive radiotherapy" in combination with "PET". Results: A ^{18}F-FDG-PET and CT-scan comparison in GTV definition for RT planning of head and neck cancer was shown in twenty-seven clinical trials with a total of 712 patients. Only two clinical trials focused on PET-guided adaptive radiotherapy (ART) with a total of 31 patients. Conclusion: ^{18}F-FDG-PET is able to achieve an accurate and precise definition of GTV boundaries during RT planning, especially in combination with CT-scan. ART strategies are proposed to evaluate tumor volume changes, plan boost irradiation on metabolically active residual neoplasm and protect organs at risk (OaRs).*

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Head and neck (H&N) cancer is the sixth most common cancer worldwide and each year more than half a million patients are diagnosed with this disease (1, 2). At diagnosis 60% of them present a non-metastatic locally advanced disease, stage III or IV, requiring a multimodality treatment (1, 3). In these cases, radiotherapy (RT) and concurrent chemotherapy (CHT) are considered the nonsurgical standard of care.

These neoplasms carry a poor prognosis with approximately 50%-60% local recurrence and 20-30% of metastases within 2 years from treatment (4). RT has the aim to improve locoregional control both in early stage disease, where RT has an elective role, and in advanced stage, in the setting of combined modality treatment (5). It has been estimated that in the majority of cases, RT treated tumors relapse within the 95% dose coverage volume, probably due to the presence of radiation-resistant hypoxic areas (6-12).

[^{18}F]-fluorodeoxyglucose-PET (^{18}F FDG-PET) is effective during the RT planning to define the Gross Tumor Volume (GTV) boundaries, especially in combination with a CT-scan. During RT, ^{18}F-FDG PET is useful to detect metabolic tumor evolution and to monitor therapy response also before clear anatomic changes. This result depends on its superior ability to detect vital cancer tissue. Therefore, it is potentially useful to develop adaptive radiotherapy (ART) with treatment replanning following not only morphological but even metabolic changes. ART is based on reassessment of macroscopic tumor volume (GTV), and of organs at risk (OaRs) (as parotid and submandibular glands) after a specific time from RT start allowing the optimization of plan conformality during treatment. This approach, especially if

combined with dose-escalation strategies directed against the residual tumor, could contrast radio-resistance leading to higher Tumor Control Probability (TCP) and reduced rates of severe acute and late effects (13-15).

Being an emerging method, only few concept studies, no literature reviews and only few clinical trials using ^{18}F-FDG PET/CT as a re-planning tool are available in literature.

In this article we report the current state of art on the use of ^{18}F-FDG PET in planning and replanning (ART) of H&N cancers to assess the impact of this new therapeutic strategy in patient's managements.

Materials and Methods

Search strategy. PubMed and Scopus electronic databases were searched for articles published until 15th August 2017. Articles published in English and with no time limits were included in this review. Reviews, case reports and non-human studies were excluded. Studies were identified and evaluated by two of the authors (E.F. and M.F.) combining the following major medical subject headings: "GTV delineation", "head and neck cancer", and "radiotherapy" or "adaptive radiotherapy" in combination with "PET". Additional eligible studies were identified by screening the reference lists of the studies found.

Inclusion criteria. Studies were excluded if the title and/or abstract was not appropriate for the aim of the review. The full text of eligible studies and of studies whose relevance was uncertain were obtained. Selected studies were eligible if they met the following criteria: (i) clinical trials, (ii) studies including patients with H&N cancer treated with ^{18}F-FDG PET-guided RT, (iii) studies including the comparison between ^{18}F-FDG PET and CT-based definition of target volumes in RT (planning studies) or studies including PET-guided ART aimed to plan boost irradiation on metabolically active residual neoplasm (re-planning studies).

Results

In literature a ^{18}F-FDG-PET and CT-scan comparison in GTV definition for RT planning of head and neck cancer is shown in twenty-seven clinical trials with a total of 712 patients. Only two clinical trials focused on PET-guided adaptive radiotherapy (ART) for head and neck cancer were available with a total of 31 patients.

Discussion

Role of ^{18}F-FDG PET in radiation oncology: benefits and potential issues. ^{18}F-FDG is the most popular radio-tracer used in oncology and its use is increased also in patients treated with RT (16). Currently, some authors nearly considered ^{18}F-FDG PET/CT as a routine test in RT practice to contour target volumes (both primary tumor and metastatic lymph nodes) in patients with H&N carcinoma, decreasing inter- and intra-observer variability and increasing the conformity to real tumor boundaries (17, 18). In fact, its use is able to achieve a more accurate and precise definition of GTV boundaries, reducing also the risk of possible under- or over-treatment of the real tumor volume based only on morphological imaging especially in combination with CT-scan. Obviously, in case of difficulties in boundaries contouring, other imaging modalities in addition to ^{18}F-FDG PET/CT can be used to better define tumor limits (19). Several studies compared the use of ^{18}F-FDG PET and CT-scan in target volumes definition showing, in the majority of cases, that ^{18}F-PET-based target volumes are smaller than CT-scan-based ones with statistically significant differences (Table I) (20-46).

Moreover, the delineation of GTV and standardized uptake value (SUV) levels evaluation allows the design of dose escalation strategies, improving the possibility to identify tumor subvolumes with higher risk of recurrences (17, 47-50). ^{18}F-FDG PET may be useful even as a prognostic factor due to the ability to early detect tumor recurrences (15-18, 51-54).

The main problem in the use of ^{18}F-FDG PET during RT is the presence of possible false positive results, due to the rise of radiation-induced inflammatory areas leading to incorrect target volumes expansion (15, 17). For Hentschel *et al*. (55) the mismatch due to inflammation between viable tumor and target volume based on a per-treatment ^{18}F-FDG PET is already evident after the delivery of >20 Gy during radio-chemotherapy. Currently, the presence of radiation-induced inflammation in normal tissues also leads to investigate the use of other radiotracers as 3'-deoxy-3'-[^{18}F]fluorothymidine (FLT), [^{18}F]-fluoromisonidazole (FMISO), [^{18}F]-fluoroazomycin (FAZA), and [^{60}Cu]-diacetyl-bis(N(4)-methylthiosemicarbazone (ATSM) (56). However, ^{18}F-FDG still remains the most frequently used molecular radiotracer mainly because of its higher availability (16).

^{18}F-FDG PET-based ART: debated aspects in head and neck radiation treatment. Although 3D-conformal radiotherapy (3D-CRT) and intensity modulated radiotherapy (IMRT) represent the gold standard for H&N cancer treatment, several aspects remain debated. Primarily, the treated volumes (volumes receiving the prescribed dose) are still wide despite their technological progress, and this has an important impact on tissue toxicity (57). Furthermore, tumor volumes and OaRs as salivary gland, mucosae and muscles may be subjected to changes during RT. Also, patient weight loss can modify the position of anatomical structures (57). Kupelian *et al*. (57) observed that these modifications are more evident in HPV positive cancers where tumor volume changes suggest a faster response to RT. Modifications occurring during RT are both anatomical and functional and they can lead to an incorrect dose distribution with a potential underdosage of tumor volumes, overdosage of OaRs, and increased volumes receiving high doses (58).

^{18}F-FDG PET-based ART: aims and characteristics. ^{18}F-FDG PET-guided ART represents a technique potentially able to reduce and correct both anatomical and metabolical changes due to improved dose coverage tailoring. In fact, ^{18}F-FDG PET is able to show metabolical changes before the occurrence of anatomical ones (59). Furthermore ^{18}F-FDG PET offers the possibility to guide ART distinguishing between radioresistant and radioresponder areas leading to dose redistribution with increased dose to the most active residual areas of the GTV (16, 53).

GTV evaluation during treatment is crucial for ART being the region with higher tumor cell density and therefore the more prone to local recurrence (11, 15). In fact, replanning of dose distribution can follow the new target volumes silhouette adapting to volume shrinks and shifts (60, 61). Geets *et al*. (60, 62) stated that this may lead to future dose escalation studies and to increased RT efficacy, especially using highly conformed techniques and a Simultaneous Integrated Boost (SIB) approach on the shrunk volume with better sparing of the adjacent healthy areas and thus respecting their dose constraints. A concept study by the same authors (62) showed the feasibility of a helical-tomotherapy-based adaptive IMRT in a pharyngolaryngeal carcinoma. The authors reported a decreased GTV throughout the radiation course using both anatomic and ^{18}F-FDG PET functional imaging ($p<0.001$) leading also to CTV and PTV reduction. On the contrary this technique had a limited impact on doses to selected OARs (spinal cord, ipsilateral and controlateral parotid, oral cavity) compared to a nonadaptive technique.

ART and dose painting technique. Potentially improved results could be theoretically achieved through dose painting technique where higher radiation doses are delivered to target subvolumes (dose painting by contours) or to single different voxels based on their SUV intensity (dose painting by numbers). In fact, taking into account the correlation between ^{18}F-FDG uptake and the risk of local recurrences, a heterogeneous dose may be delivered in order to boost specific "high risk" subvolumes (49, 63-64). The purpose is to achieve a radiation biological conformity and not only a physical one, considering also the heterogeneity of tumor biology due to differences in terms of hypoxia and proliferation (48, 56, 63).

Moreover, in the H&N region, several OaRs as oral cavity, mandible, salivary glands and inner ears are close to RT target (17). Planning modifications can lead not only to better tumor coverage but also to a better OARs sparing and thus to reduced incidence of side-effects.

Castadot (58) showed that during radiotherapy, CT-scan alone can improve target volumes delineation and can be considered as a valid approach. However, ^{18}F-FDG PET seems the better option for dose painting (65). In fact "dose painting by numbers" implies signal conversion from voxel levels to heterogeneous dose prescription and computation of the total dose (66) taking into account the possible target volumes propagation involving the growth of "newborn" and "orphan" areas (67).

Currently, only one center (68, 69) reported on clinical experience on dose painting in ^{18}F-FDG PET-guided ART.

In a comparative dosimetric study by Olteanu *et al*. (70) ART seems to be superior to non-ART treatments due to the possibility of dose painting rearrangement. This resulted in an increased minimum dose and in a reduced maximum dose to target volumes and in a lower dose to OaRs with an overall improvement of planning results. Moreover, with ART, small tumor volumes have a greater possibility for dose escalation with OaRs saving through the use of a SIB or dose painting by numbers (19).

Technical issues. Geets *et al*. (60) showed in a concept study that an automatic method of PET imaging segmentation during RT is not adequate due to the difficulty in distinguishing residual neoplasms from normal benign tissue reactions. Olteanu *et al*. (67) reported that an ART planning can also last a whole working day and thus a non-rigid image coregistration with the deformation of target volumes boundaries followed by manual control may improve feasibility. Castadot *et al*. (71, 72) confirmed the low feasibility of ART planning in clinical routine without an automatic method of volume delineation. Even these authors highlighted how the use of a deformable method of segmentation can be useful in ^{18}F-FDG PET-guided ART (71, 72). In fact, this method can spare 26-47% of total contouring time in replanning and can reduce the inter- and intraobserver variations compared to rigid registration. This different approach allows an automatic re-delineation of target volumes using a corresponding deformation map of the target volumes contoured before. In their first clinical trial, Duprez and colleagues (68) defined the total dose with a rigid image registration, while Berwouts and coworkers (69) used a deformable image co-registration method for total dose calculation, for target volumes propagation facilitating targets re-contouring, and thus decreasing the working time. Obviously, the intervention of a radiation oncologist is needed to check, monitor, and eventually correct the adapted volumes (67). The manual adjustment by the physician creates the mismatch between voxels (original voxels in pre-treatment CT-scan and their corresponding voxels in per-treatment CT-scan), creating newborn and orphan voxels (67). The tiny swallowing structures are the most common areas of adjustment (67). Deformable coregistration allows to decrease the replanning time up to 10 minutes for patients coregistration, deformation of volumes of interest, and creation of a dose map, and to around 1 hour for expert radiation oncologist review.

Table I. *^{18}F-FDG PET and CT-scan comparison in GTV definition for radiotherapy planning of H&N cancer.*

Author, year	Reference	Patients	Disease stage	PET-based contouring method	Results
Ciernik I.F. *et al*., 2003	20	12	IIb-IVa	Visual criteria based on 50% of the max value	T+N: GTV_{CT}≥25% GTV_{PET-CT} in 33% pts; GTV_{CT} ≤25% GTV_{PET-CT} in 17% pts (p=NR)
Daisne J.F. *et al*., 2004	21	29	II-IV	Automatic segmentation algorithm based on the measured s/b ratio	T: GTV_{CT} > GTV_{PET} (differrence range=28-37%) [Oropharyngeal T: GTV_{CT} > GTV_{PET} (32.0 cc *vs*. 20.3 cc)* (p=0.02); Laringeal and hypopharyngeal T: GTV_{CT} > GTV_{PET} (21.4 cc *vs*. 13.4 cc)* (p<0.01)]
Geets X. *et al*., 2004	22	23	II-IV	Adaptive threshold-based automatic method according to s/b ratio	T: GTV_{PET} < 40% GTV_{CT} [Oropharyngeal lesions: GTV_{PET} < GTV_{CT} (19.3 cc±21.4 cc *vs*. 29.0 cc±31.0cc)# (p=0.013); Laringeal and hypopharyngeal lesions: GTV_{PET} < GTV_{TC} (14.5 cc±11.3 cc *vs*. 24.9 cc±19.0 cc)# (p=0.003)]
Heron D.E. *et al*., 2004	23	21	II -IV	Visual criteria	T: GTV_{CT} > GTV_{PET} (65.0 cc *vs*. 42.7 cc)* (p=0.002) (GTV_{CT} and GTV_{PET} difference not significative for N: p=0.5)
Scarfone C. *et al*., 2004	24	6	NR	Visual criteria	T: $GTV_{PET/CT}$ > 3.3 cc (15%)* GTV_{CT} N: $GTV_{PET/CT}$ > 5.0 cc (17%)* GTV_{CT} (p=NR)
Paulino A.C. *et al*., 2005	25	40	III – IV (95% pts)	Volume based on 50% intensity level relative to the tumor max	T:GTV_{CT} > GTV_{PET} (37.2 cc *vs*. 20.3 cc)# (p=NR) [GTV_{CT} > GTV_{PET} in 75% cases; GTV_{CT} ~ GTV_{PET} in 8% cases; GTV_{CT} < GTV_{PET} in 18% cases]
Breen S.L. *et al*., 2006	26	10	NR	Visual criteria	T: GTV_{CT} > $GTV_{PET/CT}$ (27.7 cc±26.5 cc *vs*. 23.3±19.2 cc)* (α: not significative)
Wang D. *et al*., 2006	27	16	NR	Visual criteria (SUV≥2.5)	T+N: GTV_{CT} > GTV_{PET} (68.8 cc *vs*. 61.8 cc)* (p=NR)
Ashamalla H. *et al*., 2007	28	25	II-IV	Visual criteria (n if SUV≥2.5)	T+N: GTV_{CT} > $GTV_{PET/CT}$ (44% pts) (p=NR)
El-Bassiouni M. *et al*., 2007	29	25	I-IV	Visual criteria based on tumor max and background uptake	T+N: GTV_{CT} > GTV_{PET} (29.6 cc *vs*. 23.0 cc)# (p=0.0022)
Schinagl D.A.X. *et al*., 2007	30	77	II-IV	Visual criteria; volume based on: SUV of 2.5; a fixed threshold of 40% and 50%; a s/b ratio adaptive threshold	T: GTV_{CT} ~ $GTV_{PET-VIS}$ (22.7 cc *vs*. 21.5 cc)* GTV_{CT} > GTV_{PET} (GTV_{40}, GTV_{50}, $GTV_{S/B}$) (22.7 cc *vs*. 16.4 cc, 10.5 cc, 11.2 cc)* (p≤0.0001 for all comparisons)
Newbold K.L. *et al*., 2008	31	18	II-IVb	Volume based on 50% density of the max of the interest region	T+N: $GTV_{PET/CT}$ > 6.2 cc (74%)# GTV_{CT} In case of known T: $GTV_{PET/CT}$ > 6.1 cc (78%)# (p=0.008); in case of unknown T: $GTV_{PET/CT}$ > 6.3 cc (61%)# (p=0.012)
Deantonio L. *et al*., 2008	32	22	I-IVb	Fixed image intensity threshold method (40% of max intensity)	T+N: GTV_{PET} < GTV_{CT} (17.2 cc *vs*. 20.0 cc)* (p=0.2); $GTV_{PET/CT}$ > GTV_{CT} (26.0 cc *vs*. 20.0 cc)* (p<0.0001)
de Figueiredo B.H. *et al*., 2009	33	9	Advanced stage	Automatic segmentation based on s/b ratio	T: GTV_{CT}> GTV_{PET} (71.4 cc *vs*. 39.3 cc)* (p=0.004)
Dirix P. *et al*., 2009	34	15	III-IVa	Automatic contouring based on s/b ratio	T+N: GTV_{CT} > GTV_{PET} (33.6 cc *vs*. 18.7 cc)* (p=0.0005)
Guido A. *et al*., 2009	35	38	I-IVb	Visual criteria based on 50% intensity level relative to the tumor max	T+N: GTV_{CT} > GTV_{PET} (34.5 cc *vs*. 29.4 cc)* (p<0.05); not statistically significant p and n separate analyses
Iğdem S. *et al*., 2009	36	26	I-IV	Standardized SUV and visual criteria	T+N: GTV_{CT} < $GTV_{PET/CT}$ (26.5 cc *vs*. 35.5 cc)* (p=0.004)
Delouya G. *et al*., 2011	37	25	I-IVb	Visual criteria	T: GTV_{CT} > GTV_{PET} (24.0 cc *vs*. 18.0 cc)* (p=0.001) N: GTV_{CT} ~ GTV_{PET} (p=0.08)

Table I. *Continued*

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Author, year	Reference	Patients	Disease stage	PET-based contouring method	Results
Kajitani C. *et al*., 2011	38	15	II-IVA	Visual criteria	T+N: $GTV_{CT} > GTV_{PET/CT}$ in 66.7% pts (p=0.12)
Fried D. *et al*., 2012	39	91	II-IV	Visual criteriaand 40%-50% peak PET activity	T: $GTV_{CT} > GTV_{PET}$ (32.0 cc *vs*. 29.0 if visual interpretation, 10.8 if PET_{40}, 7.0 if PET_{50})# (p=NR); N: $GTV_{CT} > GTV_{PET}$ (16.0 cc *vs*. 8.0 cc)# (p: NR)
Perez-Romasanta L.A., 2012	40	19	NR	Adaptive threshold-based method according to s/b ratio	T+N: $GTV_{CT} < GTV_{PET}$ in 84.6% of lesions; $GTV_{CT} > GTV_{PET}$ in 15.4% of lesions (p=0.000)
Venkada M.G. *et al*., 2012	41	26	NR	Visual criteria	T: $GTV_{CT} > GTV_{PET}$ (54.8 ±64.5 cc *vs*. 48.4±53.2 cc)* (p<0.001); N: $GTV_{CT} < GTV_{PET}$ (11.0±14.9 cc *vs*. 12.7±15.5 cc)* (p<0.001)
Anderson C.M. *et al*., 2014	42	14	III-IVb	Visual criteria	T: $GTV_{CT} > GTV_{PET/TC}$ (45.0 cc *vs*. 35.0 cc)* (p=NR)
Arslan S. *et al*., 2014	43	37	NR	Visual criteria (n with $SUV_{max} > 2$)	T: $GTV_{CT} > GTV_{PET/CT}$ (55.8 cc *vs*. 32.7 cc)# (p<0.001) N: $GTV_{CT} < GTV_{PET/CT}$ (5.3 cc *vs*. 7.5 cc)# (p<0.001) T+N: $GTV_{CT} > GTV_{PET}$ (82.0 cc *vs*. 50.9 cc)# (p<0.001)
Bird D. *et al*.; 2015	44	11	III-IV	Semi-automated segmentation algorithm	T: $GTV_{CT} > GTV_{PET}$ (11.6 cc *vs*. 8.8 cc)# (p=0.059)
Chauhan D. *et al*., 2015	45	21	I-IV	40% of SUV_{max} as reference	T: $GTV_{CT} < GTV_{PET}$ (29.6±31.3 cc *vs*. 32.0±33.7 cc)* (p=0.468)
Leclerc M. *et al*., 2015	46	41	III-IV	Automatic gradient based method	T: $GTV_{CT} > GTV_{PET}$ (40.4 cc *vs*. 28.8cc)* (p<0.0001)

GTV: Gross tumor volume; N: nodal disease; NR: not reported; pts: patients; RT: radiotherapy; s/b: signal to background; T: primary tumor; *vs*.: *versus*; *average; # median.

Replanning time and frequency. Monitoring per-treatment target volumes, OaRs anatomical shrinkage, metabolical modifications, and the consequent replanning are at the basis of ART. However, the optimal time of replanning is not clear. The results of Duprez and colleagues clinical trial (68) suggest that PET re-imaging can be performed during the first week of treatment but they also observed that target volumes show a significant reduction appropriate for dose-painting technique after 8 fractions.

For Geets and collegues (62) a treatment plan based only on pre-treatment imaging is only a simplification of the entire treatment but even one single re-imaging and consequent replanning at the mid-treatment does not give relevant benefit. In fact anatomic and functional changes occur during the entire RT duration and it is important to take into account also the onset of actinic inflammation creating noisier imaging difficult to assess. Also, the group of Ghent University Hospital used two replanning for each radiation treatment in their two clinical trials (68, 69). In fact, a single replanning is not considered sufficient to detect all target variations occurring during the therapy.

For Geets and colleagues (62) the optimal time for reimaging and replanning is during the first 2 or 3 treatment weeks of a conventional protocol. For Differding *et al*. (66) a decrease of target volumes can be shown in the first radiation treatment week. However, replanning is considered optimal after two treatment weeks but no later due to increasing edema and inflammation and the consequent difficult to distinguish boundaries.

Dose summation. Currently, the summation of the distributed dose is a challenge (68). The dose count of all treatment plans of the whole RT cycle is a crucial point also for a correct outcome evaluation (69). Olteanu *et al*. (67) proposed different methods of dose summation taking into account, in different ways, of "orphans" and "newborn" areas (chronological and antichronological methods).

The anti-chronological method shows the summation of the total doses including those of "orphan" voxel areas as a summation of all ROIs in pre-treatment CT. On the contrary, in the chronological method the doses are calculated in a CT-scan performed the last day of RT including "newborn"

Table II. *Clinical trials: patients and tumor characteristics.*

Author, year	Medical center	Reference	Patients	Age range (yrs)	Histologic diagnosis	Site	Stage (AJCC 2010)
Duprez F. *et al.*, 2011	Ghent University Hospital, Belgium	68	21	46-72	Squamous cell carcinoma: 100%	Oral cavity: 9.5% Oropharynx: 52.4% Hypopharynx: 19.0% Larynx: 19.0%	I: 0% II: 19.0% III: 23.8% IVA: 42.9% IVB: 14.3%
Berwouts D. *et al.*, 2013	Ghent University Hospital, Belgium	69	10	48-74	Squamous cell carcinoma: 100%	Oral cavity: 10% Oropharynx: 50% Hypopharynx: 30% Larynx: 10%	I: 10% II: 0% III: 40% IVA: 30% IVB: 20%

Table III. *Clinical trials: studies design and treatment characteristics.*

Author, year	Reference	Study design	Inclusion criteria	Radiotherapy planning	Pre-treatment imaging	Per-treatment imaging and time	Median dose prescriptions (Gy)		
Duprez F. *et al.*, 2011	68	Phase I dose escalation trial	HNC M0 non-resected	Phase I (1-10 fr): DPBN IMRT based on pre-treatment imaging Phase II (11-20 fr): DPBN IMRT based on per-treatment imaging Phase III (21-32 fr): conventional IMRT based on previous per-treatment imaging	^{18}F-FDG PET/CT	^{18}F-FDG PET/CT after 8th fr.	CTV_{HD} - Dose level I Phase I: 25.0 Phase II: 30.0 Phase III: 25.9	GTV - Dose level II Phase I: 30.0 Phase II: 30.0 Phase III: 25.9	PTV_{EN} Phase I: 21.6 Phase II: 21.6 Phase III: -
Berwouts D. *et al.*, 2013	69	Phase I trial	HNC M0 non-resected	Phase I (1-10 fr): DPBN based on pre-treatment imaging Phase II (11-20 fr): DPBN based on 1st per-treatment imaging Phase III (21-32 fr): DPBN based on 2nd per-treatment imaging	^{18}F-FDG PET/CT	^{18}F-FDG PET/CT after 8th and 18th fr.	GTV and GTV_{LN} Phase I: 27.0 Phase II: 21.6 Phase III: 21.6 CTV_{EN} Phase II-II: 40		

CTV: Clinical target volume; DPBN: dose painting by numbers; EN: elective neck; GTV: gross tumor volume; HD: high dose; HNC: head and neck cancer; IMRT: intensity modulated radiotherapy; LN: metastatic lymph nodes; PTV: planning target volume.

voxel doses. Obviously, the choice of the count method is essential for treatment evaluation also because the total dose can result different depending on the used approach (69).

^{18}F-FDG PET-based ART: clinical trials. In literature only two papers, both published by authors from Ghent University Hospital, Belgium, are available (68, 69). Both clinical trials had a prospective design: one was a phase I study (69) and the other was a phase I dose escalation study (68) with a total of 31 patients. Patients and clinicopathologic features, imaging, treatment data and results of these clinical trials are summarized in Tables II-IV.

In both clinical trials radiation treatment was divided into three consecutive phases (phase I: from 1st to 10th fraction, phase II: from 11th to 20th fraction and phase III: from 21st to 32nd fraction) with three different treatment plans. Megavoltage external beam RT was delivered in both studies with "dose painting by numbers" IMRT based on pre- and per-treatment functional imaging in all phases with the exception of conventional IMRT (delivery of uniform doses) performed in the 3rd phase in Duprez *et al.* (68) study.

In both trials re-imaging was performed with ^{18}F-FDG PET/CT at 8th fraction with consequent treatment replanning. The new radiation planning started in the nearby next phase (II phase). In Berwouts study (69) a second ^{18}F-FDG PET/CT re-imaging was performed at 18th fraction performed with consequent treatment replanning in the III phase. On the contrary, in Duprez study (68) the III phase

Table IV. *Clinical trials: results.*

Author, year	Reference	Acute toxicity	Late toxicity	MDT (maximum tolerated dose)	LRC (locoregional control)	Survival
Duprez F. *et al*., 2011	68	No ≥G4	No ≥G4	Median dose of 80.9 Gy	95% local and 93% regional actuarial control (F-UP: 2 yrs); 68% actuarial freedom from distant metastasis (F-UP: 2 yrs)	42.8%pts dead (F-UP: 2 yrs) (not statistically significant the difference between actuarial DSS and DFS in dose level I and II)
Berwouts D. *et al*., 2013	69	No ≥G4	NR	-	70% CR (F-UP: 3 months); 90% CR (F-UP: 13 months)	100% OS (F-UP: 3 months); 90% OS (F-UP: 13 months)

CR: Complete response; DFS: disease-free survival; DSS: disease-specific survival; F-UP: follow-up; G: grade; NR: not reported; pts: patients; yrs: years.

was based on a RT plan created on previously identified pre-treatment volumes. In Duprez study (68) the definition of the total dose sum was performed through a rigid CT and PET registration method. On the contrary, Berwouts *et al*. (69) used a deformable image co-registration method both for the target volumes propagation and for total dose calculation.

In both studies no acute G4 toxicity able to discontinue the treatment, assessed by the CTCAE (Common Toxicity Criteria for Adverse Effects) v. 2, was recorded. An update of the dose-escalation study (73) showed also no G4 toxicity after a median of 38 and 22 months of follow-up for dose level I and II, respectively. The median dose of 80.9 Gy resulted as the maximum tolerated dose (MTD) recorded in 3-month follow-up (73). An actuarial local and regional control of 95 and 93% respectively and 68% of freedom from distant metastasis after 2 years of follow-up was recorded (73). During follow-up a 42.8% rate of patient's death was recorded (44.4% of deaths caused by progressive disease). In the most recent study Berwouts *et al*. (69) reported 70% of complete response at 3rd month follow-up and 90% complete response rate (with the exception of 1 patient who undergone pathological lymph node dissection after RT) and 90% of overall survival after a median follow-up of 13 months.

Conclusion

The growing interest in ^{18}F-FDG PET capacities in defining hypermetabolic areas has brought to an increased use of this technique in RT planning and particularly in target volumes definition of H&N cancer. Moreover ^{18}F-FDG PET-guided ART can be considered a new strategy in the treatment of H&N cancer. The integration of anatomic and metabolic data is potentially useful to evaluate cancer biology and radiation resistance during RT. The study of these features and the evaluation of mismatch between dose distribution and target volumes allow to define an adapted high dose volume significantly smaller compared to pre-treatment plan although requiring a demanding work for replanning (58). The expected results are a more individualized therapy with improved dose distribution and locoregional control, a decreased probability of recurrences and toxicity and therefore a better therapeutic ratio (18, 53). Using repeated CT-scan it is possible to achieve 70% GTV shrunk during RT (7 weeks) (74) while with ^{18}F-FDG PET this data is difficult to be defined due to the scarce number of available studies. In fact, based on the small number of published studies, no strong evidence on ^{18}F-FDG PET-guided ART is available. Though ART seems to be superior to standard planning strategies because of better target coverage and improved OaRs sparing, there are several unsolved questions such as timing and frequency of re-planning, re-planning procedures, validation of fast segmentation tools taking into account non-uniform anatomical and metabolical volume modifications, and dose summation methods (13, 70). In a recent study, Brouwer *et al*. (75) highlighted some pre-therapy predictive factors potentially used to identify patients who may benefit more from ART (*e.g*. tumor site and parotid glands planned dose). However, specific studies reporting data to identify clinical, biological and technical issues to select patients for ^{18}F-FDG PET-guided ART are still lacking (58).

Currently, the lack of strong evidence on ^{18}F-FDG PET-guided ART leads to consider it a not-routine technique and to take into account also the cost-effort/effectiveness balances. Therefore, its validation will require future phase II and III trials.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

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