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Correlation between fluorodeoxyglucose hotspots on preradiotherapy PET/CT and areas of cancer local relapse: systematic review of literature

Corrélation entre les zones de forte captation (« hotspots ») du fluorodésoxyglucose sur la tomographie par émission de positons–scanographie préthérapeutique et les sites de récurrence locale des cancers traités par irradiation : revue systématique de littérature

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Each author has contributed to the submitted work as follows: RA, US and JC designed the study; DB, FL and JCL analysed the data; PYS and PV are the guarantors of the paper. All authors contributed in drawing up the manuscript.

Abstract

The aim of the present paper is to systematically review all available literature on preradiotherapy high uptake areas (hotspots) as a potential target for dose escalation in different tumour sites, and to understand the potential role and limitations of fluorodeoxyglucose (FDG)-positron-emission tomography (PET)/computed tomography (CT) in this context. An electronic database (Medline) search was conducted to identify articles reporting on a correlation between high tracer uptake on pretreatment PET and preferential sites of local recurrence after radiotherapy. Search was limited to English language. No date range limitation was applied. Among 45 studies initially identified, nine series matching with inclusion criteria have finally been retained from the literature after reviewing (5 retrospective and 4 prospective). Primary tumour locations were head neck (n=2), lung (n=4), oesophageal (n=2) and rectal (n=1) areas. Overlaps between FDG hotspot on preradiotherapy PET/CT and site of local recurrence on post-treatment scan showed good to excellent agreement. Only studies on head neck cancer reported moderate agreement probably explained by the lack of reproducibility of the patients positioning between pre- and post-treatment FDG-PET/CT; and by the rigid registration process of images limited by post-therapeutic changes that highly affect anatomical landmarks. FDG hotspots-guided radiotherapy may allow dose escalation in respecting a robust methodology (treatment position, coregistration method, four-dimensional PET).

Keywords

PET/CT; FDG hotspots; radiotherapy; local relapse; literature review

Résumé

L'objectif de cet article est de faire une revue systématique de toute la littérature disponible pour comprendre le rôle potentiel et les limites selon les localisations tumorales de la tomographie par émission de positons (TEP)-tomodensitométrie (TDM) au fluorodésoxyglucose (FDG) pour l'escalade de dose sur les zones de forte captation du traceur (points chauds ou « hotspots ») avant radiothérapie. Une recherche dans la base de données électronique (Medline) a été menée pour identifier les articles rapportant une corrélation entre les zones de forte captation du traceur à la TEP préthérapeutique et les sites préférentiels de récurrence locale après radiothérapie. La recherche était limitée aux articles anglophones. Aucune limite de date de publication n'a été appliquée. Parmi les 45 études initialement

identifiées, neuf séries correspondant aux critères d'inclusion ont finalement été retenues après lecture (cinq rétrospectives et quatre prospectives). La localisation tumorale primitive concernait les voies aérodigestives supérieures (n=2), les poumons (n=4), l'œsophage (n=2) et le rectum (n=1). Les intersections entre le hotspot de la TEP-TDM au fluorodésoxyglucose réalisée avant la radiothérapie et le site de récurrence locale de l'examen après le traitement ont montré un accord bon à excellent. Seules les études menées sur le cancer des voies aérodigestives supérieures rapportaient un accord modéré, probablement expliqué par le manque de reproductibilité du positionnement des patients entre les TEP-TDM avant et après le traitement ; et par la méthode rigide de recalage des images, limitée par les changements tissulaires post-thérapeutiques affectant fortement les repères anatomiques. La radiothérapie guidée par les hotspots sur la TEP-TDM au fluorodésoxyglucose peut permettre une augmentation de dose de radiothérapie en respectant une méthodologie robuste (position de traitement, méthode de coregistration, TEP quadridimensionnelle).

Mots clés

TEP-TDM; FDG « hotspots »; radiothérapie; rechute locale; revue de littérature

1. Introduction

Alongside with surgery, radiotherapy is the cornerstone of treatment for many locally advanced cancers. However, local relapse can occur in many tumour types, usually within the high dose treated volume, indicating that the radiation dose delivered may be insufficient for local tumour control [1-3]. Dose escalation is often limited by the tolerance of surrounding tissues and the associated risk of radiation-induced toxicity [4-6]. In this respect, the ability to define and irradiate more accurately areas at high risk of recurrence could be useful to guide a dose escalation protocol, now possible since the development of modern techniques such as stereotactic radiotherapy, radiosurgery, image-guided and intensity-modulated radiotherapy.

Tumours consist of heterogeneous cell subpopulations that are known to be spatially distinct within the lesion [7]. These areas differ by their metabolism, hypoxia, perfusion, proliferation and are therefore not equally radiosensitive [8]. Based on this intratumoral heterogeneity, several studies aimed to predict the anatomical location of residual or relapsed tumours using functional imaging, and especially (¹⁸F)-fluorodeoxyglucose positron-emission tomography/computed tomography (FDG-PET/CT). This could indeed support a radiotherapy planning optimization strategy based on focal increased dose to these identified treatment-resistant subvolumes (“hotspot”) without impaired tolerance.

This is a systematic review of the available literature on the hotspot concept in FDG-PET/CT. The goal is to understand the potential role and limitations of FDG-PET/CT in dose escalation on preradiotherapy high uptake areas within different tumour locations.

2. Methods

2.1. Study selection

An electronic database (Medline) search was conducted to identify articles reporting the use of PET/CT to search for a correlation between areas of high tracer uptake on pretreatment scan and preferential sites of local recurrence. The following keywords, Medical Subject Headings (MeSH) terms and text words were used for Medline search: [neoplasms OR cancer OR tumours] AND [(local OR located OR locoregional) AND (recurrence OR relapse OR residual OR failure)] AND [(positron-emission tomography) OR (positron emission tomography computed tomography) OR (PET scan)] [(high uptake areas) OR (high metabolic activity) OR (high uptake sub-volumes) OR (hotspots)] AND [(radiotherapy) OR (chemo-radiotherapy)]. Search was limited to English language. No date range limitation was applied.

Abstracts were screened to check inclusion criteria: series on patient with any type of cancer treated with radiotherapy with or without chemotherapy within usual recommendations undergoing both PET/CT before and after treatment, during systematic follow-up or at the time of clinically suspected recurrence; quantified overlap analysis of pre- and post-radiotherapy metabolic tumour volume on PET/CT after images coregistration. Exclusion criteria were: case reports and any other PET tracer than fluorodeoxyglucose.

The full text of the remaining studies was reviewed.

2.2. Data collection

Data extraction table was predefined prior to literature search and populated upon revision of full text. Variables of interest were: study type, population demographics (sex and age), primary tumour location, sample size with proportion of local recurrence, PET patient positioning, volume of interest delineation method, images registration method, overlap indices and main results.

2.3. Hotspot concept

2.3.1. FDG PET/CT imaging

A first FDG-PET/CT (PET_A) is performed at initial staging and a second one (PET_R) during systematic follow-up or in cases of suspected relapse.

The main objective is to find the method delineating the smallest tumour subvolume on baseline PET with the highest overlap index compared to the relapse volumes. Different overlaps between volume

of interest on baseline tumour (A_X) and relapse subvolumes (R_X) are eventually investigated. Relapse subvolumes are only calculated in patients with local recurrence.

2.3.2. Delineation method

For delineation of the highest tumoral uptake area on baseline PET_A or of the residual metabolic activity after treatment on PET_R , standardized uptake value (SUV) based methods are the most often described. For the relative threshold method, a three-dimensional contour around voxels equal to or greater than $x\%$ of SUV_{max} is applied. For the absolute threshold method, a three-dimensional contour around voxels equal to or greater than absolute value of $SUV = x$ is applied.

Then, baseline subvolumes A_X are reported on PET_R , and recurrence subvolumes R_X are reported on PET_A , to quantify their respective overlaps as shown on Fig. 1.

2.3.3. Coregistration method

The principle underlying the hotspot concept is to measure the common volume of two uptakes in two different studies. The registration between those series is then a major step of the measurement workflow, as few pixels transformation can eliminate the existence of the overlap. A PET to PET registration would be a mistake, because uptakes can be very different, for example in case of complete response. Therefore CT to CT registration, based on anatomical landmarks, remains the preferred method. The registration matrix is then applied on PET images. A registration method is based on four components. First, the algorithm identifies common structures in the two scans. Usually, it is based on edge detection of high density areas like bones on CT. The second step is to apply a transformation method. It can be rigid (translation, rotation, scale) or non rigid (creation of a vector field between the two images). Then, an objective function measures the difference between the two sets of images. Finally, an optimization algorithm determines the transformation parameters that best solve the objective function. Rigid transformation is commonly used because it is faster, does not affect image integrity and is widely available on commercial software. Mostly, it is constrained in a localized volume of interest set by user to maximize the performances in a local area. Non-rigid transformation has to be chosen after a rigid registration. Images being deformed, the non-rigid transformation has to be as small as possible.

2.3.4. Overlap estimation

Five indices are mostly used in the literature to assess potential overlap between different volumes of interest: Dice index ($2 \cdot \frac{A_X \cap R_X}{A_X + R_X}$), Jaccard index ($\frac{A_X \cap R_X}{A_X \cup R_X}$), overlap fraction ($OF = \frac{A_X \cap R_X}{\min(A_X, R_X)}$), common volume divided by the initial volume ($A_X \cap R_X / A_X$) and common volume divided by the compared volume ($A_X \cap R_X / R_X$). The Dice, Jaccard and overlap fraction indices are widely used to compare delineated volumes obtained with different methods or by multiple investigators. Their values vary

between 0 if the volumes are completely disjointed and 1 if the volumes match perfectly in size, shape and location. They can be misleading when the sizes of the delineated volumes differ. The $A_X \cap R_X / A_X$ is used to estimate the larger subvolume A_X with high chances of containing the recurrent tumour volume (R_X), aiming to limit the irradiation of areas with low risk of recurrence. The $A_X \cap R_X / R_X$ index is used to estimate the smaller sub-volume A_X on PET_A containing the highest uptake area in the recurrent tumour (R_X), to avoid omitting areas at high risk of recurrence from the target volume.

A schematic example of the interpretation of overlap indices is represented in Fig. 2.

2.3.5. Statistics

The quality of overlap is usually assessed using Cohen k-test for agreement between investigators as follows: 0-0.2, poor agreement; 0.21-0.40, fair agreement; 0.41-0.60, moderate agreement; 0.61-0.80, good agreement; and 0.81-1.00, very good agreement [9].

3. Results

3.1. Description of studies

Thirty-five studies were identified on Medline search. After revision of abstracts, nine series have finally been identified in the literature matching with inclusion criteria (5 retrospective and 4 prospective). Primary tumour location concerned head neck (n=2), lung (n=4), oesophageal (n=2) and rectal (n=1) areas [10-18]. Study characteristics are presented in Table 1.

3.2. Methodology

Description of image analysis within series is described in Table 2.

3.2.1. Delineation method

Seven studies tested respectively five to seven volumes of interest on PET_A and two to three volumes of interest on PET_R (metabolic active residual disease or relapse) using a relative threshold method percentage of maximum standardized uptake value. On the contrary, Shusharina et al. arbitrarily defined A_{50} and R_{80} [15].

In addition, Lu et al. used absolute standardized uptake value thresholds 2.5 and 5.0 on PET_A , and Aerts et al. on PET_R as well [12,13,17].

Finally, van den Bogaard et al. used a signal to background method to define the percentage of maximum standardized uptake value threshold for both A_X and R_X delineation[18,19].

3.2.2. Coregistration method

All authors reported that the process first rely on rigid registration. Eight studies finalized registration manually and one with a deformable registration[18]. Four studies used OncoPlanet software (Dosisoft®, Cachan, France) [10,11,14,16], two used TrueD software (Siemens®, Elangen, Germany) [12,13], one used an open source ITK library (VersorRigid3DTransform) [17] and two did not notify the used package [15,18].

3.2.3. Overlap estimation

Most of the studies calculated the five indices defined above: Dice, Jaccard, OF, common volume divided by the initial volume and common volume divided by the compared volume [10,11,14,16].

Three series only studied the overlap fraction [12,13,17].

Van den Bogaard et al. used a 10 bin SUV-volume-histograms approach based on the pretreatment fluorodeoxyglucose uptake level. After deformable registration of the outlining recurrent disease R_X onto PET_A , the decrease in the amount of voxel per bin was calculated (voxel fraction, VF) [18].

3.3. Pertumour location analysis

3.3.1. Head and neck cancer

In a retrospective analysis of 19 out of 72 local recurrences of head and neck squamous cell carcinoma treated by radiotherapy with or without chemotherapy, Chaput et al. reported a moderate correlation between the volumes drawn on initial PET_A and relapse PET_R . In fact, the $OF(A_X \cap R_{40})$ and $A_X \cap R_{40}/R_{40}$ index showed a moderate agreement (0.52–0.43) for maximum standardized uptake value thresholds of 30% to 50%. Moreover, moderate agreement values (0.54–0.45) of $OF(A_X \cap R_{70})$ and $A_X \cap R_{70}/R_{70}$ indices were obtained for baseline maximum standardized uptake value thresholds between 30% and 40%[10] (Fig. 3). Although the correlation was moderate, we proposed to perform further study with patients in treatment position and deformable registration method to improve results, in testing a 50%SUVmax threshold.

With a similar PET procedure (no treatment position, rigid registration), Legot et al. reported similar results. In their 38 cases of post-treatment local recurrence, the $OF(A_X \cap R_{40})$ ranged between 0.35 and 0.55 for overlaps between R_{40} and A_{30} , A_{40} , A_{50} and A_{60} respectively. Similarly, $A_X \cap R_X/R_X$ showed a fair overlap only with values remaining between 0.3 and 0.4 for the comparison of R_{40} with A_{40} , A_{50} , A_{60} , A_{70} and A_{80} . Only 21% of patients had an overlap between various subvolumes and R_{90} [11].

In the two studies, the Jaccard and Dice and $A_X \cap R_X/A_X$ indices were consistently lower than 0.5 irrespective of the thresholds considered.

3.3.2. Lung cancer

In a first retrospective study on non small cell lung cancer, Aerts et al. reported that the overlap fraction $OF(A_X \cap R_X)$ for A_{34} to A_{60} and R_{70} to R_{90} was higher than 0.6 (good agreement). Because the pretreatment 50%SUVmax area A_{50} largely corresponded with the 70–90%SUVmax high-uptake areas within the residue, authors recommended this method to delineate the of radiotherapy boost target volume. Moreover, the hotspot within the residual area (90%SUV) had a good overlap with the pre-radiotherapy 50%SUV threshold ($OF = 71\%$)[12]. They finally confirmed these findings in a prospective analysis of 12 patients and showed that pretreatment high fluorodeoxyglucose uptake area A_{50} had an overlap fraction of 68% within the residue R_{90} [13].

Moreover, using a non-rigid registration method, Shusharina et al. prospectively studied in 19 out of 61 postradiation residual disease of non small cell lung cancer the overlap fraction of an initial subvolume defined with the 50%SUVmax threshold as well and a relapse subvolume defined with the 80%SUVmax threshold. They showed that the $OF(A_{50} \cap R_{80})$ was excellent (80%) at 2 weeks (W2) after treatment and remained good (63%) at 3 months (M3) [15].

Only Calais et al. suggested a 70% SUVmax threshold on baseline PET_A as more suitable for radiation-boosting target in a series of 17 local relapses of lung cancer treated by radiation with or without chemotherapy extracted from 39 patients included in three prospective clinical trials (RTEP1, NCT01261585; RTEP2, NCT01261598; RTEP4, RECF0645). In this study, the $A_X \cap R_{40}/A_X$ indices between PET_A and PET_R scans at the time of recurrence showed good agreement (values between 0.60 and 0.80) for A_X SUVmax thresholds between 70% and 90%. Good to excellent overlap fractions (0.60–0.93) were also obtained for the volumes delineated on PET_A with SUVmax thresholds between 30% and 60%, whereas $A_{70} \cap R_{90}/A_{90}$ was calculated at 0.56[14].

3.3.3. Oesophageal cancer

In a small cohort of 8 oesophageal cancers, Lu et al. reported a lack of performance of pretreatment FDG PET/CT to identify the residual metabolically active volumes. On average, less than 60% of the R_X was included in the original A_X while the Dice overlap between the two was even lower at 37%[17].

On the contrary in a cohort of 98 consecutive patients, Calais et al. reported good agreement (values between 0.60 and 0.80) in overlap fraction between A_X and R_{40} for threshold of 30 to 60% in the 35 patients with local recurrence (PET in treatment position). Likewise, good to excellent overlap fraction (0.61-0.89) between A_X and R_{90} for threshold of 30 to 60% were reported (Fig. 4). Authors also proposed a 60% SUVmax threshold on PET_A to delineate high fluorodeoxyglucose uptake areas on pretreatment PET/CT for dose escalation target volume[16].

3.3.4. Rectal cancer

In a series of 24 out of 28 residual disease of locally advanced rectal cancer treated by chemoradiotherapy, van den Bogaard et al. proposed a 50%SUVmax threshold on pretreatment FDG-PET/CT to define the hotspot for a potential dose-escalation. Indeed, they showed in their SUV-volume-histograms approach that the residual voxel fraction after non-rigid registration was $70.6 \pm 5.6\%$ when pretreatment fluorodeoxyglucose uptake was greater than 50% of SUVmax, unlike $51.1 \pm 6.7\%$ otherwise [18].

3.4. Prognostic significance

As a secondary objective, several studies have assessed the prognostic significance of A_x to predict local recurrence. Chaput et al. found that mean A_{40} was significantly higher in subsequently relapsing patients than in locally controlled patients with head and neck squamous cell carcinoma (10.4 cm^3 vs. 5.2 cm^3 , $P=0.002$)[10]. In another series conducted on head and neck cancer, Legot et al. confirmed that median 40%SUVmax metabolic tumour activity on baseline PET_A was significantly higher in patients with local recurrence than in those achieving a complete response (23.5 cm^3 vs. 8.9 cm^3 , $p=0.0005$)[11]. Finally, Calais et al. reported in their cohort of oesophageal tumours that A_{40} was significantly predictive of local recurrence ($P=0.024$) [16].

4. Discussion

Biology-guided radiation therapy currently represents one of the major development strategies of radiotherapy. Beside others biomarkers like hypoxia, fluorodeoxyglucose standardized uptake value is known to be significantly correlated with different histopathological parameter, especially with average nucleic area and can therefore be used as biological marker in this setting[20]. The so-called “dose-painting” radiotherapy allows indeed for a heterogeneous delivery of radiation within the tumour volume by targeting these biological target volumes defined by functional imaging to overcome radioresistant intratumoral subregions [21]. It is therefore crucial to be able to identify accurately and reliably these subvolumes.

Most of the studies included in this review focused on lung cancer. All authors highlight the interest of pretreatment PET/CT to define target areas for dose escalation based on fluorodeoxyglucose hotspot, but differed on the percentage of maximum standardized uptake value threshold applied for biological target volumes delineation. Aerts et al. firstly suggested a 50%SUVmax threshold for delineation on PET_A because the results of $OF(A_{50} \cap R_{90})$ were higher than 70% in their retrospective analysis of 16 out of 39 local recurrence of non small cell lung cancer [12]. They confirmed this threshold in a prospective series showing that pretreatment high fluorodeoxyglucose uptake area A_{50} had an overlap fraction of 68% within the residue R_{90} [13]. Shusharina et al. were also in accordance with these results but only tested one threshold on PET_A (40%SUVmax) and PET_R (80%SUVmax) [15]. However, in a

large population extracted from three prospective clinical trials (RTEP1, RTEP2, RTEP4), Calais et al. found that the baseline PET subvolume defined with the 70% SUVmax threshold was an acceptable choice for dose escalation. By combining their results, they argued this choice to avoid missing the hotspot of recurrence (OF and $A_{70} \cap R_{90} / R_{90}$ index > 51%) and limit the irradiation of areas at a low risk of relapse (OF and $A_{70} \cap R_{40} / A_{70}$ index > 70%)[14]. With this hypothesis, the same team has recently already assessed the feasibility of FDG PET-guided dose escalation with intensity-modulated radiotherapy in 21 lung cancer (RTEP5 trial, NCT01576796)[22]. In their scenario with boost to A_{70} fluorodeoxyglucose hotspot, the mean dose to planning target volume was 72.5 ± 0.25 Gy and the dose/volume constraints to organ at risk were respected.

Between the two series conducted on oesophageal cancers, only Lu et al. really concluded to a lack of interest of fluorodeoxyglucose hotspot approach for radiotherapy dose escalation[17]. But these affirmations were based on the results from a retrospective small cohort analysis (n=6). On the contrary with a rigorous methodology, Calais et al. showed in 98 consecutive patients with oesophageal cancers that pretreatment FDG-PET/CT can identify the metabolically residual active areas and also proposed a 60% SUVmax threshold to delineate target volumes for dose escalation [16]. Concerning other digestive cancer, van den Bogaard et al. also confirmed the potential role of pretreatment FDG-PET/CT in rectal cancer to identify post-treatment local recurrence, even if the calculation of overlap was not strictly comparable with the other study. In fact, they used a SUV-volume-histograms approach in calculating the residual voxel fraction but proved that 70.6% of the voxels higher than 50% SUVmax on PET_A were still metabolic in the residual tumor on PET_R [18].

The rationale for applying the “hotspot” concept to HNSCC relies on the overlap of the recurrence sites with the pretreatment biological target volume. Soto et al. reported that local recurrence was included in the pretreatment fluorodeoxyglucose biological target volumes in eight out of nine patients after radiotherapy [23]. Nevertheless, only moderate agreements of $OF(A_{40} \cap R_x)$ after rigid registration of images were found in the two retrospective cohorts of head and neck squamous cell carcinoma [10,11]. One possible explanation is that patients were not scanned in the same position, without radiotherapy head support or thermoplastic mask. Moreover, unlike other above-mentioned cancers, weight loss and post-therapeutic tissue distortions in head and neck squamous cell carcinoma can affect anatomical landmarks, making more difficult the registration process. Previously, Due et al. underlined the necessity of an elastic registration in a series of 21 out of 39 head and neck squamous cell carcinoma local recurrence originated inside initial fluorodeoxyglucose positive volume[24]. Furthermore, they determined the overlap between PET_A -gross tumour volume segmented on PET_A and recurrence-gross tumour volume segmented on the CT but not on the PET_R . In a prospective study in progress conducted by our team (with Chaput et al. population as a control cohort), preliminary analysis demonstrated a improvement of OF and $A_x \cap R_x / R_x$ index ($x= 30\%$ to 50% SUVmax) by using an elastic registration method and by acquiring PET_A and PET_R in the same radiotherapy position

(moderate to good agreements ranged from 0.41 to 0.64)[25]. Finally, whereas textural analysis on pretreatment FDG-PET/CT has already been demonstrated as a prognostic factor of head and neck squamous cell carcinoma [26], Beaumont et al. recently proposed to use this approach to predict local recurrence sites. They showed that 15 parameters extracted from a voxel to voxel analysis, combining radiomics and spatial location, allowed better predicting the gross tumour volume failure than a regional analysis, with a median area under the receiver-operating curve of 0.71[27].

In the present review, a sole study used a deformable registration method for image analysis. Rigid registration method can be effective in brain registration, as the internal structures are fixed in regards to the cranial vault[28]. This is not applicable in other anatomical areas. Rigid registration based on bone mutual information can be effective when the organs have restricted motions (i.e. oesophagus). On the contrary, rigid registration can lead to important shifts due to motions or organ filling (i.e. lung, head and neck squamous cell carcinoma, rectum). Because respiratory motions amplitude are higher in lower parts of lungs compared to apex, a rigid registration will never manage to register the whole lungs[29]. Four-dimensional PET/CT acquisitions could be a key, but it has to be available and planned [30]. Non-rigid registration could offer a great alternative as it is just image processing. Regarding head and neck squamous cell carcinoma, three-axis rotational moves can be operated between the two time points PET/CT. That gives to rigid registration low efficiency and to non-rigid registration a big potential. But this kind of registration has an impact on pixels value. Thus, more studies have to be conducted to test the integrity of quantitative parameters measured on deformed coregistered PET images[31].

For delineation of FDG tumour uptake on PET_A and PET_R , majority of studies (eight out of nine) have tested fixed absolute standardized uptake value and/or relative percentage of maximum standardized uptake value thresholds. This procedure remains a simple measurement easily accessible routinely using tools available in softwares of different vendors. Only van den Bogaard et al. used an adaptive threshold method based on signal-to-background [32] that has already shown an added value compared to cancers clinical characterization alone [33,34]. However, this technique remains more tedious to implement and requires a PET calibration phase. Nonetheless, combinations of thresholds could lead to overestimation or underestimation of overlaps and others PET segmentation methods, like automatic approaches should also be tested in the near future. In fact, several studies have suggested that gradient-based method[35] best estimates the true tumour volume in non small cell lung cancer or head and neck squamous cell carcinoma compared to standardized uptake value -based method[36,37]. The fuzzy locally adaptive Bayesian (FLAB) method is also an interesting model that has showed an improvement of metabolic tumour volume delineation of lung or oesophageal lesions [38-40].

As a secondary objective, several studies showed that initial metabolic tumour volume A_x delineated on PET_A was significantly higher in local relapse of head and neck squamous cell carcinoma or oesophageal cancer than in controlled disease. These results are also consistent with literature [40-42].

Finally, literature mainly underlined perspective in assessing tumour hypoxia that is a well-known factor for radioresistance. Lee et al. have already investigated targeting fluoromisonidazole volume in patients with head and neck squamous cell carcinoma [43,44]. Nevertheless, Thureau et al. showed that intensity-modulated radiotherapy dose-painting with pretreatment fluoromisonidazole PET/CT provides non small cell lung cancer radiotherapy plan matching with dose/volume objectives and organs at risk tolerance [22]. Finally, in the same trial, patients with fluoromisonidazole positive scan receiving a radiotherapy boost (70 to 86Gy) tend to have a better overall survival (median 26.5 vs. 15.3 months, $P = 0.71$)[45].

In conclusion, fluorodeoxyglucose hotspots-guided radiotherapy may allow dose escalation in respecting a robust methodology (treatment position, coregistration method, four-dimensional PET) and deserves investigation within prospective clinical trials powered for outcome. Further study are also needed to find a consensus on tumour delineation method in PET. Besides gastrointestinal, lung and head and neck cancer, other tumours types should also be considered, like cervix tumours, a work under progress at our institution.

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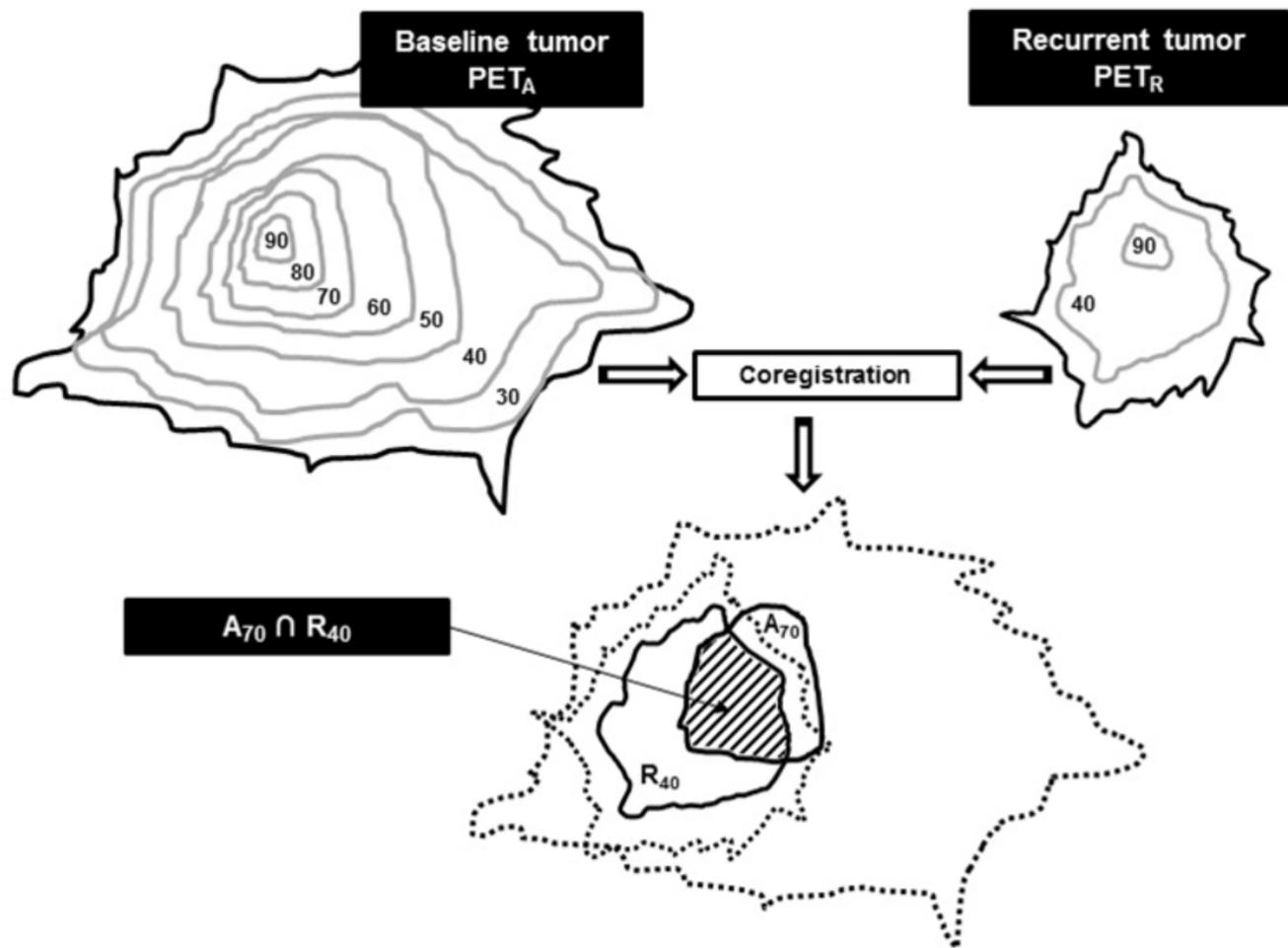
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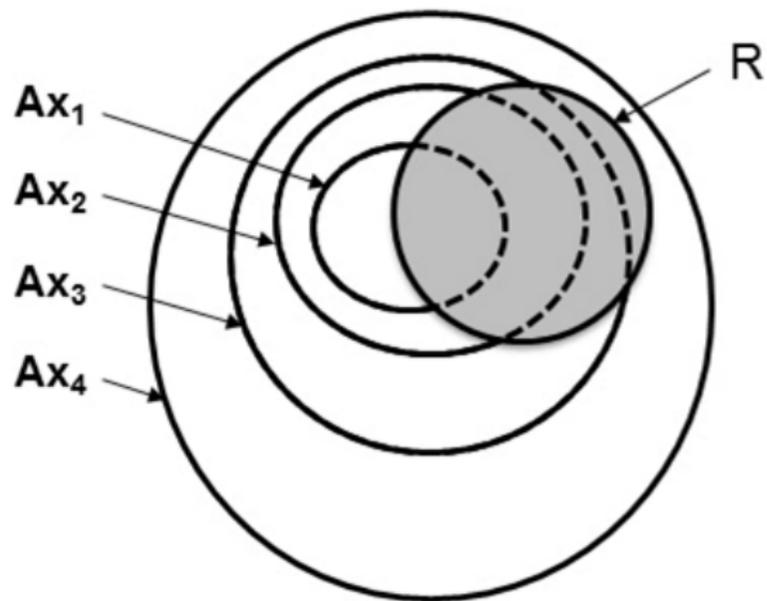
Figure 1. Fluorodeoxyguucose hotspots-guided radiotherapy for cancer local relapse: typical A_{70} and R_{40} subvolumes overlapping estimation after coregistration and reports. PET: positron-emission tomography; A_x : volumes of interest on baseline tumour; R_x : relapse subvolumes; numbers indicate the maximum standardized uptake value thresholds in percentage.

Figure 2. Fluorodeoxyguucose hotspots-guided radiotherapy for cancer local relapse: study flow for scenario of PET_A and PET_R subvolume comparisons. Indices of common volume ($A_x \cap R_x$) with A referring to staging FDG-PET/CT and R to FDG-PET/CT at recurrence. FDG: fluorodeoxyglucose; PET: positron-emission tomography; CT: computed tomography.

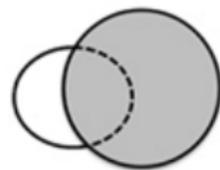
Figure 3. FDG hotspots-guided radiotherapy: example of a 45-years-old woman with an oropharyngeal head and neck squamous cell carcinoma T4N2bM0. PET_A (left) and PET_R (right) were not scanned in treatment position and were coregistered with a rigid method. Overlap fraction (A_{70} , R_{40}) and (A_{70} , R_{90}) index were calculated respectively at 0.69 and 0.96. PET: positron-emission tomography; A_x : volumes of interest on baseline tumour; R_x : relapse subvolumes; numbers indicate the maximum standardized uptake value thresholds in percentage. Used with permission from Chaput et al. [10].

Figure 4. Fluorodeoxyguucose hotspots-guided Taradiotherapy for cancer local relapse: example of a 59-years-old woman with an oesophageal squamous cell carcinoma $T_xN_xM_x$. PET_A (left) and PET_R (right) were scanned in treatment position and were coregistered with a rigid method. Overlap fraction (A_{60} , R_{40}) and (A_{60} , R_{70}) index were calculated respectively at 0.X and 0.X. PET: positron-emission tomography; A_x : volumes of interest on baseline tumour; R_x : relapse subvolumes; numbers indicate the maximum standardized uptake value thresholds in percentage. Used with permission from Calais et al. [16].





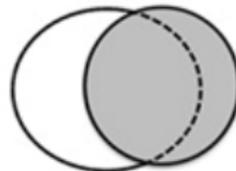
Ax_1



- $\frac{Ax_1 \cap R}{Ax_1} \approx 50\%$

- $\frac{Ax_1 \cap R}{R} \approx 20\%$

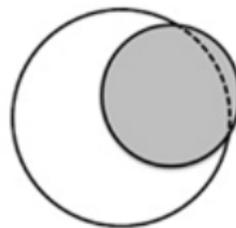
Ax_2



- $\frac{Ax_2 \cap R}{Ax_2} \approx 40\%$

- $\frac{Ax_2 \cap R}{R} \approx 70\%$

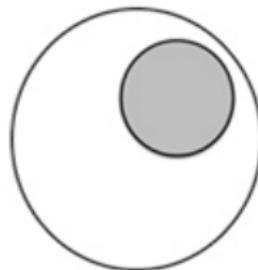
Ax_3



- $\frac{Ax_3 \cap R}{Ax_3} \approx 30\%$

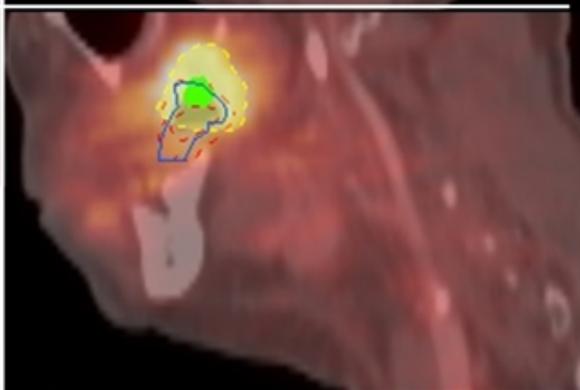
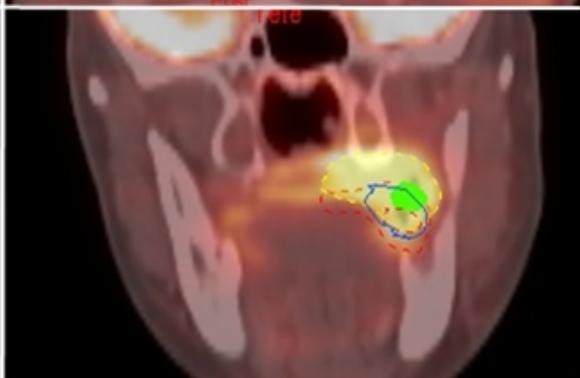
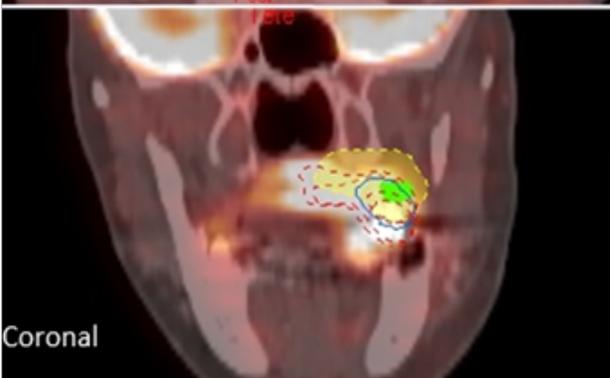
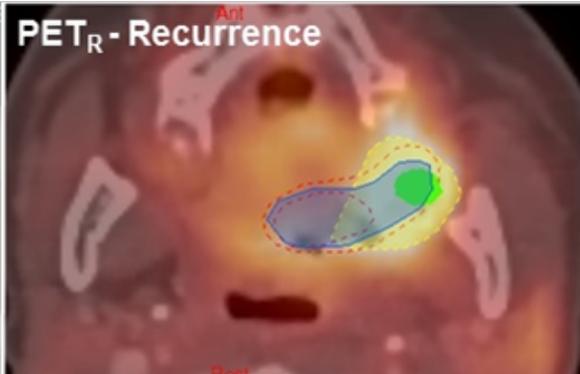
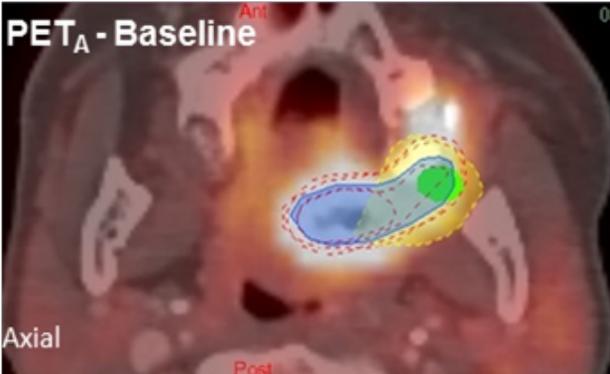
- $\frac{Ax_3 \cap R}{R} \approx 90\%$

Ax_4



- $\frac{Ax_4 \cap R}{Ax_4} \approx 15\%$

- $\frac{Ax_4 \cap R}{R} \approx 100\%$



 **A₅₀ : Initial Sub-Volume 50% SUVmax**

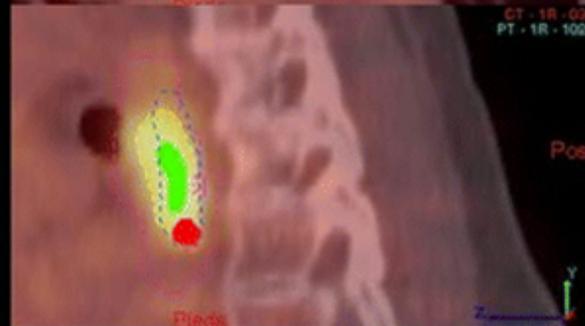
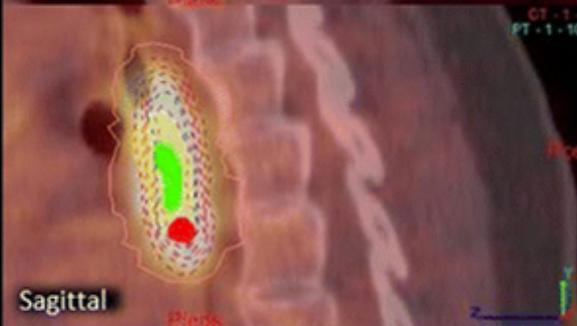
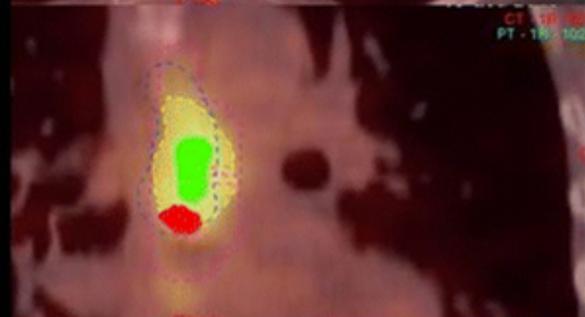
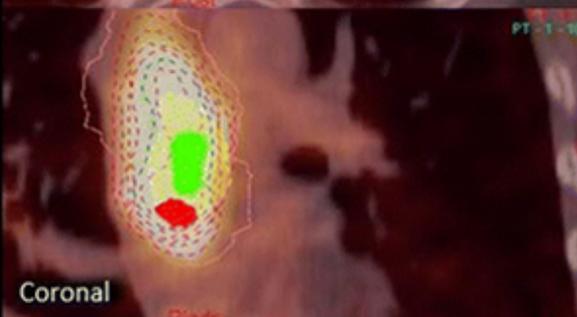
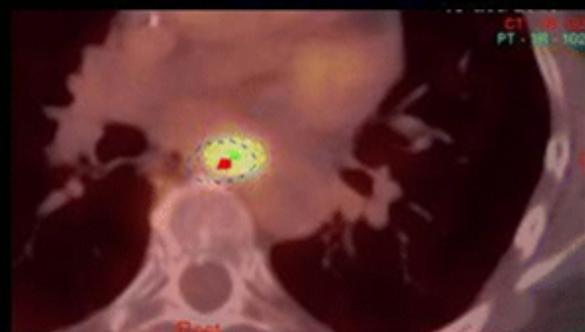
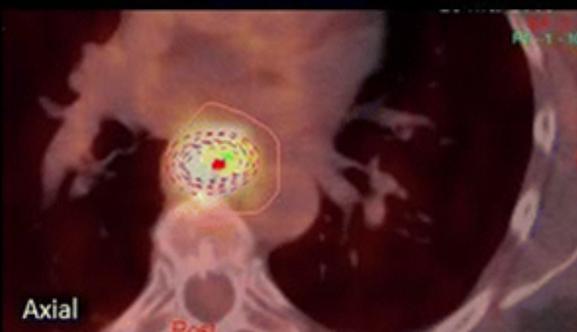
 **A_x : Multiple Initial Sub-Volumes with different SUVmax thresholds**

 **R₄₀ : Relapse MTV 40% SUVmax**

 **R₇₀ : Relapse Hotspot 70% SUVmax**

BASELINE

RECURRENCE



 A_{70} : Initial Volume 70% SUVmax

 A_{90} : Initial Hotspot 90% SUVmax

 R_{40} : Relapse MTV 40% SUVmax

 R_{90} : Relapse Hotspot 90% SUVmax

Table 1. Fluorodeoxyglucose hotspots-guided radiotherapy for cancer local relapse study characteristics.

Study	Tumour location	Study design	Population (local recurrence)	Sex : M/F	Age (y) [range]
Aerts et al., 2009 [12]	Lung	Retrospective	55 (22)	39/16	65.4 [44-83]
Van den Bogaard et al., 2011 [18]	Rectum	Retrospective	28 (24)	17/11	66±11
Aerts et al., 2012 [13]	Lung	Prospective	12 (7)	NR	66.2±9.5
Shusharina et al., 2014 [15]	Lung	Prospective	61(19)	NR	NR
Calais et al., 2015 [14]	Lung	Prospective*	39 (17)	31/8	58 [39-77]
Calais et al., 2015 [16]	Oesophagus	Prospective*	98 (35)	81/17	63±11
Lu et al., 2015 [17]	Oesophagus	Retrospective	20 (6)	18/2	64
Chaput et al., 2017 [10]	Head and neck	Retrospective	72 (19)	55/17	61.0±11.4
Legot et al., 2018 [11]	Head and neck	Retrospective	94 (38)	80/14	59.2±8.7

* post-hoc retrospective analysis in a cohort of patients included a prospective clinical trials

Table 2. Fluorodeoxyglucose hotspots-guided radiotherapy for cancer local relapse: image analysis.

Study	A _x delineation	R _x delineation	Indices	Treatment position	Registration	Overlap results	Suggested threshold
Aerts et al., 2009 [12]	A ₃₄ , A ₄₀ , A ₅₀ , A ₆₀ , A ₇₀	R ₇₀ , R ₈₀ , R ₉₀ R _{>2.5} , R _{>5}	OF	Yes	Rigid	OF(A _x ∩R _x) > 0.6 for A ₃₄ to A ₆₀ ; R ₇₀ to R ₉₀ OF(A ₅₀ ∩R ₉₀)= 0.71	50%SUVmax
Van den Bogaard et al., 2011 [18]	% SUVmax defined by stereotactic body radiation method		Residual voxel fraction (VF)	Yes	Non rigid	VF = 70.6% vs. 51.1%	50%SUVmax
Aerts et al., 2012 [13]	A ₃₄ , A ₄₀ , A ₅₀ , A ₆₀ , A ₇₀	R ₇₀ , R ₈₀ , R ₉₀ R _{>2.5} , R _{>5}	OF	Yes	Rigid	OF(A _x ∩R _x) > 0.55 for A ₃₄ to A ₆₀ ; R ₇₀ to R ₉₀ OF(A ₅₀ ∩R ₉₀)= 0.68	50%SUVmax
Shusharina et al., 2014 []	A ₅₀	R ₈₀	OF	Yes	Rigid	OF(A ₅₀ ∩R ₈₀) = 0.63 at W2 OF(A ₅₀ ∩R ₈₀) = 0.63 at M3	50%SUVmax
Calais et al., 2015 [14]	A ₃₀ , A ₄₀ , A ₅₀ , A ₆₀ , A ₇₀ , A ₈₀ , A ₉₀	R ₄₀ , R ₉₀	Dice, Jaccard, OF, (A _x ∩R _x /A _x), (A _x ∩R _x /R _x)	Yes	Rigid	A ₇₀ ∩R ₄₀ /A ₇₀ = 0.67 A ₇₀ ∩R ₉₀ /A ₉₀ = 0.56	70%SUVmax
Calais et al., 2015 [16]	A ₃₀ , A ₄₀ , A ₅₀ , A ₆₀ , A ₇₀ , A ₈₀ , A ₉₀	R ₄₀ , R ₉₀	Dice, Jaccard, OF, (A _x ∩R _x /A _x), (A _x ∩R _x /R _x)	Yes	Rigid	OF(A ₆₀ ∩R ₄₀) = 0.60 OF(A ₆₀ ∩R ₉₀) = 0.61	60%SUVmax
Lu et al., 2015 [17]	A _{>2.5}	R _{>2.5}	Dice	No	Rigid	A _{2.5} ∩R _{2.5} /R _{2.5} = 0.6 Dice = 0.37	
Chaput et al., 2017 [10]	A ₃₀ , A ₄₀ , A ₅₀ , A ₆₀ , A ₇₀ , A ₈₀ , A ₉₀	R ₄₀ , R ₉₀	Dice, Jaccard, OF, (A _x ∩R _x /A _x), (A _x ∩R _x /R _x)	No	Rigid	OF(A ₅₀ ∩R ₄₀) = 0.43 OF(A ₄₀ ∩R ₇₀) = 0.45	50%SUVmax
Legot et al., 2018 [11]	A ₃₀ , A ₄₀ , A ₅₀ , A ₆₀ , A ₇₀ ,	x R ₄₀ , R ₉₀	Dice, Jaccard, OF,	No	Rigid	OF (A _x ∩R ₄₀) > 0.35 for A ₃₀ to A ₆₀	

	A_{80}, A_{90}		$(A_x \cap R_x / A_x), (A_x \cap R_x / R_x)$				
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SUVmax: maximum standardized uptake value; OF: overlap fraction; A_x : volumes of interest on baseline tumour; R_x : relapse subvolumes; numbers indicate the maximum standardized uptake value thresholds in percentage.