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Original Research Article

Role of 18F-choline and 18F-fluorodeoxyglucose positron emission tomography in combination with magnetic resonance imaging in brachytherapy planning for locally advanced cervical cancer: A pilot study

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ABSTRACT

Background and purpose: This pilot study aims to describe the advantages of combining metabolic and anatomic imaging modalities in brachytherapy (BT) planning for locally advanced cervical cancer (LACC) and to evaluate the supplementary value of Fluoro(F)-Choline positron emission tomography/computed tomography (PET/CT) in comparison to 18F-fluorodeoxyglucose (FDG) in this setting.

Materials and methods: A prospective cohort of six patients with LACC was included in this study. Each patient underwent BT planning CT scan, magnetic resonance imaging (MRI), and both FDG and F-Choline PET/CT scans on the same day, with BT applicators in place. Patients were treated according to the standard of care. Metabolic target volumes (TV) were generated retrospectively and compared with the anatomic volumes using Dice coefficients and absolute volume comparison.

Results: The threshold at which the metabolic and anatomic volumes were the most concordant was found to be 35% maximum standardized uptake value (SUV max) for both PET/CT scans. Amongst the six patients in this cohort, three in the FDG cohort and four in the F-Choline cohort were found to have more than ten percent ratio of excess (increase) in their MRI gross tumor volumes (GTV) when incorporating the metabolic information from the PET/CT scans. However, no significant changes were needed in the high risk-clinical target volumes (CTVHR) for both PET tracers.

Conclusions: FDG and F-Choline PET/CT scans can substantially modify the BT GTV on MRI, without affecting the CTVHR. F-Choline is potentially more informative than FDG in assessing residual TV, particularly in cases with significant post-radiation inflammatory changes.

1. Introduction

Brachytherapy (BT) is an integral part of curative chemoradiation for locally advanced cervix cancer (LACC). The last 2 decades have brought important changes in BT planning by incorporating 3D-imaging and adaptive treatment concepts. The Groupe Européen de Curiethérapie (GEC) and the European SocieTy for Radiotherapy & Oncology (ESTRO) Committee has played a major role in implementing these changes worldwide [1,2]. Magnetic resonance imaging (MRI) is considered the gold standard imaging modality for cervical cancer brachytherapy due to its superior soft tissue resolution. It allows for dose escalation and improved local control in LACC with minimal additional toxicity [1–3].

During and immediately after external beam radiotherapy (EBRT), the persistence of heterogeneous T2-weighted and contrast enhancement areas may represent tumor residue, inflammation, necrosis, or radiation fibrosis [4]. In this regard, 2-[18F]-fluoro-2-deoxy-D-glucose

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(FDG) – positron emission tomography/computed tomography (PET/CT) has shown greater specificity than MRI in detecting residual tumor by providing metabolic information alongside anatomical details [4]. Several studies have explored the role of FDG PET/CT in brachytherapy planning, either with or without MRI, demonstrating its feasibility and accuracy in target definition [5–10,11].

On the other hand, 18F-Fluorocholine (F-Choline), a PET radiotracer commonly used in other cancers has received limited attention in cervical cancer research [12,13]. F-Choline offers advantages such as early tumor fixation, a prolonged half-life, and elimination primarily through the digestive system, which may be beneficial for cervix cancer located near the bladder.

While the potential benefits of combining MRI with metabolic imaging remain uncertain, no prior studies have investigated the added value of incorporating both F-Choline and FDG PET/CT alongside MRI in BT planning for LACC. This pilot study aims to explore the potential benefits of using both radiotracers and to assess any additional advantages of F-Choline PET/CT compared to FDG PET/CT within this specific context.

2. Materials and methods

2.1. Ethics and patient selection

This study was approved by the local ethics committee (#18.097). A prospective cohort of 6 patients with LACC was recruited from June 2019 to April 2020. All patients consented to participate. Inclusion criteria were adult patients with FIGO stage IB2 to IVA cervix cancer planned for treatment with concurrent weekly cisplatin and radiotherapy with intracavitary or interstitial/intracavitary brachytherapy; squamous cell, adenocarcinoma or adenosquamous histology; initial tumor size on MRI > 4 cm; Body Mass Index < 30 kg/m^2 and ECOG 0–2. Patients were excluded if they had diabetes, previous pelvic radiotherapy, hysterectomy, inflammatory bowel disease, contraindication to MRI, and allergy to gadolinium, FDG or F-Choline. Demographic characteristics including age, ECOG, FIGO stage, histological type and response to treatment were collected.

2.2. Study protocol

Two metabolic studies, F-Choline and FDG PET/CT, and multiparametric MRI were performed before the start of EBRT. The time interval between F-Choline and FDG PET/CT had to be less than a week in order to have comparable tumor volumes. All these exams were repeated prior to the first brachytherapy fraction. During brachytherapy session, the applicator, VeneziaTM or ViennaTM (Elekta Brachytherapy, Veenendaal, The Netherlands), was inserted under abdominal ultrasound guidance, and then stabilized using the applicator clamp with base plate (Elekta Brachytherapy, Veenendaal, The Netherlands). Then, all images were acquired sequentially in the same day with the applicator in place: CT scan followed by MRI, then by both PET/CT scans (FDG and then Choline). Both PET CT images were used for the study purposes only, as no brachytherapy planning was based on those images. PET Imaging data were retrospectively collected and analyzed to answer the study questions.

Treatment was done according to the standard protocol for LACC, following the GEC-ESTRO recommendations [1,2]. Patients were treated with concurrent chemoradiation, consisting of intensity-modulated radiation therapy (IMRT) with weekly cisplatin, and utero-vaginal HDR-brachytherapy that started towards the 4th week of EBRT. Total dose planning aims including EBRT plus BT were: high-risk clinical target volume (CTVHR) D90 > 85 Gy, gross tumor volume (GTV) D98 > 90 Gy, CTVHR D98 > 75 Gy, intermediate-risk clinical target volume (CTVIR) D98 > 60 Gy. Organs at risk (OAR) dose limits were D2cc < 90 Gy for the bladder and <75 Gy for the rectum, sigmoid and small bowel. All doses were calculated in equivalent dose in 2 Gy fractions (EQD2), using α/β of 10 for target volumes and α/β of 3 for OAR.

2.3. Image acquisition, co-registration and contouring

Comprehensive information regarding simulation, image acquisition protocols, co-registration process, and contouring can be found in the supplementary material, providing detailed explanations.

2.4. Comparison of metabolic and anatomic volumes

Comparison of the correlation between anatomic and metabolic BT volumes was done using the Dice coefficient (defined as quotient of similarity) calculated with MIM version 6.6 (MIM Software Inc., Cleveland, OH), and through the analysis of numerical values of the absolute volumes (regardless of their respective overlap) combined with the visual interpretation (Eclipse version 13 (Varian Medical Systems). We also used a ratio of the excess metabolic volume (not overlapping with the MRI volumes) over the MRI volumes (either GTV or CTVHR) to assess the amount of volume that is required to be added to the anatomic volumes to account for the functional uptake. This ratio is referred to as ratio of excess GTV or CTVHR for both PET scans. For example, the ratio of excess GTV for FDG is the volume of FDG uptake (cm3) minus the MRI GTV (cm3), divided by the MRI GTV (cm3). Fig. 1 shows an example of the excess metabolic volume for GTV. The goal is to quantify the ratio (%) of the FDG/F-Choline tumor volume that has been added to the MRI GTVs, after the integration of data obtained from metabolic imaging (FDG and F-Choline), in order to assess the impact of the use of PET scans and in particular F-Choline in the planning of brachytherapy for locally advanced cervical cancer. The number of patients whose contours need to be substantially changed was also reported. We prefixed a threshold of 10 % for the ratio of required changes to both MRI GTVs and CTVHRs to be considered as clinically significant in our pilot study.

3. Results

A total of six patients are included in the current study. Patient characteristics are reported in Table 1. During follow-up, all patients had complete response locally. However, two patients developed distant metastases.

Median pre-EBRT MRI, FDG and F-Choline GTVs were 57.8 (range 15.4–227.2), 39.8 (range 12.9–180.6) and 61.5 (range 16.3–188.5) cc, respectively. Fig. 2 shows the relative FDG/F-Choline GTVs as compared to the MRI GTVs. The threshold where the metabolic and anatomic volumes were the most concordant (closest to a ratio of 1) was found to be 35% SUVmax for both FDG and F-Choline PET/CT. Fig. S1 (supplementary material) shows the progression of the SUVmax values before and after EBRT for both PET/CT radiotracers.

An attempt to apply the same threshold in BT PET/CT scans resulted in a large discrepancy between the anatomic and metabolic volumes that were up to 5 times bigger than the correspondent anatomic volumes at 35% SUVmax (Fig. 3). Also, we were unable to find a single universal threshold that works for all cases like in the pre-EBRT setting. The alternative method of thresholding, consisting in visual assessment by the nuclear medicine physician who selected a customized threshold for every single case, resulted in more accurate results. BT volume analysis, using the latter method, showed that absolute metabolic volumes were smaller than anatomic ones. Median MRI, FDG and F-Choline GTVs were 17.42 cc (range 0.2–48.7), 10.2 cc (range 0.74–17.9) and 6.65 cc (range 0.7–24.8) cc, respectively. The median MRI CTVHR was 32.45 cc (range 7.7—71.3) as shown in Table 2.

Fig. 1 shows an example of contours on MRI and both PET/CT scans. Fig. 4 shows slices of a T2 sequence and an F-Choline PET scan. The GTV and CTVHR contours are shown on the T2 images and the processed region of interest on the PET scan.

All but one patient presented an interpretable residual FDG uptake in

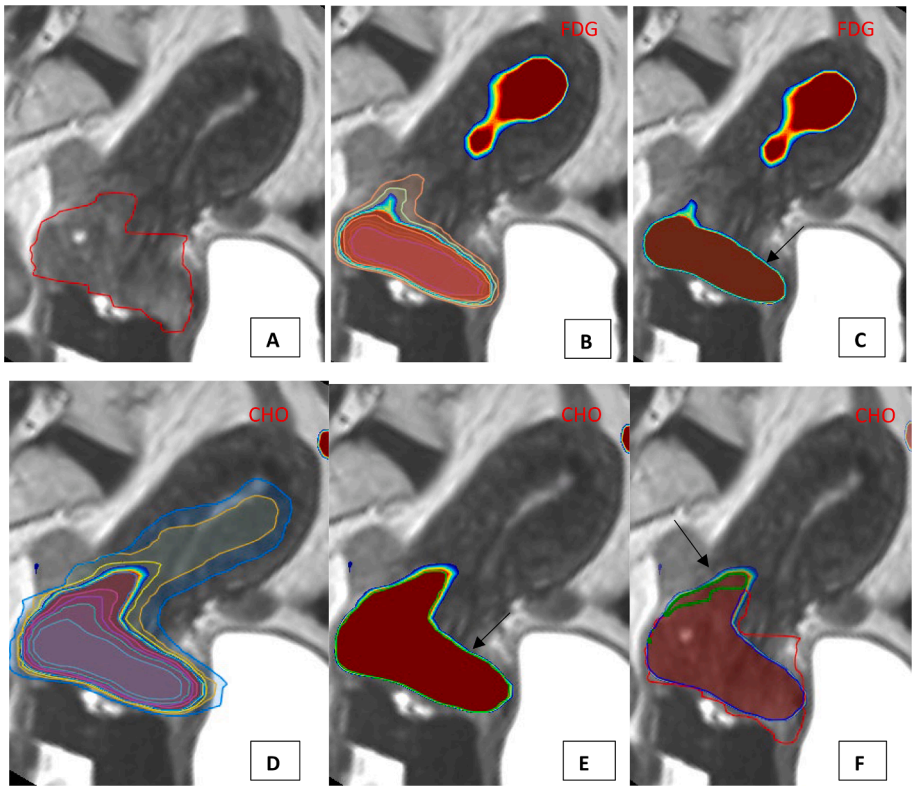

Fig. 1. Example of contours on MRI and both PET/CT scans for patient number 4. A) MRI GTV (red). B) FDG PET/CT-based contours with automatically set threshold. C) FDG PET/CT-based contour chosen by the physician (arrow). D) Choline PET/CT-based contours with automatically set threshold. E) Choline PET/CT-based contour chosen by the physician (arrow). F) Excess metabolic volume for GTV (GTV in red, Choline PET/CT-based contour chosen by the physician in blue, excess metabolic volume in green and arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Patient demographics.

Patient number	Age	ECOG	FIGO 2018 stage	Histological type	Extent of disease at time of brachytherapy
1	77	1	IIB	SCC	65% of initial volume, left proximal parametrial and vaginal involvement.
2	60	1	IIB	SCC	27% of initial volume, minimal right parametrial and vaginal involvement.
3	49	1	IIIC2 (IIB locally)	SCC	22% of initial volume, bilateral proximal parametrial involvement.
4	65	1	IIIC1 (IIIB locally)	SCC	35% of initial volume, upper uterine corpus and bilateral proximal parametrial involvement.
5	55	1	IIA2	SCC	1% of initial volume, minimal residual cervical tumor.
6	45	1	IIIC1 (IIA2 locally)	SCC	1% of initial volume, minimal residual cervical tumor.

the tumor on FDG PET/CT. In this patient, diffuse inflammatory uptake in the background, likely related to post-external beam radiation changes, prohibited accurate visualization of FDG uptake in the tumor. However, a more precise and easily defined uptake was seen in the same patient on F-Choline PET/CT scan (Fig. S2 in the supplementary material).

Despite all our efforts to minimize internal organ motion between different imaging modalities, a small but still significant range of motion of the tumor central axis was detected. Hence, the spatial correlation between the anatomic and metabolic volumes using Dice coefficient showed poor concordance (median Dice of 0.44 and 0.32 for FDG and F-Choline PET/CT scans, respectively), thus absolute volume comparison, despite its limitations, was deemed more relevant.

The absolute excess metabolic volumes are shown in Table S1 (supplementary material).

The ratios of excess GTV and CTVHR are shown in Table 2 for both FDG and F-Choline PET/CT scans.

In this cohort of 6 patients, 3 patients in the FDG PET/CT cohort and 4 patients in the F-Choline cohort were found to have >10% in the ratio of excess for GTV when incorporating the metabolic information from the PET/CT scans (Table 2). However, no significant changes were needed in the CTVHR contours in all patients for both cohorts, as the ratio of excess based on the inclusion of metabolic information was <1.1% and <2.6% for the FDG and F-Choline PET/CT scans, respectively, which is less than the 10% predetermined threshold in our study.

A comparison between pre-EBRT and BT MRI GTVs is shown in Fig. S3 (supplementary material).

4. Discussion

PET/CT usage in brachytherapy planning is feasible, but challenges persist in target definition due to low spatial resolution and variability in lesion threshold definition. [5,14]. Different segmentation techniques have been proposed for target definition on PET/CT based on SUV threshold [14–16].

Archad et al.'s recent study found that a 30% SUVmax threshold correlated optimally with MRI volume, with excellent inter-reader agreement and minimal manual adjustment [17]. Another study examining functional and histopathologic volumes in cervical cancer found the best correlation with a threshold of approximately 40% [18]. In our study, a threshold of 35% SUVmax showed the strongest correlation between anatomic and metabolic volumes in the pre-EBRT setting.

Post-EBRT, a universal SUV cut-off value for all tumors would have

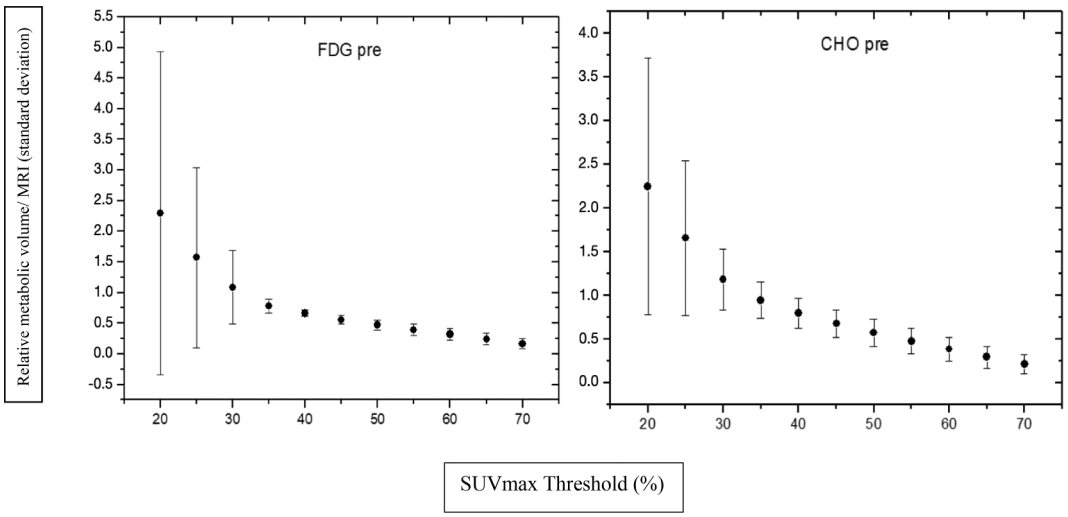

Fig. 2. Relative metabolic volume (FDG pre and Choline (CHO pre) PET/CT) in pre-EBRT versus MRI GTV represented with standard deviation.

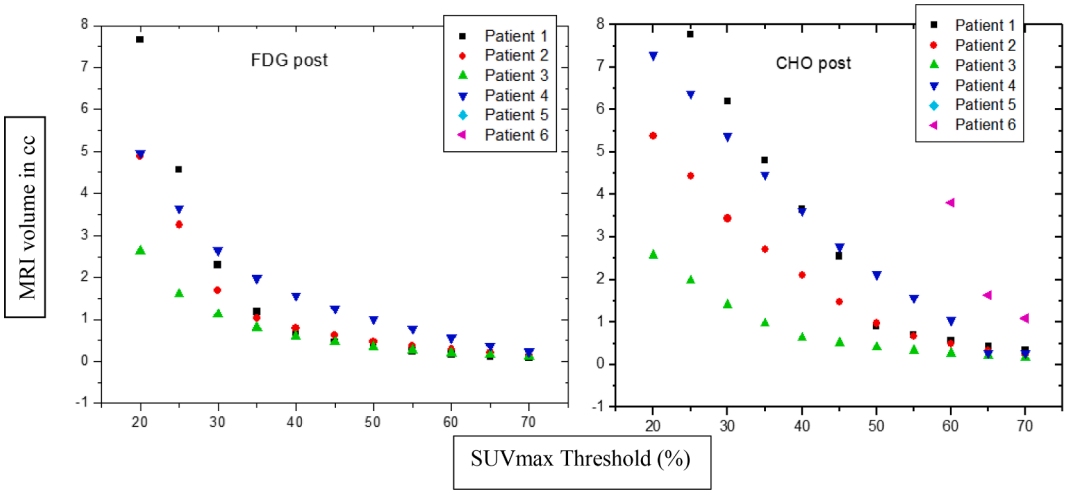

Fig. 3. BT metabolic volumes showing an attempt to apply the same threshold of 35, that was applied in pre-EBRT setting, in post-EBRT (FDG post & CHO post) resulting in a large discrepancy between the anatomic and metabolic volumes.

Table 2
Anatomic and metabolic absolute volumes and ratio of excess PET volume not overlapping with the MRI volumes (refer to Table S1 in the supplementary material for data on the absolute excess volumes).

Patient number	MRI GTV (cm^3)	CTVHR (cm^3)	FDG (cm^3)	F-CHO (cm^3)	Ratio of excess GTV for FDG (%)	Ratio of excess CTVHR for FDG (%)	Ratio of excess GTV for F-CHO (%)	Ratio of excess CTVHR for F-CHO (%)
1	12.6	19.5	4.1	4.1	3.0	0.7	2.7	1.2
2	29.0	45.4	10.2	9.2	10.0	1.1	14.5	2.6
3	48.7	65.4	17.9	24.8	0.2	0	1.8	0.3
4	22.2	71.3	17.3	15.5	23.4	0.4	41.9	0.8
5	0.2	7.7	0.7	0.8	350.0	0.3	275.0	1.3
6	0.5	13.2	NA	0.7	NA	NA	98.0	0.1
Median	17.4	32.5	10.2	6.7	10.0	0.4	28.2	1.0

yielded inappropriate volumes. However, visual assessment by the nuclear medicine physician allowed customized determination of the ideal threshold for each case, resulting in improved accuracy. These findings align with a report by Nam et al., which failed to establish a universal SUV uptake cut-off value across all cases [5]. Their study relied on visual analysis, adjusting the level and window values to discriminate between background and tumor for each patient. The median threshold value obtained was 41% SUVmax (range 23%–71%).

Our study revealed higher cut-off for both PET/CT scans (55% (range 45–65) for FDG and 65% (range 45–85) for F-Choline). Therefore, the smaller resulting metabolic volumes in 4 out of 6 patients, as compared to the anatomic GTVs (approximately 40 to 60%), could be explained by the well-established inverse relationship between the applied SUV cut-off values and the resulting metabolic volumes [18].

Despite this significant smaller metabolic volume, there is still excess FDG/F-Choline uptake not overlapping with the MRI GTVs that result in

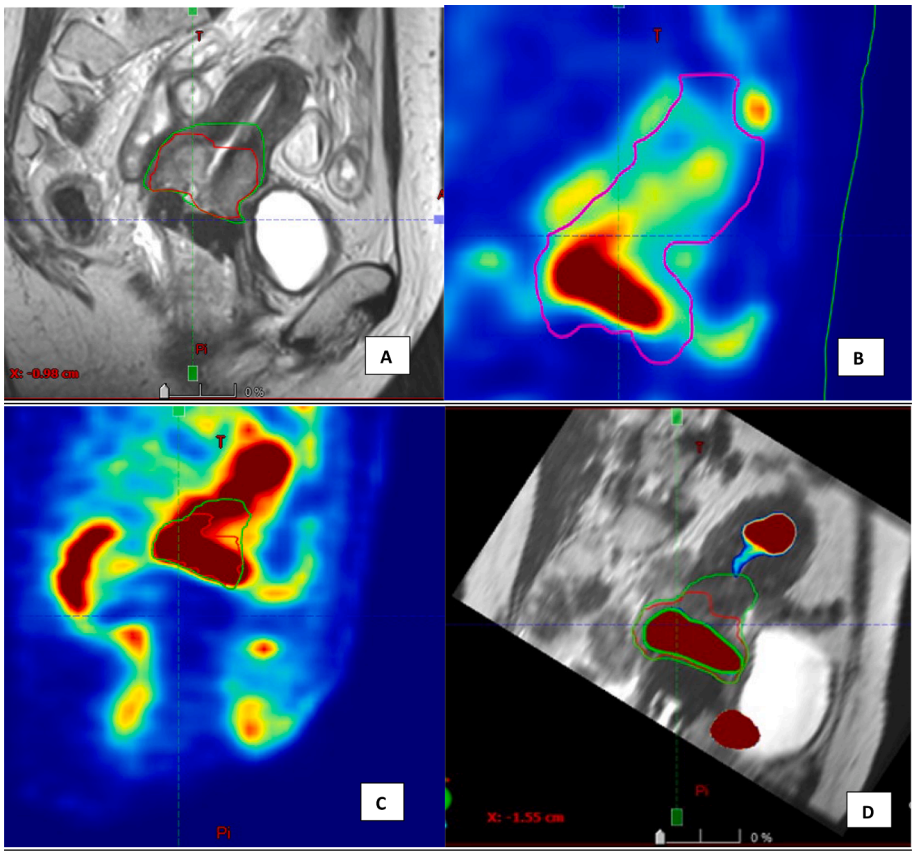

Fig. 4. Example of the contours of patient number 3. A) MRI image showing GTV (red) and CTVHR (Green). B) Choline PET image showing processed region of interest (purple). C) & D) Registration between MRI volumes and FDG image, we noted the inflammatory increased uptake inside the uterine corpus in the FDG image as compared to the Choline image. D) Automatic thresholding with emphasis on the contour chosen by the nuclear medicine physician (light green). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

significant ratio of excess when registering both imaging modalities. These changes could be explained by the improved ability of metabolic imaging to visualize residual target volumes that would have been missed by MRI alone, especially when the residual GTV signal is ambiguous [3].

The analysis of similarity coefficients (Dice) between metabolic and anatomic volumes revealed the possibility of tumor volume motion, which cannot be completely ruled out. This motion is likely attributed to shifts in tumor centers due to internal organ movement or differences in bladder filling, despite efforts for optimal registration. This effect is more pronounced in smaller BT tumor volumes. For example, the patient with the largest volume in our study had the lowest ratio of excess (0.2% and 1.8% for FDG and F-Choline PET/CT scans, respectively), while the patient with the smallest volume had the highest ratio of excess in their anatomic volume (350% and 275% for FDG and F-Choline PET/CT scans, respectively). Similar findings were reported in a study at Washington University, where MRI was found to visualize larger tumors better than smaller ones compared to FDG PET/CT. Additionally, PET/CT visualized tumor volumes differently from MRI, particularly for small tumor volumes [19]. Although the ratio of excess appears substantial in patients with small tumor volumes in our cohort, its clinical significance may be limited due to representing a small absolute volume. Therefore, adjustments to anatomic volumes based on metabolic data should be left to the discretion of the treating physician after clinical assessment. Visual assessment of the excess volume's location was performed to address this issue (refer to Table S1 in the supplementary material). Given the small sample size, larger cohorts are necessary to confirm these results statistically.

Numerous studies have explored the role of FDG PET in brachytherapy planning for LACC. One study found that combining 18F-FDG PET with multiparametric MRI reduced inter-observer variations in defining BT GTV [9]. Dynamic contrast-enhanced MRI was frequently used to modify GTV contour, particularly aiding in visualizing residual myometrial disease. Functional imaging is believed to provide more detailed information on tumor physiologic volume during brachytherapy planning, enabling potential dose escalation in areas with high residual uptake following EBRT, which may represent radiation-resistant tissues. Although multiparametric MRI sequences were acquired in our study, they were not analyzed in this preliminary report, which primarily focuses on the use of FDG and the added value of F-Choline PET/CT scans.

The high sensitivity of the FDG tracer to radiation-induced inflammatory changes poses a well-known limitation in differentiating residual tumor from inflammation in cervical cancer. Necrotic tumors may also exhibit low FDG accumulation. Additionally, physiological FDG accumulation in the bowel and bladder can hinder clear differentiation between the cervical tumor and surrounding organs, making it challenging to detect small residual lesions in cases of good response to EBRT [4]. In our series, detecting the residual FDG volume for the sixth patient was challenging due to excessive inflammatory changes, substantial bladder uptake, and a good post-EBRT tumor response. In this case, F-Choline radiotracer proved more useful, successfully distinguishing residual tumor uptake from the inflammatory background.

Choline-based PET tracers in PET/MRI applications are still in their early stages [20]. Further clinical studies with larger cohorts are necessary to establish the clinical utility of this tracer in brachytherapy planning.

This study's major limitation is the small population cohort, preventing statistical analysis. However, it serves as a pilot study to assess the feasibility of conducting such research in our department and generate preliminary results to determine the benefit of progressing to a phase II trial.

We have demonstrated the feasibility of incorporating PET/CT into the brachytherapy workflow, despite logistical challenges. Descriptive analysis of each case revealed a potential role for metabolic images in guiding and improving brachytherapy planning in LACC. While CTVHR

was minimally affected by incorporating metabolic information, BT GTV delineated on MRI was significantly impacted in 4 out of 6 cases and in 3 out of 6 cases for F-Choline and FDG radiotracers, respectively.

Notably, our visual and numerical analysis on a case-by-case basis showed smaller metabolic volumes compared to the anatomic volumes. This finding is particularly interesting in terms of dosimetric optimization through dose painting and escalation to regions with significant residual activity [21]. Increased local control in LACC is better achieved through dose escalation to the GTV [3]. As such, the EMBRACE II study protocol requires higher BT GTV dose than CTVHR [22]. PET-guided BT, alongside MRI-based planning incorporating functional imaging sequences, could identify residual active zones at risk of local relapse, enabling targeted dose escalation to these critical areas.

Confirmation of these findings would require a larger prospective study, but this pilot study demonstrated improved delineation of the residual volume by incorporating both PET/CT radiotracers, particularly F-Choline in cases with significant post-EBRT inflammatory changes and small residual volumes.

In conclusion, FDG and F-Choline PET/CT scans significantly modified the MRI GTV in 50% and 66.7% of cases, respectively. This opens up possibilities for PET-guided dose escalation, in conjunction with MRI/CT scans, targeting these biologically active regions. However, there was no significant impact on CTVHR, the primary prescription volume in cervical cancer brachytherapy planning. F-Choline PET is potentially more specific than FDG PET in identifying residual hypermetabolism, especially in the presence of substantial post-radiation inflammatory changes. Although our cohort size is limited for drawing formal conclusions, F-Choline PET/CT shows promise as a valuable tool in brachytherapy planning for LACC.

CRediT authorship contribution statement

Fadoua Rais: Formal analysis, Writing – original draft. **Karim Boudam:** Data curation, Formal analysis, Writing – review & editing. **Cynthia Ménard:** Writing – review & editing. **Marie-Claude Beauchemin:** Writing – review & editing. **Naoual Oulmoudne:** Conceptualization, Methodology. **Daniel Juneau:** Writing – review & editing. **Antoine Leblond:** Conceptualization, Methodology. **Maroie Barkati:** Conceptualization, Funding acquisition, Methodology, Data curation, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phro.2023.100467.

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