

¹⁸F-FDG PET Imaging in Posttherapy Monitoring of Cervical Cancers: From Diagnosis to Prognosis

Cervical cancer is a public health problem worldwide (1). The disease ranks second to breast cancer in incidence but accounts for the leading cause of cancer-related death among women (2). In the pretreatment setting, most oncology centers refer to the International Federation of Gynecology and Obstetrics (FIGO) recommendations for staging the disease (3). After treatment, conventional work-ups usually include a physical examination at control visits, Papanicolaou smear, tumor markers, and conventional imaging methods such as ultrasonography, CT, and MRI. However, the follow-up surveillance is not standardized and may vary considerably from one institution to another. Besides, the efficiency of routine protocols for detecting recurrences is often suboptimal, especially in asymptomatic patients (4,5). This provides an important rationale to assess the value of ¹⁸F-FDG PET in posttherapy surveillance of cervical cancers.

In the last few years, growing evidence indicates that ¹⁸F-FDG PET is feasible for the assessment of women previously treated for cervical cancers (6–16). Cumulative data from the literature in 431 patients showed that ¹⁸F-FDG PET has a mean sensitivity of 94.7% (85.7%–100%), a mean specificity of 83.7% (60%–100%), and a mean diagnostic accuracy of 87.9% (70%–97.2%) for the detection of recurrences from cervical cancers (Table 1). Moreover, metabolic imaging ap-

pears to be more sensitive and specific than the conventional work-ups, including CT and MRI.

The strength of ¹⁸F-FDG PET primarily relies on its capability to locate the disease in the entire body, thereby distinguishing a local recurrence from disseminated disease (17). As such, metabolic imaging may significantly influence the therapeutic choices in terms of pelvic exenteration ± radiation versus systemic chemotherapy ± radiation (13,16). This gives metabolic imaging a clear advantage over conventional imaging, which is usually performed with a limited field of view including the pelvis and the abdomen. Importantly, several published series showed the ability of metabolic imaging to detect clinically and radiologically unsuspected recurrences, early enough in the course of follow-up to give the patient the best chances for successful salvage therapies (15,17). This latter point is crucial in light of more efficient multimodality treatment demonstrating significant results in terms of reduced mortality and prolonged survival (18,19).

Beyond the diagnostic performances related to metabolic imaging for assessing the disease extent, however, the gynecologist needs accurate and individualized information regarding the treatment impact on the patient's survival.

Recently, Grigsby et al. showed in a large series of women with cervical cancers ($n = 152$) that any ¹⁸F-FDG uptake after the primary treatment, either at sites of persistent disease or at new sites of recurrences located outside the fields of irradiation, was the most significant predictive variable of 5-y overall survival and 5-y cause-specific survival as well (20). In other

words, in such gynecologic cancers, as observed in other types of cancers, metabolic imaging is not just a valuable diagnostic tool but it may also bring determinant prognostic information with regard to patients' outcomes (21).

In the era of health cost-savings, ¹⁸F-FDG PET may be particularly useful by selecting the most efficient therapies in patients with good prognosis, and more so by avoiding unnecessary expenses in those of women with poor prognosis. From this perspective, the study by Yen et al. (22), on pages 1632–1639 of this issue of *The Journal of Nuclear Medicine*, is an interesting contribution for optimizing the use of ¹⁸F-FDG PET in women with previously treated cervical cancers. The authors assessed the impact of ¹⁸F-FDG PET on the disease's management and the patient's survival from 2 prospective studies including 55 women with proven recurrent cervical cancers. In all patients, the relapse was confirmed either by histology or by clinical follow-up. Three main conclusions may be drawn from this study: (i) Whole-body ¹⁸F-FDG PET is confirmed as a powerful diagnostic technique for detecting a recurrent disease with an overall 84% sensitivity versus 47.9% for CT/MRI. In both situations of metastatic lesions and central or pelvic recurrent or persistent tumors, the sensitivity of metabolic imaging (89.2% and 90%, respectively) was higher than that of conventional imaging (39.2% and 80%, respectively). (ii) In nearly 65.5% of women (36/55), ¹⁸F-FDG PET modified the initial treatment plan (25% to curative intent and 75% to palliative intent). These data are in line with those published by the group from Liège in 38 patients with

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TABLE 1

Value of ^{18}F -FDG PET for the Detection of Recurrent Cervical Cancers: Cumulative Data from Literature

Reference			No. of patients	Sensitivity (%)	Specificity (%)	Accuracy (%)
Authors	No.	Year				
Park et al.	10	2000	36	100.	94.4	97.2
Sun et al.	11	2001	20	95.8*	93.7*	95*
Nakamoto et al.	12	2002	20	100.	60.	70.
Belhocine et al.	13	2002	38	100.	77.	92.
Havrilesky et al.	14	2003	28	85.7	86.7	86.2
Ryu et al.	15	2003	249	90.3	76.1	77.9
Lai et al.	16	2004	40	91.	98.	97.
			Total = 431	Mean = 94.7	Mean = 83.7	Mean = 87.9

*Results were calculated from all regions of recurrent cervical cancer detected by ^{18}F -FDG PET, including local recurrences, pelvic lymph nodes, paraortic lymph nodes, and distant metastases (46 true-positives, 2 false-positives, 30 true-negatives, 2 false-negatives).

treated cervical cancers explored by ^{18}F -FDG PET (13). Among them, 13 patients with a confirmed recurrence detected by PET had equivocal or false-negative results in the routine protocol. In 11 of 25 patients with positive PET findings (44%), metabolic imaging localized disseminated recurrences below and above the diaphragm, thereby influencing the treatment strategy from surgery \pm radiation to chemotherapy \pm radiation. (iii) When appropriately incorporated into the clinical work-up, whole-body ^{18}F -FDG PET may significantly impact the patients' outcomes. Based on a Cox proportional hazards model using multivariate analysis, 3 independent covariates were selected: (a) the patient's clinical features (symptomatic vs. asymptomatic), (b) the serum levels of tumor markers (SCC-Ag $>$ 4 ng/mL vs. SCC-Ag \leq 4 ng/mL), and (c) the initial treatment choices (surgery vs. radiation). By summing these prognostic covariates (from 0 to 3), 3 groups of patients emerged with different outcomes. Asymptomatic patients treated by surgery with a serum level of SCC-Ag \leq 4 ng/mL had the better prognosis (Cox proportional hazards ratio [HR] = 1.00). Those of patients treated by radiation who presented with clinical manifestations and serum levels of SCC-Ag $>$ 4 ng/mL had the worse prognosis (HR = 60.46). Between the 2 extreme clinical situations, patients with a covariate summing score of 2

had an intermediate prognosis (HR = 6.91).

Because ^{18}F -FDG PET is often perceived as a cost-prohibitive technique by the clinician community, the prognostic data reported by the Yen et al. (22) are critical for defining the best indications of metabolic imaging in patients with treated cervical cancers. An appropriate selection of patients based on clinical and biologic criteria during the follow-up helps indicate more logically a PET study, especially in women who may best benefit from subsequent salvage therapies and prolonged survival (score \leq 1). Interestingly, in a patient with a less favorable prognosis (score = 2), the ^{18}F -FDG PET intervention may also change the curative treatment options, thereby reducing the cancer-related mortality. Even in those of patients with a poor prognosis (score = 3), metabolic imaging may be clinically useful by reorienting the therapeutic scheme from curative to palliative, which in the end may avoid the costs and the side effects of fruitless systemic therapies. Alternatively, metabolic imaging may help select those of patients with a progressive disease, which may be included into research therapeutic protocols.

Not surprisingly, the prognostic scoring system proposed by Yen et al. (22) appears to be in line with the data reported by Bodurka-Bevers et al. from the largest cervical cancer data-

base (23). Accordingly, the detection of recurrent sites in asymptomatic patients is a key point to be considered to impact the patient's survival. Besides, the accurate assessment of recurrence patterns (i.e., local disease vs. distant metastases, nodal involvement vs. visceral dissemination) is critical for guiding the appropriate treatments in terms of salvage surgery versus chemoradiation (4).

From a research perspective, the study by Yen et al. (22) provides an important framework for the assessment of treated cervical cancers. As suggested by others, the complementary data provided by a highly sensitive *in vivo* technique such as whole-body ^{18}F -FDG PET and a highly specific *in vitro* marker such as SCC-Ag offer an attractive alternative to the routinely used protocols (17,24). Recently, the use of combined PET/CT devices was also proposed to improve the metabolic imaging accuracy (25–27)—that is, the suboptimal specificity of ^{18}F -FDG PET, especially soon after surgery or later after radiation as well as in cases of concomitant infection, may be the cause of false-positive results (9,12–15).

To optimize the clinical benefits expected from ^{18}F -FDG PET in monitoring women with cervical cancers, some issues still must be addressed: First, the adequate frequency for SCC-Ag serum measurements in parallel with the performance of ^{18}F -FDG

PET studies during the follow-up remains to be determined; second, larger controlled trials including more homogeneous groups of patients in terms of disease stages and initial treatments are still needed to refine the indications of ^{18}F -FDG PET; third, the cost-effectiveness is a key step to be considered to incorporate ^{18}F -FDG PET in a large-scale routine protocol.

Finally, there is a clinical need for improving the posttherapy monitoring of cervical cancers. Whole-body ^{18}F -FDG PET, in combination with tumor markers, may play a pivotal role in this particular indication by providing the clinician with crucial information from diagnosis to prognosis. The availability of PET/CT devices should prompt further well-designed studies for assessing the most appropriate protocols in the management of women with previously treated cervical cancers.

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