Case Report

Fused functional-anatomic images of metastatic cancer of cervix obtained by a combined gamma camera and an X-ray tube hybrid system with an illustrative case and review of the $^{18}$F-fluorodeoxyglucose literature

Anat Aizer-Dannon, M.D., a Amiram Bar-Am, M.D., b Ilan G. Ron, M.D., c Gideon Flusser, M.D., d and Einat Even-Sapir, M.D. Ph.D. a, *

a Department of Nuclear Medicine, Tel-Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
b Department of Obstetrics and Gynecology, Tel-Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
c Department of Oncology, Tel-Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
d Department of Radiology, Tel-Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

Received 15 August 2002

Abstract

Background. $^{18}$F-Fluorodeoxyglucose (FDG) assessments have provided clinically important information in cervical cancer. FDG studies can now be performed by both dedicated PET systems and by new-generation gamma cameras. Hybrid systems which consist of positron emission tomography (PET) or a gamma camera with X-ray for fusion of functional-anatomic data without changing the patient’s position are now available.

Case. A woman with newly diagnosed cervical cancer underwent preoperative FDG studies using a hybrid gamma camera. In addition to the known primary tumor, FDG detected heretofore unidentified metastatic disease at the liver, bone, and para-aortic lymph nodes: the treatment approach was consequently altered to chemo- and radiotherapy. The fused images provided precise localization of the lesions, guiding bone biopsy and radiation field planning.

Conclusion. When PET is unavailable, a modified gamma camera can provide clinically relevant data in patients with cervical cancer. © 2003 Elsevier Science (USA). All rights reserved.

Keywords: Cancer; Cervix; PET; $^{18}$F-Fluorodeoxyglucose; Gamma camera

Introduction

Once the diagnosis of carcinoma of cervix is pathologically proven, accurate staging is essential for the selection of appropriate management [1,2]. Positron emission tomography (PET) has emerged in recent years as a useful functional imaging modality for providing data on the spread of viable tumor tissue in the entire body. $^{18}$F-Fluorodeoxyglucose (FDG), the radiopharmaceutical most commonly used in PET, is a glucose analogue which accumulates in tumor cells due to the increased expression of glucose membrane transporters and the enhanced glycolysis that characterizes these cells [3]. FDG-PET has been found to be of clinical value in detecting diverse types of human cancer, including lymphoma, melanoma, lung, colorectal, esophageal, and breast cancer as well as various gynecologic malignancies [4–6]. In carcinoma of the cervix, PET-FDG was found to have an important role for staging, restaging, diagnosis of early recurrence, and monitoring response to treatment [7–13]. PET systems, however, are beyond reach for many patients who might benefit from an FDG assessment. Gamma cameras, which are used in the routine practice of nuclear medicine, have been recently modified so that they...
can also be applied to detect positron emitters such as FDG [3]. Tumor detection by a PET system is superior to that obtained by a gamma camera; in the absence of a PET system, however, it has been suggested that FDG imaging with a gamma camera can better provide data of clinical importance than an assessment by means of conventional imaging modalities, such as computerized tomography (CT) alone [3,14].

Although it is successful in providing the functional data of suspected active tumor sites, scintigraphy may be limited by its inability to define the precise anatomic localization of suspected lesions [15–17]. This limitation often requires correlation of the findings by other modalities, e.g., CT or magnetic resonance imaging (MRI), to accurately localize the site of disease. The correct alignment of the data obtained by two different modalities can be difficult and is prone to errors [18,19]. Novel systems designed as hybrids of a PET or single photon emission computer tomography (SPECT) device integrated with an X-ray tube of various powers are now available [16]. Emission (PET or coincidence) and transmission (low- or high-resolution CT) studies are performed in the same setting using the same device without changing the patient’s position, thereby allowing for correct fusion of the images that are produced by both modalities.

We describe a patient who presented with cervical cancer accompanied by extensive lymph node, liver, and bone metastatic disease to illustrate the added value of FDG whole-body assessment with a gamma camera when a dedicated PET system is not available as well as the importance of co-registration of functional and anatomic data.

Case report

A 54-year-old female was referred for a routine Pap smear examination. Due to abnormal findings suggestive of the presence of squamous cell carcinoma, she underwent a cone biopsy which revealed invasive poorly differentiated squamous cell carcinoma. Her physical examination and laboratory tests were within normal limits except for a high thyroid-stimulating hormone (TSH) level due to known hypothyroidism. The transvaginal ultrasound examination detected no abnormalities.

A CT scan of the abdomen and pelvis with intravenous (iv) contrast yielded abnormal findings: the cervix was thickened and there was infiltration of the fatty tissue adjacent to the left and right paracervical and parauterine regions, as well as enlarged pelvic lymph nodes along the iliac blood vessels (bilaterally) and a few small equivocal retroperitoneal lymph nodes. A 2.8-cm hypodense heterogenic lesion was noted in the left medial segment of the liver: this lesion was diagnosed on biopsy as a metastasis. Based on these findings, she was considered to have clinical stage IIB cervical disease. Noting her relatively young age and otherwise good general physical condition, she insisted upon exploiting all available surgical options before considering undergoing any other therapeutic approach. Thus, extensive pelvic surgery and lymph node excision in conjunction with partial hepatectomy were planned as the potential initial treatment modality. In order to ensure that, in this case, the surgical approach could be curative and not palliative, she was referred for a whole-body FDG study in order to more accurately determine the extent of the disease. The study was performed with a dual-headed gamma camera with coincidence characteristics as a hybrid system and with a low-resolution X-ray tube providing fused functional-anatomic images of the body. Abnormal sites of markedly increased FDG uptake were located in the known primary tumor, in four para-aortic lymph nodes (two on each side), in the known hepatic metastasis, in an unsuspected para-aortic lymph node, and in the vertebral body of D10. A CT-guided biopsy of the bony lesion confirmed the diagnosis of a skeletal metastatic spread. Thus, any likelihood of curative surgery was ruled out subsequent to these valuable contributions provided by the FDG study, and the patient now agreed to be referred for chemo- and radiotherapy. The FDG findings with and without fusion with CT are demonstrated in Fig. 1.

The procedure for FDG assessment using transmission emission tomography

The patient fasts for 4 h prior to the iv administration of 370 MBq (10 mCi) FDG. Patient preparation includes urinary bladder catheterization and 20 mg Lasix iv in order to minimize interference from labeled urine uptake in the bladder or in the renal collecting system. Imaging starts 1 h later. The emission-transmission study is performed on a gamma camera with coincidence imaging capacity and with a low-dose X ray tube installed in its gantry (Discover VH consisting of a VG8 gamma camera and a Hawkeye X-ray system, GE Medical System). This system allows both transmission and emission acquisitions without changing the patient’s position, and fused images overlying the transmission (CT) and emission (coincidence) data can be generated.

For the FDG coincidence study (the emission part), the system is equipped with NaI(Tl) crystals of 1-inch (25.4 mm) thickness (the thickness of the crystal in gamma cameras is normally 3/8 inch) and ultra-fast coincidence detection electronics (a CoDe VC circuitry). Both characteristics are tailored for detection of the high-energy coincidence events (511 keV). Acquisition includes the region of the head and neck, chest, abdomen, and pelvis in two fields of view, each lasting for 30 min and corresponding to 10 rotations of the gantry. The CT integrated consists of 384 crystals and photodiodes mounted on the gantry’s rotating module. The full field of view, consisting of 40 slices, is
completed in 10 min. Transmission data of the patient are corrected and reconstructed using filtered back-projection to produce cross-sectional images in which each pixel represents an attenuation of the imaged tissue. The transmission data are used both to correct the attenuation of the emission images and to create coincidence CT-fused (functional-anatomic) images. Reconstruction and fusion are performed on an eNTEGRA workstation.

**Discussion**

Accurate assessments of tumor extent and clinical staging are major factors for determining the appropriate management and the prognosis in patients with carcinoma of the cervix. Cervical cancer tends to metastasize in a predictable pattern, with retroperitoneal lymphatic spread occurring primarily along the external and internal iliac nodal route or via the presacral route to involve the para-aortic lymph nodes [2,6,20]. In patients with stage I–IV a carcinoma of the cervix, involvement of the para-aortic lymph nodes was found to be the most significant prognostic variable, followed by tumor size [21]. The overall survival rate of patients who are post-radical hysterectomy and pelvic lymphadenectomy was found to decrease from 85 to 90% for stage IB to 65% for stage II. This decrease correlates in 20–25% of the patients with a higher incidence of pelvic and para-aortic lymph node involvement. It was found that the survival rate is associated with the extent of disease in the pelvic lymph nodes, even within the same clinical stage [1].

Hematogenous dissemination, which occurs less frequently than lymphatic spread, may result in distant metastases to the lung, liver, and bone, and the prognosis of patients with distant metastases is extremely poor [2,20,22]. Based on the clinical staging, the therapeutic approach may be aimed for either cure or only palliation. The routine staging system established by the International Federation of Gynecology and Obstetrics (FIGO) includes clinical examination and limited imaging procedures [23,24]. The accuracy of this staging system is questionable and may be erroneous, particularly in the case of stages III and IV disease [2].

There is a large variation among the techniques used by clinicians for pretreatment evaluation [24,25]. The more commonly employed imaging modalities are CT and ultrasonography (US) [20]. The overall sensitivity and specificity of CT for the detection of para-aortic lymph node involvement are 34 and 96%, respectively [26]. CT and MR can suggest the presence of nodal involvement primarily when the size of the lymph nodes is increased and, therefore, these techniques are likely to overlook micro-metastases in normal-sized lymph nodes. Moreover, an increase in the size of lymph nodes is a nonspecific sign and may
occur in various benign conditions, such as reactive inflammatory changes [6].

In contrast to anatomical imaging modalities, PET imaging using FDG, a glucose analogue, is a functional modality for tumor imaging. FDG-PET exploits the metabolic differences between benign and malignant cells for imaging purposes. Accumulation of FDG in tumor cells represents the increased metabolic activity characterizing these cells, and is the result of overexpression of glucose transporter proteins in the cell membrane and the increased level of intracellular enzyme levels which promote glycolysis, such as hexokinase and phosphofructokinase [3].

Whole-body PET with FDG has rapidly become a routine imaging modality in various human malignancies and is currently used for the differentiation between benign and malignant lesions, staging, detection of recurrence, and monitoring response to therapy [3,4,27]. Several studies have been conducted to assess the role of PET-FDG in cancer of the cervix. Rose et al. [10] reported a high avidity of FDG in cervical malignancies. These authors found that 91% of the cervical tumors, including both squamous and nonsquamous types, show an increased FDG uptake. PET-FDG assessment accurately predicted both the presence and absence of pelvic and para-aortic nodal metastatic spread, using a surgical staging lymphadenectomy as the gold standard. The lack of FDG uptake was associated with a high negative predictive value for the exclusion of metastatic nodal involvement. Comparing PET and CT, Sugawara et al. [7] found a better sensitivity for PET in detecting primary cervical tumor. Grigsby and Siegel [20] reported that the most significant prognostic factor for progression-free survival was the status of the para-aortic lymph nodes. PET depicted more abnormal lymph node regions than CT. Reinhardt et al. [1] compared the diagnostic accuracy of MRI with that of PET-FDG-PET had a sensitivity of 0.91, a specificity of 1.00, a negative predictive value of 0.96, and an accuracy of 0.97 for depicting lymph node metastases, while the respective values for MR imaging were 0.73, 0.83, 0.67, 0.87, and 0.80.

There are also promising preliminary reports indicating the efficiency of FDG-PET in monitoring response to treatment and in the early detection of recurrent disease, either locally or as distant metastases [9,11–13]. In their study on 20 patients, Nakamoto et al [9] have recently shown that a PET scan detected all the sites of local recurrence. Dose et al [11] reported a patient after radical hysterectomy and external radiotherapy in which an FDG-PET scan detected an extensive recurrence in the pelvis, in the lymph nodes below and above the diaphragm, and in the bone, while a CT scan detected only abnormal para-aortic lymph nodes. Umesaki et al. [12] described several cases of recurrent cervical cancer: in one case, PET was the only imaging modality, including MRI, to detect a recurrent disease at the vaginal wall and, in another case, the FDG-PET scan confirmed the MRI findings which suggested the presence of pelvic recurrence. PET assessment was of value in monitoring response to chemotherapy in both these patients. In another report by the same authors, PET scanning identified all 13 cervical cancers, 4 of which were local recurrences [13]. All the above-cited studies used dedicated PET systems for FDG imaging. These systems are characterized by a high spatial resolution for detecting small structures. Their number is, however, still limited and, therefore, these systems are inaccessible to a large number of patients for whom assessment with FDG might be beneficial. Conventional gamma cameras, which are used in the routine practice of nuclear medicine, have been recently modified to also operated in the coincidence mode for the detection of positron emitters, enhancing the potential to image a greater number of patients by means of FDG. There are several studies on the use of camera-based coincidence imaging of FDG for the detection of various malignancies, including lymphoma, melanoma, lung cancer, colorectal cancer, and others [3,14,28,29].

Procedures applied in nuclear medicine (NM) are limited by their lack of ability to define the precise anatomic localization of suspected lesions and often require correlation with other modalities, such as CT, to accurately localize the site of disease. Attempts to fuse NM and CT images obtained separately on different devices were prone to errors in alignment due to differences in positioning, in bowel gas or urine content, in respiration, and in motion [18,30]. These potential difficulties in fusing the functional NM data with the anatomic CT data gave rise to the development of novel hybrid imaging devices combining a SPECT or a PET system with CT. In the system that was used in our currently described case, a low-dose X-ray tube had been installed within the gamma camera gantry: this setup permitted the registration of the emission images on the anatomical CT images without changing the patient’s positioning. One recent publication demonstrated that although PET-FDG is a sensitive tool for assessment of the viability of cervical cancer after radiotherapy, it has a suboptimal specificity without an anatomic correlation. These authors suggested that this limitation could be partially overcome by using a hybrid PET-CT system [9].

The case we now present illustrates two main issues regarding the pretreatment assessment of a newly diagnosed patient with cervical cancer. First, in the absence of a dedicated PET system, a gamma camera-based FDG study may detect unsuspected tumor sites, resulting in alteration of the clinical stage and the choices of the appropriate therapeutic approach. Second, there is added value in fusing the functional FDG data with anatomical data, allowing for a precise localization of the scintigraphic findings.

Finally, by virtue of our patient’s having undergone a bone biopsy based on the findings of the fused images, a more comprehensive and highly specific radiation field could be planned.
Acknowledgments

Esther Eshkol is thanked for editorial assistance.

References


