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Original

Effect of furosemide administration before F-18 fluorodeoxyglucose positron emission tomography/computed tomography on urine radioactivity and detection of uterine cervical cancer

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Abstract

BACKGROUND: In evaluating uterine cervical cancer with ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT), there may be overlap between the FDG activity at tumor sites and nonspecific radioactivity in the urine. We evaluated the efficacy of furosemide premedication with routine hydration to obtain better contrast and less overlap between cervical cancer and the urinary bladder.
MATERIAL AND METHODS: We retrospectively evaluated 166 patients who had primary or relapsed cervical cancer and underwent FDG PET/CT scanning with (133 patients) or without (33 patients) furosemide premedication (10 mg intravenous, slowly injected 30 min before the scan). We calculated bladder and tumor maximum and median standardized uptake value (SUV_{max} and SUV_{med}), and overlap between tumor and urinary activity was detected visually.
RESULTS: Overlap between urinary and tumor radioactivity was observed in 8 of 133 scans (6%) in patients who receive furosemide and in 3 of 33 scans (9%) in patients who did not receive furosemide. The SUV_{max} and SUV_{med} for the bladder were significantly lower in patients who were pretreated with furosemide (SUV_{max}, 6.3; SUV_{med}, 4.6) than patients who were not pretreated with furosemide (SUV_{max}, 8.8 [$P \leq 0.008$]; SUV_{med}, 6.5 [$P \leq 0.002$]). The tumor SUV_{max} and SUV_{med} were similar between the patient groups.
CONCLUSION: Furosemide premedication before FDG PET/CT scanning may enable improved evaluation of activity and extension of cervical cancer.

KEY words: gynecologic oncology, cervix, imaging, diuretic, bladder

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Background

Patients who have early cervical cancer can be treated with surgery or radiotherapy, but women who have more advanced cervical tumors that are metastatic to lymph nodes or pelvic tissues are treated usually with a combination of external beam radiotherapy and intracavitary brachytherapy. Evaluation with positron emission tomography/computed tomography (PET/CT) with the glucose analogue ^{18}F-fluorodeoxyglucose (FDG) may facilitate tumor detection, staging, restaging after radical therapy, prognostic assessment, and radiotherapy planning [1–4].

The major source of uncertainty in the interpretation of PET/CT images is the anatomic position of the uterine cervix contiguous with the urinary bladder. Unlike glucose, FDG is not completely reabsorbed in the kidneys, and a variable amount of radioactivity may be found in the urinary tract after FDG injection. Therefore, there may be overlap between the FDG activity at tumor sites and nonspecific radioactivity in the urine. In 15 PET/CT centers, routine bladder catheterization usually is not performed before scanning [5]. An alternative noninvasive way to decrease urine radioactivity is highly desirable.

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Better contrast between tumor FDG uptake and urine radioactivity may be achieved by decreasing urine radioactivity with standardized patient hydration protocols or the administration of diuretic drugs before PET/CT scanning [6–7]. The European Association of Nuclear Medicine guidelines suggest hydration and diuretic administration during the investigation of small pelvic tumors [8].

We hypothesized that the diuretic furosemide may improve contrast between cervical cancer and the urinary bladder during PET/CT scanning. The purpose of the present study was to evaluate the efficacy of using furosemide with routine hydration to obtain better contrast and less overlap between cervical cancer and the urinary bladder.

Materials and methods

Subjects

We retrospectively evaluated 166 patients who had primary or relapsed cervical cancer and who underwent FDG PET/CT scan at our center between December 2011 and November 2012. The scans were performed in accordance with current guidelines including intravenous injection of ^{18}F-FDG (185 to 444 MBq) at 1 hour before image acquisition [7]. The PET/CT scan was performed with 2 scanners (72 patients: Philips Gemini GXL16 scanner, Philips Healthcare, Andover, MA, USA; 94 patients: Siemens Biograph mCT128 scanner, Siemens, Malvern, PA, USA). The cross-calibration process was performed on a regular basis to ensure measurement stability between different scanners.

Procedures

All patients were routinely instructed to drink ≥ 1 L of water within 2 hours before the examination and to void just before image acquisition. Patients were divided into 2 groups: patients who received premedication with furosemide (10 mg intravenous, slowly injected 30 min before the scan; 133 patients [80%]), and patients who did not receive furosemide because of a history of furosemide hypersensitivity, kidney stones, or renal colic (33 patients [20%]). No patient who was treated with furosemide had adverse events from diuretic administration. The maximum and median standardized uptake value (SUV_{max} and SUV_{med}) for the bladder and tumor were determined for each patient in both groups by manually drawing the free region of interest. Visual analysis was performed independently by 2 nuclear medicine specialists with software (Syngovia v.1.1.0.17, Siemens AG, Munich, Germany) to identify patients who had overlap between urinary and tumor activity.

Data analysis

Data analysis was performed with statistical software (STATISTICA v10.0, StatSoft, Tulsa, OK, USA). Normality of distribution was tested with Shapiro-Wilk test for SUV_{max} and SUV_{med} for the bladder and tumor for both patient groups; only the SUV_{max} and SUV_{med} for the tumor in patients who received furosemide were normally distributed. The basic statistics such as median, minimum, maximum, and interquartile range were calculated for each of the considered variables. The Mann-Whitney test was used for comparisons between the groups, because the groups were unrelated, the data were quantitative, and the data lacked normality. The primary outcome of the study was to compare the SUV_{max} and SUV_{med} for the bladder and tumor between the 2 patient groups. The null hypothesis assumed that the median values of these variables were equal. Statistical significance was defined by $P \leq 0.05$.

Results

Overlap between urine and tumor radioactivity was observed in 8 of 133 scans (6%) in patients who received furosemide and in 3 of 33 scans (9%) in patients who did not receive furosemide (Figure 1 and 2). The bladder SUV_{max} and SUV_{med} were significantly lower in patients who were pretreated than in those who were not pretreated with furosemide (Table 1). The tumor SUV_{max} and SUV_{med} were similar between the patient groups (Table 1).

Discussion

The present result showed that SUV_{max} and SUV_{med} of the bladder, but not tumor, were significantly lower in patients who were pretreated than in those who were not pretreated with furosemide (Table 1). This suggests that pretreatment with furosemide may be

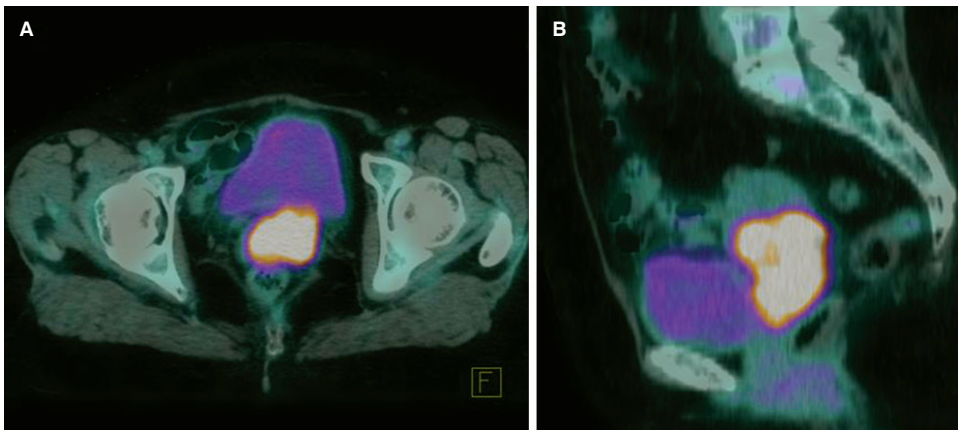

Figure 1. Transverse and sagittal fused ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography scan in a patient who had cervical cancer stage IVA with infiltration of the bladder wall. The patient received furosemide before the scan. Furosemide premedication reduced urinary radioactivity and enabled good visualization of the neoplasm (**A, B**)

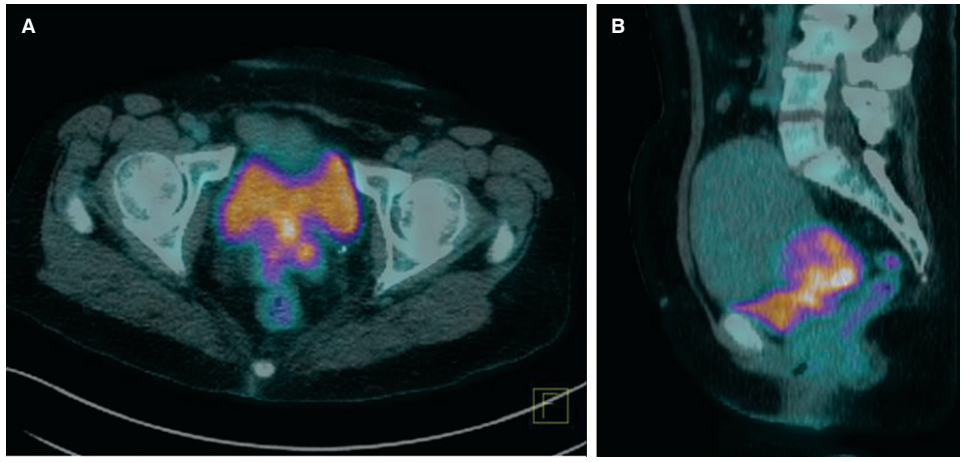

Figure 2. Transverse and sagittal fused ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography scan in a patient who had cervical cancer stage IVA with infiltration of the bladder wall. The patient did not receive furosemide before the scan. Overlap of radioactivity was observed between the bladder and the cancer

Table 1. Standardized uptake values from ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography scans in patients who had cervical cancer*

Parameter	With furosemide			Without furosemide			$P \leq$ †
	Median	(Minimum to maximum)	[Interquartile range]	Median	(Minimum to maximum)	[Interquartile range]	
No. patients	133			33			
Bladder SUV_{max}	6.3	(3.0–24.7)	[5.0–8.0]	8.8	(3.0–31.9)	[6.4–10.2]	0.008
Bladder SUV_{med}	4.6	(1.9–15.4)	[3.8–5.8]	6.5	(2.6–19.8)	[4.6–8.3]	0.002
Tumor SUV_{max}	15.4	(3.7–31.7)	[10.6–20.4]	14.6	(5.7–43.6)	[10.7–19.1]	NS
Tumor SUV_{med}	7.6	(2.0–16.6)	[5.9–9.7]	7.9	(2.9–29.0)	[6.0–10.1]	NS

*N = 166 patients. Data reported as number or median (range, minimum to maximum) [interquartile range]. Abbreviations: SUV_{max} — maximum standardized uptake value; SUV_{med} — median standardized uptake value. †NS — not significant ($P > 0.05$)

helpful in minimizing overlap between the FDG activity at tumor sites and nonspecific radioactivity in the urine.

Nonspecific accumulation of FDG in the urinary tract may interfere with the visualization of pelvic and retroperitoneal abnormalities in a PET/CT scan. In the current literature, difficulties in images interpretation were reported in a significant percentage of patients, most frequently patients who had colorectal or ovarian cancers [9, 10]. This is an important issue, especially for patients with pelvic malignancies who are referred for PET/CT scan for radiotherapy planning. Bladder catheterization is effective but it is invasive and may cause urinary tract infection [11]. In addition, bladder catheterization is time-consuming and difficult in clinical settings that have tightly scheduled examinations. Studies about the efficacy of furosemide premedication before PET/CT scanning have been performed for abdominal, bladder, and colorectal cancers, but only occasionally for cervical cancer [10–17].

The timing of diuretic injection is an important issue in order to obtain an optimal distinction between tumor and bladder [6]. In our experience, most patients had difficulties in holding back urination for > 30 minutes after furosemide intravenous injection.

Statistical analysis of tumor activity showed no difference between patients who had or did not have furosemide premedication (Table 1). The significantly lower bladder radioactivity for patients who received furosemide pretreatment (Table 1) is evidence that increased urine production effectively reduce tracer concentration in the urinary tract. These data correlate with a higher ratio of overlap between urine and tumor images on the PET/CT scan in patients who did not receive furosemide that can hinder the delineation of tumor borders. This is important for the use of PET/CT scanning in planning cervical cancer radiotherapy. Adaptive radiotherapy strategies have been proposed to minimize the effect of possible changes in cervix position because varied bladder volumes may cause displacement of pelvic organs. It is possible to measure cervical displacement by comparing pretreatment CT scans with full and empty bladder [18, 19]. Modulated adaptive radiotherapy may be coupled with furosemide premedication to improve the quality of PET/CT images and accurately measure cervical displacement.

Table 2. Overlap between urinary and tumor radioactivity in patients with and without furosemide premedication

Group	Number of patients	Patient with overlap (%)
With furosemide premedication	133	8 (6%)
Without furosemide premedication	33	3 (9%)

The findings in this report are subject to at least two limitations. First, the sample size of control group is relatively small. Furthermore, comparison with a control group of catheterized patients was not carried out.

In summary, the present study shows that a combination of hydration and furosemide premedication may enable better evaluation of cervical cancer anatomy on PET/CT imaging. The present protocol potentially may be used in planning adaptive radiotherapy.

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