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The Utility of ^{18}F-FDG PET/CT for Following Up Head and Neck Cancer

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두경부암 환자의 추적관찰에서 ^{18}F-FDG PET/CT의 유용성

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서 론

두경부암의 예후에 가장 중요한 인자는 진단시 병기와 치료 후 재발의 유무이다. 따라서, 재발 병변을 조기에 발견하는 것이 매우 중요하다. 본 연구에서는 두경부암 환자의 추적 관찰에서 ^{18}F-FDG PET/CT의 유용성에 대해 알아보고자 하였다.

대상 및 방법

2004년 4월부터 2008년 8월까지 고려대 안암병원에서 두경부암으로 치료를 완료한 후 추적관찰이 가능하였던 88예의 환자를 대상으로 하였다. 환자는 본원의 두경부암 추적관찰 양식에 따라 술 후 6, 12개월째 ^{18}F-FDG PET/CT를 시행하였으며, 원발부위 및 경부 재발, 원격전이와 중복암의 진단에 있어 ^{18}F-FDG PET/CT의 민감도, 특이도, 양성예측율, 음성예측율을 평가하였고, 기존의 추적관찰 방법과 이를 비교하였다.

결 과

원발부위 재발의 진단에 있어 민감도, 특이도, 양성예측율, 음성예측율은 각각 95%, 97%, 90%, 98% 였다. 경부전이 재발의 진단에 있어서는 각각 94%, 98%, 83%, 99%였으며, 원격전이 및 이차암 진단에 있어서는 94%, 100%, 100%, 99%였다. 원발부위 재발은 고식적인 진단 방법, 원격전이와 이차암은 ^{18}F-FDG PET/CT가 진단에 의미있게 유리하였다.

결 론

^{18}F-FDG PET/CT는 두경부암의 추적관찰 과정에서 재발 여부를 판정하는데 있어 매우 유용하며, 특히 원격전이 및 이차암의 발견에 있어 유용하다. 그러나, 위양성 및 위음성의 가능성으로 고식적인 진단 방법과 병행해야 진단의 효과를 높힐 것으로 생각된다.

중심 단어 : 양전자방출 단층촬영 · 재발 · 두경부암.

Introduction

The early detection of recurrent head and neck cancer may improve patient survival, so careful monitoring when follow-up these patients is essential. However, making the early diagnosis of recurrent head and neck cancer is difficult. Asymptomatic recurrence, and especially that for distant metastasis, is more difficult to identify with using the conventional methods.

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Many physicians have used physical examinations and structural imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) as the conventional methods. However, these methods had been found to be too equivocal in detecting recurrence because of the anatomical changes induced by therapy, and these changes may be further obscured by flap reconstruction.[1)]

PET-CT imaging, for which CT is performed in conjunction with PET, provides matching metabolic and anatomical images, and this allows precise localization of the foci of high FDG uptake. Improving the localization of high uptake foci results in better differentiation of the physiological and pathological FDC uptake.[2)] Several retrospective and prospective studies[3-8)] have shown that ^{18}F-FDG PET/CT is more effective in detecting recurrence than conventional methods. However, in these previous studies, patients were enrolled if recurrence was suspected.

The objective of the current study was to perform a retrospective evaluation of the accuracy of performing routine ^{18}F-FDG PET/CT surveillance for follow-up head and neck cancer patients.

Table 1. The patients' demographics and the tumor characteristics

	Factors	No.
Primary tumor site	Larynx	19
	Oropharynx	18
	Oral cavity	17
	Nasopharynx	10
	Hypopharynx	10
	Sinonasal	6
	Salivary gland	2
	Others	2
Cell type	Squamous cell carcinoma	73
	Low grade mucoepidermoid ca	1
	Salivary duct ca	1
	Nonkeratinizing carcinoma	5
	Undifferentiated carcinoma	2
	Melanoma	2
Stage	Stage I	13
	Stage II	18
	Stage III	18
	Stage IV*	35
Treatment modality	Surgery+postoperative radiotherapy	51
	Surgery alone	10
	Chemoradiotherapy	14
	Neoadjuvant chemotherapy+salvage surgery+radiotherapy	4
	Radiotherapy alone	5
Follow-up months	Range	3-105
	Median	29.3

* : No distant metastasis patient among the stage IV group

Materials and Methods

1. Patients

From April 2004 to April 2008, whole-body ^{18}F-FDG PET/CT were performed on 84 patients with head and neck cancer after completion of treatment to detect residual cancer or tumor recurrence. There were 61 men and 23 women, aged from 30 to 84years (mean, 59years). The patients' characteristics are given in Table 1.

A physical examination was done every month for 2 years, and then every 6 months for year and then annually if the patient was disease free during this time. Periodic neck CT scan and chest X-ray (at the 6th and 12th post-operative month, and then annually) and ^{18}F-FDG PET/CT (at the 6th and 12th month after the initial treatment and then annually) were done according to our institutional follow-up protocol. The recurrences were divided according to the location of lesion : local recurrence, recurrence in the regional area and distant metastasis/ secondary malignancy.

The conventional detection methods along with histological verification, were performed for the patients with suspected recurrence observed on their ^{18}F-FDG PET/CT. The ^{18}F-FDG PET/CT was carried out within an interval of no longer than 2 weeks from the time of finding a suspected recurrence on the conventional detection methods.

A total of 111 whole-body ^{18}F-FDG PET/CT were performed. Two scans were performed on 19 patients, three scans were performed on 3 patients and four scans were performed on 1 patient. Recurrence was confirmed histopathologically or by at least 3 months of clinical follow-up.

2. Whole-Body ^{18}F-FDG PET/CT

Scans were performed on a Gemini TF PET/CT scanner (Philips). Patients fasted 6 h before PET acquisitions, and the blood glucose level had to be less than 7mmol/L before injection of 370 MBq (5 MBq/kg) of ^{18}F-FDG. Intravenous injection was followed by a period of approximately 60 min when the patients remained in a quiet room. No muscle relaxants were administered. The ^{18}F-FDG PET/CT images were obtained over the entire body from the base of the skull to the mid-thigh. PET data were acquired in the 3-dimensional mode. Transmission CT imaging was performed for attenuation correction and anatomical localization with using the integrated PET-CT system, and the accompanying software provides the transmission CT, FDG-PET and fusion images. The Gemini scanner consists of a 16-slice multi-detector-row spiral CT scanner with a transverse field of view of 600mm.

The CT parameters-a collimation of 6×5mm, tube voltage of 120 kV, and effective tube current of 100 mAs-are standard for PET/CT studies and permit differentiation between tissues with good spatial resolution while ensuring that the patient does not receive a high radiation dose.

3. Analysis

A study was considered false-positive if no recurrence was demonstrated by biopsy or there was no disease progression on multiple following studies, or if the subsequent studies became negative without administering any therapy for recurrent disease. A study was considered false-negative if there was clinical progression of disease, or if disease was detected on another imaging modality and this was subsequently proven by biopsy or the clinical progression after the first false-negative study. Residual disease after chemoradiation (n=5) was regarded as a recurrence for statistical purpose.

The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the ^{18}F-FDG PET/CT were calculated. Statistical analysis was performed using the McNemar test and chi-square test. Statistical analysis was performed by using SPSS for Windows (version 12.0 ; SPSS Inc., Chicago, IL, USA). Statistical significance was set at $p<0.05$.

Results

1. Confirmation of the diagnosis

Recurrent disease was diagnosed in 48 cases, while there was no evidence of recurrence in 36 cases. The definitive diagnosis was obtained by means of the histology or cytology for 47 cases and the definitive diagnosis was based on the clinical follow-up for 1 case (multiple bone metastasis).

1. The diagnostic accuracy of ^{18}F-FDG PET/CT

The diagnostic accuracy of ^{18}F-FDG PET/CT is summarized in Table 2. The overall diagnostic sensitivity, specificity, PPV, NPV and accuracy for local recurrence were 95%, 97%, 90%, 98% and 96% respectively, and those for regional recurrence were 94%, 98%, 83%, 99% and 95% respectively, and those for distant metastasis/second primary cancer were 94%, 100%, 100%, 99% and 99% respectively (Table 2). There were 5 false positive cases of ^{18}F-FDG PET/CT for locoregional recurrence- Two cases of primary lesion : 1) T4a floor of mouth, surgery+postoperative radiotherapy ; 2) T4a hypopharynx, concurrent chemoradiotherapy. Three cases of regional lesion : 1) N0 tongue, elective neck dissection, SUV 3.85 ; 2) N0 tonsil, surgery+postoperative radiotherapy, SUV 3.3 ; 3) N2 Nasopharynx, concurrent chemoradiotherapy, SUV : 3.5. There were 2 cases of false negative scans for locoreginal recurrence- Primary lesion : T1b glottis cancer, surgery+postoperative radiotherapy ; Regional lesion : N1 Nasopharynx, concurrent chemoradiotherapy and 1 case of a false negative scan for distant metastasis/second primary cancer- N2a unknown primary, surgery+postoperative radiotherapy (Fig. 1). The overall sensitivity was significantly higher with ^{18}F-FDG PET/CT than conventional methods ($p=0.035$). However, there was no significant difference for overall specificity ($p=1.0$). Most of subclinical recurrent patients with routine surveillance were shown to have distant metastasis/second primary tumor with the aid of ^{18}F-FDG PET/CT (Fig. 2).

We detected primary recurrence with using the conventional methods significantly more often than we did with using ^{18}F-FDG PET/CT ($p=.007$). Distant metastasis/second primary tumor was detected significantly more often with ^{18}F-FDG PET/CT ($p=.001$). No significant difference was found for the detection of regional recurrence between ^{18}F-FDG PET/CT and the conventional methods ($p=.725$).

Discussion

The early, accurate detection of recurrent head and neck cancer is critically important for achieving successful sal-

Table 2. The results of routine ^{18}F-FDG PET/CT surveillance for follow-up head and neck cancer patients

	Local recurrence	Regional recurrence	Distant metastasis/ Secondary malignancy
True-positives	19	15	17
False-positives	2	3	0
False-negatives	1	1	1
True-negatives	62	65	66
Sensitivity (%)	95	94	94
Specificity (%)	97	98	100
PPV (%)	90	83	100
NPV (%)	98	99	99
Accuracy (%)	96	95	99

* : Sensitivity= TP/TP+FN, Specificity=TN/FP+TN, PPV=TP/TP+FP, NPV=TN/FN+TN. PPV : positive predictive value, NPV : negative predictive value, TP : true positive, TN : true negative, FP : false positive, FN : false negative

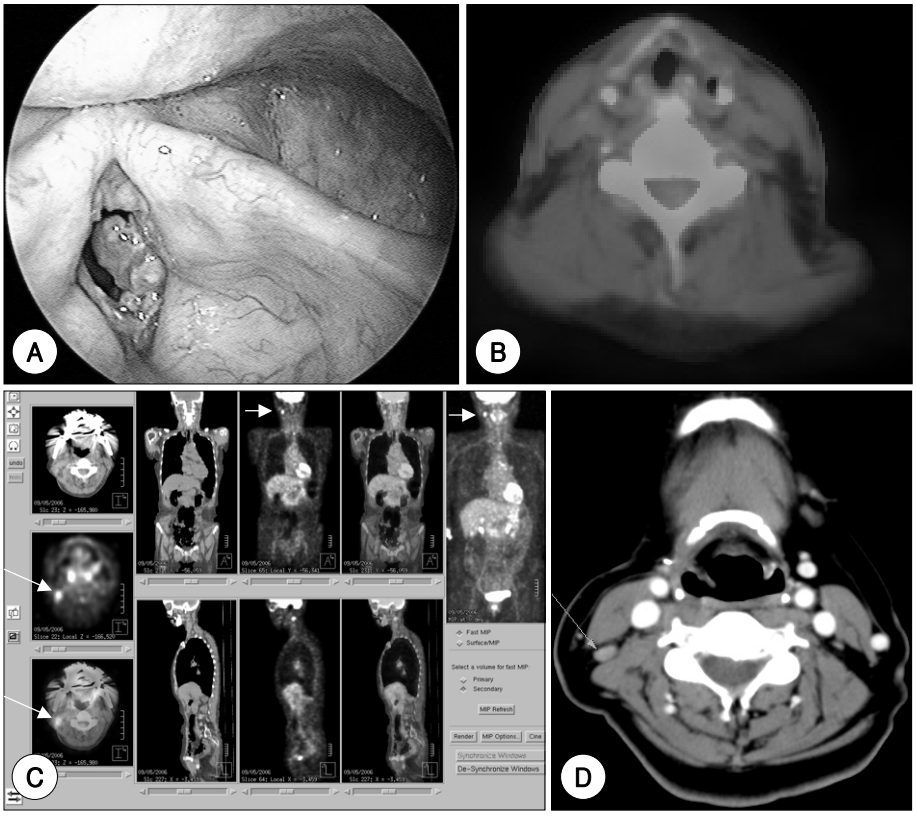

Fig. 1. False negative(A, B) and false positive(C, D) ^{18}F-FDG PET/CT. A : A 75 year-old male with glottic cancer(initial stage T1bN0M0) at 4 years after undergoing anterior commisure laryngectomy. Biopsy confirmed the recurrence. B : There is no hypermetabolic lesion in the recurrent site. C : A 58 year-old female with tongue cancer(T2N0M0) at 2 years after undergoing partial glossectomy, SND(I-III). A hypermetabolic lesion that was suspicious for recurrence was detected on the ^{18}F-FDG PET/CT scan (arrow : SUV 3.85). D : The CT scan image. The ultrasound-guided fine needle aspiration cytology and clinical follow-up(>2years) showed no evidence of recurrence.

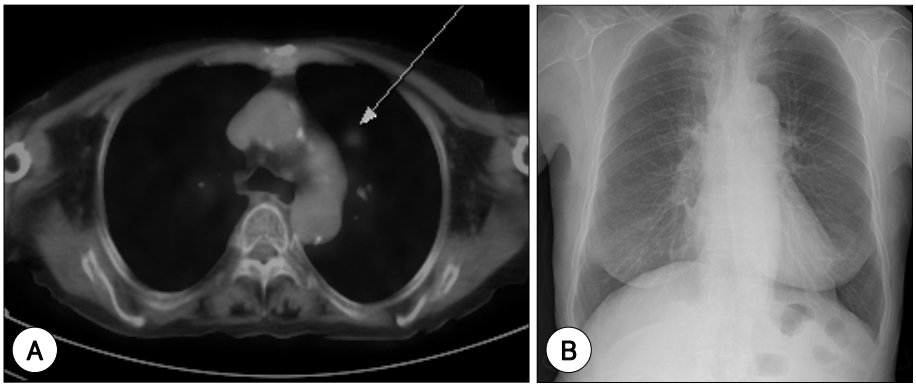

Fig. 2. A 74-year-old female with supraglottic cancer(T3N2cM0) after extended supraglottic laryngectomy, (B) MRND, and post-operative radiotherapy. Routine follow-up(A) ^{18}F-FDG PET/CT and (B) Chest X-ray at 6 months after treatment. ^{18}F-FDG PET/CT demonstrates focal hypermetabolic lesion in left upper lung field interpreted as lung metastasis(arrow). However, no evidence of lung metastasis was suspected on the chest X-ray at the same time.

vage treatment. The patients with recurrent head and neck cancer and who undergo salvage surgery at early disease stages have a 70% 2-year relapse-free survival rate, whereas those with recurrent, advanced-stage head and neck cancer have just a 22% 2-year relapse-free survival rate after salvage surgery.[9)]

Conventional imaging such as CT and MRI has been of limited value for the early detection of recurrence due to the modalities' relatively low sensitivity and specificity. The anatomical changes due to therapy and flap reconstruction are some of the main reasons for the difficulty to detect recurrent tumor. ^{18}F-FDG PET/CT, however, is able to detect areas of recurrent disease very early by demonstrating the increased FDG metabolism in tumor, and ^{18}F-FDG PET/CT is able to accurately differentiate recurrent tumor from the postoperative changes. Therefore, ^{18}F-FDG PET/CT can increase the diagnostic accuracy of the conventional methods and it

may be helpful for detecting tumor recurrence at an earlier stage. Moreover, ^{18}F-FDG PET/CT is able to detect recurrence by viewing the whole body, which can not done with the conventional methods, and this whole body ^{18}F-FDG PET/CT is valuable for detecting distant metastasis or a second primary lesion.[1,10-13)]

We evaluated the ability of ^{18}F-FDG PET/CT to identify tumor recurrence in patients seen routinely and sequentially follow-up after completion of therapy. This was done in an attempt to demonstrate any subclinical recurrent disease. Such detection may precede detection of other clinical signs or symptoms, and therefore there may be reasonable cause for using PET routinely in such patients. In the earlier studies, the sensitivity of ^{18}F-FDG PET ranged from 71% to 100%, its specificity ranged from 43% to 100%, its positive predictive value ranged from 64% to 100% and its negative predictive value ranged from 66% to 100%.[1)] In our study, ^{18}F-FDG PET/CT showed the high sensitivity, specificity, PPV and NPV, and especially for detecting distant metastasis/second primary lesion. However, a negative PET/CT result does not provide absolute assurance of a disease-free status. In our series, 3 cases with negative PET/CT scans eventually presented with recurrence. We can guess the false negative results were well-differentiated cancers. Other potential causes for these false negatives were related to the time interval after treatment, the necrotic tissue around tumor and small size that were under the detection threshold.[1,13)] We found that ^{18}F-FDG PET/CT was very sensitive, but it also displayed false-positivity. Five patients in our study had false-positive PET/CT scans. False-positive scans are usually associated with infection or inflammation.[2)] These results suggest that ^{18}F-FDG PET/CT should not completely replace the conventional evaluation methods.

In summary, a ^{18}F-FDG PET/CT can detect head and neck tumor recurrence when this tumor recurrence may be undetectable by other clinical methods. It permits highly accurate detection of head and neck cancer recurrence in the post-therapy period. With its high sensitivity, specificity, PPV and NPV, ^{18}F-FDG PET/CT may be a useful tool for performing routine surveillance for detecting the recurrence of head and neck cancer, and especially for detecting distant metastasis/second primary lesion.

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