
Synchronous Primary Neoplasms Detected on ^{18}F -FDG PET in Staging of Patients with Esophageal Cancer

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Because of improvements in diagnostic technology, the incidental detection of synchronous primary tumors during the preoperative work-up of patients with esophageal cancer has increased. The aim of this study was to determine the rate and clinical relevance of synchronous neoplasms seen on ^{18}F -FDG PET in staging of esophageal cancer. **Methods:** From January 1996 to July 2004, 366 patients with biopsy-proven malignancy of the esophagus underwent ^{18}F -FDG PET for initial staging. This series of patients was retrospectively reviewed for the detection of synchronous primary neoplasms. **Results:** Twenty synchronous primary neoplasms (5.5%) were identified in 366 patients. Eleven neoplasms were in the colorectum, 5 in the kidney, 2 in the thyroid gland, 1 in the lung, and 1 in the gingiva. One of the thyroid lesions and the lung lesion were erroneously interpreted as metastases, leading to incorrect upstaging of the esophageal tumor. **Conclusion:** ^{18}F -FDG PET detected unexpected synchronous primary neoplasms in 5.5% of patients with esophageal cancer. Sites of pathologic ^{18}F -FDG uptake should be confirmed by dedicated additional investigations before treatment, because synchronous neoplasms may mimic metastases.

Key Words: esophageal cancer; PET; synchronous neoplasms
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The association between synchronous primary tumors in the aerodigestive tract is a well-known phenomenon that has been explained by the concept of “field cancerization” (1,2). The mucous epithelium of the head and neck, lung, and esophagus is exposed to common carcinogenic agents, lead-

ing to multiple carcinomas in these regions. Strong epidemiologic evidence implicates tobacco as the main carcinogen and alcohol as a promoter of carcinogenesis (3).

The incidence of synchronous cancers in patients with esophageal cancer ranges from 3.6% to 27.1% (4,5). Most of these synchronous cancers are in the head and neck region. Other frequently reported sites of synchronous cancer associated with esophageal cancer are the stomach, lung, and urinary bladder (6,7).

The detection of incidental synchronous tumors in patients with esophageal cancer during preoperative work-up has increased along with recent improvements in diagnostic technology. Whole-body PET with ^{18}F -FDG has been used successfully with increasing frequency in the evaluation and clinical management of many tumors (8–10). Routine interpretation of ^{18}F -FDG PET scans may reveal incidental hypermetabolic foci that are probably unrelated to the neoplasms for which these patients are initially scanned. On the other hand, lesions on ^{18}F -FDG PET that are interpreted as metastatic deposits of the primary tumor may, in fact, reflect accumulated ^{18}F -FDG in a second synchronous tumor (11).

The aim of this study was to determine the rate and clinical relevance of unexpected synchronous neoplasms seen on ^{18}F -FDG PET scans obtained during the preoperative evaluation of patients with esophageal cancer.

MATERIALS AND METHODS

Patients

From January 1996 to July 2004, a total of 366 patients with biopsy-proven malignancy of the esophagus were treated in 2 academic hospitals (University Medical Center Groningen and Academic Medical Center Amsterdam) and retrospectively analyzed for this study. All patients underwent ^{18}F -FDG PET, endoscopic sonography, CT of the thorax and abdomen, and external sonography of the cervical region for the initial staging. Staging

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was according to the 2003 classification of the Union Internationale Contre le Cancer (12).

PET

PET was performed with an ECAT 951/31 or an ECAT HR+ positron camera (Siemens/CTI). The 951/31 acquires 31 planes over 10.9 cm; the HR+, 63 planes over a 15.8-cm axial field of view. All patients fasted for at least 4 h before a mean dose of 410 MBq of ¹⁸F-FDG was administered intravenously. The number of bed positions ranged from 7 to 9, depending of the length of the patient, and all patients were scanned from the crown to the mid femoral region. Data acquisition in whole-body mode started 90 min after injection, with data being acquired for 5 min per bed position from the skull to the knees. Transmission imaging for attenuation correction was performed for 3 min per bed position. Data from multiple bed positions were iteratively reconstructed (ordered-subset expectation maximization) into attenuated and nonattenuated whole-body PET images (13).

Interpretation

¹⁸F-FDG PET findings were interpreted on computer monitors by 1 of 2 nuclear medicine physicians. Possible sites of metastatic disease from esophageal cancer were reported. ¹⁸F-FDG accumulation in regions not likely to be sites of metastatic spread from esophageal cancer was reported as suggestive of synchronous tumor, depending on intensity and pattern. All PET reports were retrospectively analyzed.

RESULTS

In this series of 366 patients who underwent ¹⁸F-FDG PET during initial staging of esophageal cancer, synchronous primary lesions were identified in 20 patients (5.5%).

Except for the 5 renal tumors, the described neoplasms were not detected by routine staging procedures. Details of these 20 patients are summarized in Table 1. Sixteen unexpected foci of uptake could be pathologically confirmed. Ten patients (50%) had a malignant synchronous tumor, and the remaining 10 patients had a benign or premalignant neoplasm.

Malignant Lesions

¹⁸F-FDG PET suggested a synchronous neoplasm in the ascending colon in patients 1 and 2. Colonoscopy revealed adenocarcinoma in both patients, and they underwent trans-thoracic esophagectomy (Ivor-Lewis method (14)) and right hemicolectomy in a single surgical session.

A synchronous primary tumor was found in the kidney in 5 patients (patients 3, 4, 5, 6, and 7). In all these patients, initial abdominal CT also revealed a mass in the renal region. Patient 3 underwent a diagnostic laparoscopy revealing peritonitis carcinomatosa, and therefore, no surgical therapy was indicated. In patient 4, cytology revealed a Grawitz's tumor; however, the tumor of the esophagus was not eligible for curative therapy. Patient 5 underwent a curative esophageal resection followed by a curative nephrectomy 3 mo later. Patients 6 and 7 were considered eligible for esophagectomy and nephrectomy in a single surgical session. However, in patient 7 (Fig. 1), after a successful nephrectomy the tumor of the esophagus was considered unresectable because of unexpected invasion of the thoracic aorta. Pathologic examination revealed a Grawitz's tumor in both patients.

TABLE 1
Characteristics of 20 Patients with Esophageal Cancer and a Synchronous Neoplasm

Patient no.	Sex	Age (y)	Esophageal cancer		Synchronous primary neoplasm	
			Location	Histology	Location	Histology
1	F	69	Distal	AC	Right colon	AC
2	M	65	Distal	AC	Right colon	AC
3	M	71	GEJ	AC	Right kidney	Grawitz's tumor
4	M	67	Distal	AC	Right kidney	Grawitz's tumor
5	M	68	GEJ	AC	Right kidney	Grawitz's tumor
6	M	69	GEJ	AC	Right kidney	Grawitz's tumor
7	M	47	Mid esophagus	SCC	Left kidney	Grawitz's tumor
8	M	72	Distal	SCC	Lung	SCC
9	F	70	Mid esophagus	SCC	Thyroid	Hürthle cell tumor
10	M	58	Mid esophagus	SCC	Gingiva	SCC
11	M	55	Distal	SCC	Right colon	—
12	M	74	GEJ	AC	Right colon	—
13	M	64	Distal	AC	Left colon	Tubulovillous adenoma
14	M	63	Distal	AC	Left colon	Tubulovillous adenoma
15	M	70	Distal	AC	Left colon	Tubulovillous adenoma
16	M	70	Distal	AC	Rectum	Tubulovillous adenoma
17	M	70	GEJ	AC	Rectum	Tubular adenoma
18	M	53	Mid esophagus	SCC	Rectum	Tubular adenoma
19	M	71	Distal	AC	Rectum	—
20	M	64	Distal	AC	Thyroid	—

AC = adenocarcinoma; GEJ = gastroesophageal junction; SCC = squamous cell carcinoma.

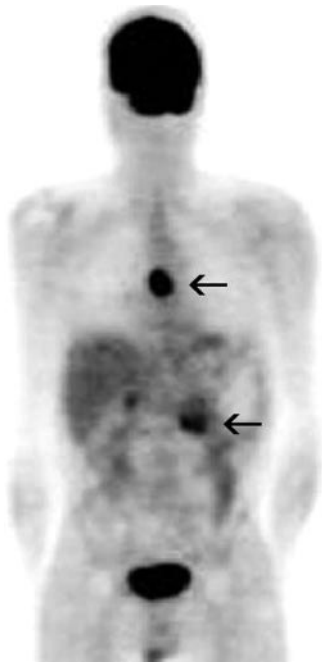


FIGURE 1. ^{18}F -FDG PET scan (coronal view) of patient 7, with synchronous carcinoma of mid esophagus (top arrow) and Grawitz's tumor of left kidney (bottom arrow).

In patient 8, with a squamous cell carcinoma of the esophagus, ^{18}F -FDG PET revealed a lesion in the right upper lobe suggestive of lung metastasis or synchronous lung carcinoma. Additional bronchoscopic examination provided cytologic evidence of a primary squamous cell carcinoma of the lung. The patient underwent right upper lobectomy and esophagectomy in a single session.

In patient 9, a supraclavicular metastasis was suspected on the basis of ^{18}F -FDG PET findings (Fig. 2). However, neither initial CT nor sonography of the cervical region showed any lymphatic abnormalities, nor did additional MRI of the cervical region. A second sonographic examination with fine-needle aspiration demonstrated a Hürthle cell thyroid tumor, for which a thyroidectomy was performed several months after the initial esophagectomy.

^{18}F -FDG PET showed in patient 10 a focus suggestive of a synchronous neoplasm in the oral cavity. Examination by a maxillofacial surgeon revealed a small squamous cell carcinoma of the gingiva. The gingival carcinoma in this patient was resected, but because of severe comorbidity the esophageal tumor was treated with combined intraluminal and extraluminal irradiation with curative intention.

Benign Lesions

Synchronous neoplasms were suspected in the ascending colon of patients 11 and 12 and in the descending colon of patients 13–15. Colonoscopy revealed tubulovillous adenoma in patients 13–15, which was resected endoscopically. In patients 11 and 12, no histologic examination was performed before surgery. Patient 11 underwent transthoracic esophagectomy with curative intent. However, because locoregional recurrence developed shortly after resection, follow-up of this synchronous lesion was not possible. In patient 12, diagnostic laparoscopy, which is standard in the

diagnostic work-up of cardia carcinoma, revealed peritonitis carcinomatosa, and the lesion in the colon was therefore not analyzed further.

In 4 patients, an unexpected ^{18}F -FDG accumulation was observed in the rectum and considered suggestive of a neoplasm. Sigmoidoscopy revealed tubulovillous adenoma in patient 16 (Fig. 3) and tubular adenoma in patients 17 and 18. All these adenomas were resected endoscopically. In patient 19, no histologic examination was performed. All the patients underwent esophagectomy with curative intention. Patient 19 died postoperatively; therefore, no histologic examination of the rectal lesion was performed.

In patient 20, ^{18}F -FDG PET showed a lesion suggestive of a neoplasm in the thyroid gland. Additional sonography of the neck showed a hypoechoic lesion suggestive of thyroid adenoma, and the lesion did not progress during 6 mo of follow-up.

DISCUSSION

The rate of synchronous neoplasms seen on ^{18}F -FDG PET in this unselected group of 366 patients with esophageal cancer was 5.5%. Most lesions were in the colon or rectum (11/20, or 55%). Sixteen lesions were evaluated histologically.

The rate of unexpected synchronous neoplasms in this study lies within the range of synchronous tumors for esophageal cancer as reported in the literature (4,6,7). In general, the occurrence of synchronous cancers strongly depends on the type of the initial cancer. Synchronous malignant tumors were detected in 9%–18% in patients with head and neck cancer, whereas in an inhomogeneous group of various cancer types the rate of malignant and premalignant tumors was 1.7% (15–17).

Misinterpretation of synchronous primary neoplasms may lead to incorrect upstaging of the primary tumor, as was demonstrated in patients 8 and 9. These patients were

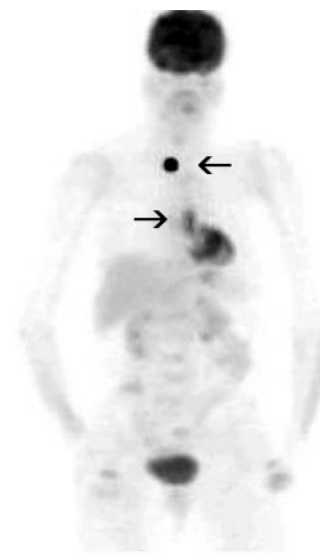


FIGURE 2. ^{18}F -FDG PET scan (coronal view) of patient 9, with tumor in mid esophagus (bottom arrow) and synchronous Hürthle cell thyroid tumor (top arrow) as confirmed by fine-needle aspiration.



FIGURE 3. ^{18}F -FDG PET scan (sagittal view) of patient 16, with distal esophageal tumor (top arrow) and synchronous rectal adenoma (bottom arrow).

initially suspected of having distant metastases (stage IV), on the basis of the PET findings, and would have erroneously been considered ineligible for surgery if histologic confirmation had not been sought. Therefore, additional investigations are mandatory to confirm the PET findings before any therapeutic decision is made. However, 4 lesions were not histologically verified in this study. In some patients, it was argued that the esophageal cancer heavily determined prognosis and that, therefore, the verification of assumed benign or premalignant lesions was not necessary. Nevertheless, the 2 lesions of the colorectum that turned out to be carcinomas are an argument in favor of verification of any positive PET finding. Another reason to verify positive PET findings is the well-known risk of false-positive results. ^{18}F -FDG is not a tumor-specific substance, and false-positive results may occur as a result of increased glucose metabolism in benign lesions (e.g., inflammatory tissue). Therefore, positive findings on ^{18}F -FDG PET must be confirmed by additional investigations, preferably by percutaneous or ultrasound- or CT-guided cytologic biopsy, or dedicated radiography, before patients are denied surgery with curative intent (11). Usually, physiologic colonic activity appears more tubular and diffuse than do separate colonic tumors, which appear more focal and of higher intensity. Because the renal excretion pattern of ^{18}F -FDG is similar to that of other radiopharmaceuticals, physiologic activities in renal collecting systems are easily detectable based on the precise location of activity, intensity of distribution, shape of the calyces and pelvis, and overall pattern of both kidneys.

The detection of synchronous tumors by whole-body ^{18}F -FDG PET poses a dilemma in the choice of the most suitable therapeutic strategy. For synchronous cancers, including esophageal cancer, the highest-priority treatment should focus on the tumor most limiting the prognosis (6). Therefore, optimal pretreatment staging of both tumors to assess their prognosis is the first step in clinical assessment.

If discrimination between 2 independent primary tumors versus metastatic disease is not possible based on conventional histology, cytogenetic analysis such as determination of loss of heterozygosity and p53 aberrations may be helpful to therapeutic decision making (18).

Resection of both neoplasms with curative intention frequently offers the best long-term survival; however, even in the case of an incurable synchronous cancer (e.g., metastatic prostate cancer), esophagectomy is not always contraindicated (19). The type of treatment for such esophageal carcinomas strongly depends on the type and prognosis of the synchronous malignancy.

Evidence-based arguments about whether to perform a simultaneous or a staged operation are not available. Suzuki et al. report that simultaneous resection of both neoplasms has acceptable morbidity and mortality rates (18). However, for each patient, the risks and benefits of simultaneous surgery should be weighed against those of a second operation (20).

The incidental detection of synchronous colorectal polyps or cancers and other malignancies by ^{18}F -FDG PET is not uncommon (17,21,22). Unfortunately, ^{18}F -FDG PET is not able to differentiate between colorectal adenoma and carcinoma (23). A true association between adenocarcinoma of the esophagus and colonic neoplasms would suggest common causes and might indicate the existence of an inherited general genetic defect. Another possible explanation might be exposure to environmental factors such as alcohol, smoking, and a fatty diet. In addition, increased expression of the cyclooxygenase 2 enzyme is central to the predisposition of both esophageal and colorectal cancers (24,25). However, a population-based cohort study in Sweden did not demonstrate an association between colorectal cancer and adenocarcinoma of the esophagus (26).

CONCLUSION

^{18}F -FDG PET may detect synchronous primary neoplasms in patients with esophageal cancer. Sites of suspected metastases should be confirmed histologically before treatment, because synchronous neoplasms can mimic metastatic disease.

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