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Brief communication

Detection of cancer recurrence in irradiated mandible using positron emission tomography

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Summary. Positron emission tomography (PET) is a promising method for pretherapeutic assessment of spread of squamous cell carcinomas (SCC) in the head and neck. A 41-year-old man with a history of operated and irradiated SCC of the tongue presented 4 years later with symptoms and signs of mandibular osteoradionecrosis. No changes related to malignancy could be seen in panoramic radiographs or computed tomography scanning with contrast enhancement. Since a biopsy of the involved region was positive for SCC, a PET study with [^{18}F]fluorodeoxyglucose (FDG) was performed. In dynamic PET images, intensive uptake of FDG was seen in a small area close to the right mental foramen. A hemimandibulectomy with reconstruction using a free vascularized graft from iliac crest was performed. In the resected specimen, histological examination showed a 1.2-mm focus of SCC in the soft tissue and bone around the mental foramen. These findings indicate that FDG-PET might be useful for presurgical evaluation of cancer recurrence in a previously irradiated mandible, especially if PET can accurately differentiate viable tumor tissue from radiation-induced fibrosis and inflammation.

Key words: Squamous cell carcinoma – Emission computed tomography – Radionuclide imaging – Osteoradionecrosis

Introduction

Radionuclide imaging of tumors in the head and neck has proven useful in selected cases for evaluation of thyroid masses, neoplastic involvement of bone, and infection [12]. Recently, new applications for cancer imaging are emerging from positron-emission tomography (PET) and the use of short-lived, cyclotron-produced radionuclides tagged in biological compounds to trace metabolic functions of cancer [3]. PET is superior to conventional radioisotope techniques in spatial resolution and ability to quantitate the distribution of the radiotracer within tissue [2]. The possibility for studying metabolic processes in vivo renders PET imaging a complementary method for clinical assessment of squamous cell carcinoma (SCC) of the head and neck [7, 9].

[^{18}F]Fluorodeoxyglucose (FDG) is the most widely used positron-emitting radiopharmaceutical for studies on cancer metabolism [14]. At present, PET scanning with the hexose analogue FDG has been found to be more sensitive than computed tomography (CT) and magnetic resonance imaging (MRI) for differentiating between recurrent tumor and necrosis after radiation treatment of gliomas [16] and colorectal tumors [15]. Our initial findings indicate that FDG is also useful for follow-up of radiation effects in patients with head and neck cancer [10]. The patient reported here illustrates the feasibility of FDG imaging for detecting small loci of SCC in the mandible and overlying mucosa following previous irradiation.

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Case report

A 41-year-old white man with a 20-year history of smoking was referred in November 1986 because of a mass in the left margin of his tongue. A 1.0 × 0.7 cm ulcerative lesion was found and biopsied. Histopathology revealed a moderately differentiated SCC. Clinical staging was then done and showed no metastatic lymph nodes. The patient was treated with a 4 MeV linear accelerator from lateral portals comprising oral cavity and upper neck to a dose of 3000 cGy. Thereafter, a left hemiglossectomy was performed but no residual SCC was found on microscopic examination of the surgical specimen. Postoperatively, external radiotherapy was continued to

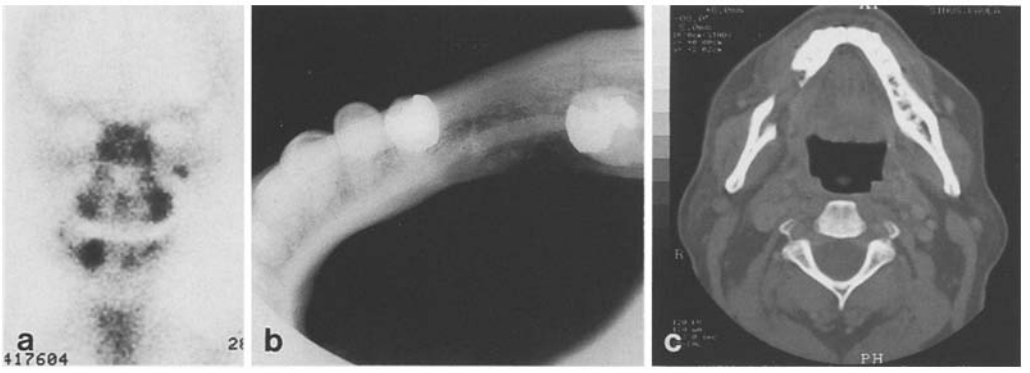

Fig. 1. a ^{99m}Tc-DPD bone scan of the mandible (AP projection). A region of increased tracer uptake can be seen in front of the right angle of the mandible. No other abnormalities are present. **b** Plain radiograph (occlusal projection) showing bone resorption in the toothless alveolar part of the mandible. **c** Axial computed tomography (CT) scan for the mandible showing an area of bone resorption in the right body of the mandible but no signs of destruction. Contrast-enhanced CT of the soft tissues (not shown) was also negative for tumor

a total dose of 6000 cGy to the tumor site and 5000 cGy to adjacent mandible.

The patient did well until 1988 when he had a left mandibular molar tooth extracted after hyperbaric oxygen treatment. In 1990 periodontal inflammation occurred in the left canine-premolar area, and since May 1991 an ulceration had persisted in the toothless premolar-molar area of the mandibular alveolar crest. The clinical picture and panoramic radiographs were suggestive of osteoradionecrosis. When symptoms became worse in September 1991, the mandible was imaged with ^{99m}Tc-DPD, which showed a hot spot in the right body of the mandible in the steady-state phase (Fig. 1a). Again, planar radiographs and CT scan (Fig. 1b, c) showed only cortical resorption in the same area but no conclusive signs of malignancy. However, a biopsy from the affected area during hyperbaric oxygen treatment was positive for SCC.

A dynamic PET study of the mandible was performed with a 931/08-12 ECAT scanner (Siemens/CTI, Knoxville, Tenn.) in the fasting state. After 10 min transmission scanning for measurement of attenuation correction, a 10-s bolus of FDG (266 MBq) was injected intravenously and sequential venous blood samples were drawn from the contralateral pre-heated arm during a 60-min acquisition time. The blood taken was then used to measure concentrations of unmetabolized tracer and glucose in plasma for calculation of FDG influx in tumor, as previously described [11]. The last frame of the acquisition (55–60 min after injection) was used for visual evaluation of the mandible and oral cavity.

FDG-PET showed a small but definite focus of increased uptake in the body of the right mandible, close to the mental foramen (Fig. 2). The uptake rate of the tracer had an influx constant of 0.017, although the true influx rate might have been 10–25% higher because of underestimation of radioactivity concentration in the small lesion due to partial volume effect. The actual pattern of the dynamic uptake was irreversible, which was considered typical of SCC in the head and neck region [11]. Behind the hot lesion, there was an area of moderately increased FDG uptake in the right mandibular body. In all other parts of the mandible uptake was very low (cf. [9]), and no other signs suggestive of malignancy were seen in tomographic PET images.

The patient underwent a hemimandibulectomy and replacement of the resected bone with a microvascular graft from ilial crest in December 1991. In the operation, a small soft-tissue tumor was seen on the mandibular bone close to the opening of the mental foramen. Histopathological examination of the removed soft tissues showed cancer only in the specimen taken from the opening of the mental foramen. The bone was examined by a cutting-grinding method. Serial longitudinal sections (10 μm) were prepared from the non-decalcified resection specimen fixed in 4% formalin and embedded in plastic [4]. At microscopic examination, bone involvement by moderately differentiated SCC was seen in the upper border of the mandible in the vicinity of the mental foramen (Fig. 3). The tumor focus within the bone tissue was surrounded by a heavy chronic inflammatory reaction. The largest dimensions of the focus as measured from the histological sections were 12 mm × 10 mm.

The postsurgical period was uneventful, and the patient was seen 12 months after treatment with no signs of residual or metastatic disease.

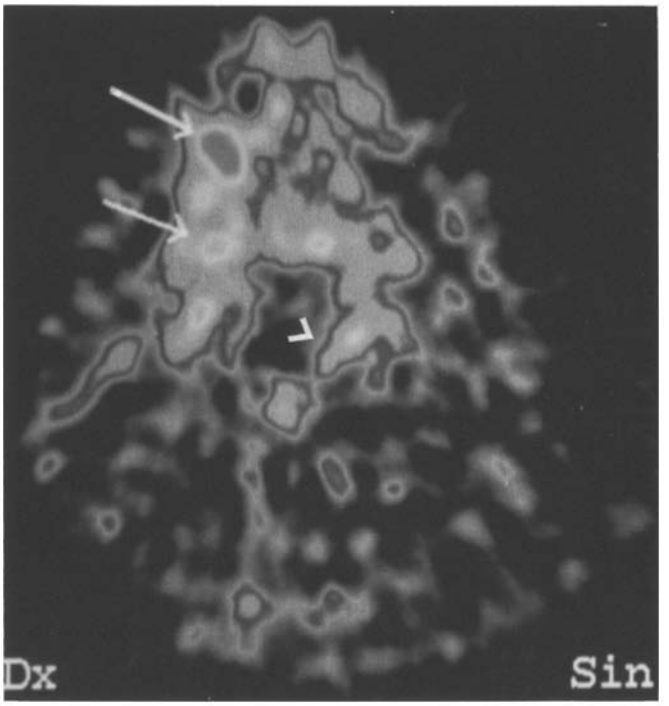

Fig. 2 Axial FDG-PET image at the level of the tongue in the steady-state phase delineating a small but definite focus of increasd uptake in the right mandible near the mental foramen *(thick arrow)*. Just behind the tumor focus, an area of slightly increased uptake is seen, most likely due to the presence of inflammatory cells *(thin arrow)*. Slighty increased physiological uptake is also seen bilaterally in the palatine tonsils *(arrowhead)*. Note that the whole left side of the mandible has low uptake, which is normal for non-diseased bony structures

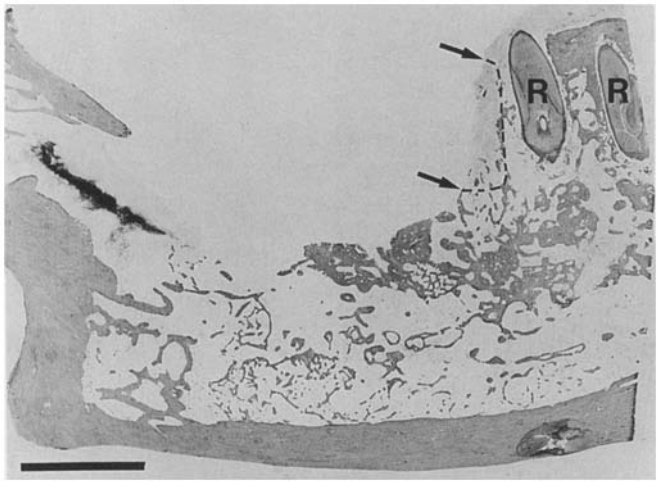

Fig. 3. Squamous cell carcinoma is present in the marked area between the *arrows* in this histological section through the middle part of the resection specimen. Behind the cancerous tissue, chronic inflamamtion is seen in accordance with slighty increased FDG uptake of the right body of the mandible. *R*, Roots of teeth. *Bar* = 10.0 mm. Toluidine blue stain, × 2.5

Discussion

The diagnosis of recurrent cancer after radiation treatment is often obscured by the presence of inflammation, edema, fibrosis and scarring which result from changes related to irradiation damage to the vasculature, stroma and surrounding normal cells [13]. Clearly, morphological imaging techniques may be insufficient to define whether or not underlying malignant disease is present. If osteoradionecrosis is evident, as was in the present case, neoplastic changes may remain undetected in standard radiographs.

A three-phase bone scanning with ^{99m}Tc-labeled biphosphonates is invaluable for the evaluation of possible extension of cancer to bone [12]. However, inflammatory lesions can also be demonstrated as areas of increased ^{99m}Tc uptake and a positive scan is found in the healing phase of bone surrounding necrosis after radiation injury [5]. Hence, findings in suspected osteoradionecrosis may be similar to those of recurrent SCC in bone, provided that osteoblastic activity is increased. Despite limitations in differential diagnosis, the good availability and low costs favor the use of bone scanning with biphosphonates in evaluating mandibular lesions after therapeutic irradiation.

In the present case, FDG-PET was found to be unequivocally positive in detecting cancer in an irradiated mandible, as compared to both conventional radiographs and ^{99m}Tc-DPD bone scanning. The tumor recurrence was most likely a second primary SCC, considering late development after initial treatment and location in a site contralateral to the original lingual lesion [1]. Although CT and MRI remain the standard imaging modalities for assessing tumors in the head and neck, PET may have some preferential use based on differential metabolic characteristics of tumor and surrounding normal tissues. Indeed, FDG-PET may be better than morphological imaging methods for evaluating superficial and submucosal tumors and for detecting neoplastic involvement of non-enlarged lymph nodes [9].

FDG uptake is related to the viability of cancer cells and reflects the increased metabolic demand of proliferating tissue [7, 8]. A presumed mechanism of tracer action is associated with enhanced aerobic and anaerobic glycolytic metabolism of malignant tumors and the fact that phosphorylated FDG is trapped intracellularly by neoplastic tissue [17]. FDG is taken up by both soft tissue and bone neoplasms, which makes it superior to bone-seeking agents in overall tumor detection [6]. Furthermore, the unsuitability of ^{99m}Tc for labeling natural compounds makes conventional gamma imaging less appealing to study tumor metabolism for monitoring treatment response to radiation [10]. Sensitivity for detecting primary tumors has been 100% in three series reporting tumor FDG uptake in patients with SCC in the oropharyngeal region [7, 9, 11]. Thus, FDG-PET might be the method of choice for radionuclide imaging of head and neck cancer for tumor detection and staging. Whether or not this is true will require further study.

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