Applied Cancer Research 2005; 25(1): 25-31

ORIGINAL REPORT

Initial Results and Clinical Application of Non Dedicated 18-FDG/PET in Head and Neck Oncology

Luiz Maurício Correia,[1] MD; Antônio Vitor Priante,[1] MD; André Lopes Carvalho,[1] MD PhD; Ivone Gonçalves Torres,[2] MD; Eduardo Nóbrega Pereira Lima,[2] MD; Luiz Paulo Kowalski,[1] MD PhD

1 Head and Neck Surgery and Otolaryngology Department, A.C. Camargo Cancer Hospital, São Paulo -Brazil

2 Radiology Department, A.C. Camargo Cancer Hospital, São Paulo -Brazil

Abstract

Imaging procedures are important methods for proper stage and treatment planning. Especially in previously treated patients, although not perfectly accurate. PET scan is a functional and imaging technique that has been used to diagnose and stage recurrent cancer from different sites. The combination of computed tomography coupled with FDG-PET (18-FDG-PET/CT) reaches high quality anatomical and functional images. OBJECTIVE: To describe the initial results of FDG-PET/CT performed at a single institution. MATERIAL AND METHODS: This technique was used in 63 patients with head and neck tumors. The purpose of the exam was: a) to rule out recurrent disease - 55 patients; b) to search for hidden primary tumor - 2 patients; and c) postoperative follow-up of residual disease - 6 patients. Computed tomography (CT) was performed in 56 cases (88.9%). Pathological confirmation was obtained in 24 cases (38.1%), all the remaining cases were considered negative based on clinical follow-up information with no evidence of recurrent disease 12 months after the PET/CT exam. RESULTS: Overall results for the accuracy of FDG-PET were: 93.9% of sensitivity, 64.2% of specificity, 75.6% of positive predictive value and 90.0% of negative predictive value. FDG-PET was able to find 1 out of 2 undetected primary tumors (base of the tongue). The best results were obtained regarding the detection of local and distant recurrences of larynx, thyroid and oral cavity cancers. CONCLUSION: The FDG-PET/CT fusion image makes anatomical localization easier and the accuracy for detection of recurrent disease was found to be higher than CT alone.

Key words: Fluorodeoxiglucose f18; Positron Emission Tomography. Head and Neck Neoplasms.

Introduction

Head and neck cancer (HNC) comprises a large group of heterogeneous and low to moderately prevalent diseases that usually require high cost diagnostic and treatment resources. High-resolution image methods are fundamental for treatment planning, ressectability evaluation, to access the presence and extension of lymphnode metastasis, to evaluate tumor response to chemotherapy and radiotherapy, as well as post-treatment surveillance.[1] Although a relatively high rate of tumor loco-regional recurrences occurs, most are diagnosed in advanced stages due to difficulties on the clinical and radiological post-treatment evaluation. This fact is more likely to reduce the number of patients to be submitted to a survival treatment.[2]

PET scan is an important method for metabolic imaging that has been used to diagnose and stage recurrent disease in the fields of oncology.[3] In addition to conventional methods, PET has also shown consistent and promising results in HNC.[3] The image is based on high glycolytic rates by tumor cells. The most employed radiotracer, ^{18}F-fluorodeoxiglucose, is a high cost and short half life glucose analog. The tumor high rates glucose uptake are secondary to glucose carriers that are overexpressed to support the high metabolic consumption.[4] Thus the use of such radiotracer provides a highly specific and non-invasive

Correspondence
Luiz Paulo Kowalski, MD, PhD
A.C. Camargo Cancer Hospital
Rua Antonio Prudente, 211
01509-900 São Paulo, Brazil
Phone: 55 11 33410325
E-mail: lp_kowalski@uol.com.br

method for a whole body scan for malignant cells. The objectives of PET scan are to locate primary tumors, clinical staging, and mainly, to monitor treatment response and recurrences. However, classical resolution limits are reported to be 4mm to 5mm, and other disadvantages are low definition images, costs and availability.[1] More recently, dedicated or non-dedicated machines connected to computed tomography (CT) have been used to generate a better anatomical image detail leading to accuracy of both exams (Figure 1).[3]

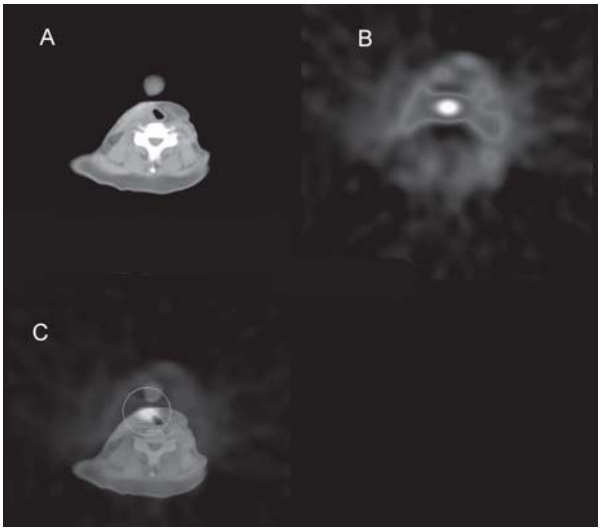

Figure 1 *– PET/CT image in a recurrent larynx cancer. 1A – CT image; 1B – PET image; 1C – PET/CT fused image*

The objective of this study is to report our experience using a non-dedicated ^{18}F-FDG high resolution PET/CT in patients with HNC treated in a single institution from July 2001 to January 2003, submitted to either conventional CT or magnetic resonance image (MRI) and FDG-PET/CT.

Material and Methods

Sixty three patients with histologically confirmed primary or previously treated HNC were included in the study. The tumor sites were: oral cavity in 11 cases; oro/hypopharynx in 12; nasopharynx in 4; larynx in 11; thyroid in 9; paranasal sinuses in 5; undetected primaries (UP) in 2 and others sites in 9 cases. Histologic diagnosis were: squamous cell carcinomas (49 cases); medullary (6 cases), papillary (2 cases) and follicular (1 case) carcinomas of the thyroid; lymphoepitheliomas (4 cases) and adenoid cystic carcinoma (1 case).

The mean age was 51.3 year-old, ranging from 29 to 75 year-old. There were 16 women (25.3%) and 47 men (74.6 %). The indications of PET/CT fusion were: pre-treatment evaluation of undetected primary (UP) in 2 patients (3.2%), possible residual tumor after treatment in 6 (9.5%) and to rule out tumor recurrence in 55 (87.3%). Among these patients, 55 (87.3%) were submitted to conventional CT scan and 6 (9.5%) to MRI as the first image method used for evaluation.

PET/CT exam was performed in a non-dedicated GE Hawkeye®PET/CT scanner with an average dose of 7.5 mCi of ^{18}F-fluorodeoxiglucose (Figure 1). The PET/CT results were considered negative or positive for tumors regarding local, regional or distant sites involved. We have considered it as the "Gold Standard" method either pathological examination of specimens (biopsy or surgery) - available for 24 patients (38.1%), or clinical follow-up with no confirmation of recurrent disease after 12 months (all remaining patients). Results were analyzed according to the accuracy, sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV). The results are reported by tumor site and purpose of the exam and then compared with conventional methods (CT or MRI). Results for PET/CT were also divided in general use (all cases together) and in specific use on cases in which the method was used to rule out recurrent disease (local, regional or distant).

Results

Diagnostic Procedures

Two patients (3.2%) with UP were submitted to image evaluation. The first one had a metastatic cervical lymph node and the primary tumor was not identified with endoscopy, CT or PET/CT exams. After one year post-treatment follow-up there was no evidence of the primary tumor location (true negative result). The other case with metastatic cervical lymph node had the diagnosis of a small lesion in the base of the tongue made only by PET/CT. This result has been confirmed by biopsy (true positive result).

Post Treatment Evaluation

Six patients (9.5%) were submitted to PET/CT scan to evaluate residual disease. The

first one had a facial sarcoma operated with close surgical margin. Both CT and PET/CT scan have shown no residual tumor. After one-year follow-up the patient remained with no evidence of disease (NED). The second case was of a patient with mandible osteosarcoma that had previously undergone radical surgery. There was no clinically suspicious recurrent disease at follow-up, but a routine CT showed an unspecific image in the local, but not specific for recurrence or fibrosis. PET/CT has shown an abnormal radiotracer concentration in the same site. A biopsy confirmed a local recurrence (true positive).

The third case was of a patient with a medullary thyroid carcinoma with persistent increase in calcitonin blood level after surgery. PET/CT has shown a mediastinal extension of the tumor that was not identified by conventional CT. Metastatic medullary carcinoma was confirmed after reoperation (true positive). The fourth one was a case of a patient with parotid gland tumor. Clinically there was a postoperative fibrotic lesion under the scar. Both CT and PET/CT have shown no significant alterations. A fine needle aspiration has confirmed no residual tumor and one-year follow-up has shown no evidence of recurrence (true negative).

The last two cases were of medullary thyroid carcinoma treated surgically. One patient had a paratracheal node detected postoperatively by MRI without PET uptake. Patient had undergone surgical procedure and histologic evaluation revealed a low-grade

Table 1 - Accuracy obtained from CT and PET/CT for general cases and for the specific recurrent cases

Histopathological Grade	General CT (n=56)	General PET/ CT (n=63)	Recurrent CT (n=53)	Recurrent PET/ CT (n=56)
Sensitivity	75.7%	93.9%	82.0%	93.1%
Specificity	48.0%	64.2%	51,8%	62.5%
Positive PV	65.7%	75.6%	63,8%	75.0%
Negative PV	60.0%	90.0%	73,6%	88.2%

Table 2 - Sensitivity and specificity of PET/CT according to the site of recurrence

Suspicious site of recurrence	PET/CT uptake	Pathological/clinical final diagnosis Positive (n)	Negative (n)	Sensitivity	Specificity
Local	Positive	20	7	100%	61%
(n=38)	Negative	0	11		
Regional	Positive	13	1	88%	50%
(n=16)	Negative	0	2		
Distant	Positive	8	3	100%	50%
(n=15)	Negative	1	3		

Table 3 - Sensitivity and specificity of PET/CT according to the site of the primary tumor (for the 5 most common sites)

	Sensitivity	Specificity
Oro/Hypopharynx (n=12)	100%	33%
Larynx (n=11)	100%	80%
Oral cavity (n=11)	100%	66%
Thyroid (n=9)	100%	75%
Paranasal sinuses (n=5)	66%	50%

sarcoma (false negative). The other patient had a local uptake detected by both DMSA-V scintygraphy and the PET/CT. The surgical procedure found no recurrent disease; calcitonin level has remained normal and, after 1 year follow-up patient was uneventful (false positive).

Tumor Recurrence Diagnosis

A total of 55 patients (87.3%) were submitted to imaging evaluation for suspicious recurrent tumors (38 local, 16 regional and 15 at distant sites). Radiotherapy was used in 39 patients (70.9%). The observed sensitivity for recurrent disease diagnosis was 93.1% and the specificity was 62.5% (Table 1). These findings varied according to the type of suspicious recurrence (local, regional or distant),the best accuracy was observed in local recurrence (Table 2). Results have also varied according to the site of the primary tumor, with the best accuracy found for larynx, thyroid and oral cavity tumors (Table 3).

The false negative and false positive results are presented in Table 4. Yet, there was 1 non-confirmed case and 1 patient was unavailable for follow-up. General results have shown that in the first three months of this experience, the accuracy was influenced by a higher number of false positive and negative results – "learning curve" (Table 5).

Table 4 – Description of the false negative and false positive results for PET/CT

PET/CT accuracy	Tumor site	CT result	PET/CT result	Clinical confirmation	Comments
FALSE NEGATIVE					
	Larynx	positive	negative	Surgery - positive	
	Maxillary	positive	negative	Biopsy - positive	
FALSE POSITIVE					
	Oropharynx	negative	positive	Biopsy - negative	Abdominal infection
	Oropharynx	negative	positive	Follow-up - negative	Mandibular plaque
	Oropharynx	negative	positive	Follow-up - negative	Inflammatory ?
	Oropharynx	negative	positive	Follow-up - negative	Inflammatory ?
	Nasopharynx	negative	positive	Biopsy - negative	Inflammatory ?
	Hipopharynx	negative	positive	Biopsy - negative	Chondronecrosis
	Larynx	negative	positive	Surgery - negative	Inflammatory ?
	Paran. Sinus	negative	positive	Follow-up - negative	
	Oral cavity	negative	positive	Surgery - negative	Radiotherapy?
	Thyroid medullary	positive	positive	Surgery - negative	

Table 5 - Sensitivity and specificity for the first 3 months (learning curve) and after this period for general use and recurrent disease diagnosis by PET/CT

	General PET/CT First 3 months	General PET/CT	Recurrent PET/CT
Sensitivity	90.0%	95.6%	94.7%
Specificity	37.5%	75.0%	75.0%
Positive PV	64.0%	81.4%	81.8%
Negative PV	75.0%	93.7	92.3%

PV – predictive value

Discussion

Image studies such as CT, MRI, ultrasound and scintigraphy are useful methods currently in use for staging, treatment planning, and follow-up in HNC patients. However these methods have several limitations, and overall accuracy is around 60%.[1-3;5] Moreover, the diagnosis of hidden disease can reach only up to 30%.[1] It is generally accepted that the limit for neck lymph nodes detection by CT is in the range of 5 and 10mm, but about 40% of metastatic lymph nodes are smaller than that.[3;6;7] MRI has not proved to be a better method.[1] The major limitation of both methods is the differentiation between scar, benign lesions and recurrent cancer in a patient submitted to multimodality treatment.[1]

Many articles have been published about FDG/PET scan, most of them in oncology, but a few using PET /CT machines. Four international consensuses held in Germany established the PET scan indications (Onko PET) and its clinical utility was classified[8]. HNC was considered a subset field in oncology where PET has shown strong accuracy in staging, diagnosis of tumor recurrence and diagnosis of undetected primaries (UP) (category 1a/1b).[8] Grouping a number of studies with a total of 325 patients the use of PET for lymph node staging had an 87-90% sensitivity and 80-93% specificity.[8] For diagnosis of the local recurrence, 216 patients were evaluated with an 80-100% sensitivity and a 64-96% specificity. The studies on investigation of UP were done in 208 patients and the diagnosis was made in 24% to 53% of the cases, depending on the study.[8] Manolidis et al.[9] had an 87% accuracy detection of primary tumors. Our results with 63 HNC patients are according to the reported results in the literature.[8]

Despite these favorable results, some authors point out negative factors of FDG/PET, such as lack of anatomic details in conventional machines, making difficult the interpretation of image details.[1] Brink et al.[10] published a study where the technique using a 90 minutes uptake was demonstrated to be more accurate in cervical lymph node detection. Another important issue concerns the differentiation between tumor and infectious/reactive tissues, which are associated with false positive results[1]. Moreover, physician interpretation and experience with the method play an important role in the accuracy of the results. However, even in the very beginning of the "learning curve" it has been shown that PET is more accurate than clinical exam and conventional image in the follow-up.[1;11;12]

In this study the most common indication for PET/CT was the suspicion of tumor recurrence or presence of distant metastasis based on clinical or conventional image methods. General sensitivity was 93.1% reaching near 100% in some subsites (larynx, thyroid, and oropharynx), comparing favorably with CT (75.7%). False positive results occurred in 10 cases (15.9%), 6 of them previously submitted to radiotherapy and 1 patient with abdominal infectious disease. Three of these false-positive cases had a normal exam 3 months after. Two false-negative cases occurred (3.2%). One patient proved to have a maxillary tumor recurrence. The PET/CT was made during palliative chemotherapy, what possibly altered glucose uptake. The second case, a patient with larynx cancer who had been previously submited to radio and chemotherapy; the PET/CT result was negative, but laryngoscopy and biopsy confirmed a local recurrence.

Stokkel et al.[5] reported sensitivity rates of 100% for larynx and hypopharynx recurrences using dual head PET scanners. In the Netherlands, costs favors the use of PET/CT, since an endoscopy and biopsy under general anesthesia costs around US$2,500 and PET/CT costs US$1,000. Critical point to the method is low specificity rates ranging from 64 to 96%.[8] False positive results are usually attributed to the detection of infectious lesions, that uptakes glucose. In case of suspicious results, new PET has been recommended in three months.[1;4;8;11-14].

For distant metastasis, Pitman et al.[6] have published results of PET to differentiate benign and malignant pulmonary nodules with sensitivity of 91% and specificity of 88%. False results secondary to tuberculosis and sarcoidosis were reported.

For regional lymph node staging, PET was considered strong evidence based on the German consensus, as it was shown in 325 patients from different studies, rates for sensitivity raging between 87-90% and for specificity 80-93%.[8] In our study there was only one patient with neck uptake that was not

confirmed as metastatic lymph node by neck dissection. In lymph node staging PET also had better results (sensitivity 82%, specificity 100%) when compared to the conventional methods. Popperl et al.[15] have shown that in 23 small lesions (<12mm) detected among 72 patients, PET failed to identify tumor in 43%. Based on these numbers, Stoeckli et al.[2] have compared PET scan with elective node dissection for larynx and oropharynx cancer. The results were not satisfactory due to low accuracy. PET was considered to have poor resolution (4-5mm) to detect micrometastasis.

Only two patients with UP were included in our study. The diagnosis of primary tumor was established by PET/CT in one of them. Manolidis et al.[9] (85) have shown that up to 56% of the patients had a primary tumor diagnosed by PET. Johansen et al.[13]have reported a 48% uptake rate in UP, but only 50% of these cases were confirmed by biopsy.

Halfpenny et al.[7] have also tried to associate high FDG uptake (HFU) standardized values with more aggressive tumors in head and neck region. Using 73 patients, they have concluded that these patients had a poorer outcome and should be treated more aggressively. Other studies have also demonstrated PET scan prognostic value.[16;17]

Our results in recurrent disease were similar to those reported in the literature.[18] Combined PET/CT has also seemed to be better than other conventional image techniques. Wong et al.[19] have reported PET results as a highly sensitive method for recurrence. They have also concluded that PET has high sensitivity for regional disease, high specificity for distant disease and in local recurrences low specificity but highly sensitivity. Positive PET-CT results were correlated with increased risk of relapse and death.

General results have shown that a higher number in false results in the first trimester, justified by the "learning curve" has influenced accuracy as shown in table 5 (poorer accuracy compared to the following period).

This report and the literature have a large number of publications showing FDG PET scan superiority to conventional image methods (mainly CT) in detecting recurrences.[18] Our results with FDG-PET were more accurate than clinical exam and/or CT to evaluate recurrent disease. Although several recommendations have been published, a well-controlled trial showing cost/benefit analysis is yet required.

References

1. Kresnik E, Mikosch P, Gallowitsch HJ, Kogler D, Wiesser S, Heinisch M, et al. Evaluation of head and neck cancer with 18F-FDG PET: a comparison with conventional methods. Eur J Nucl Med 2001; 28:816-21.
2. Stoeckli SJ, Steinert H, Pfaltz M, Schmid S. Is there a role for positron emission tomography with 18F-fluorodeoxyglucose in the initial staging of nodal negative oral and oropharyngeal squamous cell carcinoma. Head Neck 2002; 24:345-9.
3. Teknos TN, Rosenthal EL, Lee D, Taylor R, Marn CS. Positron emission tomography in the evaluation of stage III and IV head and neck cancer. Head Neck 2001; 23:1056-60.
4. McGuirt WF, Greven K, Williams D, III, Keyes JW, Jr., Watson N, Cappellari JO, et al. PET scanning in head and neck oncology: a review. Head Neck 1998; 20:208-15.
5. Stokkel MP, Terhaard CH, Hordijk GJ, van Rijk PP. The detection of local recurrent head and neck cancer with fluorine-18 fluorodeoxyglucose dual-head positron emission tomography. Eur J Nucl Med 1999; 26:767-73.
6. Pitman AG, Hicks RJ, Binns DS, Ware RE, Kalff V, McKenzie AF, et al. Performance of sodium iodide based (18)F-fluorodeoxyglucose positron emission tomography in the characterization of indeterminate pulmonary nodules or masses. Br J Radiol 2002; 75:114-21.
7. Halfpenny W, Hain SF, Biassoni L, Maisey MN, Sherman JA, McGurk M. FDG-PET. A possible prognostic factor in head and neck cancer. Br J Cancer 2002; 86:512-6.
8. Reske SN, Kotzerke J. FDG-PET for clinical use. Results of the 3rd German Interdisciplinary Consensus Conference, "Onko-PET III", 21 July and 19 September 2000. Eur J Nucl Med 2001; 28:1707-23.
9. Manolidis S, Donald PJ, Volk P, Pounds TR. The use of positron emission tomography scanning in occult and recurrent head and neck cancer. Acta Otolaryngol Suppl 1998; 534:1-11.
10. Brink I, Klenzner T, Krause T, Mix M, Ross UH, Moser E, Nitzsche EU. Lymph node staging in extracranial head and neck cancer with FDG PET—appropriate uptake period and size-dependence of the results. Nuklearmedizin 2002; 41:108-13.
11. Nowak B, Di Martino E, Janicke S, Cremerius U, Adam G, Zimny M, et al. Diagnostic evaluation of malignant head and neck cancer by F-18-FDG PET compared to CT/MRI. Nuklearmedizin 1999; 38:312-8.
12. Lowe VJ, Dunphy FR, Varvares M, Kim H, Wittry M, Dunphy CH, et al. Evaluation of chemotherapy response in patients with advanced head and neck cancer using [F-8] fluorodeoxyglucose positron emission tomography. Head Neck 1997; 19:666-74.
13. Johansen J, Eigtved A, Buchwald C, Theilgaard SA, Hansen HS. Implication of 18F-fluoro-2-deoxy-D-glucose positron emission tomography on management of carcinoma of unknown primary in the head and neck: a Danish cohort study. Laryngoscope 2002; 112:2009-14.

14. Hustinx R, Smith RJ, Benard F, Rosenthal DI, Machtay M, Farber LA, et al. Dual time point fluorine-18 fluorodeoxyglucose positron emission tomography: a potential method to differentiate malignancy from inflammation and normal tissue in the head and neck. Eur J Nucl Med 1999; 26:1345-8.
15. Popperl G, Lang S, Dagdelen O, Jager L, Tiling R, Hahn K, et al. [Correlation of FDG-PET and MRI/CT with histopathology in primary diagnosis, lymph node staging and diagnosis of recurrency of head and neck cancer]. Rofo 2002; 174:714-20.
16. Anzai Y, Carroll WR, Quint DJ, Bradford CR, Minoshima S, Wolf GT, et al. Recurrence of head and neck cancer after surgery or irradiation: prospective comparison of 2-deoxy-2-[F-18]fluoro-D-glucose PET and MR imaging diagnoses. Radiology 1996; 200:135-41.
17. Bailet JW, Abemayor E, Jabour BA, Hawkins RA, Ho C, Ward PH. Positron emission tomography: a new, precise imaging modality for detection of primary head and neck tumors and assessment of cervical adenopathy. Laryngoscope 1992; 102:281-8.
18. Gambhir SS, Czernin J, Schwimmer J, Silverman DH, Coleman RE, Phelps ME. A tabulated summary of the FDG PET literature. J Nucl Med 2001; 42:1S-93S.
19. Wong RJ, Lin DT, Schoder H, Patel SG, Gonen M, Wolden S, Pfister DG, Shah JP, Larson SM, Kraus DH. Diagnostic and prognostic value of [(18)F] fluorodeoxyglucose positron emission tomography for recurrent head and neck squamous cell carcinoma. J Clin Oncol 2002; 20:4199-208.