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# A preliminary report on the impact of $^{18}$F-FDG PET/CT in the management of paediatric head and neck cancer

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***Introduction*** **Paediatric head and neck malignancy accounts for 5% of all paediatric cancers. The choice of treatment and prediction of prognosis depend on the histological type of tumour, initial staging, evaluating treatment response and detection of early recurrence. Conventional imaging modalities have many limitations. Positron emission tomography/computed tomography (PET/CT) is more accurate; however, so far, the literature lacks reports of large groups of paediatric patients.**

***Aim*** **To report the role of PET/CT in factors affecting the choice of treatment at the newly established Children Cancer Hospital in Cairo, Egypt, which is one of the busiest dedicated paediatric oncology centres in the world. All findings were proven by histopathology, radiology and by clinical follow-up.**

***Patient population*** **Thirty-six paediatric patients (30 boys and six girls) with various histologically proven head and neck cancers were included in this study. Their age ranged from 2 to 17 years. High-resolution diagnostic CT and/or MRI of the head and neck, and in relevant cases also of the chest and the abdomen, were performed in all patients at a mean interval of 1.6 weeks (range, 1–3 months) before the PET/CT study. Results of PET/CT were compared with the findings of these conventional imaging modalities.**

***Results*** **The sensitivity, specificity, accuracy, positive and negative predictive values of PET/CT against the conventional imaging were as follows: sensitivity 100 and, 53%, specificity 89.5 and 47%, accuracy 94.5 and 50%, positive predictive value 89.5 and 47% and negative predictive value 100 and 53% respectively. PET/CT changed patient management in 50% of the cases.**

***Conclusion*** **PET/CT in paediatric head and neck carcinoma is more accurate than conventional imaging. Therefore, it also has a significant impact on further patient management. We recommend that it should be the first imaging modality for all purposes in initial staging, evaluating treatment response and follow-up in paediatric head and neck carcinoma.** ***Nucl Med Commun*** **33:21–28** © **2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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## Introduction

Head and neck cancer represents approximately 5% of all paediatric cancer cases. It is the second leading cause of death between 14 and 20 years of age [1]. At diagnosis, accurate staging is important in selecting the appropriate treatment strategy and has a significant prognostic value. After therapy, assessment of treatment response and early detection of recurrence are critical to achieving an optimal outcome. Computed tomography (CT) and MRI are the standard conventional imaging modalities (CIM) for the evaluation of patients with head and neck cancer. These tests, however, are based on morphologic diagnostic criteria, such as nodal size and contrast enhancement patterns, that do not always reflect the presence of active malignancy accurately. Although imaging is important for assessing the response after treatment of head and neck tumours, the regional anatomy is distorted by surgery and/or radiation; this makes the distinction between post-treatment changes and recurrence or residual tumour more difficult with CIM that rely on morphologic criteria [2]. Fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) is a functional imaging modality that plays an increasingly crucial role in the assessment of head and neck cancer, for both primary staging and post-therapy management [3,4]. The use of PET is based on its unique ability to assess the metabolic status of tumours. PET has proved superior to both CT and MRI in diagnosing and differentiating recurrence from post-radiation effects and surgical scars in head and neck tumours in adults [5,6] and for the detection of cervical lymph node status in these patients with head and neck cancer [7]. However, PET is limited by the lack of anatomic landmarks, and thus it is sometimes difficult to find the precise

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localization of suspicious findings. In addition, variable degrees of physiologic and inflammatory, noncancer-related uptake of FDG in the region of the head and neck, mainly after treatment, can confound interpretation of suspicious foci. The combined imaging modality of PET/CT makes it possible to sequentially acquire PET and CT in a single imaging session with the fusion of clinically significant anatomic and metabolic data. Preliminary studies have shown that PET/CT improves the anatomic localization of FDG-avid abnormalities and reduces the number of equivocal PET interpretations in head and neck tumours in adults [8]. Although the use of $^{18}$F-PET/CT has been established for early diagnosis, staging and early detection of recurrence in head and neck cancer in adults, it has, until now, been explored less extensively in paediatric patients. The growing use of PET/CT imaging in paediatrics suggests that this technique contributes significantly to the care of paediatric oncology patients.

We conducted this retrospective study at the newly established Children Cancer Hospital (CCH), Cairo, Egypt, which is one of the busiest paediatric oncology centres in the world. The aim of the study was to evaluate the performance of $^{18}$F-FDG PET/CT in paediatric head and neck cancers for the purpose of initial staging, evaluating treatment response and for long-term follow-up to detect recurrence. Furthermore, the impact of PET/CT results on subsequent care of paediatric head and neck cancer patients was evaluated.

## Patients and methods

Between January 2008 and September 2009, 36 paediatric patients (30 boys and six girls) with various histologically proven head and neck cancers had 42 PET/CT studies at the newly established PET/CT Centre at the CCH, Egypt. Their age ranged from 2 to 17 years. The clinical characteristics and referral patterns of the patient population are presented in Table 1. High-quality diagnostic CT in all patients and/or MRI of the head and neck were performed at a mean of 1.6 weeks before the PET/CT study (range, 1–3 months), and in relevant cases, CT or MRI of the chest and the abdomen were also performed. The Hospital Scientific and Ethical Committee approved this retrospective study. All the participants (or their guardians) in this study gave their informed consent before inclusion in the study.

**Table 1 Summary of patient characteristics**

| Parameter | No of patients (total $n=36$) |
|---|---|
| Tumour type | |
| Nasopharyngeal carcinoma | 14 |
| Non-Hodgkin's lymphoma | 9 |
| Rhabdomyosarcoma | 9 |
| Parotid muco-epidermoid carcinoma | 1 |
| Squamous cell carcinoma | 2 |
| Cervical nodal metastasis of unknown primary | 1 |
| Sex | |
| Male | 30 |
| Female | 6 |
| Indication for PET/CT | |
| Initial staging | 9 |
| Assessment of treatment response | 23 |
| Detection of recurrence | 4 |

PET/CT, positron emission tomography/computed tomography.

The setting of this study was more or less comparable to other nuclear medicine departments in paediatric oncology centres worldwide. The equipment, staffing, examination techniques and interpretation of the scans at the CCH PET/CT Centre have been set up to reflect the current standard of international practice. The indications for referral to PET/CT reflected the prevalence of different head and neck cancers in our paediatric population, and in the first approximation are similar to other countries.

### PET imaging

Forty-two studies were performed on a dedicated PET/CT scanner (40 slice true point Biograph; Siemens, 2007 Siemens Medical, Heidelberg, Germany). Patients fasted for at least 4–6 h before the examination. Blood glucose levels were lower than 120 mg/dl. Patient weight ranged from 9.5 to 72 kg with a mean weight of 33.6 kg. Acquisitions were started 45–60 min after an intravenous injection of 3.7 MBq/kg of $^{18}$F-FDG. Whole-body scans were acquired in overlapping bed positions usually from the mid-thighs to the base of the skull with the arms extended above the head, with 3 min acquisition time for each bed position. All patients except five were imaged without sedation. Images were processed using iterative reconstruction. Attenuation correction was applied using CT data according to the manufacturer's recommended protocol.

### CT acquisition

CT was performed either as low-dose CT for attenuation correction and anatomical localization or as high-dose CT for diagnostic purposes with CT mA adjusted accordingly. IV contrast was given in all the studies.

An initial scout view was obtained at 35 mAs and 120 kVp. For low-dose CT, this was followed by a spiral CT at 0.5 s per rotation with exposure factors 60 mAs (quality reference) and 120 kVp, a reconstructed slice thickness of 5 mm and an increment of 3 mm. Diagnostic-quality CT was obtained with 170 mAs and 120 kVp, a reconstructed slice thickness of 3 mm and an increment of 1.4 m.

The whole-body effective dose from the low-dose CT was on average 3.4 mSv, whereas that from diagnostic CT was 11.5 mSv.

### Interpretation

PET/CT studies were read by two nuclear medicine consultants independently. Every focus of increased FDG uptake was recorded and classified by visual analysis as malignant, equivocal or benign on the basis of the shape, size, intensity and localization of the focus. Semi-quantitative estimation of tumour glucose metabolism

by means of standardized uptake value (SUV) was performed for all cases with a cut-off value of 2.5 using the weight-based SUV.

CT and MR were the comparator CIMs. All patients had CT; two patients had one MR each in addition to their CT in order to improve specificity (patients no. 3 and 6 in Table 3). All the CT scans (and MR when relevant) were retrospectively reviewed and read by a consultant radiologist. CIM findings were classified as negative, malignant or equivocal in accordance with the accepted criteria for suspicion of malignancy on CIM. The criteria used for diagnosing malignant lymph nodes were loss of fatty hilum and a nodal size greater than 8 mm in a relevant nodal station. The criteria used to assess the primary mass were as follows: size change compared with previous scans; degree of contrast enhancement; symmetry with contra-lateral normal structures; presence of post-treatment oedema or inflammatory change. The reading radiologist was not aware of the findings of the PET/CT or the original reports of the CIM.

### Data analysis

The following criteria were accepted as our standard of reference: (a) histopathologic findings; (b) the combination of negative clinical findings, negative findings of other imaging studies or negative follow-up findings; (c) resolution of apparent abnormalities at subsequent PET/CT studies without intervening therapy together with negative clinical follow-up findings; and (d) the combination of positive clinical findings at the time of PET/CT and resolution of the tumour after chemotherapy or radiation therapy. Table 2 shows the criteria used to make up the composite standard of reference, and the number of patients in our patient population in whom each criterion was used.

The PET/CT results were compared with the findings of CIM on a per-patient basis. The same anatomical regions were compared (i.e. neck on CIM compared with neck on PET/CT). The performance of both PET/CT and CIM was evaluated through comparison with our reference standard. The PET/CT and CIM findings were classified as true positive [(TP), positive imaging study confirmed by the presence of cancer], true negative [(TN), normal study with no further evidence of cancer], false positive [(FP), positive imaging study with no evidence of cancer] or false negative [(FN), normal study with further proven cancer]. The criteria that represent the reference standard for the presence or the absence of cancer included histopathologic sampling in seven patients and clinical and radiologic follow-up in 27 patients. Two patients with diffuse metastatic disease on PET/CT were treated with palliative therapy without any additional diagnostic procedures. The sensitivity, the specificity, the negative and positive predictive values and the accuracy of PET/CT and CIM were calculated from the performance tables.

Changes in the clinical decision-making resulting from PET/CT were reviewed and recorded for impact on patient management for each study.

**Table 2 Number of patients according to the reference standard**

| Reference standard | No of patients |
|---|---|
| Histopathology | 7 |
| Negative clinical and radiological follow-up (minimum, maximum, range, average) | 17 |
| Resolution of PET/CT abnormality with no active treatment (no chemotherapy or radiotherapy) | 1 |
| Improvement or resolution of PET/CT lesions after active treatment | 9 |
| Widespread disease on PET/CT | 2 |

PET/CT, positron emission tomography/computed tomography.

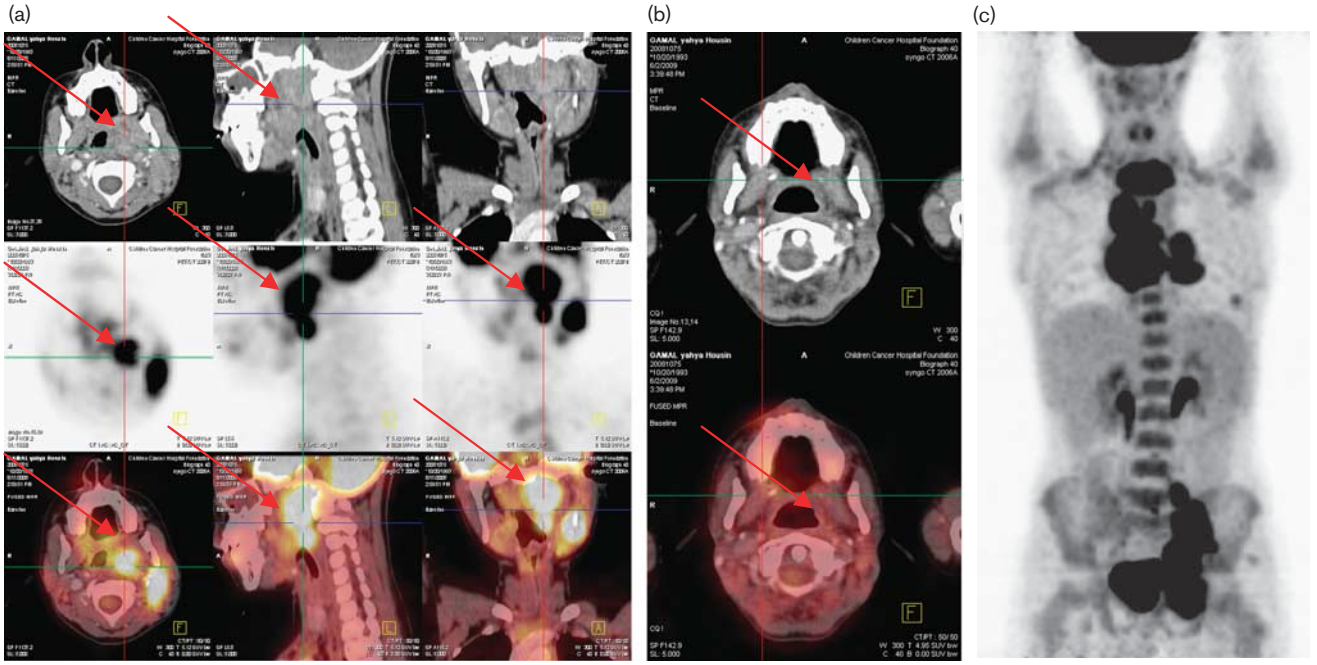
## Results

Two out of the 36 cases included in this study showed complete resolution of the primary tumour after treatment on both PET/CT and CIM. One case was a rhabdomyosarcoma of the naso-pharyngeal region that showed complete response after surgery and chemotherapy. The other case was a nasopharyngeal carcinoma that showed complete response to radiotherapy.

However, the whole-body PET/CT in both these patients showed widespread metabolically active soft tissue metastases distributed throughout the surveyed body with the maximum SUV ranging from 7.4 to 14.7 (Fig. 1a–c). These two patients then underwent palliative treatment following the findings of their PET/CT studies. No further CIM covering anatomical areas other than the head and neck were conducted on the results of PET/CT based on the presence of distant metastases on PET and visible with the low-dose CT phase of the PET/CT.

In 17 of the 36 cases after completion of treatment, PET/CT was negative at the time of response assessment (4–12 weeks range, 4 weeks after completion of chemotherapy and 12 weeks after radiation therapy) with no detectable uptake within the primary site in head and neck or elsewhere. CIM were concordantly negative in seven of these 17 negative cases, also suggesting a complete response. Serial CT of the head and neck, tumour markers and clinical evaluation were performed every 3 months until 12 months of follow-up, proving complete remission. The remaining 10 PET/CT-negative patients had discordance between CIM and PET/CT, as there was either a small residual primary mass or small residual cervical lymph nodes on CT. These 10 patients were kept under observation and underwent serial 3-monthly follow-up CT of the head and neck for a total follow-up period of 12 months, showing either a decrease in the size of the previously noted lesions or imaging stability with no newly developed lesions. In addition, six of these patients underwent follow-up PET/CT after 6 months, which was negative, and remain negative on

**Fig. 1**




(a) Initial pretherapy PET/CT showing a metabolically active left nasopharyngeal mass and cervical nodes (considered positive for malignancy on PET criteria). (b) Post-therapy PET/CT image showing complete resolution of the primary tumour. (c) Post-therapy PET whole-body multiple intensity projection image (anterior view) showing multiple distant soft tissue metastases. PET/CT, positron emission tomography/computed tomography.

serial follow-up PET/CT (range from 6 to 18 months), confirming complete remission. In these 10 discordant patients, PET/CT impacted clinical care by preventing the patients from being subjected to further treatment on the basis of residual disease shown by CIM.

PET/CT was positive in 17 studies. Two cases of 17 were FP. One case was of a nasopharyngeal carcinoma in which both PET/CT and CIM showed complete resolution of the primary nasopharyngeal mass after radiotherapy, but PET/CT showed an FDG-avid right pulmonary apical uptake with a maximum SUV of 5.7. CT chest showed a right apical lung nodule, indeterminate between inflammatory and metastatic. The nodule later proved to be caused by bacterial infection, with complete resolution in response to antibiotic therapy only, as evident on a subsequent follow-up chest CT after 2 months. The second FP PET/CT case was nasopharyngeal non-Hodgkin's lymphoma in which both PET/CT and CIM showed no residual lesions in the nasopharyngeal area after completion of therapy, whereas PET/CT showed active intense uptake at the proximal part of the oesophagus with a maximum SUV of 4.9, which was eventually confirmed to be inflammatory only on the basis of histopathological examination following endoscopic biopsy. Diagnostic CT chest was normal in this patient.

In the remaining 15 patients, PET/CT was concordantly positive with CIM in seven patients referred for initial staging and in two patients referred for assessment of response. In these nine concordant patients, the maximum SUV of the primary tumour ranged from 4.3 to 11.4.

Six of the 15 patients had a discordant positive PET/CT and negative CIM. PET/CT showed lesions that were not reported on the CIM or were reported as equivocal (did not meet the CIM criteria for malignancy; were considered negative for the purposes of clinical follow-up; and were considered negative for malignancy for our accuracy analysis). All these lesions were subsequently confirmed histopathologically to be malignant (Table 3; Figs 2 and 3). In all these six patients, PET/CT had an impact by changing further treatment plan from observation (four patients) and limited field radiation therapy (two patients) to salvage treatment with curative intent (surgery followed by radiotherapy in the two recurrent cases, modification of the radiotherapy fields in the two initial staging cases and cross over to second-line chemotherapy in the two cases of assessment of response).

On the basis of these results, we are able to state that PET/CT had an impact on the treatment plan of 18 patients (50%) out of the total 36 patients included in this study (two patients underwent palliative therapy; no further treatment in 10 negative discordant cases; modification of modality and extent of treatment in the six discordant positive cases).

**Table 3 Findings of PET/CT and CIM in six discordant positive cases**

| | Referred for | Primary | Mode of treatment | PET/CT finding | CT finding | Biopsy |
|---|---|---|---|---|---|---|
| 1 | Detection of recurrence | Rhabdomyosarcoma of the left temporal region | Surgery, chemotherapy and radiotherapy | Negative primary, positive left occipital node, maximum SUV 4.3 (12 months after completion of treatment) | Negative primary, negative lymph nodes | Positive node for rhabdomyosarcoma metastasis (Fig. 2) |
| 2 | Detection of recurrence | Left parotid mucoepidermoid carcinoma | Surgery and radiotherapy | Positive uptake at operative bed likely recurrence, maximum SUV 3.6 (6 months after completion of treatment) | Equivocal soft tissue mass in operative bed likely post-treatment sequelae – considered negative for tumour | Positive tumour recurrence (Fig. 3) |
| 3 | Initial assessment | Cervical nodal metastasis of unknown primary | Still pretreatment | Small area of active uptake in the nasopharyngeal area, maximum SUV 3.8 | Cervical nodes with no nasopharyngeal masses | Positive for nasopharyngeal carcinoma |
| 4 | Initial assessment | Nasopharyngeal carcinoma | Still pretreatment | Positive primary and positive cervical nodes maximum SUV 4.3 for the primary and 3.4 for the largest cervical node | Positive primary mass only | Positive cervical nodes |
| 5 | Assessment of response to treatment | Non-Hodgkins lymphoma of the nasopharynx | Chemotherapy and radiotherapy | Positive cervical and anterior mediastinal nodes, negative primary, maximum SUV 4.1, 5.6 (13 weeks after end of radiation therapy) | No positive nodes, negative primary | Positive cervical nodes for NHL |
| 6 | Assessment of response to treatment | Left maxillary rhabdomyosarcoma | Chemo and radiotherapy | Positive bilateral cervical nodes, negative primary, maximum SUV 3.1, 3.3, 3.5 (2 months after completion of radiation therapy) | Near total resolution of primary, negative nodes | Positive cervical nodes for rhabdomyosarcoma |

CIM, conventional imaging modalities; NHL, non-Hodgkin's lymphoma; PET/CT, positron emission tomography/computed tomography; SUV, standardized uptake value.

The sensitivities of PET/CT and CIM were 100 and 53%, respectively; the specificities were 89.5 and 47%, respectively; the accuracy was 94.5 and 50%, respectively; the positive predictive values were 89.5 and 47%, respectively; and the negative predictive values were 100 and 53%, respectively (Table 4).

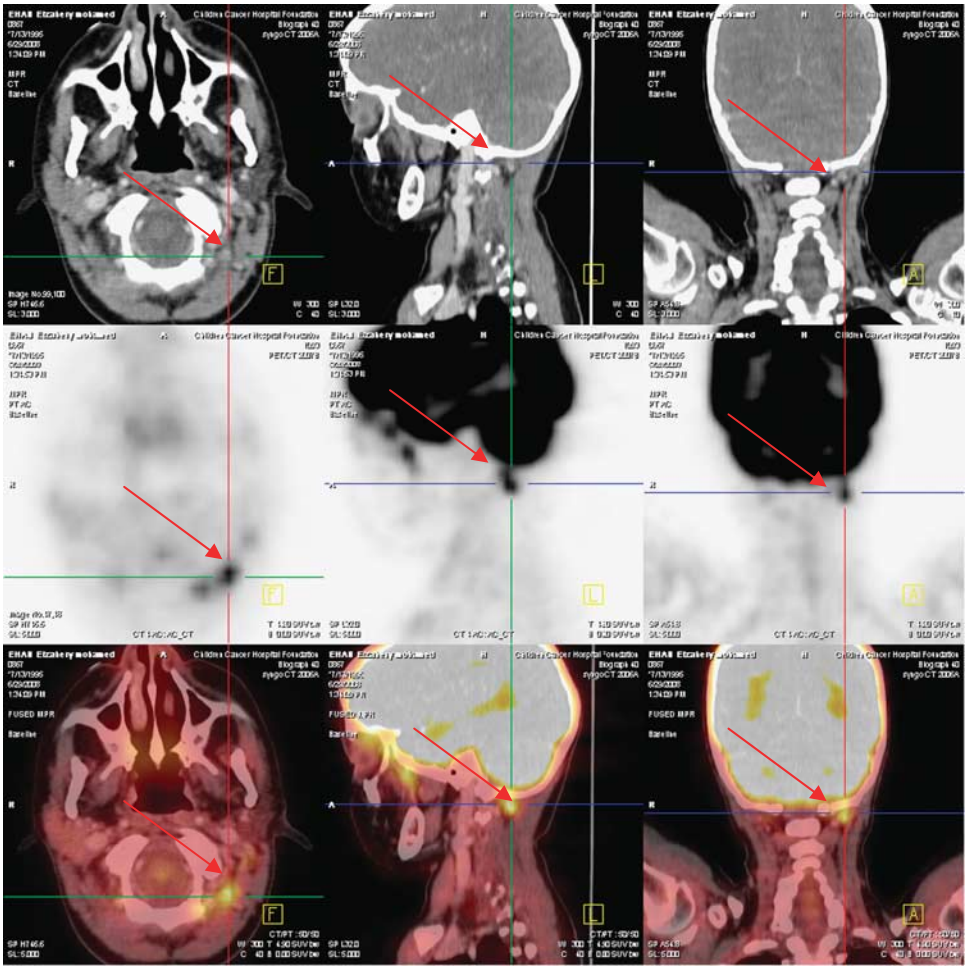
## Discussion

Imaging is an important clinical tool in the evaluation of adult patients with head and neck cancer. CIM modalities rely on morphologic criteria, such as nodal size and contrast enhancement patterns, that do not always reflect the presence of active malignant conditions accurately. The reported sensitivity, specificity and accuracy of CT for diagnosis of cervical nodal metastases were 88, 86 and 87%, respectively, for adults [9], and the specificity further decreased to 39% for CT and 48% for MRI when a 10 mm size criterion was used [10]. Surgery and radiation therapy alter the normal head and neck anatomy. Treatment-related oedema, fibrosis, inflammation and scarring are limiting factors that further hamper the performance of physical examination and CT or MRI imaging in the diagnosis of recurrent head and neck cancer. Gordin *et al.* [11] carried out a study on 90 adult patients with various types of head and neck cancer, and found that the sensitivity, the specificity, the accuracy and the positive and negative predictive values of CIM were 92, 18, 54, 51 and 71%, respectively, in comparison with 89, 95, 92, 94 and 90%, respectively, for PET/CT. In this study, we similarly found that PET/CT has higher values compared with CIM in paediatric patients. We calculated the sensitivity, specificity, accuracy and positive and negative predictive values for PET/CT to be 100, 89.5, 94.5, 89.5 and 100%, respectively, compared with 53, 47, 50, 47 and 53%, respectively, for CIM. It is worth mentioning that the 100% negative predictive value in our study may be due to the small sample size.

FDG-PET plays an increasingly crucial role in the assessment of various head and neck tumours in adults and is more accurate than CT or MRI in detecting both primary [5] and metastatic [12] disease. However, FDG-PET is limited by the lack of anatomic details and the known FDG-avidity of benign and physiologic processes, and therefore, has a relatively high FP rate and low specificity. FP PET studies are mostly due to the foci of abnormal FDG uptake in metabolically active tissues such as inflammation and infection, known as post-irradiation sequels. PET/CT is the current best-practice imaging modality that combines structural and metabolic assessment of malignant neoplasms, and it has a higher diagnostic accuracy for the evaluation of head and neck tumours in adults than PET alone [13].

On the basis of the high specificity and positive predictive value (95 and 94, respectively) of PET/CT [11], a positive study should therefore encourage the head and neck surgeon to perform further diagnostic or therapeutic steps. In this study, seven patients who had positive PET/CT and showed discordance with the results of CIM underwent histopathological sampling that proved malignancy in six cases. PET/CT guides biopsy tests accurately to the hypermetabolic foci in oedematous and scarred regions as demonstrated in seven patients in our study. PET/CT achieves two simultaneous goals: a decrease in sampling errors and less damage to normal structures.

**Fig. 2**



Follow-up PET/CT in a case of rhabdomyosarcoma of the left temporal region showing active FDG uptake within a left occipital node considered positive for recurrence (a true positive). FDG, fluorodeoxyglucose; PET/CT, positron emission tomography/computed tomography.

Ryan *et al.* [14] reported that there is an increased incidence of FP PET studies after treatment, attributed to the possibility of increased perfusion and inflammation following surgery, radiotherapy and/or chemotherapy. In this study, we had two FP PET/CT studies: one was attributed to a bacterial lung infection and the other to an inflammation in the proximal part of the oesophagus.

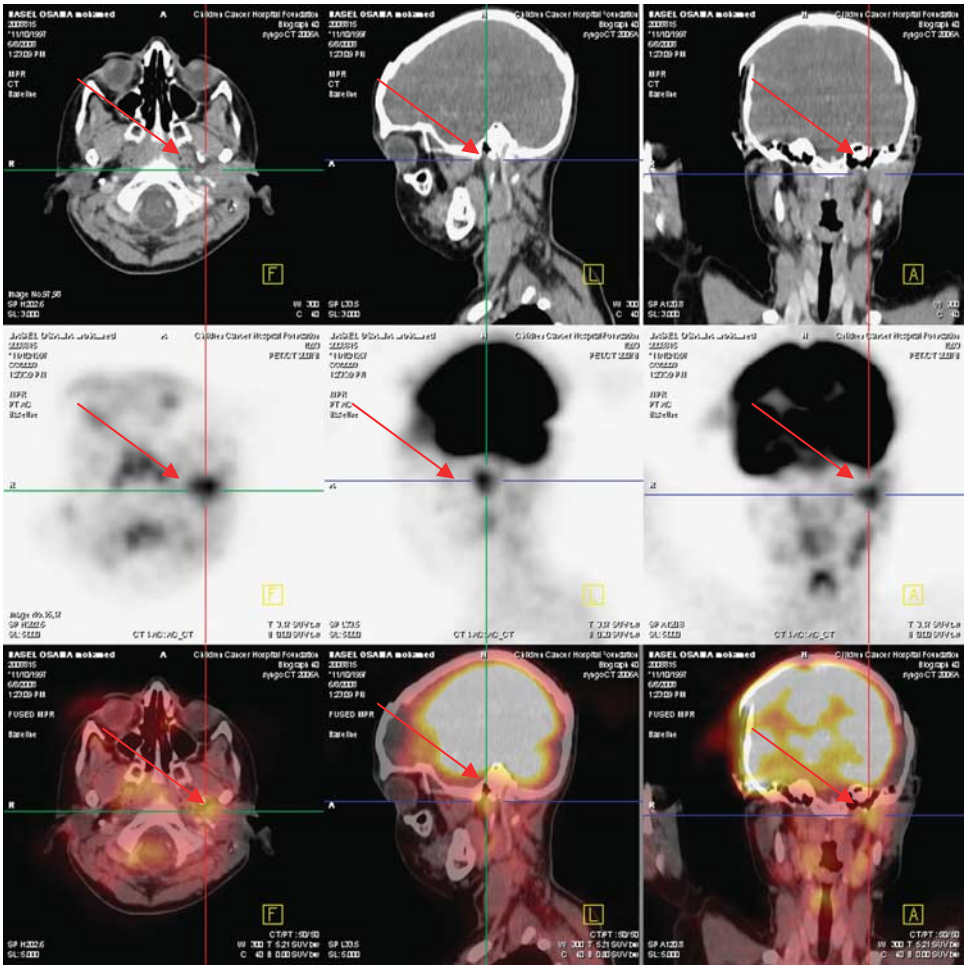
Although biopsy is the gold standard for the diagnosis of recurrence, it can cause additional oedema, pain, additional costs and emotional stress (the last one particularly relevant in paediatric patients) in previously treated patients. Further invasive procedures could be cancelled in patients who had negative PET/CT scans [11]. In this study, our results showed 100% negative predictive value, and eliminated the need for further biopsy in all the PET/CT-negative paediatric cases. Therefore, in patients with a negative PET/CT study and a suspicious CT or MR study, an ultrasound or PET/CT-guided biopsy can be postponed unless there is a high clinical suspicion for recurrent disease. In selected cases, a repeated study should be considered several months later. In this study, long-term clinical follow-up was the gold standard in this clinical scenario.

PET/CT has a high impact on patient care in cancer of the head and neck. Ha *et al.* [15] reported that PET/CT altered the treatment plan in 31% of the patients with primary head and neck squamous cell carcinoma. Gordin *et al.* [11] stated that further diagnostic or treatment plan was modified in 56% of adult patients with various head and neck tumours.

In this study, PET/CT had an impact on patient management in 18 of the 36 paediatric patients (50%).

Limitations of this study include several different radiologists reporting the CIM studies initially. However, as part of the study, all the CIM studies were re-read blindly by a consultant radiologist who was unaware of the PET/CT results. Second, we are including both CT and

**Fig. 3**



Follow-up PET/CT in a case of left parotid mucoepidermoid carcinoma showing active FDG uptake within the operative bed considered positive for recurrence (a true positive). FDG, fluorodeoxyglucose; PET/CT, positron emission tomography/computed tomography.

**Table 4 Performance of PET/CT and conventional imaging modalities on a per-patient basis for the detection of malignancy in 36 paediatric patients**

| | PET/CT | | CIM | |
|---|---|---|---|---|
| Reference standard | Positive | Negative | Positive | Negative |
| Positive 17 | True positive 17 | False negative 0 | True positive 9 | False negative 8 |
| Negative 19 | False positive 2 | True negative 17 | False positive 10 | True negative 9 |

CIM, conventional imaging modalities; PET/CT, positron emission tomography/computed tomography.

MRI under the umbrella of CIM. This may affect the statistics for CT and underestimate the accuracy of MRI. CT of the head and neck is a faster and easier first-line study in paediatric patients, many of whom are too young to keep still in the MR scanner for a sufficiently long time. Only two of our patients had MR, and the MR was performed following CT of the head and neck in cases where the clinician was seeking better specificity, and both CT and MRI were consistent.

Third, the statistical analysis of the specificity of CIM could underestimate its true performance because two patients out of the eight FN patients on CIM had an FN result because of a lack of whole-body coverage (which is routine in PET/CT). However, we recalculate the statistics after considering these two patients as true positive to give CIM the benefit of doubt. The sensitivity, specificity, accuracy and positive and negative predictive values were 64.7, 47, 55.5, 52.3 and 60%,

respectively, as compared with 53, 47, 50, 47 and 53%, respectively. This shows no significant changes.

Finally, we are comparing our results to similar adult studies as the literature lacks paediatric studies, and such a comparison is unavoidable.

## Conclusion

We conclude from this study that PET/CT is an effective diagnostic imaging modality for the assessment of paediatric head and neck carcinoma, with an overall diagnostic accuracy of 94.5%. A negative PET/CT study can eliminate the need for further biopsy unless independently clinically indicated. A positive study should encourage and guide the surgeon to obtain tissue diagnosis. PET/CT has a strong impact on further management in paediatric patients with head and neck cancer. It can modify the treatment plan and intent in a significant proportion of patients, which in our study of 36 paediatric patients was 50%.

## Acknowledgements

### Conflicts of interest

There are no conflicts of interest.

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