Original article

Interpretation of suspect head and neck fixations seen on PET/CT in lung cancer

Y. Gobel\textsuperscript{a}, G. Valette\textsuperscript{a}, R. Abgral\textsuperscript{b}, C. Clodic\textsuperscript{a}, E. Mornet\textsuperscript{a}, G. Potard\textsuperscript{a}, P.-Y. Salaun\textsuperscript{b}, R. Marianowski\textsuperscript{a,}* \\
\textsuperscript{a} Service d’ORL et chirurgie cervico-faciale, Hôpital Morvan, CHRU de Brest, 2, avenue Foch, 29200 Brest, France \\
\textsuperscript{b} Service de médecine nucléaire, Centre hospitalier universitaire de Brest, Brest, France

\textbf{A R T I C L E  I N F O}

\textbf{Keywords:} Incidentaloma \hspace{1cm} PET/CT \hspace{1cm} Head and neck cancer \hspace{1cm} Lung cancer \hspace{1cm} Second malignancy

\textbf{A B S T R A C T}

\textbf{Objectives:} Smoking is the major risk factor for lung and head and neck cancer. The purpose of the present study was to determine the clinical impact of serendipitously revealed head and neck fixation on PET/CT in patients undergoing investigation for lung cancer.

\textbf{Material and methods:} The reports from PET/CT studies for patients with lung cancer from September 2005 and April 2012 were retrospectively reviewed. Head and neck incidentaloma was interpreted as suggestive of second primary malignancy. These incidental findings were compared with the final diagnosis obtained from clinical and histological investigation.

\textbf{Results:} Five hundred and ninety-two patients were investigated on PET/CT for lung cancer in the study period. PET/CT-positive head and neck lesions suggestive of second primary malignancy were found in 65 (11%) patients. Nasoendoscopy was performed in 23 patients and biopsy in 10. In 4 patients (17.4\% of those explored), a second primary malignant lesion was proved on histology: 2 squamous cell carcinomas (larynx and oral cavity), 1 undifferentiated carcinoma (parotid), and 1 osteosarcoma (mandible). At a median 13 months’ follow-up, 3 of the 4 patients with a second primary had died from disease-related causes and 1 was free of recurrence. Metastases from lung adenocarcinoma were found in 2 patients (0.34%).

\textbf{Conclusions:} PET/CT detected incidental head and neck malignant tumors in at least 0.68\% of lung cancer patients, but in 6.4\% of those with suspect head and neck fixation.

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1. \textbf{Introduction}

\textbf{[18F]}FluoroDeoxyGlucose positron emission tomography (\textbf{[18F]}FDG) associated to CT (PET/CT) is currently implemented in bronchopulmonary and head and neck oncology. In the upper aerodigestive tract, malignant lesions exceeding 1 cm and certain benign lesions fix under PET/CT. Lung and head and neck cancers have the same principal risk factor: smoking. The upper aerodigestive tract often shows physiological fixation on PET/CT.

Between September 2005 and April 2012, 592 lung-cancer patients had at least one PET/CT examination. The present study analyzed incidental ENT fixations, how many of them led to complementary examination and what was the diagnosis of pathological lesions.

The meaning of such incidentally discovered fixation and the procedure to be adopted in consequence are discussed.

2. \textbf{Material and methods}

All patients with lung cancer of primary aspect undergoing at least one \textbf{[18F]}FDG PET/CT examination for diagnosis, assessment or follow-up in the Nuclear Medicine Department of our University Hospital between September 2005 and April 2012 were included. Patients with history of ENT neoplasia were excluded.

Examination was on a hybrid Gemini GXLi PET/CT machine (Philips\textsuperscript{\textregistered}), associating a 6-slice Brilliance CT scanner and GSO-Zr crystal PET, each measuring $4 \times 6 \times 30$ mm.

Acquisitions were taken 60 minutes after injection of approximately 370 MBq (5–6 MBq/kg) \textbf{[18F]}-FDG. All patients fasted for at least 6 hours before examination. After injection, a calm rest period was imposed, with no speaking or reading, so as to minimize physiological muscle fixation. Images were interpreted, visually and quantitatively by standardized uptake value (SUV), by a senior member of the nuclear medicine department.
Upper aerodigestive tract fixation was considered significant when the nuclear medicine specialist assessed it as “suspect”, “requiring complementary exploration” or “to be compared with clinical findings”; otherwise, it was simply mentioned in the report. Upper aerodigestive tract fixations considered “physiological” or “non-pathological” were not taken into account.

The locations studied were the facial sinuses, rhinopharynx, oral cavity, salivary glands, oropharynx, hypopharynx, larynx, thyroid and cervical lymph nodes, excluding the supraclavicular region which is the usual location for regional lymph node metastasis from lung cancers.

Patients with several PET/CT examinations were counted if there was at least one incidental fixation in the upper aerodigestive tract.

3. Results

In all, 592 patients were included: 447 male, 145 female; mean age, 62 years (range, 22–85 years; median, 62 years).

Three hundred and forty-eight patients (58.8%) showed lymph-node extension and 114 (19.2%) remote extension. Histological type was known in 193 patients at initial PET/CT: 84 adenocarcinomas (43.5%), 80 squamous cell carcinomas (41.5%), 20 small-cell carcinomas (10.2%), 3 carcinoid tumors (1.5%), 3 lymphomas (1.5%), 2 undifferentiated carcinomas (1%) and 1 fibrosarcoma (0.5%).

Eight hundred eighty-six PET/CT reports for 592 patients were analyzed. There were a mean 1.5 PET/CTs per patient (range, 1–6; Table 1). Sixty-five patients (11%) showed significant upper aerodigestive tract fixation on at least one examination: 47 male, 18 female; mean age, 60 years 9 months (median, 60 years; range, 42–84 years). On the first examination showing a sequel fix, the SUVmax value was recorded in the report in 56 cases (86.2%): mean SUVmax, 4.5 ± 3.3; median, 3.5; range, 1.5–23.3.

Only 45 of the 65 patients (69.2%) were being followed in the department. The other 20 came specifically for PET/CT, little available outside university hospitals, and were followed up clinically elsewhere; research was undertaken to find out whether they had had an ENT consultation by telephoning regional hospitals with ENT departments, or patients’ family physicians.

The following problems were encountered: patient death too far in the past; physician retired or deceased; no apparent ENT consultation; no medical records; no personal physician.

It was therefore decided to make inquiries in the regional pathology departments and offices, not about ENT consultations but about any ENT malignancy. None could be demonstrated in these 20 patients.

Only 23 of the 45 patients managed at the university hospital and presenting suspect upper aerodigestive tract fixation had a consultation for this indication in the ENT and Head and Neck Surgery Department. The other 22 had no specialist consultation, as it did not seem justifiable to the physicians managing their lung cancer, given their general health status or prognosis.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Distribution of number of PET/CTs per patient and number of ENT fixations.</th>
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<tbody>
<tr>
<td>Number of PET/CTs</td>
<td>Number of patients</td>
</tr>
<tr>
<td>1</td>
<td>406 (68.6%)</td>
</tr>
<tr>
<td>2</td>
<td>125 (21.1%)</td>
</tr>
<tr>
<td>3</td>
<td>36 (6.1%)</td>
</tr>
<tr>
<td>4</td>
<td>17 (2.9%)</td>
</tr>
<tr>
<td>5</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>6</td>
<td>2 (0.3%)</td>
</tr>
</tbody>
</table>

For each of the 23 patients, ENT examination comprised clinical and fiberoptic endoscopic examination. Ten also underwent upper gastrointestinal endoscopy under general anesthesia with biopsy.

Eighteen of the 23 patients had PET/CT reports that included SUVmax. Mean SUVmax was 4.7. Histology found 6 malignant lesions: 2 squamous cell carcinomas, 2 adenocarcinomas of pulmonary origin, 1 undifferentiated carcinoma and 1 osteosarcoma (Table 2); there were also 2 benign lesions: 1 malphighian papilloma and 1 epidermoid cyst.

Thus, 6 malignancies were detected in the 45 university hospital patients showing upper aerodigestive tract fixation (13.3%). When an ENT consultation took place, malignancy was diagnosed in 26% of cases. SUVmax was noted in 5 of the 6 PET/CT reports of ENT fixation. Mean SUVmax was 4.16 ± 1.3.

A malignant lesion of the upper aerodigestive tract unrelated to the lungs was found in 4 of the 45 patients (8.9%) (Table 3).

The first was a 68-year-old woman, presenting with left superior lobe T2N0M0 squamous cell carcinoma, managed surgically. PET/CT found fixation in the oropharynx and left ascending branch of the mandible (SUVmax, 5.1). The patient reported mandibular and oropharyngeal pain. High-malignancy T3N1M0 left mandibular osteosarcoma was diagnosed. Treatment comprised transmandibular oropharyngectomy associated to cervical lymph node resection and complementary radiation and chemotherapy. Survival was 11 months. The cause of death was evolution of mandibular osteosarcoma.

The second patient was a 73-year-old man, presenting with right superior lobe T1N1M0 squamous cell carcinoma, managed surgically. PET/CT found fixation in the right superior and medial thyroid cartilage (SUVmax, 3.6) and right vocal fold (SUVmax, 2.6). The patient was dysphonic on ENT consultation. Subglottic T4aN2bM0 squamous cell carcinoma of the laryngeal side of the epiglottis was diagnosed. Treatment comprised total laryngectomy associated to bilateral cervical lymph node resection and complementary radiation and chemotherapy. Survival was 31 months. The cause of death was local recurrence of the laryngeal lesion.

The third patient was a man of 55 years at diagnosis, presenting with right superior lobe T1aN0M0 squamous cell carcinoma, managed by radiation and chemotherapy. PET/CT (Fig. 1) found right oral cavity fixation (SUVmax, 2.8) and right sector IIa cervical fixation (SUVmax, 2.3). There was no ENT symptomatology. T2N1M0 squamous cell carcinoma of the right retromolar region was diagnosed. Treatment was exclusively radiation therapy. At

<table>
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<tr>
<th>Table 2</th>
<th>Number of ENT fixations discovered on PET/CT, of malignancies and of histologic type per ENT location.</th>
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</thead>
<tbody>
<tr>
<td>Significant ENT fixation location</td>
<td>Number of patients</td>
</tr>
<tr>
<td>Larynx</td>
<td>18 (27.7%)</td>
</tr>
<tr>
<td>Jugulocarotid lymph-node areas</td>
<td>17 (26.2%)</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>10 (15.3%)</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>9 (13.8%)</td>
</tr>
<tr>
<td>Parotid</td>
<td>6 (9.2%)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>6 (9.2%)</td>
</tr>
<tr>
<td>Rhinopharynx</td>
<td>4 (6.2%)</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>3 (4.6%)</td>
</tr>
<tr>
<td>Submaxillary gland</td>
<td>1 (1.5%)</td>
</tr>
</tbody>
</table>
the time of writing, the patient was in good health at 13 months’ follow-up.

The fourth patient was a 52-year-old woman presenting with left inferior lobe T2N2M1 adenocarcinoma, managed by chemotherapy. PET/CT found right intraparotid fixation (SUV not specified). There was no ENT symptomatology. T1N1M0 undifferentiated parotid carcinoma was diagnosed. Treatment comprised total right parotidectomy associated to right cervical lymph node resection of sectors IIa and IIb with complementary radiation therapy. Survival was 13 months. The cause of death was metastasis of the pulmonary lesion.

In these 4 patients, mean SUVmax was 3.8. Three died, with a mean 18.3 ± 11 and median 13 months’ survival.

PET/CT in a context of lung cancer led to diagnosis of a head and neck malignancy in 0.68% of cases and of primary cancer in 0.34% (Fig. 2).

### 4. Discussion

The upper aerodigestive tract typically shows physiological fixation. Asymmetric fixation, elevated SUV or an unusual location, however, will be noted in the nuclear medicine report. The clinician who ordered the examination then decided whether to undertake further exploration. In the present study, head and neck malignancy was diagnosed in more than a quarter of the patients who had ENT consultation after incidental discovery of abnormalities on PET/CT.

ENT consultation, on the other hand, concerned only 23 of the 45 patients (51.5%) with ENT fixation discovered on PET/CT who were managed in the center (51.5%). This seems a low rate, given that PET/CT detects ENT malignancy with high sensitivity and specificity [1,2] and that these patients had risk factors for such tumors. In the present series, however, patients had lung cancer, with its poor prognosis [3]. For example, at least 2 of the 45 had less than
1 month’s survival. It is therefore understandable that complementary examination may not have seemed justifiable to the clinicians managing these patients, especially when asymptomatic.

Most PET/CT examinations were carried out to assess tumoral extension as part of pre-treatment operability assessment. Thus patients already known to have metastasis or in whom surgical resection is impossible will not undergo PET/CT in this indication. Surgical resection is impossible in 80% of lung cancers at diagnosis [4]. The present study population of 592 patients was thus not representative of lung cancer patients in general, but contained a selection bias in favor of good prognosis.

SUV is used to assess the risk that PET/CT fixation reveals a malignant lesion. It is not, however, totally reliable. PET is a metabolic-based imaging technique, and SUV does not show good intersubject reproducibility; even in a given individual, variations in glycemia may affect SUV [5]. It may also vary during updating of calibration software or equipment repair [6]. It frequently varies by more than 10% for a given examination performed on different machines under identical conditions [7]. Moreover, SUV is not systematically noted in all PET/CT reports. In the present study, the mean SUVmax for suspect ENT lesions was 4.5, and 4.16 in proven malignancy. According to the literature, malignancy should be suspected when SUV exceeds 2.5 to 3.8 [5]. Nghi C. Nguyen et al. [8] reported a SUVmax threshold of 2.2 in the cervical lymph-node areas, with 98% sensitivity and 83% specificity.

Suspect fixation mainly concerned 2 locations, the larynx and the jugulocarotid areas, which accounted for about half of all fixations found. Oral cavity and oropharyngeal fixations were not unusual. Other locations were rarer. Notably, the parotid, despite showing physiological fixation on PET/CT, like the tonsils, vocal folds and tongue [9,10], represented only 9.2% of suspect fixations.

This is why analysis was based not on absolute SUV but on abnormal fixation: asymmetry or unusual location.

Repeating PET/CT in each patient seemed to increase the probability of discovering upper aerodigestive tract hyperfixation: while the mean rate was 11.7%, it was only 9.1% in patients undergoing a single PET/CT examination, and rose to 25% in those who had 3.

For the PET/CTs analyzed, initial assessments and lung-cancer surveillance reports were included without distinction, as the study did not focus on synchronicity versus metachronicity but purely on malignancy and incidental fixation.

Two of the 6 upper aerodigestive tract malignancies discovered on PET/CT were metastases of lung cancer. Only 2 of the 4 primary lesions discovered were squamous cell carcinomas of the upper aerodigestive tract. The mandibular osteosarcoma and the undifferentiated parotid carcinoma had no proven relationship with smoking, the principal risk factor for ENT and lung cancer, and the starting point of the present study [3].

All the patients in whom ENT cancer was discovered received treatment, which was surgical in 75% of cases. Survival was nevertheless less than 2 years. The study design shed no light on whether diagnosis improved survival or quality of life.

The primary malignant upper aerodigestive tract lesions discovered were large (T3 or T4) in half the cases. It is remarkable that, in patients regularly followed up for their lung pathology, such ENT lesions should have gone undetected on clinical signs, especially as the patients reported functional signs during ENT consultation.

Few studies have focused on incidental discovery of upper aerodigestive tract lesions on PET/CT [11]. In a retrospective study of 812 patients undergoing PET/CT for lung cancer, Chopra et al. [11] found unexpected suspect extrathoracic fixation in 22% of cases and in the upper aerodigestive tract in 8.8%. In the present series, the rate was higher: 11%. However, Chopra et al. analyzed only the first PET/CT in each patient. Patients with only one PET/CT in the present series showed a 9.1% rate of suspect upper aerodigestive tract fixation, close to Chopra et al.’s finding. They explored 55% of suspect upper aerodigestive tract fixation, compared to 51.1% in the present study. Advanced pulmonary pathology was the main reason given for failure to explore certain patients. A single primary upper aerodigestive tract cancer was finally diagnosed in their series: i.e., only 1.4% of suspect fixations and 0.12% of included patients, compared to respectively 8.9% and 0.68% in the present study. The low number of cancers finally diagnosed in both studies can account for this difference.

In a retrospective study of 1912 patients undergoing PET for proven or suspected malignancy at whatever location, Ishimori et al. [12] found suspect ENT fixation in 2% of cases. Upper aerodigestive tract malignancy was proved in only 0.37% of cases. Only the first PET was analyzed. These rates are lower than in the present study. Thus, a second primary of the head and neck may be more frequently discovered on PET/CT when performed in the context of lung cancer. In Ishimori et al.’s study, however, when suspect ENT fixation was explored malignancy was discovered in 41% of cases, compared to only 23% in the present study. Thus, their study involved fewer false positives, although based on PET examination without CT.

Beatty et al. [2] studied all the PET/CTs of 2219 patients, and found suspect ENT fixation or a second primary in only 3.3% of cases, regardless of the location of the tumor for which PET/CT was performed. In 20% of cases, however, PET/CT was performed in a context of upper aerodigestive tract cancer, so that discovery of a new ENT fixation cannot be counted as raising suspicion of a second primary location.

The thyroid is a common location for suspect fixation on PET/CT. It may show hyperfixation under various pathological conditions, including cancer [9,13–16]. It is the location of suspect unexpected fixation on PET/CT in 1.1% to 8.4% of cases, revealing thyroid
malignancy in 14% to 66% of cases [13–16]. In the present study, suspect thyroid fixation was found in only 1% of patients, and no thyroid cancers were diagnosed.

In the above retrospective studies, false negatives cannot be assessed, as patients without suspect head and neck fixation did not have complementary upper aerodigestive tract exploration. Jeong Won Lee et al. [17] performed PET/CT in 1587 volunteer patients with no history of malignancy, as part of a prospective cancer screening study. Other kinds of imaging, various endoscopies and tumor marker assays were performed, with at least 1 year’s clinical follow-up. There was only one false negative in the head and neck region: a papillary thyroid cancer, revealed by cervical ultrasound. This confirms the excellent sensitivity of PET/CT in detecting malignant tumors of the head and neck.

In all of these studies, despite large sample sizes, the numbers of malignancies discovered were low. It is up to the clinician to decide whether it is worthwhile performing complementary examinations on discovery of a suspect fixation. PET/CT is highly sensitive in detecting upper aerodigestive tract cancer and the population of lung cancer patients is especially exposed to the risk of upper aerodigestive tract cancer. At the same time, these patients tend to have poor general health status, so that exploring fixations may not be justifiable.

PET/CT is costly; the present study examined upper aerodigestive tract fixations on acquisitions obtained for another indication, so that no extra cost was incurred.

The present study also raises the issue of double ENT and bronchopulmonary tumor locations, with their adverse impact on prognosis [18,19]. Discovery of a double location should not, however, be taken as contraindicating the surgical treatment that would have been performed for a single location [18,19]. Treatment options in these synchronous or metachronous tumors should be discussed on a case-by-case basis, according to general health status and comorbidity. Synchronous tumors have poorer prognosis than metachronous tumors and also raise the problem of order of treatment [19,20]. When surgery is decided on, the pulmonary lesion is generally operated on first, enabling histologic diagnosis to rule out metastasis of the upper aerodigestive tract cancer and a consequently more adverse prognosis.

5. Conclusion

PET/CT in a context of lung cancer diagnosed a malignant lesion of the head and neck in 0.68% of cases and a primary cancer in 0.34%. Suspect head and neck fixations on PET/CT are frequent, and often raise the problem for the physician of how to manage them. In 23 patients who had ENT consultation, there was a 26% rate of diagnosis of malignant tumor, modifying the initial treatment attitude, with specific treatment in 4 cases (17% of patients explored), which is by no means negligible. It can therefore be affirmed that, in case of pathologic ENT fixation, ENT examination should imperatively be undertaken if the patient’s general health status and pulmonary carcinoma prognosis permits. In the present study, malignant lesions of the head and neck were diagnosed in more than a quarter of the patients who had ENT consultation after incidental discovery of abnormality on PET/CT.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Acknowledgements

Solène Querelleu-Lefranc, Nuclear Medicine Dept, Brest University Hospital Center.

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