Focal thyroid incidental uptake detected by $^{18}$F-fluorodeoxyglucose positron emission tomography

Meta-analysis on prevalence and malignancy risk

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Keywords
Positron emission tomography, PET/CT, fluorine-18-fluorodeoxyglucose, thyroid incidentaloma, meta-analysis

Summary
Aim: To perform a meta-analysis of published data on the prevalence and risk of malignancy of focal thyroid incidental uptake (FTIs) detected by Fluorine-18-Fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomography (PET) or PET/CT. Methods: A comprehensive literature search of studies published up to and including December 2012 was performed. Pooled prevalence and malignancy risk of FTIs were calculated, including a sub-analysis for the geographic areas of origin of the studies. Results: 34 studies including 215,057 patients were selected. Pooled prevalence of FTIs was 1.92% (95% confidence interval [95%CI]: 1.87–1.99%). Overall, 1,522 FTIs underwent histopathology evaluation. Pooled risk of malignancy was 36.2% (95%CI: 33.8–38.6%), without significant differences among various geographic areas. Conclusions: FTIs are observed in about 2% of $^{18}$F-FDG-PET or PET/CT scans and carry a significant risk of malignancy. Therefore, further investigation is warranted whenever FTIs are detected by $^{18}$F-FDG-PET or PET/CT.

Schlüsselwörter
Positronenemissionstomographie, PET/CT, Fluor-18-Fluordeoxyglukose, Schilddrüsen-Inzidentalom, Metaanalyse

Zusammenfassung

Thyroid incidentalomas are defined as unexpected, asymptomatic thyroid lesions that are discovered on an imaging study or during surgery unrelated to the thyroid gland. Thyroid incidentalomas represent a challenge for the clinicians; in fact, most of these lesions are benign but a malignant disease is to be excluded (22).

Thyroid lesions may be incidentally detected by several imaging modalities, such as
• ultrasonography (US),
• computed tomography (CT),
• magnetic resonance imaging (MRI),
• stand alone fluorine-18-fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomography (PET), or
• PET in combination with X-ray computed tomography (PET/CT) (22).

As $^{18}$F-FDG PET or PET/CT are increasingly used, the number of incidentalomas detected by these functional imaging methods is on the rise as well.
PET or PET/CT may sometimes reveal an unexpected $^{18}$F-FDG uptake within the thyroid gland in patients referred for other diseases (40).

Diffuse uptake of $^{18}$F-FDG in the thyroid gland is considered at low risk of malignancy and is more likely associated with thyroiditis or Graves’ disease (40). Conversely, focal thyroid $^{18}$F-FDG incidental uptake (FTI) is of greater concern since it may quite possibly represent a malignant lesion (40). Therefore, a complete diagnostic work-up including laboratory tests, US and fine needle aspiration biopsy (FNAB) is usually performed to exclude a malignant lesion whenever FTI is detected by $^{18}$F-FDG PET or PET/CT.

Over time quite a number of studies have reported data about the prevalence and the malignancy risk of FTIs detected by $^{18}$F-FDG PET or PET/CT, with sometimes discordant results. A systematic review about this topic already exists (41), without a meta-analytic approach taking into account the different weight of each included study.

Therefore, the objective of this study is to summarize published data about prevalence and malignancy risk of FTIs detected by $^{18}$F-FDG PET or PET/CT performing a meta-analysis of these data in order to derive more robust evidence.

**Methods**

**Search strategy**

A comprehensive literature search of the electronic PubMed/MEDLINE, Embase, and Scopus databases was conducted to find relevant published articles on the prevalence and malignancy risk of FTIs detected by $^{18}$F-FDG-PET or PET/CT. We used a search algorithm that was based on a combination of the terms:

a) “thyroid” AND
b) “PET” OR “positron emission tomography”.

No starting date limit was used; the search was updated until December 31st, 2012. No language restriction was used. To expand our search, references of the retrieved articles were also screened for additional studies.

**Study selection**

Original articles investigating both prevalence and malignancy risk of FTIs detected by $^{18}$F-FDG PET or PET/CT were eligible for inclusion.

The exclusion criteria were:

- a) articles not providing information about both prevalence and malignancy risk of FTIs detected by $^{18}$F-FDG PET or PET/CT, including studies using other PET tracers beyond $^{18}$F-FDG;
- b) overlap in patient data (in this case the most complete article was included).

Two researchers independently reviewed the titles and abstracts of the retrieved articles, applying the inclusion and exclusion criteria mentioned above. The same two researchers then independently reviewed the full-text version of the remaining articles to determine their eligibility for inclusion.

**Data extraction**

For each included study, information was collected concerning basic study data (authors, year of publication, country of origin), device used (PET or PET/CT), number of patients evaluated with PET or PET/CT, number of FTIs detected by PET or PET/CT, number of FTIs cytologically verified by fine needle aspiration biopsy or surgery, number and type of thyroid malignancy detected among FTIs, average standardized uptake values (SUV) in malignant and benign FTIs.

**Statistics**

Statistical analyses were performed using StatsDirect statistical software (StatsDirect Ltd; Altrincham, UK). The prevalence of patients with FTIs who underwent PET or PET/CT and the malignancy risk of FTIs detected by PET or PET/CT were obtained from individual studies using the formulas:

- prevalence of FTIs = number of patients with FTIs / number of patients evaluated with PET or PET/CT × 100
- malignancy risk of FTIs = number of malignant tumors found among FTIs / number of FTIs revealed by PET or PET/CT and verified by fine needle aspiration biopsy or surgery × 100

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**Fig. 1** Flow chart of the search for eligible studies on the prevalence and malignancy risk of focal thyroid incidental uptake detected by $^{18}$F-FDG-PET or -PET/CT
For statistical pooling of the data, DerSimonian and Laird method (random-effects model) was used. Pooled data represented weighted averages which were related to the sample size of the individual studies. Pooled data were presented with 95% confidence intervals (95%CI) and displayed using forest plots. Cochrane Q test was used for heterogeneity evaluation (p < 0.05 was considered statistically significant). To quantify the heterogeneity, I-square index was used.

A pooled sub-analysis of prevalence and malignancy risk of FTIs for different geographic areas (Asia-Oceania, Europe and North America) was carried out. Furthermore a sub-analysis comparing prevalence and malignancy risk of FTIs in iodine-deficient versus iodine-sufficient countries as classified by the World Health Organization (WHO) (45) was performed. Finally, a sub-analysis comparing the device used (PET versus PET/CT) was carried out.

Results

The comprehensive computer literature search from PubMed/MEDLINE, Embase and Scopus databases revealed 1376 articles. Reviewing titles and abstracts, 1338 articles were excluded because they did not report any data on either prevalence or malignancy risk of FTIs detected by 18F-FDG-PET or PET/CT. 38 studies were selected and retrieved in full-text version; one additional study was found screening the references of these articles (20). After reviewing the full-text articles of these 39 potentially eligible articles, 4 studies were excluded due to data overlap (2, 27, 30, 32). One further article was excluded because data about FTIs matching the definition used for the present study could not be identified (18).

Finally, 34 studies including 215 057 18F-FDG PET or PET/CT scans met all inclusion and exclusion criteria and were included in our meta-analysis (1, 3–8, 10–17, 20, 21, 23, 24, 28, 29, 33–39, 46–49) (Fig. 1). The characteristics of the included studies are presented (▶Tab. 1). These studies had a total of 4337 patients with FTIs.

The included studies were statistically heterogeneous (I-square: >75%) both for prevalence and malignancy risk of FTIs. Overall, the pooled prevalence of FTIs detected by 18F-FDG-PET or PET/CT was
Tab. 1 Characteristics of the included studies about focal thyroid incidental uptake detected by 18F-FDG PET or PET/CT

<table>
<thead>
<tr>
<th>first author (ref.)</th>
<th>country</th>
<th>imaging used</th>
<th>patients evaluated</th>
<th>number of FTIs detected by PET</th>
<th>verified*</th>
<th>thyroid malignancy found among FTIs*</th>
<th>average SUV in malignant FTIs</th>
<th>benign FTIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen (11)</td>
<td>USA</td>
<td>PET</td>
<td>4525</td>
<td>71</td>
<td>14</td>
<td>3 PC, 2 HC, 2 PDTC</td>
<td>6.92 ± 1.54*</td>
<td>3.37 ± 0.21*</td>
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<tr>
<td>Kang KW (12)</td>
<td>Korea</td>
<td>PET</td>
<td>1330</td>
<td>21</td>
<td>15</td>
<td>4 PC</td>
<td>16.5 ± 4.70*</td>
<td>6.5 ± 3.8*</td>
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<td>Hsieh (5)</td>
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<td>PET</td>
<td>477</td>
<td>12</td>
<td>8</td>
<td>1 PC</td>
<td>N.A.</td>
<td>N.A.</td>
</tr>
<tr>
<td>Ishimori (13)</td>
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<td>1912</td>
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<td>6 PC</td>
<td>N.A.</td>
<td>N.A.</td>
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<td>Chen YK (14)</td>
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<td>PET or PET/CT</td>
<td>4803</td>
<td>60</td>
<td>50</td>
<td>7 PC</td>
<td>6.7 ± 3.6*</td>
<td>2.6 ± 1.0*</td>
</tr>
<tr>
<td>Kim TY (15)</td>
<td>Korea</td>
<td>PET</td>
<td>4136</td>
<td>45</td>
<td>32</td>
<td>14 PC, 2 ML</td>
<td>5.1 ± 4.2</td>
<td>5.6 ± 6.1</td>
</tr>
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<td>Yi (16)</td>
<td>USA</td>
<td>PET/CT</td>
<td>140</td>
<td>7 (in 6 patients)</td>
<td>5</td>
<td>4 PC</td>
<td>13.7 ± 13.2</td>
<td>5.4 ± 0.8</td>
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<td>PET/CT</td>
<td>1763</td>
<td>70</td>
<td>34</td>
<td>16 PC, 1 ML, 1 Ly</td>
<td>10.7 ± 7.8*</td>
<td>6.7 ± 5.5*</td>
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<td>Chu (18)</td>
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<td>PET</td>
<td>6241</td>
<td>76</td>
<td>14</td>
<td>4 PC</td>
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<td>N.A.</td>
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<tr>
<td>Even-Sapir (19)</td>
<td>Israel</td>
<td>PET/CT</td>
<td>2360</td>
<td>59 (in 41 patients)</td>
<td>30</td>
<td>9 DTC, 1 MTC, 3 ML</td>
<td>N.A.</td>
<td>N.A.</td>
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<tr>
<td>Nam (20)</td>
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<td>19</td>
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<td>4 PC, 1 FC</td>
<td>8.4 ± 13.2</td>
<td>4.2 ± 4.0</td>
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<tr>
<td>Are (21)</td>
<td>USA</td>
<td>PET/CT</td>
<td>8800</td>
<td>101</td>
<td>42</td>
<td>12 PC, 7 FC</td>
<td>8.2 ± 7.0</td>
<td>9.2 ± 6.9</td>
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<tr>
<td>Bogsrud (22)</td>
<td>USA</td>
<td>PET/CT</td>
<td>7347</td>
<td>87 (in 79 patients)</td>
<td>44</td>
<td>12 PC, 1 HC, 1 FC, 1 ML</td>
<td>6.4 ± 3.6</td>
<td>7.9 ± 9.7</td>
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<td>Chen W (23)</td>
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<td>PET/CT</td>
<td>2594</td>
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<td>3 PC, 2 FC, 2 ML</td>
<td>4.0 ± 1.4</td>
<td>2.9 ± 1.4</td>
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<td>Bae (24)</td>
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<td>133</td>
<td>49</td>
<td>20 PC, 1 FC</td>
<td>6.64 ± 4.12*</td>
<td>3.35 ± 1.69*</td>
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<td>Kang BJ (25)</td>
<td>Korea</td>
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<td>12840</td>
<td>612</td>
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<td>54 PC, 1 FC</td>
<td>5.93 ± 5.35*</td>
<td>3.47 ± 2.89*</td>
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<tr>
<td>Eloy (26)</td>
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<td>PET/CT</td>
<td>630</td>
<td>30</td>
<td>18</td>
<td>5 PC</td>
<td>3.4 ± 2.6</td>
<td>2.9 ± 1.6</td>
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<tr>
<td>Zhai (27)</td>
<td>China</td>
<td>PET/CT</td>
<td>3580</td>
<td>115</td>
<td>96</td>
<td>35 PC, 10 FC, 2 ML, 1 Ly</td>
<td>6.7 ± 3.1*</td>
<td>3.8 ± 1.7*</td>
</tr>
<tr>
<td>Ohba (28)</td>
<td>Japan</td>
<td>PET/CT</td>
<td>1503</td>
<td>20</td>
<td>20</td>
<td>10 PC, 1 TLDC</td>
<td>5.3 ± 3.5</td>
<td>3.8 ± 1.2</td>
</tr>
<tr>
<td>Kim BH (29)</td>
<td>Korea</td>
<td>PET/CT</td>
<td>11623</td>
<td>159</td>
<td>140</td>
<td>36 PC, 1 HC</td>
<td>4.48 ± 2.13*</td>
<td>3.51 ± 1.58*</td>
</tr>
<tr>
<td>Nishimori (30)</td>
<td>Canada</td>
<td>PET/CT</td>
<td>4726</td>
<td>103</td>
<td>38</td>
<td>9 PC</td>
<td>5.8</td>
<td>5.2</td>
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<td>Pagano (31)</td>
<td>Italy</td>
<td>PET/CT</td>
<td>10881</td>
<td>191</td>
<td>36</td>
<td>13 PC, 1 FC</td>
<td>N.A.</td>
<td>N.A.</td>
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<tr>
<td>Al-Hakami (32)</td>
<td>Canada</td>
<td>PET/CT</td>
<td>1565</td>
<td>13</td>
<td>9</td>
<td>5PC</td>
<td>N.A.</td>
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<tr>
<td>Czepczyński (33)</td>
<td>Poland</td>
<td>PET/CT</td>
<td>1925</td>
<td>71</td>
<td>20</td>
<td>6 PC, 1 FC, 1 MTC, 1 ML</td>
<td>N.A.</td>
<td>N.A.</td>
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<tr>
<td>Nilsson (34)</td>
<td>Sweden</td>
<td>PET/CT</td>
<td>3641</td>
<td>41 (in 37 patients)</td>
<td>27</td>
<td>9 PC, 1 PDTC, 2 ML</td>
<td>7.05</td>
<td>6.26</td>
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<tr>
<td>Prichard (35)</td>
<td>Ireland</td>
<td>PET/CT</td>
<td>2105</td>
<td>35</td>
<td>20</td>
<td>4 PC, 2 ML, 2 Ly</td>
<td>N.A.</td>
<td>N.A.</td>
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<tr>
<td>Wong (36)</td>
<td>Australia</td>
<td>PET/CT</td>
<td>7896</td>
<td>200 (in 188 patients)</td>
<td>59</td>
<td>9 PC, 3 FC, 2 HC, 1 MTC, 1 ML, 4 Ly</td>
<td>4.3</td>
<td>3.5</td>
</tr>
<tr>
<td>Boeckmann (37)</td>
<td>USA</td>
<td>PET or PET/CT</td>
<td>23384</td>
<td>690</td>
<td>103</td>
<td>22 PC, 1 HC, 1 FC, 1 MTC, 3 ML</td>
<td>7.04 ± 7.88*</td>
<td>3.85 ± 3.06*</td>
</tr>
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<td>Bonabi (38)</td>
<td>Switzerland</td>
<td>PET/CT</td>
<td>3062</td>
<td>53</td>
<td>42</td>
<td>5 PC, 1 MTC, 1 AC, 3 ML</td>
<td>7.8</td>
<td>5.5</td>
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<tr>
<td>Lee (39)</td>
<td>Korea</td>
<td>PET or PET/CT</td>
<td>327</td>
<td>17</td>
<td>15</td>
<td>3 PC, 1 FC</td>
<td>17.8</td>
<td>6.16</td>
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<td>Pampaloni (40)</td>
<td>USA</td>
<td>PET/CT</td>
<td>8464</td>
<td>156</td>
<td>40</td>
<td>11 PC, 1 FC, 1 AC, 2 ML</td>
<td>5.5</td>
<td>7.2</td>
</tr>
<tr>
<td>Kao (41)</td>
<td>Singapore</td>
<td>PET/CT</td>
<td>942</td>
<td>21</td>
<td>6</td>
<td>2 PC, 1 MTC</td>
<td>6.6</td>
<td>5.6</td>
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<tr>
<td>Yang (42)</td>
<td>China</td>
<td>PET/CT</td>
<td>15948</td>
<td>281</td>
<td>103</td>
<td>38</td>
<td>7.0 ± 4.9*</td>
<td>5.2 ± 3.0*</td>
</tr>
<tr>
<td>Bertagna (43)</td>
<td>Italy</td>
<td>PET/CT</td>
<td>49519</td>
<td>729</td>
<td>211</td>
<td>52 PC, 8 FC, 2 HC, 2 PDTC, 1 MTC, 7 ML</td>
<td>N.A.</td>
<td>N.A.</td>
</tr>
</tbody>
</table>

*number and type (if available); **cytologically or histologically; FTIs: focal thyroid incidental uptake; N.A.: not available; PC: papillary carcinoma; FC: follicular carcinoma; HC: Hurthle cell carcinoma; MTC: medullary thyroid carcinoma; DTC: differentiated thyroid carcinoma; TLDC: thymus-like differentiated carcinoma; PDTC: poorly differentiated thyroid carcinoma; AC: anaplastic carcinoma; ML: metastatic lesions; Ly: lymphoma; *significant statistical difference between malignant and benign thyroid incidental uptake.
1.92% (95%CI: 1.87–1.99%), ranging from 0.8% to 5.2% (►Fig. 2a). Overall, 1522 FTIs detected by $^{18}$F-FDG PET or PET/CT underwent further evaluation by fine needle aspiration biopsy or surgery. Of these, 550 were diagnosed as malignant thyroid lesions. The pooled risk of malignancy was 36.2% (95%CI: 33.8–38.6%), ranging from 12.5% to 80% in the included studies (►Fig. 2b). The most frequent malignancy detected among FTIs was papillary thyroid carcinoma (►Tab. 1).

Concerning geographic distribution, the pooled prevalence of FTIs detected by $^{18}$F-FDG PET or PET/CT in Asia-Oceania (2.5%; 95%CI: 1.8–3.2%) was slightly but not significantly higher than that of North America (1.9%; 95%CI: 1.4–2.4%) and Europe (1.8%; 95%CI: 1.4–2.2%). Conversely, the pooled malignancy risk of FTIs detected by $^{18}$F-FDG-PET or PET/CT was 37.2% (95%CI: 30.9–43.6%) for Asia-Oceania, 38.7% (95%CI: 31.4–46.3%) for North America and 35.9% (95%CI: 31.2–40.7%) for Europe, without significant differences between different geographic areas.

A significant difference in pooled prevalence and malignancy risk of FTIs between iodine-deficient and iodine-sufficient countries was not found. The pooled prevalence and malignancy risk of FTIs were 2.0% (95%CI: 1.6–2.5%) and 36.3% (95%CI: 31.6–41.2%), respectively, for iodine-deficient countries, and 2.1% (95%CI: 1.7–2.56%) and 37.7% (95%CI: 33.0–42.5%), respectively, for iodine-sufficient countries.

In five articles $^{18}$F-FDG PET only was performed, whereas 26 studies used hybrid PET/CT device and three studies used both PET and PET/CT device (►Tab. 1). Excluding the studies in which both PET and PET/CT were performed, a significant difference in pooled prevalence of FTIs based on the device used (PET or PET/CT) was found. The pooled prevalence of FTIs was 2.2% (95%CI: 1.8–2.6%) when PET/CT was performed and 1.4% (95%CI: 1.1–1.7%) when PET only was performed. A significant difference in pooled malignancy risk of FTIs between PET (38%; 95%CI: 29–49%) and PET/CT (38%, 95%CI: 35–40%) was not found.

**Discussion**

With improved imaging technology and the increased use of imaging modalities, thyroid incidentalomas are being found more and more frequently. Rates of detection for thyroid incidentalomas are estimated to be 67% by neck US, 16% by CT and MRI and 9.4% by carotid Doppler scan (22). The risk of malignancy of thyroid incidentalomas is not negligible and varies according to the imaging characteristics of the thyroid findings (22).

In thyroid incidentalomas detected by US, conventional ultrasound features (such as hypoechoicity, microcalcifications, irregular margins or an absent halo, taller than wide shape, intranodular vascularity) can be used to discriminate malignant from benign lesions (22).

The rate of malignancy for thyroid incidentalomas detected by CT and MRI has been estimated to be between 3.9% and 11.3%; nevertheless, there are no imaging features on CT and MRI that are sufficiently predictive of thyroid malignancy unless neoplastic invasion of adjacent structures is demonstrated (22).

The increasing use of $^{18}$F-FDG PET and PET/CT is associated with a concomitant increase in the number of patients with FTIs. PET/CT provides simultaneous anatomic and metabolic information about incidental lesions found in the thyroid gland.

The pattern of $^{18}$F-FDG uptake in the thyroid on PET imaging influences the likelihood of malignancy: a diffuse $^{18}$F-FDG uptake in the thyroid is usually associated with benign conditions such as thyroiditis or hyperthyroidism (26, 40); such cases were not covered by this meta-analysis. We focused our analysis on FTIs because they may be associated with malignant tumors (40–42).

Several studies have reported the prevalence and the malignancy risk of FTIs detected by $^{18}$F-FDG PET or PET/CT (1, 3–8, 10–17, 20, 21, 23–25, 28, 29, 33–39, 46–49). A systematic review on this topic has been already published (41). The statistical approach of this paper has been previously discussed and criticized by our group (43). In particular, a meta-analytic approach taking into account the different weight of each included study was lacking.

**Meta-analysis** is a statistical technique for combining the findings of independent studies included in a systematic review. All meta-analyses are actually systematic reviews with components of statistical pooling of data. Conversely, not all systematic reviews have a meta-analytic component (44).

In order to derive more robust estimates, we performed a meta-analysis pooling literature data, including several articles published in the last two years (about one third of the articles included in this meta-analysis) that were not cited in the previous systematic review (41).

The pooled results of our meta-analysis indicate that FTIs are observed in about 2% of $^{18}$F-FDG-PET or PET/CT studies. Moreover, in our pooled analysis FTIs were associated with a significant risk of malignancy (36.2%), considering cytology or histology confirmation as reference standard. Therefore, whenever a focal hot spot is detected within the thyroid gland, the $^{18}$F-FDG PET or PET/CT report should suggest further investigation (including clinical examination, laboratory tests such as the measurement of thyroid stimulating hormone [TSH], thyroid US and US guided fine needle aspiration biopsy of the suspected lesion) in order to exclude a malignant tumour (19, 34).

The pooled prevalence of FTIs detected by $^{18}$F-FDG-PET or PET/CT in Asia-Oceania was slightly higher compared with other geographic areas. Although the incidence of thyroid malignancy varies between different geographic areas, the malignancy risk of FTIs seems to be similar among Asia-Oceania, North America and Europe. Similar prevalence and malignancy risk of FTIs between iodine-deficient and iodine-sufficient countries were found, in spite of the considerably higher incidence of thyroid nodules in iodine-deficient countries.

Hybrid PET/CT is usually superior in terms of diagnostic accuracy compared to PET alone for tumour imaging. Therefore, we performed a sub-analysis based on the device used (PET versus PET/CT); the prevalence of FTIs was significantly higher when hybrid PET/CT was used compared to PET alone (2.2% versus 1.4%, respectively). The significant difference in the detection of FTIs between PET and PET/CT may have different explanations. The better spatial res-
olution and contrast to noise ratio of the last generation of PET/CT scanners could have increased the detection of FTIs even though this might have been significant only for small thyroid nodules. An alternative more likely explanation is that prevalence of FTIs increased with PET/CT simply because knowledge of clinical relevance and reporting of FTIs increased with time. As a matter of fact, all PET studies were published from 2001 to 2006, whereas the vast majority of PET/CT studies after 2006. Furthermore, the lower number of FTIs detected by PET could be explained considering that a proportion of FTIs detected by PET is likely wrongly identified as extrathyroidal lesion such as cervical lymph node metastasis, though this of course remains speculative.

An advantage of the CT component of hybrid PET/CT is the possible visualization of thyroid nodules which are not detected (cold) at 18\textsuperscript{F}-FDG PET. In particular, about the thyroid malignancies, it is expected that the majority of primary differentiated thyroid carcinomas (DTCs) present as “cold” nodules at 18\textsuperscript{F}-FDG PET, due to their supposed low glucose metabolism. Nevertheless, we found that DTCs are the main cause of FTIs detected by 18\textsuperscript{F}-FDG PET or PET/CT, apparently contradicting the above described phenomenon. Further studies and prospective protocols are needed to clarify the real meaning of DTCs which present as “cold” or “hot” thyroid nodules at 18\textsuperscript{F}-FDG PET.

A significant difference in average SUV between benign and malignant FTIs was reported in some articles (→ Tab. 1). Nevertheless, a considerable overlap in SUV values was found between these two groups. As it is well known that SUV is influenced by several factors, related to the patient as well as to technical aspects and procedures, any calculation of a pooled SUV obtained by different studies – acquired with different tomographs, scan protocols, 18\textsuperscript{F}-FDG injected activity, and patient characteristics – is inappropriate in our opinion. Therefore, we did not perform a meta-analysis about SUV in benign and malignant FTIs. These factors considering, SUV alone should not be used to differentiate between malignant and benign FTIs.

### Limitations

Our study has some limitations such as a selection bias for the calculation of the risk of malignancy and the heterogeneity among studies. In the included studies only a limited proportion of FTIs detected by 18\textsuperscript{F}-FDG-PET or PET/CT underwent cytology or histology confirmation. Therefore, the calculation of malignancy risk, based on pathology data only, did not consider all the FTIs and this may represent a selection bias. It is in fact conceivable that further imaging studies already preselected those lesions at higher risk for malignancy and thus caused an overestimation of the risk of malignancy. Furthermore, the included studies were statistically heterogeneous in their estimates of prevalence and malignancy risk of FTIs. This heterogeneity is likely to stem from diversity in methodological aspects between different studies, including both the heterogeneity in PET or PET/CT methodology and the variability in the interpretation of cytology and possibly, based on this, different referral to surgery. In fact most studies were published before publication of the Bethesda classification (9). The baseline differences among the patients performing PET or PET/CT in the included studies may have contributed to the observed heterogeneity too.

A possible limitation of the pooled sub-analysis of prevalence and malignancy risk of FTIs for different geographic areas is that the vast majority of studies was performed in Asia and North America, whereas as Europe and iodine-deficient areas are underrepresented.

### Conclusions

**Focal thyroid 18\textsuperscript{F}-FDG incidental uptake is observed in about 2% of 18\textsuperscript{F}-FDG-PET or PET/CT studies and carry a significant risk of malignancy (pooled risk 36.2%).**

Further investigation is warranted whenever focal thyroid 18\textsuperscript{F}-FDG incidental uptake is detected by 18\textsuperscript{F}-FDG-PET or PET/CT.

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### Conflict of interest

The authors declare that they have no conflict of interest.

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