Fine-needle aspiration to diagnose primary thyroid lymphomas: a systematic review and meta-analysis

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Abstract

Background: Primary thyroid lymphoma (PTL) is a rare malignancy, and its prognosis depends significantly on its early diagnosis. While fine-needle aspiration (FNA) represents the gold standard to identify differentiated thyroid carcinoma, its reliability for the detection of PTL is still unclear. Here, we conducted a systematic review and meta-analysis to evaluate the diagnostic performance of FNA in PTL.

Research design and methods: A comprehensive literature search of PubMed/MEDLINE and Scopus databases was conducted to retrieve papers reporting histologically proven PTL undergone FNA. The last search was performed in February 2018 without language and time restrictions.

Results: Thirty-two studies describing 593 PTL were included and the pooled FNA sensitivity was 0.48 (95% CI = 0.38–0.58). FNA sensitivity was 0.51 in 20 studies published before 2010 and 0.39 in those published later, 0.50 in six articles with at least 20 cases and 0.44 in nine series enrolled after 2000. This performance was similar in 12 articles including diffuse large B-cell lymphoma (0.54) and those six on marginal zone lymphoma (0.56). Remarkably, FNA sensitivity increased to 0.72 when considering also FNA reports suspicious for PTL reported in 14 articles. Heterogeneity among the series was found. Publication bias was not always detected.

Conclusions: The present meta-analysis demonstrated that FNA has low sensitivity in diagnosing PTL. However, this rate increased when considering also FNA reports suspicious for PTL, which is relevant from a clinical standpoint. This result could support indirectly the use of additional imaging and/or core biopsy when PTL is suspected.

Introduction

Primary thyroid lymphoma (PTL) is a rare disease, accounting for 1–5% of thyroid malignancies and up to 2.5% of all extranodal lymphomas, with women more commonly affected than men (1, 2, 3). The majority of lymphomas arising in the thyroid gland are non-Hodgkin’s lymphomas of B-cell origin (3, 4). Most commonly, they are diffuse large B-cell lymphomas (DLBCL), which represents about half of the cases or marginal zone lymphomas of the mucosa-associated lymphoid tissue type (MALT lymphoma), accounting for up to a quarter of cases. Composite cases with both MALT lymphoma and DLBCL can occasionally be seen and may represent an ongoing histologic transformation process. Follicular lymphomas may also be found in the thyroid gland,
but are less common (approximately 10% PTL). Other histologic subtypes are rare at this site and comprise small lymphocytic lymphomas (3%), together with Burkitt’s, mantle cell and lymphoblastic lymphomas, each accounting for <1% of cases. T-cells lymphomas and Hodgkin lymphomas are extremely rare (3, 4, 5, 6, 7, 8). PTL serves (along with salivary gland lymphomas associated with myoepithelial sialadenitis) as the paradigm of the link of autoimmunity with lymphomas. The normal thyroid gland does not contain native lymphoid tissue and PTL typically arises from a background of chronic lymphocytic thyroiditis (9, 10). Indeed, patients with Hashimoto’s thyroiditis (HT) are at greater risk for developing PTL, with a relative risk of 67 compared to those without thyroiditis (9). In the context of chronic antigenic stimulation, abnormal B-cell clones acquiring successive genetic abnormalities can progressively replace the normal B-cell population of the inflammatory tissue, giving rise to the lymphoma.

The driving mechanisms might be, however, distinct in each autoimmune disease (11) and impaired immune-surveillance may also contribute to the lymphomagenesis process (12, 13).

Albeit the thyroid is not a mucosal organ, the lymphoid tissue occurring in HT shares many features with MALT (14). The differential diagnosis between a thyroid MALT lymphoma and its benign reactive precursor, HT, is not always straightforward (10, 14) and clonal B-cells can be present in (a minority of) HT (15). Detection of PTL is difficult and its early diagnosis remains challenging even in our era of emerging technologies. A PTL should be suspected in the presence of a rapidly enlarging neck mass, particularly in women with HT. Certain ultrasound features, such as enhanced posterior echoes, may also suggest the diagnosis. Fine-needle aspiration (FNA) represents the gold standard to identify differentiated thyroid carcinoma, and ultrasonography (US) and ultrasound-guided FNA are the most reliable and most commonly used first-line diagnostic procedures for risk stratification of thyroid nodules. However, the real accuracy of FNA for the detection of PTL is still unclear. FNA may lead to the diagnosis of DLBCL, while due to the continuum spectrum between HT and MALT lymphoma, it is considered less reliable for the diagnosis of MALT lymphoma. A combination of the cytological examination with flow cytometry analysis of FNA has been proposed (16), but it requires the availability of experienced specialists in hematology, flow cytometry and thyroid cytology. Therefore, biopsy is ultimately needed for a complete diagnostic work-up. Less aggressive than surgical biopsies, core needle biopsy (CNB) may provide enough tissue for both the accurate histological diagnosis and additional ancillary assays (17, 18, 19, 20), and it is currently recommended when PTL is suspected (1, 20). Nevertheless, despite its expected limitations for the diagnosis of PTL, US-guided FNA remains the most frequently used tool for the evaluation of thyroid nodules.

The actual reliability of FNA in detecting PTL has not yet been definitely assessed. Here, we report the results of a systematic review and meta-analysis on the sensitivity of FNA in the identification of PTL.

**Methods**

**Registration of review**

The present systematic review was registered in PROSPERO (n=CRD42018091734).

**Search strategy**

A five-step search strategy was planned. Firstly, we searched sentinel studies in PubMed. Secondly, keywords and MeSH terms were identified in PubMed. Thirdly, the terms ‘primary thyroid lymphoma’, ‘cytology’, ‘FNA’, ‘FNAB’, ‘FNAC’, ‘fine-needle’, ‘fine needle’ and ‘biopsy’ were searched in PubMed, in order to test the strategy. Fourthly, PubMed/MEDLINE and Scopus were screened. Finally, the references of included studies were screened for additional papers. The last search was performed on February 3, 2018. No language or time restriction was adopted.

Studies reporting the detection rate by FNA in histology-confirmed PTL were eligible for inclusion. The exclusion criteria were (a) articles not within the field of interest of this review; (b) review articles, editorials, letters or comments; (c) articles that did not provide clear study characteristics or reports that had overlapping patient data; (d) case reports and (e) case series reporting less than five PTL undergone FNA. Three investigators (P T, C V and M C) independently searched papers, screened titles and abstracts of the retrieved articles, and reviewed full-texts and selected articles for their inclusion. Incongruities were resolved in a consensus meeting involving all authors of the paper.

**Data extraction**

For each study that was included in the research, the following information was extracted independently
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by three investigators (P T, C V and M C) in a piloted form: (1) general information on the study (author, year of publication, journal, country and type of study); (2) number of patients diagnosed with PTL and who underwent FNA with year of diagnosis; (3) overall FNA results and (4) lymphoma subtype-specific FNA results. If more than one FNA was performed, the first one was considered. The main paper and Supplementary data (see section on supplementary data given at the end of this article) were searched. Since the analysis of the sentinel studies revealed a high heterogeneity in FNA results reporting, data were cross-checked and any discrepancy was discussed.

Study quality assessment
The risk of bias of included studies was assessed independently by two reviewers (P T and M C) through the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool for the following aspects: patient selection, index test, reference standard, flow and timing. Risk of bias and concerns about applicability were rated as low, high and unclear risk (21). Data presentation was arranged using the Review Manager computer program (RevMan version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Statistical analysis
The sensitivity of FNA in PTL was calculated from each article on a per-lesion-based analysis. ‘Highly suspicious’ and ‘highly suggestive’ results were input as positive. A random effect model was then used statistically to pool the data. Pooled data were presented with 95% CI. I² index was used to test for heterogeneity among the studies (significant heterogeneity was defined as having an I² value >50%). Egger’s test was used to evaluate publication bias. Statistical analyses were performed by using StatsDirect statistical software (StatsDirect Ltd; Altrincham, UK).

Results
The search yielded 843 potentially relevant articles, of which 632 on PubMed and 211 on Scopus and other seven records were retrieved by other sources. Duplicates were excluded by using a specific software, and titles and abstracts of 819 references were screened leading to the exclusion of 655 articles. The remaining 164 were evaluated in full-text, and 32 (20, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52) were finally included for the present review (Fig. 1).

Study quality assessment
The risk of bias of the included studies was shown in Fig. 2 (see also Supplementary data). Overall, a low risk of bias was found: all consecutive patients diagnosed with PTL in a specific period were included. FNA was conducted and interpreted before histology. Reference standard bias was rated as high since histology is commonly performed once the results of the index test

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Figure 1
Flow diagram of the search to retrieve eligible studies.
are known. Flow and timing biases were rated as low since PTL is a chronic condition. Finally, all studies met the predefined criteria for applicability concerns. The only exceptions to the statements above include the studies by Adhikari et al., in which 13 specimens had a prior diagnosis of lymphoma before FNA (22), those by Dustin et al., in which cases with insufficient cytological material for interpretation were not included (28) and by Matsuda et al., in which no information regarding patient selection was found (37).

### Qualitative analysis

The main characteristics of the included articles were summarized in Table 1. The studies were published between 1987 and 2018 and reported cohorts ranging from 5 to 106 patients. Twenty-seven articles were single-center, three two-center, one three-center and one four-center. Seventeen studies were performed in Asia, eight in Europe and seven in North America. Overall, a number of 593 histologically proven PTL diagnosed in

### Table 1 Characteristics of the 32 articles included in the meta-analysis.

<table>
<thead>
<tr>
<th>First author (Ref)</th>
<th>Year</th>
<th>Journal</th>
<th>Country</th>
<th>Study period*</th>
<th>Cases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adhikari (22)</td>
<td>2016</td>
<td>Journal of the American Society of Cytopathology</td>
<td>USA</td>
<td>2000–2013</td>
<td>64</td>
</tr>
<tr>
<td>Bostanci (23)</td>
<td>2017</td>
<td>Turkish Journal of Medical Sciences</td>
<td>Turkey</td>
<td>2009–2015</td>
<td>11</td>
</tr>
<tr>
<td>Colovic (27)</td>
<td>2007</td>
<td>Medical Oncology</td>
<td>Serbia</td>
<td>1994–1999</td>
<td>5</td>
</tr>
<tr>
<td>Dustin (28)</td>
<td>2012</td>
<td>Diagnostic Cytopathology</td>
<td>USA</td>
<td>1992–2009</td>
<td>15</td>
</tr>
<tr>
<td>Hirokawa (30)</td>
<td>2017</td>
<td>Endocrine Journal</td>
<td>Japan</td>
<td>2012–2015</td>
<td>32</td>
</tr>
<tr>
<td>Hwang (31)</td>
<td>2009</td>
<td>Endocrine Journal</td>
<td>Korea</td>
<td>1991–2006</td>
<td>29</td>
</tr>
<tr>
<td>Lam (33)</td>
<td>1999</td>
<td>Hematopathology</td>
<td>China</td>
<td>1968–1997</td>
<td>9</td>
</tr>
<tr>
<td>Li (35)</td>
<td>2017</td>
<td>Transcancer Research</td>
<td>China</td>
<td>2002–2012</td>
<td>9</td>
</tr>
<tr>
<td>Matsuzuka (38)</td>
<td>1993</td>
<td>Thyroid</td>
<td>Japan</td>
<td>1963–1990</td>
<td>83</td>
</tr>
<tr>
<td>Mizokami (39)</td>
<td>2016</td>
<td>Internal Medicine</td>
<td>Japan</td>
<td>2005–2014</td>
<td>9</td>
</tr>
<tr>
<td>Ruggiero (43)</td>
<td>2005</td>
<td>Otolaryngology-Head and Neck Surgery</td>
<td>USA</td>
<td>1977–2004</td>
<td>15</td>
</tr>
<tr>
<td>Sangalli (44)</td>
<td>2001</td>
<td>Cytology</td>
<td>Italy</td>
<td>1980–1998</td>
<td>17</td>
</tr>
<tr>
<td>Stacchini (47)</td>
<td>2015</td>
<td>Cytometry Part B: Clinical Cytometry</td>
<td>Italy</td>
<td>2001–2013</td>
<td>11</td>
</tr>
<tr>
<td>Wang (49)</td>
<td>2005</td>
<td>Modern Pathology</td>
<td>USA</td>
<td>1990–2005</td>
<td>5</td>
</tr>
<tr>
<td>Xie (52)</td>
<td>2017</td>
<td>Zhongguo Yi Xue Ke Xue Yuan Xue Bao</td>
<td>China</td>
<td>N/A</td>
<td>7</td>
</tr>
</tbody>
</table>

*Period of patient enrollment; *number of PTL undergone FNA; §data not available.

https://eje.bioscientifica.com
the period from 1963 to 2015 and submitted to FNA were described. Other examinations were described alongside to FNA cytology. Among cytological ancillary testing, flow cytometry was the most widely used (22, 26, 30, 43, 47); other techniques included PCR, immunocytochemistry and G-banding chromosome examination (22, 29, 44, 46, 47). In other studies, CNB/tru-cut or surgical biopsy were reported (20, 23, 26, 31, 32, 35, 36, 38, 39, 42, 43, 44, 45, 46, 47, 48, 50, 51); in one study, a lymph node biopsy was performed (51). Among histological ancillary testing, immunohistochemistry was the most widely used (26, 30, 33, 34, 35, 49, 51); only a few reports included immunoglobulin heavy-chain gene analysis and flow cytometry studies (30, 43).

Quantitative analysis

In order to calculate the pooled sensitivity of FNA in diagnosing PTL, we initially included all 32 papers (20, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52), leading to a sensitivity of 0.48 with high heterogeneity and no publication bias. In the attempt to reduce the heterogeneity, we then calculated FNA sensitivity in some subgroups. There were 14 articles describing the number of FNA reports as diagnostic of and suspicious for PTL separately (22, 23, 28, 32, 34, 35, 41, 42, 43, 44, 47, 48, 50, 51, 52); when we considered these two FNA reports as a whole, a sensitivity of 0.72 was found, with high heterogeneity and publication bias. Also, by analyzing FNA sensitivity combining only data from the six papers with at least 20 PTL cases (22, 30, 31, 38, 42, 50), we found a sensitivity of 0.50 with significant heterogeneity but no publication bias. Then, we evaluated the impact of timing of publication. Firstly, in the 12 articles published more recently (i.e., we arbitrary selected papers published after 2010) (22, 23, 28, 30, 35, 39, 45, 47, 48, 50, 51, 52), we found a sensitivity of 0.39 with heterogeneity and no publication bias (Fig. 3). Secondly, in the nine papers reporting PTL series enrolled after 2000 (20, 22, 23, 30, 32, 35, 49, 52), the pooled FNA sensitivity was 0.44 with heterogeneity, but there was no publication bias (Fig. 4). Lastly, we analyzed the pooled FNA sensitivity in the specific histologic PTL types. The most prevalent PTL variants in the 32 retrieved articles were DLBCL and MALT. The pooled FNA sensitivity in DLBCL from 12 articles (20, 22, 28, 30, 31, 34, 36, 43, 44, 47, 48, 51) was 0.54 with mild heterogeneity and no publication bias (Fig. 5). The pooled FNA sensitivity in MALT from six articles (30, 31, 39, 44, 47, 50) was 0.56 with mild heterogeneity and publication bias.

Discussion

The aim of the current study was to evaluate the available evidence on the reliability of FNA cytology in diagnosing PTL. Although PTLs include some of the most aggressive thyroid malignancies, they are very rare; consequently, evidence on the reliability of diagnostic tools is limited.

Figure 3

Forest plot of detection rate (i.e., diagnostic sensitivity) of FNAC in PTL (random effect), including 95% confidence intervals, in papers published since 2010.

Figure 4

Forest plot of detection rate (i.e., diagnostic sensitivity) of FNAC in PTL (random effect), including 95% confidence intervals, in articles reporting series of enrolled after 2000.
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Here, we focused on the FNA performance – this being the gold standard test to identify thyroid cancer. By applying a specific search strategy, we found 32 articles reporting PTL cases subjected to FNA and published over a very large period (1987–2018) by Asian, European and American authors. The most significant finding was that the FNA sensitivity in diagnosing PTL was quite low (48%) when we considered the overall series of papers and remained unchanged even after selecting various subgroups of articles or focusing on different histological PTL types. However, sensitivity increased to 72% when FNA reports ‘suspicious for’ and ‘diagnostic of’ PTL were considered together. From the clinical standpoint, this high diagnostic sensitivity is a most interesting observation because the same diagnostic approach is indicated in both FNA instances; in fact, since FNA is inadequate for initial lymphoma diagnosis, a biopsy is recommended to provide adequate tissue for the precise identification/confirmation of the histological lymphoma subtype (53). While FNA is the pivotal diagnostic tool for the assessment of thyroid nodules, it is usually performed in a clinical setting that may lack specific expertise on lymphomas. Furthermore, PTL being a rare condition, its precise identification at FNA may depend on the specific expertise of the cytologist who often is a thyroid specialist. Nevertheless, FNA performance for the lymphoma diagnosis remains lower than that observed in differentiated thyroid carcinomas, in which FNA sensitivity is reported >85% (1, 54, 55, 56). The present data also indicate that the recognized accuracy of FNA in detecting thyroid cancers must be referred only to papillary carcinoma and not to other types of malignancies (1, 56, 57, 58). Surprisingly, when we analyzed the subgroup of articles published more recently or enrolling patients in the last two decades, we found even lower FNA sensitivity. We cannot explain these findings with certainty, but it could be speculated that PTL diagnosed in earlier decades (i.e. in 80s or 90s) could have been detected in a late or more advanced stage of the disease. This condition has to be taken into account as a potential factor of risk of bias. Due to its aggressive nature, the presence of DLBCL might have been clinically suspected leading to FNA performed as a diagnostic proof rather than question (or accompanied by a core biopsy) with blinded cytopathologists.

The cytological presentation of PTL is quite variable and may be sometimes challenging due to the variability of the cytological picture and presence of thyrocytes included in the sample. The cytological features of PTL are similar to those reported for lymph nodes: the main characteristic is the presence of monomorphism of the neoplastic population in contrast with the mixture of small and large lymphocytes that are present in varying proportions in reactive lymph nodes. While large cell lymphomas are readily recognized as malignant tumors, small cell lymphomas usually require immunophenotyping of the neoplastic population to be correctly identified. This approach requires the availability of a cell block for immunohistochemistry or a cytological preparation for flow cytometry (59). In this setting, the clinical history is a crucial point to achieve the correct diagnosis: if a lymphoproliferative disorder is suspected before FNA, appropriate ancillary studies can be planned and performed. From the therapeutic point of view,
Table 2 | Results of the meta-analysis on the overall series of articles and in specific subgroups.

<table>
<thead>
<tr>
<th>Pooled analysis</th>
<th>Articles included (n)</th>
<th>PTL cases (n)</th>
<th>Sensitivity (95% CI)</th>
<th>Inconsistency - $I^2$ (95% CI)</th>
<th>Publication bias - Egger test (95% CI)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>All retrieved papers</td>
<td>32</td>
<td>593</td>
<td>0.48 (0.38–0.58)</td>
<td>82.3% (75.8–86.4)</td>
<td>−1.44 (−4.26 to 1.38)</td>
<td>0.3052</td>
</tr>
<tr>
<td>FNA diagnostic of and</td>
<td>14</td>
<td>309</td>
<td>0.72 (0.61–0.81)</td>
<td>69.9% (41.7–81.3)</td>
<td>−2.64 (−4.82 to −0.46)</td>
<td>0.0215</td>
</tr>
<tr>
<td>suspicious for PTL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papers with at least 20 PTL cases</td>
<td>6</td>
<td>334</td>
<td>0.50 (0.33–0.68)</td>
<td>90.2% (81.2–93.8)</td>
<td>−1.6 (−15.29 to 12.09)</td>
<td>0.7624</td>
</tr>
<tr>
<td>Articles published before 2010</td>
<td>20</td>
<td>294</td>
<td>0.51 (0.39–0.64)</td>
<td>78.6% (67.3–84.7)</td>
<td>−4.14 (−6.54 to −1.74)</td>
<td>0.0018</td>
</tr>
<tr>
<td>Articles published after 2010</td>
<td>12</td>
<td>299</td>
<td>0.39 (0.25–0.53)</td>
<td>82.2% (68.8–88.3)</td>
<td>1.88 (−3.45 to 7.2)</td>
<td>0.4504</td>
</tr>
<tr>
<td>Articles reporting PTL</td>
<td>9</td>
<td>158</td>
<td>0.44 (0.28–0.62)</td>
<td>76.8% (49.2–86.4)</td>
<td>2.34 (−4.34 to 9.02)</td>
<td>0.4342</td>
</tr>
<tr>
<td>series enrolled after 2000*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FNA of DLBCL*</td>
<td>12</td>
<td>128</td>
<td>0.54 (0.38–0.70)</td>
<td>68.8% (34.1–81.4)</td>
<td>3.11 (−2.3 to 8.53)</td>
<td>0.229</td>
</tr>
<tr>
<td>FNA of MALT*</td>
<td>6</td>
<td>168</td>
<td>0.56 (0.37–0.74)</td>
<td>74.8% (22.4–87.1)</td>
<td>3.51 (−0.6 to 7.62)</td>
<td>0.0767</td>
</tr>
</tbody>
</table>

Sensitivity ranged from 0 to 1.0. Absence of heterogeneity was set at $I^2$ <50%. Egger test significantly identified the presence of publication bias.

*Results reported as forest plot.

Non-Hodgkin lymphomas are distinct clinicopathological entities defined through a comprehensive evaluation of morphological, immunophenotypic and genetic features and clinical data, and their complete assessment is the base for the classification and the planning of specific treatments (60). Some authors found that flow cytometry applied to FNA might enhance the accuracy of cytological diagnosis in lymphoproliferative disorders and allow further subclassification in more than half of the cases (61). This implies that the remaining patients will need adjunctive analysis. This is also true for those patients who receive a cytological diagnosis of PTL (either suspicious or definitive) based on morphological assessment only. In such cases, FNA may serve as a screening test, which should be followed by an excisional (or core) biopsy for the appropriate histological assessment.

While ultrasound combined with FNA is pivotal in the initial assessment of thyroid nodule due to its high sensitivity and specificity to rule out primary and metastatic solid tumors, its accuracy drops significantly in the assessment of PTL. Indeed, PTL frequently presents itself as a large mass and not as a defined nodule. In addition, some of the ancillary ultrasonographic features typical for thyroid malignancy (such as microcalcifications, irregular margins, marked hypoechochogenicity, taller-than-wide shape) are often absent (1). Alternative imaging tools may be taken into account. $^{18}$F-FDG PET-CT is a functional imaging modality increasingly used for the staging and response assessment in patients with lymphomas and provides high accuracy in the detection of nodal and extranodal disease (53, 62). Nevertheless, in the PTL context also $^{18}$F-FDG PET-CT has important limitations. In fact, inflammatory cells, in particular leukocytes, show an increased glucose metabolism after antigenic activation. This phenomenon explains the high tracer uptake detected by PET in HT and may affect the specificity of the PET imaging (63, 64). In contrast with differentiated thyroid cancer, which usually depicts focal FDG uptake, a diffuse (either homogeneous or irregular) increase of thyroid uptake is the most characteristic PET feature in PTL (63, 65). However, this pattern cannot be considered pathognomonic since the same is frequently found in patients with HT or Graves’ disease (65, 66, 67) and, more rarely, in cases of metastatic cancer involvement of the thyroid (68, 69). On the other hand, focal uptake may be occasionally found also in patients with a secondary lymphomatous involvement of the thyroid gland (70). Additionally, HT is considered as the ‘etiologic background’ of PTL (9, 71), and in some cases, it is very difficult to discriminate between the two coexisting processes (72). Some authors demonstrated higher SUV$_{\text{max}}$ values in PTL compared to HT or Graves’ disease patients (73); nevertheless, a wide range of SUV$_{\text{max}}$ values (7.4–39.6) has been reported in cases of PTL (63, 74, 75, 76). The FDG uptake values of malignant lymphomas differ according to the histological subtypes and aggressive PTL such as DLBCL show higher values than indolent lymphomas (i.e. MALT) (77); this makes it difficult to use the SUV$_{\text{max}}$ to discriminate between HT/Graves’ disease and PTL. Therefore, the PET imaging may only suggest or support the clinical suspicion of PTL but cannot be used as surrogate of the pathologic diagnosis. Some authors also reported that patients with PTL exhibit decreased CT density of the thyroid gland as compared to healthy subjects and patients with autoimmune thyroiditis (73, 78, 79). Nevertheless, different CT patterns have
been associated with PTL (solitary nodule surrounded by normal thyroid tissue, multiple nodules in the thyroid and both homogeneously enlarged thyroid lobes with a reduced attenuation, with or without peripheral thin hyperattenuating thyroid tissue), such that the use of the decreased attenuation as a diagnostic parameter is problematic in clinical practice (80, 81). Hence, biopsy confirmation is always needed for the diagnosis of PTL. CT and MRI may contribute to the local stage of the disease by defining the location and extension of the primary lesion and by assessing the possible invasion of the adjacent structures in areas that are poorly assessed by ultrasonography. Since MRI has a high contrast resolution for soft tissues, it may better detect pseudocapsules and define the uninvolved thyroid tissues (82, 83). Conversely, 18FDG PET-CT plays a pivotal role in the initial staging of PTL, providing a reliable map of regional and distant disease dissemination (84). At the time of presentation, 56% of PTLs are Ann Arbor stage IE, 32% stage IIE, 13% stage III–IVE, with 5-year disease-specific survival of 86, 81, and 64%, respectively (8, 85). Stage and histological subtype are predictors of outcome and therefore also affect the therapeutic approach to PTLs. Patients with localized and indolent disease (e.g., MALT lymphoma stage IE) usually receive loco-regional treatment such as radiotherapy alone or surgery (86, 87, 88), while those with disseminated disease as well as those with aggressive histological subtypes, such as DLBCL, should be treated with chemotherapy and consolidation radiotherapy (89, 90, 91, 92). Changes of FDG uptake represent a sensitive and reliable tool for monitoring the response of the disease to treatment and for detecting early relapses with higher accuracy than CT imaging (68, 84, 93).

In view of the potential limitations of FNA and imaging tools in the detection of PTL, current guidelines suggest using other biopsy techniques; firstly, CNB and surgical excision (1). This approach is not really supported by evidence-based data, probably due to the rareness of PTL (14). However, the present study underlines FNA and ultrasound limits and indirectly corroborates the use of CNB and/or other imaging tools when PTL is clinically suspected. The results of the present meta-analysis should not be affected by these limitations. We feel that the very large number of included papers and the wide period during which they were published can reduce the publication bias. The results (and heterogeneity) were unchanged when we evaluated several subgroups of articles, also if arranged by time periods. Specifically, FNA sensitivity further decreased when we meta-analyzed the subgroup of recent studies; this can avoid the bias frequently present in meta-analyses on studies reporting preliminary and recent results, because positive findings are more likely to be published. Therefore, we are confident to have excluded significant search and statistical weakness. On the other hand, we could not evaluate FNA sensitivity in some specific contexts, such as limited versus advanced stage or with ancillary cytological examinations available; data on these issues were not reported in the retrieved articles. As a main inclusion criterion, here we selected studies reporting the detection rate by FNA in histologically proven PTL. On one hand, this study design allowed us to have a strong standard of reference (i.e. histology) for FNA assessment. On the other hand, this approach could introduce another potential bias of our data. In fact, multidisciplinary teams from many centers may rely only on FNA results, and later stage and treat their patients without core or open biopsy. Then, these studies were not found in our search due to our major inclusion criterion (i.e. histologically proven PTL).

The present meta-analysis showed that FNA cytology has a low sensitivity in diagnosing PTL, ranging between 39 and 56% of cases in a large series of articles reporting on PTL subjected to this procedure. Moreover, this percentage increased to 72% when we included also FNA reports suspicious for PTL, and this can be a useful information for clinical practice. These data indirectly suggest that the high reliability recognized for ultrasound-guided FNA in thyroid malignancy should be specifically referred to papillary carcinomas. Furthermore, these results indirectly support the use of other imaging tools and the need of core or excisional biopsy when PTL is suspected.

Supplementary data
This is linked to the online version of the paper at https://doi.org/10.1530/EJE-18-0672.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

Funding
This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Clinical Study
L. Zhang and others
FNA cytology in thyroid lymphoma


That's the end of the extracted text. It seems to be a detailed study on fine-needle aspiration cytology in thyroid lymphoma, discussing various aspects such as diagnostic pitfalls, treatment, and follow-up evaluations. The text is rich with references to other studies and journals, indicating a comprehensive review of the topic. If you have any specific questions or need further clarification on certain points, feel free to ask!


