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

Lu Zhang[1], Marco Castellana[2], Camilla Virili[3], Anna Crescenzi[4], Francesco Giorgino[2], Emanuele Zucca[5,6,7], Luca Ceriani[8], Franco Cavalli[7], Luca Giovanella[8] and **Pierpaolo Trimboli[8]**

[1]Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China, [2]Section of Internal Medicine, Endocrinology, Andrology and Metabolic Diseases, Department of Emergency and Organ Transplantation, University of Bari Aldo Moro, Bari, Italy, [3]Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy, [4]Pathology Unit, University Hospital Campus Bio-Medico, Rome, Italy, [5]Division of Medical Oncology, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland, [6]Medical Oncology, University of Bern, Bern, Switzerland, [7]Institute of Oncology Research, and [8]Department of Nuclear Medicine and Thyroid Centre, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland

Correspondence should be addressed to L Giovanella
Email
luca.giovanella@eoc.ch

European Journal of Endocrinology

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.

European Journal of Endocrinology (2019) **180**, 177–187

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,

https://eje.bioscientifica.com
https://doi.org/10.1530/EJE-18-0672

Published by Bioscientifica Ltd.

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

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. I^2 index was used to test for heterogeneity among the studies (significant heterogeneity was defined as having an I^2 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

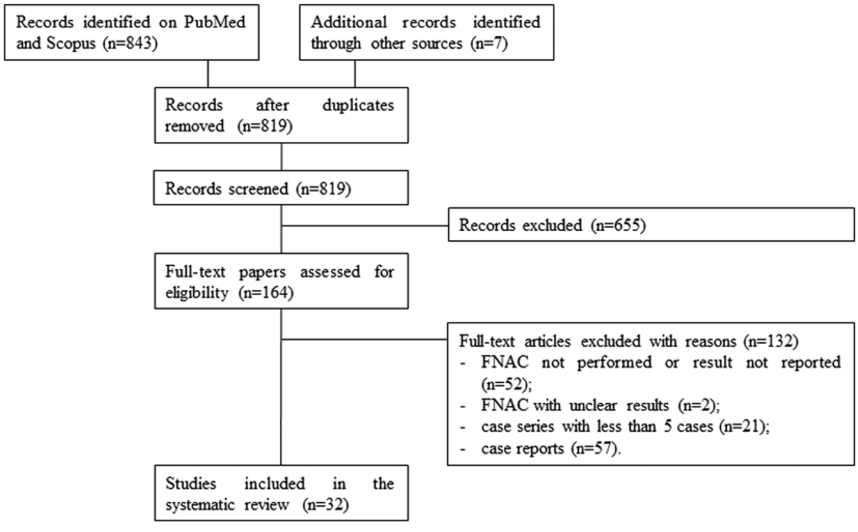

Figure 1
Flow diagram of the search to retrieve eligible studies.

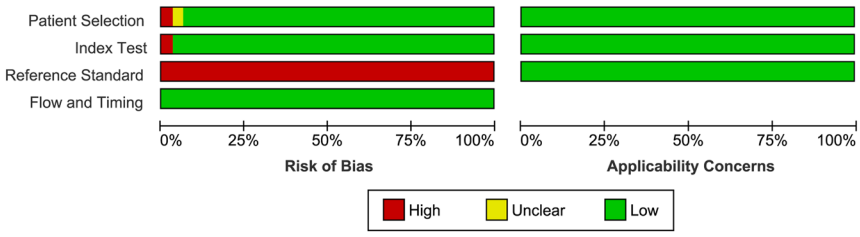

Figure 2
Risk of bias and applicability concerns graph: review authors' judgments about each domain presented as percentages across included studies.

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.

First author (Ref)	**Year**	**Journal**	**Country**	**Study period***	**Cases#**
Adhikari (22)	2016	*Journal of the American Society of Cytopathology*	USA	2000–2013	64
Bostanci (23)	2017	*Turkish Journal of Medical Sciences*	Turkey	2009–2015	11
Bula (24)	2008	*Acta Chirurgica Belgica*	Poland	1990–2005	8
Cap (25)	1999	*Clinical Endocrinology*	Czech Republic	1991–1998	6
Cha (26)	2002	*Annals of Surgical Oncology*	USA	1985–2000	12
Colovic (27)	2007	*Medical Oncology*	Serbia	1994–1999	5
Dustin (28)	2012	*Diagnostic Cytopathology*	USA	1992–2009	15
Gupta (29)	2005	*CytoJournal*	India	1998–2004	10
Hirokawa (30)	2017	*Endocrine Journal*	Japan	2012–2015	32
Hwang (31)	2009	*Endocrine Journal*	Korea	1991–2006	29
Joshi (32)	2009	*International Journal of Clinical Practice*	Great Britain	2001–2008	9
Kwak (20)	2007	*Journal of Ultrasound in Medicine*	Korea	2003–2005	6
Lam (33)	1999	*Hematopathology*	China	1968–1997	9
Lerma (34)	2003	*Acta Cytologica*	Spain	1992–2001	6
Li (35)	2017	*Transational Cancer Research*	China	2002–2012	9
Lu (36)	2001	*Journal of the Formosan Medical Association*	Taiwan	1981–2000	11
Matsuda (37)	1987	*Diagnostic Cytopathology*	Japan	1983–1985	5
Matsuzuka (38)	1993	*Thyroid*	Japan	1963–1990	83
Mizokami (39)	2016	*Internal Medicine*	Japan	2005–2014	9
Nishiyama (40)	2003	*Annals of Nuclear Medicine*	Japan	1990–2001	15
Ogawa (41)	2001	*Surgery Today*	Japan	1993–1998	5
Pyke (42)	1992	*World Journal of Surgery*	USA	1965–1989	20
Ruggiero (43)	2005	*Otolaryngology-Head and Neck Surgery*	USA	1977–2004	15
Sangalli (44)	2001	*Cytopathology*	Italy	1980–1998	17
Sarinah (45)	2010	*Asian Journal of Surgery*	Malaysia	1998–2006	15
Skarsgard (46)	1991	*Archives of Surgery*	Canada	1981–1990	18
Stacchini (47)	2015	*Cytometry Part B: Clinical Cytometry*	Italy	2001–2013	11
Sun (48)	2010	*Journal of Surgical Oncology*	China	1991–2007	11
Wang (49)	2005	*Modern Pathology*	USA	1990–2005	5
Watanabe (50)	2018	*Journal of Clinical Endocrinology and Metabolism*	Japan	1990–2009	106
Wu (51)	2016	*Formosan Journal of Surgery*	Taiwan	1992–2015	9
Xie (52)	2017	*Zhongguo Yi Xue Ke Xue Yuan Xue Bao*	China	N/A§	7
Total, *n*					593

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

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 FNA 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, 39, 47, 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 (Fig. 6). All the above results are detailed in Table 2 (view also Supplementary data).

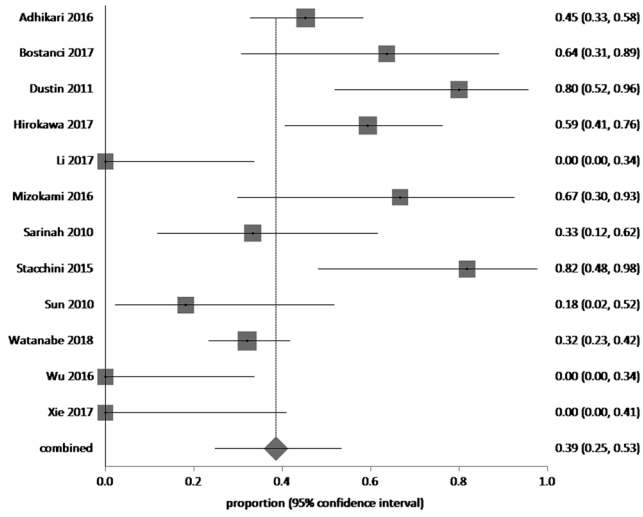

Figure 3
Forest plot of detection rate (i.e. diagnostic sensitivity) of FNAC in PTL (random effect), including 95% confidence intervals, in papers published since 2010.

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.

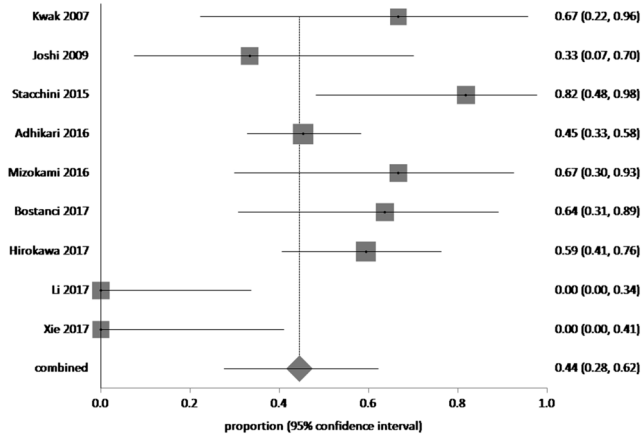

Figure 4
Forest plot of detection rate (i.e. diagnostic sensitivity) of FNAC in PTL (random effect), including 95% confidence intervals, in articles reporting series of enrolled after 2000.

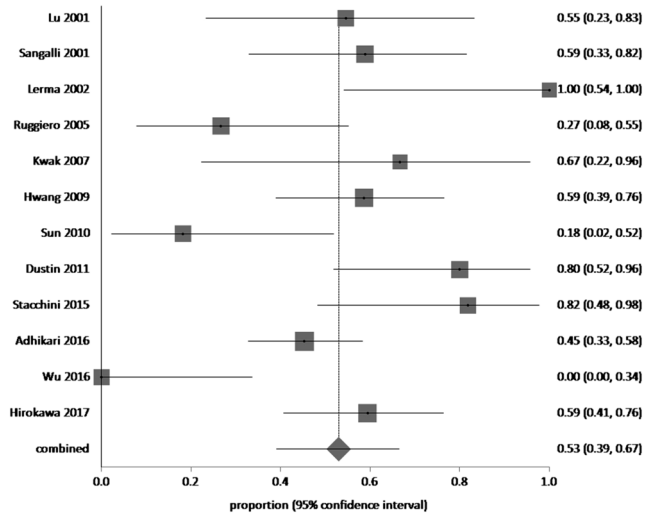

Figure 5

Forest plot of detection rate (i.e. diagnostic sensitivity) of FNAC in DLBCL (random effect), including 95% confidence intervals.

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

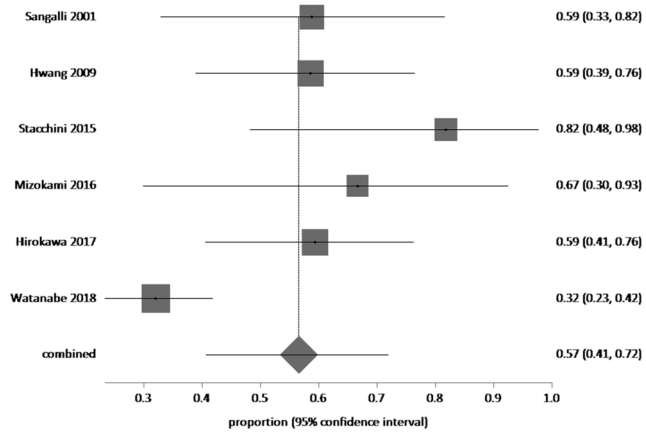

Figure 6

Forest plot of detection rate (i.e. diagnostic sensitivity) of FNAC in MALT (random effect), including 95% confidence intervals.

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.

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

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 hypoechogenicity, 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_{max} values in PTL compared to HT or Graves' disease patients (73); nevertheless, a wide range of SUVmax 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 SUVmax to discriminate between HT/Graves' disease and PTL. Therefore, the PET imaging may only suggest or support the clinical suspicion of PLT 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, ^{18}FDG 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.

References

1 Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M *et al*. 2015 American Thyroid Association Management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid* 2016 **26** 1–133. (https://doi.org/10.1089/thy.2015.0020)

2 Stein SA & Wartofsky L. Primary thyroid lymphoma: a clinical review. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 3131–3138. (https://doi.org/10.1210/jc.2013-1428)

3 Pavlidis ET & Pavlidis TE. A review of primary thyroid lymphoma: molecular factors, diagnosis and management. *Journal of Investigative Surgery* 2017 Epub. (https://doi.org/10.1080/08941939.2017.1383536)

4 Graff-Baker A, Roman SA, Thomas DC, Udelsman R & Sosa JA. Prognosis of primary thyroid lymphoma: demographic, clinical, and pathologic predictors of survival in 1408 cases. *Surgery* 2009 **146** 1105–1115. (https://doi.org/10.1016/j.surg.2009.09.020)

5 Thieblemont C, Mayer A, Dumontet C, Barbier Y, Callet-Bauchu E, Felman P, Berger F, Ducottet X, Martin C *et al*. Primary thyroid lymphoma is a heterogeneous disease. *Journal of Clinical Endocrinology and Metabolism* 2002 **87** 105–111. (https://doi.org/10.1210/jcem.87.1.8156)

6 Pedersen RK & Pedersen NT. Primary non-Hodgkin's lymphoma of the thyroid gland: a population based study. *Histopathology* 1996 **28** 25–32. (https://doi.org/10.1046/j.1365-2559.1996.268311.x)

7 Alzouebi M, Goepel JR, Horsman JM & Hancock BW. Primary thyroid lymphoma: the 40 year experience of a UK lymphoma treatment centre. *International Journal of Oncology* 2012 **40** 2075–2080. (https://doi.org/10.3892/ijo.2012.1387)

8 Onal C, Li YX, Miller RC, Poortmans P, Constantinou N, Weber DC, Atasoy BM, Igdem S, Ozsahin M & Ozyar E. Treatment results and prognostic factors in primary thyroid lymphoma patients: a rare cancer network study. *Annals of Oncology* 2011 **22** 156–164. (https://doi.org/10.1093/annonc/mdq310)

9 Holm LE, Blomgren H & Lowhagen T. Cancer risks in patients with chronic lymphocytic thyroiditis. *New England Journal of Medicine* 1985 **312** 601–604. (https://doi.org/10.1056/NEJM198503073121001)

10 Isaacson PG. Lymphoma of the thyroid gland. *Current Topics in Pathology* 1997 **91** 1–14.

11 Zucca E & Bertoni F. The spectrum of MALT lymphoma at different sites: biological and therapeutic relevance. *Blood* 2016 **127** 2082–2092. (https://doi.org/10.1182/blood-2015-12-624304)

12 Drugarin D, Negru S, Koreck A, Zosin I & Cristea C. The pattern of a T(H)1 cytokine in autoimmune thyroiditis. *Immunology Letters* 2000 **71** 73–77. (https://doi.org/10.1016/S0165-2478(99)00156-X)

13 Nanba T, Watanabe M, Inoue N & Iwatani Y. Increases of the Th1/Th2 cell ratio in severe Hashimoto's disease and in the proportion of Th17 cells in intractable Graves' disease. *Thyroid* 2009 **19** 495–501. (https://doi.org/10.1089/thy.2008.0423)

14 Hyjek E & Isaacson PG. Primary B cell lymphoma of the thyroid and its relationship to Hashimoto's thyroiditis. *Human Pathology* 1988 **19** 1315–1326. (https://doi.org/10.1016/S0046-8177(88)80287-9)

15 Saxena A, Alport EC, Moshynska O, Kanthan R & Boctor MA. Clonal B cell populations in a minority of patients with Hashimoto's thyroiditis. *Journal of Clinical Pathology* 2004 **57** 1258–1263. (https://doi.org/10.1136/jcp.2004.018416)

16 Cibas ES & Ali SZ. The 2017 Bethesda system for reporting thyroid cytopathology. *Thyroid* 2017 **27** 1341–1346. (https://doi.org/10.1089/thy.2017.0500)

17 Trimboli P & Crescenzi A. Thyroid core needle biopsy: taking stock of the situation. *Endocrine* 2015 **48** 779–785. (https://doi.org/10.1007/s12020-014-0382-z)

18 Buxey K & Serpell J. Importance of core biopsy in the diagnosis of thyroid lymphoma. *ANZ Journal of Surgery* 2012 **82** 90. (https://doi.org/10.1111/j.1445-2197.2011.05935.x)

19 Nam M, Shin JH, Han BK, Ko EY, Ko ES, Hahn SY, Chung JH & Oh YL. Thyroid lymphoma: correlation of radiologic and pathologic features. *Journal of Ultrasound in Medicine* 2012 **31** 589–594. (https://doi.org/10.7863/jum.2012.31.4.589)

20 Kwak JY, Kim EK, Ko KH, Yang WI, Kim MJ, Son EJ, Oh KK & Kim KW. Primary thyroid lymphoma: role of ultrasound-guided needle biopsy. *Journal of Ultrasound in Medicine* 2007 **26** 1761–1765. (https://doi.org/10.7863/jum.2007.26.12.1761)

21 Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA & Bossuyt PM. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Annals of Internal Medicine* 2011 **155** 529–536. (https://doi.org/10.7326/0003-4819-155-8-201110180-00009)

22 Adhikari LJ, Reynolds JP & Wakely PE Jr. Multi-institutional study of fine-needle aspiration for thyroid lymphoma. *Journal of the American Society of Cytopathology* 2016 **5** 170–176. (https://doi.org/10.1016/j.jasc.2015.11.002)

23 Bostanci H, Dikmen K, Akyurek N, Buyukkasap AC, Yavuz A, Yalcin MM & Akin M. Eleven patients with primary thyroid lymphoma: a single center experience. *Turkish Journal of Medical Sciences* 2017 **47** 1322–1327. (https://doi.org/10.3906/sag-1611-91)

24 Bula G, Waler J, Niemiec A, Trompeta J, Steplewska K & Gawrychowski J. Unusual malignant thyroid tumours – a clinical study of 20 cases. *Acta Chirurgica Belgica* 2008 **108** 702–707. (https://doi.org/10.1080/00015458.2008.11680320)

25 Cap J, Ryska A, Rehorkova P, Hovorkova E, Kerekes Z & Pohnetalova D. Sensitivity and specificity of the fine needle aspiration biopsy of the thyroid: clinical point of view. *Clinical Endocrinology* 1999 **51** 509–515. (https://doi.org/10.1046/j.1365-2265.1999.00847.x)

26 Cha C, Chen H, Westra WH & Udelsman R. Primary thyroid lymphoma: can the diagnosis be made solely by fine-needle aspiration? *Annals of Surgical Oncology* 2002 **9** 298–302. (https://doi.org/10.1007/BF02573069)

27 Colovic M, Matic S, Kryeziu E, Tomin D, Colovic N & Atkinson HD. Outcomes of primary thyroid non-Hodgkin's lymphoma: a series of nine consecutive cases. *Medical Oncology* 2007 **24** 203–208. (https://doi.org/10.1007/BF02698041)

28 Dustin SM, Jo VY, Hanley KZ & Stelow EB. High sensitivity and positive predictive value of fine-needle aspiration for uncommon thyroid malignancies. *Diagnostic Cytopathology* 2012 **40** 416–421. (https://doi.org/10.1002/dc.21802)

29 Gupta N, Nijhawan R, Srinivasan R, Rajwanshi A, Dutta P, Bhansaliy A & Sharma SC. Fine needle aspiration cytology of primary thyroid lymphoma: a report of ten cases. *Cytojournal* 2005 **2** 21. (https://doi.org/10.1186/1742-6413-2-21)

30 Hirokawa M, Kudo T, Ota H, Suzuki A, Kobayashi K & Miyauchi A. Preoperative diagnostic algorithm of primary thyroid lymphoma using ultrasound, aspiration cytology, and flow cytometry. *Endocrine Journal* 2017 **64** 859–865. (https://doi.org/10.1507/endocrj.EJ17-0111)

31 Hwang YC, Kim TY, Kim WB, Shong YK, Yi KH, Shong M, Jo YS, Kim WS & Chung JH. Clinical characteristics of primary thyroid lymphoma in Koreans. *Endocrine Journal* 2009 **56** 399–405. (https://doi.org/10.1507/endocrj.K08E-355)

32 Joshi A, Chan J, Bruch G, Jeannon JP, Mikhaeel NG, Fields PA & Simo R. Thyroid lymphoma and airway obstruction – is there a rationale for surgical management? *International Journal of Clinical Practice* 2009 **63** 1647–1652. (https://doi.org/10.1111/j.1742-1241.2009.02050.x)

33 Lam KY, Lo CY, Kwong DL, Lee J & Srivastava G. Malignant lymphoma of the thyroid. A 30-year clinicopathologic experience and an evaluation of the presence of Epstein-Barr virus. *American Journal of Clinical Pathology* 1999 **112** 263–270. (https://doi.org/10.1093/ajcp/112.2.263)

34 Lerma E, Arguelles R, Rigla M, Otal C, Cubero JM, Bague S, Carreras AM, Eulalia E, Gonzalez-Campora R, Galera H *et al*. Comparative findings of lymphocytic thyroiditis and thyroid lymphoma. *Acta Cytologica* 2003 **47** 575–580. (https://doi.org/10.1159/000326571)

35 Li L, Wáng YXJ, Shi L, Yu C & Feng X-L. Primary thyroid lymphoma: CT findings of a rare malignant tumor with pathologic correlations. *Translational Cancer Research* 2017 **6** 578–587. (https://doi.org/10.21037/tcr.2017.03.84)

36 Lu JY, Lin CW, Chang TC & Chen YC. Diagnostic pitfalls of fine-needle aspiration cytology and prognostic impact of chemotherapy in thyroid lymphoma. *Journal of the Formosan Medical Association* 2001 **100** 519–525.

37 Matsuda M, Sone H, Koyama H & Ishiguro S. Fine-needle aspiration cytology of malignant lymphoma of the thyroid. *Diagnostic Cytopathology* 1987 **3** 244–249. (https://doi.org/10.1002/dc.2840030314)

38 Matsuzuka F, Miyauchi A, Katayama S, Narabayashi I, Ikeda H, Kuma K & Sugawara M. Clinical aspects of primary thyroid lymphoma: diagnosis and treatment based on our experience of 119 cases. *Thyroid* 1993 **3** 93–99. (https://doi.org/10.1089/thy.1993.3.93)

39 Mizokami T, Hamada K, Maruta T, Higashi K, Yamashita H, Noguchi Y, Noguchi H & Tajiri J. Development of primary thyroid lymphoma during an ultrasonographic follow-up of Hashimoto's thyroiditis: a report of 9 cases. *Internal Medicine* 2016 **55** 943–948. (https://doi.org/10.2169/internalmedicine.55.5428)

40 Nishiyama Y, Yamamoto Y, Yokoe K, Satoh K & Ohkawa M. Diagnosis of thyroid lymphoma and follow-up evaluation using Ga-67 scintigraphy. *Annals of Nuclear Medicine* 2003 **17** 351–357. (https://doi.org/10.1007/BF03006600)

41 Ogawa Y, Kato Y, Ikeda K, Aya M, Ogisawa K, Kitani K, Onoda N, Ishikawa T, Haba T, Wakasa K *et al*. The value of ultrasound-guided fine-needle aspiration cytology for thyroid nodules: an assessment of its diagnostic potential and pitfalls. *Surgery Today* 2001 **31** 97–101. (https://doi.org/10.1007/s005950170190)

42 Pyke CM, Grant CS, Habermann TM, Kurtin PJ, van Heerden JA, Bergstralh EJ, Kunselman A & Hay ID. Non-Hodgkin's lymphoma of the thyroid: is more than biopsy necessary? *World Journal of Surgery* 1992 **16** 604–609; discussion 609–610. (https://doi.org/10.1007/BF02067333)

43 Ruggiero FP, Frauenhoffer E & Stack BC Jr. Thyroid lymphoma: a single institution's experience. *Otolaryngology-Head and Neck Surgery* 2005 **133** 888–896. (https://doi.org/10.1016/j.otohns.2005.07.040)

44 Sangalli G, Serio G, Zampatti C, Lomuscio G & Colombo L. Fine needle aspiration cytology of primary lymphoma of the thyroid: a report of 17 cases. *Cytopathology* 2001 **12** 257–263. (https://doi.org/10.1046/j.1365-2303.2001.00338.x)

45 Sarinah B & Hisham AN. Primary lymphoma of the thyroid: diagnostic and therapeutic considerations. *Asian Journal of Surgery* 2010 **33** 20–24. (https://doi.org/10.1016/S1015-9584(10)60004-8)

46 Skarsgard ED, Connors JM & Robins RE. A current analysis of primary lymphoma of the thyroid. *Archives of Surgery* 1991 **126** 1199–1203; discussion 1203–1194. (https://doi.org/10.1001/archsurg.1991.01410340037006)

47 Stacchini A, Pacchioni D, Demurtas A, Aliberti S, Cassenti A, Isolato G, Gazzera C, Veltri A, Sapino A, Papotti M *et al*. Utilility of flow cytometry as ancillary study to improve the cytologic diagnosis of thyroid lymphomas. *Cytometry Part B: Clinical Cytometry* 2015 **88** 320–329. (https://doi.org/10.1002/cyto.b.21204)

48 Sun TQ, Zhu XL, Wang ZY, Wang CF, Zhou XY, Ji QH & Wu Y. Characteristics and prognosis of primary thyroid non-Hodgkin's lymphoma in Chinese patients. *Journal of Surgical Oncology* 2010 **101** 545–550. (https://doi.org/10.1002/jso.21543)

49 Wang SA, Rahemtullah A, Faquin WC, Roepke J, Harris NL & Hasserjian RP. Hodgkin's lymphoma of the thyroid: a clinicopathologic study of five cases and review of the literature. *Modern Pathology* 2005 **18** 1577–1584. (https://doi.org/10.1038/modpathol.3800501)

50 Watanabe N, Narimatsu H, Noh JY, Iwaku K, Kunii Y, Suzuki N, Ohye H, Suzuki M, Matsumoto M, Yoshihara A *et al*. Long-term outcomes of 107 cases of primary thyroid mucosa-associated lymphoid tissue lymphoma at a Single Medical Institution in Japan. *Journal of Clinical Endocrinology and Metabolism* 2018 **103** 732–739. (https://doi.org/10.1210/jc.2017-01478)

51 Wu S-Y, Chu C-H, Duh Q-Y, Hsieh C-B, Yu J-C & Shih M-L. Management for primary thyroid lymphoma: experience from a single tertiary care centre in Taiwan. *Formosan Journal of Surgery* 2016 **49** 201–207. (https://doi.org/10.1016/j.fjs.2016.07.001)

52 Xie Y, Liu W, Liu Y, Wang W, Wang M, Liu H, Li X & Gao W. Diagnosis and clinical analysis of primary thyroid lymphoma. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao* 2017 **39** 377–382.

53 Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E & Lister TA. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *Journal of Clinical Oncology* 2014 **32** 3059–3068. (https://doi.org/10.1200/JCO.2013.54.8800)

54 Chung SR, Suh CH, Baek JH, Choi YJ & Lee JH. The role of core needle biopsy in the diagnosis of initially detected thyroid nodules: a systematic review and meta-analysis. *European Radiology* 2018 **28** 4909–4918. (https://doi.org/10.1007/s00330-018-5494-z)

55 Misiakos EP, Margari N, Meristoudis C, Machairas N, Schizas D, Petropoulos K, Spathis A, Karakitsos P & Machairas A. Cytopathologic diagnosis of fine needle aspiration biopsies of thyroid nodules. *World Journal of Clinical Cases* 2016 **4** 38–48. (https://doi.org/10.12998/wjcc.v4.i2.38)

56 Bongiovanni M, Trimboli P, Rossi ED, Fadda G, Nobile A & Giovanella L. DIAGNOSIS OF ENDOCRINE DISEASE: High-yield thyroid fine-needle aspiration cytology: an update focused on ancillary techniques improving its accuracy. *European Journal of Endocrinology* 2016 **174** R53–R63. (https://doi.org/10.1530/EJE-15-0817)

57 Trimboli P, Guidobaldi L, Bongiovanni M, Crescenzi A, Alevizaki M & Giovanella L. Use of fine-needle aspirate calcitonin to detect medullary thyroid carcinoma: a systematic review. *Diagnostic Cytopathology* 2016 **44** 45–51. (https://doi.org/10.1002/dc.23375)

58 Trimboli P, Treglia G, Guidobaldi L, Romanelli F, Nigri G, Valabrega S, Sadeghi R, Crescenzi A, Faquin WC, Bongiovanni M *et al*. Detection rate of FNA cytology in medullary thyroid carcinoma: a meta-analysis. *Clinical Endocrinology* 2015 **82** 280–285. (https://doi.org/10.1111/cen.12563)

59 Kalina T, Flores-Montero J, van der Velden VH, Martin-Ayuso M, Bottcher S, Ritgen M, Almeida J, Lhermitte L, Asnafi V, Mendonca A *et al*. EuroFlow standardization of flow cytometer instrument settings and immunophenotyping protocols. *Leukemia* 2012 **26** 1986–2010. (https://doi.org/10.1038/leu.2012.122)

60 Cozzolino I, Rocco M, Villani G & Picardi M. Lymph node fine-needle cytology of non-Hodgkin lymphoma: diagnosis and classification by flow cytometry. *Acta Cytologica* 2016 **60** 302–314. (https://doi.org/10.1159/000448389)

61 Zeppa P, Marino G, Troncone G, Fulciniti F, De Renzo A, Picardi M, Benincasa G, Rotoli B, Vetrani A & Palombini L. Fine-needle cytology and flow cytometry immunophenotyping and subclassification of non-Hodgkin lymphoma: a critical review of 307 cases with technical suggestions. *Cancer* 2004 **102** 55–65. (https://doi.org/10.1002/cncr.11903)

62 Barrington SF, Mikhaeel NG, Kostakoglu L, Meignan M, Hutchings M, Mueller SP, Schwartz LH, Zucca E, Fisher RI, Trotman J *et al*. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. *Journal of Clinical Oncology* 2014 **32** 3048–3058. (https://doi.org/10.1200/JCO.2013.53.5229)

63 Basu S, Chryssikos T, Moghadam-Kia S, Zhuang H, Torigian DA & Alavi A. Positron emission tomography as a diagnostic tool in infection: present role and future possibilities. *Seminars in Nuclear Medicine* 2009 **39** 36–51. (https://doi.org/10.1053/j.semnuclmed.2008.08.004)

64 Gotthardt M, Bleeker-Rovers CP, Boerman OC & Oyen WJ. Imaging of inflammation by PET, conventional scintigraphy, and other imaging techniques. *Journal of Nuclear Medicine* 2010 **51** 1937–1949. (https://doi.org/10.2967/jnumed.110.076232)

65 Karantanis D, Bogsrud TV, Wiseman GA, Mullan BP, Subramaniam RM, Nathan MA, Peller PJ, Bahn RS & Lowe VJ. Clinical significance of diffusely increased 18F-FDG uptake in the

thyroid gland. *Journal of Nuclear Medicine* 2007 **48** 896–901. (https://doi.org/10.2967/jnumed.106.039024)
66 Yasuda S, Shohtsu A, Ide M, Takagi S, Takahashi W, Suzuki Y & Horiuchi M. Chronic thyroiditis: diffuse uptake of FDG at PET. *Radiology* 1998 **207** 775–778. (https://doi.org/10.1148/radiology.207.3.9609903)
67 Chen W, Parsons M, Torigian DA, Zhuang H & Alavi A. Evaluation of thyroid FDG uptake incidentally identified on FDG-PET/CT imaging. *Nuclear Medicine Communications* 2009 **30** 240–244. (https://doi.org/10.1097/MNM.0b013e328324b431)
68 Win AZ & Aparici CM. Bilateral diffuse fluorodeoxyglucose uptake in thyroid gland diagnosed by fluorodeoxyglucose-positron emission tomography/computed tomography. *World Journal of Nuclear Medicine* 2014 **13** 138–141. (https://doi.org/10.4103/1450-1147.139147)
69 Are C, Hsu JF, Schoder H, Shah JP, Larson SM & Shaha AR. FDG-PET detected thyroid incidentalomas: need for further investigation? *Annals of Surgical Oncology* 2007 **14** 239–247. (https://doi.org/10.1245/s10434-006-9181-y)
70 Lin M, Wong C, Lin P, Shon IH, Cuganesan R & Som S. The prevalence and clinical significance of (18) F-2-fluoro-2-deoxy-D-glucose (FDG) uptake in the thyroid gland on PET or PET-CT in patients with lymphoma. *Hematological Oncology* 2011 **29** 67–74. (https://doi.org/10.1002/hon.955)
71 Kato I, Tajima K, Suchi T, Aozasa K, Matsuzuka F, Kuma K & Tominaga S. Chronic thyroiditis as a risk factor of B-cell lymphoma in the thyroid gland. *Japanese Journal of Cancer Research* 1985 **76** 1085–1090.
72 Arabi M, Dvorak R, Smith LB, Kujawski L & Gross MD. Fluorodeoxyglucose positron emission tomography in primary thyroid lymphoma with coexisting lymphocytic thyroiditis. *Thyroid* 2011 **21** 1153–1156. (https://doi.org/10.1089/thy.2011.0064)
73 Nakadate M, Yoshida K, Ishii A, Koizumi M, Tochigi N, Suzuki Y, Ryu Y, Nakagawa T, Umehara I & Shibuya H. Is 18F-FDG PET/CT useful for distinguishing between primary thyroid lymphoma and chronic thyroiditis? *Clinical Nuclear Medicine* 2013 **38** 709–714. (https://doi.org/10.1097/RLU.0b013e31829b2686)
74 Lee CJ, Hsu CH, Tai CJ & Lin SE. FDG-PET for a thyroid MALT lymphoma. *Acta Oncologica* 2008 **47** 1165–1167. (https://doi.org/10.1080/02841860701732923)
75 Chander S, Zingas AP, Bloom DA, Zak IT, Joyrich RN & Getzen TM. Positron emission tomography in primary thyroid lymphoma. *Clinical Nuclear Medicine* 2004 **29** 572–573. (https://doi.org/10.1097/01.rlu.0000134987.48416.05)
76 Mehta A & Muthukrishnan A. Stage IE non-Hodgkin's thyroid lymphoma on (18)F-FDG-PET/CT. *Hellenic Journal of Nuclear Medicine* 2011 **14** 186–187.
77 Schoder H, Noy A, Gonen M, Weng L, Green D, Erdi YE, Larson SM & Yeung HW. Intensity of 18fluorodeoxyglucose uptake in positron emission tomography distinguishes between indolent and aggressive non-Hodgkin's lymphoma. *Journal of Clinical Oncology* 2005 **23** 4643–4651. (https://doi.org/10.1200/JCO.2005.12.072)
78 Kamijo K. Clinical studies on thyroid CT number in chronic thyroiditis. *Endocrine Journal* 1994 **41** 19–23. (https://doi.org/10.1507/endocrj.41.19)
79 Derringer GA, Thompson LD, Frommelt RA, Bijwaard KE, Heffess CS & Abbondanzo SL. Malignant lymphoma of the thyroid gland: a clinicopathologic study of 108 cases. *American Journal of Surgical Pathology* 2000 **24** 623–639. (https://doi.org/10.1097/00000478-200005000-00001)
80 Kim HC, Han MH, Kim KH, Jae HJ, Lee SH, Kim SS, Kim KH & Chang KH. Primary thyroid lymphoma: CT findings. *European Journal of Radiology* 2003 **46** 233–239. (https://doi.org/10.1016/S0720-048X(02)00134-1)
81 Li XB & Ye ZX. Primary thyroid lymphoma: multi-slice computed tomography findings. *Asian Pacific Journal of Cancer Prevention* 2015 **16** 1135–1138. (https://doi.org/10.7314/APJCP.2015.16.3.1135)
82 Shibata T, Noma S, Nakano Y & Konishi J. Primary thyroid lymphoma: MR appearance. *Journal of Computer Assisted Tomography* 1991 **15** 629–633. (https://doi.org/10.1097/00004728-199107000-00019)
83 Wang JH, Chen L & Ren K. Identification of primary thyroid lymphoma with medical imaging: a case report and review of the literature. *Oncology Letters* 2014 **8** 2505–2508. (https://doi.org/10.3892/ol.2014.2542)
84 Basu S, Li G, Bural G & Alavi A. Fluorodeoxyglucose positron emission tomography (FDG-PET) and PET/computed tomography imaging characteristics of thyroid lymphoma and their potential clinical utility. *Acta Radiologica* 2009 **50** 201–204. (https://doi.org/10.1080/02841850802620689)
85 Freeman C, Berg JW & Cutler SJ. Occurrence and prognosis of extranodal lymphomas. *Cancer* 1972 **29** 252–260. (https://doi.org/10.1002/1097-0142(197201)29:1<252::AID-CNCR2820290138>3.0.CO;2-#)
86 Tsang RW, Gospodarowicz MK, Pintilie M, Wells W, Hodgson DC, Sun A, Crump M & Patterson BJ. Localized mucosa-associated lymphoid tissue lymphoma treated with radiation therapy has excellent clinical outcome. *Journal of Clinical Oncology* 2003 **21** 4157–4164. (https://doi.org/10.1200/JCO.2003.06.085)
87 Harrington KJ, Michalaki VJ, Vini L, Nutting CM, Syrigos KN, A'Hern R & Harmer CL. Management of non-Hodgkin's lymphoma of the thyroid: the Royal Marsden Hospital experience. *British Journal of Radiology* 2005 **78** 405–410. (https://doi.org/10.1259/bjr/31803121)
88 Sakorafas GH. What's the role of surgery in the management of primary thyroid lymphoma? *Acta Oncologica* 2011 **50** 319–320. (https://doi.org/10.3109/0284186X.2010.500301)
89 Watanabe N, Narimatsu H, Noh JY, Kunii Y, Mukasa K, Matsumoto M, Suzuki M, Sekiya K, Ohye H, Yoshihara A *et al*. Rituximab-including combined modality treatment for primary thyroid lymphoma: an effective regimen for elderly patients. *Thyroid* 2014 **24** 994–999. (https://doi.org/10.1089/thy.2013.0523)
90 Karlin L & Coiffier B. Improving survival and preventing recurrence of diffuse large B-cell lymphoma in younger patients: current strategies and future directions. *OncoTargets and Therapy* 2013 **6** 289–296. (https://doi.org/10.2147/OTT.S42574)
91 Miller TP, Dahlberg S, Cassady JR, Adelstein DJ, Spier CM, Grogan TM, LeBlanc M, Carlin S, Chase E & Fisher RI. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. *New England Journal of Medicine* 1998 **339** 21–26. (https://doi.org/10.1056/NEJM199807023390104)
92 Watanabe N, Noh JY, Narimatsu H, Takeuchi K, Yamaguchi T, Kameyama K, Kobayashi K, Kami M, Kubo A, Kunii Y *et al*. Clinicopathological features of 171 cases of primary thyroid lymphoma: a long-term study involving 24553 patients with Hashimoto's disease. *British Journal of Haematology* 2011 **153** 236–243. (https://doi.org/10.1111/j.1365-2141.2011.08606.x)
93 Naswa N, Sharma P, Nazar AH, Mohapatra TK, Bal C & Kumar R. (18) F-FDG PET/CT for initial assessment and response monitoring in a case of high grade primary lymphoma of the thyroid gland: a case report and review of literature. *Indian Journal of Nuclear Medicine* 2014 **29** 94–96. (https://doi.org/10.4103/0972-3919.130291)

Received 10 August 2018
Revised version received 16 November 2018
Accepted 17 December 2018