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ORIGINAL ARTICLE

Detection rate of FNA cytology in medullary thyroid carcinoma: a meta-analysis

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Summary

Background The early detection of medullary thyroid carcinoma (MTC) can improve patient prognosis, because histological stage and patient age at diagnosis are highly relevant prognostic factors. As a consequence, delay in the diagnosis and/or incomplete surgical treatment should correlate with a poorer prognosis for patients. Few papers have evaluated the specific capability of fine-needle aspiration cytology (FNAC) to detect MTC, and small series have been reported. This study conducts a meta-analysis of published data on the diagnostic performance of FNAC in MTC to provide more robust estimates.

Research Design and Methods A comprehensive computer literature search of the PubMed/MEDLINE, Embase and Scopus databases was conducted by searching for the terms 'medullary thyroid' AND 'cytology', 'FNA', 'FNAB', 'FNAC', 'fine needle' or 'fine-needle'. The search was updated until 21 March 2014, and no language restrictions were used.

Results Fifteen relevant studies and 641 MTC lesions that had undergone FNAC were included. The detection rate (DR) of FNAC in patients with MTC (diagnosed as 'MTC' or 'suspicious for MTC') on a per lesion-based analysis ranged from 12·5% to 88·2%, with a pooled estimate of 56·4% (95% CI: 52·6–60·1%). The included studies were statistically heterogeneous in their estimates of DR (I-square >50%). Egger's regression intercept for DR pooling was 0·03 (95% CI: −3·1 to 3·2, $P = 0·9$). The study that reported the largest MTC series had a DR of 45%. Data on immunohistochemistry for calcitonin in diagnosing MTC were inconsistent for the meta-analysis.

Conclusions The presented meta-analysis demonstrates that FNAC is able to detect approximately one-half of MTC lesions. These findings suggest that other techniques may be needed in combination with FNAC to diagnose MTC and avoid false negative results.

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Introduction

Medullary thyroid carcinoma (MTC) accounts for approximately 5% of thyroid malignancies.[1] MTC is a well-differentiated neuroendocrine carcinoma that arises from thyroid C-cells. It occurs as a sporadic cancer in approximately 80% of cases and is part of autosomal dominant genetic familial disorders in the remaining ones.[1] Generally, MTC has an aggressive behaviour, being responsible for 8% to 13% of total thyroid cancer deaths and correlating with a 5-year survival rate of 70%.[2,3] The early detection of MTC can improve patient prognosis, because histological stage and patient age at diagnosis are highly relevant factors. As a consequence, delay in the diagnosis and/or incomplete surgical treatment should correlate with a poorer prognosis for patients.[4,5]

Since its first demonstration, the diagnosis of MTC has represented a major challenge in clinical practice. In fact, while fine-needle aspiration cytology (FNAC) is a reliable diagnostic tool in the assessment of thyroid nodules, cytologic examination has several pitfalls related to MTC.[6,7] Moreover, the routine measurement of serum calcitonin in all patients with nodular thyroid disease is still a matter of debate,[1,5] and the application of ultrasonography lacks specificity when diagnosing these cancers.[6,8,9] Owing to these limitations, a significant number of

MTCs are not recognized until after initial thyroid surgery, with the consequent risk of an incomplete therapeutic approach.

Overall, few large series have evaluated the effectiveness of cytology to detect MTC and only a small number of MTC series have been reported. Thus, our study conducts a meta-analysis of published data focusing on the diagnostic performance of FNAC to detect MTC to provide more robust estimates on this topic.

Materials and methods

Search strategy

Initially, we searched studies that have evaluated the accuracy of cytology for MTC. A comprehensive computer literature search of the PubMed/MEDLINE, Embase and Scopus databases was conducted to find published articles on this topic. The search algorithm was based on combinations of the following terms: A) 'medullary thyroid' AND B) 'cytology', 'FNA', 'FNAB', 'FNAC', 'fine needle' or 'fine-needle'. A beginning date limit was not used and the search was updated until 21 March 2014 without language restrictions. To identify additional studies and expand our search, the references of the retrieved articles were also screened.

Study selection

Studies or subsets in studies that report data on the detection rate (DR) of MTC by FNAC were eligible for inclusion. The main exclusion criteria were (i) articles not within the field of interest of this review, (ii) review articles, editorials, letters or comments, and (iii) articles that did not provide clear study characteristics or reports that had overlapping patient data. Case reports were also excluded. Two investigators (PT, GT) independently reviewed the titles and abstracts of the retrieved articles, applying the inclusion and exclusion criteria previously described. Then, the same two researchers independently reviewed the full-text of the remaining articles to determine their inclusion. Disagreements were resolved in a consensus meeting involving a third author (LG).

Data extraction

For each included study, information was abstracted concerning study data (authors, journals, year of publication and country of origin). The number of patients evaluated, number of histologically proved MTCs and the DR of FNAC for MTC were also extracted. Moreover, the results of FNAC for each lesion were provided.

Statistical analysis

The DR of FNAC in patients with MTC was calculated from each article on a per lesion-based analysis using this formula: DR = TP/(TP + FN), where TP were 'MTC' or 'suspicious for MTC' FNAC and FN were false negative (non-MTC) FNAC results. A random effects model was then used statistically pooling the data. Pooled data are presented with 95% confidence intervals (95% CI). An I-square index was used to test for heterogeneity among the studies (significant heterogeneity was defined as having an I-square value >50%). Finally, to evaluate publication bias, funnel plots and Egger's regression intercepts[10] were used. Statistical analyses were performed using StatsDirect statistical software (StatsDirect Ltd; Altrincham, UK).

Results

The comprehensive computer literature search for MTC and FNAC (see Materials and methods) revealed 3551 articles. The

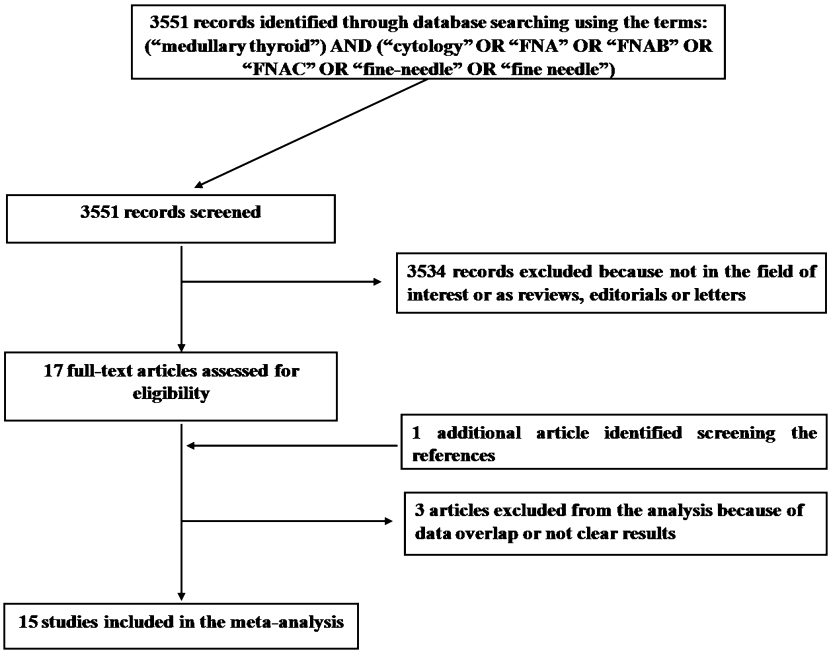

Fig. 1 Flowchart of the search for eligible studies on the detection rate of FNAC in patients with MTC.

Table 1. Characteristics of the 15 studies included in the meta-analysis

First author	Year	Country	Aim of the study	MTC lesions undergone FNAC	
				n	MTC diagnosed (%)
Elisei[11]	2004	Italy	To evaluate routine serum calcitonin measurement	44	20 (45·5)
Bugalho[12]	2005	Portugal	To assess the accuracy of FNAC in MTC	67	42 (62·7)
Chang[13]	2005	China–Taiwan	To review MTC cases	34	30 (88·2)
Vierhapper[14]	2005	Austria	To evaluate routine serum calcitonin measurement	13	2 (15·4)
Boi[15]	2007	Italy	To assess diagnostic accuracy of FNA-calcitonin	21	13 (61·9)
Kudo[16]	2007	Japan	To assess diagnostic accuracy of FNA-calcitonin	5	4 (80·0)
Seningen[17]	2010	USA	To review FNAC diagnosis	27	21 (77·8)
Kaushal [18]	2011	India	To review MTC cases	78	54 (69·2)
Colombo[28]	2012	Italy	To evaluate calcium stimulation test for calcitonin	7	2 (28·6)
Diazzi[19]	2013	Italy	To assess diagnostic accuracy of FNA-calcitonin	8	1 (12·5)
Essig[20]	2013	USA–Italy–Greece–Brazil–UK–Belgium	To assess the diagnostic value of FNAC	245	112 (45·7)
Jo[21]	2013	USA	To review FNAC diagnosis	16	13 (81·3)
Trimboli[22]	2014	Italy–Switzerland	To assess accuracy of FNA-calcitonin and FNAC	37	21 (56·8)
Samulski[23]	2014	USA	To review MTC cases	33	23 (69·7)
Boschin [24]	2014	Italy	To evaluate pentagastrin stimulation test for calcitonin	6	2 (33·3)
Overall				641	360

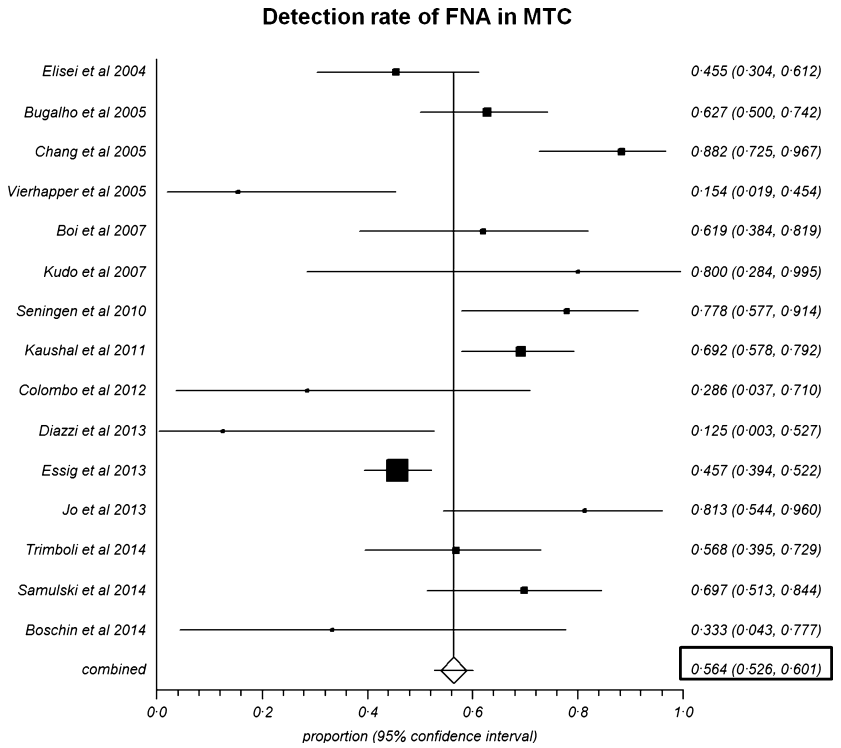

Fig. 2 Plot of individual studies and pooled detection rate of FNAC in patients with MTC, including 95% confidence intervals.

review of the titles and abstracts of these papers excluded many records according to the above-mentioned criteria. Ultimately, 17 articles were selected and their full-text versions retrieved.[11–27] Another additional study was found by screening the references of these papers.[28] However, one study was excluded because of unclear results (the MTC diagnoses were not specifically detailed between the malignant FNAC),[25] and two other papers were removed from the sample owing to overlapping data.[26,27] Altogether, 15 studies were included in our meta-analysis [11–24,28] (Fig. 1). The main characteristics of these studies are summarized in Table 1.

Overall, the sampled studies included 641 MTC lesions that had undergone FNAC. Approximately half (360/641) of these were assessed by FNAC as 'MTC' or 'suspicious for MTC'. The DR of FNAC in patients with MTC on a per lesion-based analysis ranged from 12·5% to 88·2%, with a pooled estimate of

Table 2. Cytologic reports of MTC not classified as 'MTC' nor 'suspicious for MTC'

First author	Year	*n*	Cytologic Classification			
			Other malignancies	Indeterminate	Benign	Not adequate
Elisei[11]	2004	24/44	9	–	11	4
Bugalho[12]	2005	25/67	14	5	6	–
Chang[13]	2005	4/34	1	3	–	–
Vierhapper[14]	2005	11/13	–	–	11*	
Boi[15]	2007	8/21	–	–	8	–
Kudo[16]	2007	1/5	–	–	–	1
Seningen[17]	2010	6/27	1	2	1	2
Kaushal[18]	2011	24/78	23	1	–	–
Colombo[28]	2012	5/7	–	2	1	2
Diazzi[19]	2013	7/8	Cytologic reports not available			
Essig[20]	2013	133/245	39	64	15	15
Jo[21]	2013	3/16	–	2	1	–
Trimboli[22]	2014	16/37	–	3	6	7
Samulski[23]	2014	10/33	–	10	–	–
Boschin[24]	2014	4/6	–	4	–	–

*The authors did not detail benign and not adequate FNAC reports.

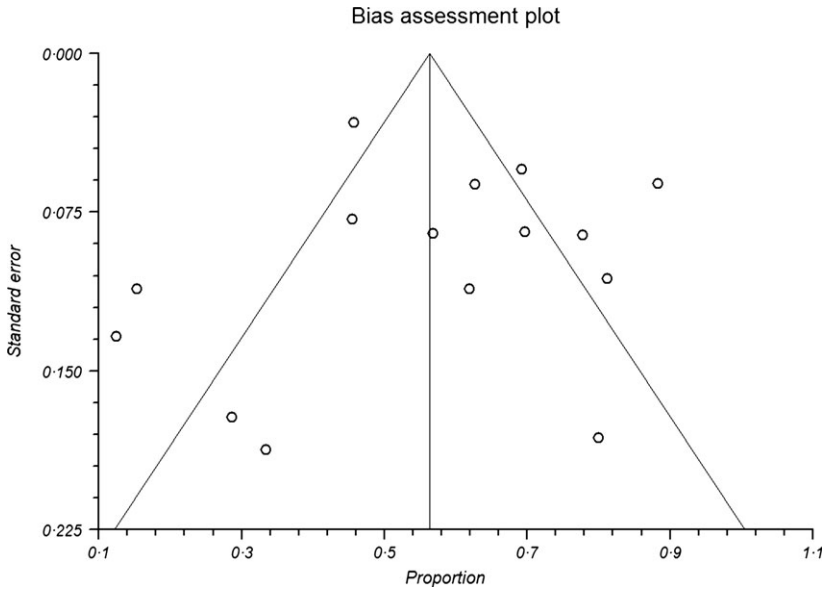

Fig. 3 Funnel plot for publication bias assessment.

56·4% (95% CI: 52·6–60·1%) (Fig. 2). The included studies were statistically heterogeneous in their estimates of DR (I-square >50%). In particular, those studies that included smaller series reported lower FNAC sensitivity. The study that reported the largest MTC series[20] had a DR of 45%. The cytologic reports of MTC not classified as 'MTC' nor 'suspicious for MTC' are described in Table 2. Excluding the study of Essig. *et al.*[20] which is a collection of patients selected from multiple centres, we found a pooled DR of 58·8% (95% CI: 48·4–68·9%), which is quite similar to the overall DR we reported including all the studies.

The funnel plot that was used to assess possible publication bias is shown in Fig. 3. Egger's regression intercept for DR pooling was 0·03 (95% CI: −3·1 to 3·2, $P = 0·9$). Only two papers[18,22] described the application of immunohistochemistry for calcitonin in diagnosing MTC, and data were inconsistent for the purposes of meta-analysis. Similarly, data about nodule size were poor to be meta-analysed. No significant difference was recorded regarding familial or sporadic MTC forms, patient gender, patient age or lesion size.

Discussion

In this study, we included 15 articles published between 2004 and 2014 that reported the capability of cytology to detect MTC. The main result from this meta-analysis is that 56% of histologically proven MTCs are correctly detected by cytologic evaluation, while the remaining MTCs are reported by FNAC as

benign, indeterminate, nondiagnostic or as other types of neoplasms. Elisei *et al.*[11] reported that 20/44 MTCs (45% sensitivity) were cytologically suspicious for this cancer. Later, Bugalho *et al.*[12] recorded a detection rate of 63% (42/67 cases) by FNAC. More recently, a large multicentre study by Essig *et al.*[20] collected 313 MTCs from 12 institutions over 29 years. Of these, 245 underwent FNAC and 112 (45·7%) were correctly read as MTC or as possible MTC. Overall, in the fifteen papers sampled in this study, about fifty per cent of MTC were assessed as other malignancies, benign or nondiagnostic. Table 2 presents these data in more detail. An important cause of a false negative FNAC diagnosis was misinterpreting MTC as other tumours, especially as a Hürthle cell neoplasm or follicular neoplasm.[7]

Two studies with different designs and aims must be mentioned here. Papaparaskeva *et al.*[29] retrospectively reviewed the aspirate reading of 'medullary carcinoma of the thyroid' in their department between 1977 and 1999; 81 of 91 cytologies reading for MTC were histologically confirmed as MTC and 10 of 91 were false positives, with a consequent positive predictive value of 89%. Similar results were reported by Forrest *et al.*[30] over the period 1976–1997, namely a positive predictive value of 81% (17/21). Based on these interesting findings, there is also a small false positive rate for MTC that needs to be taken into account.

Other techniques were reported as having been used to detect MTC in FNAC samples. The use of immunohistochemistry for calcitonin was described in only two papers included in the meta-analysis.[18,22] In both articles, the sensitivity of FNAC significantly increased up to 70%[18] and 90%[22] when immunohistochemical evaluation was added. More recently, the diagnosis of MTC has been improved by measurement of calcitonin in needle washout fluids after aspiration (FNA-calcitonin). As the firsts, two papers showed high accuracy of FNA-calcitonin in detecting MTC[15,16]; after, a multicentre study indicated that FNA-calcitonin has higher sensitivity than cytology in diagnosing MTC.[22] In clinical practice, the use of FNA-calcitonin and immunohistochemistry for calcitonin should be useful in those patients having high serum calcitonin value before nodule aspiration. Serum calcitonin is the main diagnostic tool to detect MTC in patients with thyroid nodules.[1] Work by Elisei *et al.*[11] suggested that serum calcitonin has a higher sensitivity than FNAC for detecting MTC. As an extension of these data, in the series by Bugalho *et al.*,[12] cytology was positive in only 74% of those patients with elevated serum calcitonin. These results were corroborated by subsequent studies.[1,5] Even if the sensitivity for MTC of serum calcitonin has been reported as high, its use as a routine test in patients with thyroid nodules is controversial. Examining serum calcitonin in patients eligible for thyroid nodule biopsy would likely contribute to improved detection of MTC,[31] but this approach is not included in current guidelines.[1,5] Finally, other potential serum diagnostic markers (i.e. CEA, procalcitonin or other neuroendocrine molecules) of MTC have been reported, but their role in indentifying this cancer deserves further studies.[6]

A possible limitation of our meta-analysis could be the heterogeneity between the included studies. Heterogeneity between studies may represent a potential source of bias in a meta-analysis. This heterogeneity is likely to arise through diversity in methodological aspects among studies. The baseline differences among the patients in the included studies and study quality may contribute to the heterogeneity of the results, too. In our pooled analysis, for example, the included studies were statistically heterogeneous in their estimate of the DR (I-square >50%). However, this heterogeneity has been accounted for using a random effects model.

Publication bias is another major concern in all meta-analyses, as studies that report significant findings are more likely to be published than those reporting nonsignificant results. Indeed, small-sized early studies often reported a positive relationship that subsequent larger studies failed to replicate. We assessed publication bias in our meta-analysis using qualitative and quantitative methods (Egger's regression method). Our funnel plots showed mild asymmetry for DR pooling, but Egger's regression method did not show a significant publication bias.

In conclusion, our meta-analysis demonstrates that FNAC is able to accurately detect only approximately one-half of histologically proven MTC lesions. Based on these findings, other techniques and specific approaches to patients with thyroid nodules are likely to be needed in combination with FNAC to more accurately diagnose MTC and avoid false negative results.

Conflicts of interest

The authors have no conflicts of interest to declare.

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