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ENDOCRINE METHODS AND TECHNIQUES

Thyroid core needle biopsy: taking stock of the situation

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Abstract Recently, the microhistologic evaluation by core needle biopsy (CNB) has been reported as high accurate to diagnose thyroid nodules with previous indeterminate or not adequate fine-needle aspiration cytology. In addition, sparse data have been reported regarding the use of CNB in other conditions. Aim of this review was to furnish the state of the art of this topic by summarizing published data about the diagnostic performance of CNB in thyroid lesions, and provide an easy to use reference for clinical practice. Sources encompass studies published through May 2014. Original articles were investigated and following specific aspects were discussed: 1. The "large" needle biopsy in 90's; 2. Complications by and patient's comfort with thyroid CNB; 3. Advantages provided by examination of a microhistologic sample of thyroid nodule; 4. Use of CNB in thyroid nodules with previous not adequate (Thy 1/Class 1/Category I) cytology; 5. Use of CNB in thyroid neoplasms (Thy 3/Class 3/Category III–IV) cytology; 6. Use of CNB in specific ultrasonographic presentations of thyroid nodules or in patients with peculiar clinical contexts; 7. First-line approach by CNB in thyroid nodules; 8. Immunohistochemistry and molecular tests on CNB samples; and 9. Future perspective.

Keywords Thyroid cancer · Thyroid nodules · Core needle biopsy (CNB)

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Introduction

Fine-needle aspiration cytology (FNAC) holds a main role in assessing thyroid nodules [1–4]. The large majority of thyroid lesions undergone FNAC has benign (70–80 %), suspicious for malignancy or malignant (5–10 %) diagnosis, being the negative predictive value very low (i.e., 1–2 % of benignancies). On the other hand, a not negligible rate of thyroid cytologies is read as uncertain and indeterminate for diagnosis (10–20 %) or as inadequate sample (10–15 %) [1–3]. Even if the rate of malignancy in the latter cytologic categories (Thy 3/Class 3/Category III–IV and Thy 1/Class 1/Category I according to the main International guidelines [1–3]) is low, to exclude a cancer is one of the major challenges in thyroidology. In the last decade, several single-center original papers described the use of core needle biopsy (CNB) as a second-line approach to diagnose those thyroid nodules with Thy 3/Class 3/Category III–IV or Thy 1/Class 1/Category I at FNAC. Data from these papers are interesting, and more recently, this biopsy option was included in AACE/AME/ETA guidelines [1] that should encourage a more large diffusion of CNB. Here, we reviewed the literature on this topic and outlined several aspects:

1. The "large" needle biopsy in 90's.
2. Complications by and patient's comfort with thyroid CNB.
3. Advantages provided by examination of a microhistologic sample of thyroid nodule.
4. Use of CNB in thyroid nodules with previous not adequate (Thy 1/Class 1/Category I) cytology.
5. Use of CNB in thyroid neoplasms (Thy 3/Class 3/Category III–IV) cytology.

Table 1 Overview of the thirty studies included in the present review

First author (year)	Study type	Country	Main results
Screaton (2003)	Retrospective	England	CNB is a safe outpatient procedure with a high diagnostic accuracy
Carpi (2006)	Retrospective	Italy	The integrated approach of CNB and Galectin-3 reduces unnecessary thyroid resection
Renshaw (2007)	Retrospective	USA	The adequacy rate for CNB is significantly higher than that of FNAC, and the combination of FNAC–CNB has the highest adequacy rate and sensitivity
Khoo (2008)	Retrospective	USA	The addition of CNB to FNAC confers little benefit in decreasing the non-diagnostic rates
Yousaf (2008)	Retrospective	Denmark	TPO immunostaining on CNB samples is a valuable adjunct to morphology in the diagnosis of cold thyroid nodules of the non-oxyphilic type
Strauss (2008)	Retrospective	USA	CNB is an effective method for obtaining tissue from thyroid nodules
Lieu (2008)	Retrospective	USA	All cases undergoing both FNAC and CNB are diagnostic
Zhang (2008)	Retrospective	USA	FNAC in conjunction with a CNB is a safe technique that can reduce the rate of unsatisfactory and suboptimal thyroid biopsy
Park (2011)	Retrospective	Korea	CNB is better than second FNA to evaluate indeterminate nodules at initial FNAC, especially in patients with US findings of a borderline nodule
Sung (2012)	Retrospective	Korea	CNB is more accurate than FNAC, and combined FNAC–CNB is more accurate than CNB alone in small thyroid nodules
Samir (2012)	Retrospective	USA	Combined FNAC–CNB is more accurate than either CNB or FNAC alone in patients when prior FNA reading is non-diagnostic
Na (2012)	Retrospective	Korea	CNB is more useful than repeat-FNAC for reducing the frequency of inconclusive diagnostic results
Buxey (2012)	Retrospective	Australia	CNB is more accurate than FNAC in detecting thyroid lymphoma
Nam (2012)	Retrospective	Korea	CNB accuracy in thyroid lymphoma is significantly higher than that of FNAC
Carpi (2013)	Retrospective	Italy	CNB has high tolerability
Stangierski (2013)	Retrospective	Poland	Patients' tolerability to CNB and FNAC was comparable
Yeon (2013)	Retrospective	Korea	CNB has high rate of conclusive and accurate diagnoses in patients for whom previous FNAC results are non-diagnostic, thereby reducing the need for unnecessary diagnostic surgery
Hakala (2013)	Retrospective	Finland	CNB may be beneficial for the diagnosis of papillary thyroid carcinoma and other non-follicular thyroid lesions
Hahn (2013)	Retrospective	Korea	CNB has benefit for the diagnosis of thyroid nodules with prior inconclusive FNAC results
Nasrollah (2013)	Retrospective	Italy	CNB helps discriminate encapsulated from non-encapsulated nodules with prior indeterminate FNAC
Ha (2013)	Retrospective	Korea	CNB reduces the need to repeat FNAC or diagnostic surgery in thyroid nodules with risk at US and previous benign FNAC
Yunker (2013)	Retrospective	USA	CNB does not significantly differ from FNAC with respect to sample adequacy and sensitivity in diagnosing pediatric thyroid neoplasms
Lee (2014)	Retrospective	Korea	CNB may be enough to exclude malignancy risk for patients with a non-diagnostic aspirate
Choi (2014)	Retrospective	Korea	CNB demonstrates that category "AUS" showed a higher risk of malignancy, becoming surgical candidates, having malignant US findings, and having malignant CNB readings than "FLUS"
Min (2014)	Retrospective	Korea	In the preoperative diagnosis of follicular neoplasms, CNB has no advantage over FNAC in predicting the likelihood of malignancy but helps reduce the need for repeat biopsy
Trimboli (2014)	Prospective	Italy	Using CNB as first-line biopsy reduces potential pitfalls from FNAC in nodules at risk of cancer by US
Ha (2014)	Retrospective	Korea	CNB can minimise non-diagnostic results as well as diagnostic surgery in patients with calcified thyroid nodules
Nasrollah (2014)	Retrospective	Italy	CNB has good tolerability similarly to FNAC
Zhang (2014)	Retrospective	China	CNB demonstrates high rates of conclusive and accurate diagnosis in US suspicious thyroid nodules
Crescenzi (2014)	Retrospective	Italy	CNB samples are useful for BRAF antibody immunohistochemistry

6. Use of CNB in specific ultrasonographic presentations of thyroid nodules or in patients with peculiar clinical contexts.
7. First-line approach by CNB in thyroid nodules.
8. Immunohistochemistry and molecular tests on CNB samples.
9. Future perspective.

Materials and methods

Search strategy, study selection and data extraction

We searched studies evaluating the use of CNB in thyroid nodules. 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 the combinations of the terms ("thyroid" AND "core" AND "needle" AND "biopsy"). Initially, we did not use a beginning date limit, the search was updated until May 31, 2014, and no language restriction was used. To identify additional studies and expand our search, references of the retrieved articles were also screened.

Original articles that investigated CNB in thyroid nodules were eligible for inclusion. The two authors of the present study independently reviewed the retrieved articles. The main exclusion criterion was article that did not specifically report CNB in thyroid lesions, and review papers were also excluded. For each included study, information was abstracted concerning study data (authors, year of publication, and country).

The comprehensive computer literature search revealed 125 articles. Titles and abstracts of these articles were reviewed, and 31 original papers were selected by retrieving their full-text version and screening their references list [5–35] (Table 1). All these papers was published after 2003, but one [11] which was excluded from the review because it is too old. Almost all of these papers were retrospective, and the majority was from USA, Korea, or Italy. Subtle differences were recorded regarding the type of the needle used for CNB (Ace-cut, Menghini, Quick-core, Temno evolution, or other); the gauge of these needles ranged from 18 to 22. Overall, low rate of complications from CNB was described.

The large needle biopsy in 90's

A large needle biopsy (LNB) was first proposed in thyroid nodule in the 90's. The main goal was the possibility to evaluate the nodular architecture and the potential application of ancillary techniques. Despite the advantages in result obtained from the thick core examination, LNB has not become a standard procedure because of its relatively high risk of complications, especially hemorrhages, and its consequent technical difficulties [36, 37]. The recently described CNB has roots in the LNB of the 90's but has been diffused due to the more accurate sampling and rare complications recorded (see below). In fact, in the last decade more refined cutting systems with smaller gauge have been commercialized (such as ace-cut, temno, and quick-core). These devices, with automatic or semiautomatic operation, are carefully inserted into the lesion under ultrasound guide, and the needle can be fired with high precision to obtain a nodule's core specimen.

Complications by and patient's comfort with thyroid CNB

In general, thyroid CNB has been reported as a safe procedure, and the complications rate and comfort degree using CNB was not significantly higher than that recorded by FNAC [5–10, 12–35]. Specifically, minor complications were recorded by thyroid CNB; transient hoarseness, hematoma, parenchymal edema, bleeding, and bruising were rarely (i.e., 1–3 % of cases) present after these biopsies [5–10, 12–35]. Very recently, tolerability of CNB was investigated by one research group [33]. There, a questionnaire was administrated to patients undergone both CNB and FNAC, and patient's comfort and biopsy tolerability were not significantly different. Another study reported similar results [34].

Advantages provided by examination of a microhistologic sample of thyroid nodule

Core biopsy represents an optimal complementary test for thyroid nodules with fibrous component that are difficult to be aspirated by FNAC. In these cases, CNB allows obtain adequate material from nodules [5–10, 12–35]. At microscopic level, the nodule's core sample offers the possibility to evaluate the general architecture of the lesion, the alteration of follicular structures, and the relationship with adjacent tissues [9, 20, 21]. The latter tissue–tissue examination is highly important in all histologic assessments. Moreover, CNB is advantageous in the analysis of nuclear changes, being the tissue formalin fixed and paraffin embedded similarly to the final post-surgical histology [5–10].

Use of CNB in thyroid nodules with previous not adequate (Thy 1/Class 1/Category I) cytology

The inadequacy of sample from thyroid nodule FNAC occurs in about 10–15 % of cases. In this context, the international guidelines suggest to repeat FNAC [1–4], and two inadequate FNAC should prompt to diagnostic surgery [2]. Remarkable, the likelihood of malignancy in a thyroid nodule with Thy 1/Class 1/Category I is low [1–4], and other techniques or markers able to diagnose these lesions are strongly required to avoid surgery.

Very interesting papers have reported a main role of CNB as a second-line biopsy in these lesions with Thy 1/Class 1/Category I [12–16]. The more relevant contribution was published by Samir et al. [12]. There, the authors enrolled a series of 90 nodules with prior one or two inadequate FNAC, and all nodules underwent both CNB and repeat FNAC. The combination of repeat-FNAC and CNB classified as diagnostic 87 % of thyroid lesions with one prior inadequate FNAC and 86 % of those with two prior inadequate FNAC. CNB has been also used by Zhang et al. [13] in a large series of nodules with inadequate or suboptimal cytologic outcome. Subjects underwent FNAC or both FNAC–CNB, and the latter approach could reduce the sample's inadequacy rate from 8.7 % obtained by FNAC alone to 3.4 %. Moreover, Na et al. [16] compared CNB and a second FNAC in 64 nodules previously reading of not diagnostic; a 28 % of inadequate specimens were found in FNAC, while 1.6 % was recorded by CNB.

In all, whether to repeat FNAC in nodules with previous not diagnostic cytologic report is a matter to debate [12–16]. The combined use of repeat FNAC and CNB should be strongly considered as an alternative to surgery in individuals with previous non-diagnostic cytology. This approach has been recently included in the AACE/AME/ETA guideline [1] and Italian consensus for thyroid cytology [38].

Use of CNB in thyroid neoplasms (Thy 3/Class 3/Category III–IV) cytology

Up to 20 % of thyroid nodules submitted to FNAC has an indeterminate diagnosis of follicular neoplasm [1–4]. These lesions represent one main hot topic in thyroidology [39]. In fact, only one in four of nodules with Thy 3/Class 3/Category III–IV cytology is a cancer [40, 41], but this possibility cannot be excluded before final histology. Then, surgery has been traditionally required to diagnose these lesions [1–4]. Because of the large majority of nodules with indeterminate FNAC is benign, thyroidectomy/lobectomy is often a posteriori not necessary, and several studies have attempted to analyze clinical, morphologic, instrumental, or immunocytochemical parameters to be used in the risk stratification of thyroid follicular neoplasms [41–45]; as a result, male gender, large nodule's size, irregular margins, and microcalcifications at ultrasonography, MIBI uptake, cytologic atypias, and a positive Galectin-3 were reported as predictors of cancer, but they lack to be proved as reliable tests to avoid diagnostic surgery with 100 % specificity [41–45]. Thus, current guidelines do not recommend for the use of the above mentioned tools in the workup of patients with inconclusive thyroid cytology [1–4].

Several single-center papers described CNB in thyroid lesions with previous indeterminate FNAC, with remarkable findings [16–22]. Park et al. [20] addressed a series of patients with indeterminate neoplasms to CNB, or second FNAC, or diagnostic surgery; CNB was more effective with 77.8 % benign, 20.3 % cancer, and 1.8 % uncertain samples. Na et al. [16] evaluated 161 nodules with Category III–IV according to Bethesda system [3], and CNB correctly assessed 66.7 % of benign and 67.7 % of malignant tumors, with low rate of not diagnostic or indeterminate reports. These results were corroborated by other studies [17–19, 21, 22]. Finally, a paper by the authors of the present review described a new CNB approach which allows detect nodule's capsule while present [21]; this sampling technique can distinguish among follicular lesions the adenomatous non-encapsulated nodules from truly neoplastic encapsulated lesions.

All in all, the above studies reported high accuracy of CNB to detect benign nodules with indeterminate cytology which can avoid unnecessary diagnostic surgery. Also, the rate of not adequate CNB sample is low [16–22]. At present, CNB is not recommended by guidelines in nodules with Thy 3/Class 3/Category III–IV cytology [1–4]. In fact, CNB cannot distinguish a follicular adenoma from a follicular carcinoma which should represent the majority of thyroid lesions with indeterminate cytologic outcome. The assessment of these neoplasias requires the evaluation of the whole nodule's capsule at final postsurgical histology [1, 21].

Use of CNB in specific ultrasonographic presentations of thyroid nodules or in patients with peculiar clinical contexts

Few papers evaluated the diagnostic utility of CNB with ultrasound risk presentation [23–26]. As the first, Ha et al. [23] used CNB in thyroid nodules with previous benign FNAC outcome but having high risk at ultrasound examination. Interestingly, a very high cancer rate (32 %) was found. This finding was perfectly in agreement with that previous reported by papers analyzing the likelihood for malignancy in these specific nodules [46–48]. More recently, CNB or conventional FNAC was proposed to patients with newly discovered at risk thyroid lesions [24]; the diagnostic accuracy of CNB was significantly higher than that of FNAC [24]. These data should prompt to use CNB in those nodules suspected to be a cancer to avoid false negative FNAC reports, but more studies, ideally with prospective design and multicenter setting, are needed.

The approach by CNB in calcified thyroid nodules was reported by Ha et al. [25]. There, in a series of 272 nodules with micro- or macrocalcifications undergone CNB, only 2 (0.7 %) cases had inadequate sample, other 37 (13.6 %) were indeterminate, and there were 3 cancers with false negative microhistologic report [25]. Further data on CNB in calcified thyroid lesions are necessary.

Thyroid nodules occur with low frequency in pediatric population, and malignancy rate in these subjects ranges from 16 to 43 % [49]. A single institute experience of CNB in children was reported by Yunker et al. [27]; 36 % of nodules were malignant, and CNB had 13 % of inadequacy with sensitivity and specificity for cancer of 85 and 63 %, respectively. Of interest, no complications were recorded. The authors advocated this procedure to avoid diagnostic thyroidectomy in pediatric population. Because no significant difference was found between CNB and FNAC, the authors reject their initial hypothesis.

Finally, some studies indicate that microhistologic samples from CNB are more reliable than cytologic ones from FNAC in detecting thyroid lymphoma [28, 29]. Data on this topic are sparse. In this context, it has to be cited that current guidelines suggest CNB in patients with suspicious anaplastic thyroid carcinoma, thyroid lymphoma, pathologic lymph nodes, or other malignant neck disease [1].

First-line approach by CNB in thyroid nodules

Only few studies on the specific use of CNB as first-line approach to thyroid nodules exist. Sung et al. [10] submitted 555 thyroid nodules to both CNB and FNAC; the main result was the improved accuracy obtained by combining the two procedures. Also, Trimboli et al. [24] enrolled a selected series of 72 patients with nodule at ultrasound risk for malignancy, and higher accuracy of CNB with respect to FNAC was found. At present, the first-line use of CNB remains a matter to be evaluated.

Immunohistochemistry and molecular tests on CNB samples

The CNB sampling allows obtain a tissue fragment with size up to 500 μ and length up to 1.5 cm. These specimens should be the optimal material for extensive studies and ancillary techniques [9]. In fact, on one hand the microhistologic examination detects nuclear changes, architectural alterations of follicular structures, and pathologic relations between adjacent tissues; on the other hand, the paraffin core sections permit automated immunostaining with high reproducibility and very low cost [9, 30].

Of relevance, a very recent paper by the authors of this review reported 100 % concordance between immunohistochemical examination for the BRAF(V600E) antibody VE1 on paraffin section, and the mutational analysis performed by pyrosequencing on DNA obtained by extraction from the same core samples [30]. These results look to have very high interest and advises for future studies. In fact, lower accuracy of VE1 has been recorded in cell block and thin layer cytologic preparation [50, 51]. Few papers evaluated Galectin-3 expression in core samples from cytologically indeterminate thyroid neoplasms. The accuracy of the integrated morphologic–phenotypic diagnostic approach was high [21, 22], but data on this topic are very sparse to extend its use in routine workup of thyroid nodule. Very interesting findings were also described by Yousaf et al. [32] who applied thyroperoxidase (TPO) immunostaining in CNB samples to discriminate malignant and benign thyroid lesions with cold appearance at scintiscan.

All in all, the feasibility of immunohistochemistry is maintained with poor cellular or fibrous samples, as demonstrated in small cell aggregates from BRAF-mutated cases with inconclusive genetic results [52]. Although few studies reported immunohistochemistry applied to core specimens, CNB samples should be used for these extensive research.

Future perspective

In general, future prospective multicenter studies are required to better set the use of CNB in thyroid nodule. In fact, this study setting is lacking in thyroid CNB literature. Immunophenotyping thyroid nodules represent one major challenge in thyroidology. Different cytologic preparations (i.e., cell block, thin layer) failed to reach high reliability as samples for immunohistochemistry of thyroid cancer potential markers (i.e., Galectin-3), and their routinely use has not be recommended by current guidelines due to several reasons. On the contrary, microhistologic samples should be the ideal specimens to perform these ancillary studies. Future researches are needed to confirm that.

The cost of thyroid CNB is not negligible; not published data from the authors of the present review report that CNB may achieve 1,000 euros per patient, which is higher than the cost to perform a conventional FNAC (about 150 euros). The latter issue could represent a potential limit for the worldwide diffusion of thyroid CNB.

Conclusions

CNB has been reported as more accurate than FNAC in diagnosis of thyroid nodules. In particular, the second-line use of CNB can assess as diagnostic those thyroid lesions with previous inadequate or indeterminate cytology. At present, international guidelines include CNB only for thyroid nodules with prior not adequate FNAC.

Information of first-line use of CNB is poor, and this approach should be considered only in specific conditions where conventional FNAC might be not accurate. The microhistologic samples from thyroid CNB should allow to obtain tissue fragments ideal for immunochemistry. In next future, the immunophenotype analysis of thyroid nodules should be improved by this approach.

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References

1. H. Gharib, E. Papini, R. Paschke, D.S. Duick, R. Valcavi, L. Hegedüs, P. Vitti, AACE/AME/ETA Task Force on Thyroid Nodules: American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association Medical Guidelines for Clinical Practice for the Diagnosis and Management of Thyroid Nodules. Endocr. Pract. **16**, 1–43 (2010)
2. Royal College of Physicians of London, *Guidelines for the Management of Thyroid Cancer*, 2nd edn. (The Lavenham Press, Suffolk, 2007)
3. E.S. Cibas, S.Z. Ali, The Bethesda system for reporting thyroid cytopathology. Thyroid **19**, 1159–1165 (2009)
4. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, D.S. Cooper, G.M. Doherty, B.R. Haugen, R.T. Kloos, S.L. Lee, S.J. Mandel, E.L. Mazzaferri, B. McIver, F. Pacini, M. Schlumberger, S.I. Sherman, D.L. Steward, R.M. Tuttle, Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid **19**, 1167–1214 (2009)
5. N.J. Screaton, L.H. Berman, J.W. Grant, US-guided core-needle biopsy of the thyroid gland. Radiology **226**, 827–832 (2003)
6. T.K. Khoo, C.H. Baker, J. Hallanger-Johnson, A.M. Tom, C.S. Grant, C.C. Reading, T.J. Sebo, J.C. Morris 3rd, Comparison of ultrasound-guided fine-needle aspiration biopsy with core-needle biopsy in the evaluation of thyroid nodules. Endocr. Pract. **14**, 426–431 (2008)
7. E.B. Strauss, A. Iovino, S. Upender, Simultaneous fine-needle aspiration and core biopsy of thyroid nodules and other superficial head and neck masses using sonographic guidance. Am. J. Roentgenol. **190**, 1697–2709 (2008)
8. D. Lieu, Cytopathologist-performed ultrasound-guided fine-needle aspiration and core-needle biopsy: a prospective study of 500 consecutive cases. Diagn. Cytopathol. **36**, 317–324 (2008)
9. A.A. Renshaw, N. Pinnar, Comparison of thyroid fine-needle aspiration and core needle biopsy. Am. J. Clin. Pathol. **128**, 370–374 (2007)
10. J.Y. Sung, D.G. Na, K.S. Kim, H. Yoo, H. Lee, J.H. Kim, J.H. Baek, Diagnostic accuracy of fine-needle aspiration versus core-needle biopsy for the diagnosis of thyroid malignancy in a clinical cohort. Eur. Radiol. **22**, 1564–1572 (2012)
11. J.M. Miller, J.I. Hamburger, S. Kini, Diagnosis of thyroid nodules. Use of fine-needle aspiration and needle biopsy. JAMA **241**, 481–484 (1979)
12. A.E. Samir, A. Vij, M.K. Seale, E. Halpern, W.C. Faquin, S. Parangi, P.F. Hahn, G.H. Daniels, Ultrasound-guided percutaneous thyroid nodule core biopsy: clinical utility in patients with prior nondiagnostic fine-needle aspirate. Thyroid **22**, 461–467 (2012)
13. S. Zhang, M. Ivanovic, A.A. Nemcek Jr, D.V. Defrias, E. Lucas, R. Nayar, Thin core needle biopsy crush preparations in conjunction with fine-needle aspiration for the evaluation of thyroid nodules: a complementary approach. Cancer **114**, 512–518 (2008)
14. S.H. Lee, M.H. Kim, J.S. Bae, D.J. Lim, S.L. Jung, C.K. Jung, Clinical outcomes in patients with non-diagnostic thyroid fine needle aspiration cytology: usefulness of the thyroid core needle biopsy. Ann. Surg. Oncol. **21**, 1870–1877 (2014)
15. J.S. Yeon, J.H. Baek, H.K. Lim, E.J. Ha, J.K. Kim, D.E. Song, T.Y. Kim, J.H. Lee, Thyroid nodules with initially nondiagnostic cytologic results: the role of core-needle biopsy. Radiology **268**, 274–280 (2013)
16. D.G. Na, J.H. Kim, J.Y. Sung, J.H. Baek, K.C. Jung, H. Lee, H. Yoo, Core-needle biopsy is more useful than repeat fine-needle aspiration in thyroid nodules read as nondiagnostic or atypia of undetermined significance by the bethesda system for reporting thyroid cytopathology. Thyroid **22**, 468–475 (2012)
17. Y.J. Choi, J.H. Baek, E.J. Ha, H.K. Lim, J.H. Lee, J.K. Kim, D.E. Song, Y.K. Shong, S.J. Hong, Differences in risk of malignancy and management recommendations in subcategories of thyroid nodules with atypia of undetermined significance or follicular lesion of undetermined significance: the role of ultrasound-guided core-needle biopsy. Thyroid **24**, 494–501 (2014)
18. T. Hakala, I. Kholová, J. Sand, R. Saaristo, P. Kellokumpu-Lehtinen, A core needle biopsy provides more malignancy-specific results than fine-needle aspiration biopsy in thyroid nodules suspicious for malignancy. J. Clin. Pathol. **66**, 1046–1050 (2013)
19. S.Y. Hahn, J.H. Shin, B.K. Han, E.Y. Ko, E.S. Ko, Ultrasonography-guided core needle biopsy for the thyroid nodule: does the procedure hold any benefit for the diagnosis when fine-needle aspiration cytology analysis shows inconclusive results? Br. J. Radiol. **86**, 20130007 (2013)
20. K.T. Park, S.H. Ahn, J.H. Mo, Y.J. Park, J. Park, S.I. Choi, S.Y. Park, Role of core needle biopsy and ultrasonographic finding in management of indeterminate thyroid nodules. Head Neck **33**, 160–165 (2011)
21. N. Nasrollah, P. Trimboli, L. Guidobaldi, D.D. Cicciarella Modica, C. Ventura, G. Ramacciato, S. Taccogna, F. Romanelli, S. Valabrega, A. Crescenzi, Thin core biopsy should help to discriminate thyroid nodules cytologically classified as indeterminate. A new sampling technique. Endocrine **43**, 659–665 (2013)
22. H.S. Min, J.H. Kim, I. Ryoo, S.L. Jung, C.K. Jung, The role of core needle biopsy in the preoperative diagnosis of follicular neoplasm of the thyroid. APMIS (2014). doi:10.1111/apm.12244
23. E.J. Ha, J.H. Baek, J.H. Lee, D.E. Song, J.K. Kim, Y.K. Shong, S.J. Hong, Sonographically suspicious thyroid nodules with initially benign cytologic results: the role of a core needle biopsy. Thyroid **23**, 703–708 (2013)
24. P. Trimboli, N. Nasrollah, L. Guidobaldi, S. Taccogna, D.D. Cicciarella Modica, S. Amendola, F. Romanelli, A. Lenzi, G. Nigri, M. Centanni, L. Giovanella, S. Valabrega, A. Crescenzi, The use of core needle biopsy as first-line in diagnosis of thyroid nodules reduces false negative and inconclusive data reported by fine-needle aspiration. World J. Surg. Oncol. **12**, 61 (2014)

25. E.J. Ha, J.H. Baek, J.H. Lee, J.K. Kim, J.K. Kim, H.K. Lim, D.E. Song, T.Y. Sung, T.Y. Kim, W.B. Kim, Y.K. Shong, Core needle biopsy can minimise the non-diagnostic results and need for diagnostic surgery in patients with calcified thyroid nodules. Eur. Radiol. **24**, 1403–1409 (2014)
26. M. Zhang, Y. Zhang, S. Fu, F. Lv, J. Tang, Thyroid nodules with suspicious ultrasound findings: the role of ultrasound-guided core needle biopsy. Clin. Imaging **38**, 434–438 (2014)
27. W.K. Yunker, S.F. Hassan, L.B. Ferrell, M.J. Hicks, C.M. Giannoni, D.E. Wesson, C.I. Cassady, J.A. Hernandez, M.L. Brandt, M.E. Lopez, Needle core biopsy in the diagnosis of pediatric thyroid neoplasms: a single institution retrospective review. Pediatr. Surg. Int. **29**, 437–443 (2013)
28. K. Buxey, J. Serpell, Importance of core biopsy in the diagnosis of thyroid lymphoma. ANZ J. Surg. **82**, 90–91 (2012)
29. M. Nam, J.H. Shin, B.K. Han, E.Y. Ko, E.S. Ko, S.Y. Hahn, J.H. Chung, Y.L. Oh, Thyroid lymphoma: correlation of radiologic and pathologic features. J. Ultrasound Med. **31**, 589–594 (2012)
30. A. Crescenzi, L. Guidobaldi, N. Nasrollah, S. Taccogna, D.D. Cicciarella Modica, L. Turrini, G. Nigri, F. Romanelli, S. Valabrega, L. Giovanella, A. Onetti Muda, P. Trimboli, Immunohistochemistry for BRAF(V600E) antibody VE1 performed in core needle biopsy samples identifies mutated papillary thyroid cancers. Horm. Metab. Res. **46**, 370–374 (2014)
31. A. Carpi, A.G. Naccarato, G. Iervasi, A. Nicolini, G. Bevilacqua, P. Viacava, P. Collecchi, L. Lavra, C. Marchetti, S. Sciacchitano, A. Bartolazzi, Large needle aspiration biopsy and galectin-3 determination in selected thyroid nodules with indeterminate FNA-cytology. Br. J. Cancer **95**, 204–209 (2006)
32. U. Yousaf, L.H. Christensen, A.K. Rasmussen, F. Jensen, C.L. Mollerup, J. Kirkegaard, I. Lausen, F. Rank, U. Feldt-Rasmussen, Immunohistochemical staining for thyroid peroxidase (TPO) of needle core biopsies in the diagnosis of scintigraphically cold thyroid nodules. Clin. Endocrinol. (Oxf.) **68**, 996–1001 (2008)
33. N. Nasrollah, P. Trimboli, F. Rossi, S. Amendola, L. Guidobaldi, C. Ventura, R. Maglio, G. Nigri, F. Romanelli, S. Valabrega, A. Crescenzi, Patient's comfort with and tolerability of thyroid core needle biopsy. Endocrine **45**, 79–83 (2014)
34. A. Carpi, G. Rossi, A. Nicolini, G. Iervasi, M. Russo, J. Mechanick, Does large needle aspiration biopsy add pain to the thyroid nodule evaluation? PLoS One **8**, e58016 (2013)
35. A. Stangierski, K. Wolinski, K. Martin, O. Leitgeber, M. Ruchala, Core needle biopsy of thyroid nodules: evaluation of diagnostic utility and pain experience. Neuro. Endocrinol. Lett. **34**, 798–801 (2013)
36. Q. Liu, M. Castelli, P. Gattuso, R.A. Prinz, Simultaneous fine-needle aspiration and core-needle biopsy of thyroid nodules. Am. Surg. **61**, 628–633 (1995)
37. A. Carpi, A. Sagripanti, A. Nicolini, S. Santini, E. Ferrari, R. Romani, G. Di Coscio, Large needle aspiration biopsy for reducing the rate of inadequate cytology on fine needle aspiration specimens from palpable thyroid nodules. Biomed. Pharmacother. **52**, 303–307 (1998)
38. F. Nardi, F. Basolo, A. Crescenzi, G. Fadda, A. Frasoldati, F. Orlandi, L. Palombini, E. Papini, M. Zini, A. Pontecorvi, P. Vitti, Italian consensus for the classification and reporting of thyroid cytology. J. Endocrinol. Invest. **37**, 593–599 (2014)
39. Z.W. Baloch, M.J. Sack, G.H. Yu, V.A. Livolsi, P.K. Gupta, Fine-needle aspiration of thyroid: an institutional experience. Thyroid **8**, 565–569 (1998)
40. R. Mihai, A.J. Parker, D. Roskell, G.P. Sadler, One in four patients with follicular thyroid cytology (THY3) has a thyroid carcinoma. Thyroid **19**, 33–37 (2009)
41. P. Trimboli, G. Treglia, L. Guidobaldi, E. Saggiorato, G. Nigri, A. Crescenzi, F. Romanelli, F. Orlandi, S. Valabrega, R. Sadeghi, L. Giovanella, Clinical characteristics as predictors of malignancy in patients with indeterminate thyroid cytology: a meta-analysis. Endocrine **46**, 52–59 (2014)
42. A. Bartolazzi, F. Orlandi, E. Saggiorato, M. Volante, F. Arecco, R. Rossetto, N. Palestini, E. Ghigo, M. Papotti, G. Bussolati, M.P. Martegani, F. Pantellini, A. Carpi, M.R. Giovagnoli, S. Monti, V. Toscano, S. Sciacchitano, G.M. Pennelli, C. Mian, M.R. Pelizzo, M. Rugge, G. Troncone, L. Palombini, G. Chiappetta, G. Botti, A. Vecchione, R. Bellocco, Italian Thyroid Cancer Study Group (ITCSG): Galectin-3-expression analysis in the surgical selection of follicular thyroid nodules with indeterminate fine-needle aspiration cytology: a prospective multicentre study. Lancet Oncol. **9**, 543–549 (2008)
43. P. Trimboli, E. Condorelli, A. Catania, S. Sorrenti, Clinical and ultrasound parameters in the approach to thyroid nodules cytologically classified as indeterminate neoplasm. Diagn. Cytopathol. **37**, 783–785 (2009)
44. T. Rago, G. Di Coscio, F. Basolo, M. Scutari, R. Elisei, P. Berti, P. Miccoli, R. Romani, P. Faviana, A. Pinchera, P. Vitti, Combined clinical, thyroid ultrasound and cytological features help to predict thyroid malignancy in follicular and Hürthle cell thyroid lesions: results from a series of 505 consecutive patients. Clin. Endocrinol. (Oxf). **66**, 13–20 (2007)
45. A. Heinzel, D. Müller, F.F. Behrendt, L. Giovanella, F.M. Mottaghy, F.A. Verburg, Thyroid nodules with indeterminate cytology: molecular imaging with 99mTc-methoxyisobutylisonitrile (MIBI) is more cost-effective than the Afirma® gene expression classifier. Eur. J. Nucl. Med. Mol. Imaging (2014). doi:10.1007/s00259-014-2760-4
46. J.Y. Kwak, E.K. Kim, H.J. Kim, M.J. Kim, E.J. Son, H.J. Moon, How to combine ultrasound and cytological information in decision making about thyroid nodules. Eur. Radiol. **19**, 1923–1931 (2009)
47. F.F. Maia, P.S. Matos, E.J. Pavin, J. Vassallo, D.E. Zantut-Wittmann, Value of repeat ultrasound-guided fine-needle aspiration in thyroid nodule with a first benign cytologic result: impact of ultrasound to predict malignancy. Endocrine **40**, 290–296 (2011)
48. Y.J. Choi, I. Jung, S.J. Min, H.J. Kim, J.H. Kim, S. Kim, J.S. Park, J.H. Shin, Y.M. Sohn, J.H. Yoon, J.Y. Kwak, Thyroid nodule with benign cytology: is clinical follow-up enough? PLoS One **8**, e63834 (2013)
49. C.A. Dinauer, C. Breuer, S.A. Rivkees, Differentiated thyroid cancer in children: diagnosis and management. Curr. Opin. Oncol. **20**, 59–65 (2008)
50. A.K. Zimmermann, U. Camenisch, M.P. Rechsteiner, B. Bode-Lesniewska, M. Rössle, Value of immunohistochemistry in the detection of BRAF(V600E) mutations in fine-needle aspiration biopsies of papillary thyroid carcinoma. Cancer Cytopathol. **122**, 48–58 (2014)
51. E.D. Rossi, M. Martini, S. Capodimonti, T. Cenci, P. Straccia, B. Angrisani, C. Ricci, P. Lanza, C.P. Lombardi, A. Pontecorvi, L.M. Larocca, G. Fadda, Analysis of immunocytochemical and molecular BRAF expression in thyroid carcinomas: a cytohistologic institutional experience. Cancer Cytopathol. (2014). doi:10.1002/cncy.21416
52. D. Capper, M. Preusser, A. Habel, F. Sahm, U. Ackermann, G. Schindler, S. Pusch, G. Mechtersheimer, H. Zentgraf, A. von Deimling, Assessment of BRAF V600E mutation status by immunohistochemistry with a mutation-specific monoclonal antibody. Acta Neuropathol. **122**, 11–19 (2011)