Fine needle aspiration biopsy of thyroid nodules

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Abstract

***Background*—Fine needle aspiration biopsy (FNA) is a routine diagnostic technique for evaluating thyroid nodules. Many reports in adults consider that FNA is superior to thyroid ultrasonography (USG) and radionuclide scanning (RS). Only five studies have been published on FNA of childhood thyroid nodules.**

***Aims*—To investigate the reliability of FNA in the evaluation and management of thyroid nodules, and compare the results of FNA, USG, and RS with regard to final histopathological diagnosis.**

***Methods*—FNA was performed in 46 children with thyroid nodules after USG and RS examination. We investigated the sensitivity, specificity, accuracy, and positive and negative predictive values of USG, RS, and FNA in their management.**

***Results*—Six patients who had malignant or suspicious cells on FNA examination underwent immediate surgery. The other 40 patients received medical treatment according to their hormonal status. Fifteen of these nodules either disappeared or decreased in number and/or size. Surgery was performed in 25 patients who did not respond to therapy. Statistical analysis revealed sensitivity, specificity, accuracy, and positive and negative predictive values respectively as follows: 60%, 59%, 59%, 15%, and 92% for USG; 30%, 42%, 39%, 12%, and 68% for SC; 100%, 95%, 95%, 67%, and 100% for FNAB.**

***Conclusion*—FNAB is as reliable in children as in adults for definitive diagnosis of thyroid nodules. Using this technique avoids unnecessary thyroid surgery in children.**

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Keywords: fine needle aspiration; biopsy; thyroid nodule

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As thyroid nodules have a lower incidence in children than in adults, surgery should be selective to lessen unnecessary operations. Many methods have been used to select patients, but none has efficiently predicted the pathological findings. Ultrasonography (USG) and radionuclide scanning (RS) have been used routinely to screen thyroid nodules, but many reports question their reliability.[1–3] Routine use of FNA has significantly reduced the number of adults undergoing surgery for benign disease.[4–6] With experienced physicians performing needle biopsy, and experienced cytopathologists interpreting the results, the accuracy of FNA has been reported as 95–97%.[7–9]

The technique has been used less extensively in children.[10–12] To date, only five papers pubished in English have documented series involving the use of FNA for diagnosing thyroid nodules in children.[13–17] We investigated the reliability of FNA in evaluating and managing thyroid nodules, and assessed the overall usefulness of the method.

Patients and methods

Our prospective study included 46 children who presented with nodules in their thyroid glands during a six year period. All nodules were fine needle biopsied after USG imaging and RS examination with 99m-technetium pertechnetate. The same surgeon (ISA) performed aspirations in all cases. Patients were placed in the recumbent position with a pillow under their shoulders, such that their neck was hyperextended, and the skin cleansed with povidone iodine (Betadine scrub). Local anaesthetic was not used routinely, but we have used prilocaine hydrochloride (Citanest) in uncooperative patients or in the case of inadequate material. In children with multiple nodules, we attempted to biopsy the largest one. The nodule was fixed in position manually, and a 23 gauge needle attached to a 20 ml disposable syringe inserted perpendicular to the anterior surface of the neck. Once the needle was in place, constant suction was applied and maintained while the needle was withdrawn to the level of the nodule capsule. The content was then discharged onto glass slides and smears were made. If no sample was drawn into the syringe on the first attempt, the needle was inserted in a different direction to obtain adequate material without withholding it outside the skin. We have prepared at least five smears similar to the technique for preparation of bone marrow aspirates. All smears were dried in air and Giemsa stained (Merck Laboratories, Germany). One cytopathologist evaluated the smears. The presence of more than seven groups of cells per stained smear was considered sufficient aspirate volume. FNA examination results were classified according to cell type—benign, malignant, or follicular pattern. Biopsy specimens were labelled suspicious when cell types could not be determined.

After obtaining the results of FNA examination, we administered thyroid hormone or antithyroid drugs to patients as appropriate except in those in whom we detected malignant or suspicious cells. These patients underwent immediate surgery. After six months of treatment, the nodules were re-evaluated by physical examination, USG, and RS. Patients whose nodules were the same size or had enlarged underwent surgery. Maintaining high concentrations of thyroid hormones despite therapy was another indication for surgery. We performed intraoperative frozen section examination (FSE) in patients both with solid nodules

Table 1 Definition and calculation of the statistical parameters

Type	*Cytology*	*USG*	*Scintigraphy*	*Histopathology*
TP	Malignant or suspicious	Solid	Cold	Malignant
TN	Benign cells	Cystic or mixed	Hot or warm	Benign
FP	Malignant or suspicious	Solid	Cold	Benign
FN	Benign cells	Cystic or mixed	Hot or warm	Malignant

Sensitivity	= TP/(TP+FN)
Specificity	= TN/(TN+FP)
Accuracy	= (TP+TN)/(TP+TN+FP+FN)
Positive predictive value	= TP/(TP+FP)
Negative predictive value	= TN/(TN+FN)

USG, thyroid ultrasonography; TP, true positive; TN, true negative; FP, false positive; FN, false negative.

and with malignant or suspicious cells in their FNAs. We also performed FSE in two patients whose FNA was unsuccessful. All removed thyroid glands were evaluated histopathologically. Patients with nodules who did not undergo surgery were followed at three month intervals during hormonal treatment. Their thyroid glands were examined once a year after the cessation of drugs. The follow up period ranged from one to five years.

At the end of the study, we calculated the sensitivity, specificity, accuracy, and positive and negative predictive values of thyroid USG, RS, and FNA results in the diagnosis of thyroid nodules of children (see table 1). We derived these figures using the final histopathological diagnosis as the gold standard.

Results

Nine patients were male (19%) and 37 female (81%). Mean age was 9 years (range 5–116). Diameters of the biopsied nodules were as follows: six (13%) were less than 1 cm, 28 (61%) were between 1 and 2 cm, and 12 (26%) were larger than 2 cm. We were able to aspirate adequate material in 44 of 46 patients (96%). In the two cases where we were unsuccessful, nodule sizes were 1 and 1.5 cm. Only four patients (9%) required multiple attempts; all had a nodule diameter of less than 1 cm. Although we did not use local anaesthesia routinely, six patients (13%) needed subcutaneous administration of prilocaine hydrochloride. In four the first attempt was unsuccessful. The other two were straining. All the other patients' aspirations were successful at the first attempt.

Table 2 presents results of USG, RS, and FNA. In the surgically treated group we detected 17 solid, 10 mixed, and four cystic nodules with USG. RS revealed 19 cold, six hot, and six warm nodules. Results of FNA

Table 2 Comparative results of patients undergoing surgical and medical treatment

Case	*Sex*	*USG*	*Type*	*RS*	*Type*	*FSE*	*FNA*	*Type*	*Surgery*	*Histopathology*
Patients undergoing surgical treatment										
1	F	Solid, solitary	FP	Cold	FP	Benign	Follicular	TN	RST	Follicular adenoma
2	M	Mixed, multiple	TN	Hot	TN	Benign	Unsuccessful	—	BST	Follicular adenoma
3	F	Solid, solitary	TP	Cold	TP	Malignant	Malignant	TP	BTT	Papillary carcinoma
4	F	Solid, multiple	FP	Cold	FP	Benign	Suspicious	FP	BST	Colloidal goitre
5	F	Solid, solitary	TP	Cold	TP	Malignant	Malignant	TP	BTT	Papillary carcinoma
6	M	Solid, multiple	TP	Cold	TP	Malignant	Suspicious	TP	BTT	Follicular carcinoma
7	F	Solid, solitary	FP	Cold	FP	Benign	Benign	TN	RST	Colloidal goitre
8	F	Solid, solitary	FP	Cold	FP	Benign	Benign	TN	LST	Colloidal goitre
9	F	Solid, solitary	FP	Cold	FP	Benign	Benign	TN	RST	Colloidal goitre
10	F	Mixed, multiple	FN	Hot	FN	Malignant	NHL cells	TP	BTT	NHL metastasis
11	F	Solid, solitary	FP	Cold	FP	Benign	Follicular	TN	RST	Follicular adenoma
12	F	Solid, multiple	FP	Cold	FP	Benign	Benign	TN	BST	Colloidal goitre
13	F	Solid, solitary	FP	Hot	TN	Benign	Benign	TN	RST	Colloidal goitre
14	F	Solid, solitary	FP	Warm	TN	Benign	Unsuccessful	—	RST	Follicular adenoma
15	F	Solid, solitary	FP	Hot	FN	Benign	Benign	TN	LST	Colloidal goitre
16	F	Solid, solitary	FP	Hot	TN	Benign	Follicular	TN	RST	Follicular adenoma
17	F	Solid, solitary	FP	Warm	TN	Benign	Benign	TN	LST	Colloidal goitre
18	F	Mixed, multiple	TN	Cold	FP	Benign	Suspicious	FP	BST	Follicular adenoma
19	F	Solid, multiple	FP	Cold	FP	Benign	Benign	TN	BST	Colloidal goitre
20	F	Solid, multiple	FP	Cold	FP	Benign	Benign	TN	BST	Colloidal goitre
21	F	Mixed, multiple	TN	Warm	TN	—	Benign	TN	BST	Follicular adenoma
22	F	Mixed, multiple	TN	Warm	TN	—	Follicular	TN	RST	Follicular adenoma
23	F	Cystic, multiple	TN	Cold	FP	—	Benign	TN	BST	Colloidal goitre
24	F	Mixed, multiple	TN	Cold	FP	—	Benign	TN	BST	Colloidal goitre
25	M	Mixed, multiple	TN	Warm	TN	—	Benign	TN	BST	Follicular adenoma
26	F	Mixed, solitary	TN	Cold	FP	—	Benign	TN	LST	Colloidal goitre
27	F	Mixed, multiple	TN	Warm	TN	—	Benign	TN	BST	Colloidal goitre
28	F	Cystic, multiple	FN	Cold	FP	—	Benign	TN	BST	Colloidal goitre
29	M	Cystic, solitary	TN	Cold	FP	—	Follicular	TN	LST	Follicular adenoma
30	M	Mixed, solitary	TN	Cold	FP	—	Benign	TN	RST	Colloidal goitre
31	F	Cystic, solitary	TN	Hot	FN	—	Benign	TN	RST	Follicular adenoma
Patients undergoing medical treatment										
1	F	Mixed, multiple	TN	Cold	FP	—	Benign	TN	—	Colloidal goitre
2	F	Solid, solitary	FP	Hot	FN	—	Benign	TN	—	Colloidal goitre
3	M	Mixed, multiple	TN	Cold	FP	—	Benign	TN	—	Colloidal goitre
4	M	Mixed, multiple	TN	Cold	FP	—	Benign	TN	—	Colloidal goitre
5	F	Solid, solitary	FP	Warm	TN	—	Benign	TN	—	Colloidal goitre
6	F	Cystic, solitary	TN	Cold	FP	—	Benign	TN	—	Colloidal goitre
7	F	Cystic, solitary	TN	Warm	TN	—	Benign	TN	—	Colloidal goitre
8	F	Mixed, multiple	TN	Cold	FP	—	Benign	TN	—	Colloidal goitre
9	F	Mixed, multiple	TN	Warm	TN	—	Benign	TN	—	Colloidal goitre
10	F	Solid, solitary	FP	Warm	TN	—	Benign	TN	—	Colloidal goitre
11	F	Cystic, solitary	TN	Hot	FN	—	Benign	TN	—	Colloidal goitre
12	M	Mixed, solitary	TN	Hot	FN	—	Benign	TN	—	Colloidal goitre
13	F	Mixed, multiple	TN	Warm	TN	—	Benign	TN	—	Colloidal goitre
14	M	Cystic, solitary	TN	Warm	TN	—	Benign	TN	—	Colloidal goitre
15	F	Cystic, solitary	TN	Hot	FN	—	Benign	TN	—	Colloidal goitre

F, female; M, male; TP, true positive; TN, true negative; FP, false positive; FN, false negative; BTT, bilateral total thyroidectomy; BST, bilateral subtotal thyroidectomy; RST, right subtotal thyroidectomy; LST, left subtotal thyroidectomy; NHL, non-Hodgkin lymphoma.

Table 3 Statistical analysis of the results

	USG	*RS*	*FNA*	*FSE*
True positive	3	4	3	4
True negative	15	38	24	15
False positive	21	2	17	1
False negative	7	0	2	0
Sensitivity	60%	30%	100%	100%
Specificity	59%	42%	95%	94%
Accuracy	59%	39%	95%	95%
Positive predictive value	15%	12%	67%	80%
Negative predictive value	92%	68%	100%	100%

examination were as follows: malignant cells in two patients, metastatic non-Hodgkin lymphoma (NHL) cells in one, benign cells in 18, follicular pattern in five, and suspicious cells in three. FNA was unsuccessful in two patients. In the medically treated group, nodules were solid in eight, mixed in five, and cystic in two patients with USG; and cold in 12, hot in two, and warm in one patient with RS. All biopsies revealed benign cells on FNA examination of these patients.

Following the FNA examination results, we operated immediately on six patients (13%) who had malignant, metastatic NHL and suspicious cells. While malignant aspirations showed papillary carcinoma in the final histopathological examinations, three of the patients with suspicious cells were confirmed as having follicular carcinoma, follicular adenoma, and colloidal goitre, respectively. Fifteen patients (33%) responded to medical treatment over a six month period. We have operated on 25 (54%) unresponsive patients. The indications for surgery were no change or enlargement in nodule size in 23 patients, and high concentrations of thyroid hormones despite treatment in two patients. No patient responding to medical treatment developed recurrent nodules or malignancy after treatment stopped.

We performed FSE in 20 patients: 12 with solid nodules, three with suspicious cells, two with malignant cells, one with metastatic NHL cells, and two whose FNAs were unsuccessful. All patients with solid nodules had benign cells in their FNAs. One patient with suspicious cells, one patient with metastatic NHL cells, and two patients with malignant cells on FNA had features of malignancy in their FSE. The other four patients' examinations revealed a benign lesion. Table 2 presents the results of FSE and final histopathological diagnoses of nodules. Table 3 presents the results of statistical analysis.

Discussion

RS examination has been the first choice for diagnosing thyroid nodules in the past, but the technique has significant limitations in children.[1 2] It is primarily useful for detecting ectopic tissues or hot toxic nodules.[18 19] The other well known diagnostic method, USG, is of limited value, especially for evaluating children with solitary thyroid nodules.[20 21] The popular fine needle biopsy technique, introduced in the 1950s in Scandinavia, provides adequate specimens for cytological examination.[22] The accuracy of diagnosis by FNA is dependent on the type and diameter of the lesion being sampled and the experience of those doing the sampling and evaluating the smears.[23 24] Although there appears to be no uniformity of the operative technique in performing FNA, we think our technique with a 23 gauge needle and constant suction provides adequate material for examination.

The main objective of FNA is to identify thyroid nodules that can safely be left in situ, excluding carcinoma. Before the introduction of FNA, patients with solid, cold, and/or single nodules had been candidates for surgery. In practice, diagnosis based on FNA has led to a substantial reduction in the number of patients sent to surgery.[6 25] In the current series, of 40 patients with benign or follicular cells, 21 had solid, 31 had cold, and 23 had solitary nodules. No patient either operated or not operated developed cancer at the time of operation or during follow up. As reported in recent childhood series,[13 16] we believe that FNA significantly narrows the scope of indications for surgery in children with thyroid nodules.

Correct diagnosis can be achieved in over 90% of undifferentiated, medullary, and papillary carcinomas using FNA.[7] These patients need no other investigation of the nodule and should be operated on without delay. If suspicious cells are detected, surgical excision of the nodule should be the treatment of choice to exclude malignancy.[26 27] In our series, of three patients with suspicious cells, two proved benign and one had follicular carcinoma. Accuracy of the technique in cases of follicular carcinoma is approximately 40% because of difficulty in diagnosing this neoplasm based on FNA alone.[23 28] We believe that surgery aims not only at treatment but also to be the optimal way to make a diagnosis in patients with a suspicious result on FNA examination. Some recommend repeating aspirations in patients with persistent nodularity in case of carcinoma development later in life.[29] In our study, we detected no malignancy in the final histopathological examinations of the surgically treated patients nor in patients with benign FNA receiving only medical treatment during follow

Table 4 Comparison of the childhood FNA series

Series	*No.*	*Sex*		*Age*	*FNA results*				*Overall malignancy rate*	*Statistical analysis*				
		M	*F*		*Benign*	*Malign*	*Suspicious*	*Insufficient*		*Sen*	*Sp*	*Acc*	*PPV*	*NPV*
Arda *et al*	46	9 (19%)	37 (81%)	9	38 (82%)	3 (7%)	3 (7%)	2 (4%)	7%	100%	95%	95%	67%	100%
Al-Shaikh *et al*[17]	41	35 (85%)	6 (15%)	13	30 (73%)	2 (5%)	6 (15%)	3 (7%)	5%	87%	100%	87%	29%	100%
Khurana *et al*[16]	57	11 (19%)	46 (81%)	17	36 (63%)	7 (12%)	14 (25%)	0	25%	93%	81%	84%	62%	97%
Lugo-Vicente *et al*[15]	24	4 (%17)	20 (83%)	15	11 (61%)	2 (11%)	2 (11%)	3 (17%)	21%	60%	90%	80%	75%	81%
Degnan *et al*[14]	18	4 (22%)	14 (78%)	14	7 (41%)	2 (12%)	7 (41%)	1 (6%)	33%	73%	80%	75%	89%	57%
Raab *et al*[13]	57	8 (14%)	49 (86%)	13	51 (77%)	4 (6%)	8 (12%)	3 (5%)	18%	80%	86%	85%	36%	98%

No., number of patients; M, male; F, female; Sen, sensitivity; Sp, specificity; Acc, accuracy; PPV, positive predictive value; NPV, negative predictive value.

up. We believe that repeated aspiration is unnecessary in children with benign cells on FNA. However, we advise that persistence or enlargement of nodule size or persistence of high concentrations of thyroid hormones despite medical treatment are indications for surgery.

Recent studies have assessed FNA and perioperative FSE with regard to reliability in the diagnosis of cancer and determining the limitation of excision of the gland. FSE can be omitted if FNA is reported as benign.[30] When the FNA result is uncertain, patients should undergo diagnostic surgery, and definitive surgery should be based on the FSE result. In our series, we encountered no case in which FNA revealed benign cells but FSE and consequent histopathological examinations detected malignancy. Therefore, we believe that FSE is unnecessary in patients with benign cells on FNA.

An important aspect of FNA in small children is whether sedation or anaesthesia is necessary. We found that inserting a needle for anaesthetic administration caused as much fear and discomfort as insertion of the FNA needle. We consider that local anaesthesia should be reserved for children in whom the first attempt is unsuccessful or if the child is fearful. Anaesthesia spray or cream may be another choice.

The principal reasons why FNA has not been used more widely in children are age, neck size, the need for sedation or anaesthesia, and the amount of specimen needed.[15] Table 4 compares previous series with ours. It shows that benign nodules significantly outnumber those which are malignant. Although a thyroid nodule in a child involves an underlying risk of malignancy, the majority are benign[13 15 16] with an overall rate of primary thyroid malignancy of 5–333%. The accuracy in detecting thyroid tumours is 75–995% with FNA. Our childhood malignancy rate is 7%; we believe the high figure for benign nodules in our series to be a result of the fact that endemic goitre is common in some regions in our country.[31] As the number of suspicious FNA examinations increases, the accuracy of the technique decreases. Although Degnan *et al* reported that the accuracy of FNA for diagnosing thyroid malignancy in children was similar to that of other diagnostic procedures,[14] both in children and adults,[4 7 9 13–17] we conclude that FNA was more reliable than USG and RS in the diagnosis of thyroid nodules. When comparing our results with others, it seems that our sensitivity, specificity, and accuracy is higher. As mentioned above, detection of malignant cells, especially follicular neoplasms, has a higher false positive rate. The number of malignant FNA in our series is less than in other series which helps to explain our better figures.

We conclude that FNA is as reliable a method for assessing thyroid nodules in children as in adults. The technique can be easily applied without local anaesthesia, although this should be used in selected cases such as those who are fearful, or after unsuccessful attempts. FNA prevents unnecessary thyroid surgery in children, whose nodules are more likely to be cold on scintigraphy, solid on ultrasonography, and have a greater tendency to be malignant than those found in adults. We believe that detection of malignant or suspicious cells are definite indications for surgery. FSE should be performed only in patients with malignant or suspicious cells and has no place in patients whose previous FNA examinations revealed benign cells.

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