



Diagnostic Accuracy of Fine Needle Aspiration for Solitary and Multiple Thyroid Nodules in a Tertiary Care Center

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Abstract

Background: Thyroid nodules are common in clinical practice. They are usually benign, but malignancy must be ruled out. Fine needle aspiration (FNA) biopsy of the thyroid is a rapid and cost-effective procedure in the initial evaluation of a thyroid nodule, but its results may be inaccurate in 10% to 30% of cases. This prospective observational study was conducted to determine the prevalence of thyroid cancer, its related findings, and the diagnostic accuracy of preoperative FNA in a tertiary care center.

Methods: We prospectively studied the medical records of 345 subjects, who underwent thyroid resection in the university hospital setting over a 4-year period. Age, gender, FNA and pathologic reports, and whether the lesion was multinodular or a solitary nodule were determined.

Results: The sensitivity and specificity of FNA were 64.96% and 62.76%, respectively. The positive predictive value of the test for the diagnosis of malignant nodules was 59.30% and its negative predictive value was 68.20%. In 63.5% of the patients, the preoperative FNA matched the surgical histopathology results. The presence of multinodular goiter was an important risk factor for thyroid malignancy. Fifty-two subjects had papillary microcarcinoma and the rate of aggressive behavior was considerable in this group.

Conclusions: Although fine needle aspiration biopsy is the most important step in the workup of the thyroid nodules, it may miss a significant number of malignant lesions. Therefore, there is a mandatory need to evolve other clinical and laboratory adjuncts, which assists the clinicians with the interpretation of FNA more accurately.

Keywords: Thyroid Nodule, Fine Needle Aspiration, Multinodular Goiter, Papillary Microcarcinoma, Positive Predictive Value, Negative Predictive Value

1. Background

Thyroid nodules are a common finding among patients, who seek medical help, with a prevalence of 4% to 7% in the adult population. Nodules are more common in iodine-deficient areas, in women and with aging. However, the majority of palpable nodules were found to be pathologically benign in nature according to surgical specimen analysis (1).

The major goal in the evaluation of a thyroid nodule is to identify, in a cost-effective manner, the small subgroup of individuals with malignant lesions. In the current literature, fine needle aspiration (FNA) was considered the primary method, which helps the physician decide whether a certain thyroid nodule needs to be operated or not (2, 3). Given the central role played by FNA in the initial evaluation of thyroid nodules, its reliability for providing accurate data is an important issue. However, this method has limitations, including insufficient or non-diagnostic samples or lack of FNA's differentiation between benign and

malignant lesions in the cases with follicular neoplasms (4-6). Also, FNA biopsies of large thyroid nodules (at least 4 cm) yielded a high false-negative rate (7, 8). Actually, diagnostic yield of the FNA varies significantly between different studies and medical groups as it remains highly dependent on the operator and the cytologist's skills (9). Therefore, in a significant number of cases, only after surgery and histologic examination of tissue specimens, the definitive distinction of benign from malignant nodules will become possible (5, 10). Furthermore, it has been assumed that iodine repletion may affect the prevalence and clinical behavior of thyroid cancer (11-13). In fact, no clear relationship between thyroid cancer incidence and iodine intake has been found. But, it has been demonstrated that the ratio of papillary carcinoma to the more malignant follicular and anaplastic thyroid carcinomas increases after the institution of salt iodization programs in iodine deficient regions (14).

In this regard, Belfiore et al. reported about twice more

common malignant thyroid lesions in an iodine sufficient area compared to a region with iodine deficiency. In addition, the prevalence of follicular and anaplastic carcinomas in the iodine deficient region was 3 times more than the area with adequate iodine intake (15).

Accordingly, this study was performed to assess the current status of the thyroid nodules in this region and the predictive role of FNA in correct diagnosis of malignant versus benign thyroid nodules compared to their post-operative pathology reports.

2. Methods

This prospective observational cohort study was conducted to determine the prevalence of thyroid cancer, its related findings, and the diagnostic accuracy of preoperative FNA in a tertiary care center over a 4-year period (2007 - 2011). The study population comprised 345 subjects with solitary and multiple thyroid nodules, who underwent thyroid resection in Namazee and Rajaei hospitals affiliated to Shiraz University of Medical Sciences, in Shiraz, Iran.

Patients with a prior history of thyroid surgery or thyroid carcinoma were excluded from the study. Nodule size was determined based on final surgical pathology. For each patient with a palpable nodule, serum thyroid stimulating hormone (TSH) level was measured and those with normal TSH concentration were candidate for FNA. All nodules were aspirated with palpation guidance, and cutoff size of 1cm was considered to separate papillary thyroid carcinoma from those determined as micropapillary thyroid carcinoma after operation. In patients with a multinodular goiter, the dominant nodules were aspirated. In all patients, cytopathologic, operative, and histopathologic findings were reviewed. The reasons for surgery included the presence of malignancy based on the FNA results, cases who were suspicious for malignancy, and those who had follicular neoplasm, compressive symptoms, or cosmetic problems.

For each patient, the preoperative result of fine needle aspiration was identified, retrospectively. Experienced board-certified pathologists who were blinded to the FNA results analyzed and compared the preoperative FNA to surgical histopathology results. All data were collected via a review of the patients' files. This study received local institutional review board's and the ethics committee approval (code No. EC-P-92-5038).

2.1. Statistical Analysis

Based on the previous similar research studies and their reported diagnostic accuracy of FNA, at the error level of $\alpha = 0.05$ and power = 90%, the number of required cases was determined as less than 100 persons.

Data analysis was performed, using SPSS Version 17. The mean values of continuous variables were compared using student t test and categorical data were compared with Chi-Square and Fisher tests. Also, P value less than or equal to 0.05 was considered statistically significant.

3. Results

In this study, 345 patients were included (66 men and 279 women). The mean age of the subjects was 40.93 ± 13.44 years (age range: 15 - 90), of whom 156 suffered from thyroid cancer. Table 1 shows their characteristics, including thyroid malignancy risk factors.

Table 1. Descriptive Characteristics of the Study Population

Variable	Frequency
Presence of multiple nodules	
Yes	182 (52.8)
No	163 (47.2)
Rapid growth	
Yes	251 (72.8)
No	94 (27.2)
Family history of thyroid disease	
Positive	60 (17.4)
Negative	285 (82.6)
Family history of thyroid malignancy	
Positive	61 (17.7)
Negative	284 (82.3)
Age, y	
≤ 36	136 (39.4)
> 36	209 (60.6)
Size of thyroid nodule, cm	
≤ 2	230 (66.7)
> 2	115 (33.3)
Disease duration, y	
≤ 1.5	175 (50.7)
> 1.5	170 (49.3)
Nature of disease	
Benign	189 (54.8)
Malignant	156 (45.2)

In 63.5% of the patients, the preoperative FNA matched surgical histopathology results. On the other hand, FNA falsely predicted a benign nature for thyroid nodules in 16% of subjects (false-negative), but in 20% of cases, the FNA was falsely positive for thyroid malignancy.

On the basis of our findings, the sensitivity and specificity of FNA were 64.96% and 62.76%, respectively. The positive predictive value (PPV) of the FNA for diagnosis of malignant nodules was 59.30% and negative predictive value (NPV) of this method was 68.20% (Table 2).

Table 2. True Positive and Negative Values for FNA Biopsies Versus Surgical Specimen Analyses

	FNA	Histopathology	Total (%)
Benign, %	118 (62.4)	71 (37.6)	189 (100)
Malignant, %	55 (35.3)	101 (64.7)	156 (100)

Abbreviation: FNA, fine needle aspiration.

According to this study, the most important risk factors for malignancy were positive family history of thyroid disease ($P = 0.003$) or thyroid cancer ($P = 0.001$), malignant FNA result ($P = 0.002$), the presence of multiple nodules ($P = 0.017$), disease duration > 1.5 years ($P = 0.019$), the size of thyroid nodule (> 2 cm) ($P = 0.001$), > 36 years of age ($P = 0.003$), and rapid growth of thyroid nodules ($P = 0.011$). But, there was no statistical relationship between the patients' gender and histopathologic diagnosis of nodules ($P = 0.8$).

In the present study, papillary, follicular, and medullary carcinomas were detected in 123 (35.7%), 22 (6.4%), and 12 (3.5%) patients, respectively.

Based on the post-surgical pathology, papillary microcarcinoma (PMC) was diagnosed in 52 (33.1%) of those who had papillary carcinoma. Moreover, in this subgroup, capsular invasion was detected in 17.8%, extra-thyroidal extension in 18.4%, lymphatic invasion in 12.1%, and vascular invasion in 10.2% of cases.

Also, in 58 subjects, the size of thyroid nodules was 4cm or more; of them, 39 nodules (67.2%) were benign and 19 (32.1%) were malignant on the basis of FNA results. But, after surgery, histopathology reports were benign in 27 patients (46.6%) and 31 cases were malignant (53.4%).

4. Discussion

In this prospective observational study, the preoperative FNA matched the surgical histopathology results in 63.5% of patients.

Fine needle aspiration biopsy has been proposed as the most important tool in the preoperative assessment of thyroid nodules. But, the efficiency of this method is highly dependent on the expertise of the operator as well as the pathologist, which leads to significant diversity about its sensitivity and specificity. The reported sensitivity and specificity of FNA in previous studies ranged between 57%

to 98% for sensitivity and 72% to 100% for specificity (4). In our study, we found the sensitivity and specificity of 64.96% and 62.76%, respectively.

Various studies suggested that the sensitivity will improve if the procedure and its interpretation are performed by experienced practitioners (7, 16, 17). In this regard, Stojadinovic et al. reported up to 61% inaccuracy in the initial diagnosis when the results of FNA was compared to histology or revised later by an expert cytologist (18).

Our survey revealed higher malignancy risk with increased number of thyroid nodules.

This finding was in agreement with several previous articles, which also showed the similar risk of malignancy in thyroid nodules, regardless of their number (15, 19-21). Indeed, it has been shown that approximately 23% of single nodules are dominant in the context of a multinodular goiter (22). Conversely, some other reports revealed no increased risk of malignancy for multinodular goiters (MNG) (7, 19, 21, 23). Moreover, MNGs are a common cause for lower predictive capacity and higher false negative results of FNA, as reported by Cootough and Kaliszewski. Subsequently, they recommended total thyroidectomy for most of the cases with MNG in order to reduce the rate of reoperation despite a nonmalignant FNA result (24, 25).

Another notable finding in our study was the recognition of papillary microcarcinoma (PMC) in 52 (33.1%) of malignant nodules. During the last decades, papillary thyroid cancer has shown the largest increase in incidence among all solid tumors worldwide. Interestingly, this increase is in large part attributed to more identification of nodules less than 1cm due to the routine use of high resolution ultrasonography and more application of total thyroidectomy (26-29). This issue was described by Elisei et al. who had noted a significant rise in the incidence of microcarcinomas from 8% before 1990 to 29% from 1990 to 2004 (30). However, there are extensive controversies related to the categorization of papillary microcarcinomas as benign versus malignant and their clinical course or treatment. A large number of studies in recent years have suggested more aggressive behavior in such cases, contrary to what was believed in the past (31-34). For example, Roti et al. in a prospective study, found this pathology in about 39% of all malignant thyroid nodules over a 10-year period and showed a considerably aggressive behavior in them (35). Choi et al. also in their study, reported lymph node and capsular invasion in 25.2% and 20.7% of papillary microcarcinomas, respectively (36). In this regard, Pellegriti et al. proposed that the aggressive behavior of PMC might have been overlooked in previous studies, where these small tumors were managed with lobectomy. They reported lymph node metastasis in 30% and persistent or recurrent disease in 25.7% of subjects diagnosed with PMC (37). Actu-

ally, there are several papers, confirming the adverse prognostic significance of lymph node involvement at presentation in patients with PMC (33, 38-40). We also found capsular invasion in 17.8%, lymphatic invasion in 12.1%, and vascular invasion in 10.2% of nodules with the diagnosis of PMC. Nevertheless, thyroid microcarcinomas and their appropriate management remain a topic of debate (41, 42). Recent reports have raised the question about their evaluation by FNA and screening of thyroid nodules, regardless of their size (31). Current American thyroid association guidelines recommend FNA of nodules 0.5 cm or larger in high risk subjects (e.g. family history of thyroid cancer, personal history of radiation exposure or suspicious characteristics on ultrasonography) (3). Moreover, one of the possible reasons for reported sensitivity and specificity of FNA in our study may be the inclusion of PMC cases in statistical analysis. Indeed, earlier studies had considered them a benign category with non-invasive behavior and did not include them in their statistical analyses (43, 44). In the studies conducted by Rios et al. and Kulstad, improved sensitivity but lower PPV of FNA were reported after excluding the patients with PMC. Finally, it has been suggested that although FNA is a useful test, our decision making should not be solely on the basis of its result and sometimes clinical criteria are preferred to cytologic data (45, 46).

However, the observation of such aggressive behaviors in small nodules may be related to increased iodine supplementation in recent years. In fact, it has been shown that increased iodine intake may influence the distribution of the types of thyroid cancers with fewer aggressive follicular and anaplastic carcinomas and more papillary carcinomas in iodine sufficient areas (13, 14). For example, Belfiore et al. reported malignancy in 2.9% of residents with iodine deficiency and in 5.48 % of those from an iodine sufficient area (15). We could not perform simultaneous measurement of urinary iodine as a marker of its intake. However, recent studies showed that there was no more iodine deficiency in Iran, including Fars province (47).

Of note, in another survey performed a decade earlier in our center when this area was still considered an iodine deficient region, the prevalence of thyroid cancer was 23.3% compared to 49.9% in the present study (48). Nakhjavani et al. also in a similar investigation in Tehran, Iran, carried out more than 10 years ago, reported thyroid cancer in 30.5% of the resected thyroid nodules, which was significantly higher than a prior study, conducted about 2 decades before, in their center, which reported malignancy in 10.2% of the thyroid nodules (23). Although this difference may reflect changes in diagnostic strategies, iodine repletion should also be considered a possible contributing factor.

On the other hand, sampling error of a fine needle as-

piration biopsy increases as the size of a thyroid nodule increases and FNA of large nodules (at least 4 cm) yields a high false-negative rate. However, patients with negative FNA results do not necessarily undergo surgery and are often excluded in statistical analysis; hence, this might lead to bias in the reported sensitivity of FNA in prior reports (7, 44, 49).

Tee et al. in their report on the sensitivity of FNA, showed that the sensitivity of this method is significantly associated with cancer risk in a group, whose FNA was negative for malignancy and, therefore, did not undergo surgery. Actually, when they considered the malignancy risk of these undiagnosed cases, the FNA sensitivity reduced to 66%. Furthermore, they concluded that FNA cannot detect up to one-third of malignant thyroid nodules (49).

In our study, 58 patients had large thyroid nodules (≥ 4 cm), of whom 32.1% were diagnosed as malignant by FNA, but after surgery, histopathology reports showed malignancy in 53.4%. Unfortunately, there is little consensus regarding the accuracy of FNA for therapeutic decision making of large nodules. Yeh et al. showed that a single false-negative FNA delayed the surgical treatment by 28 months and those subjects whose tumors were not detected by FNA had higher rates of capsular and vascular invasion and were more likely to have persistent disease (50).

Pinchot et al. concluded that FNA results in large thyroid nodules (≥ 4 cm) were very unreliable. Consequently, the authors suggested the performance of diagnostic lobectomy in patients with large nodules, regardless of their FNA cytology (7). Similarly, Carrillo et al. reported the nodule size ≥ 4 cm as the only clinical factor associated with preoperative false-negative FNA in patients with indeterminate FNA results (51).

In this regard, Yoon et al. proposed that the prevalent false-negative FNA results in large nodules are due to the existence of eccentric malignant foci in them, which were often not sampled (26).

On the other hand, Albuia et al. and Porterfield et al. in their studies concluded that with appropriate application of ultrasound-guided aspiration and expert cytologic analysis, the size of thyroid nodules would not affect the reliability of FNA. Accordingly, they did not recommend routine surgery for large nodules (52, 53). Moreover, Kulstad suggested that the decision for surgery of thyroid nodules should not be mainly based on their size, but additional factors, such as ultrasound characteristics and surgical risk should also be considered (46).

However, with the widespread use of ultrasound, thyroid nodules reach a more prevalent percentile. So, in order to reduce the number of unnecessary diagnostic surgeries as well as neglected suspicious cases, a more reliable

algorithm is recommended to assess the risk of thyroid malignancy.

The aim of the present study was to determine the accuracy of FNA in detecting malignant thyroid nodules in a tertiary care center. Our findings revealed suboptimal accuracy for this procedure and it was incapable for correct diagnosis of thyroid cancer in about one-third of cases. Also, we found higher prevalence of thyroid malignancy in this center several years after iodine repletion programs, and a significant percentage of malignant nodules in our study was less than 1cm. Aggressive behavior was seen in these small nodules, as well, which may be related to increased iodine supplementation in recent years. These findings highlight the need to pay more attention to this group of nodules and appropriate decision making when we are managing them. However, further research is required to investigate the incidence of malignancy in FNA negative cases and to determine the additive effect of clinical judgment and application of molecular genetics to FNA biopsies.

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Footnotes

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