

Does the site of aspiration affect the efficacy of ultrasound-guided fine needle aspiration biopsy of thyroid nodules?

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Abstract

Objective: To investigate whether the choice of a hypovascular or a hypervascular site of a thyroid nodule affects the efficacy of the ultrasound-guided fine needle aspiration procedure or not.

Methods: Sixty solid thyroid nodules in 60 patients with hypo- and hypervascular parts were included in this prospective clinical study. Under color Doppler sonographic guidance, the fine needle aspiration was made with 22-gauge needle. Radiological and cytological features as well as the adequacy of samples were noted and compared.

Results: Sonographically, 25 nodules (41.7%) were heterogenous and calcified, 21 were hypoechoic (35%), 10 were isoechoic (16.7%) and 4 were hyperechoic (6.6%). Rate of adequate sampling when only hypervascular was used or hypovascular sites were evaluated were 81.7% and 83.3%, respectively. When both sites were evaluated together, rate of adequate sampling was found to be 91.7% in total. Presence and distribution of endothelial cells in the sample seems not to influence the diagnostic value of the procedure.

Conclusion: Our results indicate that vascularity of a thyroid nodule outlined by color Doppler sonography can aid in optimizing the efficiency of fine-needle aspiration biopsy. The samples obtained from aspirates of hypo- and hypervascular sites are both complementary and assessment of these sites together yields better results in terms of diagnostic accuracy.

Keywords: Thyroid, nodule, diagnosis, ultrasonography, fine-needle aspiration, color Doppler.

Özet: Aspirasyon yerinin tiroid nodüllerinin ultrason destekli jet iğne biyopsisi verimliliği üzerindeki etkileri

Amaç: Çalışmanın amacı ultrason destekli jet iğne biyopsisinde hipovasküler ya da hipervasküler tiroid nodül tercihinin prosedür verimliliğine etkisinin incelenmesidir.

Yöntem: Bu prospektif çalışmada hipovasküler ve hipervasküler tiroid nodülleri olan 60 hasta değerlendirilmiştir. Renkli Doppler sonografik yönlendirme altında 22 numara iğne ile jet iğne biyopsisi gerçekleştirilmiştir. Radyolojik ve sitolojik faktörler ve numunelerin yeterliliği değerlendirilmiş ve karşılaştırılmıştır.

Bulgular: Sonografik olarak 25 nodül (%41.7) heterojen ve kalsifiye, 21 nodül hipoekoik (%35), 10 nodül izoekoik (%16.7) ve 4 nodül (%6.6) hiperekoik olarak tanımlanmıştır. Yalnızca hipervasküler ve hipovasküler nodüller değerlendirildiğinde yeterli örneklem oranı %81.7 ve %83.3 olarak ölçülmüştür. Her iki grup beraber değerlendirildiğinde toplam yeterli örneklem oranı %91.7 olarak bulunmuştur. Örneklerde endotelial hücrelerin bulunmasının ya da bu hücrelerin dağılımının prosedürün teşhis değerini etkilemediği görülmüştür.

Sonuç: Elde ettiğimiz sonuçlara göre renkli Doppler sonografisi ile tiroid nodüllerinin vaskülaritesinin incelenmesinin jet iğne biyopsisinin etkinliğini optimize edebileceği görülmüştür. Hipovasküler ve hipervasküler bölgelerde yapılan biyopsiler birbirini tamamlayıcıdır ve bu verilerin birlikte kullanılması teşhis doğruluğunu arttırmaktadır.

Anahtar sözcükler: Tiroid, nodül, tanı, ultrason, ince iğne aspirasyonu, renkli Doppler.

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Fine-needle aspiration biopsy (FNAB) is routinely used to evaluate nodular thyroid disease. Cytological outcome may be important for selection of the optimal treatment approach. However, since the results of blind FNAB are often inconclusive, ultrasound guided fine-needle aspiration (UG-FNA) is accepted as the least invasive and most accurate method for identification of the nature of thyroid nodules.^[1-3] The aim is to obtain the most cellular specimen that represents the target nodule during FNAB. In the literature, UG-FNA specimen cellularity ranges from 66.4% to 96.6% depending on the different specimen obtaining techniques.^[4] Even though the rate of specimen inadequacy with UG-FNA is lower than that of palpation-guided aspiration, rate of inadequacy is still about 10–20% of all procedures.^[5] Color Doppler sonography (CDS) can be used to identify the perinodular and intranodular vessels, to obtain a safe access site and to minimize the amount of blood in the aspirate during FNAB.^[1-3] For nodules consisting solid and cystic components placement of the needle into the solid part may provide aspirates with higher cellularity, resulting in a better diagnosis. The FNAB is a simple, well-known and practical intervention but the question where to place the needle tip with regard to the vascularity of the nodule during aspiration remains to be elucidated.^[2,4-6]

This study was designed to investigate whether the hypervascular site or the hypovascular site of a solid thyroid nodule reveals more cellular aspirates when UG-FNA is performed under CDS guidance.

Materials and Methods

The local institutional review board approved the study protocol and informed consents were obtained from all the patients included in the study. This prospective, clinical study included 60 consecutive euthyroid patients referred for UG-FNA for the first time in two centers (Kelkit Government Hospital, Gümüşhane, and Istanbul Dr. Lütfi Kırdar Kartal Training and Research Hospital, Istanbul). Between March 2012 and March 2013, a total of 60 cases with solid thyroid nodules >10 mm with clear distinction between the hypervascular and hypovascular sections were investigated prospectively. Nodules smaller than 1 cm were excluded since discrimination of hyper- and a hypovascular zones via Doppler US was not feasible for such lesions. Nodules that did not reflect any signals under power and color Doppler US were termed as “hypovascular zone”, while those which reflect signals were described as “hypervascular zone”. Nodules that have completely cystic,

necrotic or degenerated structure, and nodules containing >25% cystic component were excluded from the study population. Patients with subsequent UG-FNAB due to inconclusive specimens were excluded from the study. The size of each nodule was recorded on the basis of its longest diameter in the axial plane. The biggest dimensions of the nodule in transverse and longitudinal planes, and lymph nodes in bilateral jugular lymph nodes were recorded.

Imaging and UG-FNAB

Patients referred for UG-FNA of thyroid nodules to the radiology department of a state hospital were designated as study group. All patients were examined with the same Toshiba Applio XV device (Toshiba Medical Systems®, Tokyo, Japan) and by the same physician (E.C.). For the linear transducer the axial resolution was 0.5 mm, the lateral resolution was 1 mm, the maximum field of view was 39 mm, and the maximum depth of penetration was 8–10 cm.

All the biopsies were obtained under CDS guidance with the same technique. The patient was kept in supine position with the neck extended. After the localization of the nodule and cleansing of the overlying skin with iodine, a total of two passes and aspirations (one from the hypovascular and one from the hypervascular sites) were performed for FNAB.

Aspiration material obtained was puffed on stage and was gently spread with the mild pressure of a second stage. All smears were fixed in 95% ethanol and stained with hematoxylin and eosin. “Parallel position technique” for placement of the needle and subsequent vacuum aspiration were generally preferred in all procedures. Aspiration of 1 ml of air was made into the syringe prior to the access into the nodule. Afterwards, the tip of the needle was pushed into the hyper or hypovascular zone of the nodule. After proper positioning within the nodule, the needle was pushed back and forth under negative pressure. One aspiration for each site has been performed and the materials were maintained within the needle rather than the syringe.

For obtaining the hypovascular aspirate, the needle tip was located at least 10 mm to the nearest vessel and as close to centre of the nodule as possible. In the hypervascular site, the needle tip was placed in the most hypervascular part of the nodule and as close as possible to the blood vessels but without making an intravascular sampling.

The first pass for fine-needle aspiration was made from the hypovascular site with 22-gauge needle to avoid inconclusive results. When the needle was put in the target site, aspiration process was maintained until the aspirate materi-

al reached the hub. The second pass was performed on the hypervascular site with a 22-gauge needle to avoid haemorrhage of the vessels in the vicinity the hypervascular site.

All interventions were made in the outpatient department without an accompanying cytopathologist. No complications such as vascular injury, hematoma and recurrent laryngeal nerve paralysis have been encountered.

Histopathological Evaluation

The methods of classifying FNAB outcomes into categories were based on the guidelines formulated in the Bethesda system for reporting thyroid cytopathology.⁴ After a total of two samples were obtained, the smears were air-dried and stained with May-Grünwald-Giemsa (MGG) stain. Cytological evaluation parameters were cellularity, cluster formation and distribution of endothelial cells. Scoring was made with respect to the number of cell groups as follows:

- **Score 1:** the number of cell groups less than 5: inadequate specimen,
- **Score 2:** the number of thyrocyte groups between 5 to 10,
- **Score 3:** specimens with more than 10 cell groups.

Endothelial cells were classified as either randomly scattered single endothelial cells (scored as 1), or groups of endothelial cells (scored as 2). Echogenicity of the solid portion was categorized as hyperechoic, isoechoic, hypoechoic or heterogeneous and calcified (punctate echogenic foci of 1 mm or more, combined with eggshell or macrocalcification). Cytological results were class as “adequate” or “inadequate” for the interpretation of cytological evaluation. A specimen was considered to be “adequate” if there were at least six groupings of well-preserved thyroid cells consisting of ten cells per group. The “adequate” group was divided into two subgroups which were “benign” and “malignant”. “Benign” cytology included colloid nodules, nodular hyperplasia, lymphocytic thyroiditis, Graves’ disease, and postpar-

tum thyroiditis. Cytological results were designated as “malignant” when specimen revealed abundant cells with definite cytological features of malignancy.

Cytological analysis was routinely performed by the same pathologist with experience in thyroid pathology (D.E.) who was blinded to both the patient data and the site of biopsy (hypovascular or hypervascular). Cytological and sonographic features of aspirates obtained from hypo- and hypervascular sites were compared.

Statistical Analyses

Data were analyzed using the Statistical Package for Social Sciences 19.0 for Windows (SPSS Inc., Chicago, IL, USA). Parametric tests were applied to data of normal distribution and non-parametric tests were applied to data of questionably normal distribution. Kappa analysis was used to compare groups. Data were expressed as mean±SD or median (interquartile range), as appropriate. All differences associated with a chance probability of .05 or less were considered statistically significant.

Results

Sixty nodules in 60 patients (49 females, 11 males) with a mean age of 48.8±13.9 (range: 19 to 71) years were included in the study. Nodule characteristics were hypoechoic (n=21, 35%), isoechoic (n=10, 16.7%), hyperechoic (n=4, 6.7%), and heterogeneous and calcified (n=25, 41.6%). Mean nodule diameter was 35.8 mm (range: 20 to 100 mm).

Aspirates obtained from the hypervascular site revealed benign cytology in 35 patients (58.3%) and malignant cells indicative of papillary carcinoma in 14 (23.3%) cases. In 11 cases (18.3%), the specimens did not contain adequate number of cells for pathologic assessment (Table 1). Adequate sampling was limited to 81.7% (49/60) of the cases when only hypervascular site was used.

Table 1. Distribution of cytological sample features.

Histopathological interpretation	Hypervascular	Hypovascular	Together
Benign	35 (58.3%)	39 (65%)	41 (68.3%)
Malignant	14 (23.3%)	11 (18.3%)	14 (23.3%)
Inadequate	11 (18.3%)	10 (16.7%)	5 (8.3%)
Endothelial cells in clusters	24 (40%)	32 (53.3%)	32 (53.3%)
Smear cellularity score	1	11 (18.3%)	6 (10%)
	2	16 (26.7%)	11 (18.3%)
	3	33 (55%)	43 (71.7%)

Samples derived from the hypovascular site had benign cytology in 39 patients (65%) and malignant cells reminiscent of papillary carcinoma in 11 (18.3%) cases. In 10 cases (16.7%), the specimens did not contain sufficient number of cells available for pathological evaluation (Table 1). Adequate sampling was limited to 83.3% (49/60) of the cases when only hypervascular site was taken into account.

When both sites were evaluated together, overall adequate sampling was 91.7% (55/60). The yield was 81.7% for hypervascular site and 83.3% for hypovascular site. Interestingly, when results from both areas were combined, the yield was 91.7%.

Rate of inadequacy was 16.7% in the hypovascular group and 18.3% in hypervascular group. The difference between adequate and inadequate samples was in moderate agreement for hypovascular and hypervascular groups. Overall agreement rate was 70.9% (Kappa value = 0.7152; 95% CI: 0.284–0.614). Rate of inadequacy was decreased and smear cellularity scores were improved significantly when both hypo- and hypervascular site aspirates were evaluated together.

In hypovascular group, clusters of endothelial cells were observed in 53.3% (32/60) of the cases, whereas in hypervascular group, endothelial cell groups were observed in 40% (24/60) of the cases. The higher number of endothelial cell groups in hypovascular group seems not to influence the cytology scores.

Of the 60 thyroid nodules, 13 (21.7%) were found to be malignant and 47 (78.3%) were supposed to be benign according to FNAB results. The mean size of the malignant nodules was 24.3 ± 11.7 (range: 20 to 44) mm and the mean size of the benign nodules was 21.2 ± 10.2 (range: 10 to 47) mm ($p=0.773$).

The mean age of the patients with benign nodules was significantly older than that of the patients with malignant nodules (53.6 ± 9.8 yrs vs. 42.4 ± 11.8) ($p=0.024$).

Discussion

Thyroid nodules are common problems that can be detected in up to 60% of the general population by ultrasound.^[1-3] Assessment of patients with thyroid nodules can be initially made by FNAB, which has been proven to be a practical, cost-effective, and safe method of investigation.^[2-7] Fine-needle aspiration biopsy was initially performed by Cardozo and Soderstrom, but it has gained popularity in 1980s.^[8-10]

Ultrasound (US) imaging is an important procedure in the follow-up of patients with focal lesions in the thyroid

gland. Fine-needle aspiration biopsy is especially useful for posterior localized and small nodules, where diseases like Hashimoto thyroiditis or Graves disease interfere with determination of the lesion. A significant increase of lesion size and occurrence of features suggestive of malignancy are among relevant factors suggesting the necessity of control FNAB or even of surgical treatment. Adequate clinical interpretation of the observed changes in the US image of examined lesions requires information on all diagnostic or therapeutic procedures which were performed between control examinations.^[3,4,6]

The use of imaging guidance in FNAB of thyroid nodules is important, since it permits the safe passage of the needle. Thyroid nodule vascularity can be easily detected with CDS while performing UG-FNA, demonstrating the relative position of needle tip to the vessels.^[11,12] Our results indicate that FNAB attempts made through the hypovascular and the hypervascular site of a solitary nodule will provide more cell groups for the pathological assessment. In other words, aspirates obtained from the hypovascular and hypervascular sites serve as complementary and they should be performed consecutively. In addition, number of endothelial cells in the site aspirates does not alter the cytology score of the nodule.

Successful percutaneous needle biopsy has been applied to most organ systems with excellent results and few complications.^[3-5] The biopsy guidelines for masses other than thyroid recommend sampling the solid and viable parts of the tumor instead of cystic, necrotic or more sclerotic parts.^[13,14] Sites of biopsy in a tumor may reveal various cellular components. The relative high rates of inadequacy in our series may be attributed to the fact that we had made only one attempt of FNAB for a hypo or hypervascular zone. In the literature, up to 2 to 5 interventions for FNAB of a nodule have been reported.^[2,3,5]

Cystic and necrotic components of a neoplasm may yield inadequate biopsy material. In general, the viable part of a tumor is usually preferential over a necrotic or cystic part as a biopsy site. Thyroid nodules larger than 10 mm in size are frequently vascular and the increase in vascularity is usually related to the cellular proliferation in a neoplastic condition.^[8] Papillary thyroid carcinomas are reported to have some intrinsic blood flow and a completely avascular nodule is unlikely to be malignant.^[15,16] Whether sampling from the hypervascular part of a thyroid nodule would yield better cytologic results is under debate. In this study, nodules larger than 1 cm were

included to demonstrate the hypo- and hypervascular sites separately. Degirmenci et al. reported that the highest rate of adequacy was observed in nodules smaller than 1 cm, and the lowest rate was observed among nodules larger than 3 cm. They suggested that the lower rate in larger nodules may have resulted from increased vascularity which subsequently causes blood staining of the material acquired at fine-needle biopsy.^[5] Aspirates taken with thicker needles are more likely to contain blood and this makes microscopic evaluation difficult. Contradictory data exists for the size of needle to be used for FNAB. Some authors have stated that material cellularity was satisfactory for samples obtained with 21–25 or 23–27 gauge needles.^[17,18] In contrary, Rausch and Ravetto have indicated that 25 gauge or thinner needles would be more appropriate for FNAB of hypervascular lesions.^[2,19]

In our series, we noted that if the aspirate is obtained only from the hypervascular part of a nodule, adequate sampling is 81.7%. Our findings demonstrate that blood staining may be avoided by using CDS guidance during aspiration that allows appropriate selection of the aspiration site and avoidance of intravascular sampling. Thus, we state that CDS guidance should be used to avoid intravascular sampling during FNAB.

The use of color Doppler “mapping” of the nodule immediately before the FNAB helps to identify the larger blood vessels to be avoided during the procedure to reduce the amount of blood in the aspirate.^[6,7,11] The CDS assessment of the nodule vascularity may be useful to optimize sampling two clinical settings.^[5–7] Bloodstained material, which makes microscopic evaluation more difficult, is seen more often when aspiration is performed with thicker needles.^[3,5] However, there are studies that no significant difference in diagnostic yield was found between cellular specimens obtained with different needles from 23-to 27-gauge.^[15,16] Some authors have suggested the use of a 25-gauge or thinner needle for biopsy of markedly hypervascular nodules of the thyroid.^[1,17] In this study, a thin needle was preferred to avoid traumatic haemorrhage within the nodule, and the tip was kept still while performing aspiration. In our study we performed the biopsies from hypervascular zones by using a 22-gauge needle in order to avoid cellular injury and minimize bloodstaining. Fine-needle aspiration biopsies from hypovascular zones were taken by 22-gauge needles to overcome inadequacy of the sample. The similarity of adequacy rates for both hyper and hypovascular zones in our series confirm the suitability of our selection of needle size.

Specimen adequacy is supposed to be independent of the vascularity and echogenicity of the sampled thyroid nodule, but on components such as cystic change, calcification, and fibrosis.^[3,4,18] While performing FNAB, areas of fibrosis, calcification, and cystic degeneration should be avoided. If the target lesion consists of cystic part and/or mixed components, aspiration should be performed from the solid part.^[2,8,18,20]

Gharib stated that an accompanying cytopathologist during FNAB procedure can allow simultaneous evaluation of the aspirate in terms of adequacy and decrease the necessity for repeated biopsies.^[21] In contrast, O'Malley suggested that adequacy of the material was not affected by the presence of a cytopathologist during the intervention.^[22]

Sonographic features suggesting malignancy include hypoechogenicity, irregular or microlobulated margins, calcifications, greater length than width, intranodular vascularity, solitary presence and solid components.^[1,7,23,24] However, none of the features have sufficiently high positive predictive value to obviate the necessity for USFNA. It is widely accepted that, most nodules exceeding 1 to 1.5 cm in maximum diameter should be further evaluated by USFNA, regardless of physical and sonographic features.^[2,4,18] The overall incidence of cancer in patients with thyroid nodules selected for FNAB is approximately 9.2–13.0%, no matter how many nodules are present at US.^[3,7] In our series, the 23.3% of cases were presumably malignant, and this high rate may develop from the endemic high prevalence of thyroid pathologies including malignancies. Another aspect to be kept in mind is that, we have included nodules >1 cm, excluding smaller and more innocent nodules in this study.

A predominantly solid nodule, hypoechogenicity, microcalcification, ill-defined margins, intranodular vascularity, and taller-than-wide shape have all been associated with increased risk of malignancy, but no single US characteristic is sufficiently sensitive or specific to exclude or diagnose malignancy by itself. However, the use of combinations of US characteristics to stratify nodules into high- and low-risk for malignancy appears to be a promising strategy.^[3]

In our series, UG-FNAB seems to be a quite safe diagnostic modality. No significant complications or interruption of the procedure due to vasovagal syncope or hypotensive reaction were noted. However, several limitations of our study should be mentioned. First, our sample size was relatively small. Second, distinguishing the solid and cystic components in mixed echoic nodules may be challenging and measurement of the solid component can be difficult.

All in all, CDS may improve FNAB biopsy yield by enhancement of the determination of the appropriate site for biopsy. Determination of the thyroid nodule vascularity can be made with CDS. Obtaining the cytological aspirates from the hypovascular and hypervascular sites of solid nodules under US guidance should be performed consecutively for obtaining higher number of cell groups.

Conflict of Interest: No conflicts declared.

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