

BRIEF REPORT

Ultrasound Criteria of Malignancy for Cervical Lymph Nodes in Patients Followed Up for Differentiated Thyroid Cancer

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Context: Neck ultrasonography (US) has become a keystone in the follow-up of patients with differentiated thyroid cancer.

Objective: The aim of this study was to determine specificity and sensitivity of ultrasound criteria of malignancy for cervical lymph nodes (LNs) in patients with differentiated thyroid cancer.

Design: We prospectively studied 19 patients referred to the Institut Gustave Roussy for neck LN dissection. All patients underwent a neck US within 4 d prior to surgery. Only LNs that were unequivocally matched between US and pathology were taken into account for the analysis.

Results: One hundred three LNs were detected on US, 578 LNs were surgically removed, and 56 LNs were analyzed (28 benign and 28 malignant). Sensitivity and specificity were 68 and 75% for the long

axis (≥ 1 cm), 61 and 96% for the short axis (> 5 mm), 46 and 64% for the round shape (long to short axis ratio < 2), 100 and 29% for the loss of fatty hyperechoic hilum, 39 and 18% for hypoechogenicity, 11 and 100% for cystic appearance, 46 and 100% for hyperechoic punctuations, and 86 and 82% for peripheral vascularization.

Conclusion: Cystic appearance, hyperechoic punctuations, loss of hilum, and peripheral vascularization can be considered as major ultrasound criteria of LN malignancy. LNs with cystic appearance or hyperechoic punctuations are highly suspicious of malignancy. LNs with a hyperechoic hilum should be considered as benign. Peripheral vascularization has the best sensitivity-specificity compromise. Round shape, hypoechogenicity, and the loss of hilum taken as single criteria are not specific enough to suspect malignancy. (*J Clin Endocrinol Metab* 92: 3590–3594, 2007)

NECK ULTRASONOGRAPHY (US) has replaced radioactive iodine in the follow-up of patients with differentiated thyroid cancer (DTC) (1, 2). Sensitivity of US for the diagnosis of neck recurrence ranges from 70 to 100% (3–5). Metastatic lymph nodes (LNs) tend to be large, round, hypoechoic, and hypervascularized with a loss of hilar architecture (6–13). In DTC, metastatic LNs may also demonstrate specific features such as hyperechoic punctuations or microcalcifications and cystic appearance (14–16). The specificity of these US criteria in DTC is, however, not well known and difficult to assess on follow-up only because of the indolent nature of DTC. Specificity of US criteria based on pathology are, in fact, not available in DTC. Confirmation of malignancy of suspicious LN found on US is usually recommended and consists in a fine-needle aspiration biopsy (FNAB) for cytology and thyroglobulin determination in the aspirate fluid (17). There is a need for specific criteria of malignancy; otherwise, a majority of DTC patients will be

submitted to FNAB, a stressful examination with potential morbidity.

We therefore assessed both sensitivity and specificity of US criteria based on pathology in patients planned to neck LN dissection for DTC neck recurrence.

Patients and Methods

Patients

Patients referred to the Institut Gustave Roussy from February 2004 to January 2005 for surgical treatment of a neck recurrence of DTC were enrolled in this prospective study. Our institutional review board approved the study, and all patients gave written informed consent.

Ultrasonography

All patients underwent US within 4 d prior to surgery. US was performed by a single experienced radiologist, trained in neck US (E.G.), with a high-resolution ultrasound system (Aplio ultrasound machine; Toshiba Medical, Puteaux, France) equipped with a high-energy linear probe of 14 MHz (PZT; Toshiba), allowing to work in fundamental B-mode (lateral resolution: 0.17 mm; axial resolution: 0.11 mm) and in power Doppler mode (rate of 12 frames/sec, limit detection of 5 cm/sec with a pulse repetition frequency (PRF) of 17 KHz).

US examination included both central and lateral neck compartments. For each LN detected with a short axis of 2 mm or more, eight ultrasound criteria were assessed (Fig. 1): long axis, short axis (perpendicular to the long axis), round shape (defined as a long to short axis ratio of less than 2), loss of the fatty hyperechoic hilum, hypoechogenicity (by comparison with surrounding muscles), cystic appearance, hyperechoic punctua-

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Abbreviations: DTC, Differentiated thyroid cancer; FNAB, fine-needle aspiration biopsy; LN, lymph node; US, ultrasonography.

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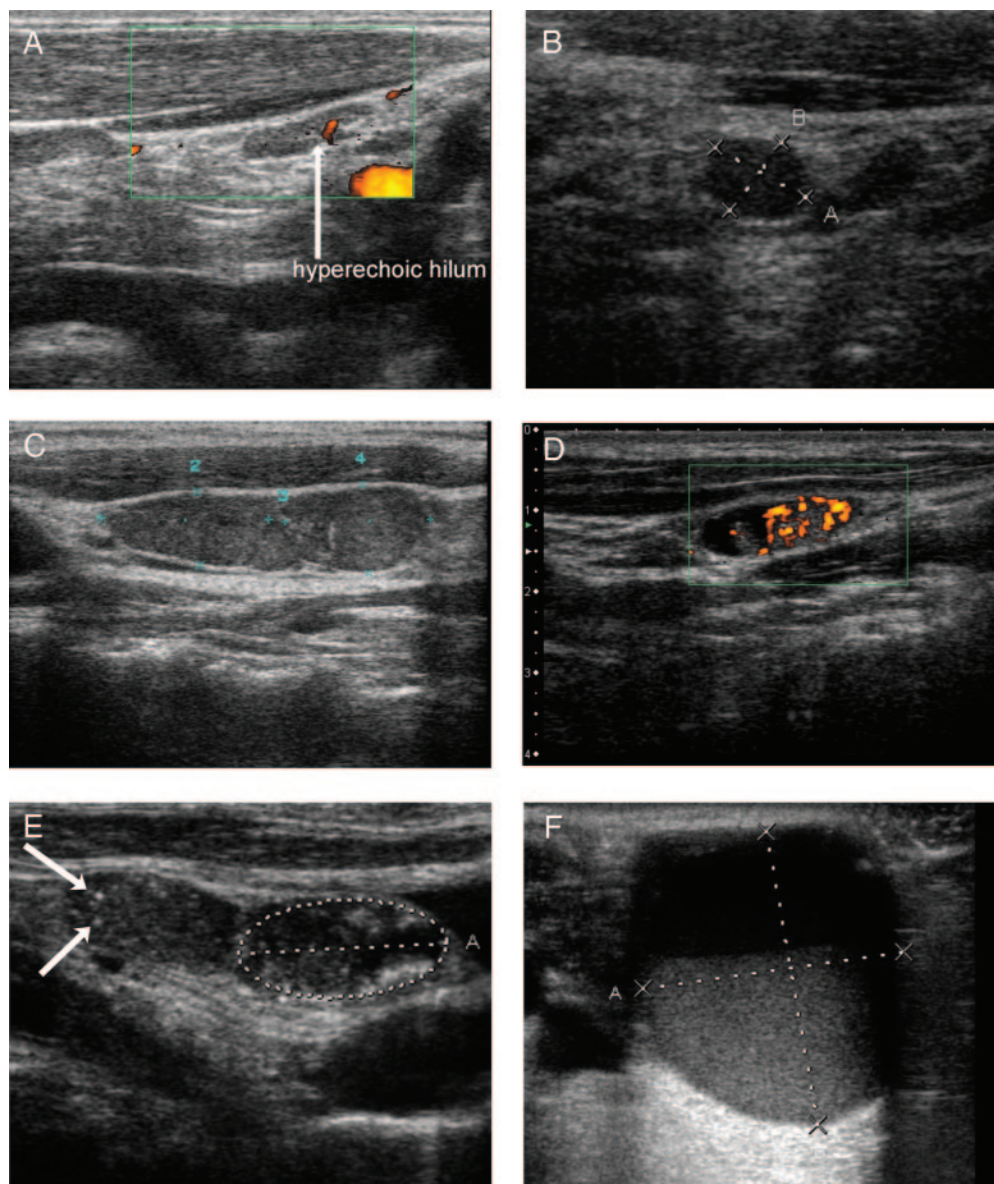


FIG. 1. Benign LN with a hyperechoic hilum and a central vascularization (A), round shape hypoechoic LN (B), LN without its hyperechoic fatty hilum (C), LN with peripheral and central vascularization (D), LN with hyperechoic punctuations (E), and LN with a cystic appearance (F)

tions (due to colloid or to microcalcifications), and peripheral vascularization either associated with central vascularization or not. All LNs were reported on a diagram.

Surgery

The surgical procedure included a dissection of the central neck (level VI). Depending on previous surgery and the location of the recurrent disease, an ipsilateral neck dissection of levels III–IV was performed. In case of bilateral tumor, a bilateral neck dissection was performed. The dissection was extended to the level II and V in case of metastases of the levels III–IV on frozen section. Surgery was macroscopically complete in all cases. Surgical specimens of the compartments III–IV were transmitted en bloc; tagged at the upper end; and separated from the surgical specimens of the compartment VI, II, and V.

Pathological diagnosis

Pathological diagnosis was confirmed by a single pathologist (B.C.). Patients were classified according to the 2002 pathological tumor node metastasis

(pTNM) scoring system. Two-millimeter sections of each LN without apparent metastasis were routinely performed. In case of macroscopic metastasis, fewer sections were performed. Pathological findings of each operated compartment were reported on the same diagram as the one used by the ultrasonographer. The pathologist was blinded to the neck US results.

US and pathology correlation

To match each LN found at pathological examination to the corresponding node on US, we took into account its location, shape, and size. Only LNs that were matched without any doubt between US and pathology were taken into account. Multiple LNs in a given neck level on US were taken into account only if all LNs of the compartment were either benign or malignant.

Statistics

The sensitivity and specificity of ultrasound criteria were calculated for the diagnosis of malignancy, on a per-node analysis, in relation to the pathological results considered as the reference standard.

Results

Patients

Nineteen patients were enrolled (six males, 13 females; mean age 44 yr, range 24–70 yr). DTC were classified as papillary and well-differentiated follicular carcinomas in 18 and one patient, respectively. Previous surgical treatment included total thyroidectomy in all patients without any neck dissection in four, with central neck dissection in 12 and lateral neck dissection in 11 patients (seven ipsilateral and four bilateral). Therapeutic radioactive iodine had been given to 17 patients. The suspicion of neck recurrence was based on previous abnormal ultrasonography (three patients) or abnormal radioactive iodine total body scan (16 patients). TSH stimulated thyroglobulin level was elevated in 13 patients (range 2–202 $\mu\text{g/liter}$). Mean time between initial thyroidectomy and surgery for recurrence was 36 months (range 4–183 months; median 14 months).

Surgery

Dissection of level II was performed seven times, level III-IV 25 times, level V four times, and level VI 19 times. The mean number of LNs resected per patient was 30 (range 2–70; median 29). Surgery removed 578 LNs among which 113 were metastatic. The number of metastatic LNs of the levels II, III-IV, V, and VI was six, 55, none, and 52, respectively.

US

US detected LNs in 18 patients. The mean number of LNs detected per patient was six (range two to 28; median four). Overall, 103 LNs were detected and were located in levels II (two), III-IV (69), V (18), and VI (14). The mean long and short axes were 10 mm (range 3–37; median 8 mm) and 5 mm

(range 2–32; median 4 mm), respectively. Ultrasound criteria of the detected LNs are shown in Table 1.

Ultrasound criteria of malignancy

There were 56 neck LNs for which US and pathological results could be undoubtedly matched. Based on pathology, the 56 LNs were classified as benign and malignant in 28 and 28 cases, respectively. They were located in level II (two cases), level III-IV (32 cases), level V (13 cases), and level VI (nine cases). Their mean long and short axes were 10 mm (range 3–37; median 9 mm) and 6 mm (range 2–32; median 4 mm), respectively. Of note, 45% (30 of 66) of the LNs of less than 1 cm and 70% (26 of 37) of the LNs of 1 cm or more were correctly identified. Their ultrasound criteria are given in Table 1.

Sensitivity and specificity of the US criteria are shown in Table 1.

Discussion

Neck US is highly sensitive for the diagnosis of neck recurrence of DTC. The specificity reported varies from 90 to 100% (3–5). However, most studies did not take into account indeterminate US results for which follow-up US or even FNAB finally demonstrate benign LNs.

This study is, to our knowledge, the first to assess specificity of LN US criteria in patients with DTC based on pathology. Biases have to be quoted. First, the study was performed on patients with known residual disease. Second, patients had been previously treated (radioactive iodine, surgery), which may have modified the sonographic appearance of the LN. Third, the diagnosis of recurrence was based on US results in three of the cases.

TABLE 1. US criteria of LN

| | All LNs detected on US, n = 103 (%) | LNs with US matched to pathology, n = 56 (%) | No. of malignant LNs based on pathology/no. of LNs with US matched to pathology | Se% (95% CI) | Sp% (95% CI) |
|--|-------------------------------------|--|---|--------------|--------------|
| Long axis | | | | | |
| Less than 1 cm | 66 (74) | 30 (54) | 9/30 | 68 | 75 |
| 1 cm or greater | 37 (36) | 26 (46) | 19/26 | (48–84) | (55–89) |
| Short axis | | | | | |
| ≤ 5 mm | 73 (71) | 38 (68) | 11/38 | 61 | 96 |
| > 5 mm | 30 (29) | 18 (32) | 17/18 | (41–78) | (82–100) |
| L/S | | | | | |
| Two or more | 52 (50) | 33 (59) | 15/33 | 46 | 64 |
| Less than 2 | 51 (50) | 23 (41) | 13/23 | (28–66) | (44–81) |
| Hyperechogenic hilum | | | | | |
| Present | 11 (11) | 8 (14) | 0/8 | 100 | 29 |
| Absent | 92 (89) | 48 (86) | 28/48 | (88–100) | (13–49) |
| Hypoechoogenicity | | | | | |
| No | 39 (48) | 22 (39) | 17/22 | 39 | 18 |
| Yes | 64 (62) | 34 (61) | 11/34 | (22–59) | (6–37%) |
| Cystic appearance | | | | | |
| No | 100 (97) | 53 (95) | 25/53 | 11 | 100 |
| Yes | 3 (3) | 3 (5) | 3/3 | (2–28) | (88–100) |
| Hyperechogenic punctuations | | | | | |
| Absent | 84 (82) | 43 (77) | 15/43 | 46 | 100 |
| Present | 19 (18) | 13 (23) | 13/13 | (28–66) | (88–100) |
| Presence of a peripheral vascularization | | | | | |
| No | 66 (64) | 27 (48) | 4/27 | 86 | 82 |
| Yes | 37 (36) | 29 (52) | 24/29 | (67–96) | (63–94) |

L/S, Long to short axis; Se, sensitivity, presence of the criterion in the presence of disease; Sp, specificity, absence of the criterion in the absence of disease.

Fourth, to match US characteristics to pathological results, we analyzed only half of the LNs detected on US, and LNs larger than 1 cm were more frequently analyzed. Finally, because of the limited number of LNs analyzed, it was not possible to combine US criteria. We, however, assessed both sensitivity and specificity of eight different US criteria.

In accordance with previous studies, we found a very high specificity (100%) and a low sensitivity (46 and 11%, respectively) for hyperechoic punctuations and cystic appearance (14–16). Hyperechoic punctuations or microcalcifications in LNs are characteristic of DTC because they seldom exist in metastatic LNs from other cancers. Differential diagnosis of cystic LNs includes lymphocele, branchial cyst, tuberculous lymphadenitis, and squamous cell carcinoma. Given these high specificities, all LNs with hyperechoic punctuations or a cystic appearance in a patient followed up for DTC should be considered as malignant.

With a specificity of 18, 29, and 54%, respectively, hypoechogenicity, loss of hyperechoic hilum, or shape were not specific enough to assess malignancy. Of note, LNs in normal individuals of the parotid and submandibular regions are often round (18). The specificity of the round shape is in fact linked to the long axis (6, 8). Similarly, the absence of fatty hilum is often seen in normal individuals, especially in young subjects and LNs located in level V (19). Interestingly, we found a sensitivity of 100%, indicating that the persistence of a fatty hilum is a major criteria that excludes malignancy. We found for hypoechogenicity a lower sensitivity than previously reported, which might be due to the systematic pathologic study of LNs, independently from US criteria (16).

The short axis has also been a malignancy criterion proposed with various cutoffs, depending on the LN location (11, 13). With a cutoff of 5 mm, we found a specificity as high as 96%, with an intermediate sensitivity of 61%, indicating that LNs with a short axis of less than 5 mm do not need FNAB, in accordance with recent recommendations (20).

Hilar or central vascularization of the LN is normal. In contrast, capsular or peripheral vascularization, either associated or not with central vascularization, is an US criterion for malignancy. In our study, the pattern of vascularization had the best sensitivity-specificity compromise (86 and 82%, respectively), making essential the use of Doppler in the follow-up of DTC, as it is for other cancers (9, 12, 13).

Given these results, we can define LNs needing FNAB. LNs with fatty hilum are benign and LNs with an absence of hilum should be carefully examined with Doppler to evaluate its vascularization pattern. Peripheral vascularization is suspicious and should lead to FNAB. A round shape, hypoechogenicity, the absence of hilum, and a short axis of 5 mm or less, as single criteria, are not specific enough to justify systematic FNAB. Finally, LNs with either a cystic appearance or hyperechoic punctuations in a patient with DTC should be considered as metastatic disease. Whether these LNs need systematic FNAB depends on the risk of recurrent disease of each patient, defined by

previous treatment, tumor characteristics, and thyroglobulin level. The location of the LN should also be taken into account because most of the metastases are found in the compartments III-IV and VI. However, because we analyzed only a small number of LNs, larger studies are needed to better identify combined US criteria for malignancy.

In conclusion, cystic appearance, hyperechoic punctuations, absence of a hilum, and peripheral vascularization can be considered as major ultrasound criteria of LN malignancy. US in DTC patients should therefore associate gray-scale and power Doppler imaging. The use of specific ultrasound criteria of malignancy of neck LN should prevent patients from undergoing unnecessary FNAB.

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The authors have nothing to declare.

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