B-FLOW TWINKLING SIGN IN PREOPERATIVE EVALUATION OF CERVICAL LYMPH NODES IN PATIENTS WITH PAPILLARY THYROID CARCINOMA

INTRODUCTION

Papillary thyroid carcinoma is the most common histologic type of differentiated thyroid cancer and accounts for 80% of all thyroid cancers [1, 2]. The disease-specific survival rate of papillary thyroid carcinoma is excellent but its recurrence rate is high [2-4]. Therefore, preoperative evaluations of the extent of the primary tumor and the presence of lymph node metastasis are crucial for optimal treatment to reduce the recurrence rate.

Incidence

Papillary thyroid cancer (PTC) is the most common form of differentiated thyroid cancer, comprising approximately 90% of the 44,670 estimated new cases of thyroid cancer in the United States in 2010 [1]. The disease-specific survival rate of PTC is excellent and may exceed 90% at 10 years, but its recurrence rate is more than 30% [5-7]. PTC and the follicular variant of PTC have a propensity for cervical lymphatic spread that occurs in 20% to 50% of patients on standard review of surgical pathologic specimens and in 90% of those examined for micrometastases [3,4]. The spread of tumors cells occurs in a predictable pattern that initiates in the perithyroidal lymph nodes (LNs) of the central neck and progresses to the LNs of the lateral cervical compartments and the superior mediastinum [8,9]. "Skip" metastases to the lateral compartment without central neck nodal involvement are rare but do occur [8,9]. Patients with nodal metastasis have higher rates of persistent and recurrent disease during postoperative surveillance [9]. Furthermore, lymph node metastasis has also been identified as a risk factor for distant metastasis. The impact of nodal metastasis on overall survival remains debatable; several studies have demonstrated no difference in mortality, while two large population-based studies have shown increased mortality in patients with regional LNs metastasis [10-14].

Detection of Nodal Metastasis

Several studies have shown that ultrasonography has higher sensitivity than palpation and the other diagnostic methods for the detection of cervical metastatic LNs in patients with PTC [15-18]. High resolution ultrasonography can detect cervical nodal metastasis in 14% to 20% of PTC patients and can detect pathologic nodes as small as 2 to 3 mm without radiation exposure [19,20]. Ultrasound is also easily repeatable and has been shown to change the surgical procedure performed in 39% of thyroid cancer patients. [21,22]. A dedicated cervical ultrasound to include nodal levels II–VI should be performed, to detect nonpalpable LNs metastases in patients undergoing surgical evaluation for any thyroid nodule. The sensitivity of cervical ultrasound to detect pathologic LNs in PTC patients is higher in the lateral neck (94%) than in the central neck (53% to 55%), and this disparity may be considered as additional support for prophylactic central neck dissection [23].

Metastatic LNs tend to be large, round, hypoechoic, and hypervascularized with a loss of hilar architecture (24-31). In differentiated thyroid cancer, metastatic LNs may also demonstrate specific features such as hyperechoic punctuations or microcalcifications and cystic appearance (32-34). 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 (35). However, the US criteria for metastatic LNs are controversial (36,37).

In patients with suspected mediastinal disease or with bulky cervical lymphadenopathy, cross-sectional imaging with CT should be considered as it can aid in the planning of nodal dissection and often identify as pathologic level VI and VII lymph nodes within the superior mediastinum that are not detected on cervical ultrasound or physical examination.

BFI

B-flow imaging (BFI) is a non-Doppler technique widely used to evaluate carotid artery stenosis and other vascular diseases [38, 39]. The main advantage of this technology lies in the direct visualization of blood reflectors without the limitations of conventional Doppler technology; this is extremely useful in the assessment of complex hemodynamics.

Recent works [40] had applied the BFI technique for evaluation of thyroid nodules. BFI can identify a new sign (the twinkling sign; BFI-TS) in "suspect" PTC nodules, which appeared to be generated by microcalcifications and increase the US accuracy in identification of malignant nodules.

The BFI-TS is a rapidly flashing white light behind such stationary objects as microcalcifications, which gives the appearance of movement.

When an incidental sonographic beam impinges a rough interface composed of sparse reflectors, the sign is generated by the phase shift, thereby causing a faint variation of the sonographic beam at the interface. The sign is also caused by the increase of pulse duration, which results in multiple reflections in the medium. In thyroid nodules these rough interface were the microcalcifications formed from aggregates of primary psammoma bodies (PBs); they consist mainly of highly reflecting crystalline aggregates of calcium [41].

The same features described in thyroid nodules, represented by microcalcifications and colloid crystals are also present in lymph node metastases.

SURGICAL MANAGEMENT

Technique

Central neck dissection is the most common neck dissection completed for patients with PTC and can be performed safely and effectively with low complication rates by experienced surgeons. Therapeutic central neck dissection is recommended for all patients with clinically evident disease. Prophylactic central neck dissection should be considered in order to provide more accurate staging in high-risk patients.

Cervical nodal dissection for PTC should include a systematic or *en bloc* nodal dissection rather than a selective or "berry picking" dissection due to higher rates of persistent and recurrent disease with the later approach [42] The ATA consensus statement [19] regarding the terminology and classification of the central neck defines the central compartment nodal dissection as all perithyroidal and paratracheal soft tissue and lymph nodes with borders extending superiorly to the hyoid bone, inferiorly to the innominate artery, and laterally to the common carotid arteries and is well described and illustrated by Grodski et al. [43] The inclusion of the level VII nodes in the superior mediastinum with the central neck dissection should be noted as this is often a site of persistent disease following central neck dissection (ND). Moo et al [44]. compared ipsilateral vs bilateral central ND for PTC and concluded that an ipsilateral dissection was sufficient in tumors less than 1 cm, while tumors larger than 1 cm required bilateral central ND based on the high incidence of contralateral central neck disease in a retrospective analysis of the pattern of nodal metastases in surgical specimens. Some additional studies demonstrated that ipsilateral central ND was adequate for tumors larger than 1 cm. [45] If lateral cervical metastases are present in levels II–V, a bilateral central nodal dissection should be included with the modified radical ND to remove the presumed central neck nodal disease based on described patterns of nodal spread.[46]. Modified radical ND is defined as excision of all LNs routinely removed by radical neck dissection with preservation of one or more nonlymphatic structures (the spinal accessory nerve, sternocleidomastoid muscle, and internal jugular vein).

Complications

Complications of central ND include injury to the recurrent laryngeal nerve or the external branch of the superior laryngeal nerve, which occurs in 1% to 2% of patients based on several studies [45,47-50]. Small retrospective studies have shown that the addition of central compartment lymphadenectomy to total thyroidectomy for thyroid cancer has not increased nerve injury rates in

experienced hands [45,47,48,51]. In cases of reoperative central lymph node dissection after either previous thyroidectomy or central node dissection, reports have noted increased nerve injury rates ranging from 1% to 12% [52,53].Temporary hypoparathyroidism following central ND occurs in 14% to 40% of cases depending on the definition of hypoparathyroidism used in the study [54-57] The higher incidence of temporary hypoparathyroidism is likely due to the increased incidence of parathyroid reimplantation and inadvertent inclusion of parathyroid glands in the nodal dissection. Reports are mixed regarding the risk of permanent hypoparathyroidism. A meta-analysis of retrospective studies reported a 1.2% incidence as defined by the requirement for calcium supplements greater than 6 to 12 months postoperatively; however, none showed a statistically significant difference in total thyroidectomy with or without central ND [58].

Aim Of The Study
The aim of this study was to determine the presence of BFI-TS in metastatic LNs and to compare it with the other ultrasound features in relation to the results obtained from the surgical specimen.
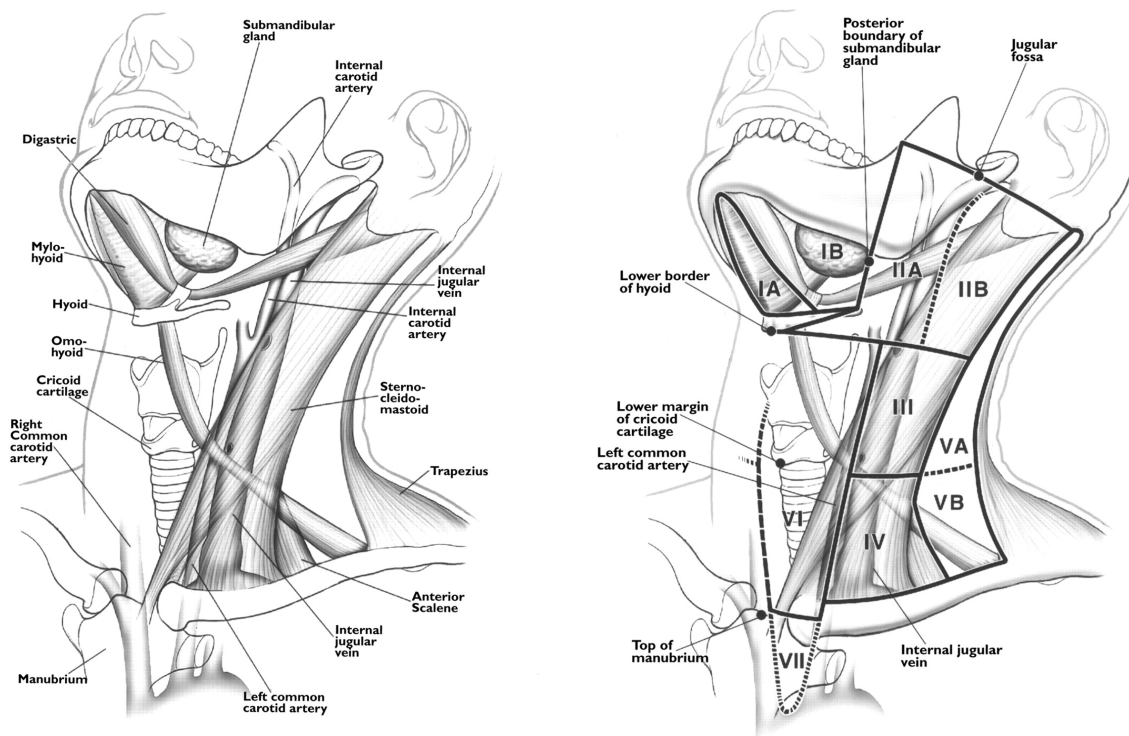
MATERIALS AND METHODS

Patients

Between September 2006 and June 2011, two hundred fifty two patients with known PTC were examined, at our institution, for preoperative sonographic evaluation with gray-scale ultrasonography (US), color Doppler US and BFI-TS. The patients with suspicious metastatic cervical LN at US examination underwent FNAB for cytology and thyroglobulin determination in the aspirate fluid. Only eighty-three patients (19 men, 64 women; mean age 52 years range, 26–79 years) with at least one metastatic LN were included in our study.

All patients included in our study underwent surgery, and the final diagnosis was based on the results of histologic examination of the resected specimens.

The mean interval between sonographic examination and surgery was 5.3 days (range, 1–17 days).

The study was conducted at the Department of Radiology and Endocrinology at the University Federico II of Naples and to the Department of Endocrinology at the Second University of Naples, according to the principles of the Declaration of Helsinki and approved by the Ethics Committee of the University of Molise. Written informed consent was obtained from all subjects.

US and Cytological Examinations

US, color flow Doppler (CFD) and BFI examinations were performed with LOGIQ 9 GE Healthcare (Chalfont St Giles, UK), a commercially available real-time US system, equipped with a 5 to 14 MHz (M12L) and 2.5 to 7 MHz (7L) linear array transducer. All examinations were performed by two blinded radiologists with 6 and 5 years of neck sonography experience separately and all data analysis was performed by another investigator. When results of the examiners were discordant, agreement was found by conjoint review of clips of the US examinations.

At gray-scale US, the following six sonographic characteristics were evaluated for all LNs examinated: a round shape (ratio of short axis to long axis > 0.5), absence of echogenic hilum, abnormal ecogenicity of LN, calcification, cystic change and a peripheral color Doppler pattern.

Of all cervical LNs were recorded shape, size and location (levels I-VI), on the basis of the American Joint Committee on Cancer and the American Academy of Otolaryngology-Head and Neck Surgery nodal classification [59,60,61].

BFI was performed at 10 MHz (M12L) and 7 MHz (7L) with the BFI capability at the level of the LNs. PRI was set at 3. BFI gain was not fixed and was adjusted to allow a better visualization of the signs. This technique focuses on high flow, with suppression of the tissue signal. BFI images were used to evaluate the presence or the absence of the signs.

The sign was considered positive when at least a twinkling was present in the LNs examined and repeatable over time.

After the US features were assessed, patients underwent a cytological evaluation and findings were recorded by a radiologist. US-guided FNA was simultaneously performed by an endocrinologist, a radiologist and pathologist.

Physicians were extremely experienced in the performance of US-guided FNA, with 27- and 22-gauge needles; the technique used is described in literature (62,63). A number of three or four smears were prepared; the first was air dried and immediately stained with Diff Quik stain Inadequate smears were immediately repeated.

After collection of the cytology samples, each FNAB needle is then washed with 0.1– 0.5 ml of normal saline; the washes from all needles are pooled (final volume 0.5–1 ml) and sent to the laboratory. Thyroglobulin was measured in fine needle washouts using an immunoradiometric assay (IRMA) based on coated tubes with monoclonal antibodies directed against distinct epitopes of the molecule of Tg (DYNO test Tg-plus, BRAHMS Diagnostic GmbH, Berlin, Germany). With this measurement, analytic sensitivity, defined as the detectable minimum concentration different from zero (mean value + 2 standard deviation), and functional sensitivity, defined as the lowest value that was measured with the precision of a maximum 20% interassay variance, were 0.08 ng/mL and 0.2 ng/mL, respectively. [64]

Surgery and Histologic Examination

All patients underwent thiroidectomy and ipsi or bilateral modified radical neck dissection to include levels II-V. All possible measurements were taken to ensure an accurate one-to-one comparison between the LNs that were imaged and those that were removed during surgery. After US examination, the location of each lymph node was mapped with respect to the surrounding anatomic structures (ie, trachea, main vessels, and sternocleidomastoid muscle) and plotted on the sketch diagram of the neck. In addition, the surgeons were assisted by a radiologist for correlation of the LN location seen on the US images with the LNs seen in the lymphadenectomy specimens. After being resected, each LN specimen was fixed in 10% formalin, embedded in paraffin, cut into thin slices, and stained with standard hematoxylin-eosin. During histologic examination, two or three histologic slices per LN were examined. The final diagnosis of metastatic lymph node involvement was made by a pathologist who had 15 years of experience performing histologic cervical LN diagnosis. Certain additional features were also recorded such as complete versus incomplete metastatic involvement and presence of necrosis and/or calcifications.

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.

Statistical Analyses

Qualitative variables were compared by using the χ^2test. The BFI characteristics of each lymph node were registered separately and processed blindly for statistical evaluation. The unit of analysis was each lymph node rather than each patient. The value of each visual and qualitative criterion that showed the highest diagnostic accuracy in the distinction between benign and metastatic lymph nodes was selected as the cutoff value. For each criterion examined, the sensitivity, specificity, positive and negative predictive values, and overall accuracy in the differentiation between benign and metastatic lymph nodes were calculated. Quantitative data are presented as means $\pm$ 1 standard deviation. Statistical significance was assumed when the p value was less than 0.05.

RESULTS

A total of 604 LNs were analyzed. 298 out of 604 were metastatic while the remaining 306 were benign, according to the histopathologic findings. The minimum diameters of LNs on sonography ranged from 2.3 to 13 mm, with mean diameter of metastatic LNs 5,8 mm and the mean diameter of nonmetastatic LNs 4.6 mm. No statistical difference was observed between the histopathologically determined diameters of metastatic and nonmetastatic LNs ($p > 0.05$).
The diagnostic performance of each ultrasound finding in this study is shown in Table 1.
Most ultrasound features had high specificity and PPV but low sensitivity and NPV. The only sonographic characteristic with high specificity and sensitivity values was the BFI-TS.
The BFI-TS was positive in all LNs with microcalcification at the US examination (93 LNs) and in 148 LNs (all metastatic) in which microcalcifications were not evident to the US but were histologically.
 Only one LN positive at the BFI and with calcifications at US was a tuberculous node after treatment with intranodal macrocalcifications at histological examination

US features	Total lymph nodes (604)	Metastatic lymph nodes (298)	Sensitivity (%)	Specificity (%)	P	PPV	NPV
Round size Short to long Axis (diameter ratio > 0.5)	183	155	52	90.8	X^2 131.3 P 0.0000	84.7	66
Abnormal Echogenicity	290	244	81.9	85	X^2 270.3 P 0.0000	84.1	82.8
Calcification	94	93	31.2	99.7	X^2 109.5 P 0.0000	98.9	59.8
Cystic Change	63	63	21.1	100	X^2 72.2 P 0.0000	100	56.6
Absent Hilum	400	274	91.9	58.8	X^2 174 P 0.0000	68.5	88.2
Peripheral Vascularity	238	142	47.6	68.6	X^2 16.7 P 0.0000	59.7	57.4
BFI-TS	242	241	80.9	99.7	X^2 407.9 P 0.0000	99.6	84.2

DISCUSSION

Neck US is highly sensitive for the diagnosis of metastatic LNs in patients with PTC. The specificity reported varies from 85 to 90% [65]. A variety of diagnostic criteria have been reported to be useful for the distinction between benign and metastatic LNs.

LN size has been previously described as a criterion for malignancy detection. By comparing three lymph node diameters, van den Brekel and coworkers [66] previously concluded that the minimum axial diameter is a better criterion than both the maximum axial diameter and the longitudinal diameter. The cutoff nodal short-axis diameters range from 5 to 30 mm [67-69]. However, some findings indicate that the size criteria used for random patient populations are not optimal for neck LNs assessment and that the same cutoff points cannot be used for all levels in the neck [70]. Because both reactive and metastatic lymph nodes in level II tend to be larger in patients with head and neck cancer . Many authors agree that the size criterion for lymph nodes in level II is larger. In our study, a cutoff short-axis diameter of 8 mm was used, yet neither univariate nor multivariate analysis results support the diagnostic accuracy of this criterion for neck lymph node classification mainly because of its low sensitivity.

Lymph node shape also has been used as a criterion for the detection of metastatic lymph nodes. In some previous studies, metastatic lymph nodes often appeared as round lesions, whereas benign nodes are usually flat or oval [71]. In current investigation, this sign has an excellent specificity (90.8%) but low sensitivity (52%). Of note, LNs in normal individuals of the parotid and submandibular regions are often round [72].

The presence of a hyperechoic hilum of the nodes are usually considered strong diagnostic criteria for benign lymph nodes [73]. It has been reported that 84%–92% of benign nodes but less than 5% of metastatic nodes have a hyperechoic hilum [74]. The absence of fatty hilum is often seen in normal individuals, especially in young subjects and LNs located in level V [75]. In our study, the metastatic LNs with visible hilum and partial involvement were at high level, while the LN metastases at low level showed in 99.5% the absence of hyperechoic hilum. Whereby, an absent LN hilum has high sensitivity (91,9%) but low specificity (58,8%). Whereas, ***the abnormal LN echogenicity*** had both high sensitivity and specificity (respectively 81,9% and 85%). In our experience 54 metastatic LNs (18%) had no abnormal ecogenicity. ***Calcification*** was a specific sign but not sensitive criterion. Calcification in metastatic lymph nodes is characteristic of PTC but generally rare. In our results nodal calcifications were detected in only 93 of the 298 metastatic LNs. Similarly, we found a very high specificity (100%) and a low sensitivity (21,1%) for ***cystic appearan***ce. All LNs with hyperechoic punctuations or a cystic appearance in a patient   with PTC should be considered as malignant.

Assessment of nodal vascularity at color Doppler US is an further criteria for the diagnosis of metastatic LNs. It has been noted that benign LNs tend to show hilar vascularity or appear avascular [76,77]. In contrast, metastatic nodes tend to have peripheral or mixed (both peripheral and hilar) vascularity [78]. In our study, color Doppler US vascularity had intermediate specificity (68,6%) but low sensitivity (47,6%). These findings correspond to previously published reports that the value of color Doppler US cannot compete with that of FNAC in the diagnosis of metastatic adenopathy.

The BFI-TS had the higher specificity and sensitivity (respectively 99,7% and 80.9%) than those of the conventional US features. The BFI-TS was positive in all LNs with calcification on US (93 LNs) and in 148 LNs (all metastatic) in which calcifications were not identified on US. We consider that the BFI-TS identify significantly more microcalcifications than B-mode US and also identify highly reflective and non-calcified structures such as colloidal crystals. Questo è

avvalorato dal riscontro istologico microcalcifications and colloidal crystals nella sede del BFI-TS.

The BFI-TS has been detected in 6 metastatic LNs resulting negative to the other conventional US features . Therefore the presence of BFI in addiction to convetional US increases the sensitivity for identifying the suspicious LNs. Its high specificity (99,7%) allows identifying more better the suspicious LNs to revaluate by surgery or US-guided FNAC. The limits of the technique consist in the influence of pulsatility of main neck vessel and the deep places of examinated LNs. These limits could explain the missed detection of 57 LNs (19%) resulted metastatic at istological examination. The other limit is the presence of non metastatic LN calcifications; in fact the BFI-TS resulted false-positive only in a LN with calcification deriving from tuberculosis.

Our results indicate that this technique can be applied to studies of cervical nodes in patients with PTC and that its sensitivity and specificity is higher than those of traditional US diagnostic techniques.

In conclusion, BFI is a promising imaging technique that can provide assistance in the differentiation of benign and metastatic neck LNs in patients with PTC. Our findings suggest that BFI can be helpful in the selection of suspicious neck LNs that should be examined at cytologic examination or open biopsy for accurate preoperative staging and individual therapy selection. However, longitudinal studies on a large population are required to verify the efficacy of BFI in the diagnosis of metastatic LNs.
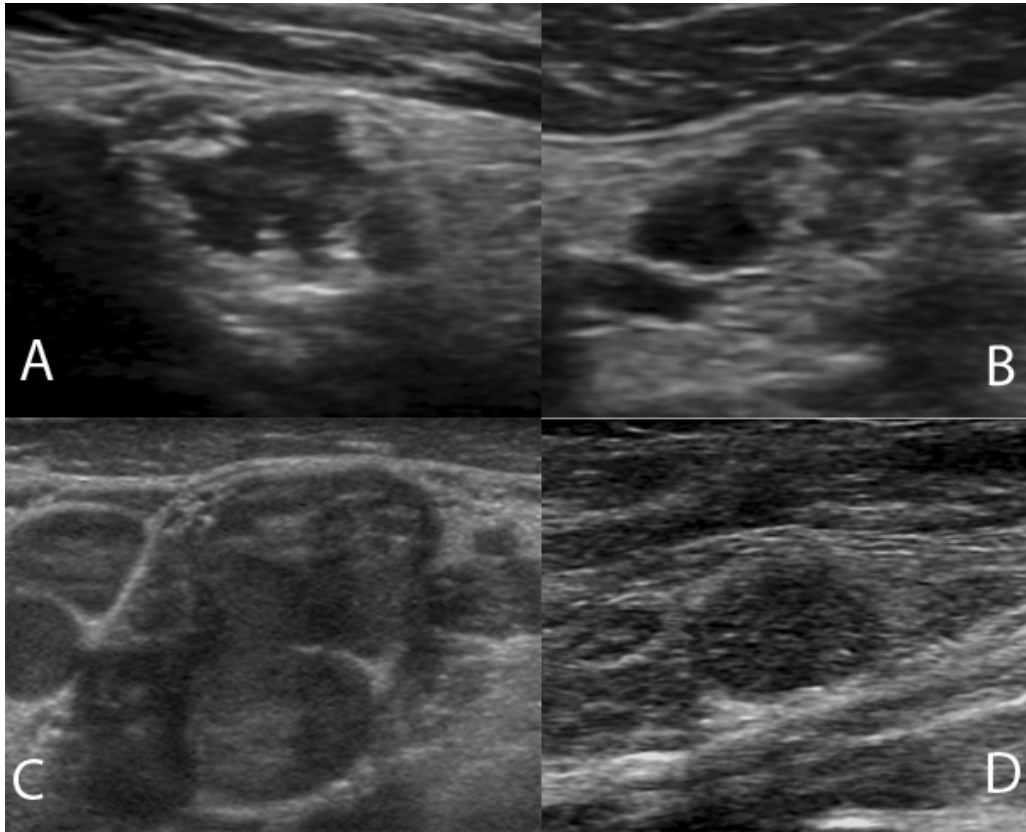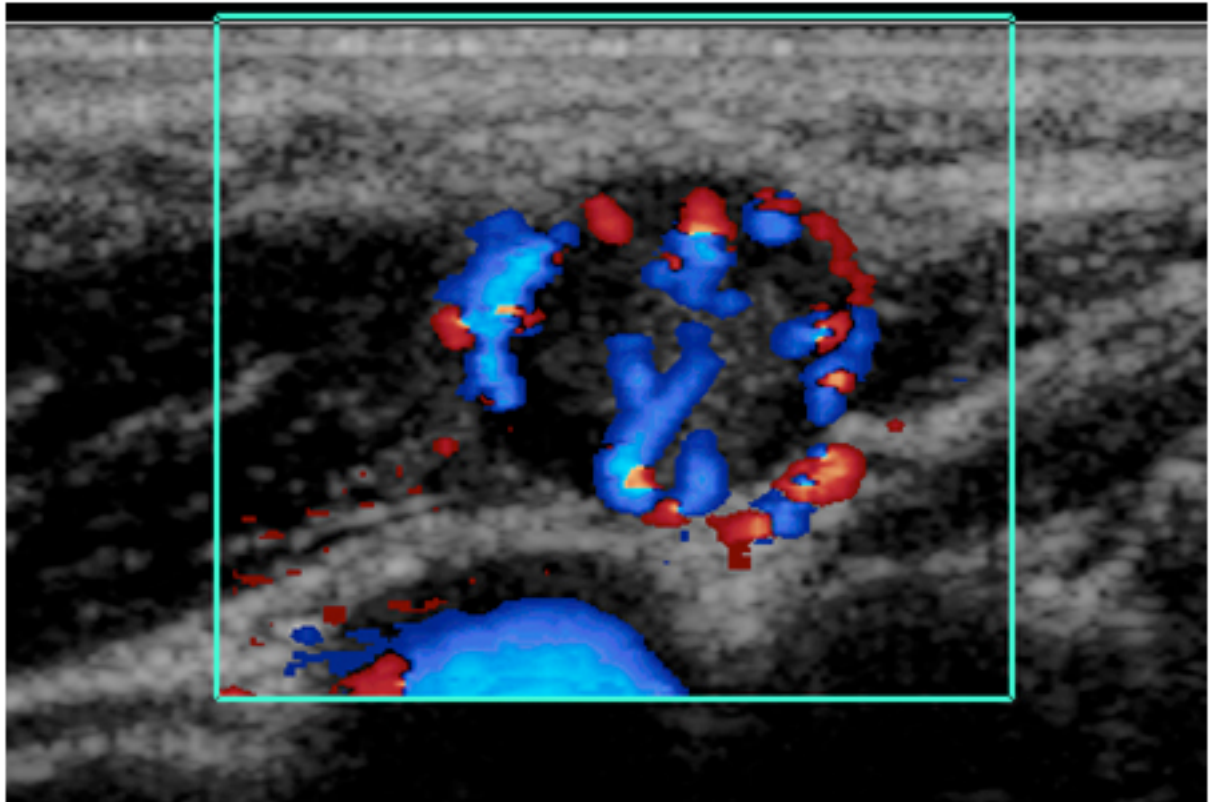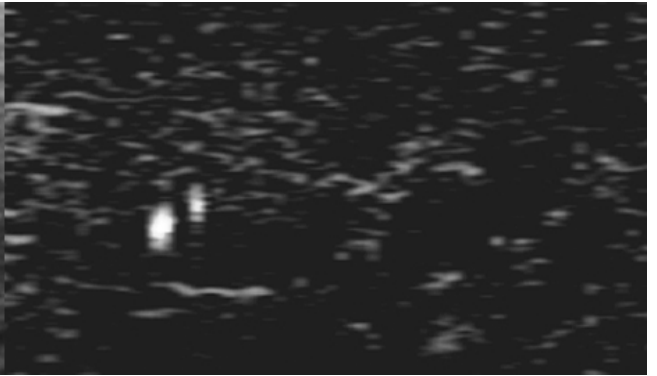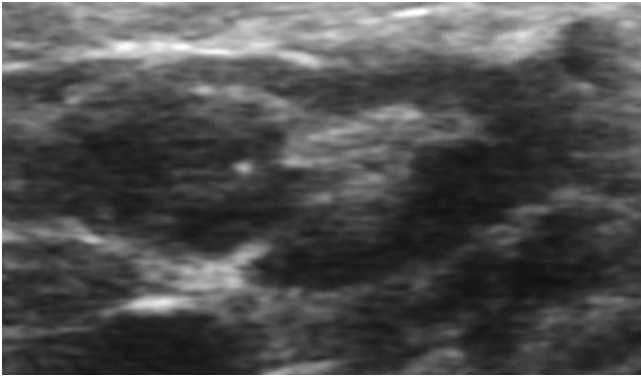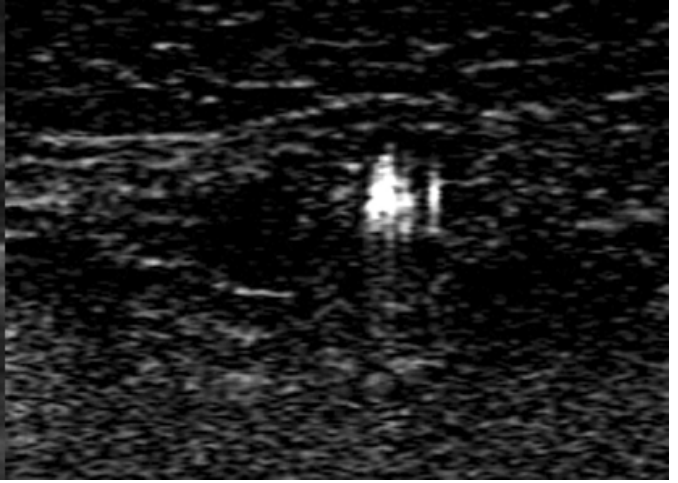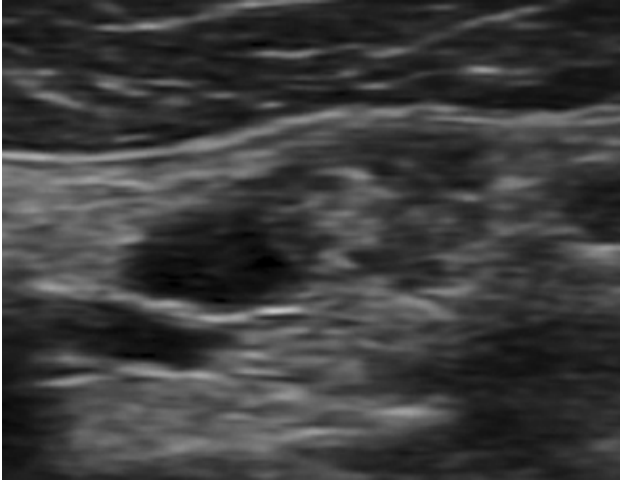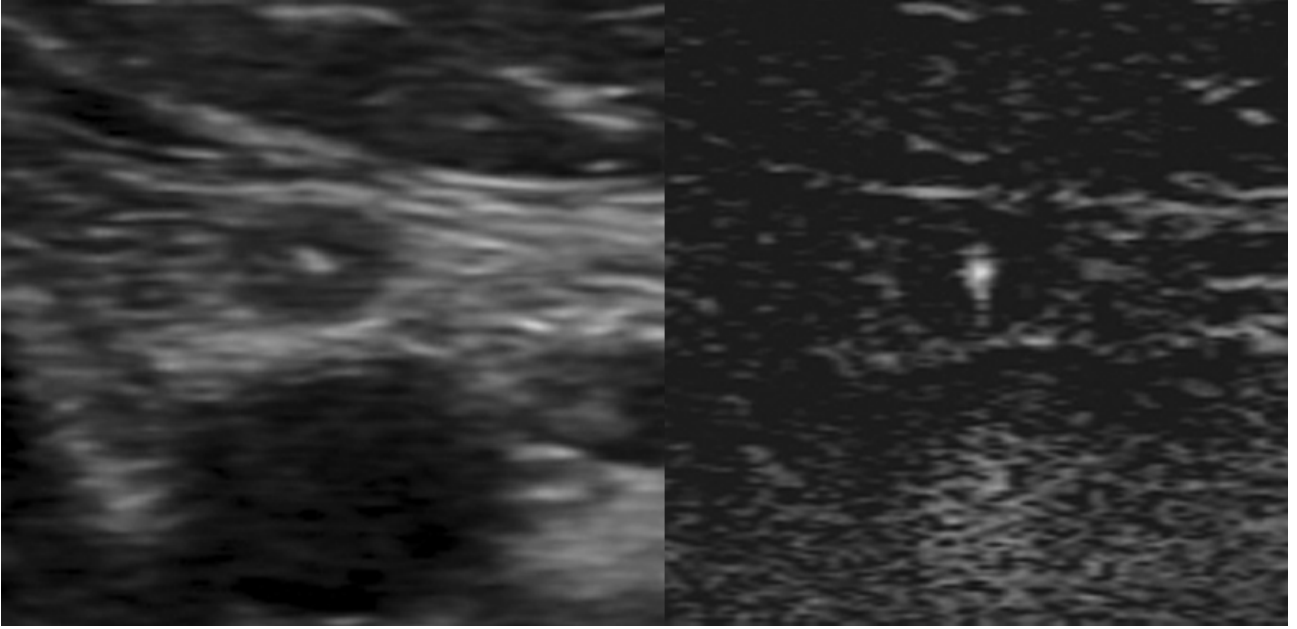
REFERENCES

1. Jemal A, Siegel R, Xu J, et al. Cancer statistics, 2010. CA Cancer J Clin. 2010;60(5):277-300.
2. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19(11):1167-1214.
3. Cooper DS, Doherty GM, Haugen BR, et al. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2006;16(2):109-142.
4. Arturi F, Russo D, Giuffrida D, et al. Early diagnosis by genetic analysis of differentiated thyroid cancer metastases in small lymph nodes. J Clin Endocrinol Metab. 1997;82(5):1638-1641.
5. Sherman SI. Thyroid carcinoma. Lancet 2003; 361:501–511
6. Samaan NA, Schultz PN, Hickey RC, et al. The results of various modalities of treatment of well differentiated thyroid carcinomas: a retrospective review of 1599 patients. J Clin Endocrinol Metab1992; 75:714–720
7. Simon D, Goretzki PE, Witte J, Roher HD. Incidence of regional recurrence guiding radicality in differentiated thyroid carcinoma. World J Surg 1996; 20:860–866
8. Gimm O, Rath FW, Dralle H. Pattern of lymph node metastases in papillary thyroid carcinoma. Br J Surg. 1998;85(2):252-254.
9. Machens A, Hinze R, Thomusch O, et al. Pattern of nodal metastasis for primary and reoperative thyroid cancer. World J Surg. 2002;26(1):22-28.
10. Rossi RL, Cady B, Silverman ML, et al. Current results of conservative surgery for differentiated thyroid carcinoma. World J Surg. 1986;10(4):612-622.
11. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med. 1994;97(5):418-428.
12. Hughes CJ, Shaha AR, Shah JP, et al. Impact of lymph node metastasis in differentiated carcinoma of the thyroid: a matched-pair analysis. Head Neck. 1996;18(2):127-132.
13. Lundgren CI, Hall P, Dickman PW, et al. Clinically signifi cant prognostic factors for differentiated thyroid carcinoma: a population-based, nested case-control study. Cancer. 2006;106(3):524-531.
14. Podnos YD, Smith D, Wagman LD, et al. The implication of lymph node metastasis on survival in patients with well-differentiated thyroid cancer. Am Surg. 2005;71(9):731-734.
15. Hajek PC, Salomonowitz E, Turk R, Tscholakoff D, Kumpan W, Czembirek H. Lymph nodes of the neck: evaluation with US. Radiology 1986; 158:739–742.
16. Sutton RT, Reading CC, Charboneau WJ, James EM, Grant CS, Hay ID. US-guided biopsy of neck masses in postoperative management of patients with thyroid cancer. Radiology 1988; 168:769–772.
17. Baatenburg de Jong RJ, Rongen RJ, Verwoerd CD, van Overhagen H, Lameris JS, Knegt P. Ultrasound-guided fineneedle aspiration biopsy of neck nodes. Arch Otolaryngol Head Neck Surg 1991; 117:402–404.
18. Do Rosario PW, Fagundes TA, Maia FF, Franco AC, Figueiredo MB, Purisch S. Sonography in the diagnosis of cervical recurrence in patients with differentiated thyroid carcinoma. J Ultrasound Med 2004; 23:915–920.
19. American Thyroid Association Surgery Working Group, American Association of Endocrine Surgeons, American Academy of Otolaryngology- Head and Neck Surgery, et al. Consensus statement on the terminology and classification of central neck dissection for thyroid cancer. Thyroid.2009;19(11):1153-1158.
20. Robbins KT, Clayman G, Levine PA, et al. Neck dissection classification update: revisions proposed by the American Head and Neck Society and the American Academy of Otolaryngology-Head and Neck Surgery. Arch Otolaryngol Head Neck Surg. 2002;128(7):751-758.

21. Stulak JM, Grant CS, Farley DR, et al. Value of preoperative ultrasonography in the surgical management of initial and reoperative papillary thyroid cancer. Arch Surg. 2006;141(5):489-494; discussion 494-496.

22. Kouvaraki MA, Shapiro SE, Fornage BD, et al. Role of preoperative ultrasonography in the surgical management of patients with thyroid cancer. Surgery. 2003;134(6):946-954; discussion 954-955.

23. Ahn JE, Lee JH, Yi JS, et al. Diagnostic accuracy of CT and ultrasonography for evaluating metastatic cervical lymph nodes in patients with thyroid cancer. World J Surg. 2008;32(7):1552 1558.

24. Tohnosu N, Onoda S, Isono K 1989 Ultrasonographic evaluation of cervical lymph node metastases in esophageal cancer with special reference to the relationship between the short to long axis ratio (S/L) and the cancer content. J Clin Ultrasound 17:101–106

25. Vassallo P, Wernecke K, Roos N, Peters PE 1992 Differentiation of benign from malignant superficial lymphadenopathy: the role of high-resolution US. Radiology 183:215–220

26. Steinkamp HJ, Cornehl M, Hosten N, Pegios W, Vogl T, Felix R 1995 Cervical lymphadenopathy: ratio of long- to short-axis diameter as a predictor of malignancy. Br J Radiol 68:266 –270

27. Ariji Y, Kimura Y, Hayashi N, Onitsuka T, Yonetsu K, Hayashi K, Ariji E, Kobayashi T, Nakamura T 1998 Power Doppler sonography of cervical lymph nodes in patients with head and neck cancer. AJNR Am J Neuroradiol 19:303–307

28. Tschammler A, Ott G, Schang T, Seelbach-Goebel B, Schwager K, Hahn D 1998 Lymphadenopathy: differentiation of benign from malignant disease—color Doppler US assessment of intranodal angioarchitecture. Radiology 208:117–123

29. Van den Brekel MW, Castelijns JA, Snow GB 1998 The size of lymph nodes in the neck on sonograms as a radiologic criterion for metastasis: how reliable is it? AJNR Am J Neuroradiol 19:695–700

30. Dragoni F, Cartoni C, Pescarmona E, Chiarotti F, Puopolo M, Orsi E, Pignoloni P, De Gregoris C, Mandelli F 1999 The role of high resolution pulsed and color Doppler ultrasound in the differential diagnosis of benign and malignant lymphadenopathy: results of multivariate analysis. Cancer 85:2485–2490

31. Wang Q, Takashima S, Takayama F, Wang JC, Kawakami S, Saito A, Matsushita T, Sone S 2001 Detection of occult metastatic lymph nodes in the neck with gray-scale and power Doppler US. Acta Radiol 42:312–319

32. Kessler A, Rappaport Y, Blank A, Marmor S, Weiss J, Graif M 2003 Cystic appearance of cervical lymph nodes is characteristic of metastatic papillary thyroid carcinoma. J Clin Ultrasound 31:21–25

33. Ahuja AT, Chow L, Chick W, King W, Metreweli C 1995 Metastatic cervical nodes in papillary carcinoma of the thyroid: ultrasound and histological correlation. Clin Radiol 50:229 –231

34. Kuna SK, Bracic I, Tesic V, Kuna K, Herceg GH, Dodig D 2006 Ultrasonographic differentiation of benign from malignant neck lymphadenopathy in thyroid cancer. J Ultrasound Med 25:1531–1537; quiz 1538 –1540.

35. Pacini F, Fugazzola L, Lippi F, Ceccarelli C, Centoni R, Miccoli P, Elisei R, Pinchera A 1992 Detection of thyroglobulin in fine needle aspirates of nonthyroidal neck masses: a clue to the diagnosis of metastatic differentiated thyroid cancer. J Clin Endocrinol Metab 74:1401–1404

36. Ahuja A, Ying M, Evans R, King W, Me- treweli C. The application of ultrasound criteria for malignancy in differentiating tuberculous cervical adenitis from metastatic nasopharyngeal carcinoma. Clin Radiol 1995;50:391–395.

37. Gritzmann N, Hollerweger A, Macheiner P, Rettenbacher T. Sonography of soft tissue masses of the neck. J Clin Ultrasound 2002;30:356 –373.

38. Roti E, Rossi R, Trasforini G, Bertelli F, Ambrosio MR, Busutti L, Pearce EN, Braverman LE, Degli Uberti EC. 2006. Clinical and histological characteristics of papillary thyroid

microcarcinoma: results of a retrospective study in 243 patients. J Clin Endocrinol Metab. 91(6):2171-8.

39. Bucek RA, Reiter M, Koppensteiner I, Ahmadi R, Minar E, Lammer J. 2002. Bflow evaluation of carotid arterial stenosis: initial experience. Radiology. Oct;225(1):295-9.

40. Brunese L, Romeo A, Iorio S, Napolitano G, Fucili S, Zeppa P, Vallone G, Lombardi G, Bellastella A, Biondi B, Sodano A. Thyroid B-flow twinkling sign: a new feature of papillary cancer. Eur J Endocrinol. 2008 Oct;159(4):447-51. Epub 2008 Jul 21.

41. Rahmouni A, Bargoin R, Herment A, et al. Color Doppler twinkling artifact hyperechoic regions. Radiology 1996;199:269–271.

42. Hay ID, Bergstralh EJ, Grant CS, et al. Impact of primary surgery on outcome in 300 patients with pathologic tumor-node-metastasis stage III papillary thyroid carcinoma treated at one institution from 1940 through 1989. Surgery. 1999;126(6):1173-1181; discussion 1181-1182.

43. Grodski S, Cornford L, Sywak M, et al. Routine level VI lymph node dissection for papillary thyroid cancer: surgical technique. ANZ J Surg. 2007;77(4):203-208.

44. Moo TA, Umunna B, Kato M, et al. Ipsilateral versus bilateral central neck lymph node dissection in papillary thyroid carcinoma. Ann Surg. 2009; 250(3):403-408.

45. Sywak M, Cornford L, Roach P, et al. Routine ipsilateral level VI lymphadenectomy reduces postoperative thyroglobulin levels in papillary thyroid cancer. Surgery. 2006;140(6):1000-1005; discussion 1005-1007.

46. Roh JL, Park JY, Rha KS, et al. Is central neck dissection necessary for the treatment of lateral cervical nodal recurrence of papillary thyroid carcinoma? Head Neck. 2007;29(10):901-906.

47. Henry JF, Gramatica L, Denizot A, et al. Morbidity of prophylactic lymph node dissection in the central neck area in patients with papillary thyroid carcinoma. Langenbecks Arch Surg. 1998;383(2):167-169.

48. Palestini N, Borasi A, Cestino L, et al. Is central neck dissection a safe procedure in the treatment of papillary thyroid cancer? Our experience. Langenbecks Arch Surg. 2008;393(5):693-698.

49. Kim MK, Mandel SH, Baloch Z, et al. Morbidity following central compartment reoperation for recurrent or persistent thyroid cancer. Arch Otolaryngol Head Neck Surg. 2004;130(10):1214-1216.

50. Moley JF, Lairmore TC, Doherty GM, et al. Preservation of the recurrent laryngeal nerves in thyroid and parathyroid reoperations. Surgery. 1999;126(4):673-677; discussion 677-679.

51. Roh JL, Park JY, Park CI. Prevention of postoperative hypocalcemia with routine oral calcium and vitamin D supplements in patients with differentiated papillary thyroid carcinoma undergoing total thyroidectomy plus central neck dissection. Cancer. 200;115(2):251-258.

52. Simon D, Goretzki PE, Witte J, et al. Incidence of regional recurrence guiding radicality in differentiated thyroid carcinoma. World J Surg. 1996; 20(7): 860-866; discussion 866.

53. Uruno T, Miyauchi A, Shimizu K, et al. Prognosis after reoperation for local recurrence of papillary thyroid carcinoma. Surg Today. 2004;34(11): 891-895.

54. Roh JL, Park JY, Park CI. Total thyroidectomy plus neck dissection in differentiated papillary thyroid carcinoma patients: pattern of nodal metastasis, morbidity, recurrence, and postoperative levels of serum parathyroid hormone. Ann Surg. 2007;245(4):604-610.

55. Steinmüller T, Klupp J, Wenking S, et al. Complications associated with different surgical approaches to differentiated thyroid carcinoma. Langenbecks Arch Surg. 1999;384(1):50-53.

56. Pereira JA, Jimeno J, Miquel J, et al. Nodal yield, morbidity, and recurrence after central neck dissection for papillary thyroid carcinoma. Surgery. 2005;138(6):1095-1100; discussion 1100-1101.

57. Gemsenjäger E, Perren A, Seifert B, et al Lymph node surgery in papillary thyroid carcinoma. J Am Coll Surg. 2003;197(2):182-190.

58. Chisholm EJ, Kulinskaya E, Tolley NS. Systematic review and metaanalysis of the adverse effects of thyroidectomy combined with central neck dissection as compared with thyroidectomy alone. Laryngoscope. 2009;119(6):1135-1139.

59. Robbins KT. Pocket guide to neck dissection and TNM staging of head and neck cancer. Alexandria,VA: American Academy of Otolaryngology–Head and Neck Surgery Foundation, 1991:1–31

60. Fleming ID, Cooper JS, Henson DE, et al. American Joint Committee on Cancer Staging manual, 5th ed., Philadelphia: Lippincott Raven, 1997.

61. Robbins KT. Classification of neck dissection: current concepts and future considerations. Otolaryngol Clin North Am 1998;31:639–655

62. Lagalla R, Caruso G, Midiri M, et al. Echo-Doppler-couleur et pathologie thyroidienne. J Echogr Med Ultrason 1992; 13: 44–47.

63. Gharib H. Diagnosis of thyroid nodules by fine needle aspiration biopsy. Curr Opin Endocrinol Diabetes 1996; 3:433– 438.

64. Giovanella L, Ceriani L, Suriano S. Lymph Node ThyroglobulinMeasurement in Diagnosis of NeckMetastases of Differentiated Thyroid Carcinoma. Journal of Thyroid Research Volume 2011.

65. Kuna SK, Bracic I, Tesic V, Kuna K, Horvatic Herceg G, Dodig D. Ultrasonographic Differentiation of Benign From Malignant Neck Lymphadenopathy in Thyroid Cancer. J Ultrasound Med 2006; 25:1531–1537.

66. Van den Brekel MWM, Stel HV, Castelijns JA, et al. Cervical lymph node metastasis: assessment of radiologic criteria. Radiology 1990; 177:379–384.

67. Lyshchik A, Higashi T, Asato R, Tanaka S, Ito J, Hiraoka M, Insana MF, Brill AB, Saga T, Togashi K. Cervical lymph node metastases: diagnosis at sonoelastography-initial experience. Radiology. 2007 Apr;243(1):258-67. Epub 2007 Feb 9.

68. Ying M, Ahuja A, Metreweli C. Diagnostic accuracy of sonographic criteria for evaluation of cervical lymphadenopathy. J Ultrasound Med 1998;17:437–445.

69. Hajek PC, Salomonowitz E, Turk R, Tscholakoff D, Kumpan W, Czembirek H. Lymph nodes of the neck: evaluation with US. Radiology 1986;158:739–742.

70. Van den Brekel MW, Castelijns JA, Snow GB. The size of lymph nodes in the neck on sonograms as a radiologic criterion for metastasis: how reliable is it? AJNR Am J Neuroradiol 1998;19:695–700.

71. Papakonstantinou O, Bakantaki A, Paspalaki P, Charoulakis N, Gourtsoyiannis N. Highresolution and color Doppler ultrasonography of cervical lymphadenopathy in children. Acta Radiol 2001;42:470–476.

72. Leboulleux S, Girard E, Rose M, Travagli JP, Sabbah N, Caillou B, Hartl DM, Lassau N, Baudin E, Schlumberger M. Ultrasound Criteria of Malignancy for Cervical Lymph Nodes in Patients Followed Up for Differentiated Thyroid Cancer. J Clin Endocrinol Metab, September 2007, 92(9):3590–3594.

73. Ying M, Ahuja AT, Evans R, King W, Metreweli C. Cervical lymphadenopathy: sonographic differentiation between tuberculous nodes and nodal metastases from non-head and neck carcinomas. J Clin Ultrasound 1998;26:383–389.

74. Rubaltelli L, Proto E, Salmaso R, Bortoletto P, Candiani F, Cagol P. Sonography of abnormal lymph nodes in vitro: correlation of sonographic and histologic findings. AJR Am J Roentgenol 1990;155:1241–1244.

75. Ying M, Ahuja A, Brook F 2002 Sonographic appearances of cervical lymph nodes: variations by age and sex. J Clin Ultrasound 30:1–11.

76. Dragoni F, Cartoni C, Pescarmona E, et al. The role of high resolution pulsed and color Doppler ultrasound in the differential diagnosis of benign and malignant lymphadenopathy: results of multivariate analysis. Cancer 1999;85:2485–2490.

77. Stramare R, Tregnaghi A, Fitta C, et al. High-sensitivity power Doppler imaging of normal superficial lymph nodes. J Clin Ultrasound 2004;32:273–276.

78. Sakaguchi T, Yamashita Y, Katahira K, et al. Differential diagnosis of small round cervical lymph nodes: comparison of power Doppler US with contrast-enhanced CT and pathologic results. Radiat Med 2001;19:119–125.