Role of Neck Ultrasonography in the Follow-Up of Children Operated on for Thyroid Papillary Cancer

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The aim of this study was to evaluate the role of neck ultrasonography compared to $^{131}$I whole-body scan (WBS) and circulating thyroglobulin (Tg) measurement after thyroid hormone withdrawal in the follow-up of children with thyroid papillary cancer, who had previously undergone total thyroidectomy for the diagnosis of neck lymph node metastases (LNM). Forty-five children were examined. Neck ultrasonography and diagnostic WBS were conclusive about the presence or absence of LNM in 35 patients. Diagnostic WBS revealed the presence of LNM in 6 cases not detected by neck ultrasonography; neck ultrasonography was positive in 3 cases that were negative at diagnostic WBS but confirmed by post-$^{131}$I therapy WBS. One patient with suspicious neck lymphnodes at neck ultrasonography not confirmed by WBS was considered as a false-positive result of neck ultrasonography. Neck ultrasonography and thyroglobulin (Tg) were conclusive about the presence or absence of LNM in 29 patients. Tg was elevated in 10 subjects with negative neck ultrasonography (7 had also lung and/or mediastinic LNM). Tg was undetectable in 5 patients in whom the presence of LNM was confirmed by neck ultrasonography and WBS. In conclusion, our study in children demonstrates that neck ultrasonography can detect LNM that are not suspected by palpation, diagnostic WBS, or serum Tg determination. Furthermore, neck ultrasonography can pinpoint the anatomic site of the LNM.

Introduction

Neck ultrasonography (1–3), together with whole-body scan (WBS) (4) and serum thyroglobulin (Tg) measurement (5), has proven to be effective in the diagnosis of neck lymph node metastases and local recurrences in the follow-up of adult patients who underwent total thyroidectomy for differentiated thyroid cancer (DTC). In contrast, to our knowledge, no information is available on the performance of neck ultrasonography compared to $^{131}$I WBS and circulating Tg levels in the follow-up of children with thyroid cancer who had previously undergone total thyroidectomy for the diagnosis of neck lymph node metastases. In the present work, we compared these diagnostic tools in a cohort of children who underwent surgery for DTC on the basis that: (1) these patients appear to be more prone to develop neck lymph node metastases and (2) the presence of large inflammatory lymph nodes in the neck is more common in children than in adults, thereby making it difficult to differentiate between metastatic and reactive lymph node involvement.

Patients and Methods

Patients

Over the last decade, we studied 45 consecutive children (29 females, 16 males; age range, 10–18 years) with DTC who had previously undergone total thyroidectomy. The initial TNM classification (6) (when available) showed stage T1 in 9, T2 in 6, and T4 in 25 patients; N0 was observed in 6 and N1 in 32 children. The grade was G1 in 24, G3 and G4 in 1 patient each (7).

The results of the first neck ultrasonography and WBS after total thyroidectomy is reported; this evaluation was performed after a mean period of 2.5 years from the initial diagnosis and surgical treatment (range, 0–6 years). Post-therapy WBS was considered as the gold standard to compare the results of neck ultrasonography and diagnostic WBS.

Informed consent was obtained from each subject included in the study.

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Whole-body scan

Diagnostic WBS was performed 3 days after the oral administration of a test dose of $^{131}I$ (3–4 MBq [0.08–0.1 mCi] per kilogram of body weight). The patients followed a strict low-iodine diet 10 days prior to administration of the radioiodine tracer and for the period of imaging and successive treatment; the urinary iodine excretion was evaluated in all patients before the WBS. Thyroid hormone suppressive therapy with thyroxine ($T_4$) was withdrawn at least 45 days before the administration of the radioiodine, and to avoid prolonged hypothyroidism the patients were maintained with triiodothyronine ($T_3$) until 2 weeks before (to obtain a serum thyrotrropin [TSH] concentration higher than greater than 30 μU/mL).

Post therapy WBS was performed 3–10 days after the administration of a therapeutic dose of $^{131}I$: 37 MBq (1 mCi) per kilogram of body weight for residual functioning thyroid tissue and 74 MBq (2 mCi) per kilogram for thyroid metastasis.

Whole-body images (20 min/m, matrix 512 x 128), anterior and lateral planar images on the neck and the thorax (matrix 128 x 128 without zoom factor) were acquired with a LFOV gamma camera (3000 Camstar, GE, Milwaukee, WI) equipped with high-energy parallel-hole collimator with a 20% window centered on the 364-KeV photopeak. Planar images on the neck of 100,000 counts or 30-minute acquisition time were obtained in combination with adequate anatomic markers to distinguish between residual thyroid tissue, salivary gland uptake, and lymph node metastasis. All scans were randomly reviewed by two nuclear medicine physicians blinded to the patient’s history, clinical data, and ultrasonography findings.

Ultrasonography of the neck

Neck ultrasound was always performed by the same operator who was unaware of the WBS and Tg results, using a probe (TOSabee, Toshiba, Tokyo, Japan) with a sectorial 7.5-MHz transducer, with the interposition of a water bag. Neck ultrasound was performed in all patients immediately before the administration of the tracer dose of $^{131}I$. The following criteria (3) were used to define sonographic suggestion of lymph node metastases: (1) diameter 1 cm or more; (2) clear hypoechoic pattern or dyshomogeneous pattern, with alternating hypoechoic and hyperechoic areas; (3) irregular cystic appearance; (4) presence of internal calcifications; (5) rounded or bulging shape with increased anteroposterior diameter; and (6) shorter/longer diameter ratio greater than 0.7. Any hypoechoic mass detected in the postoperative thyroid bed, which normally appears as an area of highly reflective echoes (2), was considered suggestive for recurrence.

Laboratory evaluation

Serum Tg was measured in all patients after thyroid suppressive therapy had been stopped and immediately before the administration of the tracer dose of $^{131}I$ needed to perform WBS. Serum Tg measurement was performed by using a commercial radioimmunoassay (RIA) kit (HTGK; Sorin Biomedica, Saluggia, Italy). The lowest limit of detection was 3 ng/mL; in thyroidectomized patients, Tg was considered negative when lower than 3 ng/mL. Antithyroperoxidase antibodies (TPOAb; normal range, 0–150 UI/mL) and antithyroglobulin antibodies (TgAb; normal range, 0–50 UI/mL) were evaluated by immunoradiometric assay (IRMA) methods (ICN Pharmaceuticals, Costa Mesa, CA). Serum thyroxine ($T_4$) and triiodothyronine ($T_3$) concentrations were assayed by commercial RIA kits (RIA coat T3; Byk-Sangtec Diagnostica, Dietzenbach, Germany). Serum TSH was evaluated by RIA (TSH MYRIA).

Results

Twenty-three patients were found to be negative for lymph node metastases both on neck ultrasonography and WBS and clinical examination. Of these patients, four (17%) had detectable levels of serum Tg whereas the others had Tg levels less than 3 ng/mL. Among the four patients with detectable levels of Tg (ranging from 20 to 89 ng/mL), three presented with lung and/or mediastinic lymph node metastases on WBS, while the fourth child had locoregional lymph node metastases found on posttherapy WBS that had not been detected at the diagnostic WBS.

Twelve patients were positive for lymph node metastases both by neck ultrasonography and WBS (Table 1); of these, eight (67%) had detectable serum Tg levels (from 8 to 438 ng/mL); two also had lung and/or mediastinic lymph node metastases, the other four had Tg levels less than 3 ng/mL. In three patients of this group, diagnostic WBS showed the presence of other metastatic lymph nodes not detected by neck ultrasonography on the same and/or on the opposite side of the neck.

Six patients were positive for lymph node metastases on WBS but not by neck ultrasonography (Table 1); all had detectable serum Tg (12 to 58 ng/mL), four also had lung metastases. In this group, neck ultrasonography detected the lymph nodes but could not distinguish between inflammatory and metastatic involvement because of a normal hypoechoic pattern, with internal echoic line coursing through the lymph node.

Three children were found to be positive for lymph node metastases on neck ultrasonography but not WBS; of them, two had detectable serum Tg (10 and 133 ng/mL, respectively), both had lung metastases, 1 had circulating TgAb. In all three cases, the posttherapy WBS was positive for locoregional lymph node metastases on the same side as shown by neck ultrasonography.

One patient had neck ultrasonography suspicious for neck lymph nodes that were not confirmed by diagnostic or posttherapy WBS; in this child, the presence of lung metastases was confirmed by high levels of serum Tg (69 ng/mL). This case was therefore considered as a false-positive neck ultrasonography result according to the study design, even if only histologic evidence could actually document a false-positive in this case.

Altogether, 15 patients had neck ultrasound images suggestive of lymph node metastasis confirmed by diagnostic or posttherapy WBS (Table 1). In 7 patients, lymph nodes had a rounded or bulging shape and a uniformly hypoechoic texture and were well separated from the surrounding, relatively hyperechoic tissues (Fig. 1); only 2 presented with lymph nodes with echogenic line coursing through the midsubstance. A dyshomogeneous echo pattern of metastatic lymphnodes was
observed in 3 patients. In another 3 children, this dyshomogeneous appearance was associated with the presence of internal calcification and, in 1 case, with internal hyperechoic spots. One child had a large (2 cm) lymph node with cystic appearance (Fig. 2). In 3 of 15 patients (20%), the lymph nodes were located in the internal jugular lymph node chain, whereas in the others they were higher up in the neck.

All children had palpable angulomandibular and/or laterocervical lymph nodes. Among the 15 patients who presented with suspicious neck ultrasonography images confirmed by diagnostic or posttherapy WBS, the metastatic lymph nodes were palpable on physical examination in 5 of 15 subjects (33%). In all patients with metastatic lymph nodes, they were detectable by palpation in 12 of 22 subjects.

The sensitivity of neck ultrasonography was 68% (15/22), while that of diagnostic WBS was 82% (18/22), and that of palpation was 55% (12/22). The positive predictive value of neck ultrasonography (true-positive/[true positive + false-positive]) was 95%.

Neck ultrasonography was positive for lymph node metastases and Tg was elevated in 10 children (1 had positive TgAb), while neck ultrasonography was negative for lymph node metastases and Tg was undetectable in 19 patients (2 had positive TgAb). Overall, neck ultrasonography and Tg were conclusive for the presence (n = 10) or absence (n = 19) of lymph node metastases in 29 of 45 patients (64%). Tg was elevated in 10 patients with negative neck ultrasonography but with diagnostic or posttherapy WBS positive for lymph node metastases in the neck (7 also had lung and/or mediastinic lymph nodes metastases). Tg was undetectable in 5 patients in whom the presence of lymph node metastases was confirmed by neck ultrasonography and di-

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**TABLE 1.** **Patients with Images Suspicious of Lymph Node Metastasis at Neck Ultrasonography, Confirmed by Diagnostic WBS or Posttherapy WBS, and Values of Circulating Thyroglobulin and Antithyroglobulin Antibodies**

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<tr>
<th>Patient number</th>
<th>Diagnostic WBS</th>
<th>Antithyroglobulin antibodies U/ml (nv &lt;50)</th>
<th>Thyroglobulin ng/mL (&lt;3)</th>
<th>Neck ultrasonography</th>
<th>Posttherapy WBS</th>
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nv, normal value; +, positive; neg, negative; bilat, bilaterally; WBS, whole-body scan.

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FIG. 1. Neck echography showing an enlarged metastatic cervical lymph node placed behind the carotid and the jugular vein.
agnostic or posttherapy WBS (4 and 1 case, respectively); 2 of them had positive TgAb. The last case was considered as a false-positive result of neck ultrasonography. No cases of local recurrence were observed.

Neck ultrasonography can indicate the precise anatomic site of lymph node metastasis. This is important overall for lymph nodes not palpable, or located behind the carotid and/or the jugular vein (Fig. 1 and Fig. 2).

**Discussion**

Neck ultrasonography has proven to be an accurate and sensitive technique for the detection of recurrence of thyroid cancer in the thyroid bed and of lymph node metastases (1-3,8). In particular, Van den Brekel et al. (9) and Boland et al. (10) demonstrated that ultrasonography and ultrasonography-guided fine-needle aspiration cytology (FNAC) may play an important role in the detection of occult lymph node metastases in the neck. Recently, we have systematically assessed the contribution of neck ultrasonography in the detection of new cases of local recurrence and lymph node metastases in patients with negative WBS or Tg levels (3). Sixty-three consecutive adult patients with DTC were examined; they had previously undergone total thyroidectomy followed by \(^{131}I\) ablation of the residual thyroid tissue and were negative on WBS. When combined with FNAC, neck ultrasonography detected 4 cases of local recurrence and 11 cases of lymph node metastases. That study demonstrated that combined neck ultrasonography and FNAC can detect cases of lymph node metastasis and local recurrence of DTC that are not found by WBS or serum Tg determination. These results have recently been confirmed by Franceschi et al. (11), who found positive neck ultrasonography/FNAC in 23 of 359 adult patients with DTC, 12 of 23 (52%) of whom had undetectable Tg levels and 19 of 23 (83%) were negative on WBS. They concluded that the combined use of serum Tg measurement, neck ultrasonography, and WBS appears to give the best results in the follow-up of patients with DTC. More recently, other studies have reported similar results (12-16).

In children operated on for thyroid cancer, the prevalence of lymph node metastases is higher than in adults (17-22). In addition, the presence of large inflammatory lymph nodes in the neck, which is more common in children than in adults, makes the differential diagnosis more difficult. Thus, the value of neck ultrasonography in the diagnosis of neck lymph node metastases and local recurrences in children who underwent total thyroidectomy for DTC has been uncertain. Our study indicates that neck ultrasonography may be useful in detecting lymph node metastases in children even when diagnostic WBS is negative (3/45; 7%) or serum Tg is undetectable (5/45; 11%). Furthermore, neck ultrasonography can locate the anatomic site of lymph node metastases precisely, which WBS does only partially and Tg determination not at all.

WBS is currently the most used imaging technique to detect local recurrence, lymph node, and distant metastasis. However, in adults only approximately three fourths of recurrences and metastases from well-differentiated thyroid cancer concentrate radiiodine (4). The current data suggest that the routine use of WBS in children results in a prevalence of false-negatives of 7% (3/45), which is lower than in adults (15%-20%) but nevertheless clinically relevant in view of the young age.

In adults, the introduction of Tg measurement increased the sensitivity of diagnosis of metastases to approximately 85% (23), and the combination of WBS and Tg determination further increases sensitivity up to 95% (24). Obviously, Tg does not provide any information about the site of the recurrence. In the present study, neck ultrasonography correctly diagnosed 5 of 45 (11%) cases with undetectable Tg and negative clinical examination. It is interesting to observe that among these 5 patients, 2 also had positive TgAb, which are known to interfere with the measurement of circulating Tg. However, because the Tg assay used was relatively insensitive (lower limit of detectability, 3 ng/mL) it could be possible that many if not all the undetectable Tg levels in patients with metastases would be detectable with more current assays.

The influence of nodal status on the outcome of DTC in adults continues to be controversial. Some studies observed "no difference in survival" and/or "recurrence" between patients with or without lymph node metastases at initial surgery (25,26). However, more recently, many studies observed that the presence of lymph node metastases at initial surgery is associated with higher recurrence rates (5,27-30) or with a shorter survival (31-37). In summary, although the importance of metastatic disease in lymph nodes is still de-
bated, most authors concur that nodal metastases should be detected early and treated. Furthermore, when there are signs of dedifferentiation, such as absence of $^{131}$I uptake and/or Tg production, this prognostic factor becomes even more significant (38–40). Also, in children the presence of lymph node metastasis has been associated with a high rate of local recurrence (41–44).

In conclusion, our study in children demonstrates that neck ultrasonography can detect lymph node metastases that are not suspected by palpation, diagnostic WBS, or serum Tg determination. Furthermore, neck ultrasonography can locate the anatomic site of the metastatic lymph nodes. Early detection of lymph node metastases may improve the quality of life and survival in children with DTC, particularly when there are signs of dedifferentiation.

Acknowledgment

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