VIA MEDICA

Nuclear Medicine Review 2014, 17, 1: 3–6
DOI: 10.5603/NMR.2014.0002

ISSN 1506–9680

Original

Contribution of ultrasound examination in the detection of neck recurrence in low-risk differentiated thyroid carcinoma patients at first follow-up visits

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The author(s) declare that they have no conflict of interests.

[Received 13 VIII 2013; Accepted 7 I 2014]

Abstract

BACKGROUND: In the most patients with differentiated thyroid carcinoma (DTC), recurrent disease occurs in the neck region, but the usefulness of neck ultrasound (US) in its diagnosis is not clear. The aim of this study was to evaluate the significance of US in the detection of neck recurrence in low-risk DTC patients at first follow-up visits.

MATERIAL AND METHODS: A total of 32 patients, who had a history of DTC and radioiodine therapy after thyroidectomy with low doses of iodine 131 (3.7 GBq), were enrolled in this study. About 6 months after first ablation, the patients underwent clinical examination, iodine 131 scanning, measurement of thyroglobulin (Tg) after T4 withdrawal, thyroid-stimulating hormone measurement, TgAb measurement, and neck sonography with US.

RESULTS: Recurrence of thyroid cancer was suspected in the neck region in 17 patients (53.1%) of the study cohort. There were six groups based on the results of posttreatment serum Tg levels, 131I whole body scan (131I WBS), and US in the detection of DTC neck recurrences. Fifteen patients had negative results of three modalities (group 1); seven patients had US evidence of neck lesions but negative 131I WBS and serum Tg results(group 2); three patients had positive results of 131I WBS but negative US and serum Tg results (group 3); four patients had positive results of serum Tg results but negative US and 131I WBS results (group 4); two patients lacked 131I WBS evidence of neck lesions, but US and serum Tg suggested the diagnosis of neck recurrence (group 5), and one subject had evidence of neck recurrence in three modalities (group 6).

CONCLUSION: These findings may imply that neck sonography together with determination of serum Tg levels and 131I WBS after thyroid-stimulating hormone therapy should be considered the diagnostic modality of choice for postoperative surveillance, even in low-risk DTC patients.

KEY words: Differentiated thyroid carcinoma (DTC), neck ultrasonography, serum thyroglobulin (Tg), 131I whole body scan (131I WBS)

Nuclear Med Rev 2014; 17, 1: 3–6

Background

Differentiated thyroid carcinoma (DTC) is distinguished by an indolent growth rate with low morbidity and mortality [1]; however, cancer recurrence increases its mortality rate [2] and 8% of patients with local recurrence will ultimately die from cancer [3].

In patients with low-risk DTC, follow-up is carried out with 131I whole body scan (131I WBS) and serum thyroglobulin (Tg) measurements [4, 5]; however, 131I WBS has insufficient sensitivity for this purpose [6–9]. Serum Tg levels in these patients can also have limited sensitivity [10].

In the most patients with DTC, recurrent disease occurs in the neck region, but the usefulness of neck ultrasound (US) in its diagnosis is not clear [11]. Some authors have proposed its routine

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use because it can overcome the limitations of serum Tg levels and 131I WBS in the detection of locoregional disease [6–8, 12–17].

The aim of this study was to assess the significance of US in the diagnosis of recurrent DTC in the neck region and the contribution of US in the early diagnosis of low-risk DTC patients.

Materials and methods

Participants and study design

In this retrospective study, we recruited 32 patients over a period of 2 years, from August 2009 to May 2011. All patients had a history of DTC and radioiodine therapy after thyroidectomy with low doses of iodine 131 (3.7 GBq). No patient had extra-thyroid uptake on the pretreatment 131I WBS scan (diagnostic scan). All patients had undetectable serum anti-Tg antibody (TgAb) levels. The patients underwent clinical examination; 131I WBS; measurements of Tg, TgAb, and thyroid-stimulating hormone (TSH) after stopping levothyroxine for 1 month and liothyronine for 2 weeks; and neck sonography. The interval between the first ablation therapy and the visits was about 6 months in all patients. Patients were cautiously questioned about any exposure to exogenous iodine before scanning, and all patients were informed to avoid drugs containing iodine during the preparation period for the diagnostic scan. Patient clothing was changed before scanning to prevent contamination. At the time of the 131I WBS, all patients had a serum TSH level above 30 mIU/L.

Clinical examination was the palpation of the neck area for the diagnosis of lymph nodes or masses located in the neck, which was always performed by the same physician (MM). Initial surgical procedures included thyroid and central neck compartment dissection. Also, in suspicious cases, lymph node dissection was performed and checked histopathologically. All the included patients did not have any lymph node involvement.

This study was approved by the institutional ethics committee of Isfahan University of Medical Sciences, and all patients gave written informed consent.

Detection of neck recurrence

Neck recurrence is defined as a lesion in a patient who previously considered free of residual neck tumors following surgical manipulation and thyroid remnant ablation [8, 18]. In our participants, diagnosis of DTC neck recurrence was based on fine-needle aspiration biopsy (FNAB). Patients with normal sonographic findings but positive Tg results or positive WBS results or both were considered to have cervical recurrence. Absence of disease was described as negative Tg, 131I WBS, and sonographic findings as well as negative Tg and 131I WBS results and negative findings for neoplasia by FNAB in the patients with abnormal sonographic findings.

Acquisition protocols

For I131 WBS scintigraphy, patients took 185 MBq 131I orally, and scanning was performed 48 h later. Planar images were acquired by a gamma camera (Scintronix, UK) with a high-energy parallel hole collimator with an energy setting of 364 keV ± 10%. Images were interpreted by two experienced nuclear medicine physicians.

Neck US examination

Sonography was carried out with a linear multifrequency 7.5––10 MHz transducer. Suspected lymph node and mass lesions were conducted by FNA with a 23-gauge needle and a 5 or 10 mL syringe. The smears were prepared with hematoxylin and eosin,

Papanicolaou, and Giemsa stains and evaluated by a cytopathologist experienced in DTC.

Measurement of serum thyroglobulin

Serum Tg and anti-Tg antibody levels were measured by radioimmunoassay using commercial kits (BRAHMS Tg-plus DYNO test and BRAHMS anti-Tgn DYNO test, respectively). Since TSH was raised in all patients, Tg levels ≥ 2 μg/L were considered abnormal [8]. Because circulating AbTg interferes with Tg assays, we routinely screened all participants for serum anti-Tg antibody, using passive hemagglutination. Patients with positive anti-Tg antibody and negative Tg were excluded from this study. In addition, serum TSH was determined with a third-generation double antibody assay.

Statistical analysis

Serum Tg levels before and after I-131 therapy were compared using the Wilcoxon signed-rank test. In addition, a Chi-square test was used to compare differences between categorical variables. A P value of 0.05 or less was considered significant. Statistical analysis was performed using SPSS version 18 (SPSS Inc., Chicago, IL).

Results

A total of 32 patients (25 females and seven males) with a mean age of 44.81 ± 11.50 years took part in the study. All patients had the papillary type of DTC (PCDTC). During the initial operation, all patients underwent total thyroidectomy.

All patients received 3.7 GBq (100 mCi) radioiodine. The mean pretreatment Tg was 17.25 ± 9.95 ng/mL (range 1–45 ng/mL), the mean posttreatment Tg was 12.31 ± 28.30 ng/mL (range 0.00–130 ng/mL), and the difference was not statistically significant ($P > 0.05$).

Recurrence of thyroid cancer was suspected in the neck region in 17 patients (53.1%). Based on the findings of the serum Tg assessment, seven patients demonstrated an increment in posttreatment Tg relative to pretreatment Tg values, while the remaining 25 patients showed a decrease in the Tg value.

In the posttreatment 131I WBS, four patients showed increased activity in the neck region. The remaining 28 cases had no abnormal activity on 131I WBS in the posttreatment survey.

There were six groups based on the results of posttreatment serum Tg levels, 131I WBS, and US in the detection of DTC neck recurrences. Fifteen patients had negative results of three modalities (group 1); seven patients had US evidence of neck lesions but negative 131I WBS and serum Tg results (group 2); three patients had positive results of 131I WBS but negative US and serum Tg results (group 3); four patients had positive results of serum Tg but negative US and 131I WBS results (group 4); two patients lacked 131I WBS evidence of neck lesions but US and serum Tg suggested the diagnosis of neck recurrence (group 5), and one subject had evidence of neck recurrence in three modalities (group 6) (Table 1).

Table 1. Six groups based on the results of posttreatment serum Tg levels, 131I WBS, and US in the detection of DTC neck recurrences

Group	Number of cases	Serum Tg levels	131I WBS	Neck US
1	15	–	–	–
2	7	–	–	+
3	3	–	+	–
4	4	+	–	–
5	2	+	–	+
6	1	+	+	+

131I WBS — 131 iodine whole body scan; US — ultrasound; DTC — differentiated thyroid carcinoma

In total, 10 patients presented a lesion in the neck region with a diameter range of 5–15 mm on US examination. Recurrences were not palpable upon clinical exam in any patient. Ultrasound-guided FNAB was performed in nine of 32 patients (seven cases in group 2 and two cases in group 5) who had US findings suspicious for DTC neck recurrence. FNAB was not performed in one patient in group 6. Cytology was indicative of malignancy in four cases in group 2 and one case in group 5; in four cases, this showed reactive lymphadenitis.

The all five patients were underwent repeated surgery and received 5.55 GBq doses of 131I.

Discussion

The classic treatment for differentiated thyroid cancer (DTC) is surgical resection followed by 131I ablation [19]. However, even with this standard therapy, the recurrence rate of thyroid cancer is 20% [20].

Serum Tg in the absence of TgAb and stimulated by raised TSH is the most sensitive marker for diagnosis of tumor recurrence after initial therapy [21, 22]. However, some patients might not be distinguished by Tg measurement alone, especially those with local recurrences [23]. In a review including eight studies in low-risk patients, Tg failed to detect 9% of recurrences, all in the neck [24]; this issue was also observed in other studies [6, 7]. In our study, levels of Tg after T4 withdrawal of 2 ng/mL or greater were observed in seven out of 14 (50%) patients with recurrence, yielding questionable sensitivity but similar to values reported in previous studies [8, 25].

Diagnostic iodine scan has inadequate sensitivity, especially for detection of cervical metastases, and is therefore of limited utility in this situation [8, 12, 26]. In our series, 131I WBS showed four out of 14 (28.6%) patients with neck recurrence.

In our low-risk series, neck recurrences occurred in six out of 32 (18.7%) patients, which was similar to previous results [8]. These data support the need for careful surveillance of the neck region, even in low-risk patients.

Moreover, an important finding in this study is that US provides early diagnosis of suspected recurrences that were not detected by serum Tg and 131I WBS. Serum Tg and 131I WBS results were negative in four out of 32 (12.5%) of the patients with neck recurrences that were detected by US examination.

Several explanations may clarify these findings. First, the small size of some tumor recurrences may reduce 131I uptake and Tg production and release as seen in our study; the maximum tumor size in our study was 15 mm. Due to their small size and/or their deep location, no patient with neck recurrence was suspected on clinical examination.

Second, the absence of tumor cell differentiation has been seen in patients with DTC local recurrences [27, 28]. Third, although patients with positive anti-Tg antibodies were not included in this investigation, slight interference from low levels of anti-Tg antibodies cannot be excluded [8].

The follow-up approach in DTC recurrence in regional lymph nodes is not clearly defined [29, 30]. After surgical resection of thyroid cancer, it is advised to have neck US after 6 and 12 months and every 3–5 years thereafter [29, 31].

The US findings are useful; however, they do not provide sufficient information to ascertain the diagnosis of thyroid cancer recurrence in the neck region [30, 32]. Some echogenic signs may help detect a malignant process in the neck; however, morphologic features must be confirmed by cytopathological survey [30, 32]. For that reason, ultrasound-guided FNAB should be carried out in any suspicious situation of cancer recurrence.

Seo et al. compared the diagnostic values of US, contrast-enhanced computed tomography (CT), and F-FDG positron emission tomography (PET)/CT for detecting recurrent DTC in the neck in 20 patients [33]. The sensitivity, specificity, and accuracy were 69.2%, 89.7%, and 80.0% for ultrasound; 63.5%, 94.8%, and 80.0% for CT; and 53.8%, 79.3%, and 67.3% for PET/CT, respectively [33]. This study demonstrated that US may detect neck recurrences in low-risk DTC patients with an otherwise negative follow-up.

On evaluating these data, we support the idea that use of US for follow-up of DTC is essential. However, US examination did not show neck recurrences in three patients with positive 131I WBS and in four patients with positive serum Tg levels. In addition, the other limitation of US examination is that the accuracy of this modality is operator dependent. Therefore, our data indicate that the combination of the three diagnostic modalities (measurement of serum Tg level, US, and 131I WBS) gives excellent follow-up results and provides optimal treatment.

It should be stated that our study had some limitations, such as its small sample size and that we could not follow up over a prolonged period of time. In addition, the PET facility was not available to obtain precise statistical parameters. However, further evidence is needed to confirm our preliminary results.

Conclusion

Our findings suggest that neck sonography together with the determination of serum Tg levels and 131I WBS after TSH stimulation should be considered the diagnostic modality of choice for postoperative surveillance, even in low-risk DTC patients.

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