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Original Scientific Paper

THE CLINICAL VALUE OF THE I-131 DIAGNOSTIC WHOLE-BODY SCAN IN THE FOLLOW-UP OF INTERMEDIATE- AND HIGH-RISK PATIENTS WITH DIFFERENTIATED THYROID CANCER

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SUMMARY – The purpose of this study was to analyze the clinical value of the I-131 diagnostic whole-body scan (WBS) during the follow-up of intermediate- and high-risk patients with differentiated thyroid cancer (DTC) with respect to new classification criteria for risk groups (American Thyroid Association, ATA 2015). The retrospective study included an analysis of 121 intermediate- and high-risk patients with well-differentiated thyroid cancer, who were treated and followed up in the Clinical Institute of Nuclear Medicine and Radiation Protection, University Hospital Centre Osijek in the period between 2004 and 2018. There were 35 (28.9%) structural recurrent or persistent diseases in the group of intermediate- and high-risk patients. The sensitivity of the I-131 diagnostic WBS in the detection of structural recurrent or persistent disease was 51.4% (18/35). The negative predictive value (NPV) of the I-131 diagnostic WBS performed 12 months after initial treatment was 82.8%. The I-131 diagnostic WBS combined with stimulated serum thyroglobulin (sTg) measurement detected structural recurrence or persistent disease in 32 out of 35 patients (91.4%). When combined, their NPV was 94.4%, which was identical to the NPV of the sTg measurement as the only test performed. In conclusion, our study showed that the I-131 diagnostic WBS in patients with negative sTg findings obtained 12 months after initial therapy did not have additional diagnostic value in detecting structural recurrent or persistent disease in the group of intermediate- and high-risk patients.

Keywords: *Thyroid cancer; I-131 whole-body scan; Thyroglobulin*

Introduction

The follow-up of patients with differentiated thyroid cancer (DTC) after initial treatment (surgery and radioiodine ablation therapy) is based on three main diagnostic tools: the measurement of serum thyroglobulin (Tg), a neck ultrasound (US)

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and a diagnostic whole-body scan (WBS). All three diagnostic methods are used in the early detection of thyroid cancer recurrence or persistent disease. The development and improvement of the risk stratification system used to estimate the risk of recurrence, primarily ATA (American Thyroid Association) 2009 and ATA 2015[1,2], contributed to a better and more individualized approach to the management of patients with DTC. Additionally, numerous guidelines for the follow-up of patients with DTC (European and other international guidelines) show a pronounced tendency to either reduce the frequency of certain diagnostic tests during follow-up or to completely omit such tests, considering the constant growth of the proportion of low-risk DTC patients[3-11]. According to ATA guidelines for the follow-up of patients with DTC, it is not recommended to use the I-131 diagnostic WBS in low-risk patients with negative stimulated thyroglobulin (sTg) and normal neck US findings[2].

The purpose of this study was to analyze the clinical value of the I-131 diagnostic WBS during the follow-up of intermediate- and high-risk patients with respect to new classification criteria for ATA risk groups in patients with DTC (ATA 2015). The following diagnostic parameters were specified: the sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) of the I-131 diagnostic WBS. The primary aim of the study was to determine whether the I-131 diagnostic WBS in the group of intermediate- and high-risk patients had additional diagnostic value in relation to other diagnostic tools; more specifically, whether it provided any additional diagnostic information with regard to recurrence or metastatic disease that could not be detected based on elevated serum Tg or neck US findings.

Patients and methods

This retrospective study included an analysis of 121 intermediate- and high-risk patients with well-differentiated thyroid cancer, who were treated and followed up in the Clinical Institute of Nuclear Medicine and Radiation Protection, University Hospital Centre Osijek in the period between 2004 and 2018. Their median postoperative follow-up period was 8 years (interquartile range 5-10.2 years). All patients with DTC underwent initial therapy that included at least total thyroidectomy (with or without neck dissection) followed by radioiodine ablation therapy using I-131. The majority of intermediate- and high-risk patients received an initial dose of 100 mCi (3700 MBq) of I-131. The standard procedure for all intermediate- and high-risk patients with DTC included the first diagnostic testing under TSH stimulation 12 months after initial treatment. This procedure included the measurement of sTg, an I-131 diagnostic WBS and neck US (with a fine-needle aspiration biopsy (FNAB) of suspicious nodules). TSH stimulation was achieved by withdrawing thyroxine therapy for 4-5 weeks and achieving the target value of TSH > 30 mU/L[12,13]. In all the patients, the I-131 diagnostic WBS was performed in the period between the third and fifth day following the administration of a diagnostic dose of 2-5 mCi (74-185 MBq) of I-131. The diagnostic WBS was performed by using a large field-of-view gamma camera with a high-energy collimator. In the period observed in this study, scintigrams were made using the Siemens "Orbiter 3700" single-detector gamma camera (since 2004), and the Siemens single-detector "e.cam" gamma camera (since 2007). Individual anterior and posterior scintigrams were made (5-10 minutes per scintigram) for most of the major anatomical regions of the body. All patients had at least six scintigrams made, which included the head and neck region (anterior projection (AP) and lateral right and left projection (LD and LS)), the thorax (AP and posterior projection) and the abdomen (AP). When there was a clinical indication to do so, additional projections of certain other anatomical regions were also included. A pathological uptake in regions outside the thyroid bed (thyroid remnant) was considered to be a positive I-131 diagnostic WBS, whereas any findings indicating activity inside the thyroid bed region were categorized as indeterminate findings (non-specific uptake of small-volume thyroid remnant). The value of the I-131 diagnostic WBS was analyzed on a total of 121 patients. Two patients had indeterminate findings. In the relevant period, several different tests for thyroglobulin measurement from the group of immunometric assays were used. All the assays had high sensitivity (minimal functional sensitivity < 0.9 ng/mL), whereas the lower limit of detection was at least 0.2 ng/mL. Also, thyroglobulin assays were standardized

against the certified reference material for human Tg (CRM 457)[14]. Values of < 1 ng/mL were considered a negative sTg and values of ≥ 2 ng/mL a positive sTg. An sTg value between 1 and 2 ng/mL was considered a limit value indicating an indeterminate test result.

Patients were categorized based on risk group, according to the ATA 2015 classification criteria for risk groups.

The assessment of the efficiency of the I-131 diagnostic WBS was performed using variables for the assessment of diagnostic test validity – sensitivity, specificity, PPV and NPV. Nominal indicators were presented using frequency distribution for each diagnostic group. Data were entered in an Excel spreadsheet and analyzed with the MedCalc ver. 18.11.3 (MedCalc Software, Ostend, Belgium) statistical software.

Results

Out of a total of 35 cases of structural recurrent or persistent disease found in intermediate- (13/35) and high-risk patients (22/35) with DTC, the largest number was detected by stimulated thyroglobulin measurement (sTg > 2 ng/mL), which yielded 32 positive findings (91.4%), followed by neck US with FNAB, which yielded 22 positive findings (62.9%) and finally by the I-131 diagnostic WBS, which yielded 18 positive findings (51.4%) (Fig. 1).

Measures of validity and the predictive value of the I-131 diagnostic WBS (performed 12 months after initial treatment) in the detection of structural recurrent or persistent disease for patients in the intermediate- and high-risk group were the following: sensitivity 51.4%, specificity 97.6%, NPV 82.8% and PPV 90% (Table 1).

Table 1. Structural recurrent or persistent disease in intermediate- and high-risk groups of patients with DTC and an I-131 diagnostic WBS performed 12 months after initial treatment

Structural recurrent or persistent disease	WBS (+)*	WBS (-)
yes	18	17
no	2	82

* (+) positive I-131 WBS: pathological uptake outside the thyroid bed; DTC = differentiated thyroid cancer; WBS = whole body scan

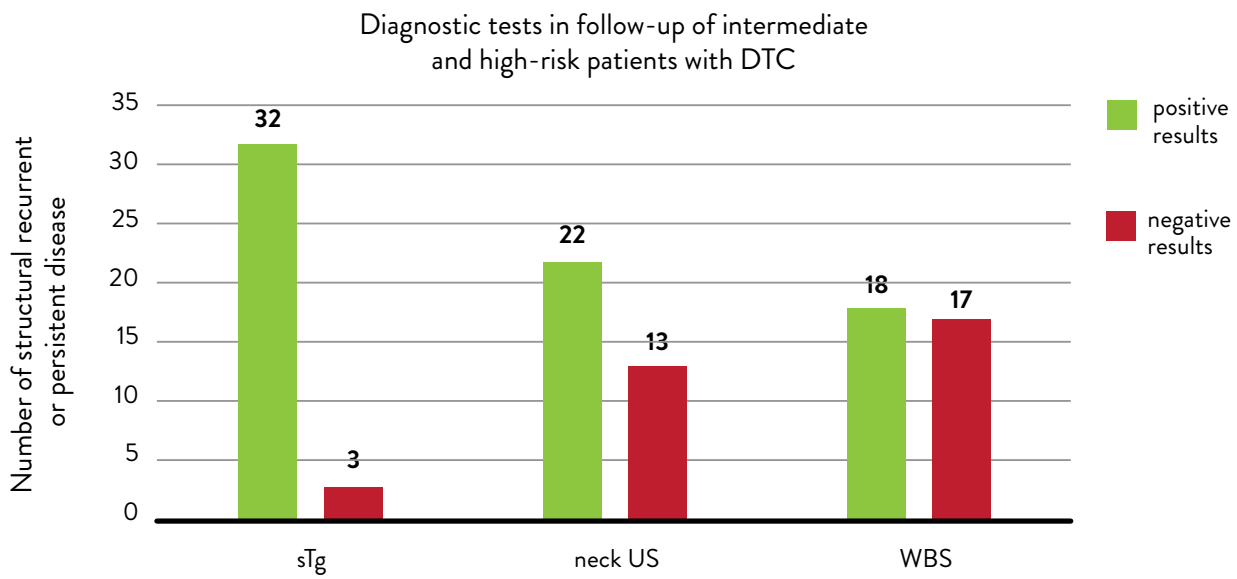

Fig. 1. Diagnostic tests in the detection of structural recurrent or persistent disease (35/121) — stimulated serum thyroglobulin (sTg), neck ultrasound (US) and I-131 diagnostic whole-body scan (WBS) in intermediate- and high-risk groups of patients with differentiated thyroid cancer (DTC) performed 12 months after initial treatment

In the group of intermediate-risk patients, the NPV of the I-131 diagnostic WBS performed 12 months after initial treatment amounted to 90.5%. In this group of patients, the sensitivity of the I-131 diagnostic WBS amounted to 38.5% with a specificity of 97.4% and PPV amounted to 71.4%.

In the group of high-risk patients, the NPV of the I-131 diagnostic WBS performed 12 months after initial treatment amounted to 40%. Additionally, the sensitivity of the I-131 diagnostic WBS amounted to 59.1% with a specificity and PPV of 100%. The NPV of the first sTg in the detection of structural recurrent or persistent disease measured 12 months after initial treatment was 94.4% in both the intermediate- and high-risk group. Separately, in the intermediate-risk group the NPV of sTg was 96.1% and in the high-risk group it was 66.7%. The I-131 diagnostic WBS combined with sTg measurement detected structural recurrent or persistent disease in 32 out of 35 patients. The sensitivity of the two tests combined was 91.4% and was identical to the sensitivity of individual sTg tests. Also, their NPV was 94.4% when combined and was identical to the value of the NPV of sTg measurement as the only test performed. The I-131 diagnostic WBS in patients with negative sTg findings did not have additional diagnostic value in detecting structural recurrent or persistent disease; each of the 3 patients with recurrent or persistent disease whose sTg test was negative also had a negative I-131 diagnostic WBS. In both the intermediate- and high-risk group, the NPV of sTg in combination with neck US in the detection of structural recurrent or persistent disease was 96.3%.

Discussion

Based on the obtained results, the I-131 diagnostic WBS had relatively low sensitivity (51.4%) in detecting structural recurrence or persistent disease, which is consistent with the results of other studies[15-18]. In a certain number of patients with DTC, specifically 2 out of 121 patients (1.7%) who had negative findings in other tests (sTg measurement and neck US), the I-131 diagnostic WBS showed uptake confined only to the thyroid bed. In this study, such findings were categorized as non-specific uptake, considering that ATA classifies such findings as an indeterminate response to initial therapy. Those patients also received additional radioiodine therapy for remnant thyroid tissue elimination, to facilitate further follow-up. There was no evidence of structural recurrent or persistent disease identified subsequently in that group of patients.

Although the NPV of the I-131 diagnostic WBS performed 12 months after initial treatment (for both risk groups) was 82.8%, it was higher in the intermediate-risk group (90.5%); in the high-risk group, NPV was very low (40%). Additionally, the NPV of the first sTg in the detection of structural recurrent or persistent disease measured 12 months after initial treatment was very high (96.1%) in the intermediate-risk group, unlike in the high-risk group, where the NPV of sTg was very low (66.7%). The NPV of the I-131 diagnostic WBS combined with sTg measurement performed 12 months after initial treatment was 94.4% and was identical to the value of the NPV of sTg measurement as the only test performed. The NPV of sTg in combination with neck US (with FNAB) was as high as 96.3%. This study confirmed that sTg measurement and neck US with FNAB are superior diagnostic tools in the follow-up of patients with DTC[19-24]. The first measurement of sTg 12 months after the initial treatment revealed only three patients with false negative test results. In one of these three patients, structural recurrent disease was detected using neck US with FNAB.

In conclusion, our study showed that the I-131 diagnostic WBS in the group of intermediate- and high-risk patients, after negative results of serum sTg, had no additional diagnostic value in detecting structural recurrent or persistent disease. Therefore, particularly in the group of intermediate-risk patients with DTC, no routine use of the I-131 diagnostic WBS is required if there is no evidence of disease based on the remaining diagnostic tests – serum sTg and neck US findings.

The authors have no conflict of interest to declare.

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Sažetak

KLINIČKA VRIJEDNOST DIJAGNOSTIČKE SCINTIGRAFIJE CIJELOGA TIJELA S I-131 U PRAĆENJU SREDNJERIZIČNIH I VISOKORIZIČNIH BOLESNIKA S DIFERENCIRANIM KARCINOMOM ŠTITNJAČE

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Svrha ovoga istraživanja bila je analizirati vrijednost dijagnostičke scintigrafije cijeloga tijela (WBS) s I-131 u praćenju srednjerizičnih i visokorizičnih bolesnika s diferenciranim karcinomom štitnjače (DTC) s obzirom na nove klasifikacijske kriterije za rizične skupine bolesnika (American Thyroid Association, ATA 2015). Retrospektivno istraživanje obuhvatilo je analizu 121 bolesnika iz skupine srednjerizičnih i visokorizičnih bolesnika s DTC, liječenih i kontroliranih u Kliničkom zavodu za nuklearnu medicinu KBC-a Osijek u razdoblju između 2004. i 2018. godine**.** Glavni cilj istraživanja bio je utvrditi je li dijagnostički WBS s I-131 imao dodatnu dijagnostičku vrijednost o strukturnom recidivu / perzistirajućoj bolesti koji nisu detektirani povišenim stimulirajućim serumskim tireoglobulinom (sTg) ili ultrazvukom vrata. U skupini srednjerizičnih i visokorizičnih bolesnika s DTC bilo je 35 (28,9 %) strukturnih recidiva / perzistirajućih bolesti. Osjetljivost dijagnostičkog WBS s I-131 u detekciji strukturnih recidiva / perzistirajuće bolesti bila je 51,4 % (18/35) dok je negativna prediktivna vrijednost (NPV) iznosila 82,8 %. NPV kombiniranih testova dijagnostičkog WBS s I-131 zajedno sa sTg bila je istovjetna vrijednosti NPV-a sTg kao samostalnog dijagnostičkog testa (94,4 %). Dijagnostički WBS s I-131 kod srednjerizičnih i visokorizičnih bolesnika s negativnim sTg nije imao dodatnu dijagnostičku vrijednost u detekciji strukturnog recidiva / perzistirajuće bolesti, odnosno svi bolesnici sa strukturnim recidivom / perzistirajućom bolesti koji su imali negativan sTg, imali su negativan nalaz i na dijagnostičkom WBS s I-131.

Ključne riječi: *Karcinomi štitnjače; Scintigrafija cijelog tijela s I-131; Tireoglobulin*