



Wartość oznaczania stężenia tyreoglobuliny w aspiratach z węzłów chłonnych szyi u chorych ze zróżnicowanym rakiem tarczycy

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Streszczenie

Wstęp: Przerzuty zróżnicowanego raka tarczycy (DTC, *differentiated thyroid cancer*) występują najczęściej w węzłach chłonnych szyi. Badanie ultrasonograficzne (USG) jest czułą metodą w wykrywaniu powiększonych węzłów chłonnych szyi, ale nie jest wystarczająco swoiste. Biopsja aspiracyjna cienkoigłowa celowana (BACC) ma większą swoistość, ale nie jest wystarczająco czuła.

Celem pracy była ocena wartości diagnostycznej stężenia tyreoglobuliny (Tg) w aspiratach z węzłów chłonnych szyi u chorych z DTC.

Materiał i metoda: Badaniem objęto 105 chorych po całkowitej tyreoidektomii i po leczeniu ablacyjnym ¹³¹I. Wszyscy chorzy wykazywali brak jodochwytności w obrębie szyi, prawidłową scyntyografię całego ciała (u większości — w warunkach endogennej stymulacji hormonem tyreotropowym [TSH, *thyroid-stimulating hormone*]) oraz powiększone w badaniu USG węzły chłonne szyi. U wszystkich pacjentów objętych badaniem oznaczono stężenie i odzysk Tg w surowicy, wykonano BACC (2–3 aspiraty z każdego węzła chłonnego szyi), a następnie przepłukano igłą 125 μ l 0,9-procentowym NaCl i oznaczono stężenie Tg w popłuczynach, używając zestawu do oznaczania Tg w surowicy. Za podwyższone stężenie Tg w popłuczynach przyjęto wartość równą średniej plus 2 odchylenia standardowe dla chorych z ujemnym wynikiem BACC (bez obecności komórek nowotworowych). Wszystkich chorych z dodatnim wynikiem BACC (z obecnością komórek nowotworowych) lub podwyższonym stężeniem Tg w popłuczynach operowano.

Wyniki: Dodani wynik BACC stwierdzono u 15 chorych (w 28 węzłach chłonnych), a podwyższone stężenie Tg w popłuczynach u 22 chorych (w 48 węzłach chłonnych).

We wszystkich węzłach chłonnych z dodatnim wynikiem BACC stwierdzono podwyższone stężenie Tg w popłuczynach. U 7 chorych (w 20 węzłach chłonnych) z ujemnym wynikiem BACC wykazano podwyższone stężenie Tg w popłuczynach. U wszystkich chorych z wyjątkiem 1 osoby (we wszystkich węzłach chłonnych z wyjątkiem 2 węzłów) z podwyższonym stężeniem Tg w popłuczynach stwierdzono wynik histopatologiczny wskazujący na przerzut DTC.

Wnioski: 1. BACC nie jest wystarczająco czuła do wykrywania obecności przerzutów DTC do węzłów chłonnych szyi. 2. Oznaczanie stężenia Tg w popłuczynach igły biopsyjnej jest metodą 100-procentowo czułą. 3. BACC charakteryzuje się 100-procentową swoistością w wykrywaniu obecności przerzutów DTC do węzłów chłonnych szyi. 4. Oznaczanie stężenia Tg w popłuczynach igły biopsyjnej może być fałszywie dodatnie. 5. Obie metody powinny być stosowane do wczesnego wykrywania przerzutów DTC do węzłów chłonnych szyi.

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Słowa kluczowe: zróżnicowany rak tarczycy, biopsja aspiracyjna cienkoigłowa celowana, stężenie tyreoglobuliny

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The diagnostic value of thyroglobulin concentration in fine-needle aspiration of the cervical lymph nodes in patients with differentiated thyroid cancer

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Abstract

Introduction: Recurrent differentiated thyroid cancer generally occurs first in the neck. Ultrasound is sensitive in detecting enlarged cervical lymph nodes but is not specific enough. Ultrasound-guided fine-needle biopsy increases the specificity but still may fail to detect a recurrence of the disease in the cystic metastatic lymph nodes.

The aim of the study was to estimate the value of Tg concentration in the needle washout after fine-needle aspiration of suspicious lymph nodes.

Material and methods: The 105 patients studied had presented one or more enlarged suspicious cervical lymph nodes. All had undergone total thyroidectomy and ¹³¹I ablative therapy. Serum thyroglobulin (Tg) concentration was within the 0.15–711.5 ng/ml range (mean 22.24 ng/ml) and Tg recovery range 94–100%. The positive Tg washout concentration cut-off value was established as equal to the mean plus two standard deviations of the Tg washout concentration of patients with negative cytology.

Results: Lymph node involvement was diagnosed by cytology in 15 patients and in 28 lymph nodes. Positive Tg washout concentration was found in 22 patients and in 48 lymph nodes. All the lymph nodes which turned out to have positive cytology had a positive Tg washout concentration. All lymph nodes with positive cytology were positive in pathology. Seven patients and 20 lymph nodes with nega-

tive cytology were positive in the Tg washout concentration test. All but one patients and all but two lymph nodes with a positive Tg washout concentration had positive pathology.

Conclusions: 1. Ultrasound-guided fine-needle biopsy is not sensitive enough to detect all metastatic lymph nodes. 2. The Tg washout concentration test is 100% sensitive in the detection of metastatic lymph nodes. 3. Cytology in ultrasound-guided fine-needle biopsy is 100% specific. 4. The Tg washout concentration test carries a risk of false-positive results. 5. Both methods should be used for early detection of metastatic lymph nodes in patients with differentiated thyroid cancer.

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Key words: differentiated thyroid carcinoma, fine-needle biopsy, Tg concentration

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Introduction

The surveillance of patients operated on for differentiated thyroid carcinoma has been limited to periodic physical examination of the neck, chest x-ray and whole-body scan (WBS), performed after withdrawal of levothyroxine (LT₄) therapy and following repeated ¹³¹I treatments. Reliable thyroglobulin (Tg) assays have revealed a large number of patients who have serological evidence of residual, recurrent or metastatic disease that is undetected in WBS [1–3]. The serum Tg concentration in patients undergoing

LT₄ therapy is not sensitive enough to detect all early recurrent cancers. Thyrotropin (TSH) stimulation increases the sensitivity but serum Tg concentration is unreliable in the presence of anti-thyroglobulin antibodies and has not proven sensitive enough to detect single or few small metastatic foci. Furthermore, elevated serum Tg detects only the presence of recurrent or metastatic cancer but not its location, which is in fact more important [4–6].

Recurrent differentiated thyroid cancer generally occurs first in the neck [5, 7]. Ultrasound is sensitive in detecting enlarged cervical lymph nodes but is not spe-

cific enough. Ultrasound-guided fine-needle biopsy increases the specificity but still may fail to detect the recurrence of the disease in the cystic metastatic lymph nodes [5, 7–10].

Radioiodine alone can effectively treat tumour foci exhibiting radioiodine uptake. This first constitutes the basis for surgical treatment of metastatic lymph nodes and this is then followed by additional ^{131}I therapy [11].

The aim of the study was to estimate the value of thyroglobulin concentration in the needle washout after fine-needle aspiration of suspicious lymph nodes.

Material and methods

A total of 105 patients (85 females and 20 males) aged 16–83 years (with a mean age of 50.8 years) were studied, 93 of whom had papillary and 12 follicular thyroid cancer. In ultrasound examination they presented one or more enlarged suspicious cervical lymph nodes. All the patients had undergone total thyroidectomy and ^{131}I ablative therapy, according to the criteria of the Association of Polish Surgeons and the Polish Society of Endocrinology. ^{131}I WBS, mostly in endogenous TSH stimulation conditions (TSH 1.28–99.82 $\mu\text{IU/ml}$; mean 71.59 $\mu\text{IU/ml}$) achieved within at least four weeks of withdrawal of LT_4 therapy was performed and showed radioiodine uptake in none of the patients. Serum Tg concentration and Tg recovery were measured in all the patients (Brahms Tg-S Dynotest) and was within the 0.15–711.5 ng/ml range (mean 22.24 ng/ml), recovery range 94–100%. Ultrasound-guided (linear probe 7.5 MHz, AU3 Partner, EsaoteBiomedica, Firenze, Italy) fine-needle biopsy by standard technique was performed in all of the patients, taking two or three aspirations of each lymph node. The material collected was prepared for cytology. Then the needle (0.5 mm thick, 2.5 cm long; 25 gauge) was washed out with 125 μl of 0.9% saline and the Tg concentration and Tg recovery were measured using the same Tg kit. A positive Tg washout concentration cut-off value was established equal to the mean plus two standard deviations of the Tg washout concentration of patients with negative cytology. Finally, all the patients with positive cytology and (or) positive Tg washout concentration were treated with surgery. The results of fine-needle Tg washout concentration were compared to cytology and pathology.

Results

Positive cytology was diagnosed in 15 patients and in 28 lymph nodes. Positive Tg washout concentration was found in 22 patients and in 48 lymph nodes. All the lymph nodes which turned out to have positive cytol-

ogy had positive Tg washout concentration. All the lymph nodes with positive cytology were positive in pathology. Seven patients and 20 lymph nodes with negative cytology were positive in the Tg washout concentration test. All but one patient and all but two lymph nodes with a positive Tg washout concentration had positive pathology.

Discussion

Differentiated thyroid carcinoma very often appears in young adults and so it is incumbent on us to find a proper method of monitoring this increasing population over the years. Early diagnosis of recurrence is a new medical challenge. Recurrent disease most frequently occurs first in the cervical lymph nodes and so a six-monthly ultrasound examination is essential screening [12]. Any cervical lymph nodes that are enlarged (greater than 5 mm in height or with a height/width ratio greater than 0.5 in the transverse view) or suspicious (with microcalcifications, punctate flecks of calcium, cystic necrosis and absence of a hilar line) should be biopsied [13–16]. Measuring Tg in needle aspirates of the neck lymph nodes is beneficial as sensitivity of Tg washout concentration increases to 100% in detecting lymph node metastases. So far there have been no reports of false-positive Tg washout concentration tests [5]. In our study we report that one patient with two lymph nodes with negative cytology was false-positive in the Tg washout concentration test. This patient had two enlarged suspicious lymph nodes biopsied (with two aspirates per node). The Tg concentration in fine-needle washouts was in the 32.46–137.0 ng/ml range, while serum Tg concentration was 2.87 ng/ml in TSH stimulation conditions (73.31 $\mu\text{IU/ml}$). The patient underwent lymphadenectomy and two biopsied suspicious lymph nodes were removed, which was confirmed in post-operative ultrasound examination performed a few days after surgery. To our surprise, these two lymph nodes were free of metastatic thyroid cancer cells in routine and also in a serial pathological examination. There were also negative results from immunohistochemistry for the presence of Tg and cytokeratine. Negative results in pathology and in immunohistochemistry ruled out metastases [17].

The presence of Tg in the lymph vessels draining the thyroid gland, has been demonstrated in rats and monkeys [18]. This indicates that probably the Tg protein particle alone can be drained through the lymphatic system, but this does not explain our false-positive result, for in this case the immunohistochemistry also turned out to be negative. Beside one "overdiagnosed" and "overtreated" patient without reasonable explanation, the study indicates that high concentrations of Tg

are present in the cervical lymph nodes when they are of metastatic thyroid cancer origin. A Tg washout concentration test should be performed routinely in the diagnostic evaluation of any suspicious cervical lymph nodes or neck masses of unknown origin outside the thyroid gland. In our study 6 out of 21 patients would have been "underdiagnosed" and eventually "undertreated", if this procedure had not been followed.

Conclusions

1. Ultrasound-guided fine-needle biopsy is not sensitive enough to detect all metastatic lymph nodes.
2. The Tg washout concentration test is 100% sensitive in the detection of metastatic lymph nodes.
3. Cytology in ultrasound-guided fine-needle biopsy is 100% specific.
4. The Tg washout concentration test carries a risk of false-positive results.
5. Both methods should be used for early detection of metastatic lymph nodes in patients with differentiated thyroid cancer.

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