Endokrynologia Polska/Polish Journal of Endocrinology
Tom/Volume 63; Numer/Number 3/2012
ISSN 0423–104X

The importance of inferior-superior thyroid veins sampling in the diagnosis of thyroid carcinomas

Znaczenie badania krwi pobranej z żył tarczowych górnych i dolnych w rozpoznawaniu raka tarczycy

Suat Kutun[1], Aybala Agac Ay[1], Alper Celik[1], Uygun Turan[2], Haluk Ulucanlar[1], Abdullah Cetin[1]

[1]Department of General Surgery, Ankara Oncology Education and Research Hospital, Turkey
[2]Department of General Surgery, Ankara Gazi Hospital, Turkey

Abstract

Introduction: We aimed to determine whether levels of thyroglobulin measured in blood from the inferior-superior thyroid veins and the peripheral antecubital vein could predict the presence of thyroid carcinoma in patients undergoing surgery for thyroid diseases.
Material and methods: Sixty-one patients were prospectively enrolled in the study. Levels of thyroglobulin were analysed. Sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) of these markers were investigated.
Results: Twenty-six out of 61 patients (42.6%) with malignancy were diagnosed. The levels of thyroglobulin in the inferior-superior thyroid veins were higher than those in the peripheral antecubital vein ($p = 0.001$). The levels of thyroglobulin in the blood taken from the antecubital vein and the inferior-superior thyroid veins did not differ between benign and malignant thyroid disorders. For thyroglobulin, sensitivity was 33.3%, specificity 60.6%, PPV 27.8%, and NPV 66.7% respectively.
Conclusion: Thyroglobulin levels in the antecubital vein compared to the inferior-superior thyroid veins were not significant either in benign or malignant disorders. **(Pol J Endocrinol 2012; 63 (3): 202–205)**

Key words: *thyroglobulin, thyroid vein sampling, thyroid cancer*

Streszczenie

Wstęp: Celem badania było ustalenie, czy oznaczenie stężeń tyreoglobuliny we krwi pobranej z żył tarczowych górnych i dolnych oraz z żyły przedłokciowej ma wartość prognostyczną w wykrywaniu nowotworów tarczycy u chorych poddawanych zabiegom chirurgicznym z powodu chorób tarczycy.
Materiał i metody: Do tego prospektywnego badania włączono 61 chorych. Analizowano wartości stężeń tyreoglobuliny. Badano czułość, swoistość oraz wartość prognostyczną dodatnią (PPV) i ujemną (NPV) tych wskaźników.
Wyniki: U 26 spośród 61 chorych (42,6%) rozpoznano chorobę nowotworową. Stężenia tyreoglobuliny w żyłach tarczowych dolnych i górnych były wyższe niż stężenia mierzone we krwi pobranej z żyły przedłokciowej ($p = 0{,}001$). Stężenia tyreoglobuliny w próbkach krwi pobranych z żyły przedłokciowej i żył tarczowych nie różniły się istotnie między osobami z łagodnymi i złośliwymi guzami tarczycy. Oznaczenie tyreoglobuliny cechowało się czułością wynoszącą 33,3%, swoistością równą 60,6%, PPV — 27,8% i NPV — 66,7%.
Wnioski: Porównanie stężeń tyreoglobuliny w żyle przedłokciowej i w żyłach tarczowych górnych i dolnych nie miało istotnego znaczenia diagnostycznego w wykrywaniu zarówno zmian łagodnych, jak i złośliwych. **(Endokrynol Pol 2012; 63 (3): 202–205)**

Słowa kluczowe: *tyreoglobulina, próbki krwi z żył tarczowych, nowotwór tarczycy*

Introduction

Thyroid cancers represent the commonest malignancy of the endocrine system, and the second commonest malignancy in the head and neck region (excluding skin cancers) [1]. The initial evaluation of the thyroid nodule continues to rely chiefly on fine needle aspiration (FNA) and ultrasound imaging. Despite the improvements in imaging methods and the wide usage of FNA, there is also a group of patients who cannot be diagnosed as differentiated thyroid carcinoma preoperatively [2]. Two of the advances in optimising operative strategy in thyroid disorders are intraoperative frozen section analysis and intraoperative touch imprint cytology [3]. They might improve outcomes in patients with suspicious nodular disorders of the thyroid gland.

Recent clinical guidelines have attempted to settle various controversies, but many inherent errors of clinical testing result in delayed diagnosis and unnecessary surgery. A better solution may ultimately involve the use of molecular markers of thyroid carcinogenesis, but further research is still needed regarding the basic biology of thyroid cancer [4]. A very well known marker for medullary thyroid carcinoma, calcitonin, is the

Aybala Agac Ay, Department of General Surgery, Ankara Oncology Education and Research Hospital, 06200 Ankara, Turkey, tel: +90 505 230 15 66, fax: +90 312 34 549 79, e-mail: draybala.a@gmail.com

most reliable marker in the course of the disease. We hypothesised that the concentrations of thyroglobulin for thyroid carcinoma would be higher in blood taken from the thyroid vein, relative to their concentrations in systemic blood.

The purpose of this study was therefore to test the hypothesis as to whether blood levels of the markers differ between the inferior thyroid vein and the peripheral circulation, and also to test whether these markers are useful in predicting the diagnosis made via microscopic exams of tissue specimens.

Material and methods

Sixty-one consecutive patients with an FNA diagnosis of suspicious for malignancy or malignant nodular goitre were prospectively enrolled in the study. The study was approved by the local ethics committee and written informed consent was obtained from each patient. Our research complied with the principles of the Helsinki Declaration.

Of the 61 patients, 48 were female (78.7%) and 13 were male (21.3%). Overall mean age was 47 years (range 23–78 years). Patients with thyroid cancers with distant metastases or a history of previous radiation exposure were excluded. All patients were preoperatively evaluated by physical examination, monitoring of serum thyroglobulin and serum thyrotropin, neck ultrasonography, and chest radiography. Thyroid scans were performed in all patients. Ultrasound-guided FNA was successfully performed using a 22-G needle prior to surgery. Smears of the FNA samples were stained by May-Grünwald-Giemsa stain and evaluated immediately by the cytologist. Patients with suspicious nodules were re-evaluated with intraoperative frozen section. Final diagnoses were confirmed postoperatively with permanent histopathological sections. Levels of serum thyroglobulin were measured in 10 ml of blood taken from the antecubital vein preoperatively, and in 10 ml of blood taken from the inferior-superior thyroid vein intraoperatively at the beginning of surgery.

The samples were centrifuged at 3,500 rpm for 5 minutes in order to separate the plasma. After separation, all samples were frozen at –30° and levels of thyroglobulin were measured with a Liaison kit (Byk-Songtec Diagnostica, Liaison thyroglobulin, 2001 USA) by immunometric assay. Normal levels for thyroglobulin were 1.5–4 ng/mL respectively. All malignant patients were separated into two groups. The separation was performed in two different ways to find out the positive predictability of independent variables (levels of thyroglobulin) for subjects due to postoperative histopathologic diagnosis. Re-arranged end results of the patients and their groups: prevalence of malignant cases; correlation of the levels of samples from benign cases (n = 35) with those of malignant patients (n = 26) according to postoperative histological examination.

Sensitivity, specificity and predictivity were assessed for thyroglobulin as follows: sensitivity (definition of the thyroid cancers detected with high marker levels) was defined as true positive / [true positive + false negative]; specificity (definition of benign thyroid diseases detected with normal levels of markers) was defined as true negative / [true negative + false positive]; positive predictive value (PPV) (probability of diagnosing the disease if the FNA is positive) and negative predictive value (NPV) (probability of diagnosing normal subjects if the FNA is negative) were calculated as follows:

— PPV: (Prevalence) × (Sensitivity) / (Prevalence) × (Sensitivity) + [(1-Prevalance) × (1-Specificity)]
— NPV: [(1-Prevalance) × (Specificity) / / [(1-Prevalance) × (Specificity)] + [(Prevalence) × × (1-Sensitivity)]
— Numeric variables between the groups were analysed using Mann-Whitney U test. The significance level was taken at p below 0.05.

Results

Preoperatively, eight patients (13.1%) were diagnosed with thyroid malignancy by FNA. According to the postoperative pathology reports, an additional 18 patients were diagnosed with malignancy. Thus in total, 26 patients (42.6%) with malignancy were diagnosed. All cases underwent surgery after achieving a euthyroid state. All nodules presented with a solid or mixed (solid-cystic) pattern. Mean nodule size was 21.1 mm (min 1.2 mm, max 9.5 cm). Mean size of the nodule was 29.4 mm in benign, and 21.3 mm in malignant, subjects. There were 42 cases with multinodular goitre, and 12 cases with single solitary nodule. We detected seven malignancies among 12 cases (58.33%) with single solitary nodule and 19 malignancies among 42 cases (45.23%) with multinodular goitre. This difference was not significant (p = 0.27). The difference in mean size of the nodules between the two groups was not significant (p = 0.11). In thyroid scans, there were only three cases of hot nodule.

Less than total thyroidectomy was performed in 32 patients (52.4%) and total thyroidectomy in 29 patients (47.6%). Papillary thyroid carcinoma was detected in 20 patients (32.8%), and follicular thyroid carcinoma in six patients (9.8%). Six of 20 cases with papillary thyroid cancer had occult carcinoma. None of the patients had enlarged cervical lymph nodes.

Mean values of thyroglobulin in blood taken from antecubital vein, inferior-superior thyroid vein, and

Table I. *Mean values of thyroglobulin in blood taken from antecubital vein, inferior-superior thyroid veins, and their ratios relative to postoperative diagnosis according to permanent section*

Tabela I. *Średnie wartości stężenia tyreoglobuliny w próbkach krwi pobranych z żyły przedłokciowej i z żył tarczowych górnych i dolnych oraz stosunek tych wartości w zależności od pooperacyjnego rozpoznania histopatologicznego*

	Thyroglobulin [ng/mL]		p
	Benign	Malignant	
ACV	9.94 ± 17.43	9.92 ± 16.34	0.33
ITV-STV	72.37 ± 34.98	68.4 ± 30.42	0.82
ACV/ITV-STV ratio	0.18 ± 0.29	0.31 ± 0.42	0.08

ACV — antecubital vein; ITV — inferior thyroid vein; STV — superior thyroid vein

their ratios relative to postoperative diagnosis according to permanent section, are shown in Table I.

According to postoperative diagnoses, the levels of thyroglobulin differed significantly between patients with malignancy and those with benign disease. In terms of the veins from which the samples were drawn, thyroglobulin levels were much higher in inferior-superior thyroid veins, and this difference was significant ($p = 0.001$) For thyroglobulin marker, the ratio of levels in peripheral antecubital vein blood to levels in inferior thyroid vein blood was calculated. The ratio of the levels of markers in antecubital vein to inferior-superior thyroid veins were not significant either in benign or malignant disorders.

Sensitivity, specificity, PPV and NPV were calculated. For thyroglobulin, sensitivity was 33.3%, specificity 60.6%, PPV 27.8%, and NPV 66.7%, respectively.

Thyroglobulin levels have provided additional information on the course of the disease beside that provided by FNA. Also, in cases with occult carcinoma, levels of thyroglobulin were within normal limits both in the antecubital vein and the inferior-superior thyroid veins. Furthermore, we detected elevated levels of thyroglobulin in cases with benign disorders that in turn prevented their use as a guide to avoid operative interventions.

Discussion

Surgical treatment is still the treatment of choice for most thyroid diseases, especially for malignant disorders. Often, surgery is carried out in the presence of a suspicious nodule [5]. Preoperative diagnosis of thyroid malignancies predicts the limits of the surgical procedure. Furthermore, early detection of asymptomatic malignancy leads to better prognosis and outcome. Cost-effective screening methods used in other solid cancers like PSA, NSE, and β-HCG are still lacking in the early diagnosis of thyroid malignancies [6]. In experienced hands, diagnostic accuracy of about 90% is obtained by FNA [7]. In general, 20–30% of patients are referred for surgery on the basis of the FNA features [8]. Approximately one third (17% to 51%) of these cases have a thyroid malignancy. False-negative rates range from 1% to more than 11% [9]. The sensitivity is about 95%, and the specificity is 95% [10]. In our series, we detected lower rates of sensitivity and specificity in cases investigated for selective venous sampling with respect to thyroglobulin levels, thereby preventing their usage as a diagnostic or screening tool. However, like FNA, detection of TSH mRNA yielded encouraging results for discrimination between benign and malignant disorders of the thyroid [11]. In the cited article, the authors found better rates of sensitivity, specificity, and PPV, even in cases with indeterminate FNA. They further concluded that detection of TSH mRNA might be beneficial in the postoperative follow-up of patients with thyroid malignancies.

Levels of calcitonin are beneficial in the prediction and follow-up of patients with medullar thyroid carcinoma [12], but similar correlation between differentiated thyroid carcinomas and biochemical markers is still lacking. Thyroid carcinomas constitute a heterogeneous group of malignancy with ambiguous outcomes. There has been a demand for molecular markers to identify thyroid cancer pathogenesis and distinguish them from benign disorders of the thyroid [13]. Thyroglobulin has been extensively investigated from this aspect. Selective sampling has been the mainstay of some studies in cases with medullar thyroid cancers.

It has been previously stated that selective venous sampling in patients with medullar thyroid carcinoma might be an effective tool in the detection of early recurrences [14]. In another study by Mohammed et al. [15], the role of calcitonin in 77 patients with medullar thyroid cancers was studied by selective venous cannulation of the thyroid, cervical, and mediastinal regions. These two studies formed the basis of the idea of cannulating the inferior thyroid vein.

Since the first demonstration by Van Herle et al. that thyroglobulin , the main iodo-protein of the thyroid gland, was detectable in the circulation of normal subjects by using specific radioimmunoassay, an impressive number of papers have been produced describing several clinical applications of Tg measurements, which is higher in some diseases such as follicular thyroid cancer [16].

Thyroglobulin (Tg) is a large molecule containing 2,750 amino acids with a molecular weight of 330 kD and 20 putative N-linked glycosylation sites. Tg gene

expression is regulated by thyroid transcription factor 1 and human paired box 8. Iodinated Tg is stored in the lumen of the thyroid follicles and is released in response to specific hormonal stimulation by thyroid stimulating hormone (TSH). Following Tg reabsorption by thyrocytes and subsequent degradation, thyroid hormones triiodothryronine (T(3)) and thyroxine (T(4)) are secreted in the bloodstream [17].

Now, because of its higher levels in follicular cancer, the measurement of Tg is a mainstay of the post-surgical follow-up of follicular thyroid cancer, After total thyroid ablation by surgery and radioiodine, the Tg level should be measured. It must be undetectable, i.e. any detectable level should alert the clinician [18].

Ringel et al. [19] observed the importance of the levels of thyroglobulin in the early diagnosis of residual and recurrent thyroid carcinomas. They investigated the m-RNA of thyroglobulin by radioimmunoassay, and concluded that positive scans result in a dismal prognosis. Even if we have observed high levels of thyroglobulin in our patients with malignancy, these high levels did not correlate with the final diagnosis. This gives rise to the question as to whether, if we had used radioimmunoassay, our results might have differed. Taking into account the high rates of thyroglobulin, both in benign and malign cases, it is disputable to make this kind of conclusion. Thorsen et al. [20] stated that preoperative levels of thyroglobulin correlated with malignant disorders of the thyroid. According to our results, we do not agree with the statement that a significant correlation can be achieved if the sampling has been made preoperatively. But high levels of thyroglobulin in benign diseases of our series are, to some degree, attributable to intraoperative over-manipulation of the thyroid gland or size of the nodule. There is also evidence to suggest that the difference in the levels of thyroglobulin in cases with a previous history of radiation exposure is significant in nodule formation [21].

Even if none of our patients was exposed to radiation, we agree that thyroglobulin levels might be altered by differential factors, beside the underlying disease. Bellantone et al. [22] have shown the presence of circulating thyroid follicle cells following thyroidectomy, by detecting thyroglobulin mRNA on rt-PCR (reverse transcriptase-Polymerase Chain Reaction) images. RT-PCR is capable of detecting only one cancer cell in 10^5 cells. Using this kind of advanced method, together with selective venous sampling, might be helpful in identifying thyroid malignancies.

Conclusion

We believe that the progress towards identifying molecular markers that might be involved in thyroid cancer pathogenesis will be the pioneering scenario in the future treatment of thyroid disease.

References

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics. CA Cancer J Clin 2007; 57: 43–66.
2. Lefevre JH, Tresallet C, Leenhardt L, Jublanc C, Chigot JP, Menegaux F. Reoperative surgery for thyroid disease. Langenbecks Arch. Surg 2007; 392: 685–691.
3. Taneri F, Poyraz A, Salman B. Using imprint and frozen sections in determining the surgical strategies for thyroid pathologies. Endocr Regul 2001; 35: 71–74.
4. Mechanick JI, Carpi A. Progress in the preoperative diagnosis of thyroid nodules: managing uncertainties and the ultimate role for molecular investigation. Biomed Pharmacother 2006; 60: 393–395.
5. Roher HD, Clark OH. Thyroid and Parathyroid. In: Wheeler MH eds. Indications and strategy for surgery of thyroid nodules. Progress in Surgery of Thyroid Tumours. Basel, Karger Press 1988; 1–20.
6. Schwartz MK. Thyroid**.** In: De Vita VT Jr eds. Cancer Markers. Cancer, Principles and Practice of Oncology. Lippincott-Raven Press 1993; 531–542.
7. Wang C, Vickery AI, Maloof F. Needle biopsy of the thyroid. Surg Gynecol Obstet 1976; 143: 365–368.
8. Gharib H, Goellner JR. Fine needle aspiration biopsy of the thyroid: an appraisal. Ann Intern Med 1993; 118: 282–289.
9. Gharib H. Fine needle aspiration biopsy of thyroid nodules: advantages, limitations, and effect. Mayo Clin Proc 1994; 69: 44–49.
10. Orell SR, Philips J. Fine needle biopsy and cytological diagnosis of thyroid lesions. Monogra Clin Cytol 1997; 14: 1–9.
11. Milas M, Mazzaglia P, Chia SY. The utility of peripheral thyrothropin mRNA in the diagnosis of follicular neoplasms and surveillance of thyroid cancers. Surgery 2007; 141: 137–146.
12. Iacobone M, Niccoli-Sire P, Sebag F, DeMicco C, Henry JF. Can sporadic medullary thyroid carcinoma be biochemically predicted? Prospective analysis of 66 operated patients with elevated serum calcitonin levels. World J Surg 2002; 26: 886–890.
13. Finley DJ, Arora N, Zhu B, Gallagher L, Fahey TJ. Molecular profiling distinguishes papillary carcinoma from benign thyroid nodules. J Clin Endocrinol Metab 2004; 89: 3214–3223.
14. Abdelmoumene N, Schlumberger M. Selective venous sampling catheterization for localization of persisting medullar carcinoma. Br J Cancer 1994; 69: 1141–1144.
15. Mohammed D, Mrad B. Value of venous catheterization and calcitonin studies in the treatment and management of clinically unapparent medullar thyroid carcinoma. Cancer 1989; 63: 133–138.
16. Pacini F, Pinchera A. Serum and tissue thyroglobulin measurement: clinical applications in thyroid disease. Biochimie 1999; 81: 463–467.
17. Lin JD. Thyroglobulin and human thyroid cancer. Clin Chim Acta 2008; 388: 15–21.
18. Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JW, Wiersinga W. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol 2006; 154: 787–803.
19. Ringel MD, Ladenson PW. Molecular diagnosis of residual and recurrent thyroid cancer by amplification of thyreoglobulin m-RNA in peripheral blood. J Clin Endocrinol Metab 1998; 83: 4435–4442.
20. Thorsen SO, Myking O. Serum thyroglobulin as a preclinical tumor marker in subgroups of thyroid cancer. Br J Cancer 1988; 57: 105–108.
21. Schneider AB. Prospective serum thyroglobulin measurements in assessing the risk of developing thyroid nodules in patients exposed to childhood neck irradiation. J Clin Endocrinol Metab 1985; 61: 547–550.
22. Bellantone R, Lombardi CP. Validity of thyroglobulin m-RNA assay in peripheral blood of postoperative thyroid carcinoma patients in predicting tumour recurrences vary according to the histological type. Cancer 2001; 92: 2273–2279.