The Frequency of Incidental Thyroid Carcinoma in Patients with Graves' Disease

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Abstract

Background: The presence of hypoactive nodules in patients with Graves? disease (GD) is an important factor in deciding on surgical treatment. Literatures are inconclusive about the increase in the risk of malignancy in cases of hypoactive nodules accompanying GD. The incidence of incidental malignancy in patients that underwent surgical treatment for GD were evaluated. Materials and Methods: This study included 108 patients that underwent thyroidectomy due to GD. Hypoactive nodules and diffuse hyperplasia were observed in 59 (54.6

Index terms— grave?s disease, thyroid nodule, incidental thyroid cancer, surgical treatment.
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1 I. Introduction

raves disease (GD) was first described by Dr. Caleb Hillier Parry and Dr. Robert James Graves' in 1825, followed by Dr. Carl A. Von Basedow in 1840 [1]. Antithyroid drugs and radioactive iodine (RAI) are the classical treatment options; near-total or TT are standard when surgery is preferred [2,3]. After Shapiro et al. observed thyroid cancer in 9% of patients with GD, a large number of studies on the relationship between GD and thyroid cancer were conducted [4]. The rate of incidental cancer in patients with GD that underwent thyroidectomy was reported to be 0%-16.6%, and the cancer was clinically more aggressive [5][6][7][8]. The variation in the frequency of incidental thyroid cancer and its aggressive clinical course led to questions about the treatment options for patients with GD.

Thyroid nodules are frequently present in patients with GD, occurring in 22%-45% of patients [9][10][11][12]. The incidence of malignancy ranges from 0.4% to 9.8% in patients with thyroid nodules; thus, the treatment of nodules in patients with GD remains a controversial issue due to an increased risk of cancer [13][14][15][16][17][18][19]. TT prevents recurrence, significantly contributes to the improvement of exophthalmia in GD, and eliminates the malignancy, as observed in the present study (10.2%). These benefits have solidified the role of TT in the treatment of patients with GD [20]. The aim of the present study was to determine the rate of histopathologically observed incidental malignancy in patients that underwent surgical treatment for GD with hypoactive nodule.

The study was reviewed by the appropriate medical ethics committee and was performed in accordance with the medical ethics standards laid down in an appropriate version of the 1964 Declaration of Helsinki. The study was approved by The Institute's Protocol Review Board.

2 II. Material and Methods

Data obtained from 1627 patients that underwent surgery due to benign pathologies of the thyroid gland at 2 different hospitals between 2003 and 2012 were retrospectively evaluated. This clinicpathological study included 108 (6.6%) of these patients that had GD and underwent TT. Clinical and laboratory findings and ultrasonography

(USG) and scintigraphy data were recorded. None of the 108 patients received RAI therapy or radiotherapy to the neck prior to surgery.

GD was diagnosed based on history, signs of hyperthyroidism, elevated free thyroid hormones (fT3 and fT4), low thyroid-stimulating hormone (TSH) and

3 III. Results

The mean ± standard deviation (SD) for GD (with or without nodule) and euthyroid patients' ages was found to be 47,1±12,7 years (16-78 years) / 37,5±12,5 years (16-76 years) and the female/male (F:M) ratio was 79/29 and 462/131 (p>0.05) Table-1. Among the 108 patients with GD TT was performed in 67 (62%) cases due to recurrence following antithyroid drug treatment, 14 (12.9%) cases that had signs of compression due to a large goiter, 9 (8.3%) cases with ophthalmopathy, and 18 (16.7%) cases due to patient preference. In 11 of the 108 patients (10.2%) incidental thyroid carcinoma was observed via histopathological examination, 7 of which were among the 59 patients with nodules (11.9%) and 4 of which were among the 49 patients (8.2%) with diffuse hyperplasia, but no nodule. As shown in Table-2, mean age of the 4 patients with GD was 41.2 ± 6.5years (37-51 years), the F: M ratio was 4:0, and ophthalmopathy was observed in 2 cases. Mean size of incidental thyroid carcinoma based on histopathological examination in the 4 patients with GD was 9.5 ± 4.7 mm (5-15 mm) (2 were ?10 mm and the other 2 were 11-20 mm). Histopathological diagnosis in all cases was papillary carcinoma (2 were microcarcinomas). One patient had a multifocal tumor and 2 patients were treated with RAI ablation. Recurrence and mortality did not occur during 30 ± 19.2 months (9-55 months) of follow-up.

Among the 7 patients with nodular GD that also had incidental thyroid carcinoma mean age was 35.1 ± 10.3 years (23-54 years), the F:M ratio was 6:1, ophthalmopathy was observed in 3 cases, mean tumor size was 11.5 ± 6.7 mm (5-25 mm) (5 were ?10 mm, 1 was 11-20 mm, and 1 was ?21 mm), histopathological diagnosis was papillary carcinoma in 6 cases (5 had microcarcinoma), and follicular carcinoma was diagnosed in 1 case (the only male patient in the study group). Histopathological characteristics of the tumors were as follows: capsular and vascular invasion (n = 1); capsular invasion only (n = 1); multifocal tumor with capsular and vascular invasion (n = 1); multifocal tumor with capsular invasion (n = 1); multifocal tumor without capsular or vascular invasion (n = 1). In all, 5 patients were treated with RAI ablation therapy. Recurrence and mortality were not observed during 25.7 ± 10.7 months (12-41 months) of follow-up (Table -2). There wasn't a significant difference in tumor size or mean age between the patients with and without nodules (P > 0.05). The clinical and histopathological characteristics of the11 patients with incidental thyroid carcinoma are shown in Table **??**

4 IV. Discussion

Thyroid nodules are very common in the general population. The incidence of palpable nodules in regions in which iodine deficiency is endemic is 15% and as high as 50% when thyroid USG is used [13,21]. The incidence of thyroid nodules in autopsy series varies between 40% and 50% [22]. In the present study 59 (54,6%) of 108 patients that underwent surgery due to GD had solid nodules, which is higher than previously reported and might have been due to the fact that in addition to physical examination imaging techniques were used to detect nodules [5,7,9,10].

The incidence of thyroid carcinoma in patients with GD was 10.2% in the present study, versus previously reported rates as high as 16.6% [5][6][7]. As the number of histological sections applied to a specimen increases so does the probability of a finding of incidental malignancy in patients with GD with or without nodules.

Papillary thyroid carcinoma is the most common pathological subtype of thyroid cancer, with an incidence of 85% [23,24]. According to World Health Organization (WHO) classification of thyroid cancers, papillary carcinomas ?10 mm are defined as papillary microcarcinoma [24]. In the present study 7 (70%) of 10 patients with incidental papillary thyroid carcinoma had microcarcinoma, which is lower than previously reported rates (75%-100%) of papillary microcarcinoma in GD and in the long-term follow-up of these patients mortality was not observed and the recurrence rates were 3.4%-7.7% in 2 studies, whereas in the present study recurrence and mortality did not occur during follow-up of 11 patients [25][26][27].

The optimal treatment of patients with nodular GD remains controversial. According to the recent studies, the risk of malignancy is higher in patients with nodular GD and, as such, thyroidectomy is recommended in the early phase of the disease which also facilitates early diagnosis of incidental thyroid carcinoma in endemic regions [28]. In the present study the rate of incidental thyroid malignancy rate was higher in the patients with nodules than in those without nodules (11.9% and 8.2%, respectively). In addition, absence of nodules in GD does not eliminate the risk of malignancy.

Incidentally detected thyroid malignancies in patients with GD are often microcarcinomas; in the present study the papillary microcarcinoma rate was 70%. Most cases of thyroid malignancies in patients with GD were characterized by an insidious clinical course and were detected incidentally; some patients had poor prognosis, developed distant metastases, and died due to disease [29,30]. The advantages of TT in GD are treatment of hyperthyroidism, prevention of relapse, treatment of compression-induced symptoms, contribution to pregnancy planning, and especially treatment of exophthalmia. In the present study TT was found to be advantageous for

Figure 1: The

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Characteristics	Graves disease patients (n:108)	Euthyroid patients (n:593)	P
Age in years (range)	47,14 ± 12.7	37.5 ± 12.5	0.332
Female: Male (F:M) ratio	79/29	462/131	0.573

Figure 2: Table 1 :

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		(2 microcarcinoma)	(5 microcarcinoma)
			1 follicular carcinoma
		50%	
	of microcarcinoma	1	83.3%
?	Multifocal tumor	0	3
?	Capsular invasion	0	4
?	Vascular invasion		2
RAI ablation therapy		2 cases	5 cases
Follow-up period in months (range)		30 ± 19.2 (9-55)	25.7 ± 10.7 (12-41)
Recurrence		-	-
Mortality		-	-

RAI: Radioactive iodine.

Figure 3: Table 2 ?

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Case	Age (years)	Gender (M, F)	Clinical Diagnosis	Tumor Size (mm)	Pathological Diagnosis	Multifocality	Capsular Invasion	Vascular Invasion	Surgery	Follow-Up Period (month
1	26.00	F	G + N	9	PC	-	+	+	BTT	23.00
2	37.00	F	G	15	PC	+	-	-	BTT	24.00
3	39.00	F	G	11	PC	-	-	-	BTT	55.00
4	23.00	F	G + N	5	PC	-	+	-	BTT	41.00
5	37.00	F	G + N	6	PC	+	+	+	BTT	26.00
6	33.00	F	G + N	25	PC	-	-	-	BTT	27.00
7	51.00	F	G	5	PC	-	-	-	BTT	32.00
8	38.00	F	G	6	PC	-	-	-	BTT	9.00
9	41.00	M	G + N	20	FC	-	-	-	BTT	12.00
10	54.00	F	G + N	5	PC	+	+	-	BTT	14.00
11	32.00	F	G + N	5	PC	+	-	-	BTT	37.00

[Note: F: Female; M: male; G: GD; N: nodule; PC: papillary carcinoma; FC: follicular carcinoma; -: negative result; +: positive result; BTT: bilateral total thyroidectomy.]

Figure 4: Table 3 :

101 preventing malignancy at a considerable rate of 10.2% and facilitating early diagnosis as well. These advantages
102 have solidified the role of bilateral TT in the treatment of GD. [1]

[Belfiore et al. ()] , A Belfiore , D Russo , R Vigneri , Filetti S Gd . *Clin Endocrinol* 2001. 55 (6) p. .

[Kasuga et al. ()] 'Clinical evaluation of the response to surgical treatment of Graves' disease'. Y Kasuga , A Sugenoya , S Kobayashi . *Surg Gynecol Obstet* 1990. 170 p. 327.

[Terzio?lu et al. ()] 'Concurrent hyperthyroidism and thyroid carcinoma'. T Terzio?lu , S Tezelman , Y Onaran , R Tanakol . *Br J Surg* 1993. 80 (10) p. .

[Koyuncu et al. ()] 'Could total thyroidectomy become the Standard treatment for GD?'. A Koyuncu , C Ayd?n , Ö Topçu , O N Gökçe , ? Elagöz , H S Dökmeta? . *Surg Today* 2011. 40 (1) p. .

[Feliciano ()] 'Everything you wanted to know about GD'. D V Feliciano . *Am J Surg* 1992. 164 (5) p. .

[Behar et al. ()] 'GD and thyroid cancer'. R Behar , M Arganini , T C Wu . *Surgery* 1986. 100 p. .

[Hedinger et al.] 'Histological typing of thyroid tumours'. C Hedinger , E D Williams , L H Sobin . *WHO International Histological Classification of Tumours*, (Berlin) Springer. 1988 p. . (2nd ed)

[Shapiro et al. ()] 'Incidence of thyroid carcinoma in GD'. S J Shapiro , N B Friedman , S L Perzik , B Catz . *Cancer* 1970. 26 (6) p. .

[Dobyns et al. (1974)] 'Malignant and benign neoplasms of the thyroid in patients treated for hyperthyroidism: a report of the cooperative thyrotoxicosis therapy follow-up study'. B M Dobyns , G E Sheline , J B Workman , E A Tompkins , W M Mcconahey , D V Becker . *J Clin Endocrinol Metab* 1974 Jun. 38 (6) p. .

[Okamoto et al. ()] 'Management of hyperthyroidism due to Graves' and nodular diseases'. T Okamoto , Iiharam , T Obara . *World J Surg* 2000. 24 (8) p. .

[Silver and Parangi ()] 'Management of thyroid incidentalomas'. R J Silver , S Parangi . *Surg Clin North Am* 2004. 84 (3) p. .

[Kraimps et al. ()] 'Multicentre study of thyroid nodules in patients with GD'. J L Kraimps , Bouin-Pineaumh , De Mathonnetm , L Calan , J Ronceray , J Visset . *Br J Surg* 2000. 87 (8) p. .

[Harach et al. ()] 'Occult papillary carcinoma of the thyroid, a 'normal' findings in Finland. A systematic autopsy study'. H R Harach , K O Franssila , V Wasenius . *Cancer* 1986. 58 p. .

[Sampson et al. ()] 'Occult thyroid carcinoma in Olmsted Country, Minnesota: prevalence at autopsy compared with that in Hiroshima and Nagasaki'. R J Sampson , L B Woolner , R C Bahn , L T Kurland . *Japan. Carcinoma* 1974. 34 p. .

[Pellegriti et al. ()] 'Outcome of differentiated thyroid cancer in Graves' patients'. G Pellegriti , A Belfiore , D Giuffrida . *J Clin Endocrinol Metab* 1998. 83 p. .

[Sakorafas et al. ()] 'Papillary thyroid microcarcinoma: a surgical perspective'. G H Sakorafas , J Giotakis , V Stafyla . *Cancer Treat Rev* 2005. 31 p. .

[Bramley and Harrison ()] 'Papiller microcarcinoma of the thyroid gland'. M D Bramley , B J Harrison . *Br J Surg* 1996. 83 p. .

[Gerenova et al. ()] 'Prevalence of thyroid carcinoma in GD: a retrospective study a cohort of 103 patients treated surgically'. J Gerenova , M Buysschaert , C Y Burbure , C Daumerie . *Eur J Intern Med* 2003. 14 (5) p. .

[Palit et al. ()] 'The efficacy of thyroidectomy for GD: a meta-analysis'. T K Palit , C C Miller , D M Miltenburg . *J Surg Res* 2000. 90 (2) p. .

[Angusti et al. (2000)] 'Thyroid cancer prevalence after radioiodine treatment of hyperthyroidism'. T Angusti , A Codegone , R Pellerito , A Favero . *J Nucl Med* 2000 Jun. 41 (6) p. .

[Mazzeferri ()] 'Thyroid carcinoma and Graves's disease'. E L Mazzeferri . *J Clin Endocrinol Metab* 1990. 70 (4) p. .

[Farbota et al. ()] 'Thyroid carcinoma in GD'. L M Farbota , D B Calandra , A M Lawrence . *Surgery* 1985. 98 p. .

[Ozaki et al. ()] 'Thyroid carcinoma in GD'. O Ozaki , K Ito , K Kobayashi , K Toshima , H Iwasaki , T Yashiro . *World J Surg* 1990. 14 (3) p. .

[Pacini et al. (1988)] 'Thyroid carcinoma in thyrotoxic patients treated by surgery'. F Pacini , R Elisei , Di Coscio , G C Anelli , S Macchia , E Concetti , R . *J Endocrinol ?nvest* 1988 Feb. 11 (2) p. .

[Chao et al. ()] 'Thyroid carcinoma with concurrent hyperthyroidism'. T C Chao , J D Lin , L B Jeng , M F Chen . *Arch Surg* 1999. 134 (2) p. .

[Brander et al. ()] 'Thyroid gland: US screening in a random adult population'. A Brander , P Viikinkoski , J Nickels , L Kivisaari . *Radiology* 1991. 181 p. .

[Cantalamessa et al. ()] 'Thyroid nodules in GD and the risk of thyroid carcinoma'. L Cantalamessa , M Baldini , Orsattia , L Meroni , Amodeiv , D Castagnone . *Arch Intern Med* 1999. 159 (15) p. .

[Carnell and Valente ()] 'Thyroid nodules in GD: classification, characterization, and response to treatment'. N E Carnell , W A Valente . *Thyroid* 1988. 8 (7) p. .

158 [Mishra and Mishra ()] 'Thyroid nodules in GD: implications in an endemically iodine deficient area'. A Mishra
159 , S Mishra . *J Postgrad Med* 2001. 47 (4) p. .

160 [Barakate et al. ()] 'Total thyroidectomy is now the preferred option for the surgical management of GD'. M S
161 Barakate , G Agarwal , T S Reeve , B Barraclough , B Robinson , L W Delbridge . *Aust N Z J Surg* 2002.
162 72 (5) p. .