Eur J Cancer Clin Oncol, Vol. 24, No. 2, pp. 299–304, 1988.
Printed in Great Britain

0277-5379/88$3.00+0.00
Pergamon Journals Ltd.

Clinical and Radio-diagnostic Aspects in the Evaluation of Thyroid Nodules with Respect to Thyroid Cancer

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INTRODUCTION

EARLY detection of biologically significant (*vide infra*) carcinoma in thyroid nodules is important since prognosis is generally very good with adequate treatment. In contrast to the former attitude: 'the only good thyroid nodules are those that have been removed', the more modern approach is to discriminate benign and malignant nodules before a thyroid operation. Several techniques have been used in this respect. All have drawbacks in the sense of relatively low specificity and sensitivity and/or dependence on (technical) experience. Therefore, many patients with thyroid cancer have to be analysed in order to obtain this experience. Since this is hardly possible within reasonable time because of the relatively low incidence of biologically significant thyroid carcinoma (especially follicular carcinoma), even in relatively large centres, the preoperative analysis should comprise a combination of data or investigations in order to increase the ultimate specificity and sensitivity of preoperative diagnosis of the malignancy of a thyroid nodule.

Before discussing the clinical and radio-diagnostic aspects in this context, one should be aware of the consequences of diagnosing thyroid carcinoma.

According to reports from the U.S.A., the incidence of diagnosed thyroid carcinoma is about 50 per 10^6 persons each year and the mortality rate about 6 per 10^6 persons each year [1, 2]. In contrast to these data and based on autopsies, the prevalence of occult carcinoma is 3–36% [3, 4]. In other words, almost all carcinomas are not detected during life and are apparently not life-threatening, thus biologically insignificant. On the basis of these figures one might expect, as is the case, that selection criteria determine the reported frequencies in the populations. Examples of these criteria are: clinical risk factors, extent of operation and histological work up.

At least one large necropsy study is indicative in this context [5]. Seventeen per cent of 1000 thyroid glands removed at consecutive routine necropsies contained *palpable* nodules (3% solitary and 14% multiple nodules), whereas the *total* prevalencies of these nodules, based on 2 mm slices, were 12% and 41% respectively. The prevalencies of thyroid carcinoma in these nodules were 12% (solitary palpable), 3% (multiple palpable), 9% (solitary non-palpable) and 3% (multiple non-palpable). Thus on histological grounds about half of all thyroids contain nodules, whereas *solitary* palpable and *solitary* non-palpable nodules harbour more cancer in contrast to their multiple counterparts. It is remarkable that of all thyroids, 7% contained one palpable in combination with multiple *non*-palpable nodules (included in the multiple non-palpable group) with a carcinoma percentage of 9, thus about the same figure as the solitary thyroid nodule. This finding might be of importance in the analysis of a patient with only one palpable thyroid nodule, in whom sonography or scintigraphy reveals multiple small lesions. Such a patient should be analysed further as having a solitary thyroid nodule with a higher probability of carcinoma than in the multiple nodule group. It should be emphasized however that in this study 26 out of a total of 28 primary thyroid carcinomas were of the 'occult' type. This prevalence of occult carcinoma is in the same order as that of carcinoma in the multiple nodule group. Only one carcinoma has been detected during life and was the cause of death.

To fulfil the need to increase the detectability of

cancer of a thyroid nodule before operation and to separate patients with a very low probability of thyroid malignancy, the impact of various clinical factors, blood analysis, sonography, X-ray investigations, scintigraphy and cytology will be mentioned.

CLINICAL FACTORS WHICH INCREASE THE PROBABILITY OF MALIGNANCY IN A THYROID NODULE ('RISK FACTORS')

A. *History*

1. *Sex.* A solitary nodule in males is more frequently malignant than in females, but the prevalence and incidence of a solitary nodule in females is higher.

2. *Growth of a nodule.* Significant continuous increase in dimension of the nodule: it is often stated that a papillary thyroid carcinoma is a slow growing tumour. However, in a report of 227 patients with thyroid malignancy, 51% of 105 patients with papillary carcinoma had an increase in tumour size within 12 months [6].

3. *X-Ray irradiation.* Previous external X-ray therapy to the head and neck of infants, children and adolescents can cause an increase in thyroid malignancies after a latent period. More than half of these tumours are of the occult type. Because of the relatively high prevalence of occult thyroid carcinoma in an unexposed population and the fact that about 55% of thyroid carcinomas in an exposed population were only detected at histological examination, the actual impact of external ionizing radiation to the thyroid is difficult to determine. However, a significant increase in prevalence of euthyroid nodular goitre has been observed (up to about 40% of exposed persons) [7, 8, Goslings BM, personal communication].

4. *Voice.* A hoarse voice and especially decreased mobility of a vocal cord: about 20% of patients with anaplastic or medullary thyroid carcinoma suffer from a hoarse voice and in case of papillary and follicular carcinoma in 10% and 3% of patients respectively. Paresis of a vocal cord can be encountered in 42% (anaplastic), 25% (medullary), 9% (follicular) and 2% (papillary carcinoma) [6].

5. *Family.* A family history of multiple endocrine neoplasia syndrome II (MEN II syndrome: medullary thyroid carcinoma, pheochromocytoma and hyperparathyroidism) and/or presence of symptoms of MEN II syndrome is indicative for this thyroid carcinoma. Calcitonine and CEA are the only tumor markers which can demostrate this thyroid malignancy before operation.

B. *Physical examination*

1. *Solitary aspect of the nodule.* Thyroid cancer is (clinically) usually restricted to one lobe (66% of anaplastic, 83% of papillary and 79% of follicular thyroid carcinoma) [9]. In 23 reports, comprising 23,000 patients with a solitary nodule, irrespective of the sono- and scintigraphic findings, 11% had a malignant thyroid tumour (*vide infra* for the impact of sono- and scintigraphic methods on the probability of thyroid cancer) [10].

2. *Consistency of the nodule.* Firm to hard consistency of the nodule is indicative of malignancy (55% of thyroid carcinoma is hard, 36% firm and 8% soft). Hard tumours have to be differentiated from calcification and lymphocytic thyroiditis. Infiltration in surrounding tissues, trachea or larynx is a characteristic feature of thyroid carcinoma (67%), although papillary cancer shows this feature in only 16%. The surface of the nodule with carcinoma has no special character; in 25% of cases it is smooth [9].

3. *Signs of metastases.* Significant palpable lymph nodes in the neck are often found (31% of all thyroid carcinomas), whereas proven metastases in neck lymph nodes are reported in 15–55% of all patients with thyroid carcinoma [6, 9].

Distant metastases are mostly found in patients with follicular carcinoma (20%), and in about 5% in cases with papillary, medullary or anaplastic cancer.

(CLINICAL) FACTORS WHICH RENDER MALIGNANCY LESS LIKELY

A. *History*

1. *Growth of a nodule.* A sudden, rapid increase in dimension of the nodule with subsequent decrease is in favour of a bleeding; symptoms of a subacute thyroiditis (SAT), like a rapid increase in thyroid volume (an anaplastic thyroid carcinoma with necrosis of normal thyroid tissue may mimic SAT!).

2. *Family.* A family history of multinodular goitre (MNG) (see below).

B. *Physical examination*

MNG. A so-called classical 'multinodular goitre' is hardly suspect of carcinoma. The following criteria should, however, be used to define the classical MNG. These are goitres of long standing with little or no progression in growth, and the absence of previous X-ray irradiation of the neck, paralysis of a recurrent nerve, lymph node enlargement in the thyroid region or a hard or firm nodule in the

thyroid. This type of MNG prevails in females and if often of familial tendency [11].

C. *Laboratory investigations*

1. *Decreased 'sensitive-TSH' value.* Hyperthyroidism due to overproduction of thyroid hormone by non-malignant thyroid tissue should be distinguished from overproduction by the malignancy itself. About 3% of patients with hyperthyroidism have been reported to have also a thyroid malignancy. Several tens of cases have been reported, in which the tumour itself caused thyrotoxicosis, of which three with a T_3-toxicosis [12, 13]. A malignancy of the thyroid can also lead, although exceptionally, to a thyrotoxicosis by causing necrosis of normal thyroid tissue: the 24 h uptake of radio-iodine is consequently low. An exception to the rule of a lower likelihood of thyroid malignancy in thyrotoxicosis is the occurrence of a diffuse toxic goitre in combination with a single palpable cold, solid nodule. The cancer likelihood is then the same as in a normal thyroid with a solitary nodule.

2. *Erythrocyte sedimentation rate (ESR).* An increased ESR might point to a subacute thyroiditis as the cause of the nodule.

3. *Serum calcium.* Signs of hypercalcaemia and the combination of an increased serum calcium and decreased serum phosphate are indicative that the nodule is possibly caused by a parathyroid tumour, but also to the presence of MEN II.

4. *Functional autonomy of a nodule.* A 'hot or toxic' nodule, thus with lesser or suppressed uptake of isotope (iodine or technetium) by the surrounding normal thyroid tissue, has a cancer probability of about 2%. The figures for the 'warm or indifferent' and 'cold' nodules are about 7% and 17%, respectively [10]. Thus the cancer-likelihood of a solitary nodule increases from 11% to 17% on the basis of the absence of tracer uptake by the nodule. Considering a hot or toxic nodule as benign and the indifferent and cold nodules as potentially malignant, then the overall sensitivity and specificity of this scintigraphy are 98% and only 10%, respectively.

5. *Ultrasonography.*

I. True cysts, which are smooth, thin-walled globular-shaped echo-free structures, are easily demonstrated by this technique and have a low probability of malignancy (below 5%). These structures have to be differentiated from semi-solid or (multi-) cystic nodules, in which the cancer prevalence is about three times higher. The prevalence of true cysts has been described to be 20% of solitary nodules, in general however, it is an infrequent finding [14].

II. Thyroid cancer is encountered in 1–4% of echo-rich nodules [15]. The percentage of solid hyperechoic nodules in solitary cold thyroid nodules is 6%.

The low prevalence of true cysts and echo-rich nodules, the lack of other ultrasonographic features, which distinguish benign and malignant nodules, and the fact that cytology is able to demonstrate the benign nature of true cysts, raise the question if there is, on a cost–benefit ratio, an indication at all to perform ultrasonography in the analysis of palpable solitary thyroid nodules, otherwise than as an expedient in thyroid biopsy.

X-RAY INVESTIGATIONS

1. *X-Ray of the chest*

In the analysis of the solitary palpable thyroid nodule (carcinoma prevalence about 11%) it is not justified to perform this investigation on a cost–benefit ratio, since of all thyroid carcinoma, about 10% have pulmonary metastases at the time of diagnosis [16], thus only 1% of all cases with a solitary palpable thyroid nodule.

2. *CT-scanning*

Like ultra-sonography, CT-scanning of the thyroid region has no characteristic features for benign or malignant thyroid disease to warrant the use of this technique in all cases with solitary thyroid nodule. Of course, local infiltration of malignant tissue into the trachea, muscles or vessels can easily be demonstrated, especially after an iodine-load. The drawback of an iodine-load is, however, absent or diminished radio-iodine uptake of thyroid tissue (e.g. metastases) for months and thus a lower efficiency of possible treatment with radio-iodine afterwards.

^{201}Tl-SCINTIGRAPHY

In recent years, ^{201}Tl-scintigraphy, about 5–15 min ('early scan') and 3–5 h ('delayed scan') after administration of ^{201}Tl, has attracted special attention, because of a reported high sensitivity (95%) and specificity (90%) in distinguishing malignant from benign lesions in the thyroid [17]. Malignant disease shows an increased uptake of ^{201}Tl in the early scan (non-specific!) *and* residual activity in the delayed scan. Absence of *decreased* activity in the delayed scan indicates a 100% prevalence of malignancy, whereas some fading but still residual activity decreases this percentage to 70%. A clear distinction between diffuse and localized residual activity has to be made, since chronic thyroiditis also shows an increased (diffuse) uptake on the delayed scan. In the study of Ochi [17] two

cases with carcinoma would have been missed if only ^{201}Tl scintigraphy would have been used (the only medullary and one of five present follicular tumours). The total number of patients with malignant disease was 37. Thirty-four of the 39 patients with benign disease had adenoma. Nine per cent of the adenomas showed some fading in the delayed scan (false-positive) and the remainder of the adenomas were true negative.

On the basis of five reports [17–21] with early and delayed ^{201}Tl-scintigraphy for cold thyroid nodules, including 96 malignant and 209 benign nodules, the overall sensitivity and specificity is 89% and 85%, respectively. The distribution of the tumour type in four of these series is: 47 papillary (3 false-negative), 10 follicular (2), 3 medullary (1), 10 undifferentiated (2) and 6 other malignancies (0). Although the sensitivity and specificity figures favours the use of this rather simple investigation, more studies are needed in order to establish these figures for all types of thyroid carcinoma more precisely.

CYTOLOGY

In the classification of cytology of the thyroid nodule three groups are distinguished: (1) negative (in about 72% of all readings, at a prevalence of cancer of 10%), (2) suspicious (±20%) and (3) positive (±8%). The probability of cancer is ±90% in positive readings and ±1% and ±11.5% in negative or suspicious readings, respectively. Combining the positive and suspicious groups as potentially malignant, then the chance on malignancy in this combined population is only 33%. These data are average values based on 11 reports, including about 2600 cases [10]. According to Heim *et al.* [22], 67% of the patients with suspicious readings have an adenoma, while 87% of patients with negative readings.

CONCLUSION AND PERSPECTIVE

At this moment cytology is the best single investigation to diagnose cancer in a thyroid nodule. A positive reading nearly always indicates a malignant nature, in contrast to a negative reading. If only all cases with positive cytology are operated then the question is what to do with the suspicious group. These are 20% of all patients and have a probability of cancer of ±11.5% (if the total cancer prevalence is 10%, e.g. in the case of a palpable solitary nodule). If the sensitivity and specificity figures of ^{201}Tl-scintigraphy turn out to be as indicated (89% and 85%, respectively), then one can use this technique in this suspicious group.

In Tables 1 and 2 the impact of several approaches of analysis of a thyroid nodule using risk factors, cytology and ^{201}Tl-scintigraphy is compared. In the approaches including risk factors, it is assumed that 10% of patients with a solitary nodule have risk factors, of whom 50% indeed have thyroid cancer [23]. For the last two investigations, the overall data of sensitivity and specificity, as mentioned in the text, are taken into account. To calculate the incidence of patients with solitary nodules the prevalence of solitary nodules (10%) [5] was divided by 50, viz the lifetime of the population at risk above 30 years of age. The calculated incidence of 0.2%/year in a population of 8×10^6 at risk amounts to 16,000 patients/year in the Netherlands. About 10% of these patients are at risk of having thyroid cancer, resulting in a figure of 110 new cases with cancer per year per 10^6 of the total general population. The five approaches in the tables clearly show that all result in detection of cancer in more than 90% of all cancer cases, however with large differences in number of operations for benign disease and thus medical (and social) costs.

Table 1. *Analysis of palpable solitary thyroid nodules with prevalence of cancer of* 10%

Operation:	Cytology (P,S)	Cyt(P)+ ^{201}Tl (S)	R.F.+Cyt (P,S)	R.F.+Cyt(P) +^{201}Tl(S)	R.F.+Cyt(P,S) +^{201}Tl(N)
% of all cancers missed	7.2	9.5	3.6	4.9	0.4
Operations in % of total number of patients	27.8	12.5	32.1	17.8	42.6
ibid for benign disease	18.5	3.5	22.5	8.3	31.6
ibid for cancer	9.3	9	9.6	9.5	±10
% cancer in total follow-up or non-operated group	1.0	1.1	0.5	0.6	0.07

R.F. = risk factors present; Cyt(P,S) = cytology positive and suspicious group; Cyt(P) = cytology positive group; ^{201}Tl(S) = positive ^{201}Tl-scintigraphy in suspicious cytology group; ^{201}Tl(N) = positive ^{201}Tl scintigraphy in negative cytology group.

Table 2. Medical costs of analysis of solitary thyroid nodules per year in the Netherlands (in 10^6/fl)

Operation:	Cytology (P,S)	Cyt (P)+^{201}Tl(S)	R.F.+Cyt. (P,S)	R.F.+Cyt (P) +^{201}Tl(S)	R.F.+Cyt (P,S) +^{201}Tl(N)
Cytology	1.44	1.44	1.3	1.3	1.3
^{201}TL-scan	-	0.8	-	0.7	2.7
Operation:					
- benign	14.0	2.7	17.1	6.3 (RF=3.8)	24.0
- malignant	7.1	6.9	7.3	7.2	8.3
Total	22.5	11.8	25.7	15.5	36.3

*Ex1: internist, TSH, ESR, social costs. See footnote to Table 1.
Costs for cytology, ^{201}Tl-scintigraphy and thyroid operation with 1 week hospitalization: fl 90, fl 250 and fl 4750, respectively. 1$ = 2 fl.

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