The Thyroid: Medical Surveillance of Exposed Workers

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ABSTRACT
In this paper the authors, on the basis of a prevalence study of thyroid diseases on a group of 234 radiation workers observed over a ten-years (1989-1999):
- discuss the issues and suggest an up-to-date approach to diagnosis and management of nodular thyroid diseases in the medical surveillance of radiation protection;
- identify and discuss, specific clinical situations, which, representing special problems, deserve a more restrictive judgement of fitness;
- intend to demonstrate that the diagnostic protocol used conciliates with due economy but with the right balance, the real requirements of medical surveillance reducing as far as possible undesirable effects such as damage from excessive protection and patient/physician delay, which is extremely dangerous in the early diagnosis of tumours.

INTRODUCTION
Because of the ability of the thyroid gland to concentrate radioiodine, it is uniquely susceptible to the biologic effects resulting from such exposures. Depending on the particular radioisotope in question, widely variable dose rates and dose distributions may be obtained.

These, along with the age of the subject, the total radiation dose delivered to the thyroid, and possibly genetic or environmental factors will have a profound effect on outcome.

The results may range from no discernible clinical effects to metabolically important processes such as acute radiation thyroiditis, and hypothyroidism and to the induction of both benign and malignant neoplasm (13).

The human data indicate clearly that 131-I is less effective on a mSv – for – mSv basis in inducting biologic effects in the thyroid even in the induction of neoplasms than is external radiation delivered at a high dose rate and with uniform distribution.

The reason for this difference between external and internal radiation is not known, but the lower dose rate of 131-I may allow repair of radiation damages.

There is no definite evidence of an increased risk of benign or malignant thyroid neoplasms after diagnostic or therapeutic administrations of 131-I. However the data at low thyroid dose levels are extremely limited, and the data at high therapeutic dose levels are confounded by the fact that at those higher levels thyroid destruction may be the predominant factor.

The hazards of short-lived iodine isotopes from atomic fallout have been confirmed from the reported data on the individuals in Belarus and Ukraine.

Huge amounts of radioactive isotopes of iodine were released from Chernobyl and radioiodine exposure must be the prime suspect for this large rise in the incidence of thyroid tumours. Several data support the concept that subjects who were younger at the time of radiation exposure had, and continue to have, a greater risk of developing thyroid carcinoma (1).

Compared with naturally occurring thyroid carcinoma, the post-Chernobyl Belarus thyroid carcinomas affected younger subjects, were less influenced by gender, were virtually always papillary, had a greater aggressiveness at presentation, and were more frequently associated with thyroid autoimmunity (2, 5).

Distinct patterns of Ret oncogene rearrangements has been observed in morphological variants of radiation-induced and sporadic thyroid papillary carcinomas in children (3). Ret rearrangements are highly prevalent in paediatric papillary carcinomas from children exposed to radiation and in those occurring sporadically. However, the types of Ret/PTC vary between these two populations, with Ret/PTC3 present more commonly in post-Chernobyl tumours (4). Furthermore, solid variants have a high prevalence of Ret/PTC3, whereas typical papillary carcinomas do not, suggesting that the different types of Ret rearrangement confer distinct phenotypic properties on neoplastic thyroid cells.

As far as medical surveillance of exposed workers is concerned, some questions must be kept in consideration.

There have been only a few studies evaluating the effects of long term, low-dose exposure to the thyroid. Most of these observed a high incidence of thyroid nodules, benign and malignant in medical x-ray workers professionally exposed to ionising radiation, probably due to the extent of diagnostic protocols (diagnostic bias).
An Italian group has recently published its results (14) suggesting that occupational exposure to radiation may be a risk factor for thyroid nodule formation. In that study thyroid nodules were detected in 41% of the exposed workers, compared with 13% of the non-exposed controls.

Furthermore, thyroid carcinoma is often preceded by other thyroid abnormalities, including endemic and sporadic goitre, benign thyroid nodules chronic autoimmune thyroiditis, and Graves’ disease, all of which are common. Whether patients suffering them should be considered at increased risk of developing thyroid carcinoma is uncertain. Despite considerable efforts to resolve this question, the results remain inconclusive.

Recent genetic data (3) suggest that thyroid tumours may progress from benign tumour stage to well-differentiated carcinomas, to anaplastic carcinomas as somatic mutations accumulate; this is particularly evident for thyroid lesions of follicular cell origin that span a wide spectrum of biologic behaviour. It must be considered that patients with small papillary carcinomas do extremely well with a low rate of recurrence and death. On the other hand, undifferentiated carcinomas, despite aggressive management, have a poor prognosis, with few survivors.

It is clearly evident the impact of the above mentioned question on the medical surveillance of radiation protection that, in the dose limitation system closely correlated to the hypothesis of a linear relation between dose and occurrence probability of stochastic damage, undoubtedly acquires obligations with regard to tumour prevention (secondary and tertiary).

**EPIDEMIOLOGY**

The thyroid is an uncommon site of cancer accounting for 0.6% of cancers among men and women. In 95% of cases, thyroid cancer presents as a nodule in the thyroid. In contrast to rare thyroid cancer, thyroid nodules are extremely common particularly among women. The prevalence of thyroid nodules is about 5% of the adult population, with a female: male ratio of 4:1. Thus most thyroid nodules are benign and it is important to identify those that are likely to be malignant. This is the main problem in the medical surveillance of radiation protection of workers exposed to ionising radiation.

Therefore in the medical surveillance of radiation protection the fundamental aims are the following:

- an early diagnosis for the optimisation of therapy;
- the evaluation of medical fitness for radiation work;

**MATERIALS AND METHODS**

During the ten-years period (1989/1999) a total of 234 exposed workers: 94 females and 140 males, ranging in age from 19 to 65 years were tested with clinical examination, FT3, FT4, TSH and ultrasound. Selected cases, in the presence of doubtful autoimmune thyroiditis were tested with thyroglobulin autoantibodies, thyroid microsomal autoantibodies and serum peroxidase autoantibodies.

Workers known by palpation or ultrasound as carriers of nodularity were studied with serum calcitonin (as marker of medullar carcinoma), scintigraphy, 131-I thyroid uptake and eventually T3 suppression test in case of doubtful differential diagnosis between hot and cold nodules. In the last two years all cold and solid nodules have been studied with echocolor-Doppler to detect an eventual intralesional flow which is considered an index of an increased risk of cancer.

Nodules less than 5 mm were not considered. In case of cold and solid nodules a fine-needle aspiration biopsy was performed to diagnose malignant nodules, benign nodules or follicular neoplasm.

**RESULTS**

A total of 74 cases of thyroid diseases were detected with a prevalence of 31.6% (female 35% - male 29.5%). (Table 1)
Table 1. Prevalence of thyroid diseases in 234 exposed workers over ten years of observation (1989-1999)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non toxic goitre:</td>
<td>5 cases</td>
<td>2.1%</td>
</tr>
<tr>
<td>Diffuse toxic goitre:</td>
<td>3 cases</td>
<td>1.2%</td>
</tr>
<tr>
<td>Hashimoto’s thyroiditis:</td>
<td>6 cases</td>
<td>2.5%</td>
</tr>
<tr>
<td>Benign nodules:</td>
<td>33 cases</td>
<td>14.1%</td>
</tr>
<tr>
<td>Malignant nodules:</td>
<td>3 cases</td>
<td>1.2%</td>
</tr>
<tr>
<td>nodular 24 cases (10.2%)</td>
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</tbody>
</table>

Among the exposed workers, only one had been previously treated with radiotherapy in childhood. Family history of thyroid disease was presented by 18 subject (7.6%). Almost all the subject presented a history of residence in iodine deficient areas for 10 years or more.

Considering the limits of fine – needle aspiration biopsy in the presurgical differential diagnosis between follicular adenoma and follicular carcinoma, we have referred to the surgeon the 2 cases of follicular neoplasm and the 3 cases of papillary carcinoma.

**DIAGNOSTIC DISCUSSION**

The possibility to clinically diagnose the presence of thyroid nodules depends on their size that must be over 1 cm, while the resolution of $\gamma$-camera using $^{99m}$Tc pertechnetate is about 0.5 cm and the resolution of small parts echography is about 1 mm.

The probability that a thyroid nodule is malignant is increased in the following cases:

- in rapidly growing nodules (unless the rapid growth is caused by a haemorrhage),
- in single nodules,
- in nodules in young patients,
- in nodules in males,
- in nodules that are scintigraphically cold,
- in nodules with a history of neck irradiation,
- in nodules cold and solid with intrallesional flow, detected by echocolor- Doppler.

However, definite proof that a thyroid malignancy is present can only be obtained before surgery by a positive FNB (9,10).

FNB is not applicable to all nodules. Some are too small and too inaccessible for accurate needle placement, or too far down in the chest to be aspirated safely. Other are so degenerated that useful material cannot be obtained. Finally, FNB diagnosis of benign for one nodule says nothing about other nodules, whether palpable or impalpable. Occult carcinomas may exist elsewhere within a gland with a benign nodule. There is no proof, however, that excising occult cancers before they are clinically detectable is important and to do so would require the removal of an absurd large number of thyroid glands. Therefore, the possibility of an occult lesion is not a practical limitation of needle biopsy. Ultrasonography is anyway of immense value in the early diagnosis of tumours, since it can easily identify small tumoral lesions already in a pre-clinic phase (11). Furthermore, echocolor-Doppler gives information about flow distribution that, when intrallesional, is considered at increased risk of cancer. Consequently a systematic application of this techniques in the medical surveillance of radiation protection on each exposed worker is advisable (8).

**MANAGEMENT OF CLINICAL SITUATIONS**

In the medical surveillance of exposed workers it is of great importance not only making a definite diagnosis at the moment of preventive visit but also reviewing and reevaluating the diagnosis at each periodical visit during all the professional exposure to ionising radiation, taking in account the risk that a single nodule, initially benign, could become malignant.

From this point of view, referring to the case contribution of the present study, it is useful, for a practical management of nodular thyroid diseases in the medical surveillance of radiation protection, to discuss some clinical situations that represent particular problems and deserve a careful evaluation and, sometimes, a more restrictive judgement of fitness.
a) **Multinodular goitre:** 5 patients evaluated for single palpable nodules were found to have additional thyroid nodules on ultrasound. It is commonly stated that demonstration of multiple nodules on ultrasound in a patient with a single palpable nodule makes malignancy unlikely. However, no carefully controlled study supports this contention, and the malignant potential of any nodule should be based on other criteria. In most cases of nodularity, this should include an echocolor-Doppler every periodical visit and, eventually, an FNB if a cold and solid nodule under thyroid hormone therapy shows growth over an extended period of time.

b) **Hyperfunctioning nodules:** such nodules, that as a rule are not malignant, have not been suspected of malignancy. However, it has to be emphasised that such nodules, although rarely, can hide follicular, papillary and even medullary carcinomas. For this reason, serum calcitonin level and eventually also fine-needle aspiration should be performed in case of hyperfunctioning nodules, either toxic or toxic, especially when they show growth over a prolonged period of time.

c) **Cystic nodules:** also cystic nodules, that as a rule are not cancer, have not been considered suspicious of malignancy, but since cancer is occasionally found in the wall of the cyst, it has been thought necessary to carry out an echographic surveillance of cystic lesions at every periodical visit.

d) **Hashimoto’s thyroiditis (HT):** since a patient with HT may develop, even if rarely, lymphoma of the thyroid gland, a protocol of caution for the follow-up is recommended. Ultrasound should be carried out semi-annually.

e) **Follicular adenoma:** considering the limits of FNB in the presurgical differential diagnosis between follicular adenoma and follicular carcinoma, we have referred to the surgeon the 2 cases of follicular neoplasm. In these 2 cases there was an increased chance of malignancy (large lesions over 2 cm, firm nodules, intralysional flow on echocolor-Doppler).

f) **History of radiation therapy:** in one case of single nodularity there was a history of radiation to the neck area in childhood. Although any given nodule has essentially the same chances of being malignant regardless of whether there has been a previous upper body radiation, caution is needed in order to it and an echo colour – Doppler should be carried out semi-annually.

**DISCUSSION**

In this case report the 2 cases of follicular neoplasm referred to surgery for the definite diagnosis and the 3 cases of papillary carcinomas show how the diagnostic protocol suggested in the management of thyroid nodular diseases could be useful also from the point of view of the secondary and tertiary cancer prevention. This diagnostic protocol conciliates with due economy but the right balance, the real requirements of medical surveillance, reducing as far as possible undesirable effects such as damage from excessive protection and patient/physician delay, which is extremely dangerous in the early diagnosis of tumours.

**MEDICAL JUDGEMENT OF FITNESS FOR RADIATION WORK**

In case of a patient known as a carrier of a thyroid nodule clinically detectable or detected on ultrasounds, the physician first of all must approach a precise diagnosis. Before the examinations have been completely performed, the subject will be consequently maintained at his normal work in controlled area without any limitation, considering the possible doses to thyroid due to radiation work (6, 7, 12). The eventuality that the subject will or will not accept the necessary diagnostic or therapeutic procedures must be faced. In this last case a judgement of unfitness should not automatically outcome, but the potential risk and actual real damage resulting from such a judgement should be evaluated case by case. As far as risks are concerned, it should be considered the possibility of a nodular cancerous degeneration caused by work exposure to ionising radiation (hypothesis with very low probability), and the possibility that in reality we are dealing with a carcinoma not detectable at the moment with the used techniques. In any case the judgement of fitness should contain the necessary prescriptions or advises for the patient in order to avoid in some psycho-social contexts the possibility of future legal controversies.

In conclusion, one has to keep always in mind some main criteria, i.e. the clinical findings; the specific risk evaluation; the social, economical and psychological parameters. Thus the physician, in his evaluation,
should always consider the risk/benefits balance.

REFERENCES