Diagnosis, Surgical Treatment and Follow-up of Thyroid Cancers

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Abstract. This paper reports the activities and the results of the research carried out by the Centers participating to the JSP4 project, within the framework of the EU program on the consequences of the Chernobyl disaster. The project was aimed to develop and to control the application of basic principles for the diagnosis, treatment and follow-up of thyroid carcinoma, with special attention to the peculiar requirement of children and adolescents. To this purpose, training in Western European Centers was offered to a number of scientists from Belarus, Ukraine and Russia. Several official meetings were organised to share views and to discuss the progress of the project. A basic protocol for the diagnosis, treatment and follow-up of thyroid carcinoma has been developed and approved by all participating Centers. Hopefully, it will be applied to the new cases and to those already under monitoring. A large part of the protocol is dedicated to the post-surgical treatment with thyroid hormones for the suppression of TSH and with calcitriol for the management of surgical hypoparathyroidism. A detailed protocol to asses iodine deficiency and, eventually, to introduce a program of iodine supplementation has been proposed.

The collection of control cases of childhood thyroid carcinoma in non-radiation exposed European countries has been initiated in Italy, France and Germany. This data will be used as control for the post-Chernobyl childhood thyroid carcinomas. Here is reported a preliminary comparison of the clinical and epidemiological features of almost all (n=368) radiation-exposed Belarus children who developed thyroid carcinoma (age at diagnosis <16 years), with respect to 90 children of the same age group, who, in the past 20 years, have received treatment for thyroid carcinoma in two centers in Italy (Pisa and Roma). Finally, by molecular biology, genetic mutations of the RET proto-oncogene have been found in several samples of thyroid carcinomas provided by the Belarus partners.

All together, this project has provided the CIS partners with the most useful information and knowledge in order to allow an effective treatment of the diseased population and, possibly, the prevention in those not yet affected.

1. INTRODUCTION

Thyroid cancer is a rare condition in childhood. When it does occur it is most usually of the papillary type, and is in general susceptible to effective treatment and cure, provided that early diagnostic and therapeutic measures are undertaken (1-3). General guidelines for the management of thyroid carcinoma in children are shared by most international centers, but protocols may differ in relation to local conditions. The unique nature of the Chernobyl accident (4-7), the pathology and the number of thyroid cancers registered to date (8,9) have outlined the importance of investigating the relationship between thyroid cancer and the causing event. This need has obtained a prompt answer from the European Community who financed the present and other projects (10).

The aim of this project was to develop and to control the application of basic principles for the following objectives: a) developing and implementing a protocol for the diagnosis, treatment and follow-up of childhood differentiated thyroid cancer, including the correct use of l-thyroxine suppressive therapy; b) developing new diagnostic imaging techniques for the post-surgical monitoring of thyroid carcinoma, including the possible use of recombinant human TSH; c) studying the autoimmune phenomena in radiation-induced childhood thyroid cancer; d) evaluating the biological and clinical behaviour of radiation-induced thyroid carcinoma as compared with non-radiation-induced thyroid carcinoma; e) assessing iodine deficiency and the need for iodine supplementation and thyroid suppressive therapy in the prevention of radiation-induced thyroid cancer.

Several exchange of visits and meetings have taken place between the Western and the CIS participating institutions. Thanks to these initiatives, several objectives and results have been reached in the years covered by this project, as summarised in the present report.

2. RESEARCH ACTIVITY AND TRAINING OF BELARUS SCIENTISTS IN EUROPEAN CENTERS.

Several scientists from Belarus had training at the Institute of Endocrinology and at the Department of Surgery of the University of Pisa. They performed an extensive number of endocrine and immunological assays in a large series of children with or without thyroid cancer or with other thyroid disorders. These children were from Belarus areas exposed or unexposed to radiation. The results obtained so far, suggest that there is a significant increase in autoimmune phenomena both in children with thyroid cancer and in unaffected children. The Belarus partners provided several samples of thyroid carcinomas which have been studied by molecular biology for the presence of genetic mutation of the RET proto-oncogene.

Other investigations on oncogenes (ras and gsp) in thyroid tumors occurring either spontaneously, or after neck external irradiation or as a consequence of the Chernobyl accident have been performed in the center of Villejuif.

Two senior physicians from Ukraine spent two weeks at Würzburg University Clinic for Nuclear Medicine to become more familiar with recent developments in the treatment and follow-up of childhood thyroid cancer. On return these colleagues were able to improve the local protocols for I-131 therapy with the equipment delivered by a CEC ECHO-2 project.

Training of medical staff from the three CIS countries in the Brussels Center is already scheduled for January 1996. The object of this visit is to became acquainted with the basic technique for the epidemiological and laboratory assessment of iodine deficiency.

3. DEFINITION OF A COMMON PROTOCOL FOR DIAGNOSIS, TREATMENT AND FOLLOW-UP OF CHILDHOOD THYROID CARCINOMA.

31. Protocols.

A protocol for diagnosis, treatment and follow-up of thyroid cancer in children has been approved by all partners and will be applied to the new cases and to those already under monitoring. A large part of the protocol is dedicated to two major problems encountered up to now by the teams involved in the treatment of the affected children in the CIS countries. These include the post-surgical treatment with thyroid hormones for the suppression of TSH and with calcitriol for the management of surgical hypoparathyroidism.

A detailed protocol for iodine supplementation and thyroid suppressive therapy has been proposed. The objectives of this protocol are two fold and are as follows:

1. Evaluating the past and present amount of iodine in the nutrition of the areas under investigation.
2. Implementing thyroid suppressive therapy and evaluating its effects. The type of therapy will be decided on the basis of the results obtained by objective 1.

32. Treatment.

In the center of Würzburg (previously in the one in Essen), 120 courses of I-131 therapy were administered to 30 children from Belarus with advanced thyroid cancer. This joint project was carried out together with the Centre for Thyroid Tumours in Minsk. The children came to Essen in groups of 4 where they stayed for a week. The group was accompanied by a physician who was trained during her/his stay in the radioiodine treatment of thyroid cancer, in the follow-up with sonography, scintigraphy and laboratory tests as well as in hormonal replacement therapy.

In addition, several new assays for thyroglobulin and TSH were tested in the laboratory of Würzburg University Clinic for Nuclear Medicine. It could now be demonstrated that the implementation of such recent techniques improves the management of patients with thyroid cancer.

A separate project focused on pulmonary fibrosis as a possible side effect of high dose I-131 therapy on children with disseminated pulmonary metastases of thyroid cancer. High resolution CT and lung function tests were used for follow-up. In 2 out of 45 children with lung metastases signs of pulmonary fibrosis developed after more than 20 GBq of I-131.

4. CLINICAL AND EXPERIMENTAL STUDIES OF THYROID CARCINOMA IN IRRADIATED BELARUS TUMORS AND IN UNIRRADIATED WESTERN EUROPEAN CONTROL TUMORS.

4.1. Data base.

The collection of control cases of childhood thyroid carcinoma in non-radiation exposed European countries has been initiated in Italy, France and Germany. In France a total of 150 cases have been registered. In Italy, a total of 120 cases ageing 16 years or less have been analyzed. These cases were compared from the epidemiological and clinical point of view with all the cases that occurred in Belarus from the year 1986 to the first 6 months of 1995.

4.2. Clinical features of radiation-induced childhood thyroid cancer from Belarus, as compared with non-irradiated childhood Italian cancer.

We studied the clinical and epidemiological features of almost all (n=368) radiation-exposed Belarus children who developed thyroid carcinoma (age at diagnosis <16 years) , compared to 90 children of the same age group, who, in the past 20 years have received treatment for thyroid carcinoma in two centers in Italy (Pisa and Roma) .

Patients

We had access to the records (from 1986 to June 1995) of most Belorussian children (n=368) who were younger than 16 when the diagnosis of thyroid carcinoma was made. The number of cases per year is shown in Table 1.

Table I. Number of Childhood thyroid cancer registered yearly from 1986 to 1995.

YEAR	NUMBER OF CASES
1986	1
1987	2
1988	4
1989	6
1990	28
1991	58
1992	65
1993	80
1994	80
1995	44 (First 6 months)

In a subgroup of 63 children (35 females, and 28 males) serum samples were available for biochemical determinations. All the patients had a histologically proven differentiated thyroid carcinoma and at the time of the Chernobyl reactor accident, were living in regions of Belarus heavily contaminated by radioactive fall outs: 201 children were living in Gomel, 81 in Brest, 41 in Minsk, 20 in Mogilev, 20 in Grodno, and 7 in Vitebsk (Table II). The diagnosis of thyroid carcinoma was done either by screening programs or by referral from the family doctor.

Table II. Distribution of cases by region.

REGION	NUMBER OF CASES
Gomel	201
Brest	81
Minsk	41
Mogilev	20
Grodno	20
Vitebsk	7

Initial treatment of all patients was carried out in Minsk and consisted in total (or near-total) thyroidectomy in 134 patients, sub-total thyroidectomy in 57, and lobectomy in 172.

The epidemiological and clinical pattern of Belarus tumors was compared with that of 88 Italian children (females, males) of the same age group treated for differentiated thyroid cancer in the past twenty years at the Institute of Endocrinology of the University of Pisa (n=33), and at the Nuclear Medicine Department, University of Roma (n=55). Initial treatment was of near-total thyroidectomy in 88 children, and sub-total thyroidectomy in 2.

Results

Belarus versus Italian tumors.

The female to male ratio was lower, but not significantly different, in Belarus children (F:M=1.6:1) compared to Italian children (F:M=2.7:1). The mean(±SD) age at the diagnosis was significantly younger in Belarus (10.0±2.5 years) than in Italy (11.5±3.2 years; $p<0.0001$ by unpaired Student's t test).

Most Belarus tumors (n=351, 95.3%) were papillary thyroid carcinomas, with or without follicular component, 15 were pure follicular carcinomas (4.1%), 1 was medullary thyroid carcinoma (0.3%), and 1 was Hurthle cell carcinoma (0.3%). In the Italian series, 72 tumors (81.8%) were papillary and 16 (18.2%) were follicular. According to TNM classification, in the Belarus cases, tumors extending outside the thyroid gland were 178 (48.3%); lymph node involvement was present in 241 (65.4%) cases, and distant metastases were found in 33 (8.9%).

Belarus children: age at radiation exposure and age at diagnosis.

As shown in Fig. 1, the mean age of the children at the time of the Chernobyl accident and at the time of diagnosis was 3.57±2.6 years (range 0-13.0) and 10.0±2.5 years (range 3.1-14.1 years), respectively

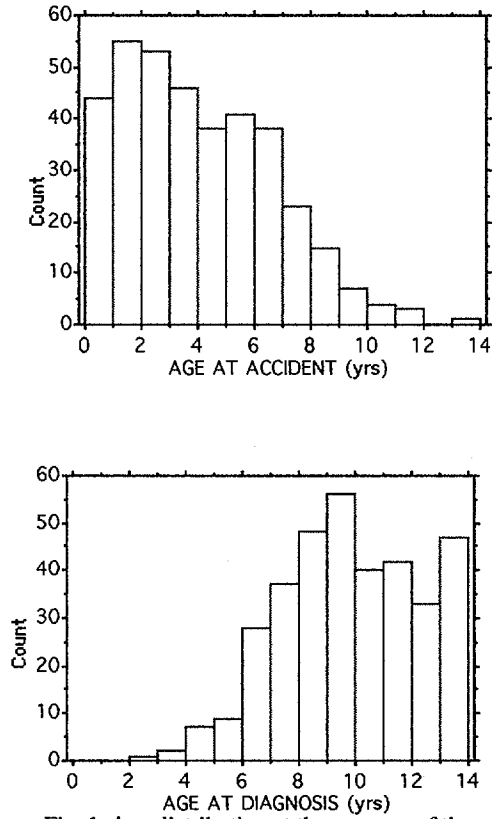

Fig. 1. Age distribution at the moment of the accident (upper panel) and at diagnosis (lower panel).

The mean time elapsed between exposure and diagnosis was of 6.47±1.6 (range 1-9) years with a strong positive correlation ($r=0.79$; $p<0.0001$; Fig. 2) between the two parameters, indicating that the latency period between exposure and diagnosis of thyroid cancer was similar in all children.

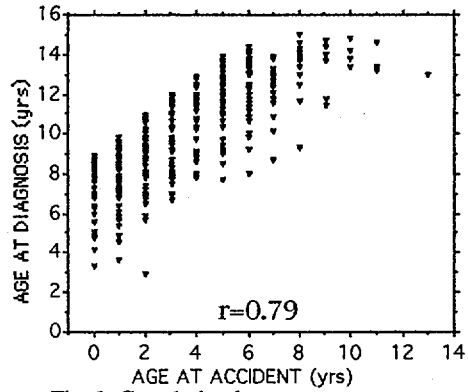

Fig. 2. Correlation between age at exposure and age at diagnosis.

Lymphocytic infiltration

Lymphocytic infiltration was assessed in 52 Belarus tumors and was present in a total of 27 (50.9%) cases. In 5 cases it was defined as diffuse infiltration typical of lymphocytic thyroiditis, and as focal in the other cases.

As shown in Fig. 3, circulating anti-TPO autoantibodies were more frequently found in Belarus patients (44.4%) than in Italian patients (23.3%; $p<0.01$), while anti-Tg autoantibodies were equally found in both populations (11.7% and 9.6%, respectively).

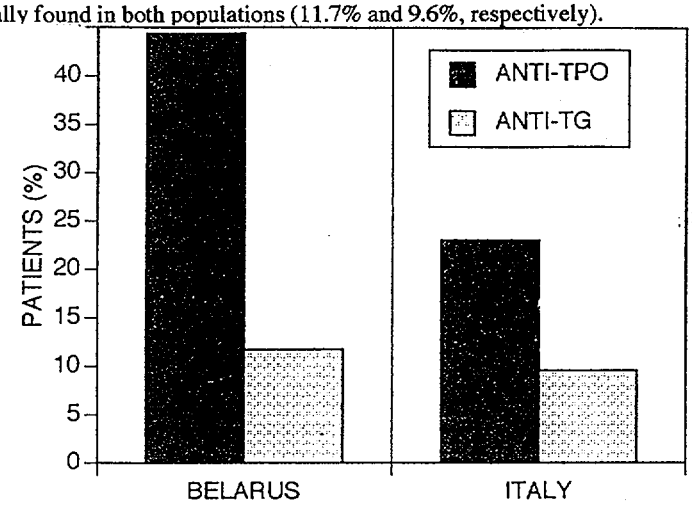

Fig.3 Incidence of anti-TPO and anti-TG autoantibodies in children with thyroid carcinoma from Belarus (radiation exposed) compared to children from Italy (unexposed). The incidence of anti-TPO, but not of anti-TG, antibodies is significantly higher ($p<0.001$) in Belarus children.

4.3. ONCOGENES in Belarus papillary thyroid carcinomas. (11,12)

Through different molecular techniques, six papillary thyroid carcinomas of children living in Belarus at the time of the Chernobyl accident were studied (These experiments were carried out in the laboratory of Dr. M. Pierotti, Istituto Nazionale Tumori, Milano, Italy). This was in order to identify tumor-specific gene rearrangements of the proto-oncogenes *RET* and *TRK*, previously found activated in papillary thyroid carcinoma. As shown in Table III, using the Southern blot analysis, in four cases we detected specific rearranged bands indicating an oncogenic activation of *RET* .

TABLE III. RET rearrangements in 6 Belarus children with papillary thyroid carcinoma after Chernobyl.

Patient/Sex	Age at accident	Age at diagnosis	Rearrangement
1/F	14 mo	6 yr	Ret/PTC3
2/F	7 yr	13 yr	None
3/F	8 yr	14 yr	None
4/M	5 yr	11	Ret/PTC2
5/F	8 yr	14	Ret.PTC3
6/F	7 yr	13	Ret/PTC3

The DNA of 3 tumors was also able to induce transformation of the NIH-3T3 cells after the DNA-mediated transfection assay, and the respective NIH-3T3 transfectants were found to express the oncogenic fusion transcripts. These results, although preliminary, support the possibility that the *RET* oncogenic activation could represent a major genetic lesion associated with radiation-induced thyroid carcinoma. The question of whether, and to what extent, young age *per se* rather than radiation, or the combination of both, is responsible for a *RET* activation remains to be established.

5. CONCLUSIONS

The JSP4 Project was mainly concerned with the clinical aspects of the post-Chernobyl childhood thyroid carcinoma. A protocol for diagnosis, treatment and follow-up has been devised. It is expected that the adoption of such protocol in its final version by all treatment Centers will greatly facilitate an optimisation of the management of thyroid cancer. Because of the limited experience acquired in this disease in most hospital Centers, it was important that the specific expertise of major European referral institutions could be made available to Belarus and other CIS countries in order to cope with the multiple and difficult aspects of the post-Chernobyl outbreak of childhood thyroid cancer. The program for training of CIS medical specialists and technicians in EU Centers has been successfully carried out and is expected to contribute to the effectiveness of the diagnostic and therapeutic procedures and to the standardisation of laboratory procedures. Clinical and molecular aspects of Belarus childhood thyroid carcinoma have been investigated and compared with unirradiated control populations.

The question of whether and to what extent the greater aggressiveness and the higher frequency of the RET oncogene activation observed in the post-Chernobyl thyroid cancer cases is related to radiation remains to be established. Furthermore, the impact of iodine deficiency on the development of the post-Chernobyl thyroid carcinoma is under evaluation. Iodine prophylaxis corrects iodine deficiency and thus may be considered an effective preventive measure for decreasing the risk of radiation-induced thyroid cancer.

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