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Thyroid cancer in children: a 20-year study at a Romanian oncology institute

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Abstract. Thyroid carcinoma (TC) has an increasing incidence in the last decade and continues to represent the most frequent form of endocrine tumor. The aim of the study was to analyze the pediatric files of TC from the registry of "Prof. Dr. Ion Chiricută" Institute of Oncology Cluj-Napoca, Romania (IOCN) and to provide the data related to the impact of nuclear fallout of Chernobyl on this pathology. We studied 72 children with TC treated between 1991 and 2010. The mean age was 15.3 years; the ratio female/male was 6.2:1. Twenty-nine children (40.2%) revealed metastasis in regional lymph nodes or lungs at the initial diagnostic. There were 63 differentiated thyroid carcinoma (DTC), 6 cases with medullary cancer (MC), 1 case with anaplastic carcinoma (AC), and 2 mixed cases. All patients underwent total thyroidectomy and the radioiodine was administered in 64 cases (activities between 1.1 - 28.1 GBq I-131). Fifty-two children (80.5%) are free of disease, 8 are in partial remission and 4 children are in evolution of the disease at minimum 12 months of follow-up. The incidence of TC was significantly increased 10 years after the accident. In the years after, the increasing trendline was stopped and at 25 years, the number of cases is stationary. The diagnosis of pediatric TC is made frequently in metastatic disease and the therapies must be conducted for many years till complete remission. A more clear strategy adapted to children is needed in the future.

Key words: Pediatric, Thyroid carcinoma, Chernobyl

THYROID cancer continues to represent the most frequent endocrine tumor. Even if this cancer increased dramatically in the last decade [1-4] it is still considered between the rare cancers. According to the European surveillance of rare cancers project (RARECARE), a rare cancer is defined as a tumor with an annual incidence lower than 6 cases per 100,000 persons [5], an incidence that in worldwide studies [6-14, 25] is achieved by thyroid cancers. Thyroid cancer comprises 0.5-1.5% of all childhood tumors and represents the most common head and neck malignant tumor in young people [15, 16]. An accurate treatment strategy can cure this disease, can minimize recurrence risks, and give an excellent prognosis to these patients [17-19].

Compared with adults, the epithelial-derived differentiated thyroid cancers (DTC), which include papillary (PTC) and follicular (FTC) thyroid cancers, occurring in children are more aggressive, are discovered in advanced stages, and are associated with higher rates of recurrencs [16-21, 23, 25, 32]. Lymph node involvement at diagnosis is very frequent in children [17, 22, 24, 25]. Distant metastases, most commonly to the lungs, are present in 20-30% of cases [26-31]. Long-term follow-up data show 20-year survival rates of 90-99% for children with DTC [18, 25], but up to 30% of children with DTC have recurrent disease [32].

The relation between thyroid cancer and irradiation is well defined. The position of Romania between the countries affected by the radioactive cloud after the nuclear accident of Chernobyl [33], justified the interest regarding the impact of the irradiation on the pediatric population 25 years after the disaster.

Patients and Methods

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Napoca (IOCN) is one of the most important national tumor centers with a considerable high number of new cancer cases growing yearly. In 2010 thyroid carcinoma was the 4th cancer pathology in IOCN, representing 6.67% of all newly registered malignancies. Between 1991 and 2010 in IOCN were treated 3,424 patients with thyroid carcinoma, with exponential increase in the last decade; among them 72 cases were children.

Patients

We analyzed the medical history of 72 children with thyroid carcinoma, representing 2.1% of all cases of thyroid carcinoma from the period 1991-2010. There were 10 boys and 62 girls, this representing a ratio of 1:6.2 male/female. The age at the moment of cancer diagnosis was ranged between 8-18 years old, and mean age was 15.3 years and median age was 15.5 years (standard deviation 2.6055). The clinical signs were: enlargement of the thyroid gland and the lymph node detection in the cervical area (64 cases; 88.8%), dyspnea and cough in 3 cases (4.1%), hemoptysis in 1 case (1.3%), and familial screening in 4 cases of MTC (5.5%). Thyroid cancer histology was reported as follow: 53 cases of PTC (49 cases of follicular variant of papillary carcinoma and only 4 pure papillary carcinoma), 10 cases of FTC, 6 cases of medullar thyroid cancer (MTC), 1 case of anaplastic thyroid cancer (ATC); 1 case was a mixed form of medullar and follicular carcinoma and 1 case mixed PTC and ATC. Regarding the stage distribution, according to the TNM classification system [34], it was as follows: stage I, 65 cases (90.3%); stage II, 4 cases of DTC with lung metastases (5.6%); stage III, 1 case with MTC (1.4%); and stage IV A, 2 cases (2.8%).

The follow-up interval ranged from 1 to 20 years. All patients from this study were treated and followed-up in IOCN. The legal representative of children, in all cases the parents, have been requested to sign an informed consent for the collection of clinical and pathological data and for being used in scientific reports.

Treatments and follow-up of patients

The treatment was adapted to histology. DTC surgery (the total or near total thyroidectomy +/- selective lymphadenectomy) was followed by the I-131 radioiodine (RIT) ablation 1 month after surgery, in the absence of any thyroid hormonal replacement; doses ranged between 30-100 mCi (1.1-3.7 GBq) of I-131, with an average activity of 61.31 mCi (2.26 GBq) I-131. Patients referred after initial surgery were submitted to completion thyroidectomy if the first operation has been less than a near-total thyroidectomy, except 1 case, considered very low risk and being previously submitted to total lobectomy. Patients with metastatic disease underwent additional treatments consisting of multiple I-131 therapeutic doses (the maximum cumulative dose was of 760 mCi-28.12 GBq) repeated at interval times not shorter than 6 months, until the evidence of a negative post therapeutic whole-body scan (WBS) and undetectable serum thyroglobulin (Tg) level. Neck recurrences were treated by surgery, whenever technically possible. No external radiotherapy was indicated in any of these differentiated cases. All patients were submitted to levo-thyroxine (LT4) therapy. Thyroid stimulating hormone (TSH) suppressive doses (TSH < 0.1 mIU/L) of LT4 were administered until evidence of a disease-free status; after that, a TSH level at the lower normal limit (0.4-1 mIU/L) was maintained.

In MTC all patients underwent total thyroidectomy (TT) and substitution with LT4; the radioiodine therapy (RIT) was performed in the case with mixed form of MTC and FTC. In the case with pure ATC, the patient's family refused any kind of treatment and in the mixed form of ATC with PTC after TT and RIT, the patient was referred for external beam radiotherapy with a total dose of 25 Gy.

The monitoring protocol of these patients was very homogenous, performed in the same department. The first control was done after 6 weeks in order to assess the thyroid hormone suppressive dose (TSH and free thyroxine (FT4) on LT4 therapy) in the case of DTC, and the normal substitutive dose in the case of MTC and ATC. In the case of DTC the first oncology control was carried out at 6 months after irradiation and consisted of clinical exam, neck ultrasound and laboratory evaluation after 2-3 weeks of hormonal withdrawal of LT4: TSH, thyroglobulin (Tg) and anti-thyroglobulin antibodies (TgAb) serum measurements. If TSH was not elevated enough (minimum level of 40 mIU/L or at least 100 times higher than was under LT4 therapy) the control was repeated after continuing the hormonal withdrawal period 2 weeks more. There were no patients evaluated by recombinant TSH stimulation. Patients were considered disease-free when WBS I-131 was negative and TSH-stimulated Tg and TgAb were undetectable, Tg < 0.1 μg/L and TgAb < 115 IU/mL. Patients with dynamic increasing of detectable levels of serum Tg or elevated titers of TgAb were defined with persistent dis-

ease, even if I-131 WBS and other imaging techniques were unable to detect any lesion. Recurrence was defined as the evidence of the disease at least 6 months after the definition of a disease-free status. Recurrence was considered if there was detectable or dynamic rising of serum level of Tg or anti-Tg; presence of clinical signs of disease (palpable tumor, lymph nodes); WBS I-131 positive; or positive neck ultrasound. When a suspicious lymph node was found, fine-needle aspiration (FNA) cytology was performed [35]. In case of recurrence the treatment sequences were reconsidered: surgery or radioiodine, or both. After the first negative WBS I-131, no other diagnostic WBS with radioiodine was performed in case of normal tumor markers.

In MTC clinical, ultrasound exam under LT4 therapy and serum calcitonin (Ct) level were performed. If a pathologic value of Ct was revealed, other imaging techniques were carried out in order to find the persistent or recurrent disease (computed tomography (CT) and/or magnetic resonance imaging (MRI)). In mixed form of FTC and ATC the same protocol as for DTC was applied. No FDG PET/CT was indicated in these patients.

Laboratory and imaging tests

Analyses were performed on Roche kits and Cobas instruments. Normal values for differentiated thyroid carcinoma patients with radical treatment according to the producers are: Tg < 0.1 μg/L and anti - Tg < 115 IU/mL. Ct normal values after radical surgery is < 0.6 pmol/L [36, 37].

WBS 1-131 was performed at all patients on Siemens gamma camera Ecam Signature, high energy collimator, at 48 h after the oral administration of 3 mCi (111 MBq) of I- 131, with 1 million counts acquisition on each image. The same protocol of acquisition was used in the case of post-therapy WBS. Conventional CT were performed in IOCN on GE spiral CT. Thyroid ultrasound was performed on Toshiba echo-Doppler.

Statistical analysis

Clinical data are presented with descriptive statistical analysis. *P* values < 0.05 were considered significant. Statistical methods used were based on EpiMax Table, Log Rank (Mantel Cox) tests.

Results and Discussions

The incidence of thyroid cancer (TC) in IOCN is considerable increased in the last years. The total 1,938 cases registered in the period 1996-2010 represents a number 9.2 times higher than the cases treated in the period 1991-1995. Among these cases the children diagnosed with TC represents only 2.1 %; even so the number of cases being in the evidence in the last 5 years is 6.5 times higher than the number from the period 1991-1995 (Fig. 1 A, B). The area of residency was from all over the country, but 17 children (23.6%) were from the Central and North Eastern part of Romania (Moldova, Mures and Covasna counties) known as being affected by the nuclear fallout from Chernobyl [33]. The official report of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) presents the map of radionuclides distribution in Europe after the Chernobyl accident: Romania is one of the countries with important contamination of Cs-137 both in NE part and central area [38]. No substantial epidemiological studies regarding the thyroid-absorbed dose

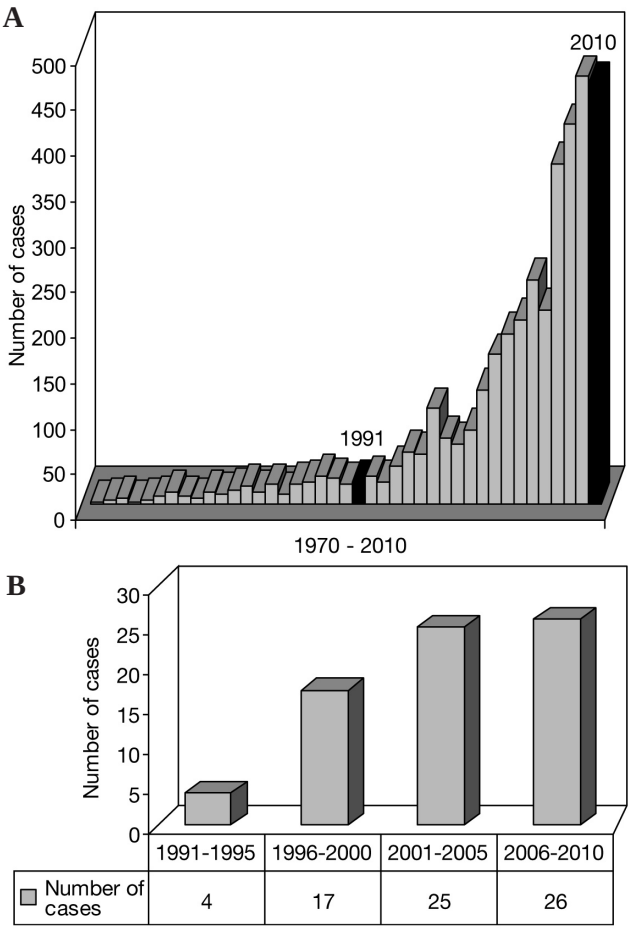

Fig. 1 Incidence of adult thyroid carcinoma (A) and of pediatric thyroid carcinoma (B) at the Institute of Oncology "Prof. Dr. Ion Chiricuță" (IOCN) 1970-2010

are available for this area.

An important issue to be underlined is that the incidence of pediatric thyroid cancer has a different pattern compared with that of the adults 25 years after Chernobyl. The number of pediatric cases 5-10 years after the nuclear accident is not significant (only 4 cases registered between 1991-1995). Between 1996-2000, after 10-15 years, the number is increased four times (17 cases). In the period 2001-2005 the number of cases was slightly increased compared with the previous period (25 cases) and was almost stationary between 2006-2010 (26 cases). In the case of adults, the number of thyroid cancer cases continues the significant increasing trendline, as is shown in Fig. 1A, potentially due to more extensive diagnostic procedures. These data suggest that the increasing incidence due to irradiation, not to screening is more accurately demonstrated in the pediatric group, than in adults.

In our study, 37 (51.38%) out of the 72 children were born before 1986, the year of the accident of Chernobyl and 35 children were born after the disaster. The age of the patients, correlated with the moment of the accident, showed that the average age in 1986 was 3.59 years. For those born after 1986, the average interval between the nuclear fallout and the naissance was 5.12 years (minimum 1; maximum 12 years).

The histology distribution showed that DTC is still the most frequent form of TC also in the pediatric files (88.8%). MTC represents 8.3% of all cases; 4 out of 6 cases were discovered in the course of familial screening of adult patients. It is interesting to note that the appearance of an unusual ATC in children. The single case with pure ATC (1.4%), with a very aggressive presentation and with dramatic outcome, refused any treatment and represented the single death that has occurred in this study. Another interesting note is the presence of the mixed forms of cancer (MTC+FTC and PTC+ATC), cancers that needed combined treatment strategies.

An important number of cases (38.8%) had lymph node involvement (27 cases out of 72) and lung metastasis (4 cases out of 72) at the discovery of the disease. This data underlines the fact that TC in children is characterized by rapid evolution and has aggressive behavior. But, even if the clinical presentation in many cases was severe, during the 20 years of the present study, all children except one are alive. Considering these results, the survival rates are excellent, so the statistical analyses were carried out on the disease-free interval, not on survival rates. Tables 1, 2, and 3 present the statistical analysis of disease-free interval at 1 year, 3 years, and 5 years, with reference to histology. It is interesting to note that, by applying the test Log Rank (Mantel-Cox) at 1 year and 3 years, the "*p*" value has statistical significance regarding the histology (*p* - 0.006 and *p* - 0.000). At 5 years, histology is a factor that presents a *p* value with no statistical significance (*p* - 0.655).

Table 1 One-year disease-free interval according to histology

HP code statistics	Total N	N of events	Censored	
			N	Percent
Anaplastic	2	2	0	0.0%
Follicular	9	0	9	100.0%
Medullary	7	0	7	100.0%
Papillary	50	11	39	78.0%
Overall	68	13	55	80.9%

Overall Comparisons

	Chi-Square	df	*p* -Sig.
Log Rank (Mantel-Cox)	12.328	3	0.006

Test of equality of survival distributions for the different levels of histology.

Table 2 Three-year disease-free interval according to histology

HP code statistics	Total N	N of events	Censored	
			N	Percent
Anaplastic	2	2	0	0.0%
Follicular	9	0	9	100.0%
Medullary	7	0	7	100.0%
Papillary	37	7	30	81.1%
Overall	55	9	46	83.6%

Overall Comparisons

	Chi-Square	df	*p* -Sig.
Log Rank (Mantel-Cox)	23.094	3	0.000

Test of equality of survival distributions for the different levels of histology.

Table 3 Five-year disease-free interval according to histology

HP code statistics	Total N	N of events	Censored	
			N	Percent
Follicular	8	3	5	62.5%
Medullary	6	1	5	83.3%
Papillary	32	11	21	65.6%
Overall	46	15	31	67.4%

Overall Comparisons

	Chi-Square	df	*p* -Sig.
Log Rank (Mantel-Cox)	0.847	2	0.655

Test of equality of survival distributions for the different levels of histology

Considering the guidelines of TC therapy in DTC cases and the 2 cases with mixed forms, 64 out of the 72 children received RIT. In 1 case of very low risk of TC, the RIT was not indicated, the patient being only followed-up after total lobectomy. The minimum amount was 30 mCi (1.11 GBq) and the maximum activity/dose was 120 mCi (4.44 GBq), the maximum cumulative dose was of 760 mCi (28.12 GBq), the mean activity/patient was 161.9 mCi (5.99 GBq) and mean activity/dose was 61.3 mCi (2.26 GBq) I-131.

Seventeen (23.6%) out of the 72 children received one single dose of I-131, with mean activity of 64.2 mCi (2.37 GBq) I-131, achieving disease-free status after the therapy; more than a quarter of the patients were completely treated with less than 70 mCi (2.59 GBq) I-131. Multiple doses of I-131 were administered as follow: 2 doses, 19 cases; 3 doses, 16 cases; 4 doses, 5 cases; more than 5 doses, 7 cases. We wish to underline the low activities of radioiodine used in this cohort of patients. It is also important to note that in this database we did not experience any lung fibrosis or hematological side effects.

Fig. 2 presents the statistical results of disease-free interval at 5 years according to the total activity of radioiodine, divided in 4 groups of activity: less than 50 mCi (1.85 GBq) I-131; activity of I-131 between 51 and 70 mCi (1.88-2.59 GBq) I-131; activity of I-131 between 71-100 mCi (2.62-3.7 GBq) I-131, and activity of I-131 higher than 100 mCi (3.7 GBq) I-131. The radioiodine doses have no statistically important value at 5 years, $p = 0.052$. The level of low and medium radioiodine activity has the same results as the high levels of activity.

Considering the entire group at the moment of the study, 57 (79.2%) out of the 72 children were free of disease, even considering the severe clinical presentation of more than one third of the group. The parameter that keeps the important statistical value at 5 years is the stage of the disease (p - 0.001 at 5 years) (Fig. 3). In pediatric files, the stage is related to the presence of distant metastases, this factor being the most important element in the prognostic analysis. Persistent disease was observed in 9 patients (12.5%), with detectable values of Tg, between 1.6-7 μg/L, but no evidence of the disease and no dynamic rising of Tg. Evolution of the disease is present in 2 cases (2.8%), both with DTC and lung metastasis.

Recurrences occurred in 3 cases (4.2%), 14 months, 5 years, 7 years, respectively, after the first decision of

Statistics

Statistics Dose	Total N	N of Events	Censored	
			N	Percent
< 50 mCi I-131	6	4	2	33.3%
51 – 70 mCi I-131	5	4	1	20.0%
71 – 100 mCi I-131	9	3	6	66.7%
> 100 mCi I-131	26	4	22	84.6%
Overall	46	15	31	67.4%

Means for Survival Time

Statistics	Mean(a)			
			95% Confidence Interval	
	Estimate	Std. Error	Lower Bound	Upper Bound
< 50 mCi I-131	52.000	2.309	47.474	56.526
51 – 70 mCi I-131	50.400	2.147	46.193	54.607
71 – 100 mCi I-131	53.333	3.823	45,840	60.827
> 100 mCi I-131	51.346	3.997	43.512	59.180
Overall	51.717	2.414	46.987	56.448

a Estimation is limited to the largest survival time if it is censored.

Overall Comparisons

	Chi-Square	df	p - Sig.
Log Rank (Mantel-Cox)	7.728	3	0.052

Test of equality of survival distributions for the different levels of radioiodine

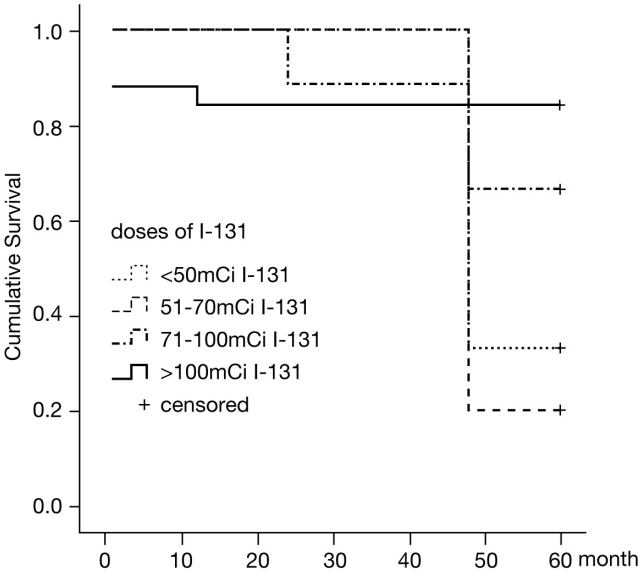

Fig. 2 Statistical results of 5-year (60 months) disease-free interval according to radioiodine doses

Case Processing Summary at 5 years

Stage	Total N	N of Events	Censored	
			N	Percent
1	44	14	30	68.2%
3	1	0	1	100.0%
4	1	1	0	0.0%
Overall	46	15	31	67.4%

Overall Comparisons

	Chi-Square	df	*p* - Sig.
Log Rank (Mantel-Cox)	14.720	2	0.001

Test of equality of survival distributions for different stages

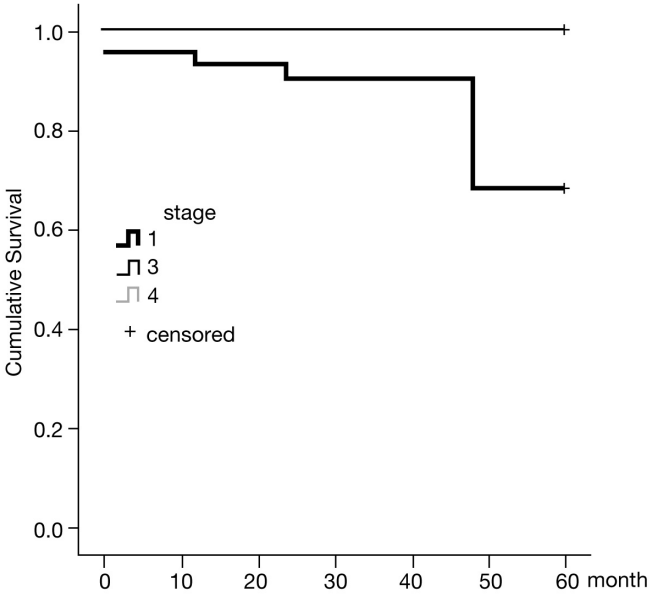

Fig. 3 Statistical results of 5-year (60 months) disease-free function according to stage

free disease status. In these situations, the recurrence was observed only at immunological level, with detectable Tg in stimulated TSH conditions and no clinical evidence of TC. The RIT was applied after a confirmation of dynamic evolution of Tg in at least 2 consecutive determinations at 6 month intervals. In all these cases we could identify long periods of inappropriate LT4 therapy and chronically elevated serum TSH levels, above 2 mIU/L.

Conclusions

Thyroid cancer in children is rapidly aggressive, but despite that, the survival rates are not influenced by the severe clinical status. The nuclear irradiation influenced a number of cases, but the increasing trendline has stopped. Appropriate treatment succeeds in curing the disease in the first year, in more than two thirds of the cases, the most important predictor factor being the stage. Low and medium doses of radioiodine used in the therapy have the same efficiency as high doses.

Declaration of Interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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