The thyroid cancer in children: a 20 years study in a Romanian oncology institute

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Abstract. The thyroid carcinoma (TC) has an increasing incidence in the last decades and continues to represent the most frequent endocrine tumor. The aim of the study was to analyze the pediatric files of TC from the registry of “Prof. Dr. Ion Chiricuță” 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 wa...
Patients and Methods

The Institute of Oncology “Prof. Ion Chiricuta” Cluj-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 new registered malignancies. Between 1991 and 2010 in IOCN were treated 3424 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, ranged between 8-18 years old, the mean age was 15.3 years and the median age was 15.5 years (standard deviation 2.6055). The clinical signs were: enlargement of the thyroid gland and lymph nodes detection in the cervical area (64 cases-88.8%), dyspnea and cough in 3 cases (4.1%), hemoptysis in 1 case (1.3%) and the familial screening in 4 cases of MTC (5.5%). The 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 anaplazic thyroid cancer (ATC); 1 case was a mixed form of medullary 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 was ranging 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. In DTC surgery (the total or near total thyroidectomy +/- selective lymphadenectomy) was followed by I-131 radioiodine (RIT) ablation at 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 previous 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 FT4 on 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.

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The thyroid cancer in children

The incidence of thyroid cancer (TC) in IOCN has considerable increased in the last years. The number of 1938 total 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 represent 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 the country, but 17 children (23.6%) were from the Central and North Eastern part of Romania (Moldova, Mures and Covasna counties) knowing as being affected by the nuclear fallout from Chernobyl [33]. The official report of the United Nations Scientific Committee of the Effects of Atomic Radiation (UNSCEAR) presents the map of radionu-

Results and Discussions

The analyses were performed on Roche kits and Cobas instruments. Normal values for differentiated thyroid carcinoma patients with radical treatment according to the producers are: \( \text{Tg} < 0.1 \mu\text{g/L} \) and \( \text{anti-TgAb} < 115 \text{IU/mL} \). \( \text{Ct normal values after radical surgery is} < 0.6 \text{pmol/L} \) [36, 37].

The WBS I-131 was performed in 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 case of post therapy WBS. Conventional computer tomographies (CT) were performed in IOCN on GE spiral CT. The 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. Statistic methods used were based on EpiMax Table, Log Rank (Mantel Cox) tests.
clude distribution in Europe after 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 are available for this area.

As an important issue to be underlined is that the incidence of the pediatric thyroid cancer has a different pattern compared with that of the adults at 25 years after Chernobyl (Fig. 1 B). The number of pediatric cases at 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 by four (17 cases). In the period 2001-2005 the number of cases was slightly increased comparing 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. 1 A, potentially due to more extensive diagnostic procedures. These data suggest that the increasing incidence due to irradiation, not to screening is more accurate demonstrated in the pediatric group, than at adults.

In our study, a number of 37 patients (51.38%) 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 birth was 5.12 years (minimum 1 – maximum 12 years).

The histology distribution showed that the DTC is still the most frequent form of TC also in the pediatric files (88.8%). The MTC represented 8.3% of all cases; 4 out 6 cases were discovered in the course of familial screening of adult patients. Interesting is the appearance of an unusual ATC at 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 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 nodes involvement (27 cases out 72) and lung metastasis (4 cases out 72) at the discovery of the disease. This data underlines the fact that TC in children is with 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 analysis were carried out on interval of free disease, not on survival rates.

The Tables 1, 2 and 3 present the statistical analysis of disease free interval at 1 year, 3 years and 5 years, referred to histology. It is interesting the fact, that applying the test Log Rank (Mantel-Cox) at 1 year and

### Table 1 The 1-year free disease interval according to histology

<table>
<thead>
<tr>
<th>HP code statistics</th>
<th>Total N</th>
<th>N of events</th>
<th>Censored</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Percent</td>
<td>N</td>
</tr>
<tr>
<td>Anaplastic</td>
<td>2</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Follicular</td>
<td>9</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Medullary</td>
<td>7</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Papillary</td>
<td>50</td>
<td>11</td>
<td>39</td>
</tr>
<tr>
<td>Overall</td>
<td>68</td>
<td>13</td>
<td>55</td>
</tr>
</tbody>
</table>

Overall Comparisons

<table>
<thead>
<tr>
<th>Chi-Square</th>
<th>df</th>
<th>p -Sig.</th>
</tr>
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<tbody>
<tr>
<td>Log Rank (Mantel-Cox)</td>
<td>12.328</td>
<td>3</td>
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</table>

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

### Table 2 The 3-years free disease interval according to histology

<table>
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<th>Censored</th>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>Percent</td>
<td>N</td>
</tr>
<tr>
<td>Anaplastic</td>
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<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Follicular</td>
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<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Medullary</td>
<td>7</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Papillary</td>
<td>37</td>
<td>7</td>
<td>30</td>
</tr>
<tr>
<td>Overall</td>
<td>55</td>
<td>9</td>
<td>46</td>
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</table>

Overall Comparisons

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<tr>
<th>Chi-Square</th>
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</thead>
<tbody>
<tr>
<td>Log Rank (Mantel-Cox)</td>
<td>23.094</td>
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Test of equality of survival distributions for the different levels of histology.

### Table 3 The 5-years free disease interval according to histology

<table>
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<th>HP code statistics</th>
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<th>Censored</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>Percent</td>
<td>N</td>
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<tr>
<td>Follicular</td>
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<td>Papillary</td>
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<tr>
<td>Overall</td>
<td>46</td>
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<td>31</td>
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Overall Comparisons

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<tr>
<th>Chi-Square</th>
<th>df</th>
<th>p -Sig.</th>
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<tbody>
<tr>
<td>Log Rank (Mantel-Cox)</td>
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Test of equality of survival distributions for the different levels of histology.
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).

Considering the guidelines of TC therapy in DTC cases and the 2 cases with mixed forms, a number of 64 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.

A number of 17 patients (26.6%) received one single dose of I-131, with mean activity of 64.2 mCi (2.37 GBq) I-131, attempting the disease free status after the therapy; more than 1/4 of the patients were complete treated with less than 70 mCi (2.59 GBq) I-131. Multiple doses of I-131 were administered as follows: 2 doses – 19 cases; 3 doses-16 cases; 4 doses- 5 cases; more than 5 doses – 7 cases. We underline the low activities of radioiodine used in this cohort of patients. It is also important the fact that in this database we don’t experienced any lung fibrosis or hematological side effects.

The Fig. 2 presents the statistical results of interval free disease 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 statistic important value at 5 years, \( p = 0.052 \). The level of low and medium radioiodine activities has same results as high levels of activities.

Considering the entire group at the moment of the study, a number of 57 children (79.2 %), where free of disease, even considering the severe clinical presentation of more than 1/3 of the group. The parameter that keeps the important statistic 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...
Recurrences occurred in 3 cases (4.2%) at 14 months, 5 years, respectively at 7 years after the first decision of free disease status. In all this 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 months intervals. In all these cases we could identify long periods of inappropriate LT4 therapy and chronic elevated serum TSH levels, above 2 mIU/L.

**Conclusions**

The thyroid cancer at children is rapid aggressive, but despite that, the survival rates are not influenced by the severe clinical status. The nuclear irradiation influenced the number of cases, but the increasing trendline stopped. An appropriate treatment succeeds to cure the disease in the first year, in more than 2/3 of cases, the most important predictor factor being the stage. Low and medium doses of radioiodine used in the therapy have 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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**References**


