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Prognostic factors for differentiated thyroid carcinoma in young patients

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Introduction. Standard therapy of differentiated thyroid cancer (DTC) comprises thyroid surgery, radioiodine treatment and L-thyroxine suppressive treatment. However, in the case of young patients the extent of surgery and the need for radioiodine treatment are questioned by some authors on the basis of the overall good prognosis in this group.
Aim. The aim of the study was to perform a retrospective analysis of prognostic factors for differentiated thyroid cancer in patients in the first three decades of their life.
Material and methods. The study included 274 patients who were younger than 28 years at the day ofdiagnosis of DTC and were observed for a mean time of 5 years. Uni- and multivariate analysis of prognostic factors for disease – free survival was performed with Cox's regression method.
Results. The actuarial survival rate was 100%, the 5 and 10-year actuarial disease free survival was 85% and 75%, respectively. In a multivariate analysis lymph node metastases, the extent of surgery and radioiodine therapy were estimated as statistically significant, independent prognostic factors for DTC relapse.
Conclusions. Radical treatment of DTC more advanced than pT1N0M0 should include total thyroidectomy and postoperative complementary radioiodine therapy. Such procedure is also justified in young patients, as it ensures a decrease of the risk of recurrence.

Czynniki prognostyczne w przebiegu zróżnicowanego raka tarczycy u młodych osób

Cel. Leczenie operacyjne z następowym leczeniem radiojodem i stosowaniem supresyjnych dawek hormonów tarczycy ma ustalone miejsce w leczeniu zróżnicowanego raka tarczycy (ZRT). Jednak zakres operacji jak i wskazania do leczenia radiojodem wciąż wzbudzają wiele kontrowersji, zwłaszcza u młodych osób, u których rokowanie w przebiegu ZRT jest szczególnie dobre.
W pracy przeprowadziliśmy retrospektywną analizę czynników prognostycznych wpływających na przebieg ZRT, rozpoznanego w pierwszych trzech dekadach życia.
Materiał i metodyka. Analizę przeprowadzono wśród 274 chorych, u których zróżnicowanego raka tarczycy rozpoznano przed ukończeniem 28 roku życia. Średni czas obserwacji wynosił 5 lat. Wpływ czynników prognostycznych na przeżycie bezobjawowe oceniano jedno- i wielowariantową analizą regresji według Cox'a.
Wyniki. W całej grupie chorych przeżycie całkowite wynosiło 100%, a przeżycie bezobjawowe po 5 i 10 latach obserwacji odpowiednio 85% i 75%. W analizie wielowariantowej zawansowanie choroby nowotworowej, zakres zabiegu operacyjnego oraz leczenie radiojodem miały istotny wpływ na przeżycie bez objawów nawrotu choroby.
Wnioski. Radykalne leczenie ZRT, w stopniu zaawansowania innym niż p T1N0M0, powinno obejmować całkowite usunięcie gruczołu tarczowego z następowym leczeniem radiojodem. Dotyczy to również młodych osób, u których postępowanie takie w sposób istotny zmniejsza ryzyko nawrotu choroby nowotworowej.

Key words: diferentiated thyroid cancer, prognostic factors
Słowa kluczowe: zróżnicowany rak tarczycy, czynniki prognostyczne

Introduction

In most studies long term survival in differentiated thyroid carcinoma (DTC) is excellent, especially in patients under 40-50 years of age [1, 2, 3]. Patients under 45 years of age are defined as a low risk group risk by TNM classification [4, 5]. Yet, the age range of this group is very wide and encompasses children as well as patients in their

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forties. In the recent years many controversies arose and some authors claim that DTC in children tends to be more aggressive than in adults [2].

Only about 3 – 10% of all thyroid carcinomas occur in patients younger than 20 years of age [6, 7]. Since the first report of thyroid cancer in a child in 1902, for the first several decades thyroid carcinoma in children was regarded as a medical curiosity. A rapid increase in the number of children with thyroid cancer observed in the 1960's was related to the previous exposure of the neck region to ionisation irradiation, mostly applied as the treatment of various benign diseases [8, 9]. A very distinct increase in prevalence of thyroid cancer among European children has surfaced in Belarus, Ukraine and Russia after the Chernobyl nuclear accident [10-12]. The peak of post-Chernobyl incidence of DTC moves now towards adolescence and the first years of adulthood. No similar rise has been observed in Poland. However a steady rise in the prevalence of thyroid carcinoma has been observed, beginning with the 1980's [13]. Thus the number of the new cases has increased from 200-300 to more than 1000 per year. The fact of increasing prevalence of thyroid cancer in young patients underscores the importance of defining the adverse prognostic factors and the appropriate treatment for this group of patients. The low incidence of the disease, its protracted course and the need for a long period of follow up to establish risk factors, make prospective studies difficult to perform. Thus, the best possible way seems to be a uni- and multivariate regression analysis of retrospective data in a homogenous population.

Material and methods

Patients

Medical records from 274 patients treated for differentiated thyroid cancer between 1972 and 1995 were reviewed retrospectively (Tab. I). There were 109 children (group I) and 165 adults (group II) less than 28 years of age at the diagnosis of DTC. This age limit was chosen to cover all patients who were younger than 18 years in May 1986, during the Chernobyl-induced contamination. The follow-up time ranged between 1 and 23 years; an average of 5 years in group I and 3.5 years in group II. Seven children and 37 young adults had thyroid cancer diagnosed shortly before the time of analysis and they were all excluded from the study. The results obtained for children were also a subject of a separately published analysis [14].

Tab. 1. Characteristics of the studied groups

		Children	Young adults	all patients	p
age		6-17 years mean 13.6	18-27 years mean 23,2	19.3	/
gender	female	76 (69%)	137 (83%)	213	0.012
	male	33 (31%)	28 (17%)	61	
Histo-pathology	papillary	77 (71%)	88 (54%)	165	0.096
	follicular	32 (29%)	77 (46%)	109	
lymph node metastases		64 (59%)	64 (39%)	128	0.037
distant metastases		17 (16%)	7 (4%)	24	0.006
total thyroidectomy		81 (79%)	107 (83%)	188	ns
radioiodine treatment		70 (69%)	103 (80%)	173	0.038

Surgery

Standard treatment of DTC applied at our centre was total thyroidectomy followed by radioiodine therapy. Primary total thyroidectomy was performed using an extracapsular approach [15,16]. Resection of the central lymph-node compartment and bilateral biopsy of lateral neck lymph nodes were performed routinely. If the latter was positive, it was followed by radical modified neck dissection on the affected side. The cervical vein and sternocleido-mastoid muscle were preserved.

Many patients were operated in other centres, 86 of them underwent sub-total surgery. We assessed the radicality of previous thyroid surgery by ultrasound and ^{131}I scan performed after 4 weeks of thyroxine withdrawal. In patients with thyroid remnants larger than 1 ml by ultrasound on either side of the neck or showing significant ^{131}I neck uptake, secondary radical thyroidectomy was performed.

In those cases where surgery had been carried out in other centres lymph node biopsy was not always performed and in some cases only lymph node excision was applied. In those cases radical lymphadenectomy was performed only when enlarged lymph nodes were detected by clinical or ultrasound examination.

Ultimately, radical thyroid surgery was administered to 188 (68.6%) patients: 81 children and 107 young adults. There were no differences in the extent of thyroid operation with reference to the lymph nodes status (Tab. II).

Tab. II. Extent of thyroid surgery in relation to lymph node status

Lymph nodes		Extent of operation		p
		total	less than total	
N0	Group I	37 (86%)	6 (14%)	ns
	Group II	58 (83%)	12 (17%)	
N1	Group I	44 (75%)	15 (25%)	ns
	Group II	49 (84%)	9 (16%)	

Histopathology and staging

On the basis of postoperative histopathologic examination 165 (60%) tumours were classified as papillary carcinoma and 109 (40%) as follicular carcinoma (Tab. I). Every diagnosis was re-evaluated by another pathologist from the Department of Tumour Pathology in our Institute according to the WHO 1986 classification.

All patients were diagnosed with a palpable neck mass before operation. The exact tumour diameter (T stage) was not always reported, thus in Table I we reported only the prevalence of lymph node and distant metastases.

Lymph node metastases were diagnosed in 128 (46%) patients. 24 (8.8%) patients suffered from distant metastases, lung metastases were prevalent (Tab. III). In 12 patients lung metastases were recognised on the basis of positive whole body ^{131}I scan (WBS) but negative chest x-rays – in those cases micronodular lung dissemination was diagnosed. In all but one patient the distant metastases were functional and could be observed on ^{131}I whole body scan.

Complementary treatment

Patients with radioiodine uptake >1% in thyroid bed and/or in lymphonodal localisation or with distant metastases were given postoperative radioiodine treatment. Fixed ^{131}I doses (mostly 60 or 100 mCi) were applied. 157 patients were treated to ablate thyroid remnants or to treat remnants after surgery of lymph node metastases. In another 16 (6%) patients the first radioiodine treatment was applied to treat distant metastases together

Tab. III. The site of initial presentation and the outcome of distant metastases

Site		No	WBS	X-ray	CR	R
lung*	Group I	14*	12	5	11	2
	Group II	5	5	3	3	2
bone	Group I	2	2	2	1	1
	Group II	1	1	1	0	1
liver (1 child)		1	1	0	1	0

*one in one child parents did not give their consent on radioiodine diagnostic examination or treatment
WBS – whole body scintigraphy
X-ray – X ray examination
CR – complete remission
R – partial remission

with thyroid or lymph node remnants. TSH suppressive therapy with L-thyroxine was introduced in all patients.

Follow-up

After treatment all patients underwent regular follow – up. When radioiodine therapy was given for ablation of thyroid remnants and no distant metastases were detected on the postherapeutic whole body scintigraphy, remission was evaluated at a check-up carried out six months after ^{131}I treatment. The check-up consisted of clinical evaluation, neck ultrasound, chest X ray, thyroglobulin (Tg) estimation and ^{131}I whole body scintigraphy (WBS) performed after 4 weeks of thyroxine withdrawal. When the results of these examinations were negative, the patients were followed-up regularly at six month intervals (after 5 years at 12 month intervals) while on thyroxine suppressive therapy. Clinical examination, TSH and Tg estimations were performed each time, and neck ultrasound and chest X-ray at annual intervals. ^{131}I WBS and Tg estimations during endogenous TSH stimulation were routinely performed after 2 and 5 years and then at 5 year intervals.

In patients treated with ^{131}I therapy for lymph node or distant metastases, the remission was evaluated at check-up carried out six months after the last ^{131}I therapy. Radioiodine therapy was discontinued when no foci of ^{131}I uptake were observed on posttherapeutic ^{131}I WBS. The accumulated ^{131}I activity ranged between 60-580 mCi. When remission was achieved, the subsequent follow-up was carried out according to the scheme outlined above.

Recurrences were recognised in 25 patients – 16 children and 9 young adults (Tab. IV). In most cases locoregional relapses were stated, in three patients with concurrent distant relapse. In nine patients the recurrence was detected at the follow up after the primary treatment performed or evaluated in our centre. The other 16 (6% of all patients) were referred to our centre only after the diagnosis of relapse.

Methods for evaluation of disease status

1. Ultrasound neck examination was performed with different ultrasound equipment, which in all cases was supplied with a 7.5 MHz linear head.
2. Diagnostic WBS was performed with 1-2 mCi of ^{131}I. Until 1995 a rectilinear whole body scanner was used (Picker Nucleograph). In 1995 a dual head γ camera with parallel high energy collimators was introduced (Siemens, Multispect 2). AP and PA projections were obtained with additional spot projections of the neck area and the chest. TSH level was evaluated simultaneously and was expected to exceed 25 mU/L. 24-hour neck uptake was measured by a scintillation probe (Scaler P21) or with region of interest (ROI) technique. The cut-offs used were 1% and 0,4% respectively. Posttherapeutic WBS was carried out on day 4 with a MB 9200 camera with reverse pinhole collimator until 1995 and thereafter with the Multispect 2.
3. Thyroglobulin estimations have been done with immunofluorometric Wallac Delfia kits on a routine basis since 1993. The functional sensivity of this assay is 1 ng/ml. Our own cut-off values were estimated by ROC analysis at a 95% specificity level [17]. During L-thyroxine therapy the cut-off value was 4 ng/ml, off therapy 30 ng/ml. The recovery of added Tg was routinely measured. Our own cut-off limit for Tg recovery was 70% and serum thyroglobulin estimations were evaluated as valid only when this condition was met.
4. TSH examinations were performed with Abbot hTSH II generation assay. A value of 0.05-0.3 IU/L was accepted as evidence for suppression of endogenous TSH. Levels above 25 IU/L were expected for endogenous TSH stimulation.

Tab. IV. Characteristics of the recurrences

site	group I	group II	all	p
distant	3	0	3	0.028
distant and local relapse	3	1	4	0.100
local relapse	10	8	18	0.092
all sites	16	9	25	0.003

Statistical analysis

Because there were no deaths, the end point of the analysis was disease free-survival, defined as the period between the first negative examination carried out after the primary treatment (thyroidectomy or thyroidectomy followed by radioiodine) and the last examination confirming the disease-free state. For relapsed patients, the end of the disease free period was the time of detection of the recurrence. All local recurrences were confirmed by histopathological examination. Distant relapses were diagnosed on the basis of ^{131}I whole body scintigraphy, increase in serum Tg, X ray and/or computer tomography and, in rare cases, 99m Tc methylene diphosphonate scintigraphy.

Prognostic factors listed below were first studied separately using the Cox proportional hazard model in a single-step analysis and then the multiple regression model was obtained for each combination of factors to compare their joined prognostic impact on DFS. P values <0.05 were considered statistically significant. Independent variables assessed for their influence on disease free-survival included:

1. Patient-related factors
   - age: 6-10/11-13/14-17/18-27,
   - sex: female/male.
2. Tumour-related factors
   - histopathology: papillary/follicular,
   - lymph node metastases: present/not present.
3. Treatment-related factors
   - extent of thyroidectomy – total/less than total,
   - postoperative radioiodine treatment – applied/not applied.

Results

There were no deaths in the studied group. Actuarial disease-free survival after 5 and 10 years of observation was 85% and 75% respectively (Fig. 1).

The best prognosis was observed in the group of young adults, where disease-free survival after 5 and 10 years was 90% and 87% respectively. Children had distinctly less favourable prognosis in relation to disease-

-free survival ($p<0.05$, Fig. 1). When they were subdivided into age groups (Fig. 2) the difference between small children (younger than 10 years of age) or young teenagers (11 to 13 years of age) and adults still remained significant. Adolescents (14 to 17 years) who formed the most numerous group did not show the significantly worse course of disease than young adults.

In univariate analysis gender and tumour histopathology did not correlate with the disease free-survival. Lymph nodes metastases adversely affected disease free-survival in the entire group of patients, but the difference was only of borderline significance ($p=0.056$, Fig. 3). In children the risk of recurrence did not differ between children with or without lymph node metastases and in the young adults group this was only of borderline significance.

A significant correlation was found between the therapeutic approach and the rate of recurrences by univariate comparison. Total thyroidectomy resulted in 91% DFS after 10 years while a non-radical operation was connected with 41% and 60% risk of relapse after 5 and 10 years respectively (Fig.3). When radical thyroidectomy was applied, there were no differences in disease free-survival between children and young adults. However, in children without radical surgery, disease free-survival was significantly worse than in young adults.

The subsequent radioiodine treatment also significantly influenced disease free-survival (Fig. 4). After 5 years of observation 94% of patients in the ^{131}I treated group were disease free while 32% and 50% of patients without radioiodine treatment relapsed after 5 and 10 years of observation. When treated with the same treatment modality, there were no statistically significant differences observed between children and young adults.

When multivariate analysis was applied, lymph node status, extent of operation and radioiodine treatment had statistically significant impact on disease free-survival (Tab. V).

Lymph nodes metastases increased the risk of relapse by a factor of 4. However, the impact was visible only when the entire group of patients under the age of 28 was analysed. In children the confidence interval was wide and p-value was higher than 0,05.

The factors with favourable significance in the multivariate analysis were total thyroidectomy and radioiodine treatment (Tab. V). The risk of recurrence was 6 times higher among patients operated with the less extensive approach and the difference was highly significant statistically. Postoperative radioiodine treatment independently reduced the risk of recurrence by a factor of 5.

Discussion

Age is recognised as one of the most important prognostic factors for disease free-survival in differentiated thyroid

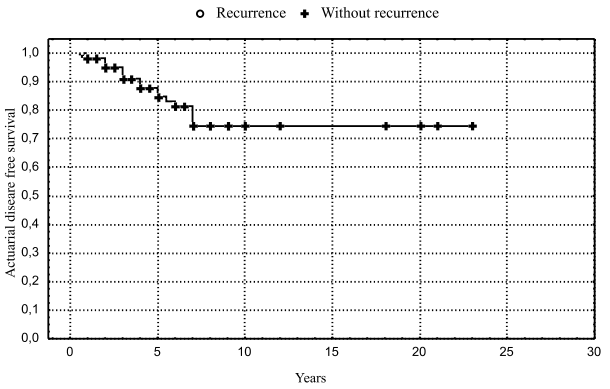


Fig 1. Actuarial disease free survival in DTC patients younger then 28 years of age

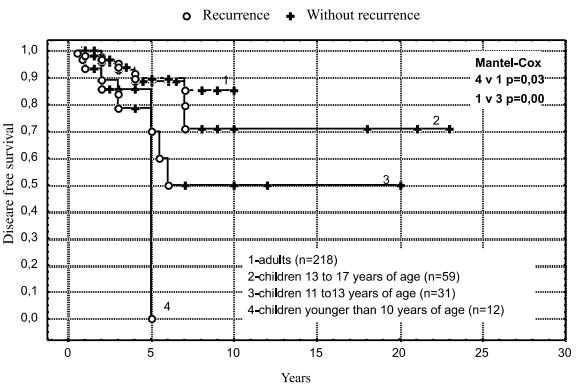


Fig. 2. Disease free survival by age

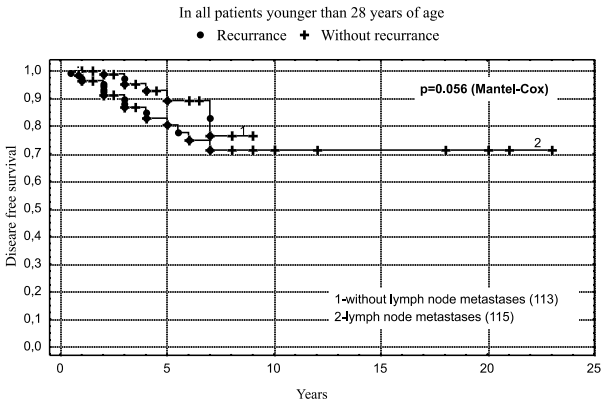
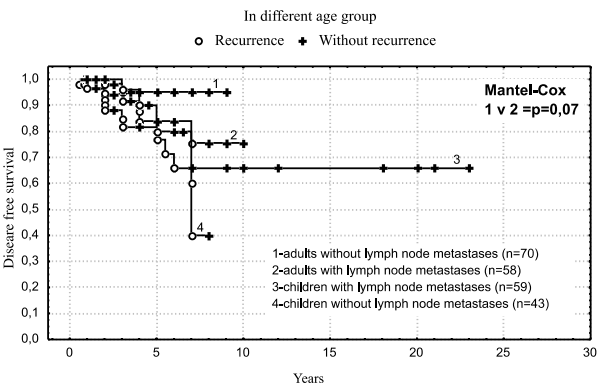


Fig. 3. Disease free survival by lymph node metastases



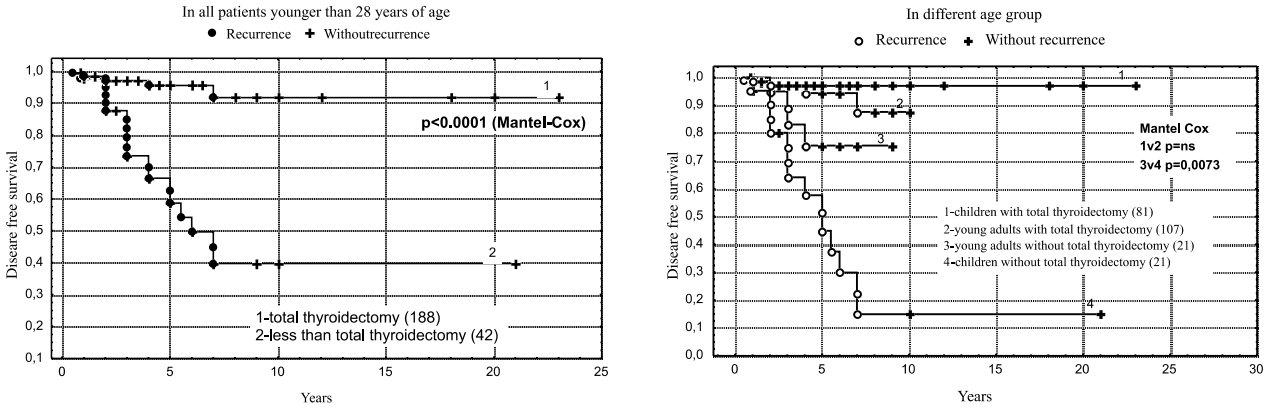


Fig. 4. Disease free survival by extent of operation

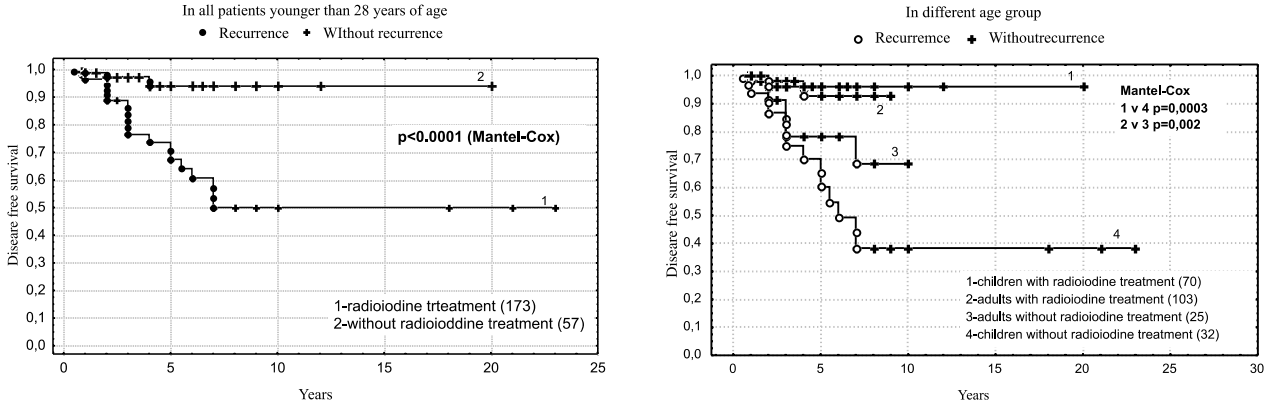


Fig. 5. Disease free survival by radioiodine treatment

carcinoma. Patients younger than 45 years of age show longer periods of survival and a lower incidence of recurrence. Although children tend to be diagnosed at a more advanced stage of the disease and have higher recurrence rates [2, 18-20] the rate of survival seems to be unaffected [2, 18]. This has caused many controversies concerning the adequate therapeutic strategy in the cases of DTC diagnosed in young patients.

In our study we analysed 274 patients with differentiated thyroid cancer, who were younger than 28 years of age at the time of disease diagnosis. Several factors affecting the prognosis of DTC were evaluated first in the entire group of patients and then compared with our previous results [14] obtained for the children's group. The patients were treated with ^{131}I and followed in the same medical centre for a mean time of 5 years. To determi-

Tab. V. Multivariate Cox regression analysis of prognostic factors

Factor	All patients younger than 28 years of age		Young adults		Children	
	p	Risk factor (90% confidence interval)	p	Risk factor (90% confidence interval)	p	Risk factor (90% confidence interval)
Age at diagnosis [years]	0.964	0.99 (0.92-1.0)	0.560	1.1 (0.82-1.4)	0.080	0.79 (0.63-0.99)
Gender [female / male]	0.959	0.97 (0.38-2.4)	0.550	2.1 (0.26-1.4)	0.800	0.83 (0.26-2.6))
Histopathology [papillary / follicular]	0.160	0.51 (0.23-1.1)	0.101	0.2 (0.06-1.0)	0.777	0.82 (0.27-2.5)
Lymph node metastases at DTC diagnosis [present / not present]	0.027	3.1 (1.3-7.2)	0.020	9.0 (1.8-43)	0.373	1.8 (0.6-5.4
Extent of operation [total / less than total]	0.0001	6.2 (2.8-13.7)	0.017	7.6 (1.8-31.1)	0.007	9.6 (2.3-39.1)
Radioiodine treatment [yes / no]	0.001	5.8 (2.4-14.1)	0.014	7.4 (9.1-28.3)	0.073	5.1 (1.1-32.2)

ne death rate, the follow up time should be, in a majority of patients, longer then 5 years [21-24] and the observation of no cancer-related death in our study is only a preliminary one. Therefore the importance of prognostic factors was calculated in relation to disease free survival.

Disease-free survival was closely related to the patient's age and was the longest in young adults. Mazzafferi et al. [2] noted the highest rate of recurrences in patients younger than 10 or older then 60 years. Similarly, the report from Children Cancer Study Group [25] and other reports have claimed that the younger the child at diagnosis the higher the rate of relapse. This was confirmed in our study. Children in the youngest group, less then 10 years of age, had the worst prognosis and all of them relapsed. The difference was statistically significant both when compared with adolescents 14 to 17 years of age and young adults. However, multivariate analysis did not prove any significant correlation between age at diagnosis and disease-free survival. Instead it revealed extent of surgery as the most potent prognostic factor for the disease-free survival. Accordingly the effect of the latter factor could have been stronger than the influence of age.

Children revealed more metastases than young adults. For a long time the presence of lymph node metastases at diagnosis was not considered a negative prognostic factor in DTC [26-31]. Recently, more and more authors have claimed that local metastases adversely influence disease-free survival [1, 29, 32-34]. Mazaferri and Jhang [2] showed an increased risk of relapse in young patients with lymph node metastases without any influence on overall survival. Similar observations may be found elsewhere [1, 35]. Some authors claim that along with the presence of node metastases, their site, size, number and extension beyond the capsule probably also exert their impact on prognosis [34, 36]. However, these factors were not taken into account in most series. Also in the present study we analysed only the presence or absence of lymph node metastases. Half of the lymphangiectomies were performed at other institutions and more specific data was often lacking. The exact extent of lymph node dissection was not always stated as well. Even though our criteria of lymph node status were very rough, patients with lymph nodes metastases suffered from significantly worse prognosis, but the difference was statistically significant only in the entire group, but not in the subgroup of children. We must stress that all but two children, and all young adults with distant metastases suffered also from neck metastases. This fact should also draw our attention to lymph node metastases as a possible adverse prognostic factor.

In our study we did not observe any correlation between histology or gender and prognosis of DTC. However in many papers such correlation has been suggested [2, 19, 34, 35].

Considering treatment-related factors, our results remain in strong opposition to authors opting for conservative surgery in young patients. Our rate of recurrence was very distinctly related to the extent of surgery both in the entire group of patients and in subgroups. The results of non- total thyroidectomies were much worse in children than in adults (DFS 15% vs 75%, $p<0.05$).When total thyroidectomy was performed, there were no differences in DFS between children and young adults. This observation supports the necessity for radical thyroid surgery both in children and young adults.

Many authors are convinced that in children and young adults (as in adults), total thyroidectomy is the most adequate treatment for any DTC, with the exception of unifocal papillary microcarcinoma [1, 2, 37]. Opponents of an extensive surgery in young patients cite the low mortality rate in this age group [14, 26, 34, 40, 41]. They opt for a conservative surgical approach, despite the high rate of recurrences in non-radically operated patients. However, their studies can be biased by a selection of patients with more extensive disease for treatment with radical surgery. Robie et al [34] in their study from 1998 advocated total or subtotal thyroidectomy only in patients with distant metastases, extensive lymph node involvement, or invasive extracapsular tumours. Only a year later they reanalysed the results in children with thyroid carcinoma confined to the thyroid gland and showed that disease-free survival improved in patients treated with total or subtotal thyroidectomy when compared with lobectomy [42].

The therapeutic benefit of complementary treatment with radioiodine for differentiated thyroid carcinoma was clearly showed by Mazzaferri et al. [2, 43]. Also in our study the favourable effect of radioiodine treatment was highly significant, both in uni- and multivariate analysis. These results are meaningful for two reasons. Firstly, radioiodine treatment was mainly given after total thyroidectomy, but despite that fact the independent effect of ^{131}I therapy was still observable. Secondly, all postoperative ^{131}I treatments were included in our analysis, including those performed in the presence of distant metastases. The presence of radiological signs of lung metastases in 4 children and 3 young adults receiving ^{131}I post thyroidectomy hampered their prognosis in comparison to the group of patients, who were not treated postoperatively with radioiodine[2, 44]. Nevertheless, their disease-free survival increased in comparison to patients without complementary ^{131}I therapy. Both these facts speak in favour of wide indications for ^{131}I complementary therapy after radical surgery also in young patients. It is well known that ^{131}I treatment does not impair fertility or induce inborn defects and it is not contraindicated in females in child bearing age [45, 46].

In conclusion, our observations show that treatment of DTC in the first three decades of life should include total thyroidectomy and postoperative complementary radioiodine therapy in every case of thyroid carcinoma more advanced than pT1N0M0 papillary carcinoma.

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