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COMPARATIVE RESULTS OF THE TREATMENT OF CHILDREN AND ADOLESCENTS WITH THYROID CANCER AT ST PETERSBURG ENDOCRINE SURGERY CENTER AND MAYO CLINIC

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Abstract. *Introduction*. Thyroid cancer (TC) is the most prevalent malignant tumor identified in childhood and comprises 1.5%–3.0% of the entire population of children and 45.3% of pediatric endocrine epithelial cancers. Of the multiple questions concerning the extent of thyroid surgery, the need for postoperative radioiodine therapy should be discussed. *Material and methods*. During 1970–2011, 105 children and adolescents with TC (up to 18 years of age) were operated in the St Petersburg Endocrine Surgery Center (Group 1) and 188 individuals were operated at the Mayo Clinic (Group 2) during 1940–2000. Since the 1980s, the same perioperative examinations were performed at these clinical centers, including thyroid stimulating hormone (TSH), T4, and T3 blood levels; ultrasound examination; fine needle aspiration biopsy; CT; and morphological examinations. *Results and discussion*. Average age of the patients from both groups was the same (16.3 ± 0.3 and 16.0 ± 0.5 years, respectively). In both groups, there was a higher prevalence of girls: 73.3% (M:F, 1:2.7) in Group 1 and 70.7% (M:F, 1:2.4) in Group 2. During the preoperative examination regional metastases were found in 53.0% and 81.4% of patients, respectively; extrathyroid TC spreading was confirmed in 9 (9.6%) and 37 (19.7%) patients, respectively; and distant metastases in lungs and bones were more frequent in group 1 compared to group 2 (9.6% vs 4.8%, respectively). At the St Petersburg Endocrine Surgery Center, the hemithyroidectomies and subtotal thyroidectomies with an ipsilateral central neck dissection (CND) were performed in 58.1% of patients. At the Mayo Clinic, all patients with TC have been receiving a thyroidectomy (TE) since 1950. TC relapses were not observed in Group 1 patients, whereas they did occur in 6.9% of the Group 2 patients; recurring lymphatic metastases occurred in 8.4% and 20.7% of the Group 1 and Group 2 patients, respectively. Radioiodine therapy (RIT) was performed in 21.1% and 25.5% patients, respectively. In group 1, 95 (96%) of the 99 operated patients were alive during the 5–36-year follow-up period. In Group 2, death due to TC occurred in only two patients, but death due to another malignant tumor occurred in 14 patients. *Conclusion*. Childhood TC is associated with more locally aggressive and more frequent distant disease compared to adults. Recurrence rates tend to be higher in children, but cause-specific mortality remains low. Optimal initial treatment of childhood TC should include TE and CND. RIT in childhood has increased the possibility of developing other malignant tumors during the follow-up period.

Key words: thyroid cancer; children; adolescents; surgical treatment; radioiodine treatment.

СРАВНИТЕЛЬНЫЕ РЕЗУЛЬТАТЫ ЛЕЧЕНИЯ ДЕТЕЙ И ПОДРОСТКОВ, СТРАДАВШИХ РАКОМ ЩИТОВИДНОЙ ЖЕЛЕЗЫ, В ЦЕНТРЕ ЭНДОКРИННОЙ ХИРУРГИИ САНКТ-ПЕТЕРБУРГА И В КЛИНИКЕ МЕЙО

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Резюме. *Введение*. Несмотря на длительную историю лечения рака щитовидной железы (РЩЖ) у детей и подростков, который встречается в 1,5–3,0 % и составляет 45,3 % детских эндокринных эпителиальных раков, остается ряд дискуссионных вопросов, связанных с выбором объема хирургических вмешательств на ЩЖ и регионарном лимфатическом аппарате шеи, проведением послеоперационной терапии радиойодом. *Материал и методы*. В период с 1970 по 2011 г. в Санкт-Петербургском центре эндокринной хирургии и онкологии находилось на лечении 105 детей и подростков (в возрасте до 18 лет) РЩЖ (1 группа). В клинике Мейо с 1940 по 2000 г. оперированы 188 РЩЖ в возрасте до 20 лет (2 группа). С начала 80-х годов в клиниках применялись одинаковые методы периоперационной диагностики (контроль уровней ТТГ, Т4, Т3; УЗИ, пункционная биопсия, срочное и плановое гистологические исследования). *Результаты и обсуждение*. Средний возраст больных составил в 1-й и 2-й группах 16,3 ± 0,3 и 16,0 ± 0,5 года соответственно. В обеих группах превалировали девочки.

В 1-й группе их было 73,3 % (М:Ж 1:2,7), во второй – 70,7 % (М:Ж 1:2,4). Более чем у половины больных до операции выявлялись регионарные метастазы (в 1-й группе – 53,0 % наблюдений, во второй – 81,4 %). Рост опухоли за пределы ЩЖ отмечен у 9 (9,6 %) детей в Санкт-Петербурге и 37 (19,7 %) больных в Рочестере. Отдаленные метастазы в легкие и кости чаще отмечены у пациентов 1-й группы (9,6 % и 4,8 % соответственно). В 1-й группе известна судьба 99 (94,3 %) больных в сроки от 5 до 36 лет после хирургического лечения. Из них живы 95 (96,0 %) человек. Во 2-й группе в сроки до 60 лет умерло двое (1,0 %) больных от РЩЖ. В обоих случаях отмечены отдаленные метастазы в легкие. 14 (7,0 %) пациентов умерли от других злокачественных новообразовании. Из этих больных 8 (38,0 %) детей получили радиойодтерапию по поводу РЩЖ. *Заключение.* Рак щитовидной железы у детей и подростков обладает высокой биологической агрессивностью с частым поражением регионарных лимфатических узлов, прорастанием капсулы железы и наличием отдаленных метастазов. Адекватное хирургическое лечение с последующим радиойод лечением, при необходимости, и ТТГ-супрессивной терапией способно обеспечить выживание абсолютного большинства больных. Применение терапии I^{131} диктует необходимость пожизненного наблюдения за пациентами с целью ранней диагностики возможных карцином других локализаций.

Ключевые слова: рак щитовидной железы; дети; подростки; хирургическое лечение; лечение I^{131}.

INTRODUCTION

Thyroid cancer (TC) is the most common epithelial neoplasm in children and adolescents with a prevalence of 1.5%–3% accounting for 45.3% of all malignant endocrine gland tumors at this age [6, 8, 10, 18, 20], and 8%–22% of pediatric head and neck cancers [5, 7].

According to the international data, the incidence of TC in the pediatric population accounts for approximately 0.04 cases per 100,000 versus 5 cases per 100,000 in the adult population [14]. In Russia, the incidence of pediatric TC is slightly higher reaching, 0.17 cases per 100,000 in 2000 [11].

Children most commonly develop differentiated TC with papillary carcinoma being the most prevalent histological form, which accounts for >90% of all pediatric TC cases [2, 8, 12, 16, 17]. Occasional cases of anaplastic TC in children have also been reported [13, 14].

Thyroid gland (TG) malignant neoplasms in children are generally asymptomatic [1, 8, 21]; however, childhood carcinomas tend to be highly aggressive. Thus, the estimated frequency of regional metastases by the time of surgery is 37%–93% [3, 9, 12, 15, 18]. The local tumor progression beyond the TG capsule is observed in 24%–52% of pediatric patients [4, 9, 18, 19]. The multifocal growth is reported in more than half of the cases (up to 65%) [8, 9, 15, 19], and distant metastases occur in 6%–28% of cases [21].

Despite a long history of TC treatment in children and adolescents, several aspects of treatment are still debated, such as the optimal volume of surgical excision, the extent of regional lymph node dissection, and the benefits of postoperative radioiodine therapy [21].

MATERIALS AND METHODS

From 1970 to 2011, 105 children and adolescents with TC were treated in the St Petersburg Endocrine Surgery Center of the Saint Petersburg State Pediatric Medical University (Group 1). In the surgical department of the Mayo Clinic (Rochester, MN) from 1940 to 2000, the surgical treatment of TC was performed in 188 <20-year-old patients (Group 2).

Multiple examination methods were used for both groups preoperatively. An ultrasound examination of TG allowed the assessment of the size and location of the and possible enlargement of the regional lymph nodes. Thyroid function was assessed by measuring triiodothyronine, thyroxine, and thyroid stimulating hormone (TSH) levels in the peripheral blood. Thin-needle aspiration biopsy (TAB) with subsequent cytological examination was shown to be the most informative method for the differential diagnosis of TC and benign neoplasms at the preoperative stage. In patients with enlarged neck lymph nodes ultrasound examination with targeted TAB was used for determining the volume of initial surgical resection. TG scanning was performed only in patients with low TSH levels and before repeated surgeries. Radiological study, computerized tomography, magnetic resonance imaging (MRI), and I^{131} scanning were used for the diagnosis of distant metastases in the lungs and bones.

RESULTS AND DISCUSSION

The age of patients at the time of first surgery varied between 8 and 20 years in Group 1 and from 3 to 20 years in 2, but the mean age did not differ (16.3 ± 0.3 years *vs* 16.0 ± 0.5 years, respectively), indicating that TC more frequently occurs in children of senior school age. Females were more prevalent in both groups, accounting for 73.7% (70/105) in Group 1 and 70.7% (133/188) in Group 2. Boys less frequently suffered from TC: 25 (26.3%) cases were observed in group 1 compared to 55 (29.3%) in group 2. The ratio of males to females was 1:2.8 in Group 1 and 1:2.4 in Group 2.

Table 1

Biological characteristics of thyroid cancer in both groups

	Group 1		Group 2	
	Total	%	Total	%
Regional metastases	36	53.0	153	81.4
Distant metastases	9	9.6	9	4.8
Growth beyond the capsule	9	9.6	37	19.7

TG carcinoma in children and adolescents of both groups was shown to be highly aggressive (Table 1). Regional metastases were found preoperatively in more than half of the patients in Group 1 (53.0%) and in the majority (81.4%) of the patients in Group 2. Tumor growth beyond the TG capsule was found in nine children (9.6%) in Group 1 and 37 children (19.7%) in Group 2. Thus, TC extending beyond the TG capsule was twice as frequent in Group 2, and growth into the regional lymph nodes was 1.5 times more frequent in Group 2. Distant metastases to the lungs and bones were more frequent in Group 1 than Group 2 (9.6% vs. 4.8%).

The volume of surgically removed TG also differed between groups. In Group 1, most surgeries were organ-preserving (hemithyroidectomy or subtotal TG resection) — 61 cases (58.1%). However, 44 cases (41.9%) were treated by complete thyroidectomy. It must be noted that in the past few decades (since 1991 in St Petersburg Endocrine Surgery Center), complete resection of the TG with central lymphadenectomy has been performed with increasing frequency for TC due to high cancer aggressivity. Moreover, during the past decade, early laboratory diagnosis of distant metastases using thyroglobulin level in the peripheral blood has become possible in Russia. This has also contributed to the greater use of thyroidectomy. At the Mayo Clinic (Group 2) hemithyroidectomy was the procedure of choice for pediatric TC until 1950. However, since 1950, thyroidectomy has been the procedure of choice for all children and adolescents with TG carcinomas.

In the postoperative period, radioiodine therapy was used in approximately the same proportion of Group 1 patients (20% or 21.1%) as Group 2 patients (48% or 25.5%) despite differences in the surgical procedures. The indicators for I^{131} treatment included tumor growth into the surrounding organs and tissues (T 4), presence of distant metastases, and increased thyroglobulin level after thyroidectomy. All patients with TC in the postoperative period received TSH-suppressive therapy using TG hormone drugs, with dosage control according to the TSH level in the peripheral blood. The TSH level ranged from 0.1–1.0 IU/L. In the absence of malignant tumor progression for 5–10 years after surgery, patients were given a replacement dose of hormonal drugs.

TC recurrence, defined as a reoccurrence of a tumor at the same site due to tumor tissue or cells remaining in the bed of removed TG, was observed in Group 2 (Table 2) but not in Group 1. In Group 2, tumor regrowth at the same site was detected in 13 cases (6.9%). The emergence of regional metastases due to continued tumor cell growth in the regional lymph nodes was observed in eight patients of Group 1 (8.4%) and 39 patients of Group 2 (20.7%). Distant tumor metastases were found in two patients of Group 1 (2.4%) and nine patients of Group 2 (4.8%). Patients with regional metastases underwent fascial compartment dissection of the neck tissue (modified radical neck dissection) on the affected side. Patients with distant metastases received I^{131} therapy.

Long-term outcomes were available for most patients of both groups. In Group 1, the outcomes of 99 patients (94.3%) over the period from 5 to 36 years after surgical treatment are known. Of these patients, 95 are still alive (96.0%), whereas four (4.0%) died of tumor progression. Among them, one female patient died within 2 years after surgery due to brain metastases, one female patient with papillary TC died within 2 years after surgery of lung metastases, and of the remaining two female patients with follicular carcinomas, one died 8 years after surgical treatment due to lung me-

Table 2

Recurrence rate of thyroid cancer in both groups

Metastasis sites	Group 1		Group 2	
	Total	%	Total	%
Repeated regional metastases	8	8.4	39	20.7
Distant metastases in the postoperative period	2	2.4	9	4.8
TC recurrences	–	–	13	6.9

Table 3

Causes of death in Group 2

Causes of death	N	%
Thyroid cancer	2	9.5
Other malignant tumors	14	66.7
Acute myocardial infarction	3	14.2
Drowning	1	4.8
Criminal deaths	1	4.8
Total no. of deaths	21	100

tastases and another died 16 years after surgical intervention due to bone metastases. All these patients had received external radiotherapy as radioiodine therapy was not possible.

In Group 2, 21 patients died during the follow-up period of up to 60 years (10.0% of the total) (Table 3). Two patients (1.0%) died of TC progression 27 and 30 years after surgery. In both cases, distant lung metastases were noted. The remaining 19 patients died from other causes, including 14 (7.0%) from malignant neoplasms at other locations. Among them, eight patients (38.0%) received radioiodine therapy for TC. The majority of these patients died due to malignant neoplasms at other locations from 3 to 50 years after surgical treatment. The cause of death was lung cancer in four cases and adenocarcinoma in three cases. One case of each died of to mesothelioma, breast cancer, duodenal cancer, trachea cancer, hepatocellular adenocarcinoma, extraorgan neck tumor, and leukemia. Among the 14 patients who died from extrathyroid malignant neoplasms, 11 (79%) received radiotherapy in the postoperative period. In three of these patients, only external irradiation was used; in four cases, only I^{131} was used; and in four cases, radioiodine therapy was administered along with external irradiation. Radiotherapy was not administered to any Group 2 patient who died from other causes.

Therefore, it may be assumed that use of radioiodine therapy in the postoperative period for children and adolescents with TG carcinoma is unsafe as it may result in the emergence of malignant neoplasms at other locations. This problem has been widely discussed in the literature for the past 20 years.

CONCLUSIONS

1. TC in children and adolescents is highly aggressive, with frequent involvement of the regional lymph nodes, invasion beyond the TG capsule, and distant metastases.
2. Adequate surgical treatment in specialized healthcare facilities with subsequent radioiodine therapy when indicated and TSH-suppressive therapy leads to long-term survival in the majority of patients.
3. Use of I^{131} therapy in the postoperative period necessitates life-long patient follow-up for an early diagnosis of possible neoplasms at other locations.

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