Surgical management of follicular thyroid carcinoma in children and adolescents: A study of 30 cases

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Background/Purpose: The purpose of the study is to describe the anatomoclinical, diagnostic, therapeutic and prognostic aspects of pediatric follicular thyroid carcinoma (FTC) in order to choose the best therapeutic strategy.

Methods: Our study includes patients ≤18 years old surgically treated for FTC in four Italian Pediatric Surgery Centers from January 2000 to March 2017. The collected data were compared with those of 132 patients matched for age with a histological diagnosis of papillary thyroid carcinoma (PTC) surgically treated in the same institutions during the same period and with the data of patients diagnosed with FTC found in the literature; p-values < 0.05 were considered significant.

Results: 21 (70%) of the 30 patients with a histological diagnosis of FTC underwent hemithyroidectomy while 9 (30%) underwent total thyroidectomy. 11 (55%) out of 21 patients were subjected to a completion of thyroidectomy. All patients are alive (OS = 100%) without recurrence or relapse of the disease. Compared with PTC, FTC is significant for capsule infiltration (p < 0.0001), vascular invasion (p = 0.0014), and T-stage T3-T4 (p = 0.013). However, multifocality (p < 0.001), extrathyroid extension (p < 0.0001) and lymph node metastasis (p < 0.0001) are more evident in PTC.

Conclusion: The conservative approach seems to be a valid surgical treatment for pediatric patients diagnosed with MI-FTC. For patients with wide vascular invasion and/or a tumor >4 cm, especially with high after-surgery Tg rate, a completion of thyroidectomy is recommended. In patients with multifocal neoplasia, and/or tumor size ≥4 cm, and/or extrathyroid extension, and/or lymph node metastasis, and/or distant metastasis, total thyroidectomy followed by radioiodine therapy is generally indicated.

Levels of Evidence: II.

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FTC is classified in Minimally Invasive-FTC (MI-FTC) and in Widely Invasive-FTC (WI-FTC). Encapsulated neoplasms with microscopic tumor capsule invasion and/or limited vascular invasion are defined as MI-FTC. Large invasive neoplasms, lack of complete tumor encapsulation, multifocality, extended vascular invasion, widespread invasion in thyroid parenchyma and/or adjacent tissues are features of WI-FTC [34–38]. The postoperative histological diagnosis is based on the identification of these features. Fine needle aspiration cytology (FNAC) is insufficient for the diagnosis of FTC, although diagnostic sensitivity is included between 65% to 98% while specificity is 73% to 100% [37,39]. However, an intraoperative histological examination on frozen sections is not recommended for a diagnosis of MI-FTC owing to the difficulty in differentiating an MI-FTC from a follicular adenoma or from a FTC encapsulated follicular variant [40]. Although WI-FTC has generally a worse prognosis in adult patients, it is reported similar to MI-FTC in children and adolescents [11,12,41,42]. A bias owing to a misdiagnosis of PTC, a follicular variant, cannot be excluded.

There are only a few articles on FTC in pediatric and adolescent age in the literature. Many studies associate FTC to PTC in their surgical approach, although the two neoplasms have different clinical and pathological characteristics. Furthermore, thyroidectomy extension in FTC treatment is still debated [9,42,43]. Our study describes the anatomoclinical, therapeutic and prognostic characteristics of pediatric and adolescent patients affected by FTC compared with our pediatric patients affected by PTC and with pediatric patients affected by FTC reported in the literature from 1997 to 2017. The most relevant articles published in PubMed and/or Google Scholar on pediatric FTC consist mostly of case reports [43,44] with the exception of Enomoto et al. [42], who report the surgical experience of 20 patients aged between 11 and 20 years old. The purpose of our study is to significantly contribute to the surgical approach of FTC in pediatric and adolescent patients.

1. Materials and methods

This retrospective study is based on the observation of FTC patient ≤18 years old, in a 17 year period (January 2000–March 2017), operated at the Pediatric and Adolescent Surgery Division of the University of Pisa, the Pediatric Surgery Division of the University of Padua, the Pediatric Surgery Division of Bambino Gesù Children Hospital in Rome and the Surgery Division of “Istituto Nazionale dei Tumori” in Milan. The studied variables were: age at diagnosis, sex, medical history, clinical presentation, diagnostic tests (thyroid US; chest X-Ray; FNAC; thyroid scintigraphy; neck MRI), surgical therapy (total thyroidectomy TT; hemithyroidectomy HT; completion of thyroidectomy TC), surgical therapy (total thyroidectomy TT; hemithyroidectomy HT; completion of thyroidectomy TC), cervical lymphadenectomy (central lymph nodes compartment and lateral lymph nodes compartment), histological type (FTC classical form, FTC Hurteau cell variant), WHO classification (minimally invasive MI-FTC, widely invasive WI-FTC), tumor capsule invasion, vascular invasion, multifocality and TNM staging [45]. Furthermore, postoperative complications (transitory hypoparathyroidism; definitive hypoparathyroidism; injury of the recurrent laryngeal nerve), postoperative treatment (hormonal manipulation and radioactive iodine-therapy, RAI) and follow-up were analyzed. All patients, after both radical and conservative surgery, were subjected to hormonal therapy (thyroid-stimulating hormone suppression) with a Levo-Thyroxin dose (according to the patients’ age and weight) to obtain an optimal value of TSH ≤0.3 UI/ml, to control neoplastic proliferation and to prevent the progression and recovery of disease [46]. Radioactive iodine remnant ablation was performed within 6 weeks after radical surgery, following ATA guidelines [47]. The follow-up after TT consisted in laboratory tests and instrumental exams: calcium serum level, dosage of thyroid hormones (TSH, FT3, FT4, Tg, anti-Tg Ab), thyroid US and total-body scintigraphy. The monitoring of thyroglobulin (Tg) levels was employed for the detection of disease recurrences [48].

The first postoperative follow-up was done after about 6 weeks in a hypothyroid state using a total-body scintigraphy with iodine-131. A total body scintigraphy was repeated after 6–12 months from the first one, after an appropriate suspension of the suppressive therapy. At the end of the follow-up, patients were considered without clinic evidence of disease if they had: serum suppression of the thyroglobulin (Tg <1 ng/mL), lack of antithyroglobulin antibodies (anti-Tg Ab), total lack of local or distant disease at imaging (US, CT, X-Ray) and/or positivity of disease to control biopsy. The follow-up after HT included: a clinical test, a yearly chest X-Ray and a serum dosage of thyroid hormones (FT3, FT4, TSH, Tg and anti-Tg Ab) every 6 months during the first 2 years, then annually. The reference value for Tg obtained one month after surgical treatment was considered between 0 and 5 ng/mL. The thyroid US was performed two times a year during the first 5 years, then yearly [6]. The data of patients diagnosed with FTC were compared with those of 132 patients of the same age with histological diagnosis of PTC, subjected to TT in the same institutes and during the same years and with the data of 20 young patients operated for FTC found in the literature [42].

1.1. Data analysis

Categorical data were described by frequency, whereas continuous data were described by mean and standard deviation. To evaluate the normality of the quantitative data distributions, the Kolmogorov–Smirnov test was performed. The assessment of the qualitative variables was realized by the z-test for proportions and by the chi-square test, whereas the quantitative variables were analyzed with the t-test (two-tailed). Finally, a correlation analysis between tumor size and age was carried out with the Pearson Method. The value of p < 0.05 was considered statistically significant and the p-value between 0.05 and 0.1 indicated a “trend toward significance”. All analyses, descriptive and inferential, were performed using SPSS v.24 technology.

2. Theory

To date, surgical indications for FTC and PTC in pediatric age have not been very dissimilar. An in-depth knowledge of the anatomoclinical and prognostic aspects of both carcinomas, obtained through our statistical correlation on patients treated in the same period in four major university centers, contributes to a more appropriate management of these neoplasms and helps select patients who need to be treated with a conservative approach from those who need to be treated with a radical surgical one. This study also deals with the relevant issues concerning the evaluation and treatment of cervical lymph nodes and the postoperative radioiodine therapy adopted. Moreover, it lays the groundwork for further investigation so that every pediatric patient affected by thyroid carcinoma may have a tailored surgical treatment.

3. Results

Between January 2000 and March 2017, 30 patients with a histological diagnosis of FTC were surgically treated and diagnosed in referral centers for thyroid pathologies. Dedicated pediatric thyroid pathologists performed all diagnoses. There were 8 (27%) males and 22 (73%) females. The age range was 5–18 years: 18 cases (60%) ≤15 years old and 12 (40%) >15 years old. Mean age at the time of diagnosis was 13.73 ± 3.83 years: 13.75 ± 4.86 years old for males, and 13.73 ± 3.52 years old for females. The age division is reported in Table 1. Nine patients (30%) were familiar to thyroid disease and all of them reported a history of multinodular goiter.

At the objective examination, 21 patients (70%) had a cervical tumefaction in the anterolateral region of the neck, while the diagnosis was accidental in the remaining 9 patients (30%), because a thyroid examination was performed during total body screening US. These patients did not present a statistically significant difference from the rest of the
cohort, either by gender, age or familiarity. The size of the follicular lesion was generally smaller in patients with an incidental diagnosis: average size of tumor was 16.1 mm (range 7–24 mm) vs. 25.8 mm (range 7–75 mm).

All 30 patients underwent thyroid US (100%), and 25 of them also underwent FNAC (83%). 13 patients (43.3%) had a chest X-Ray, one patient (0.3%) had a thyroid scintigraphy and one patient (0.3%) had an MRI. Patients were surgically treated by four pediatric surgeons, each belonging to one of the four hospitals; 21 patients were operated in Pisa, 4 patients in Padua, 3 in Milan and 2 in Rome.

The surgical therapy was conservative (HT) in 21 patients (70%) and radical (TT) in 9 patients (30%). For the 21 patients subjected to a conservative surgical treatment as a first approach, 11 (52%) were operated a second time with completion of thyroidectomy (TC) after their definitive histological report. A lymphadenectomy of the central and lateral cervical region was performed in 3 patients (10%) owing to clinically suspected metastatic lesions. Postoperative complications occurred in 2 (28%) and a lesion of the recurrent laryngeal nerve occurred in one patient (15%). As detailed in Table 2, parathyroidism occurred in 2 (28%) and a lesion of the recurrent laryngeal nerve occurred in one patient (15%). As detailed in Table 2, parathyroidism occurred in 2 (28%) and a lesion of the recurrent laryngeal nerve occurred in one patient (15%).

Table 1
Frequency of patients for age at diagnosis and sex.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Number of patients</th>
<th>Pts %</th>
<th>Males %</th>
<th>Females %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–5</td>
<td>2</td>
<td>7</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>6–10</td>
<td>5</td>
<td>17</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>11–15</td>
<td>11</td>
<td>36</td>
<td>18</td>
<td>82</td>
</tr>
<tr>
<td>16–18</td>
<td>12</td>
<td>40</td>
<td>33</td>
<td>67</td>
</tr>
</tbody>
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Table 2
FTC and PTC histological types and classification.

<table>
<thead>
<tr>
<th>FTC type</th>
<th>Number of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimally Invasive Follicular thyroid carcinoma (MI-FTC)</td>
<td>28 (93.4)</td>
</tr>
<tr>
<td>Minimally Invasive Follicular Carcinoma, NOS</td>
<td>20 (66.7)</td>
</tr>
<tr>
<td>Minimally Invasive Follicular Carcinoma, Hurthle-cell variant</td>
<td>8 (26.7)</td>
</tr>
<tr>
<td>Widely Invasive Follicular thyroid carcinoma (WI-FTC)</td>
<td>2 (6.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PTC type</th>
<th>Number of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional variant of PTC</td>
<td>75 (56.8)</td>
</tr>
<tr>
<td>Follicular variant of PTC</td>
<td>37 (28)</td>
</tr>
<tr>
<td>Diffuse sclerosing variant</td>
<td>7 (5.3)</td>
</tr>
<tr>
<td>Tall cell variant</td>
<td>7 (5.3)</td>
</tr>
<tr>
<td>Trabecular variant</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Poorly differentiated variant</td>
<td>2 (1.6)</td>
</tr>
</tbody>
</table>

This was not statistically significant (p = 0.434) compared to the Enomoto et al. study FTCs, while it was significant compared to the PTCs (p = 0.014). In the literature, the negative impact of the vascular invasion is not the same for all the authors [53,54]. The histotype, tumor size, capsular and/or vascular invasion, age, sex, prognosis and survival rate of our patients were excellent. We registered an OS = 100% with absence of recurrence, while in the Enomoto et al. study [42] all the patients were alive (OS = 100%) but 15% of them had
relapse. There was a different and significant surgical approach in the two studies (p = 0.071) for TT and HT. The percentage of patients subjected to a TT, including thyroidectomy completion, was significantly greater in our cases compared to the Enomoto et al. study patients. In our series, the histological examination of the residual lobe, after thyroidectomy completion, did not reveal neoplastic spread in any of the 11 cases. Therefore, we believe that the choice of the initial surgical procedure between a radical approach and a conservative one must be tailored to each pediatric patient. A precise presurgical ultrasonography is needed to estimate dimensions, localization, multifocality, lymph nodal metastasis and extrathyroidal extension. The presurgical sensitivity of this evaluation method for these parameters is low while US sensitivity in the evaluation of regional lymph nodes is high. These parameters are known postoperatively in the histopathological reports and they are essential for the surgeon when choosing a thyroidectomy completion after a conservative approach [55–60]. Based on our excellent results in terms of the absence of relapses (compared with the results of Enomoto) it is preferable to perform a hemithyroidectomy and then a CT, instead of performing an immediate TT, because there is a lower frequency of complications. According to Francis GL et al. [37], conservative surgery can be indicated in patients with lesions microscopically bounded to a lobe, with dimensions ≤4 cm, without evident extrathyroidal extension and minimal vascular invasion (≤3 vascular foci). In patients with wide vascular invasion (>3 vascular foci) and/or if the tumor size is >4 cm, especially with high postoperative Tg levels, a thyroidectomy completion is recommended. Patients with multifocal neoplasm and/or dimensions >4 cm and/or lymph nodal metastasis and/or distant metastasis should be treated with TT and staged postoperatively with RAI.

5. Conclusions

Regardless of the surgical approach, the FTC prognosis in the children and adolescents of our study (about 90%) by MI-FTC was excellent. Despite the limitations of our study, which are our limited series of cases and the very few cases reported in the literature, lobectomy seems to represent a valid surgical approach in pediatric patients diagnosed with MI-FTC. Moreover, the conservative surgical choice has the advantage of reducing the risk of postoperative complications, which can be particularly severe in children. The follow-up of young patients diagnosed with FTC and treated with TT includes: RAI therapy, postoperative scan, neck US and thyroid serum levels monitoring. After a conservative treatment (HT), a postoperative RAI therapy is no longer requested and the follow-up includes clinical exams, an annual chest X-ray, thyroid US and specific laboratory tests every six months in the first 2 years and then annually in the following 5 years. The use of thyroid hormone (Levo-thyroxin) for the suppression of TSH secretion, owing to the high sensitivity of the pediatric DTC to hormonal manipulation, represents an efficient therapeutic aid after conservative surgical treatment [6].

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