Treatment of sporadic nonmedullary thyroid carcinomas in pediatric age

Paola Collini, Franco Mattavelli, Claudio Spinelli and Maura Massimino†

Nonmedullary thyroid carcinomas are rare malignancies in pediatric ages. The vast majority of them are papillary carcinomas with an overall survival of approximately 100%. Their outcome is independent of strong prognostic factors of adults, such as papillary carcinoma histological subtype, invasion into soft tissue of the neck, presence and site of distant metastases, relapse and type of surgery. In these ages, follicular carcinomas and poorly differentiated carcinomas are exceptional. Undifferentiated (anaplastic) carcinomas are practically absent. In most institutions, the therapy of choice for all pediatric thyroid carcinomas is the radical approach, aimed at the eradication at diagnosis of all clinical and subclinical neoplastic foci, both at thyroid, lymph node and distant level. It consists of total thyroidectomy and lymphadenectomy in children with clinically evident lymph-node metastases, followed by radioactive iodine therapy independent of histotype and stage. Recently, owing also to the high sensitivity to hormonal manipulation shown by pediatric papillary carcinomas, a conservative approach has been proposed for selected cases, consisting of the removal of only the grossly detectable disease followed by thyroid-stimulating hormone-suppressive hormonal therapy to control subclinical disease. Today, the existence of two therapeutic approaches, radical versus conservative therapy, should be considered whenever treating a child or adolescent with a nonmedullary thyroid carcinoma. Not least, permanent post-treatment complications of radical surgery and radioactive iodine therapy should be taken into account. The future tasks include the stratification of thyroid carcinomas into low- and high-risk cases, also including their molecular alterations and the possibility of a molecularly targeted therapy against tyrosine kinases involved in the pathogenesis of thyroid carcinomas.

histotypes and variants on the basis of overall survival (OS). In the low-risk group, there are the vast majority of PCs and the minimally invasive (encapsulated) FCs (MIFCs) with only capsule and/or minimal vascular invasion, while in the high-risk group there are the PCs of the tall-cell and columnar-cell variants, the MIFCs with extensive vascular invasion, the widely invasive FCs, PDCs and undifferentiated (anaplastic) carcinomas [2,3]. The vast majority of pediatric thyroid carcinomas are PCs. It is a well-known phenomenon that the outcome of pediatric PCs is independent of strong prognostic factors of adults, such as low- versus high-risk histological subtype, extrathyroidal local invasion into soft tissue of the neck, presence of distant metastases, site of distant metastatic spread, occurrence of relapse and type of surgery [1]. Generally, pediatric PCs follow an indolent course with an OS of approximately 100% in spite of high percentages of extrathyroidal invasion into the soft tissue of the neck, nodal metastases, distant metastases and relapses [1]. In these ages, FCs are exceptional and occur as low-risk MIFCs only, and PDCs are exceptional. Many thyroid carcinomas that in the past have been diagnosed as FCs or PDCs (i.e., insular carcinomas, solid/trabecular FCs and moderately differentiated FCs) are indeed low-risk PCs of the follicular, encapsulated follicular or solid/trabecular variants [2]. In childhood, high-risk histotypes of thyroid carcinomas such as widely invasive FCs and undifferentiated (anaplastic) carcinomas are practically absent.

Along these lines, in this review, we will take into account PCs, MIFCs and PDCs. Also, the group of Hürthle cell carcinomas is considered briefly. Whereas in the radical approach, these histotypes are considered altogether under the headings of ‘differentiated thyroid carcinomas’ (that is the term applied to all nonmedullary carcinomas including PCs, FCs and PDCs taken together as a whole and set against undifferentiated carcinomas), in the conservative approach, the histotype of thyroid carcinoma is relevant to the choice of the type of treatment. For practical purposes, we will describe the therapeutic options for each histotype separately. We will not discuss postirradiation and familial cases, since they undergo a particular diagnostic approach and follow-up.

**Therapeutic approaches**

The best therapeutic approach to pediatric thyroid carcinomas is still a debated issue as regards the extension of thyroidectomy and neck node dissection, need and dosage of radioactive iodine (RAI) therapy, and type and duration of follow-up.

Two options are possible: the radical or the conservative approach [1,4,5].

**Radical therapeutic approach**

In most institutions, the therapy of choice for pediatric differentiated thyroid carcinomas is the same as for adults, still aimed at the eradication at diagnosis of all clinical and subclinical neoplastic foci, both at the thyroid, lymph-node and distant level. It is routinely applied independently of histotype and variant (PCs vs FCs vs PDCs) and stage of tumor. Indeed, since more than 90% of thyroid pediatric cancers are PCs, this approach is targeted mainly to treat this histotype. Subsequent to a diagnosis of carcinoma performed on preoperatory fine-needle aspiration cytology (FNAC) of the thyroid nodule or enlarged lymph-nodes, or during surgery on peroperatory frozen section examination, all patients undergo routine radical surgery independently of the clinically detectable extension of the neoplasm, followed by RAI scintigraphic scan to detect metastases at a subclinical stage, treated postoperatively with 131I.

The reasons for such an approach are:

- To have a better progression-free survival (PFS) and OS
- To detect subclinical metastases by RAI scintigraphic scan and treat them by RAI ablation
- To make the value of serum thyroglobulin level a very sensitive marker of post-treatment relapse
- To avoid possible dedifferentiation of occult neoplastic microfoci over time.

**Conservative therapeutic approach**

Owing to the rarity of thyroid carcinomas in children and the fact that more than 90% of them are PCs, a conservative therapeutic approach has been validated mainly in childhood PCs. Taking into account the approximately 100% OS of pediatric PCs, the long expectation of life, the significant permanent morbidity of radical surgery and RAI therapy, and the high sensitivity to hormonal manipulation of pediatric PCs, a conservative approach for pediatric PCs has been proposed and applied to selected cases, no more aimed at the eradication of all clinical and subclinical neoplastic foci by surgery plus RAI therapy, but consisting in the removal of only the grossly detectable disease followed by thyroid-stimulating hormone (TSH)-suppressive hormonal therapy to control subclinical disease. Even if already known for a few decades, this conservative approach has been routinely applied at our institution since the 1990s [1,4].

Along this approach, for which microscopic disease is not searched for since it is supposed to be controlled by suppressive therapy, staging should be performed as a ‘macroscopic staging (macrostaging)’ and not a ‘microscopic staging (microstaging)’, and the application of means necessary to highlight microscopic disease, such as RAI scan, in addition to clinical examination, ultrasounds and chest standard x-rays, is no longer required.

Cases of PCs suitable for a conservative approach are:

- Pediatric patients with a tumor limited to one lobe, with or without clinically evident monolateral nodal metastases
- Absence of clinically or x-ray-detectable distant metastases
- Compliance to a life-long follow-up.

This approach could be applied to all pediatric PCs, at least those arising in the younger patients. In fact, unlike with adult cases, PCs in younger children are all highly sensitive to hormonal manipulation and dedifferentiation along time is not registered [6]. This very different biological behavior is probably due to different genetic alterations between adult and pediatric...
cases of PCs. In fact, in pediatric cases, alterations in BRAF are not present, while they are a marker of high-risk and dedifferentiated PCs of adults [6]. There are no reports on large series of childhood MIFCs and PDCs. Applying the knowledge obtained in adult series, low-risk MIFCs could be treated conservatively owing to their indolent behavior, whereas high-risk PCs (i.e., tall-cell and columnar cell PCs), high-risk MIFCs (that is MIFCs with extensive vascular invasion) and PDCs should be treated with a radical approach taking into account their high aggressiveness, together with a lower sensitivity to hormonal manipulation [2,3]. For these high-risk histotypes, radical surgery plus RAI therapy has become the mainstay of therapy. In children the initial treatment should be conservative in suitable cases, with a complete thyroideectomy and/or RAI therapy to be carried out for selected histotypes. Along these lines, the role of a pathologist experienced in thyroid pathology and in particular in the diagnosis of pediatric thyroid carcinomas becomes critical in the application of the conservative approach. In fact, while all the adult histotypes and variants of thyroid carcinomas occur in pediatric ages with the same morphology as in adults, the low-risk solid/trabecular variant of PC is typical of childhood and occurs rarely in adults, being easily mistaken for a high-risk, ominous PDC with an insular/solid/trabecular morphology [2,6]. Nonetheless, the extent of the surgical approach is still a debated issue, with evidences based on retrospective studies, and requests future perspective trials.

Diagnosis & staging

After a clinicopathological diagnosis of carcinoma, in the radical approach, a 'macrostaging' (aimed at the detection of the clinically evident neoplastic burden) and a 'microstaging' (aimed at the detection of the subclinical neoplasm, for instance, by CT or MRI) are performed.

In the conservative approach only, a 'macrostaging' is required, considering only the grossly evident diffusion of the tumor [7].

- In the presence of a thyroid or laterocervical nodule in the neck of a child or an adolescent, the first diagnostic step is a thorough clinical neck examination, with clinical assessment of the site of the nodule (thyroid vs node vs other) and its characteristics (site, size, consistency and mobility), and direct or indirect evaluation of laryngeal or esophageal involvement by the neoplasm through the evaluation of their functional alteration (dysphonia and dysphagia).

- Laboratory examination: neither biochemical assays nor the evaluation of circulating free thyroid hormones, thyroglobulin or TSH are able to detect or differentiate a malignant thyroidal tumor. Although, the assessment of the thyroglobulin levels at diagnosis is relevant to the follow-up in case of a thyroid carcinoma.

- Ultrasound scan is useful to evaluate the nodule dimensions and possible involvement of cervical nodes, which, nevertheless, are better evaluated through clinical examination.

- FNAC could be done on the thyroid nodule or cervical lymph nodes. Regardless of their ultrasound pattern and cystic components, all childhood thyroidal nodules are worth of a cytological examination. FNAC can be diagnostic in many cases of PC, but is of scarce or no use in the differential diagnosis in case of follicular proliferations (adenoma vs encapsulated FC vs hyperplastic nodule).

- Special examination, such as neck computed tomography (CT) or magnetic resonance imaging (MRI), have an indication only in cases of suspicious involvement of respiratory structures or recurrent nerves by the tumor. CT and MRI are not applied for the detection of subclinical metastases, searched for by RAI scan in the radical approach and not relevant in the conservative approach.

- Chest x-rays: the traditional radiological survey is done to detect possible lung metastases.

- Scintigraphy: there is no indication for this exam in the preoperative phase.

Papillary carcinoma

Radical therapeutic approach

Radical surgery

At the thyroid level, the 'radical surgical approach' consists of a total thyroidectomy independently of the grossly detectable extension of disease. The subtotal thyroidectomy differs from the total thyroidectomy because a rim of normal thyroid tissue is left, and subsequently sidetracked by RAI therapy if showing more than 5% of total activity.

At the lymph node level, in the 'radical surgical approach' a lymphadenectomy is carried out in patients with evidence of lymph node metastases in the lateral or central compartment region. All motor and sensory nerves, as well as the sternocleidomastoid muscle and internal jugular vein are preserved unless invaded by tumor [5].

According to some authors, radical thyroidectomy is supported by three points:

- Radical surgery removes all thyroid tissue potentially at risk of containing multiple neoplastic foci, in the same lobe or contralaterally, again potentially at risk of developing local relapses or metastases [8].

- The presence of physiological thyroid tissue does not allow the use of thyroglobulin dosage, in an efficacious way, as a marker of tumor relapse [9].

The absence of thyroid tissue allows the use, in an efficacious way, of radiiodine therapy in the treatment of metastatic foci, especially in the lungs. Normal thyroid tissue, in fact, is much more efficient in concentrating radiiodine with respect to tumor, and a small percentage (2%) of physiological tissue is enough to concentrate the iodinated drug and hide the metastases. Therefore, according to some authors, total thyroidectomy makes it easier to use total body scan in diagnosing metastases, especially those arising in lungs that are rarely appreciated by chest imaging at an early stage [10,11].

www.future-drugs.com
Radioactive iodine therapy

Patients treated with the aim of obtaining the eradication of all clinical and subclinical neoplastic foci undergo surgery followed by metabolic ablation of thyroid remnants evaluated by routine postsurgical RAI scan.

Around 6 weeks from surgery, in hypothyroidism (which means without administering L-thyroxin at substitutive doses), a dose of 1123 is administered according to the weight of the child.

If there is local residual parenchyma:
- With ≤5–10 ng/ml: TSH-suppressive L-thyroxin is prescribed and follow-up is begun
- With >10 ng/ml: metabolic ablation of remnants with 131I is prescribed.
- This procedure consists of administering a fixed dose of 30 mCi or a weight-dependent dose of 1 mCi/Kg. Subsequent follow-up has to include whole bone scan evaluation again.
- In case of metastases as seen on radio scan, the dose can be a 100 mCi fixed one or a weight-dependent one up to 2 mCi/kg.

Hormonal manipulation (thyroid stimulating hormone suppression)

Functioning of the thyroid is dependent on TSH, whose synthesis and release depends on thyroid-releasing hormone (TRH), produced in the hypothalamus and secreted into the pituitary [12,13]. The increase of TRH or TSH results in hypertrophy and hyperplasia of thyroid cells, increased trapping of iodine and increased synthesis of thyroid hormones. Exogenous thyroid hormone or increased thyroid hormone synthesis inhibits TSH production. The use of thyroid hormone (L-thyroxin; commercially available) for the suppression of TSH secretion is adopted frequently to control differentiated thyroid cancers and their metastases growth. It is also known that the majority of thyroid cold nodules depend on TSH for their growth.

Optimal L-thyroxin dose is the minimum that can suppress TSH (<0.3 mCU/ml) and is approximately 2–2.5 µ/kg/day. These dosages are easy to be assumed by children, without inducing hyperthyroidism. For all the patients the indication is to give L-thyroxin at a dose between 1.5 and 3 µ/kg/day according to the age and weight of the patients to reach a value for TSH less than 0.3 µU/ml.

Suppressive hormonotherapy has the aim to control hidden microfoci of residual tumor and prevent overt metastasization.

Follow-up

Total body scan is repeated after 6–12 months from the metabolic treatment, and the therapeutic dose can be repeated in case of persistence of disease. The goal of this strategy is to obtain a negative scan and a thyroglobulin with an undeterminable value.

Postoperative complications & their treatment

Subsequently to radical surgery, high percentages of permanent postoperative complications are documented. After total thyroidectomy, permanent hypoparathyroidism and recurrent laryngeal nerve paralysis often occur, while after neck dissection, spinal accessory nerve paralysis is the major complication. In addition, iatrogenic effects of RAI therapy are reported.

Postoperative complications are high in almost all pediatric series, especially after total thyroidectomy, also if performed by pediatric surgeons or by neck surgeons devoted to thyroid surgery. Hypoparathyroidism accounts for 0–36% [4] and recurrent nerve palsy from 0 to 28% [4,14]. Age below 16 years is at risk of being accompanied by major complications. In children, recurrent nerves are at major risk of being injured, and parathyroid glands are very small, often hidden into the thyroid parenchyma, difficult to recognize and with a light vascularization. These complications can be very severe in developing age. To make a pragmatic example, also their support can be difficult and expensive. An adolescent girl, around the age of menarche, when deprived of parathyroid normal function, needs frequent electrolyte assays, more than bi-weekly to have a valid calcium, vitamin D and/or parathormone support. Any calcium/phosphorus balance alteration can reflect in alteration of the body mass and in possible later consequences on the harmonic body growth. All these issues suggest that the management of children with thyroid carcinoma should be performed in selected centers.

Conservative therapeutic approach

Conservative surgery

At the thyroid level, the ‘conservative surgical approach’ is defined as the removal of only the thyroid lobe involved by the clinically detectable disease and isthmus (hemithyroidectomy). At the lymph node level, the ‘conservative surgical approach’ consists of a selective neck dissection of only the clinically involved node levels, with preservation of the internal jugular vein, the sternocleidomastoid muscle, the spinal accessory nerve and the greater auricular nerve. The selective neck dissection approach has a curative intent. To lower the risk of locoregional recurrence and reoperation, at our institution, we routinely perform the selective neck dissection of the metastatic levels plus the dissection of the two free stations immediately before and after the involved ones. Along these lines, the ‘berry picking’ technique is disregarded [1,4].

The arguments in favor of hemithyroidectomy are:
- PCs in children and adolescents are a particular and different disease with a different genetic and molecular pattern and a different course from adults when unfavorable features are matched homogeneously [15]
- Mortality for PCs in children is close to zero in all series, in spite of a presentation with a greater amount of extrathyroid extension, and a bigger number of lymph nodal metastases and lung dissemination than adults
- The presence of microscopic dissemination into the thyroid and lymph nodes is the rule and does not impair prognosis
- Vascular invasion is also frequent (a third of cases) and does not influence prognosis, at variance with adult series
- The chance of dedifferentiation of microscopic disease over the years is only theoretical.
Hormonal manipulation (thyroid-stimulating hormone suppression)

In the conservative approach, this therapeutic tool becomes a mainstay of treatment following surgery. Owing to the high sensitivity of pediatric PCs to hormonal manipulation, the suppression of TSH secretion is adopted to control hidden microfoci of residual tumor and prevent overt metastasization. As after radical surgery, optimal L-thyroxin dose is the minimum that can suppress TSH (<0.3 mcU/ml) and is approximately 2–2.5 µg/kg/day. These dosages are easy to be assumed by children, without inducing hyperthyroidism. For all the patients the indication is to give L-thyroxin at a dose between 1.5 and 3 µg/kg/day according to the age and weight of the patients to reach a value for TSH less than 0.3 uU/ml.

Radioactive iodine therapy

There is no indication to use this tool as first-line treatment if applying the conservative treatment approach.

Follow-up

After a conservative treatment, the routine RAI scan after surgery is no longer requested. L-thyroxin at TSH-suppressive doses (2–2.5 µg/kg/day) is given. An optimal follow-up should include clinical examination, yearly chest x-ray, and serum tests for fT3, fT4, TSH, and thyroglobulin every 6 months during the first 2 years, then yearly. Thyroid ultrasound scans should be performed for the first 5 years only, twice in the first year and then yearly. In these instances, the normal value for thyroglobulin is considered as the result obtained a month after surgery that is in the range of 0–5 ng/ml. Cardiac function and bone metabolism markers were checked with an appropriate follow-up [1,4].

Therapy at relapse

Similarly, at relapse, the options in treating the patient again can follow a radical or a conservative approach [7].

Radical approach

In cases of local, nodal or distant relapse following the radical approach, the same guidelines as at diagnosis are followed.

Conservative approach

Surgery

In case of local or lymph nodal relapse, the conservative therapeutic approach follows the rules of the beginning, which is to say that all the macroscopic disease only should be excised. In addition to the resection of local relapse in the soft tissue of the thyroid bed, completion thyroidectomy in case of contralateral relapse, and further nodal dissection, in case of radiologically evident distant metastases it will be necessary completion thyroidectomy, even in absence of thyroid neoplastic involvement, to allow the use of RAI therapy for the treatment of distant metastases.

Hormonal manipulation (thyroid-stimulating hormone suppression)

The administration of L-thyroxin should be continued according to the guidelines already expressed.

Radioactive iodine therapy

RAI therapy after complete thyroidectomy should be used only in cases of radiologically evident metastases, which are found prevalently in lungs followed by bone. In our experience, this condition is to be considered absolutely exceptional if metastases are not determined with the use of total body RAI scan in the diagnostic phase.

Minimally invasive (encapsulated) follicular carcinoma

The therapeutic options are the same as for PCs, with the same intent. Regarding PC, it is noteworthy that PCs follow hematogenous dissemination instead of lymphatic diffusion and distant metastases are mainly at bone followed by lung. In this histotype lymph node metastases are exceptional. MIFCs are encapsulated neoplasms that involve one thyroid lobe or the isthmus and can show capsular invasion and/or vascular invasion. This latter can involve only a very few vessels (minimal vascular invasion) or many vessels (extensive vascular invasion). In the experience with adult series, MIFCs showing only capsular and/or minimal vascular invasion follow an indolent behavior, while the presence of extensive vascular invasion confers a higher risk of distant metastases [3]. This histotype is rare in pediatrics, and almost all the MIFCs diagnosed in the past are indeed PCs of the encapsulated follicular variant.

Radical therapeutic approach

It consists of total thyroidectomy independently of the presence of minimal vs extensive vascular invasion or only capsular invasion, followed by RAI scan. Lymph-node dissection is not requested.

Follow-up and therapy of relapse are the same as for PCs.

Conservative therapeutic approach

It could be applied if:

• MIFC shows only capsular invasion and/or minimal vascular invasion
• There is absence of radiologically evident distant metastases
• There is the compliance of the patient and her/his family

It consists of hemithyroidectomy followed by TSH suppression. Lymph node dissection is not requested.

Follow-up and therapy of relapse are the same as for PCs.

Hürthle cell carcinomas

The behavior and outcome of these neoplasms are reported as the same as their non-Hürthle cell counterpart in adults. There are not large series reports in pediatrics. Our suggestion is to follow the same guidelines of treatment as for the non-Hürthle cell counterpart.
Poorly differentiated carcinomas

PDCs are very rare in pediatrics. As already underlined, many carcinomas reported as high-risk PDCs (insular carcinomas, solid/trabecular FCs and moderately differentiated FCs), highly aggressive and less sensitive to hormonal manipulation, are indeed low-risk PCs of the solid/trabecular variant, highly invasive, but highly sensitive to hormonal manipulation and suitable for conservative treatment. In this distinction, the role of a pathologist well-trained in pediatric thyroid carcinoma diagnosis becomes critical. PDCs as a group show a behavior that merges the lymphophilia characteristic of PCs with the hematogenous spread of FCs. In these cancers there is tendency to local spread into the soft tissue of the neck and lymph node metastasization together with vascular diffusion and frequent distant metastases, these latter also in sites uncommon for thyroid carcinomas for example pleura, brain and liver. A diagnosis of true PDC deserves a radical approach.

Conclusions

Nowadays, the existence of two therapeutic approaches, that is radical versus conservative therapy, is still an area of great controversy [1,4,5,7,16,17–20]. Nonetheless, also based on our monoinstitutional experience during a 30-year period [1,4], we think that this option should be considered whenever treating a child or adolescent with a nonmedullary thyroid carcinoma. Not least, permanent post-treatment complications of both surgery and RAI therapy should be taken into account, with all the damage in the quality of life and the economic costs that are implied. At variance with the radical approach, the application of a conservative surgical approach is modulated also on histotype, which implies that the role of the pathologist becomes very critical in this choice of therapy. Thyroid carcinomas are histologically divided into a low-risk group (PCs and MIFCs) and a high-risk group (MIFCs with only capsular and/or minimal vascular invasion), suitable of a conservative approach if also all the other conditions are satisfied (tumor grossly limited to one lobe, absence of clinically detectable distant metastases, compliance of the patient to a life-long follow-up), and a high-risk group (MIFCs with extensive vascular invasion, true PDCs) deserving a radical approach. Our hope is that in the future, the conservative approach will be considered in the suitable cases, with a decrease of overtreatment of a type of cancer that still shows an about 100% OS independently of stage, occurrence of relapse and type of approach applied.

Expert commentary

The vast majority of sporadic nonmedullary thyroid carcinomas in pediatrics are PCs. Their OS is independent of prognostic factors of adults [1]. In spite of the very high percentages of cases with extrathyroid spread into the soft tissues of the neck, distant metastases and relapses, approximately 100% of patients are usually alive. Also, both PFS and OS proved to be independent of the type of surgery (prophylactic vs conservative) [4]. In fact, hormonal therapy is very successful in the control of these carcinomas, either by itself or in addition to RAI therapy. This sensitivity to hormonal manipulation seems to represent an important biological difference with respect to the adult cases. This is also supported by genetic findings, which show a different pattern of gene alterations in adult vs childhood PCs, these latter lacking BRAF involvement, found instead in high-risk PCs of adults and in particular in cases showing dedifferentiation [6]. All these observations are in keeping with the suggestion of Cady that thyroid carcinomas in children and adults are different diseases and not merely different stages in a single disease, with specific prognosis and therapy needs [17,18].

Key issues

- Pediatric sporadic nonmedullary thyroid carcinomas are rare tumors, accounting for the 0.5–3% of all pediatric cancers.
- Approximately 90% of them are papillary carcinoma. Rare cases of minimally invasive follicular carcinomas are reported. Poorly differentiated carcinomas are exceptional and widely invasive follicular carcinomas and undifferentiated carcinomas are practically absent in this range of ages.
- Papillary carcinomas show an approximately 100% overall survival independent of stage, site of distant metastases and occurrence of relapse.
- Two therapeutic options are possible, the radical and the conservative approach.
- The radical approach is aimed at the eradication of all clinic and subclinic neoplastic foci, and consists of total thyroidectomy plus lymphadenectomy in patients with clinical evidence of nodal metastases, followed by radioactive iodine therapy. This approach is independent of any other parameter of disease. After this approach, a high number of post-treatment complications are reported.
- The conservative approach, applicable to selected cases, for example a low-risk carcinoma clinically limited to one lobe, with or without clinically evident lymph node metastases in absence of clinically detectable distant metastases and with the compliance of the patient and her/his family, is aimed at the ablation of only the clinically evident tumor mass, controlling the microscopic neoplastic foci by hormonal manipulation and thyroid-stimulating hormone suppression. A life-long follow-up is required to adjust doses over time. With this approach the number of post-treatment complications is reduced without an impact on survival.
- Future tasks are the molecular stratification of papillary carcinomas into low- and high-risk forms, the possibility of a molecularly targeted therapy and the creation of tissue banks.
The percentage of permanent complications is distressingly higher following total thyroidectomy even if performed by experienced surgeons. This is also due to the anatomical features of the childhood thyroid and recurrent nerve pathway [7].

The impact (also economic) of the morbidity of chronic therapy and follow-up of endocrine disabilities (hypoparathyroidism and later on calcitonin deprivation) as well as the possible iatrogenic effects of RAI therapy are noteworthy [1]. By applying a conservative approach with a selective lymph-node dissection, it is possible to considerably reduce the percentage of postoperative complications without a deleterious influence on survival [1].

The application of a conservative approach requires the involvement of a team of experienced and trained professionals, including a pediatric oncologist, surgeon, pathologist and nuclear medicine physician, ready to diagnose and treat the disease at diagnosis and during follow-up. Also the selection of the patients suitable to this approach is relevant, taking into account of the need of compliance to a life-long follow-up.

Five-year view

The future tasks include the stratification of thyroid carcinomas along their molecular alterations into low-risk and high-risk cases. This setting could be included in the criteria applied in separating cases suitable for a conservative approach from those deserving a radical approach.

Another task is the possibility of a molecularly targeted-therapy against tyrosine kinases involved in the pathogenesis of thyroid carcinomas. This latter task implies the creation of Tissue Banks, with the routine collection of material for biological studies.

References

Papers of special note have been highlighted as:
• of interest
** of considerable interest


** One of the largest monoinstitutional series of pediatric patients with papillary carcinoma with a median follow-up of 16 years. An overall survival of 100% is reported, regardless of stage, site of metastases and occurrence of relapse.


** Latest updated classification of thyroid tumors.


** One of the most detailed reports on conservative therapeutic approach in children with papillary carcinoma of the thyroid gland.


** The impact of morphologic subtypes of papillary carcinoma on the biologic behavior at onset and during follow-up and on prognosis.


14 Reever T, Thompson NW. Complications of thyroid surgery: how to avoid them, how to manage them, and observations on their possible effect on the whole patient. World J. Surg. 24, 971–975 (2000).


** These two papers by Cady report on the newest approach to thyroid carcinomas, with emphasis on risk subcategorization, genetic differences and the paramount influence of age on thyroid cancer behavior.

