Thyroid Carcinomas

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Maura Massimino, Antje Redlich, Paola Collini, and Peter Vorwerk

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16.1 Introduction

Thyroid cancers account for the most frequent tumors of endocrine glands in childhood and adolescence; however, these solid tumors are rare in this population. Currently, about 10% of all thyroid cancers occur in patients under 21 years of age (Buckwalter et al. 1981). The annual incidence as derived from the Surveillance, Epidemiology, and End Results (SEER) registry is 0.54 cases per 100,000 persons (Hogan et al. 2009).

The classification of thyroid carcinomas follows the World Health Organization (WHO) Classification of Tumours edited in 2004, which considers both pathology and genetics in defining the histotypes (Table 16.1) (Rosai et al. 2011; DeLellis et al. 2004a). In childhood, the vast majority of follicular cell–derived thyroid cancers are differentiated thyroid carcinomas, i.e., papillary and follicular carcinomas. Both poorly differentiated and undifferentiated (anaplastic) carcinomas are practically absent in this age and are not discussed in this chapter (De Keyser and Van Herle 1985).

16.2 Differentiated Thyroid Carcinoma

16.2.1 Epidemiology and Etiology

Differentiated thyroid cancer (DTC), which derives from follicular epithelial cells, includes papillary and follicular carcinomas and accounts for more than 90% of thyroid cancer in childhood (Danese et al. 1997). Among DTC, papillary thyroid carcinoma (PTC) is the most common type, with ionizing radiations appearing to be an important causal factor (Ron et al. 1989). Accordingly, a steep rise in the incidence of PTC was

M. Massimino (✉)
Pediatric Unit, Fondazione IRCCS Istituto Nazionale Tumori, Via Venezian 1, 20133 Milano, Italy
e-mail: maura.massimino@istitutotumori.mi.it

P. Vorwerk • A. Redlich
Department of Pediatric Oncology, Otto-von-Guericke University Magdeburg, Leipziger Str. 44, 39120 Magdeburg, Germany
e-mail: peter.vorwerk@medizin.uni-magdeburg.de

P. Collini
Pathology Department, Fondazione IRCCS Istituto Nazionale Tumori, Via Venezian 1, 20133 Milano, Italy

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Table 16.1 Classification of thyroid carcinoma

1. Malignant tumors of follicular cells
   - 1.1 Differentiated thyroid carcinoma (DTC)
     - 1.1.1 Papillary thyroid carcinoma (PTC)
     - 1.1.2 NOS
       - 1.1.2.1 Histopathological variants
         - 1.1.2.1.1 Follicular variant
         - 1.1.2.1.2 Macrofollicular variant
         - 1.1.2.1.3 Oncocytic variant
         - 1.1.2.1.4 Clear cell variant
         - 1.1.2.1.5 Diffuse sclerosing variant
         - 1.1.2.1.6 Tall cell variant
         - 1.1.2.1.7 Columnar cell variant
         - 1.1.2.1.8 Solid variant
         - 1.1.2.1.9 Cribriform carcinoma PTC with focal insular component
         - 1.1.2.1.10 PTC with squamous cell or mucoepidermoid carcinoma
         - 1.1.2.1.11 PTC with spindle and giant cell carcinoma
         - 1.1.2.1.12 Combined papillary and medullary carcinoma
         - 1.1.2.1.13 Papillary microcarcinomas
     - 1.1.3 Follicular thyroid carcinoma (FTC)
     - 1.1.4 Minimally invasive (encapsulated)
     - 1.1.5 NOS
       - 1.1.5.1 Oncocytic variant
       - 1.1.5.2 Clear cell variant
       - 1.1.5.3 Widely invasive
       - 1.1.5.4 NOS
       - 1.1.5.5 Oncocytic variant
       - 1.1.5.6 Clear cell variant
   - 1.2 Poorly differentiated carcinoma (PDC)
   - 1.3 Undifferentiated (anaplastic) carcinoma
2. Malignant tumors of C cells
   - 2.1 Medullary thyroid carcinoma (MTC)

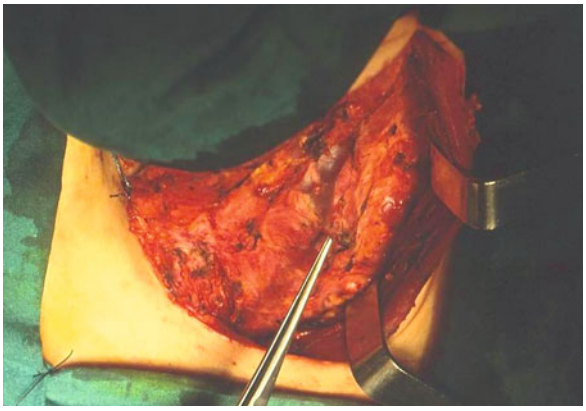

Fig. 16.1 Early operatory field showing secondary adenopathies

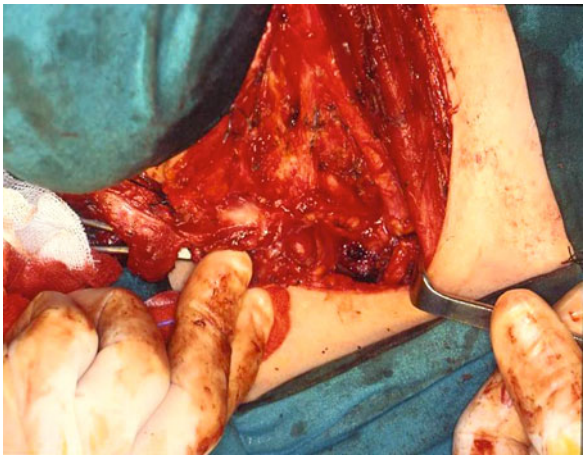

Fig. 16.2 During recurrent node resections

observed in the young population following the 1986 Chernobyl nuclear accident (Kazakov et al. 1992; Mettler et al. 1992). Also, children treated with radiation therapy on the neck for malignant diseases, such as Hodgkin lymphoma or medulloblastoma, or in the past for benign pathologies such as thymic hyperplasia, are at risk for subsequent PTC (Bhatia et al. 2003). Other risk factors are Hashimoto thyroiditis or genetic syndromes, such as Gardner's syndrome (Bell and Mazzaferri 1993; Okayasu et al. 1995; Ott et al. 1985). The preponderance of affected females throughout the literature is likely to be related to estrogen sensitivity of the thyroid gland (Hogan et al. 2009; Farahati et al. 1998; dos Santos Silva and Swerdlow 1993). In fact, in prepubertal children, the gender influence is not that clearly detectable (Jarzab et al. 2005). Follicular thyroid carcinoma (FTC) are of the minimally invasive type, being the widely invasive type exceptional (Figs. 16.1–16.3).

16.2.2 Clinical Presentation and Diagnosis

Among DTC, PTC and FTC show a different presentation and biologic behavior. Both of them can present with a thyroid mass, and lung and bone metastases are possible. Nodal metastases are very frequent in PTC but practically absent in FTC.

Along these lines, children with DTC most commonly present with asymptomatic thyroid mass or

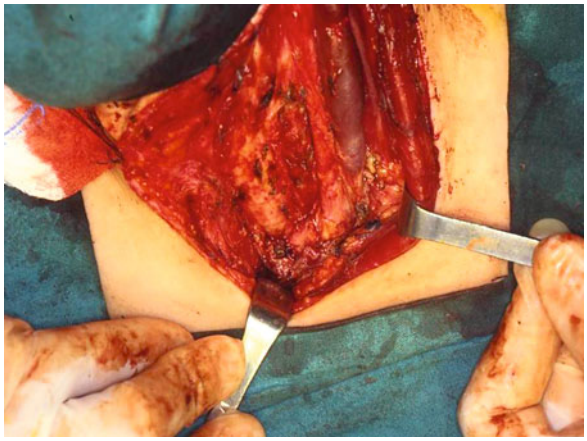

Fig. 16.3 Final result

palpable cervical lymphadenopathy (Danese et al. 1997; Chen et al. 1994; Chaukar et al. 2005). Hoarseness, dysphagia, and bronchial obstruction are not frequently found as initial symptoms.

Differentiating DTC from benign thyroid nodules challenges pediatricians, pediatric endocrinologists, and pediatric oncologists. Thyroid nodules are uncommon in childhood, affecting 0.5–0.7% of children and adolescents (Aghini-Lombardi et al. 1999; Liesenkotter et al. 1997). Since the frequency of malignancy in pediatric thyroid nodules is not quite clear, a carcinoma has to be ruled out as reliable in any case (Yip et al. 1994). In a meta-analysis, the mean incidence of DTC in pediatric thyroid nodules which were operated on was 26.4% (Niedziela 2006). Any nodule discovered in this age group should therefore be viewed with suspicion, and the diagnostic approach should be more extensive than in adults.

In the presence of a cervical mass, clinical assessment of the site of the nodule (thyroid vs node vs other), its characteristics (size, consistency, and mobility), and laryngeal or esophageal involvement (dysphonia and dysphagia) should be checked performed. Fixation of the mass to adjacent structures and lymphadenopathy are suspicious of malignancy (Lugo-Vicente and Ortiz 1998; Lassaletta et al. 1997).

In laboratory examinations, no preoperative marker is able to distinguish DTC from benign nodules. Nevertheless, laboratory evaluation of thyroid function and serum thyroglobulin is useful. Thyroglobulin is used to detect recurrence of DTC after total thyroidectomy and ablative radioiodine therapy (Herle and Uller 1975; Ng Tang Fui et al. 1979).

Ultrasonography characterizes size and appearance of the gland and the nodules (see Figs. 16.4 and 16.5). The only reliable indicators for malignancy are invasive growth into surrounding tissue and metastases to cervical lymph nodes (Hegedus and Karstrup 1998).

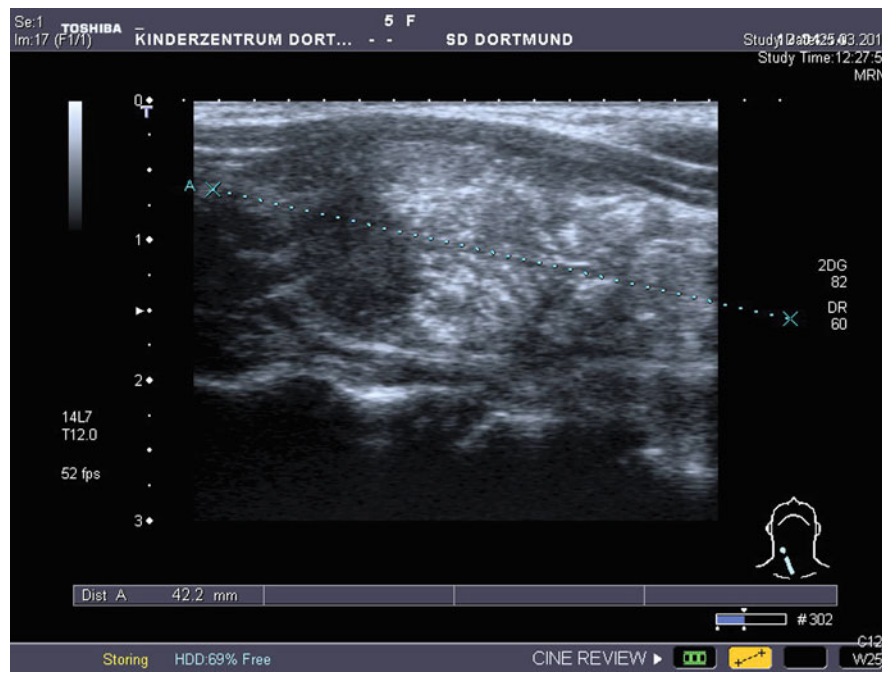

Fig. 16.4 Ultrasound of a thyroid carcinoma in right lobe of the thyroid

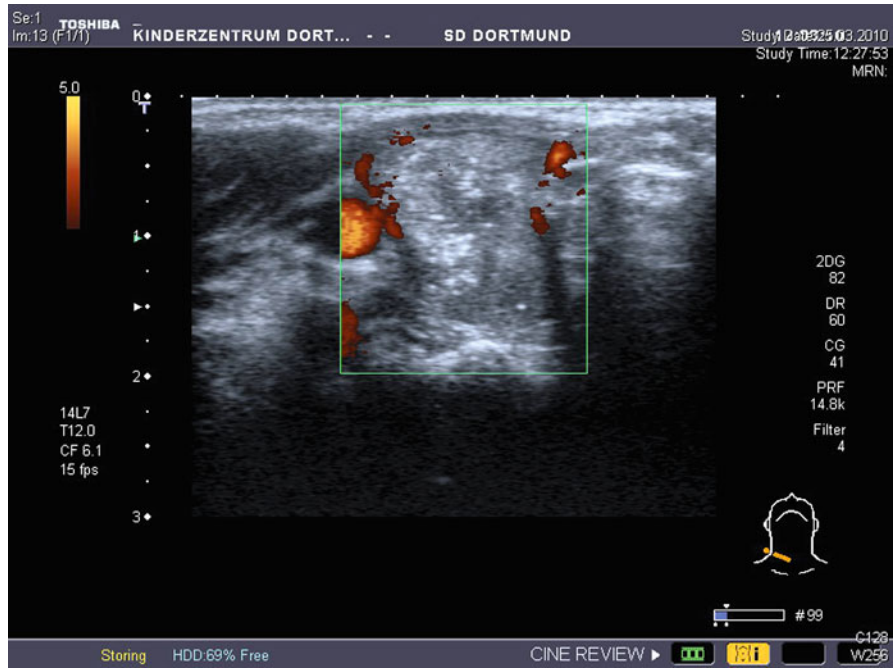

Fig. 16.5 Ultrasound of lymph node involvement of patient with thyroid carcinoma

Other sonographic findings such as hypoechogenicity, solid composition, irregular margins, or microcalcifications are associated with an increased risk of malignancy but usually can not distinguish benign from malignant nodules accurately.

In adults, numerous reports confirm that the introduction of fine-needle aspiration biopsy (FNAB) reduced thyroid surgery and increased the yield of carcinoma in patients who underwent surgery dramatically (Gharib and Goellner 1993). In young patients, FNAB has not been utilized extensively, and the scanty studies reported are often in disagreement. Nevertheless, a meta-analysis certified FNAB as a sensitive diagnostic test and a useful tool in diagnosing malignancy in pediatric thyroid nodules (Stevens et al. 2009). The procedure should only be performed by experienced physicians and cytologists.

16.2.3 Special Considerations

Several studies have shown that DTC in pediatric patients differs from that in adults with respect to its presentation and outcome (Table 16.2).

The malignant disease in childhood is associated with more locally aggressive behavior and more frequent distant metastases than its adult counterpart (Zimmerman et al. 1988; Jarzab and Handkiewicz-Junak 2007; Schlumberger et al. 1987). As the thyroid gland is smaller in children than in adults, earlier involvement of the thyroid capsule and the surrounding tissue of the neck is possible (Farahati et al. 1999). Recurrence rates tend to be higher in the pediatric population, but nevertheless, cause-specific mortality remains low.

16.2.4 Pathology

Nonmedullary, follicular-derived thyroid carcinomas, encompassing papillary thyroid carcinomas (PTC), follicular thyroid carcinomas (FTC), poorly differentiated carcinomas (PDC), and undifferentiated (anaplastic) carcinomas, represent biologically and genetically different and distinct entities (WHO, Collini et al. 2006a).

While PTC are characterized by a prevalent lymphatic spread, FTC follows a vascular way of diffusion. PTC show a high tendency to intrathyroidal microscopic pluricentricity, intrathyroidal and nodal microscopic lymphatic diffusion, infiltration beyond the thyroid capsule into the soft tissue of the neck, and

Table 16.2 Differentiated thyroid cancer: differences in children and adults

	Children	Adults
Annual incidence (Hogan et al. 2009; Wiersinga 2001)	0.2–2:1,000,000	50–100:1,000,000
Staging at presentation		
Extrathyroidal tumor spread into the soft tissue of the neck (pT4)	52%	15% (low-risk variants) 45% (high-risk variants)
Lymph node metastases (Zimmerman et al. 1988; Farahati et al. 1997)	40–70% (–90%)	30–73%
Distant metastases at onset (Schlumberger et al. 1987; Ruegemer et al. 1988)	12–20% (lung, miliar; bone)	2–10% (lung; rarely bone)
Histology		
Histological subtype (Newman et al. 1998; Welch Dinauer et al. 1998)	PTC 80–90% (low-risk variants)	PTC 80% (also high-risk variants)
Multifocality (Spinelli et al. 2004)	50–80%	30–60%
Size (Wiersinga 2001; Chow et al. 2004; Miccoli et al. 2008)	Larger	Smaller
Outcome		
Event-free survival (5 years) (Jarzab and Handkiewicz-Junak 2007)	60%	80%
Overall survival (Jarzab and Handkiewicz-Junak 2007; Showalter et al. 2008; Parisi and Mankoff 2007)	95–100%	90%

presence of nodal and distant metastases mainly in lungs. FTC are characterized by vascular invasion, distant metastases in bone and lungs, and absence of tendency to invade soft tissue of the neck or nodal metastases (DeLellis et al. 2004b). Genetically, PTC show involvement of RET, TRK, and BRAF, whereas in FTC, RAS mutations are present (DeLellis et al. 2004b). PDC are high-risk tumors that show the biological characteristics of both PTC and FTC and can arise de novo or as progression of malignancy in PTC or FTC (DeLellis et al. 2004b). As with the adult disease, follicular-derived thyroid carcinomas can be divided into low- and high-risk histotypes and variants on the basis of overall survival (OS). In the low-risk group, the vast majority of PTC and the minimally invasive (encapsulated) FTC (MIFTC) with only capsular and/or minimal vascular invasion are included. In the high-risk group, the PTC of the tall cell, columnar cell, and high-risk variants; the MIFC with extensive vascular invasion; and the widely invasive FTC, PDC, and undifferentiated (anaplastic) carcinomas are included (DeLellis et al. 2004b; Collini et al. 2004). The vast majority of pediatric thyroid carcinomas are PTC. In these ages, FTC are exceptional and occur as low-risk MIFC only. PDC are exceptional. Many thyroid carcinomas which have been diagnosed as FTC or PDC (i.e., insular carcinomas, solid/trabecular FTC, and moderately differentiated FTC) in the past are indeed low-risk PTC of the follicular, encapsulated follicular, or solid/trabecular variants (DeLellis et al. 2004b). In childhood, high-risk histotypes of thyroid carcinomas such as widely invasive FTC and undifferentiated (anaplastic) carcinomas are practically absent.

16.2.5 Therapy

The management strategies for differentiated thyroid carcinoma in children remain to be debated. In general, the radical approach utilizing radical surgery (thyroidectomy plus lymph node dissection) followed by radioiodine therapy and TSH suppression aims for control of both macro- and microscopic diseases. This strategy has been adopted from corresponding trials in adult patients. However, considering potential long-term sequelae of this treatment, a more conservative approach might also be considered for selected patients. This strategy aims for control of only macroscopic disease with limited surgery (hemithyroidectomy plus limited neck dissection) without radiotherapy but always followed by TSH suppression. In the perspective of the excellent (almost 100%) overall survival with both approaches, these two options have to be carefully weighed in each patient, since no prospective

Table 16.3 Comparison between the radical versus conservative approach in thyroid carcinoma of children and adolescents

Radical (same as for adults)	Therapeutic approach	Conservative [tailored for selected pediatric patients (tumors limited to one lobe, ± clinical evidence of monolateral N)]
Initial eradication of all clinical and subclinical neoplastic foci (at T, N, and M)	Strategy	Removal only of grossly detectable disease, without searching for microscopic disease after surgery
Improve progression-free survival by detecting and treating all tumor cells, and preventing any dedifferentiation of occult neoplastic micro-foci	Aims	Contain treatment morbidity, without jeopardizing the zero mortality rate (the risk of tumor dedifferentiation from microscopic disease seems to be merely theoretical in children)
Total thyroidectomy (regardless of the tumor extent)	Thyroid resection	Removal of the thyroid lobe affected by clinically detectable disease and the isthmus (hemithyroidectomy)
Prophylactic lymphadenectomy	Lymphadenectomy	Selective neck dissection of only the clinically involved node levels
RAI scintigraphic scan to seek any subclinical metastases	Staging	No RAI scintigraphic scan (macrostaging instead of microstaging)
Treatment with 131I ablation, where necessary	Post-operative treatment	Lifelong TSH suppression therapy to control subclinical disease
Serum thyroglobulin level is a very sensitive marker of post-treatment relapse	Follow-up	Presence of thyroid tissue could prevent the effective use of thyroglobulin assay as a marker of tumor relapse, even if a higher cut-off than 0 could be used
Hypoparathyroidism (36%) Recurrent laryngeal nerve paralysis and spinal accessory nerve paralysis (28%) Risk of iatrogenic effects of metabolic radiotherapy	Risk of permanent morbidity	Very low, if ever

studies are currently available that would provide definite evidence in favor of one or the other strategy. Both strategies are discussed in detail and summarized in Table 16.3.

16.2.5.1 Surgery

The development of a standard treatment strategy for the treatment of childhood thyroid cancer suffers from the same affliction that affects other rare pediatric tumors: the reliance on retrospective studies and the absence of prospective clinical trials (Spinelli et al. 2004; Dinauer et al. 2008; Collini et al. 2007). Though the optimal primary surgical intervention is still unclear, future prospective trials comparing various procedures should be the goal. One very important factor for successful treatment of childhood thyroid cancer is the availability to receive treatment at a facility with the appropriate specialists with a large experience in the treatment of thyroid cancer. A multidisciplinary effort, that may include surgeons, pediatric oncologists, medical oncologists, and nuclear medicine physicians, would be ideal.

The vast majority of patients undergo total thyroidectomy with or without lymph node dissection. Advantages of this radical approach are:

- Upgrading progression-free survival (PFS) and overall survival (OS).
- Ablative radioiodine therapy can be performed.
- Metastases can be sensitively detected by whole-body scintigraphy.
- Use of thyroglobulin as sensitive marker of post-treatment relapse.
- Numerous children with PTC have multifocal disease, so all thyroid tissue potentially at risk of containing multiple neoplastic foci is removed (Welch Dinauer et al. 1998; Miccoli et al. 1998; De Jong et al. 1992).

Some authors recommend total thyroidectomy even in microcarcinoma (Ogilvie et al. 2010). For selected cases, a more conservative approach is discussed (Massimino et al. 2006). A more conservative treatment approach has not been universally applied. This approach has been developed at several institutions and should be done as part of an organized clinical

trial. Only selected patients with tumor limited to one lobe with or without clinical evidence of monolateral nodal metastases are eligible. The main argument for the conservative approach is the excellent prognosis of DTC in children and adolescents despite a more advanced stage at presentation and a more aggressive clinical course (Danese et al. 1997; Chow et al. 2004). Presence of lymph node or distant metastases does not influence mortality in children. The chance of dedifferentiation of microscopic disease over the years is only theoretical. More aggressive procedures, especially if applied in children under 16 years of age, are closely related to a morbidity increase (permanent hypoparathyroidism and recurrent nerve palsy) (La Quaglia et al. 1988; van Santen et al. 2004). Minimal approach is hemithyroidectomy consisting of lobectomy plus isthmectomy. If further surgery is required, no resection in an already operated bed associated with higher complications must be performed (Shaha 2008; Levin et al. 1992).

So as long as there are no prospective trials investigating different therapeutical regimes, the debate will continue. If a conservative approach is to be followed, 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.

16.2.5.2 Radioiodine Therapy and Hormonal Manipulation

The radioactive isotope 131I can be administered for selective irradiation of remnant thyroid tissue, microscopic foci of carcinoma, and distant metastases if a radical surgical approach has been used. Radioiodine uptake in carcinoma cells depends on the expression of the sodium–iodide symporter (NIS). In pediatric DTC, the NIS is expressed stronger when compared with adult tumors (Jarzab et al. 2005). That may be one of the reasons why DTC in children are more sensitive to hormonal manipulation and have a better prognosis despite more advanced disease at diagnosis.

The first ablative radioiodine therapy (RIT) after total thyroidectomy is an adjuvant modality to eliminate regularly remaining thyroid tissue and increase sensitivity of thyroglobulin assay and whole-body scintigraphy in follow-up. RIT requires adequate TSH stimulation. It can be achieved endogenously via L-thyroxin withdrawal within 14 days in children (Kuijt and Huang 2005). The use of recombinant thyrotropin (rhTSH) in children is safe; well-tolerated and adequate TSH levels can be achieved (Luster et al. 2009; Ralli et al. 2005).

Functioning of the thyroid is dependent on TSH, whose synthesis and release depend on thyroid-releasing hormone (TRH), produced in the hypothalamus and secreted into the pituitary (Crile 1966; Gharib et al. 1987). Suppression of TSH secretion (TSH < 0.1 mU/l) has the aim to prevent growth of hidden microfoci, residual tumor, or metastases, respectively.

Used activities vary from 50 MBq/kg for ablation to 100 (–150) MBq/kg for metastatic disease (Franzius et al. 2007). Monitoring of the pulmonary function is recommended to detect radiation-induced pulmonary fibrosis, which is a rare sequela of RIT.

16.2.6 Follow-up

Whole-body scintigraphy is repeated after 6–12 months from the metabolic treatment, and the RIT can be repeated in case of persistent disease. The goal of this strategy is to obtain a negative scan and a thyroglobulin with an undeterminable value. Thyroglobulin concentration after ablative RIT is a strong predictor of disease recurrence (Pelttari et al. 2010). Low-risk patients with undetectable basal thyroglobulin should receive at least one rhTSH-stimulated thyroglobulin because of the low predictive value for recurrence of basal thyroglobulin (Diaz-Soto et al. 2011).

16.2.7 Postoperative Complications and 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% (Bargren et al. 2009; Machens and Dralle 2009; Massimino et al. 2006; Reeve and Thompson 2000) and recurrent nerve palsy from 0% to 28% (Crile 1966;

Table 16.4 Manifestations in MEN 2 syndrome and their frequencies

	MEN 2A (%)	MEN 2B (%)
MTC (Brandi et al. 2001; Iihara et al. 1997)	90–100	100
Pheochromocytoma (Brandi et al. 2001; Modigliani et al. 1998)	50	50
Hyperparathyroidism (Brandi et al. 2001; Modigliani et al. 1998)	20–30	–
Intestinal ganglioneuromatosis	–	40–100
Marfanoid habitus	–	>95
Stigmata	–	>95

Verburg et al. 2009). 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 biweekly, 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.

16.2.8 Prognosis

Children and adolescents with DTC have an excellent prognosis despite the more aggressive behavior when compared with adults (Jarzab and Handkiewicz-Junak 2007). Nevertheless, fatal outcome occurs in some cases. It is a well-known phenomenon that the outcome of pediatric PTC is independent of strong prognostic factors of adults, such as low- versus high-risk histological subtype, extrathyroid local invasion into soft tissue of the neck, presence of distant metastases, site of distant metastatic spread, occurrence of relapse, and type of surgery (Verburg et al. 2009; Collini et al. 2006b).

16.3 Medullary Thyroid Carcinoma

Medullary thyroid carcinoma (MTC) arising from the parafollicular C cells is associated with inherited tumor syndromes. The multiple endocrine neoplasias (MEN) type 2A, 2B, and also familial medullary thyroid carcinoma (FMTC) are characterized by bilateral multifocal MTC invariably in a background of C-cell hyperplasia, the inherited predisposing abnormality. In MEN 2A, besides the calcitonin-producing thyroid tumor, pheochromocytoma and parathyroid adenoma/hyperplasia causing hyperparathyroidism are found. MTC, pheochromocytoma, and typical stigmatas characterize patients suffering from MEN 2B (Table 16.4). The FMTC is diagnosed if at least four cases occur in a family in the absence of other MEN 2 manifestations.

MTC usually is the first tumor to develop in patients with MEN 2 and is the most common cause of death among these patients (Szinnai et al. 2007). The malignancy is particularly aggressive in patients with MEN 2B and may occur even in infancy (Yin et al. 2006). Different germline point mutations of the REarranged during Transfection (RET) proto-oncogene are involved in the pathogenesis of MTC and MEN 2, respectively, with consequences on management of affected children (Raue and Frank-Raue 2009; Machens and Dralle 2007). Screening for MEN 2 of affected kindreds reveals children with MEN 2, who should undergo prophylactic thyroidectomy before developing MTC (Table 16.5). A strong genotype–phenotype correlation is known, leading to the discrimination in highest-, high-, and least-high-risk mutations, respectively (Table 16.5). MEN 2A is frequently caused by mutation in codon 634 and MEN 2B by mutation in codon 918.

More than 90% of patients with MEN 2B harbor de novo mutations in the RET proto-oncogene. These index cases without any family history are at high risk for developing advanced MTC with high mortality. The distinct physical appearance of children with MEN 2B, e.g., mucosal neuromas of the tongue, lips, inner eyelids, marfanoid body habitus, are not appreciated before the occurrence of the thyroid tumor.

Table 16.5 Timing of prophylactic thyroidectomy in MEN 2 (Machens and Dralle 2007; Brandi et al. 2001; Frank-Raue et al. 2006)

RET mutation	Time of surgery	Operation
Least-high-risk level (609, 768, 790, 791, 804, 891)	<5–10 years or pPT	Total thyroidectomy
High-risk level (611, 618, 620, 630, **634**)	<5 years	Total thyroidectomy
Highest-risk level (883, **918**)	<1/2–1 years	Total thyroidectomy with central lymph node dissection

Premonitory symptoms preceding metastatic MTC are constipation since infancy and inability to cry tears (Brauckhoff et al. 2004). Children with sporadic MTC commonly present with palpable thyroid nodule.

In MEN 2A, no accompanying visible signs are found. An association with Hirschsprung disease or cutaneous lichen amyloidosis is described (Cohen et al. 2002; Verga et al. 2003).

Calcitonin levels represent an accurate and sensitive marker for both preoperative diagnosis and follow-up of MTC (Cohen et al. 2000; Melvin et al. 1971). Pentagastrin testing may be helpful in differentiating C-cell hyperplasia from MTC in cases of moderately elevated basal calcitonin (Milone et al. 2010).

The most important therapeutical option is the radical approach, with the surgical resection of all tumor localizations, since no curative medical therapy is available (Kloos et al. 2009). In recent years, targeted therapy with small molecules such as tyrosine kinase inhibitors and RET kinase inhibitors have been studied in clinical trials with partial responses in up to 30% (Lanzi et al. 2009; Puxeddu et al. 2011; Sherman 2010). The most important prognostic factor is clinical stage at diagnosis. Patients with lymph node or distant metastases are at risk of relapse or fatal outcome (Bergholm et al. 1997).

16.3.1 Pediatric Thyroid Cancer: A Model for Collaboration

The treatment of pediatric thyroid cancer is complex and should be managed by a medical team with appropriate experience and skills. The treatment of thyroid cancer in adult patients has been informed by several studies, and general guidelines exist. Pediatric oncologists have tried to extrapolate from these guidelines, but sufficient data do not exist. One aspect of the treatment debate is the fear of exposing children to potential late toxicity. It is known that pediatric thyroid cancer may be more aggressive than thyroid cancer in adults. However, pediatric patients respond well to hormonal manipulation with TSH suppression, and the mortality from pediatric thyroid cancer is very low. In the US, the Children's Oncology Group realizes that, for many "rare" cancers, clinical trials are unlikely. For these tumors, clinical guidelines are being developed. The same strategy is being pursued in other countries. It is important to emphasize that as one develops guidelines, one must try to validate them with careful attention to outcomes. For this reason, the Italian approach to a more conservative approach serves as an excellent example (Table 16.3). Guidelines were established, and data are being collected that might inform future international collaborative trials.

References

Aghini-Lombardi F, Antonangeli L, Martino E et al (1999) The spectrum of thyroid disorders in an iodine-deficient community: the Pescopagano survey. J Clin Endocrinol Metab 84(2):561–566

Bargren AE, Meyer-Rochow GY, Delbridge LW, Sidhu SB, Chen H (2009) Outcomes of surgically managed pediatric thyroid cancer. J Surg Res 156(1):70–73

Bell B, Mazzaferri EL (1993) Familial adenomatous polyposis (Gardner's syndrome) and thyroid carcinoma. A case report and review of the literature. Dig Dis Sci 38(1):185–190

Bergholm U, Bergstrom R, Ekbom A (1997) Long-term follow-up of patients with medullary carcinoma of the thyroid. Cancer 79(1):132–138

Bhatia S, Yasui Y, Robison LL et al (2003) High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: report from the Late Effects Study Group. J Clin Oncol 21(23):4386–4394

Brandi ML, Gagel RF, Angeli A et al (2001) Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab 86(12):5658–5671

Brauckhoff M, Gimm O, Weiss CL et al (2004) Multiple endocrine neoplasia 2B syndrome due to codon 918 mutation: clinical manifestation and course in early and late onset disease. World J Surg 28(12):1305–1311

Buckwalter JA, Gurll NJ, Thomas CG Jr (1981) Cancer of the thyroid in youth. World J Surg 5(1):15–25

Chaukar DA, Rangarajan V, Nair N et al (2005) Pediatric thyroid cancer. J Surg Oncol 92(2):130–133

Chen WK, Lee CH, Wang HC, Lui WY, Wei CF (1994) Thyroid cancer in children and adolescents. Zhonghua Yi Xue Za Zhi (Taipei) 54(6):400–406

Chow SM, Law SC, Mendenhall WM et al (2004) Differentiated thyroid carcinoma in childhood and adolescence-clinical course and role of radioiodine. Pediatr Blood Cancer 42(2):176–183

Cohen R, Campos JM, Salaun C et al (2000) Preoperative calcitonin levels are predictive of tumor size and postoperative calcitonin normalization in medullary thyroid carcinoma. Groupe d'Etudes des Tumeurs a Calcitonine (GETC). J Clin Endocrinol Metab 85(2):919–922

Cohen MS, Phay JE, Albinson C et al (2002) Gastrointestinal manifestations of multiple endocrine neoplasia type 2. Ann Surg 235(5):648–654

Collini P, Sampietro G, Pilotti S (2004) Extensive vascular invasion is a marker of risk of relapse in encapsulated non-Hurthle cell follicular carcinoma of the thyroid gland: a clinicopathological study of 18 consecutive cases from a single institution with a 11-year median follow-up. Histopathology 44(1):35–39

Collini P, Massimino M, Leite SF et al (2006a) Papillary thyroid carcinoma of childhood and adolescence: a 30-year experience at the Istituto Nazionale Tumori in Milan. Pediatr Blood Cancer 46(3):300–306

Collini P, Mattavelli F, Pellegrinelli A, Barisella M, Ferrari A, Massimino M (2006b) Papillary carcinoma of the thyroid gland of childhood and adolescence: morphologic subtypes, biologic behavior and prognosis: a clinicopathologic study of 42 sporadic cases treated at a single institution during a 30-year period. Am J Surg Pathol 30(11):1420–1426

Collini P, Mattavelli F, Spinelli C, Massimino M (2007) Treatment of sporadic nonmedullary thyroid carcinomas in pediatric age. Expert Rev Anticancer Ther 7(1):23–30

Crile G Jr (1966) Endocrine dependency of papillary carcinoma of the thyroid. JAMA 195(9):721–724

Danese D, Gardini A, Farsetti A, Sciacchitano S, Andreoli M, Pontecorvi A (1997) Thyroid carcinoma in children and adolescents. Eur J Pediatr 156(3):190–194

De Jong SA, Demeter JG, Lawrence AM, Paloyan E (1992) Necessity and safety of completion thyroidectomy for differentiated thyroid carcinoma. Surgery 112(4):734–737

De Keyser LF, Van Herle AJ (1985) Differentiated thyroid cancer in children. Head Neck Surg 8(2):100–114

DeLellis RA, Lloyd RV, Heitz PU, Eng C (eds) (2004a) Pathology and genetics. Tumours of endocrine organs. In: World Health Organization Classification of Tumours. IARC, Lyon

DeLellis RA, Lloyd RV, Heitz PU, Eng C (2004b) World Health Organization Classification of Tumours. Pathology and genetics of tumours of endocrine organs. IARC, Lyon

Díaz-Soto G, Puig-Domingo M, Martínez-Pino I, Martínez de Osaba MJ, Mora M, Rivera-Fillat F, Halperin I (2011) Do thyroid cancer patients with basal undetectable Tg measured by current immunoassays require rhTSH testing? Exp Clin Endocrinol Diabetes 119:348–352.

Dinauer CA, Breuer C, Rivkees SA (2008) Differentiated thyroid cancer in children: diagnosis and management. Curr Opin Oncol 20(1):59–65

dos Santos Silva I, Swerdlow AJ (1993) Sex differences in the risks of hormone-dependent cancers. Am J Epidemiol 138(1):10–28

Farahati J, Bucsky P, Parlowsky T, Mader U, Reiners C (1997) Characteristics of differentiated thyroid carcinoma in children and adolescents with respect to age, gender, and histology. Cancer 80(11):2156–2162

Farahati J, Parlowsky T, Mader U, Reiners C, Bucsky P (1998) Differentiated thyroid cancer in children and adolescents. Langenbecks Arch Surg 383(3–4):235–239

Farahati J, Reiners C, Demidchik EP (1999) Is the UICC/AJCC classification of primary tumor in childhood thyroid carcinoma valid? J Nucl Med 40(12):2125

Frank-Raue K, Buhr H, Dralle H et al (2006) Long-term outcome in 46 gene carriers of hereditary medullary thyroid carcinoma after prophylactic thyroidectomy: impact of individual RET genotype. Eur J Endocrinol 155(2): 229–236

Franzius C, Dietlein M, Biermann M et al (2007) Procedure guideline for radioiodine therapy and 131iodine whole-body scintigraphy in paediatric patients with differentiated thyroid cancer. Nuklearmedizin 46(5):224–231

Gharib H, Goellner JR (1993) Fine-needle aspiration biopsy of the thyroid: an appraisal. Ann Intern Med 118(4):282–289

Gharib H, James EM, Charboneau JW, Naessens JM, Offord KP, Gorman CA (1987) Suppressive therapy with levothyroxine for solitary thyroid nodules. A double-blind controlled clinical study. N Engl J Med 317(2):70–75

Hegedus L, Karstrup S (1998) Ultrasonography in the evaluation of cold thyroid nodules. Eur J Endocrinol 138(1):30–31

Herle AJ, Uller RP (1975) Elevated serum thyroglobulin. A marker of metastases in differentiated thyroid carcinomas. J Clin Invest 56(2):272–277

Hogan AR, Zhuge Y, Perez EA, Koniaris LG, Lew JI, Sola JE (2009) Pediatric thyroid carcinoma: incidence and outcomes in 1753 patients. J Surg Res 156(1):167–172

Iihara M, Yamashita T, Okamoto T et al (1997) A nationwide clinical survey of patients with multiple endocrine neoplasia type 2 and familial medullary thyroid carcinoma in Japan. Jpn J Clin Oncol 27(3):128–134

Jarzab B, Handkiewicz-Junak D (2007) Differentiated thyroid cancer in children and adults: same or distinct disease? Hormones (Athens) 6(3):200–209

Jarzab B, Handkiewicz-Junak D, Wloch J (2005) Juvenile differentiated thyroid carcinoma and the role of radioiodine in its treatment: a qualitative review. Endocr Relat Cancer 12(4):773–803

Kazakov VS, Demidchik EP, Astakhova LN (1992) Thyroid cancer after Chernobyl. Nature 359(6390):21

Kloos RT, Eng C, Evans DB et al (2009) Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid 19(6):565–612

Kuijt WJ, Huang SA (2005) Children with differentiated thyroid cancer achieve adequate hyperthyrotropinemia within 14 days of levothyroxine withdrawal. J Clin Endocrinol Metab 90(11):6123–6125

La Quaglia MP, Corbally MT, Heller G, Exelby PR, Brennan MF (1988) Recurrence and morbidity in differentiated thyroid carcinoma in children. Surgery 104(6):1149–1156

Lanzi C, Cassinelli G, Nicolini V, Zunino F (2009) Targeting RET for thyroid cancer therapy. Biochem Pharmacol 77(3): 297–309

Lassaletta AL, Melchor Diaz MA, Gavilanes PJ, Martin HG, de Vergas GJ (1997) Thyroid nodules: factors suggestive of malignancy. Acta Otorrinolaringol Esp 48(3):220–224

Levin KE, Clark AH, Duh QY, Demeure M, Siperstein AE, Clark OH (1992) Reoperative thyroid surgery. Surgery 111(6):604–609

Liesenkotter KP, Kiebler A, Stach B, Willgerodt H, Gruters A (1997) Small thyroid volumes and normal iodine excretion in Berlin schoolchildren indicate full normalization of iodine supply. Exp Clin Endocrinol Diabetes 105(Suppl 4):46–50

Lugo-Vicente H, Ortiz VN (1998) Pediatric thyroid nodules: insights in management. Bol Asoc Med P R 90(4–6):74–78

Luster M, Handkiewicz-Junak D, Grossi A et al (2009) Recombinant thyrotropin use in children and adolescents with differentiated thyroid cancer: a multicenter retrospective study. J Clin Endocrinol Metab 94(10):3948–3953

Machens A, Dralle H (2007) Genotype-phenotype based surgical concept of hereditary medullary thyroid carcinoma. World J Surg 31(5):957–968

Machens A, Dralle H (2009) Age disparities in referrals to specialist surgical care for papillary thyroid cancer. Eur J Surg Oncol 35(12):1312–1317

Massimino M, Collini P, Leite SF et al (2006) Conservative surgical approach for thyroid and lymph-node involvement in papillary thyroid carcinoma of childhood and adolescence. Pediatr Blood Cancer 46(3):307–313

Melvin KE, Miller HH, Tashjian AH Jr (1971) Early diagnosis of medullary carcinoma of the thyroid gland by means of calcitonin assay. N Engl J Med 285(20):1115–1120

Mettler FA Jr, Williamson MR, Royal HD et al (1992) Thyroid nodules in the population living around Chernobyl. JAMA 268(5):616–619

Miccoli P, Antonelli A, Spinelli C, Ferdeghini M, Fallahi P, Baschieri L (1998) Completion total thyroidectomy in children with thyroid cancer secondary to the Chernobyl accident. Arch Surg 133(1):89–93

Miccoli P, Minuto MN, Ugolini C et al (2008) Papillary thyroid cancer: pathological parameters as prognostic factors in different classes of age. Otolaryngol Head Neck Surg 138(2):200–203

Milone F, Ramundo V, Chiofalo MG et al (2010) Predictive value of pentagastrin test for preoperative differential diagnosis between C-cell hyperplasia and medullary thyroid carcinoma in patients with moderately elevated basal calcitonin levels. Clin Endocrinol (Oxf) 73(1):85–88

Modigliani E, Cohen R, Campos JM et al (1998) Prognostic factors for survival and for biochemical cure in medullary thyroid carcinoma: results in 899 patients. The GETC Study Group. Groupe d'etude des tumeurs a calcitonine. Clin Endocrinol (Oxf) 48(3):265–273

Newman KD, Black T, Heller G et al (1998) Differentiated thyroid cancer: determinants of disease progression in patients <21 years of age at diagnosis: a report from the Surgical Discipline Committee of the Children's Cancer Group. Ann Surg 227(4):533–541

Ng Tang Fui SC, Hoffenberg R, Maisey MN, Black EG (1979) Serum thyroglobulin concentrations and whole-body radioiodine scan in follow-up of differentiated thyroid cancer after thyroid ablation. Br Med J 2(6185):298–300

Niedziela M (2006) Pathogenesis, diagnosis and management of thyroid nodules in children. Endocr Relat Cancer 13(2):427–453

Ogilvie JB, Patel KN, Heller KS (2010) Impact of the 2009 American Thyroid Association guidelines on the choice of operation for well-differentiated thyroid microcarcinomas. Surgery 148(6):1222–1226

Okayasu I, Fujiwara M, Hara Y, Tanaka Y, Rose NR (1995) Association of chronic lymphocytic thyroiditis and thyroid papillary carcinoma. A study of surgical cases among Japanese, and white and African Americans. Cancer 76(11):2312–2318

Ott RA, Calandra DB, McCall A, Shah KH, Lawrence AM, Paloyan E (1985) The incidence of thyroid carcinoma in patients with Hashimoto's thyroiditis and solitary cold nodules. Surgery 98(6):1202–1206

Parisi MT, Mankoff D (2007) Differentiated pediatric thyroid cancer: correlates with adult disease, controversies in treatment. Semin Nucl Med 37(5):340–356

Pelttari H, Valimaki MJ, Loyttyniemi E, Schalin-Jantti C (2010) Post-ablative serum thyroglobulin is an independent predictor of recurrence in low-risk differentiated thyroid carcinoma: a 16-year follow-up study. Eur J Endocrinol 163(5): 757–763

Puxeddu E, Romagnoli S, Dottorini ME (2011) Targeted therapies for advanced thyroid cancer. Curr Opin Oncol 23:13–21.

Ralli M, Cohan P, Lee K (2005) Successful use of recombinant human thyrotropin in the therapy of pediatric well-differentiated thyroid cancer. J Endocrinol Invest 28(3):270–273

Raue F, Frank-Raue K (2009) Genotype-phenotype relationship in multiple endocrine neoplasia type 2. Implications for clinical management. Hormones (Athens) 8(1):23–28

Reeve T, Thompson NW (2000) 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(8):971–975

Ron E, Modan B, Preston D, Alfandary E, Stovall M, Boice JD Jr (1989) Thyroid neoplasia following low-dose radiation in childhood. Radiat Res 120(3):516–531

Rosai J, Carcangiu ML, DeLellis RA (2011) Tumors of the thyroid gland. In: Rosai J, Sobin H (eds) Atlas of tumor pathology. Armed Forces Institute of Pathology, Washington DC

Ruegemer JJ, Hay ID, Bergstralh EJ, Ryan JJ, Offord KP, Gorman CA (1988) Distant metastases in differentiated thyroid carcinoma: a multivariate analysis of prognostic variables. J Clin Endocrinol Metab 67(3):501–508

Schlumberger M, de Vathaire F, Travagli JP et al (1987) Differentiated thyroid carcinoma in childhood: long term follow-up of 72 patients. J Clin Endocrinol Metab 65(6): 1088–1094

Shaha AR (2008) Revision thyroid surgery - technical considerations. Otolaryngol Clin North Am 41(6):1169–1183, x

Sherman SI (2010) Targeted therapy of thyroid cancer. Biochem Pharmacol 80(5):592–601

Showalter TN, Siegel BA, Moley JF, Baranski TJ, Grigsby PW (2008) Prognostic factors in patients with well-differentiated thyroid cancer presenting with pulmonary metastasis. Cancer Biother Radiopharm 23(5):655–659

Spinelli C, Bertocchini A, Antonelli A, Miccoli P (2004) Surgical therapy of the thyroid papillary carcinoma in children: experience with 56 patients < or =16 years old. J Pediatr Surg 39(10):1500–1505

Stevens C, Lee JK, Sadatsafavi M, Blair GK (2009) Pediatric thyroid fine-needle aspiration cytology: a meta-analysis. J Pediatr Surg 44(11):2184–2191

Szinnai G, Sarnacki S, Polak M (2007) Hereditary medullary thyroid carcinoma: how molecular genetics made multiple endocrine neoplasia type 2 a paediatric disease. Endocr Dev 10:173–187

van Santen HM, Aronson DC, Vulsma T et al (2004) Frequent adverse events after treatment for childhood-onset differentiated thyroid carcinoma: a single institute experience. Eur J Cancer 40(11):1743–1751

Verburg FA, Mäder U, Luster M, Reiners C (2009) Histology does not influence prognosis in differentiated thyroid carcinoma when accounting for age, tumour diameter, invasive growth and metastases. Eur J Endocrinol 160:619–624

Verga U, Fugazzola L, Cambiaghi S et al (2003) Frequent association between MEN 2A and cutaneous lichen amyloidosis. Clin Endocrinol (Oxf) 59(2):156–161

Welch Dinauer CA, Tuttle RM, Robie DK et al (1998) Clinical features associated with metastasis and recurrence of differentiated thyroid cancer in children, adolescents and young adults. Clin Endocrinol (Oxf) 49(5):619–628

Wiersinga WM (2001) Thyroid cancer in children and adolescents–consequences in later life. J Pediatr Endocrinol Metab 14(Suppl 5):1289–1296

Yin M, King SK, Hutson JM, Chow CW (2006) Multiple endocrine neoplasia type 2B diagnosed on suction rectal biopsy in infancy: a report of 2 cases. Pediatr Dev Pathol 9(1):56–60

Yip FW, Reeve TS, Poole AG, Delbridge L (1994) Thyroid nodules in childhood and adolescence. Aust N Z J Surg 64(10):676–678

Zimmerman D, Hay ID, Gough IR et al (1988) Papillary thyroid carcinoma in children and adults: long-term follow-up of 1039 patients conservatively treated at one institution during three decades. Surgery 104(6):1157–1166