Rare endocrine tumour guidelines

Paediatric Differentiated Thyroid Carcinoma

UK National Clinical Practice Consensus Guideline

Children's Cancer and Leukaemia Group | the EXPERTS in CHILDHOOD CANCER

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Differentiated thyroid carcinoma: Guideline for the management of children and young people (CYP) aged <19 years with differentiated thyroid carcinoma (DTC).

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Paediatric Differentiated Thyroid Carcinoma

UK National Clinical Practice Consensus Guideline

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Abstract

This guideline is written as a reference document for clinicians presented with the challenge of managing paediatric patients with differentiated thyroid carcinoma up to the age of 19 years. Care of paediatric patients with differentiated thyroid carcinoma differs in key aspects from that of adults, and there have been several recent developments in the care pathways for this condition; this guideline has sought to identify and attend to these areas. It addresses the presentation, clinical assessment, diagnosis, management (both surgical and medical), genetic counselling, follow up and prognosis of affected patients. The guideline development group formed of a multi-disciplinary panel of sub-speciality experts carried out a systematic primary literature review and Delphi consensus exercise. The guideline was developed in accordance with The Appraisal of Guidelines Research and Evaluation Instrument II criteria, with input from stakeholders including charities and patient groups. Based on scientific evidence and expert opinion, 58 recommendations have been collected to produce a clear, pragmatic set of management guidelines. It is intended as an evidence base for future optimal management and to improve the quality of clinical care of Paediatric patients with differentiated thyroid carcinoma.

Introduction

Differentiated thyroid cancer (DTC), whilst the commonest endocrine cancer in children, occurs in only a small number of patients in the UK. Approximately 13 cases per year are seen in children aged less than 15 years, and about 105 cases per year in those aged 15 to 24 years (Children, teenagers and young adults UK cancer statistics report 2021: http://www.ncin.org.uk/cancer_type_and_topic_specific_work/cancer_type_specific_work/cancer_in_children_teenagers_and_young_adults/; accessed 28.3.2021).

It increases in frequency with age: of the total cases seen in those aged 0-24 years, 1% occur in those aged 0 to 4 years, 2% in those 5 to 9 years, 8% in those 10 to 14 years, 28% in teenagers 15 to 19 years and 61% in young adults 20 to 24 years. There is a female predominance which increases with age: 69% of cases aged 0 to 14 years, and 80% of cases aged 15 to 24 years, are female (Children, teenagers and young adults UK cancer statistics report 2021: http://www.ncin.org.uk/cancer_type_and_topic_specific_work/cancer_type_specific_work/cancer_in_children_teenagers_and_young_adults/; accessed 28.3.2021).

The sex ratio is near equivalent in children under 10 years of age (Harach and Williams, 1995). The overall incidence of thyroid cancer in the 0-24 age group is 1.2 per 100,000 in females and 0.5 per 100,000 in males (National Registry of Childhood Tumours, 1991-2010). The incidence appears to be increasing (Vergamini, Frazier et al., 2014, Golpanian, Perez et al., 2016), and this is largely thought to be due to better detection of asymptomatic disease through increasing use of medical imaging.

Less than 1% of thyroid cancers are linked to a risk factor such as previous thyroid irradiation (Lazar, Lebenthal et al., 2009). Familial non-medullary thyroid cancer is described in 3-9% of cases presenting at any age (Moses, Weng et al., 2011, Peiling Yang and Ngeow, 2016). Genetic predisposition syndromes account for around 5% of non-medullary thyroid cancers (Vriens, Suh et al., 2009, Richards, 2010, Peiling Yang and Ngeow, 2016). 95% is accounted for by non-syndromic forms (Peiling Yang and Ngeow, 2016, Kamani, Charkhchi et al., 2022). 80-90% of differentiated thyroid cancers in children are papillary carcinoma and 5-20% follicular carcinoma (Hogan, Zhuge et al., 2009, Papendieck, Gruñeiro-Papendieck et al., 2011, Mussa, Salerno et al., 2013, de Jong, Gaze et al., 2021).

In all age groups in the UK overall DTC mortality has decreased by 46% since the early 1970's (Lee, Sharabiani et al., 2019). Although the risk of aggressive and recurrent disease in children and young people (CYP) with DTC is higher than in adults (Alessandri, Goddard et al., 2000, Jarzab, Junak et al., 2000, Hay, Gonzalez-Losada et al., 2010, Al-Qahtani, Tunio et al., 2015, Lee, Jung et al., 2015), the 10-year cause-specific survival is better (Brink, van Heerden et al., 2000, Chow, Law et al., 2004, Steliarova-Foucher, Stiller et al., 2006, Huang, Chao et al., 2012, Shayota, Pawar et al., 2013). No deaths were reported in children, teenagers and young adults with DTC from 2012 to 2014, and the age standardised mortality rate for all thyroid cancer per 100,000 population is 0 for the 0-24 age group (data from the National Registry of Childhood Tumours). However, deaths from DTC in childhood may still occur after this age range.

In order to promote best practice standards for the diagnosis and management of thyroid cancers, The American Thyroid Association (ATA) (Haugen, Alexander et al., 2016), the American Association of Clinical Endocrinologists (AACE) (Gharib, Papini et al., 2016), the National Comprehensive Cancer Network (NCCN) (Haddad, 2016), and the British Thyroid

Association/Royal College of Physicians (Perros, Boelaert et al., 2014), have published guidelines specifically addressing the evaluation, treatment and follow up of thyroid nodules and DTC in adults.

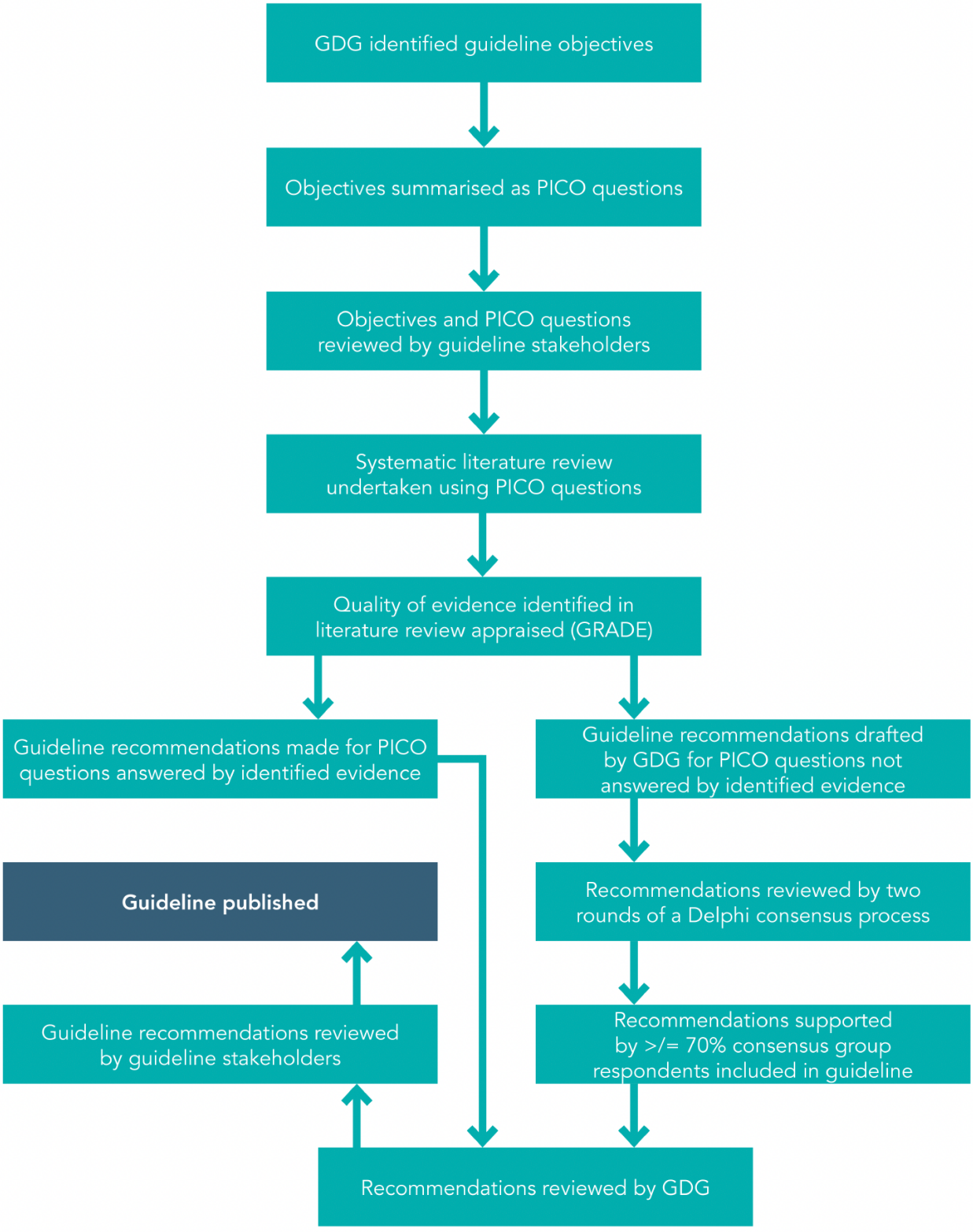
In most cases, the evaluation, treatment and follow up of children with thyroid cancer has followed adult guidelines. This approach results in excellent short and intermediate term outcomes but may have resulted in overtreatment for a disease with excellent prognosis in CYP, with significant late effects including second malignancy. More recently, specific Paediatric guidelines have been provided by the American Thyroid Association (Francis, Waguespack et al., 2015) and from the Netherlands (Lebbink, Dekker et al., 2020), but many areas of the treatment of CYP with DTC remain controversial. With recent progress in the management of CYP with this condition there is an ongoing need for up-to-date age-appropriate guidelines for the management of DTC in CYP that acknowledges the specific needs of this patient group.

Methods

A multidisciplinary Guideline Development Group (GDG) oversaw guideline development. The GDG members, as well as stakeholders and Delphi consensus panel, are listed in Supplementary Appendix 1. This guideline was developed in accordance with The Appraisal of Guidelines Research and Evaluation Instrument II (AGREE II) criteria, as specified in the Children's Cancer and Leukaemia (CCLG) guideline development standard operating procedure, version 6 (Group, Enterprise, Accessed May 12, 2021). The methodology is summarised in Figure 1. Different stages of the guideline development process were overseen and appraised by the Quality Improvement Committee of the Royal College of Paediatrics and Child Health (RCPCH).

Figure 1 – Guideline Development Process

GDG – guideline development group; GRADE - Grading of Recommendations, Assessment, Development and Evaluations (Guyatt, Oxman et al., 2011)



Conflicts of interest

All GDG and Delphi consensus group participants were asked to declare any conflicts of interests as per the National Institute of Health and Care Excellence (NICE) conflicts of interest policy. Conflicts were reviewed and no relevant conflicts identified. The CCLG provided administrative support throughout the guideline and the RCPCH provided advice and appraised the guideline at different stages.

Developing the Clinical Questions

The GDG devised the scope and, subsequently, the Population, Intervention, Comparison, Outcome (PICO) questions (Akobeng, 2005), which were sent out to stakeholders to ensure no relevant area had been omitted. Feedback from stakeholders was taken into account by the GDG in the finalisation of the PICO questions, which were used to direct a systematic literature search (Supplementary Appendix 2). Stakeholder Involvement: Views from the target population (DTC patients, survivors and their families) were sought via the stakeholder consultation process through various patient support groups including the Royal College of Physicians Young Adult and Adolescent Steering Group. Stakeholders were given the opportunity to comment on the PICO questions being asked and on the final guideline recommendations made, to facilitate brevity, clarity and fairness. Recommendation 22 and the section on health benefits (recommendation 38) are specific to the needs of children and their parents.

Identifying the Evidence

Literature searches were conducted as detailed in Supplementary Appendix 3. Of 2565 papers found using the search strategy (detailed in Supplementary Appendix 3) 238 papers met the inclusion criteria and were included in the guideline evidence base. The search strategy was limited by prior agreement of the overarching Project Board for all eight National Rare Paediatric Endocrine Tumour Guidelines to publications pertaining to CYP with DTC-related pathology before 19 years of age, including fully published case reports and case series. Full inclusion/exclusion criteria can be found in Supplementary Appendix 3. An additional 26 papers were included following the peer-review process prior to publication.

Reviewing and Synthesising the Evidence

The quality of evidence identified in the systematic search was appraised using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) criteria (Guyatt, Oxman et al., 2011). Details of this process can be found in Supplementary Appendix 4.

Developing Recommendations

Where the literature search identified evidence to answer the PICO questions, the GDG made a guideline recommendation. The strength of the recommendation was determined by the trade-off between the potential benefits and potential harms of the recommendation, taking into account the quality of the underpinning evidence. Where an evidence base to formulate recommendations was lacking (i.e. no evidence, contradictory evidence, or very low-quality evidence), an expert consensus was necessary. These recommendations were evaluated using a formal Delphi consensus process (Supplementary Appendix 5) (Okoli, 2004). A recommendation was deemed to have achieved consensus if 70% or more of the Delphi respondents (excluding those who indicated inadequate expertise in the posed question area to be able to comment) supported the recommendation as framed, or with minor modification.

The evidence supporting each recommendation is summarised following the recommendation. In situations where no or low-quality evidence was available, but a Delphi consensus was not achieved and there was no possibility of near-future comparison trials, the recommendation was made by GDG consensus. If there was additionally a clear widespread clinical best practice, that was also used to support strengthening the recommendation. We followed a consistent NICE terminology, using the verbs "offer" and "consider" respectively, for strong and less strong interventions/actions, and the verbs "should" for strong, "may" and "consider" for moderate recommendations. All recommendations were reviewed by the Project Board and four selected peer experts, prior to guideline publication. Areas highlighted by the literature review and consensus process in which the GDG felt further research would be valuable are reported under the heading, Research Recommendations (Supplementary Appendix 6).

Recommendations

The GDG made 40 recommendations based on identified evidence. 30 further recommendations were made based on GDG expert opinion, and these were reviewed by two rounds of a Delphi consensus process (Supplementary Appendix 5). Following this, 18 recommendations achieved consensus and were included in the guideline. Each recommendation is directly followed by a section discussing the related evidence and citations for this recommendation. One recommendation was made on the basis of GDG consensus only. Areas highlighted by the literature review and consensus process where the GDG felt further research would be valuable have been proposed as research recommendations (Supplementary Appendix 6).

Health benefits, side effects and risks have been considered for all recommendations on diagnosis, management and follow up. The relevant factors are discussed for each recommendation in the general text. Examples include recommendations to assess vocal cord function pre-operatively; diagnosing and managing post-operative complications; safety precautions when using radioiodine, including fertility preservation; and how to follow up these patients safely to balance over-investigation with timely diagnosis of recurrent disease. The guideline also highlights the need for surgery to take place at high-volume tertiary centres.

External Review

The guideline was then externally peer reviewed by four independent reviewers to improve the quality and applicability of the guideline (see Supplementary Appendix 1). The RCPCH, via the Quality Improvement Committee Clinical Leads for Evidence Medicine and Appraisals provided advice on guideline development and appraised the draft for quality at different stages. Feedback from the endorsing body and experts was used to complete the final document.

Results (recommendations)

Differentiated thyroid cancer – presentation

1. **Refer CYP with a diffusely or focally enlarged thyroid to an age-appropriate centre with expertise in the management of thyroid disease that can undertake all necessary investigations and treatment** *(Strong Recommendation, Delphi consensus 93%)*

2. **Care for CYP with suspected or proven DTC in an age-appropriate tertiary centre linked to a paediatric or teenage and young adult oncology centre. A designated specialist clinician who has expertise in the investigation and treatment of patients with thyroid cancer should coordinate multidisciplinary care (endocrinology, surgery and oncology)** *(Strong Recommendation, Delphi consensus 100%)*

   Recommendations 1 and 2 are based on national policy endorsed by NICE Improving Outcomes in Children and Young People with Cancer guidelines, 2005 (NICE, 2005).

3. **Investigate CYP with the following presentations for DTC:**
   a. **a solitary thyroid nodule (whether symptomatic or incidentally identified on imaging of the neck)**
   b. **an enlarged nodular thyroid**

   (Strong Recommendation, Very Low-Quality Evidence, Delphi Consensus 100%)

   Less common presentations of thyroid cancer include cervical lymphadenopathy, dysphonia, dyspnoea, stridor, as reported in several retrospective cohort studies (Lazar, Lebenthal et al., 2009, Papendieck, Gruñeiro-Papendieck et al., 2011). There is no reported association between nodule size and malignancy risk (Chiu, Sanda et al., 2012, Corrias and Mussa, 2013).

4. **Clinicians should have a higher index of suspicion for DTC in CYP with a history of prior head and neck irradiation or family history of DTC (see Genetics section below)** *(Strong Recommendation, Very Low-Quality Evidence, Delphi Consensus 100%)*

   Retrospective cohort studies of children and young people previously treated for cancer with head and neck radiotherapy, especially those where the thyroid gland is included in the treatment field, have been shown to be at increased risk of developing DTC (Sigurdson, Ronckers et al., 2005, Brignardello, Corrias et al., 2008, Lazar, Lebenthal et al., 2009, Taylor, Croft et al., 2009, Bhatti, Veiga et al., 2010, Papendieck, Gruñeiro-Papendieck et al., 2011, Veiga, Lubin et al., 2012, Kiratli, Volkan-Salanci et al., 2013, Goldfarb and Freyer, 2014, Klein Hesselink, Nies et al., 2016). Those at risk include patients treated for Hodgkin lymphoma, leukaemia, CNS tumours (Soberman, Leonidas et al., 1991, Solt, Gaitini et al., 2000, Sigurdson, Ronckers et al., 2005, Metzger, Howard et al., 2006, Taylor, Croft et al., 2009, Rose, Wertheim et al., 2012) and neuroblastoma patients treated with ^{131}I-mIBG (Clement, van Rijn et al., 2015). Environmental radiation, such as occurred after the Chernobyl accident, significantly increases the risk of DTC in CYP (Nikiforov and Gnepp, 1994). Endemic hypothyroidism secondary to iodine deficiency may also predispose to DTC (Santos, Freitas et al., 2017).

Differentiated thyroid cancer – assessment of CYP with thyroid enlargement

5. **Consider testing thyroid function in CYP presenting with a thyroid nodule or enlargement (Moderate Recommendation, Low-Quality Evidence, GDG consensus)**

   Assessment of thyroid function is standard practice in CYP presenting with thyroid abnormalities such as a nodule or goitre, in order to diagnose hypo- or hyperthyroidism. However, most children with differentiated thyroid cancer are euthyroid at diagnosis (Papendieck, Gruñeiro-Papendieck et al., 2011, Suzuki, Nakamura et al., 2016). A correlation between higher TSH levels and risk of malignancy has been identified in one low and four very low quality cohort studies of children with thyroid nodules (Chiu, Sanda et al., 2012, Mussa, Salerno et al., 2013, Mussa, De Andrea et al., 2015, Papendieck, Gruñeiro-Papendieck et al., 2015, Ly, Frates et al., 2016) and between TSH levels and cervical lymph node metastases in a very low quality cohort study of children diagnosed with differentiated thyroid carcinoma (Papendieck, Gruñeiro-Papendieck et al., 2011). In a CYP with a thyroid nodule found to have a low serum TSH, thyroid scintigraphy Iodine 123 or Technetium 99m pertechnetate can help to determine whether the nodule contains autonomously functioning tissue (Niedziela, Breborowicz et al., 2002). Scintigraphy should be reserved only for children whose serum TSH is low. The majority of patients present with normal or high serum TSH thyroid, with ultrasound being the optimal modality to confirm or refute the presence of thyroid nodule (see recommendation 11).

6. **Consider measurement of thyroid autoantibodies in CYP with thyroid enlargement, including those undergoing investigation for a thyroid malignancy** *(Moderate Recommendation, Delphi consensus 73%)*

   Investigation of a CYP with thyroid enlargement will involve the measurement of thyroid autoantibodies to diagnose autoimmune disease. However, children with differentiated thyroid carcinoma may present with co-existing autoimmune thyroid disease (Lazar, Lebenthal et al., 2009, Papendieck, Gruñeiro-Papendieck et al., 2011, Baş, Aycan et al., 2012). Additionally, a high pre-operative thyroid autoantibody titre in an euthyroid patient indicates an increased risk of hypothyroidism post-surgery (Verloop, Louwerens et al., 2012).

7. **Do not routinely measure calcitonin in CYP undergoing investigation of thyroid abnormalities** *(Strong Recommendation, Delphi Consensus 91%)*

   Calcitonin should be measured if a diagnosis of Medullary Thyroid Cancer (MTC) is suspected or diagnosed, or if the patient has a genetic predisposition to MTC. Routine measurement of calcitonin in patients who present with a thyroid abnormality is not recommended by these Guidelines, in view of the very low likelihood of detecting MTC in the absence of other clinical indicators and risk of false positive or indeterminate results, and the associated anxiety provoked by such results.

8. **Discuss CYP diagnosed with DTC in both the adult thyroid and paediatric / Teenager and Young Adult (TYA) multidisciplinary team (MDT)s, or in a properly constituted all-age thyroid MDT** *(Strong Recommendation, Delphi Consensus 87%)*

   DTC is rare in children. The combination of specialist expertise in the diagnosis and treatment of thyroid cancer in the adult thyroid MDT, in addition to expertise in the care of CYP with malignancy in the paediatric /TYA MDT will provide best care for young patients.

9. **Take a three-generation family history for relevant conditions in CYP with DTC** *(Strong Recommendation, High Quality Evidence)*

10. **Refer to a clinical geneticist all CYP who have syndromic features (see Table 1), a family history of DTC or a family history of syndromic features associated with DTC** *(Strong Recommendation, High Quality Evidence)*

    Approximately 5% of CYP with familial DTC will have an underlying syndromic genetic predisposition (Peiling Yang and Ngeow, 2016). There is high quality evidence for the association between certain syndromes and the development of DTC (Yamashita and Saenko, 2007, Morrison and Atkinson, 2009, Richards, 2010, Lauper, Krause et al., 2013, Rutter, Jha et al., 2016) - Cowden syndrome (PTEN hamartoma syndrome-) (Marsh, Coulon et al., 1998, Ngeow, Mester et al., 2011, Smith, Marqusee et al., 2011), Familial Adenomatosis Polyposis (FAP) (Kennedy, Potter et al., 2014), Carney complex (Stratakis, Courcoutsakis et al., 1997), and Multinodular goitre families (DICER1 pathogenic variants) (Rio Frio, Bahubeshi et al., 2011, de Kock, Sabbaghian et al., 2014, Stewart, Best et al., 2019). Putative low-moderate penetrant non-medullary thyroid cancer (NMTC) susceptibility genes have recently been described in dominant papillary thyroid carcinoma (PTC) families (Fallah, Pukkala et al., 2013, Zivaljevic, Tausanovic et al., 2013, Peiling Yang and Ngeow, 2016). Werner syndrome, a rare autosomal recessive disease, is known to predispose to DTC (median age of onset 20 years) (Lauper, Krause et al., 2013). A CYP with DTC and syndromic features and no family history of the condition may represent a case of de novo presentation or somatic mosaicism. A de novo presentation of Familial Adenomatous Polyposis (FAP) is known to occur in 20-25% of cases (Aretz, Uhlhaas et al., 2004).

    Clinical examination of a CYP with DTC should include measurement of their height, weight and head circumference (maximum occipito-frontal diameter), with the results plotted on an appropriate growth centile chart. The clinical features associated with rare syndromic forms of DTC predisposition are summarised in Table 1. Clinicians may be able to identify those patients with an underlying syndromic cause for their DTC by careful examination. However, as the penetrance of these features is variable and many clinical features will develop in older childhood or adulthood, the diagnosis may only become apparent if other family members are also examined. Family history should include details of previous genetic testing if cases of DTC or syndromic causes of DTC, multinodular goitre or thyroidectomy are identified in the patient's relatives. All possible efforts should be made to establish the precise thyroid tumour pathology and that of other relevant tumours previously diagnosed in the family.

    The UK Genomic Medicine service strongly supports diagnostic testing in the clinical setting i.e. within the paediatric endocrine, surgical or oncology teams as well as within the genetics service. There are now several genetic panels that can be tested for in patients

with paediatric DTC or multinodular goitre within the current test directory https://www.england.nhs.uk/publication/national-genomic-test-directories/ [v3 April 2022]. Therefore, in the UK referral to the clinical genetics service is not a requirement to carry out genetic testing on children with DTC or multinodular goitre, and the MDT can direct early genetic testing with additional referral to clinical genetics if there are variants of interest identified.

Table 1 - Genetic syndromes associated with Differentiated Thyroid Cancer.

Syndromic features are listed in approximate order of appearance, with some features only appearing in adulthood. Gene names are shown in italics

Syndrome	Germline pathogenic variant and mode of inheritance	Type of Thyroid cancer	Syndromic features noted on clinical examination	Further clinical features
PTEN Hamartoma Tumour Syndrome (Includes Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome and *PTEN*-related Proteus syndrome. These overlapping phenotypes are all known to be due to pathogenic *PTEN* variants)	*PTEN* (Autosomal dominant)	Multinodular goitre, adenomatous nodules, and follicular adenomas Papillary thyroid cancer (classical and follicular variant) Follicular thyroid cancer	Macrocephaly (OFC>97th centile) and dolichocephaly, learning difficulties, autism and developmental delay, lipomas, vascular features including haemangiomas and arteriovenous malformations, gingival hypertrophy, oral papillomas, facial papules, acral keratoses, palmoplantar keratosis, trichilemmomas, pigmented macules of the glans penis and overgrowth of tissues.	Benign and malignant tumours of the breast, colon, endometrium and kidney, adult Lhermitte-Duclos disease due to cerebellar dysplastic gangliocytoma.

Familial Adenomatous Polyposis [FAP] (Includes Gardner syndrome and Turcot syndrome. These overlapping phenotypes are all known to be due to pathogenic *APC* variants)	*APC* (Autosomal dominant, with 20% cases arising *de novo*)	Papillary thyroid cancer including cribiform pattern subtype	Congenital hypertrophy of the retinal pigment epithelium (CHRPE), congenital absence of teeth, delayed eruption of teeth, dentigerous cysts, supernumerary teeth, odontomas, epidermoid cysts, fibrous dysplasia of the skull, mandibular osteomas, fibromas, desmoid tumours and pilomatrixomas.	Hepatoblastoma, medulloblastoma, multiple adenomatous polyps throughout the gastrointestinal tract, principally affecting the colon with high likelihood of malignant transformation, as well as upper GI tract adenomas and adrenal adenomas.
Carney Complex	*PRKAR1A* (Autosomal dominant, with 30% cases arising de novo)	Papillary thyroid cancer, follicular thyroid cancer and follicular adenoma	Pale brown to black lentigines of skin, lips and oral mucosa, soft tissue myxomas, schwannomas and epithelioid-type blue nevi.	Benign adrenal tumours (Primary pigmented nodular adrenocortical disease), pituitary tumours (often somatotropinomas), large cell calcifying Sertoli cell tumours, breast ductal adenoma, osteochondromyxoma and Psammomatous melanotic schwannoma of the nerve sheath.

DICER1	*DICER1* (Autosomal dominant)	Multinodular goitre and papillary thyroid cancer	None	Pleuropulmonary blastoma, ovarian Sertoli-Leydig cell tumours, cystic nephroma, ciliary body medulloepitheliom a, botryoid-type embryonal rhabdomyosarcom a, nasal chondromesenchy mal hamartoma, pituitary blastoma, pineoblastoma, Wilms tumour and juvenile intestinal hamartomas.
Werner	*WRN* (Autosomal recessive)	Papillary thyroid cancer, Follicular thyroid cancer and anaplastic thyroid cancer	Short stature (lack of pubertal growth spurt), cataracts, premature aging, tight atrophic skin, ulceration, hyperkeratosis, pigmentary alterations, regional subcutaneous atrophy, and characteristic 'bird-like facies', hypogonadism, secondary sexual underdevelopment, premature greying and thinning of scalp hair, pes planus and abnormal voice.	Malignant melanoma, meningioma, soft tissue sarcomas, leukaemia and pre-leukaemic conditions of the bone marrow, primary bone neoplasms, osteoporosis, soft tissue calcification, evidence of premature atherosclerosis and diabetes mellitus.

Differentiated thyroid cancer – imaging of CYP with thyroid enlargement

11. **Undertake neck ultrasound in all CYP with thyroid enlargement with normal thyroid function if malignancy is suspected.** *(Strong Recommendation, High Quality Evidence)*

Ultrasound (US) characteristics, as identified by an experienced head and neck or thyroid radiologist, are important in the differentiation of benign from malignant disease in CYP (Lyshchik, Drozd et al., 2005, Corrias, Mussa et al., 2010, Saavedra, Deladoey et al., 2011, Goldfarb, Gondek et al., 2012, Gupta, Ly et al., 2013). Ultrasound findings that predict increased risk of thyroid cancer (Figure 2) include solid nodules, nodules with internal

calcification, the presence of enlarged or abnormal lymph node/s, irregular nodule margins, nodules that are taller than wide on transverse view (Al Nofal, Gionfriddo et al., 2016), hypoechoic nodules, and increased intranodular blood flow on colour Doppler (Mussa, De Andrea et al., 2015, Koltin, O'Gorman et al., 2016, Moudgil, Vellody et al., 2016). Ultrasound can assist to distinguish enlarged reactive lymph nodes, preventing their unnecessary biopsy, from DTC lymph node metastases, which have characteristic US appearances (Abbasian Ardakani, Reiazi et al., 2018).

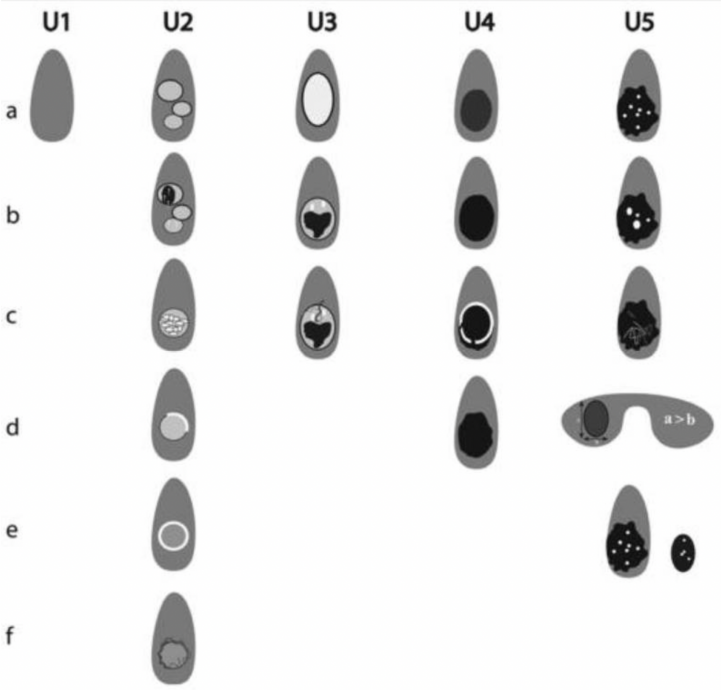
The differential diagnosis of multinodular goitre in CYP includes diffusely infiltrating papillary thyroid cancer that presents with enlargement of a lobe or the entire thyroid, very frequently associated with microcalcifications on neck US (Wang, Chang et al., 2022). Multinodular thyroid enlargement in CYP, especially if associated with palpable cervical lymph nodes, in a CYP with normal thyroid function therefore requires investigation by neck US.

The benefits of this recommendation are that ultrasound provides excellent visualisation of structures in the neck without exposure to further ionising radiation and facilitates cytological examination of abnormal findings. There are no anticipated risks or side effects of following this recommendation.

12. Report neck ultrasounds using the U1-U5 US reporting system as recommended by the British Thyroid Association *(Strong Recommendation, Moderate Quality Evidence, GDG consensus)*

The use of the U1–U5 scoring/grading system is recommended for assessing risk of malignancy in adults with thyroid enlargement (Figure 2) (Perros, Boelaert et al., 2014) . The GDG agreed it was appropriate to apply the same system to CYP undergoing investigation for DTC.

Figure 2 - British Thyroid Association 2014 classification ultrasound scoring of thyroid nodules, reproduced from literature (Perros, Boelaert et al., 2014)



U1. Normal.

U2. Benign:
(a) halo, iso-echoic / mildly hyper-echoic
(b) cystic change +/- ring down sign (colloid)
(c) micro- cystic / spongiform
(d & e) peripheral egg shell calcification
(f) peripheral vascularity.

U3. Indeterminate/Equivocal:
(a) homogenous, hyper-echoic (markedly), solid, halo (follicular lesion).
(b) ? hypo-echoic, equivocal echogenic foci, cystic change
(c) mixed/central vascularity.

U4. Suspicious:
(a) solid, hypo-echoic (cf thyroid)
(b) solid, very hypo-echoic (cf strap muscle)
(c) disrupted peripheral calcification, hypo-echoic
(d) lobulated outline

U5. Malignant
(a) solid, hypo-echoic, lobulated / irregular outline, micro-calcification. (? Papillary carcinoma)
(b) solid, hypo-echoic, lobulated/irregular outline, globular calcification (? Medullary carcinoma)
(c) intra-nodular vascularity
(d) shape (taller >wide) (AP>TR)
(e) characteristic associated lymphadenopathy

Differentiated thyroid cancer – pre-operative investigation of patients with known DTC

13. **Use ultrasound guidance in CYP undergoing Fine Needle Aspiration (FNA) for the investigation of DTC** *(Strong Recommendation, High Quality Evidence)*

    The BTA and ATA paediatric guidelines both recommend US guided fine needle aspiration cytology (FNAC) to minimise rates of indeterminate samples and reduce rates of unsatisfactory samples (Izquierdo, Shankar et al., 2009, Perros, Boelaert et al., 2014, Francis, Waguespack et al., 2015). As the use of ultrasound guided FNAC is well established in the adult population to accurately identify targets for cytological assessment, it is logical to apply ultrasound guided FNAC in CYP.

14. **Offer sedation or general anaesthesia if FNA is required, depending on the needs of the individual child** *(Moderate Recommendation, Low Quality Evidence, GDG Consensus)*

    There is no literature to clearly address the question of age cut off for tolerating FNAC under local anaesthesia. In children under 10 years of age, and/ or in CYP who are unable to tolerate FNAC under local anaesthesia for other reasons, who require thyroid /neck FNA, sedation or general anaesthesia should be considered (Redlich, Boxberger et al., 2012). Whilst general anaesthesia in a specialist centre caries a very low risk of harm, the associated risks and potential side effects should be discussed with patients and families as for any other procedure requiring general anaesthesia.

15. **Undertake US-guided FNA on a thyroid nodule reported on ultrasound as U3 - indeterminate, U4 – suspicious or U5 – malignant** *(Strong Recommendation, High Quality Evidence)*

    The utility of pre-operative FNAC of thyroid nodules in CYP in differentiating benign and malignant disease has been evaluated via multiple studies including one meta-analysis (Raab, Silverman et al., 1995, Khurana, Labrador et al., 1999, Hosler, Clark et al., 2006, Stevens, Lee et al., 2009, Altincik, Demir et al., 2010, Bargren, Meyer-Rochow et al., 2010, Hoperia, Larin et al., 2010, Kapila, Pathan et al., 2010, Gutnick, Soldes et al., 2012, Monaco, Pantanowitz et al., 2012, Redlich, Boxberger et al., 2012, Cole and Wu, 2014, Rossi, Straccia et al., 2014, Buryk, Simons et al., 2015, Norlen, Charlton et al., 2015, Partyka, Huang et al., 2016, Trahan, Reddy et al., 2016). In CYP, pre-operative FNAC has high sensitivity and specificity, as well as high positive predictive and negative predictive values for the diagnosis of malignancy (Stevens, Lee et al., 2009, Moudgil, Vellody et al., 2016), although there is variability in interpretation of cytopathology findings between institutions (Jia, Baran et al., 2021, Vuong, Chung et al., 2021, Cherella, Hollowell et al., 2022). In CYP, as in adults, the finding of follicular cytology on FNAC is not able to distinguish follicular adenoma from follicular carcinoma (Smith, Pantanowitz et al., 2013), and thus diagnostic hemithyroidectomy will be required. Observation with an interval ultrasound as an alternative to FNAC can be offered if a solitary sub-centimetre U3 indeterminate lesion is identified.

16. **Report cytology samples using the Thy 1-5 grading system. Thyroid cytology must be reported by a cytopathologist with expertise in thyroid disease** *(Strong Recommendation, Delphi Consensus 93%)*

    The Royal College of Pathology document recommends thyroid cytology be reported in prose, together with an allocated Thy category (Thy 1−Thy 5) (https://www.rcpath.org/resourceLibrary/g089-guidancereportingthyroidcytology-jan16.htmln) (Table 2). If FNA sampling is inadequate (Thy1), in the absence of clinical or radiological features of concern, US guided FNA may be repeated between 3 and 6 months (Perros, Boelaert et al., 2014, Francis, Waguespack et al., 2015).

Table 2 – Royal College of Pathologists thyroid cytology reporting system

(https://www.rcpath.org/resourceLibrary/g089-guidancereportingthyroidcytology-jan16.htmln)

Thyroid 1	Non diagnostic for cytological diagnosis
Thyroid 1c	Cystic lesion
Thyroid 2	Non neoplastic
Thyroid 2c	Non neoplastic, cystic lesion
Thyroid 3a	Neoplasm possible-atypia/ non diagnostic
Thyroid 3f	Neoplasm possible, suggesting follicular neoplasm
Thyroid 4	Suspicious of malignancy
Thyroid 5	Malignant

17. **Consider diagnostic hemi-thyroidectomy in CYP if there is a discrepancy between clinical and/or radiological features and cytology** *(Moderate Recommendation, Delphi consensus 71%)*

    Benign cytology (Thy2) that does not correlate with clinical /radiological findings of concern, or repeated findings of indeterminate cytology (Thy3f), indicates a need for diagnostic surgery (hemithyroidectomy) (Lale, Morgenstern et al., 2015). If cytology demonstrates Thy3a, but clinical /radiological suspicion is assessed by the MDT to be low, US guided FNA may be repeated between 3 and 6 months. This recommendation is supported by adult thyroid cancer guidelines (ATA & BTA) and ATA guidelines for children with thyroid nodules (Perros, Boelaert et al., 2014, Francis, Waguespack et al., 2015, Haugen, Alexander et al., 2016). The MDT will need to review management of patients with cytology that repeatedly demonstrates Thy3a on an individualised basis. There is growing evidence of the potential utility of somatic oncogene analysis to aid management decision in FNA with indeterminate cytology (Mostoufi-Moab, Labourier et al., 2018, Pekova, Sykorova et al., 2021, Mollen, Shaffer et al., 2022) (see recommendation 34).

18. **Consider the use of MRI neck with contrast prior to surgery in CYP with known DTC with evidence of local invasion or lymph node metastases** *(Moderate Recommendation, Low Quality Evidence, GDG consensus)*

    In CYP with DTC and features suggestive of extrathyroidal invasion, lymph node involvement is common (Jarzab, Junak et al., 2000, Koo, Hong et al., 2009, Hay, Gonzalez-Losada et al., 2010). In the presence of clinically or radiologically detected nodal disease e.g. bilateral cervical lymphadenopathy, especially with the involvement of lower cervical and supraclavicular nodes, a large or fixed thyroid swelling, or symptoms of vocal cord paralysis (stridor, hoarse voice), further imaging with MRI contrast should be performed pre-operatively . This is particularly due to the importance of imaging the lateral neck and upper mediastinum, as knowledge of the extent of lymph node metastases is vital prior to surgery. Furthermore, and local invasion of a tumour into local structures (trachea, oesophagus), whilst rare, is essential to guide surgery (e.g. length of surgery, appropriate specialist backup).

    Although the incidence of lung metastases in CYP presenting with DTC is much higher than in adults at approximately 12-23% (Vassilopouloii-sellin, Klein et al., 1993, Bal, Kumar et al., 2004, Leboulleux, Baudin et al., 2005, Vali, Rachmiel et al., 2015a, de Jong, Gaze et al., 2021, Nies, Vassilopoulou-Sellin et al., 2021), these will be accurately imaged at the staging radioiodine scan (Kim, Gelfand et al., 2011, Mostafa, Vali et al., 2016, Jiang, Xiang et al., 2021), which now includes a SPECT/CT as well as planar scintigraphy as a matter of course. Rarely, large volume metastases visible on a plain chest radiograph may require cover with steroid therapy to avoid issues with flare/oedema with RAI (Fard-Esfahani, Emami-Ardekani et al., 2014).

19. **Consider the use of pre-operative laryngoscopy to assess vocal cord function in CYP with DTC who have voice symptoms or extra-thyroidal disease or who have had previous neck surgery** *(Moderate Recommendation, Moderate Quality Evidence)*

    The Clinical Practice Guideline on improving voice outcomes after thyroid surgery (Chandrasekhar, Randolph et al., 2013) recommends pre-operative examination of vocal

fold mobility in patients with a normal voice when there is thyroid cancer with suspected extra- thyroidal extension or prior neck surgery. Children under age 18 years were specifically excluded from the target population of the Guideline although the authors state that many of the findings might be applicable. The National Comprehensive Cancer Network and the British Thyroid Association, have recommended pre-operative laryngeal examination for patients with proven or suspected thyroid malignancy.

Reasons given to support the use of pre-operative laryngoscopy are 1) to confirm in the event of a finding of post-operative vocal cord palsy (VCP) that it is indeed new caused by the procedure and 2) when a pre-operative VCP is identified, to raise awareness in the patient and surgeon of the risk of bilateral palsy if contralateral surgery is planned. Routine laryngoscopy prior to thyroid surgery performed on adult patients identified a 2.3-2.8% prevalence of pre-operative VCP (Lang, Chu et al., 2014, Heikkinen, Halttunen et al., 2019).

Studies that include routine pre-operative (and post-operative) laryngoscopy in paediatric patients prior to thyroidectomy are rare. Machens et al do not report finding VCP on routine pre-operative laryngoscopy in 230 surgically treated CYP (Machens, Elwerr et al., 2016). A recent study of complication rates after 464 paediatric thyroidectomies reports pre-operative laryngoscopy was performed on patients due to undergo completion surgery or on those with hoarseness or dysphagia pre-operatively (Baumgarten, Bauer et al., 2019). The patient group included 178 operations for malignant disease. The paper does not include the number of pre-operative laryngoscopies performed or a finding of pre-operative VCP.

There is increasing evidence in adults that trans-laryngeal ultrasound is as effective as laryngoscopy in screening patients pre-operatively for VCP, especially if there is no clinical suspicion (Gambardella, Offi et al., 2020). It has very high sensitivity and specificity and is likely to be better tolerated than laryngoscopy, especially in younger children. Moreover, there is recent evidence in favour of the use of intra-operative neuromonitoring, particularly if continuous, to reduce the risk of VCP in CYP (Ritter, Hod et al., 2021, Schneider, Machens et al., 2021).

Differentiated thyroid cancer – surgical management

20. **Surgery in CYP with DTC must be undertaken by a high-volume thyroid surgeon (>30 cervical endocrine procedures per year in adults and children) with collaborative care between adult and paediatric surgeons** *(Strong Recommendation, Moderate Quality Evidence, GDG consensus)*

Low quality evidence from the United States indicates that high volume surgeons (>30 cervical endocrine procedures per year in adults and children) have the best outcomes for CYP with DTC (Sosa, Tuggle et al., 2008, Burke, Sippel et al., 2012, Breuer, Tuggle et al., 2013, Al-Qurayshi, Hauch et al., 2016, Baumgarten, Bauer et al., 2019, Maksimoski, Bauer et al., 2022), especially in cases with active collaboration between endocrine and paediatric surgeons (Wood, Partrick et al., 2011). In one US study, case volume of the endocrine surgeons was an independent predictor of length of stay and costs, as well as reducing complications (Tuggle, Roman et al., 2008). Therefore, the risks of not following this recommendation are an increased incidence of short- and long-term complications of thyroid surgery (see recommendation 22 for more details).

21. **The surgical team must be led by a thyroid MDT nominated all-age thyroid surgeon (with paediatric, adolescent and adult experience)** *(Strong Recommendation, Delphi Consensus 88%)*

    The GDG agreed that a thyroid surgeon from the adult thyroid MDT nominated to operate on CYP with DTC should lead the designated surgical team. Due to the absence of UK evidence, this question was reviewed by a Delphi consensus process.

22. **Discuss with patients and their carers the risks of thyroid surgery. These include hypocalcaemia (transient or permanent hypoparathyroidism), recurrent laryngeal nerve injury (transient or permanent), post-operative bleed requiring emergency surgery, wound infection and the need for lifelong levothyroxine. If lateral neck lymph node dissection is planned, risks include injury to the spinal accessory / phrenic / sympathetic nerves, and lymphatic leak** *(Strong Recommendation, Low Quality Evidence, GDG Consensus*)

    The most commonly reported complications in CYP undergoing thyroid surgery are post-operative hypocalcaemia associated with transient or permanent hypoparathyroidism), and injury to the recurrent laryngeal nerve/s (transient or permanent hoarse voice, aspiration on swallowing, post-operative chest infection) (Newman, Black et al., 1998, van Santen, Aronson et al., 2004, Morris, Waguespack et al., 2012). Post-operative bleeding and wound infection are rare (1%) (Hanba, Svider et al., 2017, Schneider, Machens et al., 2018). Damage to the spinal accessory / phrenic or sympathetic nerves and lymphatic leak are specific complications of lateral neck dissections. Additionally, there is a risk of injury to the external branch of the superior laryngeal nerve which produces more subtle voice changes such as weakness of voice, or inability to raise or project the voice.

    CYP have higher endocrine-specific complication rates than adults after thyroidectomy (Sosa, Tuggle et al., 2008). Younger children (aged 0-6 yr) have higher complication rates than those in mid childhood (7-12 yr) and older CYP (13-17 yr). Analysis of nationwide outcomes (from the USA) after thyroidectomy in children < 1 year old revealed infection rates of 29.9%, respiratory sequelae in 35.2%, and a high incidence of VCP—14.3% (Hanba, Svider et al., 2017).

    The incidence of transient hypoparathyroidism ranges from 4.5 to 35%, permanent hypoparathyroidism from 0 to 32%, recurrent laryngeal nerve (RLN) injury from 0-25%, tracheostomy 8%, and Horner's syndrome 2-8% (Newman, Black et al., 1998, van Santen, Aronson et al., 2004, Savio, Gosnell et al., 2005, Massimino, Collini et al., 2006, Burke, Sippel et al., 2012, Morris, Waguespack et al., 2012).

    Consent for surgery should be obtained as detailed in Section 3.5.1 -Establish and maintain partnerships with patients in 'Good Surgical Practice' (page 40-3 - The Royal College of Surgeons of England 2014) - https://www.rcseng.ac.uk/standards-and-research/gsp/.

23. **Record in the surgical operation note whether or not the recurrent laryngeal nerves are dissected and preserved, and the number of parathyroid glands identified, preserved and autografted** *(Strong Recommendation, Delphi Consensus 100%)*

    Minimum standards for the content of operative notes are detailed in 'Good Surgical Practice' (page 21-2 - The Royal College of Surgeons of England 2014) - https://www.rcseng.ac.uk/standards-and-research/gsp/

24. **Offer total thyroidectomy for surgical management of CYP with cytologically proven DTC** *(Moderate Recommendation, Moderate Quality Evidence)*

    There are no randomised controlled trials to assess the optimal initial surgical management of DTC in CYP and there is no definitive evidence for the recommendation of more radical versus more conservative surgery. A systematic review (Jin, Masterson et al., 2015a) of 7 retrospective case series (489 patients) found no evidence in CYP that overall survival is influenced by total thyroidectomy as compared to less extensive surgery such as hemithyroidectomy. Overall survival in 3861 cases from the National Cancer Database similarly failed to show advantage from total thyroidectomy (Nice, Pasara et al., 2015). However, selection bias may account for some of the lack of survival benefit from total thyroidectomy, and in some studies follow up may not have been sufficient to draw this conclusion (Nice, Pasara et al., 2015). Nevertheless, there is some recent evidence to suggest there may be criteria by which to define very-low risk patients who may be candidates for lobectomy rather than total thyroidectomy (Kluijfhout, Pasternak et al., 2017).

    Papillary Thyroid Cancer (PTC): In CYP, PTC is multifocal / bilateral in approximately 65% and 30% of patients respectively. Lymph node metastasis at the time of diagnosis is evident in 40-90% and 20-30% present with distant metastasis (Dinauer, Breuer et al., 2008, Rivkees, Mazzaferri et al., 2011). Total thyroidectomy performed by a high-volume surgeon is the optimal treatment for PTC in CYP (Welch, Mcclellan et al., 1999, Jarzab, Junak et al., 2000, Haveman, van Tol et al., 2003, Kowalski, Goncalves Filho et al., 2003, Hay, Gonzalez-Losada et al., 2010, Astl, Chovanec et al., 2014). This surgical technique allows resection of the presenting macroscopic lesion in addition to the frequent microscopic foci of cancer, which can be found in the ipsilateral and contralateral lobes. Total or near total thyroidectomy is advised to reduce the risk of local recurrence, to enable the use of radioiodine for ablation and therapy and allow subsequent monitoring of serum thyroglobulin (Bignol-Kologu, Tanyel et al., 2000, La Quaglia, Black et al., 2000, Jarzab, Handkiewicz-Junak et al., 2005, Hogan, Zhuge et al., 2009, Mihailovic, Nikoletic et al., 2014). As a significant number of CYP with PTC present with distant metastases, total or near total thyroidectomy is advised in these patients as they will require radioiodine therapy. Management of patients who will require specific radiation protection (for example pregnant mothers) should be by an experienced paediatric molecular radiotherapy service.

    Neck recurrence is more common in patients with lymph node involvement or multifocal disease at presentation, extrathyroidal invasion and distant metastases (Palmer, Zarroug et al., 2005, Demidchik, Demidchik et al., 2006, Spinelli, Rossi et al., 2016). Low quality studies have identified that lower recurrence rates and decreased need for reoperative surgery are associated with near/total thyroidectomy as compared to more conservative surgical approaches (Welch, Mcclellan et al., 1999, Jarzab, Junak et al., 2000, Haveman, van Tol et al., 2003, Spinelli, Bertocchini et al., 2004, Hay, Gonzalez-Losada et al., 2010, Astl,

Chovanec et al., 2014). Reoperative surgery is associated with higher rates of complications e.g. recurrent laryngeal nerve injury and long term hypoparathyroidism (Bignol-Kologu, Tanyel et al., 2000).

Follicular Variant Papillary Thyroid Carcinoma (FVPTC): FVPTC in CYP has a low risk for bilateral disease and metastasis (Lerner and Goldfarb, 2015a, Samuels, Surrey et al., 2018). The surgical treatment of these patients should be decided on a case-by-case basis.

Follicular Thyroid Cancer (FTC): In two retrospective series of CYP with FTC which included 50 patients (Enomoto, Enomoto et al., 2013, Spinelli, Rossi et al., 2016) with mean follow up of 23.7 years and 6 years respectively, cause specific survival was 100% although recurrent tumour was identified in 3 patients (2 with distant metastases). Total thyroidectomy (single or two stage) was performed in 21 patients, external beam radiotherapy was used in 8 cases and therapeutic RAI in 8 cases. Only the patients in the more recent study received levothyroxine for TSH suppression. Total thyroidectomy was advised for patients with multifocal tumours, tumour diameter > 4cm, and for patients with > 3 foci of vascular invasion, extrathyroidal tumour extension and distant metastases. Thyroid lobectomy and isthmectomy is appropriate treatment for patients with minimally invasive FTC and none of the above risk factors (Spinelli, Rallo et al., 2019).

Data from observational studies suggests that the use of total thyroidectomy has increased from 50-60% to 85% in the last 20 years (Raval, Bentrem et al., 2010). Total thyroidectomy is more likely to be performed in high volume centres (hospital factor) and if large tumours or nodal metastases are present at time of resection (tumour factors) (Newman, Black et al., 1998, Massimino, Collini et al., 2006, Raval, Bentrem et al., 2010, Burke, Sippel et al., 2012).

Patients, parents and carers should be counselled that total thyroidectomy is associated with higher rates of permanent hypoparathyroidism and recurrent laryngeal nerve injury (Newman, Black et al., 1998, Welch, Mcclellan et al., 1999, Collini, Massimino et al., 2006, Massimino, Collini et al., 2006, Canadian Pediatric Thyroid Nodule Study, 2008, Enomoto, Enomoto et al., 2012) than lesser surgical procedures. This may be especially pertinent in young children (Scholz, Smith et al., 2011).

25. **Undertake therapeutic central neck dissection in CYP with DTC and confirmed neck lymph node metastases (N1)** *(Strong Recommendation, Moderate Quality Evidence, GDG Consensus)*

Increasing tumour size, extrathyroidal extension, and multifocal disease are independent factors associated with nodal metastases in paediatric DTC. If these risk factors are present, children with DTC should undergo careful pre-operative evaluation for evidence of lateral cervical lymph node metastases, and the central compartment should be evaluated intraoperatively (Kim, Sun et al., 2017).

Cervical lymph node metastases (N1) are associated with reduced disease-free survival (Wada, Sugino et al., 2009, Enomoto, Enomoto et al., 2012, Sugino, Nagahama et al., 2015, Spinelli, Tognetti et al., 2018). When therapeutic lymphadenectomy is performed, disease free survival is equivalent to those patients without pre-operative evidence of lymph node disease (cN0) (Handkiewicz-Junak, Wloch et al., 2007, Wada, Sugino et al., 2009).

Central neck dissection (CND) has been demonstrated to reduce the rate of subsequent locoregional disease and increases the efficacy of radioiodine therapies in CYP with known lymph node metastases (Jarzab, Junak et al., 2000, Popovtzer, Shpitzer et al., 2006, Handkiewicz-Junak, Wloch et al., 2007). Central neck dissection and the number of central nodes removed are significantly associated with permanent hypoparathyroidism in CYP with DTC (Ben Arush, 2000, Machens, Elwerr et al., 2016) and it is important that the procedure is undertaken by an experienced surgeon.

Skip metastases (lateral neck node metastasis in the absence of central neck node involvement) in PTC is reported in adults in 7% - 20% (Chung, Kim et al., 2009, Park, Lee et al., 2012). On that basis, and that of low-quality evidence in CYP, central neck dissection should be considered when there is evidence of lateral neck node disease (Vassilopoulou-Sellin, Goepfert et al., 1998, Landau, Vini et al., 2000, Demidchik, Demidchik et al., 2006, Handkiewicz-Junak, Wloch et al., 2007).

26. **Consider selective lymphadenectomy of the lateral compartment in CYP with DTC with confirmed lateral neck node metastases** *(Moderate Recommendation, Moderate Quality Evidence)*

    Moderate quality evidence suggests that lateral neck lymphadenectomy is associated with a significantly reduced rate of locoregional recurrence in cases of confirmed lymph node metastasis (Landau, Vini et al., 2000, Handkiewicz-Junak, Wloch et al., 2007).

27. **Consider prophylactic central neck node dissection in CYP with Papillary Thyroid Carcinoma (PTC), particularly those with multifocal disease** *(Moderate Recommendation, Moderate Quality Evidence)*

28. **Do not consider prophylactic lateral neck lymphadenectomy in CYP with DTC** *(Moderate Recommendation, Low-Moderate Quality Evidence)*
    CYP with DTC often have locoregional and distant spread at presentation, especially those with bilateral, multifocal or extrathyroidal disease (Ito, Kihara et al., 2012, Jin, Masterson et al., 2015b, Balachandar, La Quaglia et al., 2016, Jiang, Newbury et al., 2016, Qu, Zhang et al., 2016). However, it may be difficult to identify which cases are particularly at risk, in view of the observation that in CYP smaller tumour size may not correlate with reduced metastatic risk (Farahati, Parlowsky et al., 1998, O'Gorman, Hamilton et al., 2010). Although the efficacy of radioiodine therapy can be increased after prophylactic node dissection, the MDT should consider carefully the morbidity of the procedure and potential benefits, particularly in younger children, with individualized decision making (Machens, Elwerr et al., 2016). Recent evidence suggests there is no indication for prophylactic dissection in paediatric patients with FVPTC (Samuels, Surrey et al., 2018).

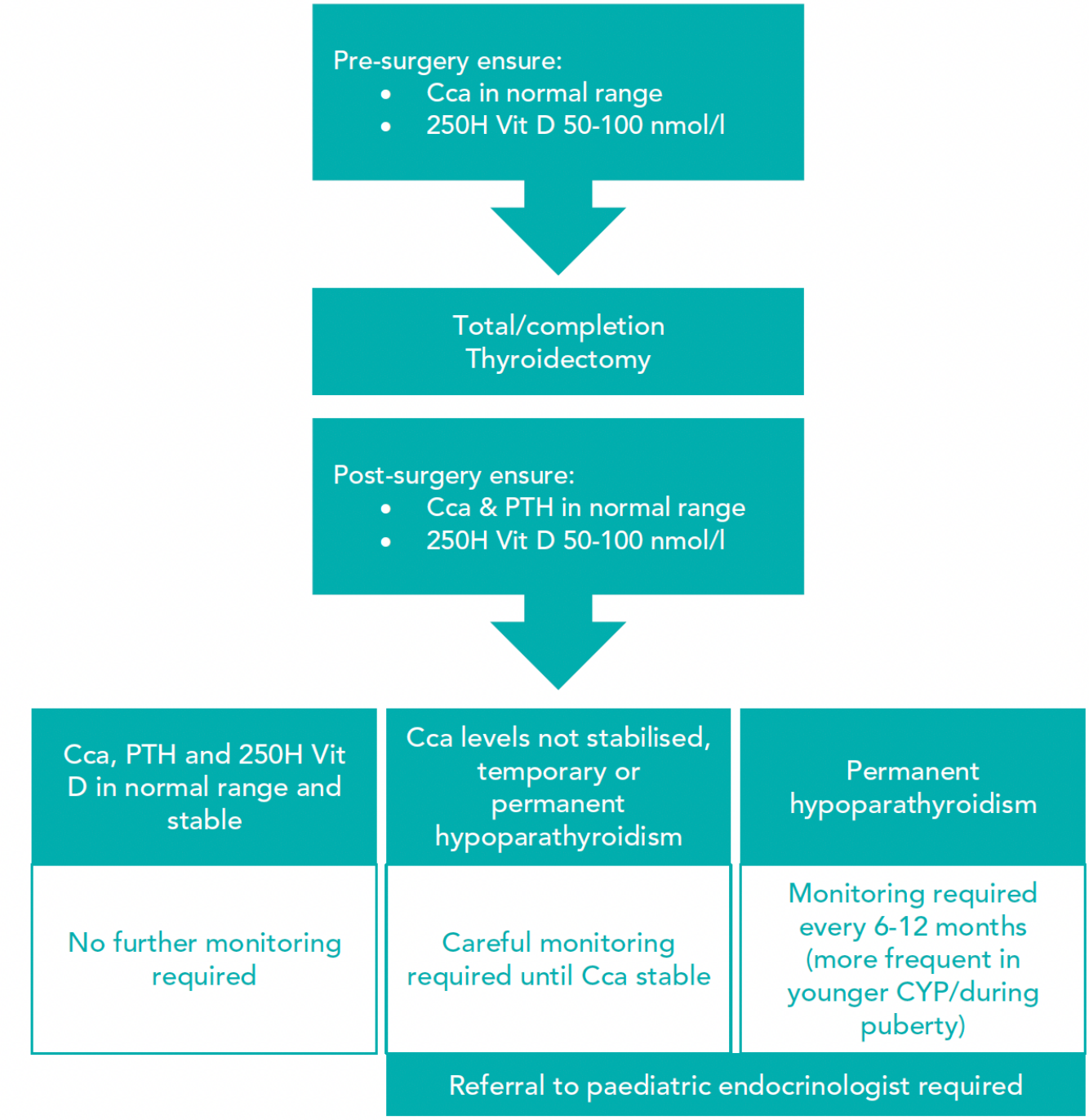
29. **Monitor serum calcium levels after total/ completion thyroidectomy in the peri- and post-operative period until levels are stable and within the normal range** *(Strong Recommendation, Low Quality Evidence, GDG Consensus)*

    Hypocalcaemia consequent to transient or permanent hypoparathyroidism may follow thyroid surgery in CYP; monitoring of serum calcium and intact parathyroid hormone levels is advised in the peri- and post- operative periods (Astl, Chovanec et al., 2014, Freire,

Ropelato et al., 2014, Patel, Bly et al., 2018). 25-hydroxy Vitamin D levels should be measured prior to surgery, and treatment or supplementation given as appropriate (Figure 3).

Figure 3 – Calcium monitoring flowchart for total/ completion thyroidectomy;

CCa – corrected serum calcium, PTH – parathyroid hormone



30. **Monitor calcium levels every 6-12 months in CYP with permanent hypoparathyroidism and stable calcium levels on treatment** *(Strong Recommendation, Delphi Consensus 92%)*

31. **Monitor calcium levels more frequently than every 6-12 months in younger patients and during puberty** *(Strong Recommendation, Delphi Consensus 92%)*

    The literature search did not identify any published evidence to support the surveillance frequency of CYP with permanent hypoparathyroidism, with biochemical plasma and urine calcium monitoring, or with renal US to monitor for nephrocalcinosis. This was therefore reviewed by the Delphi consensus group who advised 6-12 monthly assessments. More frequent monitoring is advised in younger CYP and during puberty (Figure 3).

    There is one study with low quality evidence that calcium and vitamin D supplementation improve bone-muscle proportionality in boys (but not in girls) with hypoparathyroidism following total thyroidectomy (Handkiewicz-Junak, Wloch et al., 2007). There was no consensus on utility or frequency of dual energy X-ray absorptiometry (DEXA) scanning in this group. If permanent hypoparathyroidism is confirmed CYP should be referred to and regularly reviewed by a paediatric endocrinologist (Schneider, Biko et al., 2004). This care should be transitioned to an adult endocrinologist when appropriate.

32. **Undertake formal laryngeal examination in CYP who have a post-operative voice change following thyroidectomy and/or central neck dissection** *(Strong Recommendation, Low Quality Evidence, Delphi Consensus 90%)*

    The incidence of post-operative VCP may be underestimated unless routine evaluation is performed. Institutions that practice routine post-operative laryngoscopy report almost two times higher rates of cord palsy than those that do not (Bergenfelz, Jansson et al., 2008). Studies that report routine post-operative vocal fold examination post thyroidectomy identify transient and permanent VCP in 5.2-12.6% and 1.1-3.3% of patients respectively (Lo, Kwok et al., 2000, Joliat, Guarnero et al., 2017, Heikkinen, Halttunen et al., 2019). Routine post thyroidectomy laryngoscopy in CYP has not been reported.

    Studies of post thyroidectomy outcomes in the paediatric setting that did not include routine examination of the larynx include 186 paediatric thyroidectomies over a 20-year period, in which there were 3 cases (1.6%) of temporary recurrent laryngeal nerve injury, but none were permanent (Chen, Masiakos et al., 2015).

    Intraoperative and/or post-operative concern for nerve injury resulted in laryngoscopy in 16 of 464 patients (median age 15 years: range 2–24 years) post thyroidectomy (Baumgarten, Bauer et al., 2019). 10 patients were identified with unilateral vocal cord paresis and 1 patient with bilateral paresis. Two patients had persistent unilateral RLN deficit 6 months post-operatively (0.4%). The 'Kids Inpatient Database' study on thyroidectomy patients aged 1-20 years identified vocal cord paralysis in 1.7% of >2000 patients over a 2-year period. In patients <1 year the incidence of VCP was 14.3% (Hanba, Svider et al., 2017).

    Guideline recommendations for the adult population state that the surgeon should document whether there has been a change in voice between 2 weeks and 2 months following thyroid surgery (Chandrasekhar, Randolph et al., 2013, Perros, Boelaert et al., 2014, Haugen, Alexander et al., 2016, Sinclair, Bumpous et al., 2016).

Differentiated thyroid cancer – histology

33. **Report DTC in CYP using The Royal College of Pathologists dataset for thyroid cancer histopathology reports** *(Strong Recommendation, High Quality Evidence)*

    The Royal College of Pathologists' dataset for thyroid cancer should be used to report thyroid pathology in CYP (https://www.rcpath.org/resourceLibrary/g089-guidancereportingthyroidcytology-jan16.htmln) (RCPATH).

34. **Do not routinely use molecular genetic pathology testing (DNA/RNA tests looking for specific tumour mutations) in the assessment of histopathology samples for diagnostic purposes** *(Strong Recommendation, Delphi Consensus 93%)*

    Molecular testing as an ancillary investigation for the diagnosis of thyroid nodules in the adult population is currently under investigation. There is increasing evidence that molecular testing for somatic oncogenes in CYP with DTC may provide additional diagnostic information to aid management (Mostoufi-Moab, Labourier et al., 2018, Pekova, Sykorova et al., 2021, Mollen, Shaffer et al., 2022) but this should be as advised by histopathology experts within the context of the MDT.

    The evidence for mutations in the paediatric population includes studies of alterations of BRAF, RAS, RET/PTC, PAX8/PPAR, ALK, p53, CLIP2 and the sodium-iodide symporter (Suchy, Waldmann et al., 1998, Beimfohr, Klugbauer et al., 1999, Fenton, Lukes et al., 2000, Patel, 2002, Hess, Thomas et al., 2011, Vriens, Moses et al., 2011, Sassolas, Hafdi-Nejjari et al., 2012, Leeman-Neill, Brenner et al., 2013, Henke, Perkins et al., 2014, Cordioli, Moraes et al., 2016, Patel, Bly et al., 2018, Nies, Vassilopoulou-Sellin et al., 2021, Stosic, Fuligni et al., 2021). In children, the BRAFV600E mutation has been demonstrated with a variable prevalence in DTC, and it has not been associated with more aggressive tumour behaviour (Penko, Livezey et al., 2005, Rosenbaum, Hosler et al., 2005, Vriens, Moses et al., 2011, Finkelstein, Levy et al., 2012, Henke, Perkins et al., 2014, Ballester, Sarabia et al., 2016, Gertz, Nikiforov et al., 2016, Mostoufi-Moab, Labourier et al., 2018). RET fusion oncogenes have wide ranging prevalence reported in CYP with DTC (Nikiforov, Rowland et al., 1997, Fenton, Lukes et al., 2000, Ricarte-Filho, Li et al., 2013, Ballester, Sarabia et al., 2016, Gertz, Nikiforov et al., 2016), with differences in the specific types of rearrangements linked to radiation-induced and sporadic tumours (Nikiforov, Rowland et al., 1997). Neurotrophic tyrosine kinase receptor (NTRK) fusion oncogenes are more common in paediatric than adult DTC and were found in recent cohort studies to be associated with 100% probability of malignancy, as well as more extensive disease and aggressive pathology in CYP with DTC (Prasad, Vyas et al., 2016, Pekova, Sykorova et al., 2021).

    Potential therapeutic options for management of DTC in CYP are continuing to evolve, and availability of molecular genetic testing, both for inherited germline variants via panel testing (https://panelapp.genomicsengland.co.uk/panels/171/) and somatic oncogene sequencing for small sequence and structural variants on pathology samples (https://www.england.nhs.uk/publication/national-genomic-test-directories/) is expanding in the UK and elsewhere. Whilst it is rare in CYP with DTC to require non-standard therapy, molecular genetic testing is likely to be increasingly used to direct targeted palliative therapies (see recommendation 57). Future trials can also consider the inclusion of molecular subtype into risk stratification (Franco, Ricarte-Filho et al., 2022).

35. **Report DTC in CYP using the TNM staging system** *(Strong Recommendation, Delphi Consensus 92%)*

    The Royal College of Pathologists recommends that TNM version 8 is used for classification of all thyroid cancer after January 2018 (https://www.rcpath.org/profession/guidelines/cancer-datasets-and-tissue-pathways.html). The TNM system describes well the extent of disease and predicts mortality in adults, but there is less good correlation in CYP (Zimmerman, Hay et al., 1988, Dottorini, Vignati et al., 1997, Chow, Law et al., 2004, Vaisman, Bulzico et al., 2011). In the absence of a CYP specific scoring system the GDG recommends following Royal College of Pathologists guidelines. It is important to note that age is an important predictor in CYP in that most, albeit low quality, studies show that young children have a worse prognosis compared to young adult or adolescent patients (Welch-Dinauer, Tuttle et al., 1998, Bal, Padhy et al., 2001, Borson-Chazot, Causeret et al., 2004, Powers, Dinauer et al., 2004, Palmer, Zarroug et al., 2005, Jang, Lee et al., 2012, Silva-Vieira, Santos et al., 2015).

    TNM particularly lacks accuracy to determine disease free survival in low risk CYP, due to the high rate of lymph node involvement in this group, leading to the risk of under-diagnosis and under-treatment of this group (Oommen, Romahn et al., 2008, Wada, Sugino et al., 2009).

36. **Consider recording a prognostic score (TNM) for CYP with DTC in the MDT** *(Moderate Recommendation, Delphi Consensus 73%)*

    There is no literature evidence to support this best practice recommendation and it was therefore reviewed by a Delphi consensus process and 73% of respondents supported this recommendation.

Differentiated thyroid cancer – post-operative management

37. **Assess the need for and nature of further treatment in the MDT (adult thyroid cancer and paediatric or TYA MDTs, or properly constituted all-age thyroid MDT). This will be determined by the histopathology, TNM stage and risk stratification** *(Strong Recommendation, Moderate Quality Evidence, GDG Consensus)*

    Differentiated thyroid cancer in CYP is not a uniform entity, and the post-operative treatment course, assuming optimal surgery, needs to be individualised on a number of factors including age, stage and completeness of surgery. The patient's post-operative histology should be therefore discussed at an age-appropriate thyroid cancer MDT.

    The BTA guidelines (Perros, Boelaert et al., 2014) recommend an adaptation of the ATA risk grouping, whilst the ATA paediatric guidelines recommend a specific paediatric risk grouping (Francis, Waguespack et al., 2015). There is no evidence that one system is superior to the other.

    While both the BTA and ATA offer guidelines for risk stratification after surgery, these are not identical. There is therefore an option for individual clinicians or for MDTs to use one rather than the other, or to take both into account, and offer choices to patients' families. For example, a patient with pT1b pN1a M0 R0 disease may be classified as intermediate

risk by the BTA system, and low risk by the ATA system. While radioactive iodine ablation has historically been recommended for the majority of DTC patients following surgery, there is recent evidence that some CYP with low-risk disease may not require it (Sohn, Kim et al., 2017, Sung, Jeon et al., 2017). Further evidence is awaited from randomised trials. With this uncertainty, it would be reasonable to offer either radioactive iodine or close surveillance instead.

Health Benefits: Children with DTC have specific paediatric needs, and also specific disease related needs. Expertise in both aspects is required. Their best care therefore requires expert input into both paediatric aspects of care, and also disease related aspects of care. A properly constituted all-age thyroid MDT will bring all the necessary expertise together in one setting, alternatively this can be achieved by discussion in two different MDTs. There are no anticipated side effects or risks if this recommendation is followed. If children with DTC are considered only in an adult thyroid MDT, the focus may simply be on the disease, with neglect of paediatric aspects of care; if considered only in a paediatric or TYA MDT, then the disease specific expertise may be lacking, so discussion in both is required to provide the best holistic care.

38. **Undertake radioiodine remnant ablation (RAA) according to post-operative risk assessment** *(Strong Recommendation, Delphi Consensus 87%)*

RRA is only applicable in those patients who have had either total thyroidectomy or lobectomy followed by completion thyroidectomy. Following total thyroidectomy, some radioiodine uptake is usually seen within the thyroid bed reflecting normal thyroid remnant tissue. Radioiodine-induced destruction of this remnant is known as 'radioiodine remnant ablation' (RRA). This term should not be used to describe subsequent treatment, which is referred to as radioiodine 'therapy' where the intention is to treat residual, recurrent or metastatic disease. The principles and procedures are similar for the administration of RRA or therapy (Perros, Boelaert et al., 2014).

The advantages of RRA are defined by the BTA (Perros, Boelaert et al., 2014) as follows:

- Eradication of all residual thyroid cells post-operatively with subsequent reduced risk of local and distant tumour recurrence
- Possible prolonged survival
- Reassurance to patients provided by the knowledge that serum thyroglobulin is undetectable and neck ultrasound or diagnostic iodine scan imaging is negative, implying that all thyroid tissue has been destroyed
- Increased sensitivity of thyroglobulin monitoring, facilitating early detection of recurrent or metastatic disease
- Increased sensitivity of subsequent iodine scanning if required

Following definitive surgery, CYP with DTC will fall into one of the following groups:

- No indication for radioiodine remnant ablation (RRA) – observation only
- Uncertain indication for RRA, management discussed with patient and family, with an individualized approach and consideration for trial entry.
- Definite indication for RRA and then, follow up and dynamic risk stratification.
- Definite indication for RRA and subsequent radioactive iodine therapy administration

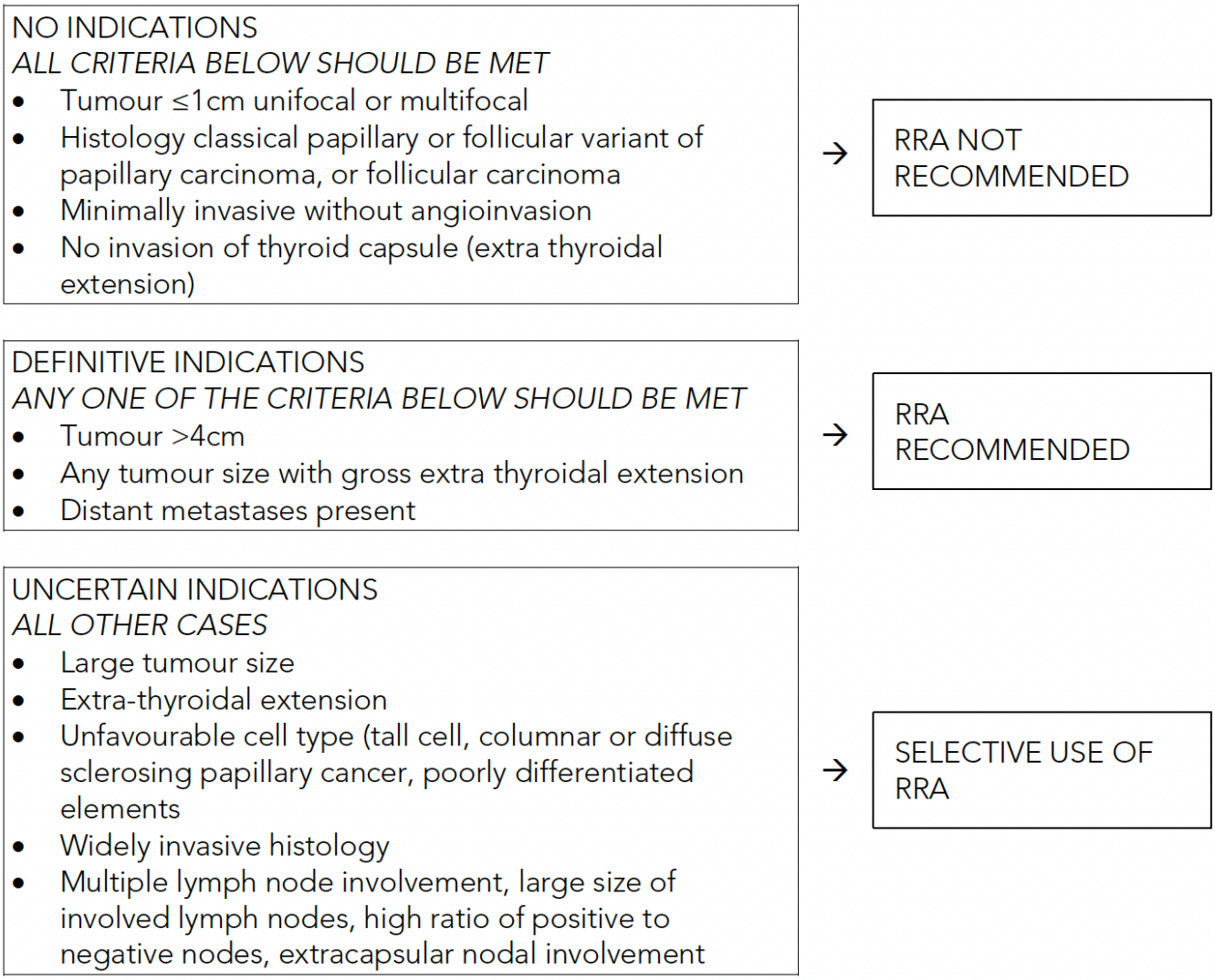
The indications for RRA are mainly TNM stage dependent with additional information from the pathological risk factors also contributing to the decision-making (see Table 3). The BTA guidelines define the indications for RRA in adults with DTC into three groups based on available evidence; 'no indication', 'definite indication' and 'uncertain indication' (Figure 4) (Perros, Boelaert et al., 2014).

Table 3 – Comparison of risk stratification systems in British Thyroid Association (Perros, Boelaert et al., 2014) and American Thyroid Association Paediatric (Francis, Waguespack et al., 2015) guidelines for DTC.

Risk Group	BTA adapted ATA Guidelines	ATA Paediatric Guidelines
Low risk	No local or distant metastases All macroscopic tumour has been resected i.e. R0 or R1 resection (pathological definition) No tumour invasion of loco-regional tissues or structures The tumour does not have aggressive histology (tall cell, or columnar cell PTC, diffuse sclerosing PTC, poorly differentiated elements), or angioinvasion	Disease grossly confined to the thyroid with N0/Nx disease or patients with incidental N1a disease (microscopic metastasis to a small number of central neck lymph nodes)
Intermediate Risk	Microscopic invasion of tumour into the perithyroidal soft tissues (T3) at initial surgery Cervical lymph node metastases (N1a or N1b) Tumour with aggressive histology (tall cell, or columnar cell PTC, diffuse sclerosing PTC, poorly differentiated elements) or angioinvasion	Extensive N1a or minimal N1b disease
High Risk	Extra-thyroidal invasion Incomplete macroscopic tumour resection (R2) Distant metastases (M1)	Regionally extensive disease (extensive N1b) or locally invasive disease (T4 tumours), with or without distant metastasis

Figure 4 – Decision making flow chart for use of radioiodine remnant ablation (RRA)

Adapted from British Thyroid Association guidelines (Perros, Boelaert et al., 2014)



Most CYP with DTC present with locally advanced disease, with TNM tumour staging of T3 or T4, and/ or N1 (Machens, Lorenz et al., 2010, Fridman, Savva et al., 2012, Markovina, Grigsby et al., 2014) and it is far less common to see microcarcinoma in the paediatric population (Lerner and Goldfarb, 2015b). It is likely that most CYP with DTC will fall into the 'definite' or 'uncertain' indication groups on the basis of the BTA classification. Those falling into the uncertain group are likely to have RRA recommended following case review due to greater rates of high-risk pathological features (as described in Table 3) seen in this population.

Following RRA, previously unknown disease status, for example unsuspected metastatic disease, may be detected on the post ablation scan, or an incomplete response on dynamic risk assessment may indicate the need for subsequent radioactive iodine therapy.

However, evidence to support the use RRA, particularly in early intra-thyroidal disease (cT1-T2 cN0 cM0), is limited (Newman, Black et al., 1998, Welch, Mcclellan et al., 1999, Jarzab,

Junak et al., 2000, Chow, Law et al., 2004, Demidchik, Demidchik et al., 2006, Handkiewicz-Junak, Wloch et al., 2007). In CYP there is low quality and conflicting evidence on the impact of RRA on disease free survival (Powers, Dinauer et al., 2003). Evidence on whether RRA is associated with increased risk of secondary malignancy is to date conflicting (Newman, Black et al., 1998, Welch, Mcclellan et al., 1999, Jarzab, Junak et al., 2000). Data from the Iodine or Not (IoN) study in which patients aged 16 or older with low risk thyroid cancer were randomised to receive RRA or not, will provide further guidance as to which patients can safely avoid RRA (Mallick, Harmer et al., 2012a). Until this evidence is available, the standard UK approach in CYP is to treat any localised disease with definite or uncertain indications with RRA. However, there is room for individualisation of decision making for the uncertain indications group (Perros, Boelaert et al., 2014) (see Figure 4).

The ATA adult guidelines consider the use of post-operative thyroglobulin and ultrasound in relation to the need for RRA. This is on the basis that in adults, a post treatment (surgery and RRA) stimulated thyroglobulin level <2ng/mL and/or undetectable basal serum thyroglobulin measured with a highly sensitive assay are strong indicators of definitive cure and a very low risk of recurrent disease. A negative ultrasound scan adds to the sensitivity of this (Pacini, Molinaro et al., 2003, Smallridge, Meek et al., 2007, Spencer, Fatemi et al., 2010).

The optimal cut off value or whether the stimulated or unstimulated thyroglobulin level should be used has not been defined, either in adults or children. It is critical to have full discussion with the family to ensure all options and the risks and benefits of surveillance or treatment are conveyed.

The timing of RRA post thyroidectomy is governed more by availability of facilities and convenience for the patient than biology of the tumour. There is no evidence that a delay of one to 2 months changes outcome. Factors around schooling, childcare for siblings and preparing the child for a period of separation from family usually contribute to the selection of date for treatment. NHS cancer waiting targets stipulate treatment should be administered within 31 days of the decision to treat, but this is not based on the biology or outcomes of the disease.

Whilst this recommendation is strongly made, it is important to acknowledge that decision making is not always easy, especially when the indications for treatment are uncertain. Individual clinicians and families may have preconceived ideas, and families may have been influenced by what other clinicians have said, or by what they have read about the disease and its treatment. In these circumstances, when faced with the option of either radioactive iodine ablation or surveillance, it is the responsibility of the MDT to approach the family with options, and to have a full and frank discussion of the uncertainties surrounding the evidence base. Some families will wish to be active participants in decision-making and will not wish to be told that they 'must' follow a certain course of action. Other families may feel unable to contribute to the decision making, possibly for fear of making the wrong choice, and would like the clinician to make a definite decision. While families typically make the decisions on behalf of younger children, older teenagers who are Gillick competent, should be encouraged to express their opinions, and contribute actively to decision making where there are reasonable options.

39. **Radioiodine must be prescribed and administered by professionals experienced in the dosing and administration of radioiodine in CYP** *(Strong Recommendation, High Quality Evidence)*

    This recommendation ensures the least risk of the incorrect treatment being given. There is also a statutory responsibility in the prescription of radioactive iodine, as regulated by the Administration of Radioactive Substances Advisory Committee of the Department of Health and Social Care. There are no anticipated risks or side effects if this recommendation to limit prescribing and administration to experienced professionals is followed, but there is a significant risk of medication errors if this recommendation is not followed.

40. **Administer radioiodine to children less than 16 years within a paediatric oncology centre with twenty-four hour medical and nursing care** *(Strong Recommendation, High Quality Evidence)*

    Children aged less than 16 years should receive radioiodine within a paediatric oncology centre with twenty-four hour paediatric medical and nursing care. Older teenagers, from the age of 16 up to their 19th birthday, should receive care in a designated principal treatment centre for young people. From the age of 19 to 24 years (up to the 25th birthday), young adults should be offered radioiodine in a designated teenage and young adult cancer service but may elect for care in an adult environment which may be closer to home.

    These recommendations are based on the Royal College of Radiologists Good Practice Guide for Paediatric Radiotherapy (https://www.rcr.ac.uk/system/files/publication/field_publication_files/bfco182_good_pract_paed_rt_second_ed.pdf accessed 28.3.2021), the NHS England: 2013/14 NHS Standard Contract for Cancer: Teenagers & young adults Section B Part 1 - service specifications (https://www.england.nhs.uk/wp-content/uploads/2013/09/b17.pdf accessed 28.3.3021), and also guidelines from the Intercollegiate Standing Committee on Nuclear Medicine (https://www.rcr.ac.uk/system/files/publication/field_publication_files/bfco199-icscnm-molecular-radiotherapy-guidance.pdf accessed 28.3.2021).

    While there is a strong recommendation for younger children to be treated in a paediatric environment, older teenagers (over 18 years) should have the option to be treated in a specialist TYA centre with all the appropriate support for people in that age group, or to be treated in an 'adult' centre which lacks TYA support.

41. **Consider adjustment of the radioiodine activity for thyroid ablation and therapy based on the size of the CYP** *(Moderate recommendation, Low Quality Evidence, Delphi Consensus 78%)*

    There are no standardised activities of RRA for children and there is no data to guide this. Following two randomised controlled trials in adult patients, HiLo (Mallick, Harmer et al., 2012b) and Estimabl 1 (Schlumberger, Catargi et al., 2012), the standard activity for RRA in adults has reduced from 3.7GBq to 1.1GBq for patients at low risk of recurrence of their thyroid cancer. In higher risk disease 3.7GBq remains the standard administered activity.

    Historically the same activity has been considered for children and adults, but some adaptation according to body weight, body surface area and age has been applied by

many specialists (Handkiewicz-Junak, Wloch et al., 2007, Pawelczak, David et al., 2010), and Delphi consensus and stakeholder review both gave further support for this practice.

For subsequent radioactive iodine for therapy in the setting of persistent or recurrent disease the recommended empirical administered activity is 5.5GBq in adults (Perros, Boelaert et al., 2014). As with RRA there is no good data for the adjustment of activity for children. Although there is interest in dosimetric prescription of radioiodine, there is no evidence to date to show superiority over empiric activity prescription. Reports have suggested that treatment with at least 200MBq/kg (5.4 mCi/kg) is possible without a risk of exceeding bone marrow tolerance limits (Verburg, Biko et al., 2011). Many patients will tolerate much higher activities. However, in children with extensive metastatic disease whole body dosimetry may be employed to ensure total blood dose does not exceed 2Gy and that the whole body retention at 48 hours does not exceed 4.44Gy or 2.86Gy (in the case of no or miliary lung metastases respectively) (Verburg, Biko et al., 2011, Verburg, Reiners et al., 2013). CYP with DTC, particularly those with pulmonary metastases and coexisting micronodular disease, often show excellent RAI uptake and thus may be more sensitive to 131I therapy than adults (Xu, Liu et al., 2016). In conclusion, there is no high-quality evidence to advise for or against prescription of radioiodine based on empiric activity or informed by dosimetry. GDG consensus opinion suggests that experts prescribe RRA as an empiric activity and reserve dosimetric methodology for patients with extensive disease and repeated therapies in centres with this expertise.

For the majority of patients there are very few complications of radioiodine. The long-term toxicities are believed to be related to the absorbed radiation dose as a function of the administered activity and therefore the risk of toxicity will increase with cumulative radiation dose and with cumulative administered radioiodine activity. The risks of RRA are relatively low following a single administration. While the majority of DTC patients are teenagers for whom the adult activity is appropriate, very small children may get a good response from a size-adjusted dose and avoid the risks of radiation exposure beyond that which is necessary. There are no anticipated risks or side effects if this recommendation is followed.

42. **Perform a blood or urine pregnancy test on all post-menarchal female patients prior to radioactive iodine administration** *(Strong Recommendation, Moderate Quality Evidence, GDG Consensus)*

The Royal College of Radiologists Good Practice Guide for Paediatric Radiotherapy (https://www.rcr.ac.uk/system/files/publication/field_publication_files/bfco182_good_pract_paed_rt_second_ed.pdf) states that radioactive iodine may not be administered to pregnant women. Post pubertal girls should be advised to avoid pregnancy for 6 months after radioiodine (although it may be wise to advise to wait until post risk assessment at 9 - 12 months as this will determine response to ablation and whether further treatment is required).

43. **Consider fertility preservation with post-pubertal CYP if they are likely to receive more than 2 administrations of radioiodine (including the ablation administration)** *(Moderate Recommendation, Delphi Consensus 75%)*

    A single ablation dose of radioiodine should have no effect on male or female fertility (Landau, Vini et al., 2000). Sperm banking should be discussed with all post-pubertal males if they are likely to receive more than 2 administrations of radioiodine (including the ablation administration) (Wallace, 2011). Referral to fertility units for expert advice may be warranted in young women with multiple treatments with radioiodine. Delphi consensus supported this recommendation, although emphasised that the risks of infertility are low in those patients not requiring high cumulative activities of radioiodine.

    While it is important to discuss fertility preservation options with post-pubertal patients and their families, the absolute risk of fertility impairment is low, and following discussion, patients and families should have the option of undergoing fertility preserving features, or not.

44. **Consider preparing CYP for radioactive iodine (RRA or therapy) with either thyroid hormone withdrawal or recombinant thyroid stimulating hormone** *(Moderate Recommendation, Moderate Quality Evidence)*

    Historically, radioactive iodine was always administered after thyroid hormone withdrawal. Typically, levothyroxine is stopped 28 days prior to radioactive iodine administration, and/or liothyronine 10 days before. Most children tolerate thyroid hormone withdrawal well and reach the target TSH of >/= 30iu for radioiodine administration without problems (Kuijt and Huang, 2005). More recently, recombinant TSH (Thyrogen) has become the standard of care in adult practice (Mallick, Harmer et al., 2012b). However, it is not licensed for use in children and the data relating to its effectiveness has mostly related to the adult population. There is now increasing retrospective data suggesting the safety and efficacy of recombinant TSH in the paediatric population (Iorcansky, Herzovich et al., 2005, Luster, Handkiewicz-Junak et al., 2009, Rosario, Mineiro Filho et al., 2012, Handkiewicz-Junak, Gawlik et al., 2015).

    Uptake of radioactive iodine is poor without a raised TSH level. This recommendation ensures the maximum uptake of radioactive iodine and gives the best chance of successful treatment. Whilst thyroid hormone withdrawal results in a feeling of tiredness and lethargy and may be associated with abnormal kidney function indicators on blood tests, thyrotropin alfa does not cause any significant side effects. However, two intramuscular injections are required.

45. **Advise a low iodine diet prior to radioiodine treatment in CYP with DTC** *(Strong Recommendation, High Quality Evidence, Delphi Consensus 100%)*

    The promotion of low iodine diets prior to radioiodine treatment in CYP with DTC is supported by adult (Perros, Boelaert et al., 2014) and paediatric guidelines (Pluijmen, Eustatia-Rutten et al., 2003, Francis, Waguespack et al., 2015) and our Delphi consensus. A high dietary iodine intake may reduce the therapeutic efficacy of radioactive iodine, and therefore a low iodine diet for 14 days before radioiodine treatment should maximise the chance of successful ablation or therapy (see https://www.btf-thyroid.org/low-iodine-diet).

46. **Perform a whole-body iodine 131 scan following RRA** *(Strong Recommendation, High Quality Evidence)*

    Following RRA, a whole-body iodine 131 scan (preferably SPECT/CT with the CT component focusing on of the neck and thorax, and any other body areas with possible abnormal uptake on planar scans) is indicated (Bal, Kumar et al., 2004, Kim, Gelfand et al., 2011). This scan permits further staging of the disease, which may identify the presence of unsuspected distant metastases requiring subsequent therapy (Mostafa, Vali et al., 2016, Jiang, Xiang et al., 2021). This will demonstrate localisation of uptake in the thyroid bed, thyroglossal tract remnants, cervical lymph nodes, and pulmonary or other distant metastases. This is therefore an essential investigation for complete staging of the disease, and to predict prognosis. There are no side effects or risks anticipated if this recommendation is followed. There is a risk of missing metastatic disease if the recommendation is not followed.

47. **Investigate residual disease on post RRA 131 scan with additional imaging. Further management will be determined by imaging findings** *(Strong Recommendation, High Quality Evidence)*

    Neck uptake within cervical lymph nodes requires anatomical imaging to localise uptake with SPECT CT/ ultrasound / MRI as available to assess for macroscopic disease (Antonelli, Miccoli et al., 2003, Bal, Kumar et al., 2004, Kim, Gelfand et al., 2011). If residual disease or distant metastases are identified, the CYP should be referred back to the MDT for consideration of further treatment, surgical or RAI. All other patients will then proceed to Dynamic Risk Stratification (see below).

Differentiated thyroid cancer – follow up

48. **Perform a dynamic risk assessment following RRA. Use this to guide further management and ongoing follow up** *(Strong Recommendation, High Quality Evidence)*

    At 9-12 months post-surgery and RRA, response to treatment should be assessed. If the suppressed thyroglobulin is undetectable, an ultrasound of the thyroid bed and bilateral neck together with the thyroglobulin following TSH stimulation should be performed. This is known as Dynamic Risk Stratification, as recommended in the BTA and ATA Paediatrics guidelines (Perros, Boelaert et al., 2014, Francis, Waguespack et al., 2015). This assesses the response to treatment in low-risk disease. There is very low quality evidence that recombinant human TSH stimulated thyroglobulin level is useful for disease surveillance in CYP (Hoe, Charron et al., 2006).

    Patients are allocated to one of three groups following dynamic risk stratification: excellent response (no evidence of disease), indeterminate response (biochemical evidence of disease only) and incomplete response (imaging/structural evidence of disease with or without biochemical evidence) (see Table 4). These investigations allow an assessment of the completeness of ablation and facilitate allocation to a risk group for purposes of deciding the level of TSH suppression required, and the frequency and intensity of follow up going forwards. There are no anticipated side effects or risks if this recommendation is followed. If the recommendation is not followed, patients may be under-treated, with the risk of disease progression, or overtreated with the risk of treatment related morbidity.

Table 4 – Follow up schedule for management of CYP with DTC

DRA – dynamic risk assessment, MDT – multi-disciplinary team, Tg – thyroglobulin, US – ultrasound, CT - computerised tomography, TFTs – thyroid function tests, TSH – thyroid stimulating hormone

	Dynamic Risk Assessment		
Baseline risk group	Excellent Response	Indeterminate Response	Incomplete Response
Low-Risk	(a) 6-12 monthly follow-up (b) at least 5 years (c) clinic visit, TFTs and Tg. No routine imaging (d) TSH in normal range	(a) 6 monthly follow-up (b) at least 5 years – possibly longer depending on imaging and Tg trend. Consider repeating DRA at 5 years (c) clinic visit, TFTs and Tg. Repeat US initially 6 monthly if abnormal – increasing to annually if stable over time (d) TSH suppressed for at least 5 years	Consider further treatment in MDT depending on DRA findings. If active surveillance chosen over further treatment: (a) 3-6 monthly follow-up (b) at least 5 years – more likely longer depending on imaging and Tg trend. Consider repeating DRA at 5 years (c) clinic visit, TFTs and Tg. Repeat US initially 6 monthly if abnormal – increasing to annually if stable over time (d) TSH suppressed indefinitely, unless repeat assessment shows improvement
Intermediate Risk	(a) 6 monthly follow-up (b) at least 5 years (c) clinic visit, TFTs and Tg. Annual US (d) TSH suppression may be slightly relaxed: target low-normal range	(a) 6 monthly follow-up (b) at least 5 years – possibly longer depending on imaging and Tg trend. Consider repeating DRA at 5 years (c) clinic visit, TFTs and Tg. Repeat US initially 6 monthly if abnormal – increasing to annually if stable over time (d) TSH suppressed for at least 5 years	Consider further treatment in MDT depending on DRA findings. If active surveillance chosen over further treatment: (a) 3-6 monthly follow-up (b) at least 5 years – more likely longer depending on imaging and Tg trend. Consider repeating DRA at 5 years (c) clinic visit, TFTs and Tg. Repeat US initially 6 monthly if abnormal – increasing to annually if stable over time (d) TSH suppressed indefinitely, unless repeat assessment shows improvement

High-Risk	(a) 3-6 monthly follow-up (b) at least 10 years (c) clinic visit, TFTs and Tg. US 6 monthly for 2 years, then annually to 5 years (d) TSH <0.1 to 10 years	(a) 3-6 monthly follow-up (b) at least 10 years – possibly longer depending on imaging and Tg trend. Consider repeating DRA at 5 years (c) clinic visit, TFTs and Tg. Repeat US initially 6 monthly – increasing to annually if stable over time (d) TSH <0.1 to 10 years	Consider further treatment in MDT depending on DRA findings. If active surveillance chosen over further treatment: (a) 3-6 monthly follow-up (b) At least 10 years, probably lifelong (c) clinic visit, TFTs and Tg. Repeat US initially 6 monthly if abnormal – increasing to annually if stable over time. Other imaging e.g. CT chest may need to be repeated periodically if clinically indicated (d) TSH <0.1 to at least 10 years, consider need for life-long suppression if there is still evidence of controlled disease

49. Use neck ultrasound as the first line imaging modality for post-operative follow up of CYP with DTC *(Strong Recommendation, Moderate Quality Evidence, GDG consensus)*

In CYP with DTC, US is sufficient for evaluation of loco-regional involvement in follow up (Vali, Rachmiel et al., 2015b), with sensitivity 85.7%, specificity 89.4%, negative predictive value 94.4% and positive predictive value 75%. Neck US can be used to pinpoint the anatomic site of lymph node metastases (Antonelli, Miccoli et al., 2003). In adults, the combination of neck US and fine needle aspiration cytology has been shown to detect cases of lymph node metastasis and local recurrence not found by whole body scan or serum thyroglobulin determination (Durante, Costante et al., 2013). Neck ultrasound is also useful, particularly in young children, post operatively to help differentiate pathological from reactive lymph nodes.

50. Measure thyroglobulin antibody in conjunction with serum thyroglobulin *(Strong Recommendation, High Quality Evidence)*

Even very low thyroglobulin antibody concentrations can interfere with assay results and thyroglobulin antibodies are found in up to 25% of adult patients (Spencer, Takeuchi et al., 1998, Vali, Rachmiel et al., 2015b, Haugen, Alexander et al., 2016). Each specimen sent for thyroglobulin measurement requires concomitant thyroglobulin antibody testing, because thyroglobulin antibody status can change over time. As variability exists between different thyroglobulin assays, there is a need to use the same assay for serial measurements. Thyroglobulin antibody titres can also correlate with disease burden.

51. **Use the baseline risk grouping and subsequent dynamic risk stratification to determine frequency and duration of follow up** *(Strong Recommendation, Moderate Quality Evidence, GDG consensus)*

There is a lack of high-level paediatric evidence on which to make clear-cut and highly detailed follow up recommendations, but it is reasonable and pragmatic to base the long-term follow up schedule of CYP evidence from adults with DTC. Prognostic stratification will be based on both the baseline risk group, and also the results of dynamic risk assessment after treatment (see Table 4). CYP will be followed-up until transition to adult services, and for low-risk adult patients a decision can be taken about discharge to primary care. Life-long follow up is advised in high-risk groups given that recurrence of DTC can occur 40 years after initial disease (Landau, Vini et al., 2000, Hay, Gonzalez-Losada et al., 2010).

The suggested follow up schedule is given in Table 4 below, modified from BTA (Perros, Boelaert et al., 2014) and ATA Paediatrics (Francis, Waguespack et al., 2015) guidelines and recent review (Lee, Sharabiani et al., 2019). Follow up of patients will be in one of three groups. These are, as above: no evidence of disease (excellent response), biochemical evidence of disease only (indeterminate response), and imaging/structural evidence of disease with or without biochemical evidence (incomplete response). The purpose of surveillance is to detect evidence of relapse/progression at a time point when further intervention may be of value, and to ensure TSH levels are optimised to reduce the risk of recurrence.

If no structural disease is present and stimulated thyroglobulin is not detectable this represents an excellent response to treatment and follow up intervals can be extended to six monthly during childhood (92% agreement on Delphi consensus) and relaxation of TSH suppression may be considered (as per Table 4).

In patients with low-level TSH-stimulated thyroglobulin (<10 ng/ml), continued follow up with serial TSH-suppressed thyroglobulin is indicated. The role of imaging with ultrasound in this situation is unclear and this should be an individualised decision by the treating clinician.

If the unstimulated thyroglobulin is detectable an US should be performed to localise persistent disease that may be surgically resectable (Vali, Rachmiel et al., 2015b). If no structural disease is present a therapy dose of RAI may be considered (Francis, Waguespack et al., 2015).

Following this recommendation allows for personalisation of care, based on the extent of disease at the time of diagnosis and the response to treatment. This facilitates individualised follow up schedules, which ensure those at the highest risk are followed more intensively to detect progression, while those at low risk are spared unnecessary hospital visits.

Differentiated thyroid cancer – metastatic, recurrent or persistent disease

52. **Use serial thyroglobulin measurement with additional imaging if required to monitor CYP with DTC** *(Strong Recommendation, Moderate Quality Evidence, GDG consensus)*

    Serum thyroglobulin may continue to be detectable following RRA but may decline over time without additional therapy (Dottorini, Vignati et al., 1997, Biko, Reiners et al., 2011). A rise in thyroglobulin or thyroglobulin antibodies should trigger initial confirmation with repeat measurement within two months, followed by investigation with ultrasound of the thyroid bed and neck to exclude disease recurrence (Kirk, Mort et al., 1992, Xu, Liu et al., 2016). If neck ultrasound is normal additional imaging such as CT or MRI can be considered to look for distant metastatic disease, especially lung metastases, if thyroglobulin levels suggest disease may be present at a distant site. 123-I whole body scintigraphy and SPECT/CT may be added if the thyroglobulin measurement is considered to be unreliable because of a high antibody titre (Kim, Gelfand et al., 2011).

    Sometimes the low administered activity of 123-I used for diagnostic imaging, and the resolution of the imaging techniques used, may result in small volume disease being overlooked or mistaken for being iodine resistant. The use of 18F-FDG PET/CT may be a helpful additional investigation as it has high diagnostic accuracy for the detection of recurrent and/or metastatic diseases in DTC patients with thyroglobulin elevation and negative iodine scintigraphy (Larg, Barbus et al., 2019, Qichang, Lin et al., 2019, Wang, Dai et al., 2021).

53. **Consider further surgical resection for persistent local structural disease** *(Moderate Recommendation, GDG consensus)*

    Structural disease refers to a definite abnormality on imaging, identifying that cancer has infiltrated anatomical structures such as jugular vein, trachea or oesophagus, or metastatic lymph nodes. If structural disease is detected on the neck US, MDT discussion about the role of further surgery is recommended.

54. **Consider therapeutic radioiodine after further surgical resection** *(Moderate Recommendation, Moderate Quality Evidence)*

55. **Administer radioiodine as first line treatment for unresectable metastatic disease in** CYP *(Strong Recommendation, High Quality Evidence)*

    Therapeutic choices after further surgical resection should be individualised, discussed with the MDT and agreed with the patient/family who may have strong views. The use of radioiodine should be considered, and would normally be regarded as indicated if, following surgery, there is imaging or biochemical evidence of residual disease which was not felt to be amenable to surgery; whereas in the absence of such evidence, a policy of careful observation might be regarded as a safe and more conservative approach, although there is no evidence to show that the use of radioactive iodine is necessarily wrong. Most DTC in this age group responds well to radioactive iodine therapy and repeated therapy doses of radioactive iodine can be used after further surgical resection and to treat metastatic disease as long as response is seen (Biko, Reiners et al., 2011, Verburg, Reiners et al., 2013). It is rare for DTC in CYP to become radioiodine refractory.

56. **Consider chest imaging (chest x-ray or chest CT) in patients with high-risk disease or those with evidence of persistent or recurrent disease to diagnose and monitor metastatic lung disease** *(Moderate Recommendation, Moderate Quality Evidence)*

Chest x-ray is used to visualise macroscopic lung metastases. There remains controversy as to whether iodinated contrast should be used if a CT scan is undertaken due to concerns that this may lead to a delay in radioiodine therapy (Perros, Boelaert et al., 2014). If contrast enhancement will help define extent of disease and help management decision-making it should be used. Evidence is not clear as to washout time required following intravenous contrast to prevent 'stunning' and reduced uptake of radioiodine therapy, but adult guidelines suggest waiting 8 weeks (Perros, Boelaert et al., 2014).

57. **Consider the use of palliative targeted therapy in CYP with progressing radioiodine refractory DTC** *(Moderate Recommendation, Moderate Quality Evidence)*

Radioiodine refractory disease includes either the presence of at least one lesion that does not take up I-131, or clinical evidence that I-131 is no longer providing benefit. There is no evidence that traditional chemotherapeutic agents are an effective treatment of radioiodine refractory DTC in CYP. Targeted agents, sorafenib and lenvatinib, have been licensed more generally for treatment of radioiodine refractory disease in adults but have not been proven in the paediatric population. In young adults over the age of 16 with progressing (i.e. with radiographic evidence of disease progression), radioiodine refractory DTC, sorafenib and lenvatinib can be considered as per marketing approval and based on phase III data from DECISION (Brose, Nutting et al., 2014) and SELECT (Schlumberger, Tahara et al., 2015) trials respectively. These drugs should be administered under the supervision of clinicians with experience in managing these drugs and associated toxicities (Brose, Smit et al., 2012).

The use of next generation sequencing to identify gene alterations, including BRAF mutations, RET, ALK and NTRK gene fusions, depends on availability of such testing and NHS England is currently establishing a national test directory service over seven genomic hubs UK-wide to carry out cancer genomic testing by next generation sequencing and interpret all results. Currently, the service offers testing in paediatric DTC via multi-target next generation sequencing panel for RET small and structural variants and NTRK1/2/3 structural variants (https://www.england.nhs.uk/publication/national-genomic-test-directories/). Future studies in CYP will likely help to direct targeted therapies for treatment of individuals with particular somatic point mutations and fusion genes (Nies, Vassilopoulou-Sellin et al., 2021).

NICE has recommended the use of Larotrectinib (https://www.nice.org.uk/guidance/ta630) within the Cancer Drugs Fund as an option for treating neurotrophic tyrosine receptor kinase (NTRK) fusion-positive solid tumours in adults and children, if the disease is locally advanced or metastatic, or surgery could cause severe health problems and they have no satisfactory treatment options. Entrectinib has been recommended for use under similar circumstances in children over 12 years of age if they have not had treatment with a NTRK inhibitor previously (https://www.nice.org.uk/guidance/ta644). Clinical trials of RET inhibitors are ongoing.

In the rare situation where CYP are not cured of their DTC, palliative care teams should be involved in care at an early stage. Symptom control may include palliative radiotherapy, in a

similar manner to as described above in recommendation 55. Other locally ablative treatment modalities such as surgery, radiofrequency ablation and vertebroplasty can be considered to treat deposits of disease that are causing specific symptoms.

58. **Consider use of external beam radiotherapy for symptom control in the palliative setting** *(Moderate Recommendation, Low Quality Evidence, Delphi Consensus 73%)*

External beam radiotherapy is very rarely indicated in CYP with DTC in the primary or adjuvant setting because their disease is usually very iodine avid and sensitive so there is no benefit from the addition of external beam radiotherapy (Hay, Gonzalez-Losada et al., 2010).

External beam radiotherapy to the neck can be of use in the palliative setting for symptom control, for example in cases of unresectable disease invading the larynx, trachea or oesophagus, where uncontrolled growth of the disease will cause life threatening or distressing symptoms. There may also be a role for palliating the effects of more distant metastases for example painful bone metastases, bleeding or obstructing deposits of tumour or brain metastases. Any external beam radiotherapy administered should be delivered in a dedicated paediatric radiotherapy centre (Landau, Vini et al., 2000).

Discussion

The rarity of paediatric endocrine tumours like DTC makes their management challenging. During the process of guideline development, we have confirmed a general lack of high-quality evidence relating to this age group and identified, through the consensus surveys necessarily undertaken, a professional mandate for both national speciality advisory panels and most importantly, a national register and evaluation of key management outcomes in these rare, eminently curable young patients. If we are to enhance clinical trials and quality of evidence, improve the health-related quality of survival and improve access to, and equity of, expertise in care, such a national register and centralised, advisory panel needs to be expedited alongside the development of tertiary, dedicated and age appropriate, endocrine oncology multidisciplinary teams and services.

The GDG believe that in the UK no child should be looked after without a full thyroid cancer MDT. If no CYP-specific MDT is available, then these patients should be discussed at an adult thyroid cancer MDT. Working through and in collaboration with existing MDTs for adult and paediatric thyroid cancer will ensure best use of resources in the current financial climate. We also recommend treatment at a high-volume tertiary centre where technologies and expertise can be most easily accessed, and the process streamlined with regards to ease of decision making and patient flow. Some additional funding may be needed, for the attendance of additional personnel at the existing MDTs and an ongoing programme of evaluation and audit, but any cost implications for health care budgets must be considered alongside the likely benefits inherent in concentrating management of rare conditions in specific expert MDTs. These include improvements in clinical outcomes and reduced complication rates both of which also greatly improve patient experience. Financial savings are also produced by more efficient referral pathways, reduction in unnecessary and inappropriate investigations and avoiding unnecessary surgical interventions. As the aim of these guidelines is to improve patient care and experience, long-term complications should be reduced with potentially associated improved cost.

Declaration of Interests

Dr Helen Spoudeas: founder of SUCCESS Charity - Life After Cure, www.successcharity.org advocating for the unmet health needs of patients surviving childhood brain tumours registered as LC in January 2019; founder of the national HPAT Virtual interest forum, piloting multidisciplinary virtual decision making for children with complex hypothalamo-pituitary tumours. The other authors have no conflicts of interest to declare.

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Endorsing organisations: RCPCH.

Author contributions

HAS chaired the project board, obtained the funding and co-ordinated the GDG set up. SRH, TRK and MG led the GDG. SRH, TRK and MG were responsible for the study concept and design and drafted the manuscript. SRH and SF undertook the literature search. All authors took part in the grading process, interpreted the data, revised the manuscript critically for important intellectual content, approved the final version to be published, and agreed to be accountable for all aspects of the work.

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Glossary

ATA	American thyroid association
BTA	British thyroid association
CND	central node dissection
CYP	children and young people
DEXA	dual energy X-ray absorptiometry
DNA	deoxyribonucleic acid
DTC	differentiated thyroid carcinoma
FNA	fine needle aspiration
FNAC	fine needle aspiration cytology
FTC	follicular thyroid carcinoma
FVPTC	follicular variant of papillary thyroid carcinoma
GA	general anaesthesia
GDG	guideline development group
MDT	multidisciplinary team
MRI	magnetic resonance imaging
MTC	medullary thyroid carcinoma
NICE	National Institute for Health and Care Excellence
NMTC	non-medullary thyroid carcinoma
PTC	papillary thyroid carcinoma
RAI	radioiodine therapy
RLN	recurrent laryngeal nerve
RNA	ribonucleic acid
RRA	radioiodine ablation
TNM	tumour node metastases
TSH	thyroid stimulation hormone
TYA	teenagers and young adults
Tg	thyroglobulin
US	ultrasound
VCP	vocal cord palsy

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