Thyroid problems in pediatric oncology: damage, prevention and consequences
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I. Endocrine care for the child with cancer

Improved treatment protocols and knowledge on behavior of pediatric malignancies have resulted in a survival of around 70% of children diagnosed with a malignant disease. However, due to the malignant disease or its treatment, acute and late side effects may occur, which often include the endocrine system. Next to disturbances in the thyroid state, also the state of the other endocrine glands regulated by the hypothalamus and pituitary gland may be distorted, especially the somatotrope and gonadotrope state.

The primary aim of maintaining the endocrine integrity of a child with cancer is to guarantee the most optimal development of a child into adolescence, despite the illness or necessary toxic treatments. Secondly, the aim may be to prevent the development of treatment-induced endocrine malignancies. The preventive strategy will depend on the individual situation, e.g. the tumor type, the treatment modalities used and the age of the patient. The severity of the expected side effect should be balanced against the toxicity of the preventive intervention. This makes preventive strategies for children different from those for adults. An example is the protection of the thyroid against radio-iodide with KI in a young child versus an 80-year old person; for the child the primary aim is the prevention of thyroid cancer, in the 80-year old person, considering the latency time of thyroid cancer, the exposure to radio-iodine perhaps does not require prevention, and the administration of KI may even induce hyperthyroidism as adverse effect.

If prevention of endocrine (e.g. thyroid) damage is not possible in the child or has failed, prevention of further damage (e.g. the development of a benign nodule into a carcinoma) or consequences of this damage (e.g. growth or mental retardation due to hypothyroidism) is indicated. This stresses the need for close follow-up, to detect endocrine disturbances in an early phase aiming to maintain an optimal development into adulthood.

The best endocrine advice on when, what and how often to screen the endocrine functions or glands is different for each child. This, because it depends on the cytotoxic drugs that are administered, the radiation treatment, the tumor-type and the age of the patient. For this reason, for each oncological treatment scheme a specific endocrine protocol should be developed, including evaluation of the thyroid, the gonadotrope and the somatotrope axes, based on experiences and evidence gathered from literature.
Also of every child that is or has been treated for a malignant disease, the growth chart should be used, including parental heights, as this will help to detect disturbances of the endocrine system. This endocrine protocol should be included as standard part of the diagnostics and treatment scheme for every child, before, during and after treatment of the malignant disease.

In this general discussion, the ways to prevent thyroid damage, considering the results of the previous chapters, will be discussed, firstly during exposure to radiation and subsequently after exposure to radiation. Also, regarding the effects of chemotherapy the discussion will firstly be about the prevention and implications of negative effects on the thyroid state during treatment and subsequently after treatment with chemotherapy. Considering the impact and frequency of gonadal damage, the ways of prevention and early detection of gonadal damage are also discussed. And lastly, the ways to prevent damage that may occur when a child is confronted with a thyroid malignancy are considered.

II. Prevention of thyroid damage due to irradiation

The aim of protecting the thyroid gland against radiation exposure in children is to minimize the development of hypothyroidism, thyroid nodules and thyroid malignancies. The most optimal way of radiation prevention is eliminating the radiation exposure. As described in the introduction and in chapter 11, this has already been done by replacement of radiotherapy by chemotherapy or by hyperfractionation of the dose. Of course the condition must be made that the change in oncologic treatment is just as effective and it must be evaluated whether the alternative treatment modality does not have other (more) serious adverse effects, such as infertility.

Despite the reduction in use, radiation treatment will remain necessary for several childhood malignancies, and for those cases preventive strategies are needed. The main aspects regarding protection against radiation induced thyroid damage have already been discussed in several previous chapters (2, 3, 4, 6, and 11). Some additional items are discussed in this section.
II.1. Protection of the thyroid during exposure to radio-iodine (e.g. coupled to MIBG)

Prevention of uptake of radio-iodide by the thyroid gland is an important subject, because targeted radiotherapy with $^{131}$I coupled to different compounds is a promising treatment modality, as it gives, in comparison to external irradiation, minimal irradiation damage to surrounding tissues. In children, it is mainly used coupled to MIBG, but in the future it may also be used coupled to other compounds, such as anti-CD20 antibodies to combat lymphoma (currently only used in adults) \(^1\). Also, in the future, transfection of the gene coding for the sodium iodide symporter (NIS), which is responsible for active iodide uptake in the thyroid gland, may be possible in other malignant tissues. After transfection of NIS, $^{131}$I will also be actively taken up by these tissues, so that $^{131}$I-treatment may be an option if this is also subsequently bound to proteins. This is under investigation for future treatment of melanoma, ovarian, liver, colon or prostate cancer \(^2\). Of course, in this case, when $^{131}$I is used in NIS-expressing tumors, thyroid protection can not be done by the administration of compounds that inhibit NIS, as it will also interfere with the therapy. In these situations, thyroid protection will have to be done by inhibition of the thyroid-specific iodide organification or diminishing the concentration of TSH by the administration of thyroid hormone. Alternatively, in this situation, one could outweigh ablation of thyroid tissue with subsequent thyroid hormone substitution therapy to absolutely minimize the chance to develop thyroid tumors.

The protection against radio-iodide during $^{131}$I-MIBG treatment in children with NB is insufficient with KI only, resulting in hypothyroidism (56%) and thyroid nodules (29%) (chapters 2 and 3). As demonstrated in the review, the reduction in uptake of radio-iodide into the thyroid may be up to 97% if KI is administered one hour in advance (chapter 11). If this optimal timing would be feasible in clinical practice, a reduction in uptake of 97% for children must still be considered as a failing thyroid protection, because of the fact that the risk for thyroid carcinoma is high especially in the low to moderate irradiation doses. The newly developed protection with KI, methimazole and T$_4$ (DBR) has improved the thyroid protection in children with NB. However, the protection again failed in 14% of the children, who developed an elevation of TSH, and in 5% of scintigraphic images (13 of 247, chapter 4) in which
uptake on the scintigram was seen (although in the subsequent cohort in addendum 3, the number of scintigraphic images on which the thyroid was visualized was even less). For this patient-group, the prevention of hypothyroidism due to radio-MIBG is important because of their young age, in which an adequate thyroid function is required for a normal development and growth. Protection against radiation exposure of the thyroid gland is even of special importance in children with NB because of the possible increased susceptibility to develop radiation-induced thyroid malignancies. This implies that the prevention of uptake needs further improvement.

A further reduction of thyroid radio-iodide uptake during $^{131}$I-MIBG may be done by adding perchlorate ($\text{ClO}_4^-$), which blocks NIS. As we know from diagnostics in children with a total iodide organification defect, the administration of $\text{NaClO}_4$ intravenously results in a 100% inhibition of the NIS. The administration of $\text{KClO}_4$ orally was tolerated well (chapter 11A). We should consider the addition of $\text{KClO}_4$, orally, for 14 days, to the DBR-protection, to children with NB during exposure to $^{131}$I-MIBG, with careful monitoring of, especially hematological, side effects.

An entirely different way of thyroid protection, would be to replace the radio-iodide in MIBG by other, non-thyroidal specific, radio-nuclides (comparable to the possibility, for the treatment for Hodgkin's disease, to replace $^{131}$I-tositumomab by $^{90}$Y-ibritumomab tiuxetan). For MIBG, an alternative radioconjugate has been searched with the alpha-emitter $^{211}$At (forming meta-astatobenzylguanidine, $^{211}$At-MABG), which was in vitro shown to be very potent and potentially suited for the treatment for micro-metastases due to its short range. However, the short physical half-life ($t_\text{1/2} = 7.2\text{ h}$) and logistic problems are limitations for use of $^{211}$At-MABG for radio-nuclide therapy. Other radio-nuclides might be looked for in the future. Obviously, uptake in NB cells must be warranted and this should first be evaluated in animal models.

A possible cause for a failing thyroid protection in children with NB treated with radio-MIBG that must be considered is the possibility of MIBG entering the C-cells of the thyroid, resulting in radiation damage to the surrounding follicles. Arguments in favor of this hypothesis are that the C-cells have the same origin as the NB cells (neural crest) and that some medullary thyroid carcinoma (MTC) can take up MIBG. If this is the case, prevention of uptake will not be possible with DBR or by blocking
NIS, and early detection of thyroid damage will have to prevent further consequences.

Next to radiation damage from $^{131}$I-MIBG, the possible damage from diagnostic $^{123}$I-MIBG must be discussed. Currently, thyroid protection is administered for 3 days during diagnostic $^{123}$I-MIBG. Due to the short $t_{1/2}$ (8 hours) of $^{123}$I and the relative low dose that is given (110-160 MBq, with 2 to 3% free $^{123}$I$^-$), the chance to develop thyroidal radiation damage will be very low. In comparison, children who are suspected of congenital hypothyroidism (CH) receive $^{123}$I$^-$ in the diagnostic work-up, with an average dose of 1 MBq. This implies that the children with NB are exposed to approximately a 3-fold dose of the considered safe dose given to children with CH. In children with CH, thyroid damage has never been reported (but it can be commented that it is perhaps not observed because they receive T$_4$ substitution for thyroid dysfunction). In our prospective cohort of children with NB, one child developed thyroid dysfunction after a single dose of $^{123}$I-MIBG during admission on the ICU (with KI, methimazole and T$_4$ for thyroid protection), which appeared to be transient when it was evaluated two years later. Whether this period of thyroid dysfunction can be attributed to the $^{123}$I-MIBG administration, to the administration of KI (failing escape mechanism) or that it was mere coincidence is unclear. To answer the question about the possible damaging effect of $^{123}$I-MIBG, the thyroid function of all children that have received only diagnostic MIBG should be evaluated.

As parents are actively involved in the care-taking of the child during $^{131}$I-MIBG treatment, also the thyroid protection of the parents must be discussed. For radiation protection, special precautions are taken, such as disposable gloves, gowns and shoes, instructions to restrict time of exposure, and continuous measurements of radiation dose by pocket dosimeter. For prevention of thyroid uptake of radio-iodide, parents and all other care-takers such as grand-parents are given 200 mg KI for 4 days. It is very unlikely that parents will ingest any radio-iodide, however. They are probably more exposed to the $\gamma$-radiation emitted by $^{131}$I taken up by the child, than to internal radiation. In an evaluation of radiation safety for parents, radiation doses in 13 children and their parents during 34 therapeutic doses of $^{131}$I-MIBG were measured. From this evaluation, it was concluded that the participation of parents in patient care during $^{131}$I-MIBG treatment is safe. In our cohort, one mother has developed hypothyroidism
in the years following $^{131}$I-MIBG treatment of her child, during which, as she has stated, ate the same popsicle as her child. The cause for this hypothyroidism has not been defined, but the chance that her thyroid dysfunction was caused by irradiation or contamination is not likely. Next to the low chance for radiation damage, also the possible side-effects of KI must be considered, especially for the grand-parents who are at increased risk to develop hypo – or hyperthyroidism due to excess iodine (as discussed in the introduction, section 1.1.c).

II.2. Protection of the thyroid during X-radiation

Lowering but not suppressing plasma TSH, does not result into less thyroid damage in rats (chapter 6). A limitation of our rat model may be the radiation dose, i.e. that the occurrence of thyroid tumors in the non-protected irradiated group would have been higher after irradiation with lower doses and the possibility for prevention would have been better when lower irradiation doses were given. In the treatment for childhood cancer, minimal doses of 18-25 to 40 Gy (in case of a brain tumor) are necessary to eradicate the tumor cells, and reduction of total dose will not always be possible, although damage to surrounding tissues can be limited by fractionation of the dose. Our model was appropriate for studies of hypothyroidism, which is also a frequent observed late effect, and the occurrence of hypothyroidism could also not be reduced by endocrine interventions.

These results, combined with the results of the literature review for human and animal studies (chapters 11A and B), leads us to conclude that there is not enough evidence to support the hypothesis that suppression of TSH during exposure to radiation, except by hypophysectomy, leads to less thyroid damage. Recently, however, an abstract was presented in which TSH suppression during cranio-spinal radiation for medulloblastoma and PNET diminished the occurrence of hypothyroidism. These results have to be awaited. An important aspect in lowering the TSH level for radiation protection, is that by lowering the threshold for radiation, the occurrence of thyroid malignancies in the long run might increase, in spite of the fact that hypothyroidism has diminished (chapter 6). This must be evaluated. An alternative for the lack of TSH after hypophysectomy could be the administration of TSH antagonists, which
have been produced mainly for the treatment of TSH producing adenomas. This should be investigated in animals before applying it in humans.

Further research should not only be aimed at suppressing TSH during exposure to radiation, but also other methods should be considered, such as the use of free radical scavengers or anti-oxidants. For future research on this subject, however, it is important to be aware that the prevention must be specific for the thyroid gland, so that the tumor does not benefit from this protection.

II.3. Prevention of thyroid nodules and cancer after exposure to irradiation

An increased TSH after exposure to radiation stimulates the development of thyroid nodules and malignancies. In chapter 11, it was shown that the administration of $T_4$ (lowering TSH) decreases the development and number of benign thyroid nodules after exposure to irradiation. This has also been demonstrated for non-irradiated individuals. For patients (adults and children) with a history of differentiated thyroid carcinoma (DTC) $T_4$ suppression therapy reduces the risk for recurrent disease, although it is still controversial to what extent, how long and for which tumors (low or high risk, papillary versus follicular) this therapy is indicated.

We did not find any evidence, however, that the administration of $T_4$ and subsequent lowering of TSH after irradiation prevents the development of thyroid malignancies (chapter 11 A). These results indicate that in a child that has been irradiated (with radio-iodine or X-radiation to the head-neck region) it is important to monitor TSH to be sure it is not elevated, but there is no evidence that it should be suppressed.

The fact that suppression of TSH, in contrast to hypophysectomy, does not prevent the development of thyroid malignancies after exposure to irradiation may be explained by the fact that thyroid oncogenesis is only partly under influence of TSH and that also other growth factors such as IGF-1 play a role in this process.

In our rat study, we did not include a group with $T_4$ administration for life to prevent the development of thyroid malignancies because, in our opinion, life-long administration of $T_4$ to children in order to prevent thyroid malignancies has many disadvantages (chapter 6). It implies daily medication, regular checks of thyroid function, venae punctures and thyroid ultrasounds, with always the possibility and uncertainty to
develop a thyroid tumor plus the chance to develop side effects due to chronic TSH suppression (such as bone loss \(^{23}\)). If radiation makes the thyroid a potentially malignant organ (substantiated with incidence studies) which causes frequent worries and is a burden to the patient, we believe it may be better to remove all thyroid tissue prophylactically. Of course, this would also imply daily medication with regular checks, but it reduces the risk for a thyroid malignancy to zero. \(T_4\) supplementation to athyroid children can be done very well as there is much experience in children with congenital hypothyroidism. Removal of the thyroid can be done by surgery or by ablation with radio-iodine. Considering the many frequent adverse events of thyroid surgery described in chapter 7, our first choice would be thyroid ablation. An elevated TSH, which is necessary for thyroid ablation can be realized with the administration of recombinant hTSH \(^{24}\). Of course, this strategy would have to be performed in a well-designed prospective trial.

For children with NB, the risk to develop a thyroid malignancy after \(^{131}\)I-MIBG treatment has to be evaluated in the course of time, especially considering their possible increased susceptibility for radiation. This implies that all children who have been treated with MIBG must be followed in time for longer periods.

**III. Prevention and detection of thyroid dysfunction due to chemotherapy**

**III.1. During treatment**

In the introduction and in chapter 9, the many possible effects of (cytotoxic) drugs on the thyroid state have been described. In our cohort, the mean concentrations of TSH, \(T_3\), Tg and cortisol decreased to 53, 67, 69 and 15 % of the baseline value respectively, with an increase in the mean plasma \(rT_3\) to 217 % of baseline. In contrast to what we expected, these alterations in the thyroid state could not be correlated to the physical well-being as scored by a daily questionnaire. This may have several reasons. Perhaps the biochemical changes that we measured did indeed not reflect the actual physical well-being and can all be explained by the effects of glucocorticoids. Another reason, however, could be that the questionnaire is not the appropriate way to evaluate physical well-being, because the children are used to feeling this way and score well,
while in fact their physical well-being is much worse than is reflected in the questionnaire. If this is the case, a more objective way could be to measure IGF-1. The IGF-1 level was low in 53% of patients, which may support the hypothesis that these children were in a worse metabolic state than told by the questionnaire. However, it must be realized that the concentration of IGF-1 is influenced by many factors (e.g. medication) and is therefore also not a very reliable factor.

The impact of finding these alterations in thyroidal state during chemotherapy is unclear, partly due to the many limitations of this study. Firstly, the studied group is very heterogeneous with many different treatment protocols, chemotherapy and tumor types which may all have its own impact on the thyroid state determinants. Furthermore, in 85% of all courses, dexamethasone was administered, interfering with the thyroid state determinants. Lastly, sampling was not done on a regular time interval, making it difficult to determine the period of time and severity of the changes. In spite of these limitations, it is clear that the thyroid hormone state is altered strongly in these children.

It can be hypothesized that having frequent episodes of an altered thyroid state in combination with low IGF-1 levels is unfavorable for a growing and developing child who is receiving cancer treatment during several years, in disregard of the cause (iatrogenic or bad metabolic state). It might, consequently, be beneficial to administer thyroid hormone and/or growth hormone to these patients.

In severe illness, it has been demonstrated that changes in endocrine determinants are partly explained by the hypothalamic releasing factors. This implies that, in order to restore thyroid function, treatment should be done with the administration of TRH. In adults, treatment with TRH alone or in combination with other releasing factors is currently being studied. Also peripheral conversion of $T_4$ to $T_3$ is decreased, implying that replacement of thyroid hormone must be done with the administration of $T_3$ and not $T_4$. The administration of $T_3$ to children with chemotherapy should be investigated in a well designed prospective randomized trial, with adequate monitoring of beneficial and adverse effects (physical condition, height, hair loss, tumor growth and response to oncologic treatment). The finding that thyroid hormone transporters may also be affected during NTI, however, resulting in a decreased transport of thyroid hormone into the cell, would imply that restoring the plasma level of $T_4$ or $T_3$ will be inadequate.
Regarding the low levels of IGF-1, treatment with GH might be beneficial. However, of course firstly the levels of IGF-1 in regard to the malignant disease must be outweighed. At the moment, there is no reason to believe that GH treatment in children after treatment for a primary diagnosis of cancer increases the risk for developing a recurrence of their disease. In a retrospective follow-up study, however, an increase of second neoplasms in oncology patients was found (RR 3.21). It has been commented, that the results of this study must be carefully interpreted, as the Confidence Interval's are wide and unrecognized biases may have been present. Even so, these results indicate that the role of GH in these patients has still not completely been determined and that there is need for continued surveillance.

GH supplementation during cancer treatment is a completely different matter. It has been reported that cancer cachexia may be associated with GH resistance, which has initiated the consideration of GH or IGF-1 to be a therapeutic agent in (adult) cancer patients with cachexia. In mice, stimulation of the GH-IGF-1 axis did not promote tumor growth and was suggested to be a viable treatment for cancer cachexia.

Whether GH-treatment is indicated in children during cancer treatment has never been studied and this should thoroughly be evaluated. Firstly, it must be determined how low IGF-1 levels are and secondly, whether low levels of IGF-1 during cancer treatment are unbeneificial. Dependent on the results, GH supplementation in cancer patients should first be studied in more detail in animal models and adults before children may be treated.

III.2. Prevention and detection of thyroid dysfunction due to chemotherapy after treatment

In contrast to our study (chapter 10), several studies have described an increased risk to develop hypothyroidism after treatment with chemotherapy, with or without irradiation, in childhood cancer survivors (see also introduction, section 1.3.b). Also hypothalamic dysfunction has been described to occur after treatment with chemotherapy.

In some of the studies that reported on hypothyroidism, a high % of thyroid abnormalities could be attributed to the syndrome of non-thyroidal illness (NTI) and were reversible or were considered to be minor abnormalities. In our study, only
a one time measurement of TSH and T<sub>4</sub> was used, so we cannot exclude transient or subtle thyroid abnormalities. However, we feel that normal thyroid function determinants with a lack of clinical symptoms indicate that, for the patient at least, there is no thyroid disease. It must be considered that the radiation exposure overruled all damaging effects of chemotherapy on thyroid function. For this reason, we may not completely exclude the possible negative effects of chemotherapy on the thyroid gland and this should be prospectively evaluated in survivors of childhood cancer, who did not receive any irradiation to the head-neck region.

IV. Prevention of gonadal dysfunction after treatment for childhood cancer

Gonadal damage may develop in girls and boys after treatment with cytotoxic drugs and/or radiation treatment, resulting in hypergonadotropic hypogonadism (gonadal hormone insufficiencies; estrogen or testosterone) and infertility (see introduction, section 1.3.c and 1.4.g)\textsuperscript{34}. Also hypogonadotropic hypogonadism may be present after treatment for craniopharyngioma, other brain tumors near to the hypothalamic-pituitary region or following cranial irradiation.

In the cohort that we evaluated after multi-modality treatment for NB (chapter 3), two boys were diagnosed with hypergonadotropic hypogonadism. Although Leydig cell function loss has been reported to be often mild (consisting of a raised LH level with a low to normal testosterone level)\textsuperscript{34}, it must be a point of attention in all children given cytotoxic agents, especially alkylating agents, because testosterone substitution treatment is relatively simple and can give much quality of life to the patient (all the advantages of prevention of delayed puberty).

For prevention of gonadal damage no established method has been reported yet, although progress has been made at scientific level. Protection of the gonads has been attempted by suppression of the pituitary-gonadal axis by the administration of GnRH analogues both during radiation and during the administration of cytotoxic agents. Studies in animals demonstrated promising results\textsuperscript{27,33,36}. Most studies in humans were disappointing, although several positive results in humans have also been obtained\textsuperscript{35,36}. An example of a positive result is the study performed by Blumenfeld and
colleagues, who demonstrated a protective effect of GnRH-analogue for premature ovarian failure (6% vs. 56%) in women treated with chemotherapy for lymphoma, leukemia or non-malignant diseases. Pregnancy rates were, however, almost identically low for GnRH-treated and non-treated women. Because controversy on the subject still exists, a large prospective study is needed to substantiate the role of GnRH analoga.

It has been suggested, for males, that prevention of fertility relies on the survival of stem cells during the gonadotoxic insult and the subsequent recovery of spermatogenesis, instead of protecting them for cytotoxic damage. This may indicate that the suppression of gonadal function needs to be given for a longer time to provide a sufficient recovery time for the stem cells and that hormonal manipulation will be most beneficial in those patients with the less severe testicular insult (with preservation of stem cells).

Physical prevention of ovarian damage against radiation may be achieved by moving the ovaries from the radiation field, laparoscopically. However, fertility may still be compromised if the uterus has been in the radiation field. The results on storage and re-implantation of (pre- or post pubertal) ovarian and prepubertal testicular tissue look very promising but must still be considered experimental. The tissue can be removed, frozen and stored, then the cytotoxic or radiation treatment can be given and later in life the gonadal tissue can be re-implanted. For results on ovarian tissue it is even more advantageous to be young; the younger the patient, the more follicles are present.

Ovarian function and a first four-cell embryo after ICSI was reported in a 36 year-old woman after reimplantation of cortical pieces of her ovary, 6 years after cryopreservation. In a 32-year old woman with Hodgkin's disease, re-implantation of ovarian tissue restored ovarian function with estrogen production. Very recently, a pregnancy was reported in a woman with Hodgkin's disease after re-implantation of ovarian tissue which restored normal ovarian function with estrogen production and fertility. It was commented, however, that conception in this woman might also have been the result of one of her ovaries that had remained in vivo, which survived the chemotherapy and produced eggs on its own. Furthermore, regarding this technique there are still several important safety concerns. The possibility that malignant cells (especially hematological) are transferred and the possible risks for neonatal deaths
cannot be excluded. However, these very promising results warrant further studies to create options for fertility in those patients who require gonadotoxic drugs or radiation. Another different option to achieve pregnancy when ovarian failure has occurred is ovum donation.

For girls that are post pubertal the only real established method to ensure offspring is embryo cryopreservation. This will, however, not often be realistic for the pediatric field of oncology as many girls will not have a committing relationship at time of disease or will not be able to make such decisions in such short (and emotional) time. An alternative for post-pubertal girls is the option for superovulation and mature oocyte collection. However, little oocytes survive the freeze and thaw process and live birth rate is below one in every 100 oocytes harvested.

For post-pubertal boys, sperm banking remains the only proven efficient prevention strategy for fertility, and should be offered to all post-pubertal boys. This may be a problem though, as malignant disease is often accompanied by poor sperm quality. Sperm testicular extraction techniques have also been developed, which may allow recovery of spermatogenic cells and can subsequently be used with intracytoplasmatic sperm injection (ICSI).

Regarding the hormonal deficiencies after chemo- or radiotherapy, for both girls and boys, detection can be done by measuring plasma LH and FSH concentrations and monitoring puberty. Hormone supplementation is very well possible with estrogens and progesterone for girls and testosterone in boys. Early recognition and treatment of hypogonadism may prevent delayed puberty and improve pubertal development and growth into adolescence. For this reason, hypogonadism should be checked in all girls and boys after cancer treatment.

V. Prevention of adverse events in the treatment of thyroid carcinoma during childhood

V.1 Differentiated thyroid carcinoma (DTC)

For children with differentiated thyroid carcinoma (DTC), although their prognosis is very good (no mortality in our treated cohort), the frequency of adverse events that we found was much larger than was expected (84 %). The most often occurring late
effects were hypoparathyroidism (32%) and recurrent nerve injury (24%) (chapter 7). The low incidence of thyroid carcinomas results in a low number of thyroidectomies a year per surgeon. The surgeon's expertise is one of the main risk factors to develop hypoparathyroidism or recurrent nerve injury after thyroidectomy. This may be overcome by operating all children by one team in Holland or even abroad or including an adult endocrine surgeon to the operating team to share expertise of the thyroidal operation field (which is currently done in Emma Children's Hospital, AMC). Another way of prevention of these adverse events can be by surgically removing the bulk of the tumor but leaving a small remnant behind, reducing the extent of the surgical intervention. The remnants can be ablated with radio-iodine.

Radio-iodine ablation is routinely done in all children to destroy any occult metastases and any residual thyroid tissue, after which monitoring of recurrent thyroid tumor with plasma Tg is possible. In a recent performed systematic review on the effectiveness of radio-iodide remnant ablation on decrease of thyroid-cancer related death or recurrence of disease, a suggestive significant decrease of recurrences and distant metastases were found. However, many confounding factors and inconsistent results were mentioned, so the real benefit from radio-iodide remnant ablation is still to be determined in a prospective randomized trial.

A hypothetical way to completely prevent damage due to the surgical intervention is to treat DTC with radio-iodine ablation only ("upfront ablation"). This has never been done in humans and should firstly be evaluated in an animal model. With ablation therapy, no surgical complications are to be expected. It must be evaluated whether the number of \(^{131}\text{I}\) treatments remain the same, because if the number of \(^{131}\text{I}\) treatments would increase, it might be an argument against "upfront ablation" due to the phenomenon of stunning.

The phenomenon of stunning was first reported in 1951, and described the fact that the administration of a diagnostic dose of \(^{131}\text{I}\) (75-400 MBq) reduces the efficacy of the subsequent \(^{131}\text{I}\) therapy (1.1-11 GBq). It is still controversial whether this phenomenon actually has any effect on therapeutic efficacy. The fact that stunning does not occur after diagnostics with \(^{123}\text{Tm}\) (740 MBq), however, implies that if stunning occurs, it must be caused by radiation damage resulting in a decrease in
number of cells or in the ability of the cells to accumulate radio-iodine \(^{46}\). This also implies that to prevent stunning, diagnostics should be done with \(^{123}\)I\(^-\) or that, following thyroidectomy, ablation should be done immediately without previous diagnostics accompanied by scintigraphic images during therapy.

Next to stunning after diagnostics, evidence has also been provided that repeated \(^{131}\)I\(^-\)-treatments are, in time, less effective ('the first strike has the highest therapeutic benefit') \(^{49}\). This may partly be caused by oncobiologic changes. Part of the tumor transforming into undifferentiated carcinoma will result in diminished \(^{131}\)I\(^-\) uptake or organification \(^{22,49,50}\). In contrast with these reports, several studies have reported that stunning has no impact on therapeutic outcome \(^{15}\).

For the discussion about the possibility of upfront \(^{131}\)I\(^-\) ablation, it is important to evaluate the number of \(^{131}\)I\(^-\)-treatments needed to ablate the thyroid gland with DTC completely and whether the effect of stunning is a real contra argument and how far this effect has implications on therapeutic efficacy.

The second aspect, next to therapeutic efficacy is the safety aspect of treatment with \(^{131}\)I\(^-\). Adverse events such as leukemia have been discussed in chapter 7. Long term follow-up will have to determine the significance for an increased risk of leukemia. Considering the fact that the dose of radiation will not be different if it is given upfront, the safety aspect does not seem to be an argument against upfront ablation. In conclusion, treatment for DTC must be done as radical and as safe as possible. Prevention of adverse events might be the upfront treatment with radio-iodide ablation. This must be evaluated in an animal model.

V.2. Medullar thyroid carcinoma (MTC)

As explained in the introduction and in chapter 8, prevention of MTC in MEN-2A patients is based on genetic screening. For carriers of this mutation, it is currently advised to perform thyroidectomy before the age of 5 years. However, since also MTC in younger patients (age 1, age 2.8 and 3.7 years) have been reported \(^{51}\) and , as we have demonstrated, many problems can occur when prophylaxis is performed too late, we feel that it should be considered to perform thyroidectomy as soon as possible after diagnosis of MEN-2A. There are several arguments in favor of performing
prophylactic thyroid surgery already at the age of one or two years. The first is the above mentioned case of early MTC. The second is the emotional aspect for the child for whom surgery at very young age is easier than at age 4 or 5 years. Also, $T_4$ supplementation therapy from young age (even from birth) is very well feasible. An argument against surgery at these young ages is that the operation field is, of course, smaller, which might increase the risk for hypoparathyroidism and recurrent nerve injury and this should be carefully outweighed. "Prophylactic" upfront ablation for these patients does not seem appropriate, as the C-cells do not take up $^{131}$I and there might be a chance that not all C-cells will be destroyed. Regarding the fact that the histological evaluation can be extremely difficult, as illustrated in chapter 8, it may be wise to always perform central lymph node dissection at time of prophylactic surgery. Although metastases have been reported to be very rare at these young ages, the benefit of being really prophylactic is so much greater than having to perform additional operations afterwards. Of course the balance between the risk for metastases against the risk of complications due to lymph node dissection must be carefully outweighed.

It is not wise to wait for calcitonin (CT) levels to rise, as an increased CT production is already a sign of C-cell hyperplasia and possible MTC. In case of post-operative levels of elevated CT, a total cervical and central lymph node dissection should be performed as soon as possible, as this may still be curative. If, after total lymph node resection CT is still elevated, it must be considered on time to withdraw from all further additional investigations and await clinical signs, with of course, a maximum of supportive care. This may be considered "secondary" prevention of further damage. For the treatment of MTC, further therapies must be developed, such as gene therapy (NIS, p53, RET-mutants and others).  

VI. Suggestions for further research

In the different chapters of this thesis, the frequency and prevention of (especially) thyroid problems, during or after treatment for childhood malignancies were evaluated. Some answers to questions were found, but also many questions remain unanswered. Also, during this research new questions evolved. For future research, the following suggestions may be useful.
Research on the consequences and prevention of damage due to radio-MIBG

Although the prevention of thyroid damage was improved by the introduction of DBR, the addition of (Na or K)-ClO₄, orally, for 14 days, to the DBR-protection, to children with NB during exposure to ¹³¹I-MIBG, with careful monitoring of, especially hematological, side effects must be evaluated. Regarding the development of thyroid nodules, there seems to be an increased frequency of thyroid nodules after treatment with ¹³¹I-MIBG, however, it is unsure how this will develop in the long run and if there is an increased risk to develop thyroid malignancies. For this, all children treated with ¹³¹I-MIBG must be followed for a longer period in prospective clinical trials, with ultrasound imaging of the thyroid gland, and, in case of suspect nodules, with FNAC. An important limitation, which we encountered, however, is that the frequency of thyroid nodules in healthy children anno 2004 is not known. This should be evaluated. Furthermore, to answer the question about the possible damaging effect of diagnostic ¹²³I-MIBG, the thyroid function of all children that have received only diagnostic MIBG should be evaluated.

Research on the prevention of thyroid damage due to X-radiation

Although the reduction or even elimination of radiotherapy is, for the thyroid gland, the best possible way to prevent radiation damage, the effect of elimination of radiotherapy versus the increase in administration of chemotherapy (type of drugs and increasing dose) must be thoroughly evaluated in a prospective trial with regards to survival and occurrence of (other) late effects, such as gonadal damage. For protection of the thyroid during and after radiation therapy, although we have argued that it is in our opinion not feasible to treat a child with suppressive doses of T₄ for life without the 100% security of prevention of thyroid malignancies, it may be scientifically relevant to investigate in a prospective well designed study in animals whether continuous treatment with T₄ can prevent the occurrence of thyroid malignancies after radiation exposure. Also, the role of TSH antagonists for the prevention of radiation induced thyroid carcinoma as alternative for hypophysectomy should be investigated in an animal model. Other ways to protect the thyroid may be the administration of free radical scavengers or anti-oxidants, such as amifostine and selenium-salts. This should be evaluated in an animal model.
For early detection of patients who are at increased genetic risk to develop thyroid malignancies after radiation exposure, screening techniques such as the COMET assay should be further developed. In this way, patients with an increased risk may be offered prophylactic thyroidectomy or thyroid ablation.

Something completely different was the observation that the hair loss of animals given T_4 during and two weeks after irradiation seemed less severe than of the rats who did not receive T_4 (non published data). As alopecia is a distorting side effect of chemo- and radiotherapy, this should be evaluated in a prospective study in animals, and subsequently, if this is confirmed, a trial should be done on the administration of thyroid hormones during radiation and chemotherapy to prevent hair loss.

Research on the effects of chemotherapy on the thyroid gland

To obtain more insight in the disturbances of the endocrine system during treatment with chemotherapy, a prospective study on the frequency and severity of endocrine disturbances in children during chemotherapy must be done, which relates these disturbances to development into adulthood. Within this evaluation, a special evaluation of low IGF-1 concentrations in children should be done, which relates these concentrations to growth, weight, clinical well-being and tumor progression. If this research has demonstrated that the endocrine determinants are severely disturbed, a prospective randomized study should be considered which compares T_4 or T_3 supplementation to no supplementation of thyroid hormone in children during treatment for cancer on long term outcome, well being and growth. Also, in animals the supplementation of GH during cancer treatment must be further evaluated.

To evaluate the possible negative late effects of chemotherapy, in patients who have not been irradiated, a cross-sectional analysis should be done on all childhood survivors who have received chemotherapy but no irradiation to the head-neck region.

Research on differentiated thyroid carcinoma

To prevent side effects of surgical intervention in differentiated thyroid carcinoma, an animal model should be made for differentiated thyroid carcinoma in which the upfront treatment with ablation instead of surgical removal is evaluated.
VII. Recommendations for clinical practice based on the current available evidence

For all children with malignant diseases

1. For each oncological treatment protocol, a corresponding endocrine protocol should be developed for early detection of endocrine damage.

2. Of every child treated for malignant disease, a growth chart (with knowledge of parental height) should be used in the follow-up for early detection of endocrine disturbances.

3. Thyroid function should not be screened during treatment with dexamethasone as this will interfere with the thyroid state and interpretation of the results.

For children with neuroblastoma

4. Before the first $^{131}$I-MIBG treatment, the thyroid function should be determined to know the thyroid plasma determinants for the individual patient (the patients' own setpoint).

5. During diagnostics and treatment with $^{123/131}$I-MIBG the thyroid should be protected with KI (3 dd 30 mg KI), methimazole (2 dd 0.5 mg/kg) and thyroxine (125 μg/ m² per day) (see addendum 2).

6. After $^{131}$I-MIBG treatment the thyroid function should be checked every three months in the first two years after stopping therapy, then every 6 months, including plasma TSH and FT₄. An ultrasound of the thyroid gland for the detection of nodules and monitoring of their behavior should be performed at diagnosis and at one year intervals.

7. Follow-up of thyroid function should not be done during diagnostic procedures with $^{123}$I-MIBG.

For children who are treated with X-radiation to the head-neck region

8. All children that have been irradiated in the head-neck region should be screened for thyroid function (FT₄, TSH and Tg) at least every 6 months for the first 5 years and annually thereafter. Considering the latency time of thyroid malignancies, screening for thyroid carcinoma should be done by routine ultrasonography of the thyroid gland, annually, life-long.
For children with thyroid carcinoma

9. Because the remnants of thyroid tissue after thyroidectomy for differentiated thyroid carcinoma (DTC) can be ablated with radio-iodide, only the large bulk of tumor should be removed. This may reduce the occurrence of hypoparathyroidism and recurrent nerve lesions. Also transplantation of the parathyroid glands should be considered.

10. Because medullary thyroid carcinoma (MTC) in MEN-2A patients has been described in a patient of age 1 and the consequences of disseminated MTC are severe, prophylactic thyroid surgery for patients with MEN-2A should be done as soon as possible in life (preferably between age 1 and 4).
References


