radiation-induced stem cell sterilization. In adult salivary gland stem cells it is known that post-radiotherapy stimulation of cell proliferation results in improved saliva secretion when part of the tissue has been spared or when the dose to the salivary gland remains below a certain level [53]. A recent publication provided evidence on the existence of thyroid stem cells and of thyroid progenitors [54]. Antonica et al. [55] even found that embryonic stem cells of the mouse could be induced to differentiate into thyroid follicular cells and to generate functional thyroid tissue in vitro and to promote subsequent symptomatic recovery in vivo in athyroid mice. Clearly more research needs to be done with stem cell replacement of patients with radiation-induced hypothyroidism.

**Summary**

The incidence of hypothyroidism is high in patients treated for laryngeal or hypopharyngeal carcinoma and varies in different studies depending on site, stage, treatment and time after treatment.

Hypothyroidism can cause a variety of symptoms affecting quality of life negatively. Physical and physiological problems due to hypothyroidism can be wrongly attributed to the oncological treatment. Subclinical hypothyroidism has not only been shown to predispose to clinical hypothyroidism but can cause wound healing problems and atherosclerotic disease as well.

Although hypothyroidism is a well-known complication following treatment of laryngeal or hypopharyngeal carcinoma the condition is often misdiagnosed and no detailed consensus regarding thyroid testing is available.

In this thesis we describe the incidence of hypothyroidism in patients treated for laryngeal or hypopharyngeal carcinoma in a cross-sectional and a prospective study. We investigated risk factors in the development of hypothyroidism and the effect of substitution therapy in patients with (sub)clinical hypothyroidism. Furthermore we performed a survey among head and neck physicians in The Netherlands, treating laryngeal or hypopharyngeal carcinoma patients, to evaluate the current management in thyroid function testing.

In **Chapter 2** the results of a cross-sectional study are presented. We found in 28.2% patients treated for laryngeal or hypopharyngeal cancer undiagnosed (18.6% subclinical and 9.6% clinical) hypothyroidism and 11.3% of these patients were already known with hypothyroidism (overall hypothyroidism 39.5%).
Furthermore we found that patients treated with laryngectomy, hemithyroidectomy and radiotherapy were more at risk to develop hypothyroidism (63.6%) as compared to patients treated with laryngectomy without hemithyroidectomy and radiotherapy (33.3%) and radiotherapy only (15.7%). Although univariate analysis showed that laryngectomy, hemithyroidectomy, ipsilateral neck dissection and autoantibodies were associated with hypothyroidism, in multivariate analysis only hemithyroidectomy remained a prognostic factor.

Patients filled out a questionnaire regarding symptoms associated with hypothyroidism: only weight gain and cold intolerance were associated with (subclinical) hypothyroidism.

We found in 10.5% of patients circulating anti-thyroid antibodies. Fifty percent of the patients with circulating anti-thyroid antibodies had hypothyroidism.

The results of the study indicate that thyroid function should be tested; especially after combination treatment of surgery and radiotherapy. It was concluded that the role of anti-thyroid antibodies in the development of hypothyroidism should be further investigated.

Based on these initial results we started a new prospective study as described in Chapter 6.

In Chapter 3 we evaluated the management of thyroid function testing in the major institutions treating head and neck cancer in The Netherlands (nineteen hospitals including all eight head and neck centers of the Dutch Head and Neck Society (Nederlandse Werkgroep Hoofd-Halstumoren; NWHHT)). Eighty-four percent of questionnaires were returned. Seventy-five percent of the physicians tested only thyroid function when symptoms were mentioned. Most physicians who screen on thyroid function, test annually (32%) or every six months (24%). Although, at the time of the survey in 2007, 75% of physicians were aware of the guidelines of the NWHHT, 65% would appreciate more clear and detailed guidelines.

In Chapter 4 we evaluated the effect of substitution therapy in patients with (sub)clinical hypothyroidism on various psychological and physical effects. Ninety-four percent of the patients returned a study specific questionnaire. Moodiness, emotional and physical problems were most often reported. Substitution therapy only resulted in an improvement of energy, sense of general interest and enjoyment and a reduction of a puffy face. With this knowledge of this health related questionnaire a better understanding of patients’ symptoms with hypothyroidism is possible.
In Chapter 5 we describe a retrospective study in which we selected patients with laryngeal or hypopharyngeal carcinoma who underwent paratracheal lymph node (PTLN) dissection in combination with a laryngectomy, hemithyroidectomy and radiotherapy. Seventy percent of the tested patients had hypothyroidism (34% subclinical hypothyroidism; 36% clinical hypothyroidism) and 33% had hypoparathyroidism. We found no additional risk of a contralateral PTLN dissection for the development of hypo(para)thyroidism.

In Chapter 6 we present our prospective study with a follow-up time of two years. We tested thyroid function, parathyroid function and anti-thyroperoxidase antibodies (before treatment) of a laryngeal or hypopharyngeal carcinoma (was started) and every six months thereafter. Several patient, tumor and treatment characteristics were analyzed. We found an incidence of hypothyroidism of 47.4% (27.7% subclinical hypothyroidism; 19.7% clinical hypothyroidism) and 7.3% for hypoparathyroidism. Only 5 patients developed positive anti-thyroid antibody, therefore no association between hypothyroidism and circulating antibodies could be found. We found a higher incidence of hypothyroidism (81.8%) in patients treated with combination treatment of surgery and radiotherapy. Because all our patients with total laryngectomy underwent hemithyroidectomy as well, and hemithyroidectomy is the most important risk factor in the development of hypothyroidism, we examined the removed thyroid tissue. The incidence of thyroid gland invasion was only 10.8% and the incidence of pathological changes other than tumor involvement (radiation changes, fibrosis, inflammation, goiter or colloid cyst) was 54.1%. Although the incidence of hypothyroidism in patients with pathological changes in the thyroid was 60-90%, no significant association was found between pathological changes and the development of hypothyroidism. We did not find radiation dose or the addition of chemotherapy to radiotherapy to increase the incidence of hypothyroidism. As found in other studies, neck dissection appeared to be an important risk factor. We did find paratracheal lymph node (PTLN) dissection to be a risk factor in the development of hypothyroidism as well although our previous study (Chapter 5) showed no additional risk of a contralateral PTLN dissection.

In this study we detected 80% of hypothyroidism within 6-12 months after treatment with a median time of 10 months. Based on the time interval between detection of hypothyroidism and oncological treatment the following screening protocol was advocated: every 3 months in the first year after treatment, every 6 months in the second year and annually thereafter. From this study it
was concluded that the incidence of hypothyroidism is high after treatment especially after combination treatment of surgery and radiotherapy. Besides the combination of laryngectomy and hemithyroidectomy, neck dissection, PTLN dissection and increasing age are associated with an increased risk of hypothyroidism. No relation between hypothyroidism and circulating anti-thyroid antibodies or hypothyroidism and hypoparathyroidism was found.

Conclusions

Based on the research described in this thesis we conclude the following:

1. The incidence of hypothyroidism is high, especially after combination treatment.

2. Laryngectomy, hemithyroidectomy, neck dissection and paratracheal lymph node dissection are the most important risk factors.

3. Psychological and physical symptoms attributed to oncological treatment may be due to hypothyroidism as well. Results of questionnaires may point to hypothyroidism and may indicate testing of thyroid function.

4. No uniformity in the management of thyroid testing after treatment of laryngeal or hypopharyngeal carcinoma was found in The Netherlands.

5. Thyroid screening pre-treatment, every 3 months the first year, every 6 months the second year and annually thereafter in patients treated for laryngeal or hypopharyngeal carcinoma is recommended.