SAARA METSO

Long-term Prognosis of Patients Treated with Radioactive Iodine for Hyperthyroidism

ACADEMIC DISSERTATION
To be presented, with the permission of the Faculty of Medicine of the University of Tampere, for public discussion in the small auditorium of Building K, Medical School of the University of Tampere, Teiskontie 35, Tampere, on October 19th, 2007, at 12 o’clock.
To patients treated with radioactive iodine for hyperthyroidism
ABSTRACT

Radioactive iodine (RAI) has been commonly used to treat hyperthyroidism since the 1940’s. Hypothyroidism has become an accepted outcome of RAI treatment. Most clinics therefore prefer a fixed dose regimen in RAI treatment instead of calculating the dose on grounds of the size of the thyroid gland and the uptake of RAI. However, no consensus exists regarding the ideal first dose of RAI in the treatment of hyperthyroidism. In previous long-term follow-up studies, cardiovascular morbidity and mortality have remained increased years after the treatment of hyperthyroidism. However, it is not known, which cardiovascular diseases cause the increased risk of cardiovascular morbidity and death. Previous long-term follow-up studies of cancer risk in patients treated with RAI for hyperthyroidism have been conflicting, reporting either increased, decreased or equal cancer risk in RAI-treated patients compared with the general population. Moreover, it is not known, whether the etiology of hyperthyroidism, the dose of RAI, or the effectiveness of the RAI treatment contribute to the cardiovascular and cancer morbidity and mortality. The aim of this thesis was to clarify these aspects concerning the long-term safety of RAI treatment for hyperthyroidism.

Details on the etiology of hyperthyroidism, the treatments, and the outcome of 2793 patients treated with RAI therapy at the Tampere University Hospital between 1965 and 2002 were entered into a computerized register. After the RAI treatment, the thyroid status of the patients was monitored every 1-3 months during the first year, and subsequently at 1-3 years’ intervals until June 2002 or until the patient died or moved out of the Tampere University Hospital district. The outcome after RAI treatment was studied on 2043 patients followed-up for more than one year after the first RAI treatment (I). The cumulative incidence of hypothyroidism in patients with Graves’ disease was 24% at one year and 82% at 25 years, respectively. Hypothyroidism developed in 4% of patients with toxic nodular disease by one year and in 32% by 25 years after RAI treatment. Administration of a single dose of RAI resulted in the control of hyperthyroidism in 75% of patients in both etiologic groups.

A population-based cohort study was conducted among all 2793 hyperthyroid patients treated with RAI at the Tampere University Hospital between 1965 and 2002, and 2793 age- and gender-matched reference subjects. The follow-up period of patients started at the end of the year of the first RAI treatment. The follow-up period of the control subject started at the same time as that of the corresponding patient. For both patients and controls, the follow-up ended on the date of the first hospitalization (II), cancer diagnosis (III), death (II-IV), emigration from Finland (II-IV), or the common closing date (December 31, 2003), whichever occurred first. Median follow-up time was 9 years. Information on hospitalizations was obtained from the Hospital Discharge Registry (HILMO) (II), cancer incidence from the Finnish Cancer Registry (III), and mortality from the Finnish Population Register Centre and the Statistics Finland (II-IV).

The rate of hospitalization due to cardiovascular diseases was higher among the patients with hyperthyroidism than among the control population (637.1 vs. 476.4 per 10,000 person-years, with a rate ratio (RR) of 1.12 (95% CI 1.03-1.21), II). The risk remained elevated up to 35 years after RAI treatment. Hospitalizations due to atrial fibrillation (RR 1.35, 95% CI 1.11-1.64), cerebrovascular diseases (RR 1.31, 95% CI 1.14-1.51), diseases of other arteries and veins (RR 1.22, 95% CI 1.05-1.43), hypertension (RR 1.20, 95% CI 1.02-1.41), and heart failure (RR 1.48, 95% CI 1.24-
1.76) were more frequent in the patients than controls, whereas no such difference was found for coronary artery disease (II).

Cancer incidence among hyperthyroid patients treated with RAI was higher than in the population-based control group (118.9 vs. 94.9 per 10,000 person-years, with a RR of 1.23 (95% CI 1.08-1.46), III). The difference in cancer incidence started to emerge five years after the first RAI treatment. The cancer incidence after 10 or more years of follow-up was 154.4 per 10,000 person-years in the patients and 126.4 in the control group (RR 1.22, 95% CI 1.00-1.53). The incidence of stomach (RR 1.75, 95% CI 1.00-3.14), kidney (RR 2.32, 95% CI 1.06-5.09), and breast (RR 1.53, 95% CI 1.07-2.19) cancer was increased among RAI-treated patients (III).

All-cause mortality was higher in the patients than the controls (453 vs. 406 per 10,000 person-years, with a RR of 1.12 (95% CI 1.03-1.20), IV). Cerebrovascular diseases accounted for most of the increased mortality among patients (RR 1.40, 95% CI 1.16-1.69), and mortality from cancer increased (RR 1.29, 95% CI 1.07-1.57) as well (IV).

In Cox regression analysis, RAI-treated hyperthyroidism and age increased the risk of cardiovascular morbidity, cancer, and death, while the development of hypothyroidism reduced the risk (II-IV).

In summary, patients treated for hyperthyroidism constitute a high-risk group for cardiovascular diseases, and the excess risk is sustained decades after the treatment of hyperthyroidism. Furthermore, cancer risk slightly increases after 5 years from the treatment with RAI. The objective of RAI treatment should be eradicating hyperthyroidism at the lowest effective dose of RAI. Patients may benefit from life-long follow-up targeting at the early recognition and treatment of hypothyroidism, and primary and secondary prevention of cerebrovascular risk factors and arrhythmias. Furthermore, patients treated with RAI should be encouraged to attend the cancer screening programs available in Finland.
TIIVISTELMÄ


aivoverenkierron sairauksien (RR 1.31, 95% CI 1.14-1.51), muiden
verisuonisairauksien (RR 1.22, 95% CI 1.05-1.43), verenpaineen (RR 1.20, 95% CI
1.02-1.41) ja sydämen vajaatoiminnan (RR 1.48, 95% CI 1.24-1.76), mutta ei
sepelvaltimotaudin vuoksi.

Kaikkien syöpien ilmaantuvuus oli korkeampi potilailla kuin kontrolliryhmällä
(118.9 vs. 94.9 10,000 potilasvuotta kohti, RR 1.23 (95% CI 1.08-1.46), III). Ero
syöpäilmaantuvuudessa alkoi näkyä 5 vuotta ensimmäisen RAJ-hoidon jälkeen.
Syövän ilmaantuvuus yli 10 vuoden seurannan jälkeen oli 154.4 10,000
henkilövuotta kohti potilailla ja 126.4 kontrolleilla (RR 1.22, 95% CI 1.00-1.53).
Maha- (RR 1.75, 95% CI 1.00-3.14), munuais- (RR 2.32, 95% CI 1.06-5.09)
jaa rintasyövän (RR 1.53, 95% CI 1.07-2.19) ilmaantuvuus oli potilailla korkeampi
kuin verrokeilla (III).

Hypertyreoosin vuoksi RAJ-hoidon saaneiden potilaiden kokonaiskuolleisuus
oli korkeampi kuin väestöpohjaisen kontrolliryhmän (453 vs. 406 10,000
potilasvuotta kohti, RR 1.12 (95% CI 1.03-1.20), IV). Aivoverenkiertosairaudet
selittivät valtaosan potilaiden ylikuolleisuudesta (RR 1.40, 95% CI 1.16-1.69). Myös
syöpäkuolleisuus oli potilailla korkeampi kuin verrokeilla (RR 1.29, 95% CI 1.07-
1.57, IV).

Coxin regressioanalyysissä RAJ-hoidettu hypertyreoosi ja ikä lisäivät
ja hypotyreoosin kehittyminen vähensi riskiä sairastua ja kuolla sydän-
ja verisuonisairauteen tai syöpään (II-IV).

Yhteenveto: Hypertyreoosin vuoksi hoidetuilla potilailla on lisääntynyt riski
sairastua ja kuolla sydän- ja verisuonisairauksiin. Lisääntynyt riski säilyy
vuosikymmeniä hypertyreoosin hoidon jälkeen. Lisäksi syöpärisi lisääntyy jonkin
verran 5 vuotta RAJ-hoidon jälkeen. RAJ-hoidon tavoite tulisi olla hypertyreoosin
tehokas hoito mahdollisimman pienellä RAJ-annoksella. Potilaat saattavat hyötyä
elämän mittaisesta seurannasta, jonka tavoitteena on hypotyreoosin varhainen
toteaminen ja hoito, sekä aivoverenkiertosairauksien ja rytmihäiriöiden primaari-
ja sekundaaripreventio. Lisäksi RAJ-hoidon saaneita on syytä
kehoittaa osallistumaan Suomessa saatavilla oleviin yleisiin syöpäseulontoihin.
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ABBREVIATIONS

$^{131}$I radioactive iodine
AF atrial fibrillation
CI confidence interval
DNA deoxyribonucleic acid
ECG electrocardiogram
Gy Gray; unit for absorbed dose of radiation
ICD International Classification of Diseases
INR international normalized ratio
MBq Mega Bequerel; unit for radioactivity ($10^6$ disintegrations per second)
NIS sodium-iodine symporter
NNH number needed to harm
mCi millieCurie; unit for radioactivity ($3.7 \times 10^7$ disintegrations per second)
RAI radioactive iodine
RR rate ratio
SMR standardized mortality ratio
SI international system of units
SIR standardized incidence ratio
TSab thyroid stimulating antibodies
TSH thyrotropin
T3 tri-iodothyronine
T4 thyroxine
US The United States of America
LIST OF ORIGINAL COMMUNICATIONS

This thesis is based on the following four original publications, which are referred to in the text by their Roman numerals I-IV.


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INTRODUCTION

Hyperthyroidism is a substantial health issue, affecting approximately 2% of women and 0.2% of men (Tunbridge et al. 1977). Hyperthyroidism is a pathological syndrome in which the body of the affected individual is exposed to an excessive amount of circulating thyroid hormones (Cooper 2003). The most common cause of hyperthyroidism is Graves’ disease (Weetman 2000), followed by toxic multinodular goitre, and solitary hyperfunctioning nodules (Siegel and Lee 1998). The diagnosis of hyperthyroidism is generally straightforward, with clinical suspicion confirmed by raised serum free thyroxine (T4) and suppressed serum thyrotropin (TSH) (Cooper 2003). Antithyroid drugs, radioactive iodine ($^{131}$I, RAI), and surgery are the traditional treatments for hyperthyroidism. None of these represents an optimal treatment for the hyperthyroidism, and potential complications are associated with each therapeutic option. Antithyroid drug therapy with thionamides is associated with side-effects and a high relapse rate even after prolonged therapy (Cooper 2005). Thyroidectomy achieves a high rate of remission, yet it is an invasive procedure that can result in hypoparathyroidism or dysphonia in 1-2% of patients (Sosa et al. 1998, Palit et al. 2000).

RAI has been commonly used as a therapy for hyperthyroidism since the 1940’s (Chapman 1983), and it was proved clinically efficient, simple, and cost-effective in comparison with the other therapeutic alternatives, i.e. long-term antithyroid medication and surgery (Ljunggren et al. 1998, Patel et al. 2006). Originally, the aim of the RAI treatment was to destroy thyroid tissue sufficiently to cure hyperthyroidism and to render the patient euthyroid. However, it was soon realized that while RAI treatment was highly effective, it led to the development of hypothyroidism in up to 70-80% of the patients (Dunn and Chapman 1964, Green and Wilson 1964, Nofal et al. 1966, Holm et al. 1982). For years, clinicians tried to titrate the dose of RAI individually on the basis of the size and RAI uptake of the thyroid gland to guarantee a euthyroid outcome. Despite the potential benefits of the calculated doses, several studies failed to demonstrate improvements in the cure rate or development of hypothyroidism over fixed doses of RAI (Smith and Wilson 1967, Jarlov et al. 1995, Peters et al. 1995, Leslie et al. 2003). Nowadays, most clinics
use a fixed dose of RAI in the treatment of hyperthyroidism. However, no consensus exists about the optimum dose of RAI to be used in the fixed dose scheme.

Hyperthyroidism has been regarded as a reversible disorder without long-term consequences, when treated effectively. However, long-term follow-up studies have revealed an increased cardiovascular mortality in those with a past history of hyperthyroidism treated with RAI compared with the general population (Goldman et al. 1988, Goldman et al. 1990, Hall et al. 1993, Franklyn et al. 1998). Instead of RAI treatment, hyperthyroidism per se probably accounts for the elevated cardiovascular mortality, since hyperthyroidism is known to exert direct effects on the myocardium and the autonomic nervous system (Klein and Ojamaa 2001, Osman et al. 2002). Recently, an increased risk of hospitalization due to cardiovascular disease was reported to persist years after the treatment of hyperthyroidism suggesting that the cardiotoxic effects of hyperthyroidism are not fully reversed by restoring euthyroidism (Nyirenda et al. 2005). However, it is not known, which cardiovascular diseases cause the persistently increased risk of death and morbidity after the treatment of hyperthyroidism.

Even though RAI has been used for the treatment of hyperthyroidism for decades, concerns remain about the subsequent risk of malignant disorders, since the patients are exposed to ionizing radiation. Previous long-term follow-up studies on cancer risk in patients treated with RAI for hyperthyroidism have yielded conflicting results. Studies have reported either an increased risk (Holm et al. 1991, Hall et al. 1992a), a decreased risk (Franklyn et al. 1999), or an unchanged risk of cancer (Goldman et al. 1988, Ron et al. 1998) in patients treated with RAI for hyperthyroidism, compared with the general population.

The purpose of this thesis was to clarify the long-term safety aspects of RAI treatment for hyperthyroidism. We assessed the cure rate and cumulative incidence of hypothyroidism among patients treated with RAI for hyperthyroidism during a long-term follow-up. The special focus was on the cardiovascular and cancer morbidity and mortality of the hyperthyroid patients treated with RAI. We also studied, whether the etiology of hyperthyroidism, the dose of RAI, or the outcome of the RAI treatment contributed to the cardiovascular and cancer morbidity and mortality of the patients.
REVIEW OF THE LITERATURE

1. Hyperthyroidism

1.1. Definitions

The term thyrotoxicosis refers to the biochemical and physiological manifestations of excessive amount of circulating thyroid hormones, irrespective of the underlying cause. The term hyperthyroidism has been restricted to the diseases in which the thyroid gland synthesizes and secretes increased amounts of hormones. However, the distinction in the literature between thyrotoxicosis and hyperthyroidism has not always been clear and does not necessarily refer to the pathophysiology of the condition (Larsen 1998).

1.2. Historical overview

Thyrotoxicosis was first described by Caleb Hillier Parry in England in 1786, but his report was not published until after his death in 1825 (Fye 1992). Thyrotoxicosis was again described by Robert Graves in Ireland in 1835 (Taylor 1986), and by Carl A. von Basedow in Germany in 1848 (Hennemann 1991).

Subtotal thyroidectomy was the oldest form of therapy for hyperthyroidism, with the Nobel prize awarded to doctor Theodor Kocker in 1909 for his innovations in this area (Cosimi 2006). Drug therapy for hyperthyroidism was introduced in the early 1940’s by doctor E.B. Astwood (Astwood 1984). Radioactive iodine (RAI) therapy for hyperthyroidism was first introduced in the 1940’s by a Massachusetts General Hospital group and a University of California-Berkeley group, independently (Chapman 1983). Treatment of hyperthyroidism with RAI has been available in Finland since the 1950’s (Lamberg 1959).

1.3. Causes of thyrotoxicosis

In most cases, thyrotoxicosis is caused by a disease of the thyroid gland leading to increased synthesis and secretion of thyroid hormones. The most common causes of hyperthyroidism are Graves’ disease, toxic multinodular goitre and toxic adenoma. In
this thesis I will concentrate on the treatment and long-term prognosis of these
diseases.

However, there are less common causes of thyrotoxicosis, in which
the mechanism and treatment of thyrotoxicosis differs from that of hyperthyroidism.
Various forms of thyroiditis, in which thyroidal inflammation damages thyroid
follicles, result in an uncontrolled release of thyroid hormones into the circulation.
Other rare conditions causing thyrotoxicosis include pituitary tumors secreting TSH,
struma ovari, hyperthyroidism mediated by human chorionic gonadotropin, iodine-
induced hyperthyroidism, metastatic well-differentiated thyroid cancer, and factitious
thyrotoxicosis caused by ingestion of excessive amounts of thyroid hormone, and
pituitary resistance to TSH. (Larsen 1998, Cooper 2003)

1.4. Etiology and clinical presentation of hyperthyroidism

There are two major active forms of thyroid hormones in humans, thyroxine (T4) and
tri-iodothyronine (T3). T3 is the main mediator of the action of thyroid hormones in
the cell. Thyroid hormones regulate energy and heat production, as well as
the synthesis of proteins essential to, e.g., hepatic, cardiac, neurological, and muscular
functions. In addition, thyroid hormones facilitate the development of the central
nervous system, somatic growth, and puberty. Typical symptoms of hyperthyroidism,
\textit{i.e.} fatigue, anxiety, weight loss, palpitations and tachycardia, heat sensitivity, and
slight tremor, indicate an increased action of thyroid hormones and enhanced \(\beta\)-
adrenergic activity. When hyperthyroidism is clinically suspected, the diagnosis
should be confirmed by a measurement of serum TSH, the concentration of which is
usually below the limit of detection, and serum free T4 or free T3, which are elevated.

The disorder known as Graves’ disease in the English-speaking world, and as
von Basedow’s disease in continental Europe, is the most common cause of
hyperthyroidism (Larsen 1998). Graves’ disease is an autoimmune disorder caused by
spontaneous development of thyroid stimulating antibodies (TSab) that mimic
thyrotropin (TSH) action and lead to an excessive synthesis and secretion of thyroid
hormones (Davies et al. 2005). It is typically characterized by diffuse goitre,
hyperthyroidism and ophthalmopathy. However, the size of the thyroid gland can also
be normal (Weetman 2000).
The second most common cause of hyperthyroidism is a toxic multinodular goitre, which refers to a thyroid gland that has at least two autonomously functioning thyroid nodules that secrete excessive amounts of thyroid hormones (Krohn et al. 2005). The clinical manifestations of a toxic multinodular goitre are growth of the thyroid gland leading to cosmetic and pressure symptoms, and functional autonomy of the gland leading to hyperthyroidism (Hegedus et al. 2003). A third, less common form of hyperthyroidism is caused by a toxic adenoma. A solitary autonomous thyroid nodule produces enough thyroid hormones to suppress the secretion of TSH from the pituitary, with a consequent suppression of the extranodular thyroid gland (Siegel and Lee 1998). Solitary thyroid nodules usually grow to at least 3 cm in diameter before they result in overt hyperthyroidism (Siegel and Lee 1998, Cooper 2003). The exact cause of toxic nodular thyroid disease is not known, but it is probably related to activating mutations of the TSH receptor gene or the genes coding the associated G proteins, leading to autonomously functioning thyroid nodules (Krohn et al. 2005).

1.5. Epidemiology of hyperthyroidism

Hyperthyroidism is a common endocrine disorder, with a prevalence of approximately 2% in women and 0.2% in men (Tunbridge et al. 1977). In addition, undiagnosed clinical hyperthyroidism occurs in approximately 0.5% of randomly selected individuals, and subclinical hyperthyroidism in 0.7% (Hollowell et al. 2002). Mild to moderate iodine deficiency is associated with an increased incidence of hyperthyroidism. The optimal iodine intake to avoid both hypo- and hyperthyroidism is approximately 120-220µg measured by 24-hour urinary iodine excretion (Laurberg et al. 2001).

The development of the various forms of hyperthyroidism depends on the genetic predisposition and the iodine intake of the population. In areas of normal iodine intake, Graves’ disease accounts for at least 80% of new cases of hyperthyroidism (Laurberg et al. 2001). In Finland, the main cause of hyperthyroidism has changed since the late 1950’s when iodine prophylaxis was activated. Whereas more than 80% of hyperthyroid patients had multinodular goitre in
the 1950’s, the main cause of hyperthyroidism has been Graves’ disease since the 1980’s (Lamberg 1986). Today, the mean daily intake of iodine is 285µg in the male and 212µg in the female Finnish population (Findiet 2002).

2. Treatment of hyperthyroidism

The treatment of hyperthyroidism is directed at the thyroid gland rather than at the basic mechanism of the disease, for example the dysregulated immune system in Graves’ disease. Each of the three major therapies for hyperthyroidism, i.e. antithyroid drug therapy, surgery and RAI treatment, has its own advantages and disadvantages, indications and contraindications. Surprisingly few controlled clinical trials have been carried out in order to clarify the differences between the treatment options, and the current treatment strategies are mostly opinion-based. Consequently, the treatment preferences vary substantially by region. In Europe, antithyroid drugs have been preferred as the first line treatment, while RAI therapy is the most commonly used means of treatment for hyperthyroidism in the United States (US) (Glinoer et al. 1987, Solomon et al. 1990, Wartofsky et al. 1991).

2.1. Antithyroid drug therapy

Antithyroid drugs (carbimazole, methimazole, and propylthiouracil) are thionamide derivatives. Thionamides reduce thyroid hormone synthesis by interfering with iodination of tyrosine residues in thyroglobulin. Furthermore, propylthiouracil decreases the 5’-deiodination of T4 in peripheral tissues. Thionamides may also interfere with T3 binding to nuclear thyroid hormone receptors and inhibit T3 action at the transcriptional level (Moriyama et al. 2007). In addition, antithyroid drugs may have clinically important immunosuppressive effects (Cooper 2005). Antithyroid drugs are used as the primary treatment for hyperthyroidism in patients with Graves’ disease and severe ophthalmopathy, in pregnant and breast-feeding women, and in children and adolescents (Cooper 2005). Furthermore, antithyroid drugs are used as pretreatment before radiiodine treatment and surgery (Välimäki 2004, Bonnema et al. 2006).

In Finland, a common practice is to initiate the drug therapy of hyperthyroidism with 20-40mg of carbimazole per day (Välimäki 2004). Antithyroid
drugs control hyperthyroidism within 6 weeks in 90% of the patients (Reinwein et al. 1993). At this stage, treatment can be continued either with a block-replace regimen or a titrated dose regimen. For a block-replace regimen, a replacement dose of thyroxine is added, and the antithyroid drug is continued with an unchanged dose. For a titrated dose regimen, the dose of thionamide is reduced, and the endogenous production of thyroxine is maintained by the partial block to thyroid hormone synthesis (Razvi et al. 2006). Thyroid function should be assessed every 4-6 weeks for the first 4-6 months. After that, follow-up can be performed every two or three months (Välimäki 2004, Cooper 2005).

Remission rates of 50-60% have been reported after the usual 12 to 18 months of antithyroid drug therapy. Relapses usually occur within the first six months after the medication is stopped (Allannic et al. 1990, Berglund et al. 1991, Benker et al. 1998, Abraham et al. 2005). Attempts to increase the remission rate by the use of high doses of antithyroid drugs (Benker et al. 1998), long duration of treatment (Maugendre et al. 1999), or concomitant thyroxine treatment (McIver et al. 1996, Abraham et al. 2005) have not proved useful.

Antithyroid drugs can cause minor side-effects including cutaneous reactions, arthralgia, and gastrointestinal symptoms, in approximately 5-25% of patients (Cooper 2003). Agranulosytosis, drug-induced vasculitis, and liver damage are the major side-effects of antithyroid drugs. Agranulocytosis arises in 0.2-0.5 %, and hepatotoxicity in 0.1-0.2 % of patients receiving antithyroid drugs (Cooper 2005).

2.2. Surgery

Although surgery was for many years the only treatment for hyperthyroidism, it is now used in specific circumstances only. Surgical treatment should be considered, if a patient has compressive symptoms, a large goitre, suspicion of a malignant thyroid nodule, or hyperthyroidism with severe eye symptoms of Graves’ disease (Cooper 2003, Välimäki 2004). After subtotal thyroidectomy, cure of hyperthyroidism is achieved in 89-92% of patients, and hypothyroidism develops in 25-30% of individuals (Sridama et al. 1984, Franklyn et al. 1991, Palit et al. 2000). Whereas subtotal thyroidectomy was advocated in previous years, total thyroidectomy is increasingly recommended to reduce thyroid autoimmunity and the risk of relapsing hyperthyroidism, especially in patients with Graves’ ophthalmopathy (Winsa et al.
Thyroidectomy is a complicated surgical procedure, and the incidence of complications depends largely on the skills and the experience of the surgeon (Sosa et al. 1998). Complications include permanent hypoparathyroidism and recurrent laryngeal nerve damage, which can take place in 1-3% of the patients (Sosa et al. 1998, Palit et al. 2000, Bellantone et al. 2002, Gaujoux et al. 2006). Transient hypocalcemia, bleeding and infection are also potential complications of thyroid surgery (Bellantone et al. 2002, Gaujoux et al. 2006).

2.3. Treatment with radioactive iodine (RAI)

2.3.1. Quantities used in RAI treatment

A radioactive source, e.g. RAI, is described by its activity, which is the number of nuclear disintegrations per unit of time. Mega Becquerel (MBq) is the SI unit for radioactivity ($10^6$ disintegrations per second). MillieCurie (mCi) is another unit for radioactivity ($3.7 \times 10^7$ disintegrations per second). One mCi equals to 37MBq. The basic quantity used to express the exposure of human body to ionizing radiation is the absorbed dose (the energy transferred divided by the mass of material, 1 Joule/kilogram), for which the SI unit is gray (Gy). Rad is an old unit for the absorbed dose. The biological effect per unit of absorbed dose varies with the type of radiation and the part of the body exposed, i.e. different tissues react differently to ionizing radiation. To take into account those variations, a weighted quantity called an effective dose is used. A quantity called millieSievert (mSv) is used in radiation protection, and it estimates the radiation exposure (effective dose) of the whole body. (Rantanen 2000, Kalinyak and McDougall 2003)

2.3.2. Treatment protocol and radiation protection

A common approach is to administer a fixed dose of 7-15mCi RAI orally as a capsule in an out-patient clinic (Weetman 2000). In Finland, most patients receive antithyroid drug therapy in order to achieve euthyroidism before treatment with RAI. Patients are informed to discontinue antithyroid drug therapy 2-4 days before RAI treatment (Välimäki 2004).
A patient receiving RAI may be treated as an out-patient if the radiation exposure caused to family members by the residual activity in the patient is less than 1mSv for children and less than 3mSv for adults (STUK 2003). The patients receiving less than 400MBq (10.8mCi) dose of RAI must avoid close contact with children and pregnant women (within less than 2 metres for more than half an hour) for 9 days and prolonged contact (more than 3 hours within less than 2 metres) for 21 days (STUK 2003). After administration of higher doses of RAI, the security times are even longer. Fifteen mCi is the largest dose of RAI that can be administered in an out-patient clinic. Every patient must receive written and oral instructions for radiation protection. (STUK 2003) These requirements of radiation protection may cause inconvenience and increase fear among the patients concerning the potential dangers of RAI.

### 2.3.3. Indications and contraindications

RAI is the primary definite therapy for most patients with Graves’ disease, toxic multinodular goitre and toxic adenoma (Cooper 2003, Välimäki 2004).

RAI is contraindicated for pregnant and breast-feeding women (STUK 2003). Currently no evidence shows that RAI treatment is associated with increased infertility, mutagenesis, or teratogenesis (Bal et al. 2005). However, it is recommended that both male and female patients avoid conception for 4 months after the treatment of hyperthyroidism with RAI (STUK 2003), since the gonads receive approximately 50mGy of radiation after a 60-100Gy dose of RAI for the thyroid gland (Holm et al. 1991). RAI treatment is also relatively contraindicated for children and adolescents because of the paucity of data regarding the long-term risks associated with radiation (Rivkees et al. 1998, Lee et al. 2007, Rivkees and Dinauer 2007). In the longest follow-up study concerning children treated with RAI for hyperthyroidism, none of the 98 patients developed cancer of the thyroid gland or leukaemia up to 36 years after treatment. In the same study, pregnancies of the patients treated under the age of 20 years did not result in an unusual number of congenital anomalies or abortions (Read et al. 2004).

Prospective studies have shown that RAI may worsen a pre-existing ophthalmopathy, especially in patients with severe hyperthyroidism and in smokers (Tallstedt et al. 1992, Bartalena et al. 1998). The worsening of a mild thyroid
ophthalmopathy might be prevented by the administration of glucocorticoids (Bartalena et al. 1998). A potential concern is an exacerbation of hyperthyroidism due to a radiation-induced thyroiditis and leakage of thyroid hormones from the damaged thyroid gland into the circulation. The precise frequency of this complication is unknown, but it is probably less than 10% (Cooper 2003).

2.3.4. Metabolism and effect of RAI

The effect of RAI in treating hyperthyroidism is based on the capacity of the thyroid gland to concentrate iodine, which is required for the formation of thyroid hormones. The sodium-iodine symporter (NIS) is an intrinsic plasma membrane protein that mediates active iodine transport into the thyroid gland (Larsen 1998). RAI emits β-radiation, which affects the cells trapping RAI and by-stander cells within the path length of 1-2mm (Rivkees et al. 1998). A vast majority of the radiation exposure is localized in the thyroid gland, where it causes destruction of the follicular cells trapping RAI. The histological findings in the thyroid gland after RAI treatment include epithelial swelling and necrosis, edema, and leukocyte infiltration. The acute inflammation is followed by fibrosis of the thyroid gland (Rivkees et al. 1998).

Other organs capable of concentrating iodine include the salivary glands, the urinary bladder, and the stomach (Holm et al. 1991). The radiation dose different organs are exposed to due to RAI therapy depends on: 1) the local concentration of RAI in iodine concentrating tissues; 2) circulating RAI derived from the part of the administered RAI activity which has not been concentrated by the thyroid gland; 3) RAI organically bound by the thyroid gland and released within thyroid hormones; and 4) radiation emitted from an organ concentrating RAI to an organ in the immediate neighbourhood (for example the parathyroid glands) (Edmonds and Smith 1986). Eighty percent of RAI is excreted renally (Katz et al. 1975). The mean effective half-life of RAI is 6 days, and it depends on the physical and biological half-life of RAI (Holm et al. 1991, Kalinyak and McDougall 2003). The physical half-life of RAI is 8 days and is determined by the decay rate of the RAI isotope. The biological half-life of RAI is determined by the clearance of iodine from the thyroid gland and is therefore highly variable (Kalinyak and McDougall 2003). Because of the prolonged effective half-life of RAI, the radiation dose is received
gradually over time, with nearly 95% of the dose being delivered in 4 weeks (Holm et al. 1991).

2.3.5. Effect of RAI on thyroid function

Thyroid function returns to normal within 2-6 months after RAI treatment in 50-95% of patients after a single dose of RAI (Holm et al. 1982, Kendall-Taylor et al. 1984, Franklyn et al. 1991). Patients not cured with the first dose of RAI usually receive a second dose 3-6 months after the initial treatment (Cooper 2003, Välimäki 2004). After the first post-therapy year, approximately 3% of patients develop hypothyroidism annually. In the longest follow-up studies, the cumulative incidence of hypothyroidism has been 42 - 76% 10 - 25 years after the first RAI therapy (Holm et al. 1982, Franklyn et al. 1991).

The proportions of patients cured with a single dose of RAI and developing hypothyroidism after the treatment of hyperthyroidism are presented in Table 1. The broad range of figures within different dose regimens makes it apparent that the outcome after RAI treatment for hyperthyroidism is unpredictable. Variability in the outcome after RAI treatment for hyperthyroidism is related to factors that influence the actual radiation effect in the thyroid gland, and to clinical factors. Factors affecting the actual radiation effect are the size of the thyroid gland (Holm et al. 1982, Sridama et al. 1984, Watson et al. 1988, Allahabadia et al. 2000, Ahmad et al. 2002, Erem et al. 2004), the avidity of the thyroid gland to iodine measured by the 24-hour RAI uptake (Bockisch et al. 1993), the effective half-life of RAI in the thyroid gland (Kung et al. 1990), and the dose and number of RAI treatments (Holm et al. 1982, Goolden and Stewart 1986, Franklyn et al. 1991, Ahmad et al. 2002). Clinical factors reported to affect the outcome of RAI therapy include the age (Holm et al. 1982, Allahabadia et al. 2000) and the gender of the patient (Allahabadia et al. 2000, Ahmad et al. 2002), the etiology (Allahabadia et al. 2001, Ahmad et al. 2002), the severity, and the duration of the underlying thyroid disease (Holm et al. 1982, Watson et al. 1988, Kung et al. 1990, Allahabadia et al. 2001, Erem et al. 2004), a previous thyroidectomy (Holm et al. 1982, Watson et al. 1988), and a preceding antithyroid drug therapy (Kung et al. 1990, Allahabadia et al. 2001).
## Table 1. Long-term follow-up studies on the outcome after RAI treatment for hyperthyroidism

<table>
<thead>
<tr>
<th>Study</th>
<th>First dose of RAI</th>
<th>Low dose of RAI</th>
<th>High dose of RAI</th>
<th>Intermediate dose of RAI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cure rate after the first dose of RAI, %</td>
<td>Hypothyroidism at 1 year, %</td>
<td>Hypothyroidism at 10 years, %</td>
<td>First dose of RAI</td>
</tr>
<tr>
<td>Sridama et al. 1984</td>
<td>66</td>
<td>12</td>
<td>65</td>
<td>148 MBq 187*</td>
</tr>
<tr>
<td>Watson et al. 1988</td>
<td>72</td>
<td>16</td>
<td>35</td>
<td>185 MBq 199*</td>
</tr>
<tr>
<td>Franklyn et al. 1991</td>
<td>91</td>
<td>2</td>
<td>35</td>
<td>200 MBq 1119</td>
</tr>
<tr>
<td>Nygaard et al. 1995</td>
<td>67</td>
<td>25</td>
<td>60</td>
<td>185-200 MBq 117*</td>
</tr>
<tr>
<td>Read et al. 2004</td>
<td>64</td>
<td>32</td>
<td>60</td>
<td>185 MBq 116*</td>
</tr>
<tr>
<td>Dunn and Chapman 1964</td>
<td>NA</td>
<td>15</td>
<td>40</td>
<td>165 μCi/g 1391</td>
</tr>
<tr>
<td>Kendall-Taylor et al. 1984</td>
<td>96</td>
<td>64</td>
<td>80</td>
<td>555 MBq 225*</td>
</tr>
<tr>
<td>Tzavara et al. 2002</td>
<td>100</td>
<td>55</td>
<td>55</td>
<td>1221 MBq 126†</td>
</tr>
<tr>
<td>Ceccarelli et al. 2005</td>
<td>94</td>
<td>8</td>
<td>46</td>
<td>513 MBq 346‡</td>
</tr>
<tr>
<td>Green and Wilson 1964</td>
<td>51</td>
<td>10</td>
<td>29</td>
<td>7,000 rad 925</td>
</tr>
<tr>
<td>Nofal et al. 1966</td>
<td>71</td>
<td>45</td>
<td>70</td>
<td>370-480 MBq 848</td>
</tr>
<tr>
<td>Holm et al. 1982</td>
<td>56</td>
<td>6</td>
<td>45</td>
<td>185-370 MBq 4473</td>
</tr>
<tr>
<td>Goolden and Stewart 1986</td>
<td>54</td>
<td>10</td>
<td>40</td>
<td>100 μCi/g 261</td>
</tr>
<tr>
<td>Danaci et al. 1988</td>
<td>94</td>
<td>61</td>
<td>66</td>
<td>369 MBq 201*</td>
</tr>
<tr>
<td>Kung et al. 1990</td>
<td>60</td>
<td>10</td>
<td>54</td>
<td>370 MBq 1028‡</td>
</tr>
<tr>
<td>Berglund et al. 1991</td>
<td>56</td>
<td>20</td>
<td>60</td>
<td>8,000 rad 106*</td>
</tr>
<tr>
<td>Nygaard et al. 1999b</td>
<td>75</td>
<td>0</td>
<td>8</td>
<td>310 MBq 62‡</td>
</tr>
<tr>
<td>Nygaard et al. 1999c</td>
<td>62</td>
<td>0</td>
<td>14</td>
<td>313 MBq 130‡</td>
</tr>
<tr>
<td>Ahmad et al. 2002</td>
<td>89</td>
<td>56</td>
<td>86</td>
<td>400-550 MBq 274</td>
</tr>
</tbody>
</table>

Low dose: fixed dose < 200 MBq or adjusted dose < 80 μCi/g or absorbed dose < 50Gy (5,000 rad)
High dose: fixed dose >500 MBq or adjusted dose > 120 μCi/g or absorbed dose < 100Gy (10,000 rad)

*Graves’ disease
†Patients with toxic multinodular goitre
‡Patients with toxic adenoma

During the past few decades, a lot of attention has been focused on achieving euthyroidism and avoiding hypothyroidism by adjusting the dose of RAI individually. Despite the numerous associations found between outcome after the RAI treatment and different pre-treatment variables, no single variable or combination of variables has been shown to predict the cure rate or the development of hypothyroidism with sufficient confidence (Kung et al. 1990, Doi et al. 2001). Most dose calculation regimens are based upon the size and the iodine uptake of the thyroid gland. In a few randomised clinical trials, the advantages of the dose calculation methods have been small and of little clinical significance compared with a fixed dose of RAI (Smith and Wilson 1967, Jarlov et al. 1995, Peters et al. 1997, Leslie et al. 2003). When the thyroid size, iodine uptake, and effective half-life of RAI have been taken into account, a correlation between the administered dose (mCi/Mbq) and the organ dose...
(Gy) has been obtained \((r = 0.3)\) (Catargi et al. 1999). However, the outcome has still been imprecise due to individual variation in the sensitivity of the thyroid to RAI (Catargi et al. 1999). Furthermore, a low dose of RAI may have decreased the cure rate but it has not protected from a later development of hypothyroidism, although it may have delayed it (Table 1). The early effect of RAI treatment is caused by the direct toxicity of radiation (interphase death), while the subsequent effects of radiation are determined by the rate of cell division (mitotic death). In adults, thyroid cells have a very long life-span, \(i.e.,\) human thyroid cells divide about five times in adulthood (Dumont et al. 1992). Thus, mitotic cell death may therefore not impair thyroid function until after a delay of many years (Goolden and Stewart 1986). Furthermore, the natural course of Graves’ disease with subsiding levels of stimulating TSH antibodies, the effect of TSH blocking antibodies, and autoimmune thyroiditis may contribute to the development of hypothyroidism several years after RAI treatment (Tamai et al. 1989).

In conclusion, the development of late hypothyroidism after RAI treatment for hyperthyroidism seems to be common and unpredictable. The administration of a calculated dose of RAI involves patient inconvenience and additional costs due to the need to measure RAI uptake of the thyroid gland. Many clinics therefore prefer a fixed dose regimen in the RAI treatment for hyperthyroidism. The goal of RAI treatment in hyperthyroidism should be to cure hyperthyroidism by the lowest effective dose of RAI. An initial dose of 10mCi is most commonly used (Nordyke and Gilbert 1991, Kalinyak and McDougall 2003, Weetman 2007). However, no consensus exists on the ideal first dose of RAI in the treatment of hyperthyroidism.

2.4. Current treatment strategies for hyperthyroidism

There are no randomized studies comparing outcomes after antithyroid drug therapy, surgery, and RAI treatment as the primary treatment of hyperthyroidism. Even non-randomized studies comparing the long-term outcomes after treatment with RAI, thyroidectomy, and antithyroid drugs for hyperthyroidism are few in number (Sridama et al. 1984, Berglund et al. 1991, Franklyn et al. 1991). Both patient and disease characteristics affect the choice of treatment, and they may have induced confounding in these studies. RAI treatment was mostly used for older patients,
surgical treatment for young patients with large goitres, and long-term antithyroid drugs for young patients with mild to moderate symptoms and small thyroid glands.

In the study of Sridama et al. (1986), surgery and RAI treatment were effective in the treatment of hyperthyroidism (cure rate 66 and 78%, respectively), but antithyroid drug therapy cured only 40% of the patients. Hypothyroidism developed in 72% of RAI-treated, 27% of surgically treated, and 10% of medically treated patients in long-term follow-up (Sridama et al. 1984). In the study of Berglund et al. (1991), hyperthyroidism recurred in 5% of patients treated with RAI, 9% of patients treated with surgery, and 43% of patients treated with antithyroid drugs only. Hypothyroidism developed in 32% of patients treated with RAI and 32% of those treated surgically. Franklyn et. al. (1991) reported a cure rate of 90% both in patients treated with RAI and in those treated surgically, and a 42% vs. 28% prevalence of hypothyroidism by 20 years of follow-up, respectively.

Since long-term remission rate after antithyroid drug therapy is low in Graves’ disease, and antithyroid drugs do not induce remission in toxic nodular goitre, most subjects with hyperthyroidism proceed to either surgery or RAI treatment. Although surgery is somewhat faster in restoring euthyroidism and hypothyroidism may be less frequent, the RAI therapy is simpler, and no hospital admission is required. In addition, RAI has proved cost-effective in comparison with other therapeutic alternatives, i.e. long-term antithyroid medication or surgery (Ljunggren et al. 1998, Patel et al. 2006). All the three major treatments have similar effects on the quality of life of the hyperthyroid patients (Ljunggren et al. 1998).

The current strategies for the treatment of hyperthyroidism in Finland have been reviewed recently (Välimäki 2004). Most patients are primarily treated with antithyroid drugs to restore euthyroidism. RAI is chosen as the first-line curative treatment for most patients. Pregnant and breast-feeding women, children, young adults, and patients with ophthalmopathy are primarily treated with antithyroid drugs. For hyperthyroidism relapsing after the treatment with antithyroid drugs, RAI treatment can be considered unless the patient is pregnant or has severe ophthalmopathy. In mild ophthalmopathy, RAI can be considered with corticosteroid prophylaxis. Surgery is used as the first-line curative treatment for patients with a large goitre, or with a suspicion of malignancy. Surgery is used as a secondary line of treatment in patients with severe eye symptoms and relapsing hyperthyroidism after antithyroid drug treatment. If a patient refuses RAI treatment, is not operable, or
has a short life-expectancy, a treatment with antithyroid drugs indefinitely can be considered, but a regular laboratory monitoring every 3-6 months is required (Azizi et al. 2005).

3. Morbidity and mortality after RAI treatment for hyperthyroidism

3.1. Overall mortality

Mortality studies of hyperthyroid patients treated with RAI are few in number and based on three different patient cohorts: an American (Hoffman et al. 1982a, Goldman et al. 1988, Goldman et al. 1990), a Swedish (Hall et al. 1992a, Hall et al. 1993), and an English one (Franklyn et al. 1998, Franklyn et al. 1999, Franklyn et al. 2005).

The Cooperative Thyrotoxicosis Therapy Follow-up Study included a total of 36,050 hyperthyroid patients treated with RAI, thyroidectomy, antithyroid drugs, or various combinations of these therapeutic options between 1946-1968 in 26 clinics in the US. Since the 1980’s, long-term follow-up studies on the mortality of several subsets of these patients have been published. Hoffman et al. (1982a) from the Mayo Clinic reported no difference in the overall, cardiovascular, or cancer mortality between 1005 women treated with RAI and 2141 women treated with surgery for hyperthyroidism. Goldman et al. (1988) observed an increased standardized mortality rate (SMR) for all causes of death and for deaths due to endocrine, circulatory, and respiratory diseases, but not from malignant tumors in 1762 hyperthyroid women treated at the Massachusetts General Hospital. The overall mortality increased after all the treatment modalities of hyperthyroidism, i.e. RAI (80%), thyroidectomy, or antithyroid drugs, when each treatment group was compared with the general population (Goldman et al. 1988). In a report of the whole original Cooperative Thyrotoxicosis Therapy Follow-up Study including 35,593 hyperthyroid patients (65% were treated with RAI and 91% had Graves’ disease), the total cancer mortality did not differ from that of the general US population (Ron et al. 1998).

Among 10,552 Swedish hyperthyroid patients treated with RAI, a significant excess of overall mortality was observed compared with the expected rates. The risk of dying from cancer and cardiovascular, respiratory, and endocrine diseases was
elevated up to 10 years after the treatment of hyperthyroidism (Hall et al. 1992a, Hall et al. 1993). In a cohort of 7,209 subjects with hyperthyroidism treated with RAI in 1950-1991 in Birmingham (UK), the all-cause mortality and mortality due to cardiovascular, cerebrovascular, and thyroid diseases, and due to hip fracture was increased, but cancer mortality was decreased compared with the general population of England and Wales (Franklyn et al. 1998, Franklyn et al. 1999). Later on, Franklyn et al. (2005) reported an increased overall mortality and mortality from cardiovascular diseases in 2,668 hyperthyroid patients treated with RAI for hyperthyroidism in 1984-2002. In a recent study of 3,888 hyperthyroid patients treated during 1994-2001 in Tayside Scotland, no increase in all-cause, cardiovascular or cancer mortality was observed compared with the general population of Scotland. However, the mortality was reported for all hyperthyroid patients, and the proportion of patients treated with RAI was not known. (Flynn et al. 2006)

Mortality studies concerning thyroidectomy and anti-thyroid drug therapy in the treatment of hyperthyroidism are scarce. Mortality rate after thyroidectomy has been 0-0.3% (Foster 1978, Gaujoux et al. 2006). In 0.1-0.5% of cases, the side-effects of antithyroid drugs, e.g. agranulocytosis and hepatoxicity, can be serious or even fatal (Cooper 2005). Previously, only one study has been published comparing the mortality of patients treated with RAI and those treated with surgery for hyperthyroidism, with no difference between the treatment groups (Hoffman et al. 1982a).

In conclusion, the previous long-term follow-up studies have reported an increase in all-cause mortality among hyperthyroid patients treated with RAI, but the results on the specific causes of death have been conflicting (Goldman et al. 1988, Hall et al. 1993, Franklyn et al. 1998). Furthermore, it is not clear whether the hyperthyroidism *per se* or the RAI treatment causes the increased mortality.

### 3.2. Cardiovascular morbidity and mortality

Short-term effects of overt hyperthyroidism on the circulatory system are well recognized. T3 is the biologically relevant thyroid hormone also in the myocardium, where it modulates the transcription of multiple genes and affects the ion channels for sodium, potassium, and calcium (Klein and Ojamaa 2001). Furthermore, thyroid hormone excess exerts direct effects on the autonomic nervous system and increases
peripheral oxygen consumption. The consequent increase in cardiac contractility and heart rate, a decrease in systemic vascular resistance, and activation of the renin-angiotensin-aldosterone system lead to the hyperdynamic circulation that is commonly seen in overt hyperthyroidism (Klein and Ojamaa 2001, Osman et al. 2002). Furthermore, acute hyperthyroidism represents a hypercoagulable state characterized by an increased hematocrit, enhanced thrombin and plasmin activity, and dehydration (Hofbauer and Heufelder 1997, Erem et al. 2002). Endothelial dysfunction is also commonly seen in hyperthyroidism (Erem et al. 2002, Coban et al. 2006). Finally, Graves’ disease is associated with other autoimmune diseases increasing the risk of thrombosis, such as diabetes and antiphospholipid syndrome (Perros et al. 1995, Hofbauer and Heufelder 1997). By these mechanisms, hyperthyroidism can aggravate an existing cardiovascular disease or contribute to the development of a new cardiovascular disease.

Overt hyperthyroidism has been associated with tachycardia and arrhythmias, systolic hypertension, changes in ventricular systolic and diastolic function, and pulmonary hypertension (Klein and Ojamaa 2001, Osman et al. 2002, Merce et al. 2005, Armigliato et al. 2006, Siu et al. 2007). The reported prevalence of atrial fibrillation (AF) at time of diagnosing hyperthyroidism has been 6-15% (Petersen and Hansen 1988, Klein and Ojamaa 2001, Frost et al. 2004, Osman et al. 2007). AF occurs more frequently in males than in females (Shimizu et al. 2002). The incidence of AF increases with age, irrespective of any underlying heart disease (Petersen and Hansen 1988, Shimizu et al. 2002, Frost et al. 2004). Acute cardioembolic stroke is a well-described manifestation of AF in hyperthyroid patients (Staffurth et al. 1977, Bar-Sela et al. 1981, Petersen and Hansen 1988, Presti and Hart 1989, Squizzato et al. 2005). There is some evidence that the rate of cardiogenic embolism in thyrotoxic AF exceeds that of non-thyrotoxic AF (Presti and Hart 1989). However, there are no controlled studies on the use of anticoagulants in hyperthyroid AF.

The cardiovascular effects have been regarded to be eliminated by effective treatment of hyperthyroidism. However, the risk of death from cardiovascular diseases has been higher than expected among the patients treated with RAI for hyperthyroidism (Goldman et al. 1988, Goldman et al. 1990, Hall et al. 1993, Franklyn et al. 1998, Franklyn et al. 2005). The risk of dying from cardiovascular diseases has been reported to increase up to 10 years after the treatment of hyperthyroidism (Hall et al. 1993, Franklyn et al. 1998). Increased mortality from
ischemic heart disease (Goldman et al. 1988, Franklyn et al. 1998), cerebrovascular
disease (Franklyn et al. 1998), rheumatic heart disease (Goldman 1990, Franklyn et al.
1998), hypertensive disease (Franklyn et al. 1998), and diseases of the pulmonary
circulation (Franklyn et al. 1998) has been reported in hyperthyroid patients. Moreover, an increased cardiovascular morbidity was observed in RAI-treated hyperthyroid patients compared with controls in a long-term follow-up study, suggesting that the cardiotoxic effects of hyperthyroidism are not fully reversed by the treatment of hyperthyroidism (Nyirenda et al. 2005). It has also been shown that despite the restoration of biochemical euthyroidism, previously hyperthyroid patients continue to experience dyspnea, palpitation, AF, and heart failure (Osman et al. 2007, Siu et al. 2007). In another study, only 60% of patients with AF and hyperthyroidism reverted to sinus rhythm within 8-10 weeks after the treatment of hyperthyroidism, and after 3 months only a few resumed sinus rhythm spontaneously (Nakazawa et al. 1982, Shimizu et al. 2002). An increased risk of arrhythmia has been shown to persist up to 5 years after the treatment of hyperthyroidism (Flynn et al. 2006).

In conclusion, a persistent increase in cardiovascular mortality and morbidity has been reported among hyperthyroid patients treated with RAI. Instead of the RAI treatment, hyperthyroidism per se is probably the major explanation for the elevated cardiovascular mortality, since no increased mortality from cardiovascular diseases has been found in patients treated with RAI compared with patients treated with surgery, and an excess of cardiovascular morbidity and mortality has been seen after all treatment modalities for hyperthyroidism. Although AF seems to be a major contributor, no long-term studies have been published to confirm which cardiovascular diseases cause the increased morbidity after the treatment of hyperthyroidism.

3.3. Ionizing radiation and cancer risk

3.3.1. Sources and effects of ionizing radiation

Ionizing radiation represents electromagnetic waves and particles that can ionize, that is, remove an electron from an atom or a molecule of the medium through which they propagate. Ionizing radiation may be emitted in the process of natural decay of some unstable nuclei or following excitation of atoms and their nuclei in nuclear reactors,
cyclotrons, or x-ray machines. For historical reasons, the photon (electromagnetic) component of ionizing radiation emitted by the excited nucleus is termed $\gamma$-rays and that emitted from machines is termed x-rays. The charged particles emitted from the nucleus are referred to as $\alpha$-particles (helium nuclei) and $\beta$-particles (electrons) (UNSCEAR 2000).

All living organisms are continually exposed to ionizing radiation. The sources of natural radiation exposure are cosmic rays that come from outer space and from the surface of the Sun, and terrestrial radionuclides that occur in the Earth’s crust, in building materials, air, water, foods, and in the human body itself.

The mean annual global per caput effective dose due to natural radiation sources is 2.4mSv (range 1-10mSv). Some of the exposures are fairly constant and uniform for all individuals everywhere, other exposures vary widely depending on location (UNSCEAR 2000, Charles 2001). The second largest contribution to exposures of individuals worldwide is from medical radiation procedures. The mean annual global per caput effective dose due to diagnostic medical examinations is 0.4mSv (UNSCEAR 2000, Charles 2001). In Finland, the mean per caput effective dose due to both natural radiation and medical use is slightly higher than the global average (Table 2).

Table 2. The effective doses due to various sources of radiation in the Finnish population

<table>
<thead>
<tr>
<th>Source of radiation</th>
<th>Effective dose, mSv</th>
</tr>
</thead>
<tbody>
<tr>
<td>The annual per caput dose due to different radiation sources</td>
<td>4</td>
</tr>
<tr>
<td>The annual per caput dose due to diagnostic medical examinations</td>
<td>0.5</td>
</tr>
<tr>
<td>Annual per caput radioactive fall-out because of Tshernobyl disaster</td>
<td>0.04</td>
</tr>
<tr>
<td>x-ray of thorax</td>
<td>0.1</td>
</tr>
<tr>
<td>Computerised tomography of thorax</td>
<td>5.1</td>
</tr>
<tr>
<td>Maximum annual radiation dose in radiation work</td>
<td>20</td>
</tr>
<tr>
<td>Mean annual dose in medical radiation work</td>
<td>0.4</td>
</tr>
<tr>
<td>Mean annual dose of the aircrew</td>
<td>2-4</td>
</tr>
<tr>
<td>Thyroid scintigraphy and 24-hour uptake of RAI</td>
<td>63</td>
</tr>
<tr>
<td>RAI treatment for hyperthyroidism per 1mCi</td>
<td>888</td>
</tr>
<tr>
<td>Family members in close contact with patients undergoing RAI treatment</td>
<td>0.5</td>
</tr>
</tbody>
</table>

This table is adapted from Rantanen 2000 and Komppa and Korpela 2000
Radiation exposure can damage living cells, causing death especially in dividing cells. This is called the deterministic effect, and it correlates with the dose of radiation. A threshold dose, above which the deterministic damage will occur, can be determined. Moreover, radiation may cause long-term harm to organs and tissues by causing double-strand breaks of the deoxyribonucleic acid (DNA) in the nucleus. Cells have a number of biochemical pathways capable of recognising and dealing with specific forms of DNA damage. For example, tumor suppressor genes control the cell cycle and apoptosis, i.e. programmed cell death, which is instrumental in preventing damaged cells from progressing to the transformed, malignant growth stage. Thus, the damage in cells is usually repaired. If it is not, damage will be transmitted to further cells creating a clone of cells that all have the same damage in their DNA. If the damage is in a somatic cell, this may eventually lead to cancer. If the cells modified are those transmitting hereditary information to the descendants of the exposed individual, anomalies or hereditary disorders may arise. Even the exposure to the lowest doses of ionizing radiation has the potential to cause double-strand breaks in the DNA, which in the absence of a fully efficient repair system may result in long-term damage. This is called the stochastic harm of radiation. There is a latent period of at least a couple of years after the radiation exposure before a malignancy will develop if the stochastic harm occurred. The risk of DNA damage increases with the life-long cumulative dose of radiation exposure. However, there is no threshold dose for the stochastic harm of radiation. Thereby, the goal of radiation protection is to keep radiation exposure as low as possible in order to reduce the risk of stochastic harm. (Paile 2000, UNSCEAR 2000)

Ionizing radiation can cause any kind of cancer, but the most common radiation-induced cancers are leukaemia and cancers of the thyroid, breast and lung (Isola 2007).

3.3.2. Radiation exposure after RAI treatment

On the basis of the available knowledge on the metabolism of the absorbed dose of RAI together with measurements of the concentration of RAI in the thyroid and other tissues, it is possible to estimate the radiation dose to various organs after RAI treatment for hyperthyroidism (Holm et al. 1991, Ron et al. 1998). When the dose of RAI to the thyroid gland is aimed at 60-100Gy in treating hyperthyroidism,
an average dose of less than 10mGy is delivered to colon, liver, pancreas, lungs, breasts, uterus, ovaries, testes, kidneys, and bone marrow. Radiation exposure is estimated to be slightly higher in salivary glands (200mGy), stomach (250mGy) and bladder (140mGy). Consequently, these sites may be particularly vulnerable to RAI-induced cancer.

3.3.3. Overall cancer incidence and mortality

Concerns remain about the risk of cancer following RAI treatment for hyperthyroidism, especially in organs that concentrate iodine, since an increased cancer risk of the urinary bladder (Edmonds and Smith 1986), genital organs (Hall et al. 1991, Rubino et al. 2003), kidneys (Hall et al. 1991), digestive tract (Hall et al. 1991, Rubino et al. 2003), and the salivary glands (Hall et al. 1991, Dottorini et al. 1995, Rubino et al. 2003) has been reported in patients treated with high doses of RAI (3,000-6,000MBq) for thyroid cancer. Radiation exposure of non-thyroid tissues of the hyperthyroid patients differs from that of the thyroid cancer patients who receive RAI after total thyroidectomy to destroy the residual thyroid tissue. In a hyperthyroid state, the renal clearance of radioactive iodine is higher than in a post-surgical hypothyroid state (Barbaro and Boni 2007). On the other hand, the trapping of RAI into the thyroid gland is probably higher in the patients with hyperthyroidism than in the post-ablative thyroid cancer patients, although the residual thyroid tissue in cancer patients is more avid to RAI because of hypothyroidism (Barbaro and Boni 2007). In general, the radiation dose received by the body increases as the uptake in the thyroid increases, due to the release of increased amounts of organic compounds of RAI, which provide the principal source of irradiation (Edmonds and Smith 1986). Thus, the radiation exposure of non-thyroid tissues would be higher in hyperthyroid patients than in post-ablative thyroid cancer patients, if the cumulative dose of RAI was similar.

In the first reports of the Cooperative Thyrotoxicosis Therapy Follow-up Study, treatment of hyperthyroidism with RAI did not increase the risk of malignant thyroid tumors or leukemia, but the average follow-up time was only 8 years (Saenger et al. 1968, Dobyns et al. 1974). Since the 1980’s, long-term follow-up studies of cancer risk in patients treated with RAI for hyperthyroidism have been reported with conflicting results. The first two long-term studies were continuations of
the Cooperative Thyrotoxicosis Therapy Follow-up Study (Hoffman et al. 1982b, Goldman et al. 1988). Hoffman et al. (1982b) reported no difference between 1005 women treated with RAI and 2141 women treated with surgery for hyperthyroidism in the overall cancer incidence, or in the incidence of breast cancer or leukemia. Although based on a small number of cases, an elevated risk of cancer was observed in the thyroid gland and in other organs that concentrate RAI (salivary glands, digestive tract, kidney and bladder). In a study of Goldman et al. (1988), the cancer incidence of 1762 hyperthyroid women treated with RAI (80%) or surgery did not differ from that of US white women. In the report of the whole original Cooperative Thyrotoxicosis Therapy Follow-up Study including 35 593 hyperthyroid patients (65% were treated with RAI and 91% had Graves’ disease), total cancer mortality did not differ from that of the general US population (Ron et al. 1998). However, there was a small excess of mortality from cancers of the lung, breast, kidney, and thyroid. In an analysis restricted to the hyperthyroid patients treated with RAI, the overall cancer incidence was unchanged but an increased thyroid cancer mortality was reported (Ron et al. 1998).

In a large population-based study of 10,552 Swedish patients who received RAI therapy for hyperthyroidism, significantly elevated overall cancer incidence and mortality was observed compared with the Swedish population (Hall et al. 1991, Holm et al. 1991). Among 10-year survivors, significantly elevated risks were seen for cancers of the stomach, brain and kidney. In a population-based study of 7,417 patients treated with RAI for hyperthyroidism in Birmingham (UK), the overall cancer incidence and mortality decreased, but the incidence and mortality of cancers of the small bowel and the thyroid gland were increased compared with the expected rates (Franklyn et al. 1999).

3.3.4. Stomach cancer

In Finland, 760 new cases of stomach cancer are diagnosed annually. The incidence of stomach cancer has been declining since the 1950’s (Finnish Cancer Registry). The risk of stomach cancer has been associated with helicobacter pylori infection, pernicious anemia, atrophic gastritis, gastric ulcer, resection of the stomach, and some dietary factors, e.g. excessive use of salt and insufficient use of vegetables. Ninety-five per cent of stomach cancers are adenocarcinomas. The prognosis of stomach
cancer is poor, only 30% of patients surviving 5 years after the diagnosis. (Roberts 2007)

An increased risk of stomach cancer has been found in thyroid cancer patients treated with RAI, but not in those receiving other types of treatment (Hall et al. 1991). Significantly elevated incidence and mortality from stomach cancer was seen in a Swedish population of patients treated with RAI for hyperthyroidism (Holm et al. 1991, Hall et al. 1992a). In this study, the risk of stomach cancer increased both with time and with increasing doses of radioactivity. Furthermore, an elevated risk of cancer was observed in a combined group of organs that concentrate RAI, including the digestive tract (Hoffman et al. 1982b).

When a 60-100Gy dose of RAI has been targeted on the thyroid gland, a 250mGy dose of radiation has been estimated for the stomach (Holm et al. 1991, Ron et al. 1998). Consequently, the stomach might be particularly vulnerable to RAI-induced cancer. The stomach accumulates iodine and it’s radiation exposure depends mainly on the RAI ingested and is not appreciably influenced by the variation of RAI in the blood (Edmonds and Smith 1986). NIS, an intrinsic plasma membrane protein that mediates active iodine transport into the thyroid gland, has been detected in the gastric mucosa and probably mediates active iodine transport from the serum to the gastric fluid (Riesco-Eizaguirre and Santisteban 2006).

The thyroid disease *per se* might also contribute to the development of stomach cancer in various ways. Thyroid hormones inhibit gastric acid production and cause hypergastrinemia (Wiersinga and Touber 1980, Dahlberg et al. 1981). Gastrin is a pro-proliferative, anti-apoptotic hormone with a central role in the acid secretion and carcinogenesis of the gastric mucosa (Watson et al. 2006). Atrophic gastritis is an autoimmune disorder related to an increased risk of stomach cancer. It has been seen more frequently in patients with autoimmune thyroid diseases than in the general population (Centanni et al. 1999). Thus, patients with Graves’ disease may have an increased risk of stomach cancer. However, Holm et al (1991) reported an increased risk of stomach cancer among RAI-treated patients with nodular thyroid disease but not among those with Graves’ disease.
3.3.5. Breast cancer

Breast cancer is the most common cancer of women in Finland, and the incidence has been increasing since the 1960’s. Annually, 3,800 new cases of breast cancer are diagnosed (Finnish Cancer Registry). Increasing age, female sex, radiation exposure, smoking, alcohol abuse, and reproductive factors, e.g. age at menarche and menopause, age at first and last childbirth, parity, and long-term use of hormone replacement therapy, are known risk factors for breast cancer (Holli 1995). Furthermore, 5-10% of breast cancer cases are estimated to be attributable to hereditary factors (Holli 1995, Syrjäkoski et al. 2000). Five years after the diagnosis of breast cancer, 85% of patients are alive (Finnish Cancer Registry, Holli 1995).

There have been concerns regarding a potential increase in the incidence of breast cancer after RAI treatment for hyperthyroidism, since an elevated risk of breast cancer has been observed among women treated for thyroid cancer (Chen et al. 2001, Rubino et al. 2003). Goldman et al. (1988) found a non-significant increase in breast cancer incidence and mortality in women treated for hyperthyroidism (80% received RAI) after 10 years of follow-up, persisting up to 30 years of follow-up. Furthermore, increased breast cancer mortality was seen in the report of the whole original Cooperative Thyrotoxicosis Therapy Follow-up Study population (Ron et al. 1998).

Both the thyroid disease and its’ treatment may increase the risk of breast cancer in hyperthyroid patients. Quiescent mammary glands do not concentrate iodine, and radiation doses received by the mammary glands are estimated to be low (Holm et al. 1991, Ron et al. 1998). However, the breast tissue is especially sensitive to radiation carcinogenesis, and dose fractionation does not decrease the risk of breast cancer per unit dose (UNSCEAR 2000). Breast cancer and thyroid disease predominantly affect females and both have a postmenopausal peak incidence. An increased prevalence of thyroid peroxidase (TPO) antibodies and an increased rate of goitre have been reported in patients with breast cancer (Turken et al. 2003). However, there is no evidence that thyroid disorders and breast cancer would be causally related (Goldman 1990, Smyth 2003). In addition, breast cancer mortality increased only after the treatment of hyperthyroidism both in patients with Graves’ disease and those with toxic nodular disease (Ron et al. 1998). One area, in which thyroid and breast functions overlap, is the uptake and utilization of dietary iodine. There are some experimental and epidemiological findings suggesting that dietary...
iodine may protect from breast cancer development (Smyth 2003). Thus, iodine
deficiency might contribute to the development of both multinodular goitre and breast
cancer. Interestingly, NIS is expressed in more than 80% of breast cancers (Riesco-
Eizaguirre and Santisteban 2006). In Finland, the mean daily intake of iodine has been
adequate since the late 1950’s when iodine prophylaxis was introduced (Findiet
2002).

3.3.6. Renal cancer and cancer of the urinary bladder

In Finland, 760 new cases of renal cancer are diagnosed annually, and the incidence is
increasing (Finnish Cancer Registry). Smoking, exposure to arsenic in industrial
processes and drinking water, obesity, and radiation exposure are known risk factors
of renal cancer. The five-year survival after renal cancer is 60%. (Sequeiros 2007)

Most of the circulating RAI is excreted by the kidneys (Katz et al. 1975).
Tubular cells reabsorb up to 60-80% of the iodine excreted in primary urine, and renal
distal and collecting tubules have been found to express NIS (Riesco-Eizaguirre and
Santisteban 2006). The risk of renal cancer has been shown to increase in the patients
treated with high doses of RAI for thyroid cancer (Hall et al. 1991, Rubino et al.
2003). An increased renal cancer risk has also been reported after RAI treatment of
hyperthyroidism, although the average radiation dose of the kidneys has been
estimated to be quite low (0.05Gy) (Hoffman et al. 1982b, Holm et al. 1991).

High concentrations of RAI have been estimated to occur in the urinary
bladder, because most of the circulating RAI is excreted into urine, and the bladder is
known to express NIS and to accumulate iodine (Holm et al. 1991, Riesco-Eizaguirre
and Santisteban 2006). A slightly increased incidence of cancer of the urinary bladder
has been seen in patients treated with high doses of RAI for thyroid
carcinoma (Edmonds and Smith 1986). However, the risk of the bladder cancer has
not been increased in previous long-term studies of patients treated with RAI for
hyperthyroidism (Holm et al. 1991, Ron et al. 1998, Franklyn et al. 1999). To
the urinary bladder, the ionizing radiation comes chiefly from RAI contained in
the urine, which will be reduced if more RAI is concentrated in the thyroid (Edmonds
and Smith 1986). Hence, the urinary bladder dose falls as the uptake in the thyroid
increases, unlike the stomach dose, which depends on the RAI ingested and is not
influenced by variation of RAI in the blood.
3.3.7. Leukemia

Leukemia is the most frequently observed radiation-induced malignancy due to its early onset after exposure, and high sensitivity of the bone marrow. A higher risk has been reported among the patients under 40 years of age at time of radiation exposure, and within 2-9 years after the exposure (UNSCEAR 2000). An increase in the incidence and mortality of leukemia has been observed in patients treated with high-dose RAI (3,000-6,000MBq) for thyroid cancer (Edmonds and Smith 1986, Rubino et al. 2003). However, no increased risk for malignancies of the hematopoietic system (leukemia and lymphoma studied separately) has been found in studies on patients treated with RAI (370-555MBq) for hyperthyroidism (Hoffman et al. 1982b, Holm et al. 1991, Franklyn et al. 1999). Furthermore, the absence of a dose-response relation or any relationship between cancer incidence and age at exposure or time since exposure has been reassuring (Hall et al. 1992b). The dose of RAI received gradually over time (effective half life of 6 days) may be a less effective carcinogen and give more opportunity to cellular repair than high doses of radiation given over a short time (Holm et al. 1991)

3.3.8. Thyroid cancer

A total of 350 new cases of thyroid cancer are diagnosed annually in Finland, (Finnish Cancer Registry). Primary thyroid malignancies include papillary (90%), follicular, medullary, or anaplastic carcinomas. A juvenile thyroid gland is one of the most radiosensitive organs in the body, presumably due to its superficial location and a relatively high cell turnover rate (Rivkees et al. 1998). An increased incidence of thyroid cancer after the atomic bomb explosions in Japan and the Chernobyl nuclear accident has been reported, especially among children exposed before the age of 10 years (UNSCEAR 2000).

Given the considerable increase in the risk of thyroid cancer in children exposed to 0.2-2Gy of external radiation (Ron et al. 1995, Rivkees et al. 1998) and the higher occurrence of thyroid adenomas in children treated with RAI for hyperthyroidism (Dobyns et al. 1974), a concern has lingered about an increased risk of thyroid cancer after RAI treatment for hyperthyroidism, especially in children and adolescents. Moreover, several reports have shown that patients with Graves’ disease
had a higher incidence of thyroid cancer than normal subjects. Thyroid malignancies developing in patients with Graves’ disease may also be more aggressive than cancers occurring in individuals without Graves’ disease (Belfiore et al. 1990, Mazzaferri 1990).

No increase in the risk of thyroid malignancies has been observed in patients treated with RAI for hyperthyroidism in most of the published long-term follow-up studies (Holm et al. 1991, Angusti et al. 2000). In a 36-year follow-up of 98 patients treated with RAI for hyperthyroidism under the age of 20, no cases of thyroid cancer were observed (Read et al. 2004). However, in a few studies an elevated risk of thyroid cancer (including papillary, follicular and anaplastic carcinomas) has been reported, though based on a small number of cases (Hoffman et al. 1982b, Ron et al. 1998, Franklyn et al. 1999).

3.4. Morbidity and mortality due to other diseases

In studies comparing RAI-treated hyperthyroid patients with the national background population, an increase in mortality due to fractures (Franklyn et al. 1998), respiratory diseases (Goldman et al. 1988, Hall et al. 1993), and endocrine diseases (Goldman et al. 1988, Hall et al. 1993, Franklyn et al. 1998) has been reported.

A past history of hyperthyroidism has been associated with decreased bone mineral density and increased risk of fracture, which may relate to the duration of exposure to excess thyroid hormones (Bauer et al. 2001, Vestergaard and Mosekilde 2002, Murphy and Williams 2004). In hyperthyroidism, the duration of the bone remodeling sequence is reduced, resulting in a negative balance between bone resorption and formation, i.e., in bone loss and a more fragile microarchitecture of bone (Murphy and Williams 2004). Furthermore, intestinal calcium and phosphate absorption is reduced, while urinary, fecal and dermal calcium excretion is increased leading to a negative calcium balance. Both thyroid hormone excess and low TSH levels may contribute to bone loss in hyperthyroid patients (Murphy and Williams 2004). During RAI treatment for hyperthyroidism, the parathyroid glands are exposed to radiation (Bondeson et al. 1989). Both hypoparathyroidism and hyperparathyroidism have been reported in several patients treated with RAI for
hyperthyroidism or thyroid carcinoma (Bondeson et al. 1989, Winslow and Meyers 1998).

The increased mortality from respiratory diseases after treatment of hyperthyroidism has been presumed to result mainly from respiratory infections (Hall et al. 1993). In most studies, no data on smoking habits has been available. In the only study reporting smoking habits, overall mortality was elevated in both smokers and non-smokers compared with the general population (Goldman et al. 1988).

Thyroid diseases and diabetes have accounted for the excess deaths due to endocrine and metabolic diseases (Hall et al. 1993, Franklyn et al. 1998). Diabetes is a well-known cause of increased mortality (Huxley et al. 2006), and type 1 diabetes is associated with autoimmune thyroid diseases (Perros et al. 1995). Although a thyroid storm might actually be lethal, the causes of death associated with hyperthyroidism may have been overestimated because of the knowledge of a previous thyroid disease (Goldman et al. 1988, Hall et al. 1993, Franklyn et al. 1998).

3.5. Clinical characteristics affecting mortality and morbidity after RAI treatment for hyperthyroidism

The information on the effect of the etiology of hyperthyroidism, treatment of hyperthyroidism, and age at treatment on the mortality and morbidity after RAI treatment is mostly lacking or conflicting. Younger patients and those receiving higher RAI activity were at an increased risk of death or cancer compared with older patients and those receiving lower activity RAI in one cohort (Holm et al. 1991, Hall et al. 1993), while in another cohort no such associations were observed (Franklyn et al. 1998). Patients with a toxic multinodular goitre had a higher overall and cancer mortality than those with Graves’ disease in several studies (Goldman et al. 1988, Hall et al. 1993, Ron et al. 1998). A recent systematic review reported a trend towards lower cardiovascular morbidity and mortality in patients with adjunctive antithyroid drugs compared with those not receiving antithyroid drugs before RAI treatment, though this was not significant and neither event was a primary outcome in the studies (Walter et al. 2007). Hypothyroidism has been suggested to increase the risk of death by causing hypercholesterolemia, diastolic hypertension and left ventricular dysfunction (Cappola and Ladenson 2003). However, levothyroxine-treated hypothyroidism after RAI treatment seems to protect against death instead of
predisposing to it (Franklyn et al. 2005). This might reflect the impact of an effective
cure of hyperthyroidism. An initial hypothyroid state induced by effective treatment
has been reported to be a predictor of successful reversion to sinus rhythm in those
with AF during hyperthyroidism (Osman et al. 2007).
AIMS OF THE STUDY

The aim of this study was to establish the long-term outcome of Finnish patients treated with RAI for hyperthyroidism. The specific objectives were:

1. to assess the cumulative incidence of hypothyroidism during long-term follow-up after RAI treatment for hyperthyroidism

2. to compare the morbidity, especially due to cardiovascular diseases, of hyperthyroid patients treated with RAI with that of an age- and gender-matched reference population

3. to compare the cancer incidence and mortality of hyperthyroid patients treated with RAI with that of an age- and gender-matched reference population

4. to compare the mortality and causes of death of hyperthyroid patients treated with RAI with that of an age- and gender-matched reference population

5. to study the possible modification of the risk of morbidity and death by the clinical characteristics of the patient, the etiology of hyperthyroidism, the dose of RAI, recurrent hyperthyroidism, and the development of hypothyroidism
SUBJECTS AND METHODS

1. Subjects

The present study was based on a computerized register where the details of all hyperthyroid patients treated with RAI for hyperthyroidism at the Tampere University Hospital have been collected since 1965. When a patient was referred to the department of nuclear medicine at the Tampere University Hospital to get RAI treatment, a form for the register follow-up was filled for every patient and details of the etiology of hyperthyroidism, previous treatment of hyperthyroidism, and the dose of RAI were added to the computerized register (Appendix 1).

A total of 2793 patients (457 men and 2336 women) were treated with RAI for hyperthyroidism at the Tampere University Hospital between January 1965 and June 2002. The Tampere University Hospital provides tertiary medical care for a population of approximately 460,000 people, and due to the public health care system available for all residents it has been practically the sole provider of RAI treatment for this population. The case series therefore represents all incident cases of RAI-treated hyperthyroidism in the base population. The mean number of RAI treatments per year between 1965-2002 was 75. Since the 1990’s, the annual number of RAI-treated patients has been approximately 100 per year.

2. Follow-up

The development of hypothyroidism and recurrent hyperthyroidism were studied in 2043 patients treated with RAI for hyperthyroidism in 1965-2002, and followed-up at least one year after the first RAI treatment (I). The follow-up period began at the time of the first RAI treatment and continued until the patient developed hypothyroidism, died or moved out of the Tampere University Hospital district, or until June 2002. From the original study population, 750 patients who did not participate in the follow-up for at least twelve months were excluded. The distribution of excluded patients was uniform throughout the data collection period, except for years 2001-2002 when most of the patients were excluded because of a short follow-up period (Figure 1).
Excluded (register follow-up less than 1 year, n = 750)

Deceased until 6/2002
(n = 1148)

Moved away from hospital district (n = 202)

Follow-up continues up to 6/2002 (n = 693)

Excluded (treated before 1969, n = 182)

Hospitalized due to cardiovascular disease (n = 1305)

Deceased until 12/2003
(n = 290)*

Moved away from Finland (n = 4)

Follow-up continues up to 12/2003 (n = 1012)

Cancer diagnosed (n=367)

Deceased until 12/2004
(n = 1120)**

Moved away from Finland (n = 4)

Follow-up continues up to 12/2004 (n = 1302)

Deceased until 12/2003 (n = 1390)

Moved away from Finland (n = 4)

Follow-up continues up to 12/2003 (n = 1399)

Figure 1. Schematic presentation of the hyperthyroid patients treated with RAI in the present series of studies

* deceased without hospitalization due to cardiovascular disease

** deceased without a diagnosis of cancer
A population-based cohort study was conducted among all 2793 hyperthyroid patients treated with RAI in 1965-2002 at the Tampere University Hospital to study the hospitalization rate and causes of hospitalization (II), cancer incidence (III), and mortality (IV). The follow-up period started at the end of the year of the first RAI treatment. A reference group was formed by choosing an age- and gender-matched control subject for each patient from the Population Register Centre. The control subject had to be alive at the time when the patient received the first RAI treatment. The follow-up period of the control subject started at the same time as that of the corresponding patient (Figure 1).

In order to study the rate and causes of hospitalization, 182 patients treated with RAI before 1969 were excluded, because no data on hospitalization was available until January 1969. Consequently, 2611 patients treated with RAI for hyperthyroidism, and 2611 age-and gender matched controls were studied (II). The disease-specific hospitalization rate was calculated with follow-up until the first hospitalization due to that disease, regardless of any other causes of hospital admission. If the subject was not hospitalized because of that disease, the follow-up ended on the date of death, emigration, or the common closing date (December 31, 2003), whichever occurred first. If a subject was treated in a hospital several times because of the same disease, only the first admission was included. When studying cancer incidence and mortality, the follow-up of both patients and controls started at the first RAI treatment (since 1965) and ended on the date of the first cancer diagnosis, death, emigration from Finland, or the common closing date (December 2004), whichever occurred first. The person-years at risk were 30,878 among the patients and 32,452 among the controls. In the analysis of mortality, the follow-up started at the first RAI treatment (since 1965) and continued until date of death, date of moving out of Finland or until the study closing date in December 2003. The person-years at risk were 30,669 among the patients and 31,972 among the controls.
3. Methods

3.1. Etiology of hyperthyroidism

Hyperthyroidism was diagnosed when classical symptoms and signs of hyperthyroidism coexisted with biochemical evidence, i.e., high total T4 or free T4 (above the current reference values) associated with a decreased level of TSH (below 1mU/l until 1986 and below 0.4mU/l thereafter). The etiology of hyperthyroidism was determined by clinical examination. The diagnosis of Graves’ disease was made if a diffuse goitre or ophthalmopathy was present. The diagnosis of toxic nodular goitre was made if examination of the neck revealed nodularity within an enlarged thyroid. Toxic thyroid adenoma was diagnosed if a solitary nodule within otherwise normal thyroid gland was present. If the cause of hyperthyroidism was not apparent by clinical examination, thyroid antibodies were measured. Furthermore, the etiology was verified by thyroid scintigraphy in 59 % of cases. In thyroid scintigraphy, the iodine avidity of the thyroid gland was measured visually from the scintigrams (diffuse or focally increased uptake) by the 24-h uptake of RAI (proportion of the RAI dose trapped by the thyroid gland). RAI uptake is diffuse and high in Graves’ disease, while nodular thyroid disease is characterised by focal areas of increased uptake. RAI uptake is very low or undetectable in thyrotoxicosis resulting from an exogenous administration of thyroid hormone or from a thyrotoxic phase of thyroiditis (Cooper 2003). In the present study, 57 % of 2973 patients had Graves’ disease, 34 % had a toxic nodular goitre, and 8 % had a toxic adenoma. For the statistical analyses, the etiology of hyperthyroidism was classified as Graves’ disease or nodular thyroid disease, the latter one including toxic multinodular goitre and toxic adenoma. From the 1960’s till the 1970’s the most common etiology of hyperthyroidism was nodular thyroid disease (72%), while in the 1980’s-2000’s 75% of the patients had Graves’ disease.

3.2. Treatment of hyperthyroidism

According to a common policy in Finland, the RAI treatment was given to most patients with hyperthyroidism unless they were pregnant or breastfeeding or had severe eye symptoms of Graves’ disease. Young patients, as well as patients with eye
symptoms of Graves’ disease usually received long-term antithyroid drug therapy, and RAI was chosen only for those who suffered a relapse of hyperthyroidism after a long-term antithyroid treatment. Surgical treatment was chosen, if a patient had a very large multinodular or diffuse goitre causing symptoms of compression in the neck, or if there was a suspicion of a malignancy in the thyroid gland. The proportion of patients treated with thyroidectomy and long-term antithyroid drug therapy for hyperthyroidism was less than 10% of all hyperthyroid patients in the Tampere University Hospital district during the study period.

Until the end of the 1980’s, thyroid scintigraphy with a measurement of RAI uptake and the weight of the thyroid gland estimated by palpation were used to calculate the dose of RAI at the Tampere University Hospital. Thereafter, the dose has been chosen empirically. Since 1990, a fixed 7mCi (259MBq) dose of RAI has been recommended as the first dose for all hyperthyroid patients. In the whole population, the mean first dose of RAI administered was 241MBq (median 259MBq, min 55MBq, max 740MBq). Only four patients received more than 555MBq of RAI as their first treatment dose.

Most patients (88%) were given antithyroid drug therapy in order to achieve euthyroidism before the treatment with RAI. The drug of choice was carbimazole unless the patient was allergic to it. The patients were informed to discontinue the antithyroid drug therapy four days before their RAI treatment and to continue it again four days after the RAI treatment. Subsequently, the antithyroid medication was tapered off within three to four weeks after the RAI treatment. Of the 313 patients, who did not receive antithyroid drug therapy before RAI treatment, 59% had toxic nodular disease, and 57% were treated before the 1980’s.

3.3. Assessing the development of hypothyroidism and recurrent hyperthyroidism during the follow-up

After the RAI treatment, the thyroid status of the patients was monitored by blood samples every 1-3 months during the first year, and subsequently at 1-3 years’ intervals. In addition, the patients filled in a questionnaire on the symptoms of hypo- or hyperthyroidism, and reported their present medication for the thyroid illness (thyroxine or antithyroid drugs) and when the medication had been started (Appendix 2-3).
Patients were classified as hypothyroid when symptoms and biochemical evidence, *i.e.*, low total T4 or free T4 associated with an elevation of TSH (> 6mU/l), suggested hypothyroidism and resulted in the initiation of thyroxine replacement therapy. Transient hypothyroidism after RAI therapy was not recorded. Patients were classified as having a relapse of hyperthyroidism when their symptoms and biochemical evidence, *i.e.*, a high total T4 or free T4 (above the current reference value) associated with a decreased level of TSH (below 1mU/l until 1986 and below 0.4mU/l thereafter), necessitated a repeated RAI therapy or a continuous antithyroid medication lasting for more than one year after the RAI therapy. The remission was determined as becoming euthyroid or hypothyroid after the RAI treatment. Follow-up data was entered into the computerized register on the basis of a follow-up form and the results of blood samples (Appendix 4).

### 3.4. Evaluation of rate and causes of hospitalization

The causes of hospitalization as well as the diagnosis and date of hospital admission were obtained from the nation-wide Hospital Discharge Register (HILMO) maintained by the Research and Development Centre for Welfare and Health (STAKES) using a computerized record linkage, with the personal identification number as the key. The HILMO database covers all dates and causes of hospitalization (hospital admission requiring an overnight stay) of the Finnish citizens since January 1969. The diagnoses have been coded according to the 8th revision of the International Classification of Diseases (ICD) between 1969 and 1986, the Finnish version of ICD-9 between 1987 and 1995, and the Finnish version of ICD-10 thereafter. A translation between the different ICD versions was made, and the causes of hospitalization were classified into 13 disease groups. The classification of infectious diseases used in the present study differed from that of the ICD. In our study, hospital admissions due to all infections of the cardiovascular, central nervous, respiratory, genito-urinary, gastrointestinal, and musculoskeletal systems were classified as infectious diseases. In the ICD the infectious diseases are classified according to the origin of infectious disease. Furthermore, seven different cardiovascular disease classes were analyzed separately: hypertension, coronary artery disease, diseases of the pulmonary circulation, arrhythmias, heart failure,
cerebrovascular diseases, diseases of other arteries and veins, and other cardiovascular
diseases (non-bacterial endo-, peri- and myocardial diseases, cardiomyopathy, and
conduction disorders of the heart). Both the primary and secondary diagnoses
recorded at discharge from the hospital were used in the analysis. If a disease caused
hospitalization prior to the beginning of the follow-up, the patient was classified as
having a prevalent disease. The rate ratios (RR) for hospitalization (II) and
cardiovascular mortality (IV) were adjusted using a prevalent disease as a covariate.

3.5. Evaluation of cancer incidence

Incident cancer cases occurring among patients and controls were identified from
the Finnish Cancer Registry. The Finnish Cancer Registry is a population-based,
nation-wide cancer registry established in 1952. Each cancer regarded as
an independent new primary malignancy was registered separately. The unspecified
tumors included metastatic tumors with unknown or unspecified primary site.
Prevalent cancers at baseline, i.e., those diagnosed prior to the beginning of
the follow-up, were excluded. Site-specific cancer incidence was calculated with
follow-up until the diagnosis of the site-specific cancer, regardless of any other cancer
diagnosed. As for prostate, breast and gynecological cancer, the person-years at risk
were counted only for the sex at risk.

3.6. Evaluation of mortality and causes of death

Data on the causes of death of the patients and the controls was obtained from
the Statistics Finland. The dates and causes of death of all Finnish citizens certified by
a physician have been included in this register since 1971. The death certificate
data was compared with the Population Register by means of the personal
identification code of the deceased, which ensures the coverage of the statistics.

In the Finnish Cause of Death Register the causes of death have been coded
according to the 8th revision of the International Classification of Diseases (ICD)
between 1971 and 1986, the Finnish version of ICD-9 (Tautilukitus 1987) between
the different versions was made, and the underlying causes of death were classified
into nine groups: infectious diseases, malignant tumors, endocrine diseases,
cardiovascular diseases, dementia, respiratory diseases, traumata, other causes of death, and unknown cause of death. Because the diseases of the central nervous system consisted mainly of cerebrovascular diseases, infectious diseases, and dementia in the present study, we used these separate classes instead of the overall category of central nervous system diseases, as in the ICD. We used the underlying cause of death for the classification. In addition, the mortality due to atrial fibrillation was analyzed using also the contributory causes of death.

In the present study, 55 deaths (29 patients and 26 controls) occurred before 1971, when the cause of death was not recorded in the national cause-of-death database. Ninety-six persons (10 patients and 86 controls) died abroad or their cause of death was otherwise unspecified or unknown.

3.7. Statistical analyses

We used the statistical software Stata for Windows (StataCorp, College Station, Texas, USA) to calculate the incidence of hypothyroidism and cancer, as well as the hospitalization and mortality rates. The hospitalization, cancer incidence and mortality rate ratios were calculated by the Mantel–Haenszel method. Other statistical analyses were performed using SPSS for Windows Versions 11.0 -14.0 (SPSS Inc., Chicago, Illinois, USA). Normality of the distribution of the variables studied was tested by the Kolmogorov-Smirnov test. The distributions of all the continuous variables were skewed and therefore non-parametric tests (Mann-Whitney and Kruskal-Wallis tests) were used to assess the relationship between continuous and categorical variables. The Chi-square test was used to determine, whether an association between two categorical variables was statistically significant. Hospitalization rates, cancer incidence and mortality were illustrated by Kaplan-Meier analyses with log rank tests. Cox regression analyses were performed to evaluate the significance of different factors in predicting the risk of hypothyroidism, hospitalization, cancer, and death. Hospitalization rates, cancer incidence and mortality were also counted in the following subgroups of patients using only the corresponding age- and gender matched controls: etiology of hyperthyroidism (Graves’ disease, nodular thyroid disease), total dose of RAI (55-258MBq, 259-369MBq, 370-2664MBq), recurrence of hyperthyroidism after the first dose of RAI (yes, no), development of hypothyroidism during follow-up (yes, no), and age at
the beginning of follow-up (13-50, 50-59, 60-69, and 70-98 years). In all studies, a two-sided p-value of less than 0.05 was considered statistically significant.

3.8. Ethical considerations

The study was undertaken in accordance with the Declaration of Helsinki. Informed consent could not be collected, because of the large number of participants and a high proportion of deceased subjects. The ethics committee of the Pirkanmaa Hospital District approved the study protocol. In addition, the National Research and Development Centre for Welfare and Health gave permission to use data from the Population Register Centre and the Hospital Discharge Registry, and the Statistics Finland gave permission to the use of the Cause of Death Register.

RESULTS

1. Development of hypothyroidism

During the follow-up, hypothyroidism was diagnosed and treated in 38% of the 2043 patients who participated in the register follow-up for more than one year (I). Out of the 750 patients who participated in the register follow-up for less than one year, 40 patients were known to develop hypothyroidism. In 710 patients the status of thyroid function remained unclear because of the lack of the follow-up data on thyroid function. Hypothyroidism was known to develop in 30% of the 2793 patients in studies III and IV, and in 31% of the 2611 patients in study II.

The median time to the development of hypothyroidism was two years (minimum one month, maximum 25.4 years, I). The cumulative incidence of hypothyroidism in the patients with Graves’ disease and those with a nodular thyroid disease at one, 10 and 25 years were 24 vs. 4%, 59 vs. 15% and 82 vs. 32%, respectively. In a Cox regression model, a previous partial thyroidectomy increased the risk of hypothyroidism, and the risk decreased with age both in patients with Graves’ disease and in those with a nodular thyroid disease. Antithyroid medication preceding RAI therapy decreased and female gender increased the risk of hypothyroidism only in patients with Graves’ disease (I).
2. Recurrence of hyperthyroidism

In the whole population, the mean first dose of RAI administered was 241MBq (min 55MBq, max 740MBq) and the mean total dose was 305 MBq (min 55, max 2664 MBq). Remission was achieved with a single dose of RAI in 80% of the patients. A total of 435 patients (15.6%) were given two doses of RAI, 76 patients (2.7%) three doses, 39 patients (1.7%) four or more doses. Twenty-one patients received antithyroid treatment for more than a year after the first RAI treatment to maintain a euthyroid state (II-IV).

When the patients who were followed up for less than a year were excluded, administration of a single dose of RAI resulted in the control of hyperthyroidism in 76% of patients (76% of the patients with Graves’ disease, 74% of those with toxic multinodular goitre, and 77% of those with toxic adenoma), while two to six RAI treatments were needed in 24% of patients to achieve either a hypothyroid or a euthyroid state (I). The second dose of RAI was given for persistent hyperthyroidism after a median of 10 months (minimum 4 months, maximum 33 years). The etiology of hyperthyroidism, gender, surgical treatment or antithyroid medication preceding RAI therapy, duration of antithyroid medication, first dose of RAI, or age at the first RAI treatment did not differ between the patients cured with a single dose of RAI and those who needed more than one dose of RAI or prolonged antithyroid treatment to achieve remission.

The remission rate did not differ between the patients who received a dose of RAI calculated according to the uptake of RAI and thyroid size (n = 1477) and those who received an empirical dose of RAI (n = 566), either in patients with Graves’ disease or in those with nodular thyroid disease (I). A total of 364 patients received the recommended 7mCi dose. However, other empirical doses were also used. The remission rate did not differ statistically significantly between the dose groups (80% in patients who received 7mCi, 77% in patients who received 5mCi and 69% in patients who received 10mCi). (I).
3. Morbidity and mortality after RAI-treated hyperthyroidism

3.1. Cardiovascular diseases

The median age of the patients at RAI-treatment and the reference group at the beginning of the follow-up was 62 years (interquartile range 49-72 years for both groups). The median follow-up time was 9.0 years for the patients and 9.1 years for the controls (interquartile range 4.3-16.0 years for the patients and 5.0-16.4 years for the controls).

The risk of the first hospital admission (adjusted for prior hospitalizations) due to cardiovascular diseases was significantly higher in the patients than in the control group up to 35 years after the RAI treatment (hospitalization rate 637.1 vs. 476.4 per 10,000 person years in the patients and the controls with a RR of 1.12 (95% CI 1.03-1.21)). The absolute increase in the risk (rate difference) of hospitalization due to cardiovascular diseases was 84 hospital admissions per 1000 patients by 10 years of follow-up (II).

The most frequent cardiovascular disease leading to hospitalization was arrhythmia. The risk of hospitalization due to arrhythmia was significantly higher in the patients than in the controls (RR 1.22, 95% CI 1.07-1.39) up to 35 years of follow-up (II). AF accounted for the increased risk of hospital admissions due to arrhythmia (RR 1.35, 95% CI 1.11-1.64). The second most common cardiovascular disease leading to hospitalization was coronary artery disease, but it was not increased in the patients compared with the controls (II). The third most common cardiovascular disease was cerebrovascular disease. Adjustment for AF did not markedly affect the increased risk of hospitalization due to cerebrovascular disease (II). In addition, the effect of RAI-treated hyperthyroidism on cerebrovascular morbidity remained practically unchanged, when adjusted for diabetes and hypertension (II).

Cardiovascular diseases were the most frequent causes of death both in the RAI-treated patients and the controls (IV). Cerebrovascular diseases accounted for the increased risk of death from cardiovascular diseases in the patients compared with the control group (Figure 2). Adjusting for prevalent cerebrovascular disease, diabetes, and age did not change the patients’ risk of death from cerebrovascular disease (IV).
Figure 2. Cardiovascular mortality (deaths/10,000 person-years) by the underlying cause of death in the RAI-treated patients and in the population-based control group (RR is given only for statistically significant differences)

*Chronic rheumatic and non-rheumatic valve diseases
**Conduction disorders of the heart, diseases of the pulmonary circulation, unspecified cardiac arrhythmias
The risk of death from endocardial diseases (chronic rheumatic and non-rheumatic valve diseases) and other cardiovascular diseases (conduction disorders of the heart, diseases of the pulmonary circulation and unspecified cardiac arrhythmias) was also significantly higher among the patients, but they accounted for only a small fraction of the cardiovascular mortality (Figure 2). AF was equally common as an underlying cause of death among the patients and the controls. However, when the contributory causes of death were included in the analysis, the patients had an increased risk of dying due to AF compared with the controls (mortality 29.3 vs. 17.5 per 10,000 person years in the patients vs. controls with a RR of 1.68 (95% CI 1.20-2.34), IV).

3.2. Cancer

At least one cancer diagnosis after the beginning of the follow-up was identified in 367 patients and in 308 controls. More than two different cancer types were diagnosed in 21 patients and 8 controls. The overall cancer incidence was higher among the patients than in the control group (RR 1.23, 95% CI 1.08-1.46). The absolute difference in the incidence rates was 24/10,000, which corresponds to the number needed to harm of 418 (95% CI 391-446, i.e., one excess case of cancer induced by treating 418 patients with RAI). The difference in cancer incidence between the studied groups started to emerge five years after the first RAI treatment (III). The cancer incidence after 10 or more years of follow-up was 154.4 per 10,000 person-years in the patients and 126.4 in the control group (RR 1.22, 95% CI 1.00-1.53). Cancer had been diagnosed in 125 patients and 93 controls prior to the beginning of follow-up. When adjustment for previous cancer was used in the Cox regression analysis, the risk related to RAI treatment remained unchanged (RR 1.27 (95% CI 1.09-1.47), III). The risk of cancers of the stomach, kidney, breast, and unspecified site was increased in the patients compared with the control group (Figure 3).
**Figure 3.** Cancer incidence per 10,000 person-years at risk in the RAI-treated patients and in the age- and gender-matched control group (RR is given only for statistically significant differences)
Mortality from cancer increased in the patients compared with the controls, as well (RR 1.29, 95% CI 1.07-1.57). Adjustment for previous cancer did not markedly affect the result (RR 1.36 (95% CI 1.12-1.65), IV). The increase in mortality from cancer in the patients was mainly explained by gastro-esophageal tumors, out of which esophageal cancer caused the death of 7 patients and 2 controls, and stomach cancer the death of 24 patients and 11 controls, respectively (Figure 4).

3.3. Other diseases

The risk of the first hospital admission (adjusted for prior hospitalizations) due to infectious (RR 1.23, 95% CI 1.11-1.37) and gastrointestinal diseases (RR 1.15, 95% CI 1.00-1.32), and fractures (RR 1.18, 95% CI 1.01-1.39) was significantly higher in the patients than in the control group (II), but mortality due to these diseases did not differ between the patients and controls (IV). Hyperthyroid patients had an increased risk of being hospitalized due to infectious diseases up to 20 years after the RAI treatment. However, hyperthyroidism was not an independent predictor of hospitalization due to infectious diseases when adjusted for both previous infectious disease and cardiovascular disease (II). Although the risk of hospital admission due to gastrointestinal diseases was slightly increased in the patients compared with the controls, there was no difference between the groups, if diseases of the upper and lower gastrointestinal tract and liver and pancreas were analyzed separately (II). Hospitalizations due to fractures were more common among RAI-treated patients than among the respective controls in women, but not in men. In addition, hospitalizations due to fractures were increased only in female patients treated at the age of 50 years or older, but not among younger women. However, when adjusted for both the prevalent fracture and cardiovascular disease, the fracture risk related to RAI-treated hyperthyroidism was not statistically significant (II). The risk of pregnancy complications did not differ between the patients and the controls (II).
All malignant tumours
Other malignant tumors
Intestinal tumours
Tumours of liver and pancreas
Respiratory tumours
Breast cancer
Genito-urinary tract tumors
Thyroid tumors
Hematological malignancies
Gastro-esophageal tumors

Figure 4. Cancer mortality per 10,000 person-years at risk in the RAI-treated patients and in the age- and gender-matched control group (RR is given only for statistically significant differences)
3.4. Mortality

Record linkage with Statistics Finland identified an all-cause mortality of 453 vs. 406 per 10,000 person-years in the patients vs. the controls (RR 1.12, 95% CI 1.03-1.20). The risk of death was higher in the RAI-treated hyperthyroid patients compared with the controls up to 25 years of follow-up (IV).

The risk of death from malignant tumors, and from cardiovascular, endocrine, and respiratory diseases was higher in the patients than in the controls (Figure 5). Cardiovascular diseases and malignant tumors accounted for most of the increased risk of death in the patients compared with the control group. Mortality due to endocrine and respiratory diseases only accounted for a minor part of the difference in mortality between the patients and the controls. The excess endocrine mortality in the patients was mainly attributable to hyperthyroidism. All 15 deaths from thyroid disease occurred between 1971-1986 and were caused by toxic multinodular goitre or adenoma with a thyroid crisis mentioned in the death certificate. The increased risk of death from respiratory diseases was due to asthma and chronic obstructive pulmonary disease. The mortality from unknown causes was significantly lower in the patients than in the control group. When the mortality analysis was repeated with the assumption that deaths from unknown causes were distributed similarly as the known causes of death (i.e., similar proportion from each cause in both known and unknown deaths), the results remained unchanged (IV).

When mortality among men and women was considered separately, the overall mortality was higher among RAI-treated patients in both men (521/10,000 vs. 424/10,000, RR = 1.23, 95% CI = 1.02-1.48) and women (442/10,000 vs. 403/10,000, RR = 1.10, 95% CI = 1.01-1.19). Mortality from cardiovascular diseases was elevated in both male and female patients. Mortality from endocrine and respiratory diseases increased only among female patients, while mortality from malignant tumors increased only in male patients (IV).
Figure 5. Mortality (deaths/10,000 person-years) by the underlying cause of death in the RAI-treated patients and in the population-based control group (RR is given only for statistically significant differences)
3.5. Clinical characteristics affecting morbidity and mortality after RAI-treated hyperthyroidism

The cardiovascular morbidity, cancer incidence, and overall mortality were higher among the RAI-treated patients than among the controls in both genders.

Other clinical characteristics and their effect on the prognosis of the patients compared with the controls are presented in Table 3. The risk of cardiovascular morbidity, cancer, and death increased with the cumulative dose of RAI. The risk of cardiovascular morbidity and death increased significantly only in the subjects older than 60 years at the time of RAI compared with the corresponding controls. The incidence of cancer was statistically significantly higher in the RAI-treated patients than in the control group in two age groups, namely those who were 50-59 or 70-98 years old at the beginning of the follow-up. Twenty-one patients were treated with RAI under the age of 20. None of them or their controls had a cancer or died during the follow-up (median 13 years in both the patients and the controls).

Hyperthyroidism was caused by Graves’ disease in 57% of the patients and by nodular thyroid disease in 43%. The overall cancer incidence was increased in the patients compared with the corresponding control group in both etiologic groups. The hospitalizations due to cardiovascular diseases and overall mortality were elevated in the patients with nodular thyroid disease, but not in those with Graves’ disease, compared with the corresponding controls. The patients with nodular thyroid disease were older (median age 67 vs. 57 years, p<0.001), received a higher cumulative dose of RAI (median dose of RAI 259 vs. 222 MBq, p<0.001), and were treated historically earlier (median year of the first RAI 1976 vs. 1991, p<0.001), but were followed-up as long as those with Graves’ disease (median follow-up time 9 years 10 months vs. 9 years 2 months, p=0.57).

The risk of cancer in the patients whose hyperthyroidism recurred after the first treatment with RAI compared with the corresponding controls was slightly higher than in those whose hyperthyroidism was cured with a single dose of RAI. In the patients who were known to develop hypothyroidism during the follow-up, hospitalization rate due to cardiovascular disease, cancer risk, and mortality were lower than in the corresponding controls. The risk of cancer and mortality were slightly lower in the patients previously treated with partial thyroidectomy than in the non-operated ones. The antithyroid medication prior to RAI treatment did not
markedly affect the risk of death, but slightly reduced the risk of hospital admission due to cardiovascular disease, and was associated with an increased risk of cancer.

In order to evaluate the significance of different clinical factors in predicting the risk of cardiovascular morbidity, cancer, and death the clinical characteristics presented in Table 3 were used as covariates in a Cox regression analysis. RAI-treated hyperthyroidism and age increased the risk of hospitalization due to cardiovascular disease (II), cancer (III), and death (IV), while hypothyroidism decreased these risks. In addition, nodular thyroid disease increased the risk of hospital admission due to cardiovascular disease (II).
Table 3. Clinical factors affecting the morbidity and mortality after RAI-treated hyperthyroidism

<table>
<thead>
<tr>
<th>Clinical factor</th>
<th>Percentage of all patients (n)</th>
<th>RR for cardiovascular morbidity</th>
<th>RR for overall cancer incidence</th>
<th>RR for all-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total dose of RAI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55-258 MBq†</td>
<td>39% (n=1083)</td>
<td>0.97 (0.84-1.12)</td>
<td>1.11 (0.89-1.39)</td>
<td>1.05 (0.94-1.81)</td>
</tr>
<tr>
<td>259-369 MBq</td>
<td>37% (n=1033)</td>
<td>1.20 (1.07-1.34)*</td>
<td>1.32 (1.00-1.75)*</td>
<td>1.15 (1.00-1.33)</td>
</tr>
<tr>
<td>370-2664 MBq</td>
<td>24% (n=677)</td>
<td>1.21 (0.98-1.50)</td>
<td>1.47 (1.09-1.99)*</td>
<td>1.18 (1.03-1.36)*</td>
</tr>
<tr>
<td><strong>Age at treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13-49 years</td>
<td>25% (n=694)</td>
<td>1.12 (0.87-1.45)</td>
<td>1.49 (0.88-2.53)</td>
<td>0.86 (0.58-1.26)</td>
</tr>
<tr>
<td>50-59 years</td>
<td>18% (n=506)</td>
<td>1.14 (0.94-1.39)</td>
<td>1.44 (1.05-1.97)*</td>
<td>1.10 (0.90-1.34)</td>
</tr>
<tr>
<td>60-69 years</td>
<td>26% (n=731)</td>
<td>1.17 (1.01-1.35)*</td>
<td>1.06 (0.83-1.36)</td>
<td>1.18 (1.04-1.35)*</td>
</tr>
<tr>
<td>70-98 years</td>
<td>31% (n=862)</td>
<td>1.37 (1.20-1.56)*</td>
<td>1.38 (1.05-1.82)*</td>
<td>1.17 (1.05-1.31)*</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td></td>
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<tr>
<td>Graves’ disease</td>
<td>57% (n=1604)</td>
<td>0.95 (0.85-1.08)</td>
<td>1.25 (1.00-1.58)*</td>
<td>1.07 (0.94-1.22)</td>
</tr>
<tr>
<td>Toxic nodular disease</td>
<td>43% (n = 1189)</td>
<td>1.35 (1.21-1.52)*</td>
<td>1.27 (1.04-1.56)*</td>
<td>1.17 (1.06-1.28)*</td>
</tr>
<tr>
<td><strong>Recurrence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>20% (n=571)</td>
<td>1.09 (0.91-1.31)</td>
<td>1.40 (1.02-1.94)*</td>
<td>1.10 (0.94-1.30)</td>
</tr>
<tr>
<td>No</td>
<td>80% (n=2222)</td>
<td>1.13 (1.03-1.23)</td>
<td>1.21 (1.02-1.44)*</td>
<td>1.12 (1.03-1.22)*</td>
</tr>
<tr>
<td><strong>Hypothyroidism</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>40% (n=831)</td>
<td>1.03 (0.88-1.29)</td>
<td>1.18 (0.89-1.56)</td>
<td>0.89 (0.75-1.05)</td>
</tr>
<tr>
<td>No</td>
<td>60% (n=1250)</td>
<td>1.22 (1.10-1.34)*</td>
<td>1.32 (1.11-1.58)*</td>
<td>1.24 (1.14-1.35)*</td>
</tr>
<tr>
<td><strong>Previous partial thyroidectomy</strong></td>
<td></td>
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<tr>
<td>Yes</td>
<td>12% (n=303)</td>
<td>1.11 (0.87-1.45)</td>
<td>1.13 (0.74-1.73)</td>
<td>0.97 (0.77-1.22)</td>
</tr>
<tr>
<td>No</td>
<td>88% (n=2179)</td>
<td>1.12 (1.02-1.23)*</td>
<td>1.28 (1.08-1.53)*</td>
<td>1.14 (1.05-1.24)*</td>
</tr>
<tr>
<td><strong>Antithyroid drug</strong></td>
<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>88% (n=2362)</td>
<td>1.11 (1.01-1.21)*</td>
<td>1.65 (1.06-2.58)*</td>
<td>1.12 (1.03-1.21)*</td>
</tr>
<tr>
<td>No</td>
<td>12% (n=313)</td>
<td>1.28 (1.01-1.63)*</td>
<td>1.19 (1.00-1.40)*</td>
<td>1.14 (0.94-1.34)</td>
</tr>
<tr>
<td><strong>All</strong></td>
<td>100% (n=2793)</td>
<td>1.12 (1.03-1.21)*</td>
<td>1.25 (1.08-1.46)*</td>
<td>1.12 (1.30-1.20)*</td>
</tr>
</tbody>
</table>

*Statistically significant difference between the patients and the corresponding controls
†55-258MBq = 1.5-6.9mCi, 259-369MBq = 7.0-9.9mCi, 370-2664MBq = 10.0-72.0mCi
DISCUSSION

1. Completeness and validity of the data

1.1. Register of the patients treated with RAI for hyperthyroidism

Information on the patients treated with RAI for hyperthyroidism in the Tampere University Hospital district has been collected into a computerized register in collaboration with the department of nuclear medicine at the Tampere University Hospital and internists in the Tampere University Hospital district since 1965. The Tampere University Hospital has been practically the sole provider of RAI treatments for the population of approximately 460,000 people living in the hospital district since 1965. In 1995-1999 part of the RAI treatments were given in the city hospital of Tampere, but the patients were included in the register. The case series therefore represents all incident cases of RAI-treated hyperthyroidism in the base population.

1.2. Clinical characteristics affecting prognosis after RAI treatment

In the present study, hyperthyroidism was diagnosed when classical symptoms and signs of hyperthyroidism coexisted with biochemical evidence, i.e., high total T4 or free T4 associated with a decreased level of TSH. Until 1986, a first generation method for measuring TSH was used at the Tampere University Hospital. The patients treated historically earlier may have suffered from a more prolonged and severe hyperthyroidism before receiving effective treatment because of less accurate methods of diagnosing hyperthyroidism compared with the patients treated after 1986. Because nodular thyroid disease was the most common diagnosis until the 1980’s, the delay of the diagnosis might have attributed to the poorer prognosis of these patients.

In the present study, the etiology of hyperthyroidism was determined by clinical examination in most cases. The clinical diagnosis of the etiology of hyperthyroidism is usually apparent, and no further tests are needed (Cooper 2003, Välimäki 2004). However, some variety in determination of the etiology of hyperthyroidism may have occurred between physicians referring patients for RAI
treatment in the present study. Furthermore, toxic nodular disease and Graves’ disease may occasionally manifest in the same patient (Nygaard et al. 1999a, Ceccarelli et al. 2005). In the present study, the proportion of patients with Graves’ disease (57%), toxic nodular goitre (34 %), and toxic adenoma (8%) was in line with the figures reported previously in Europe (Reinwein et al. 1988). While most of the hyperthyroid patients had multinodular goitre in the 1960’s-1970’s, the main cause of hyperthyroidism was Graves’ disease (75%) since the 1980’s (I).

Late-onset hypothyroidism after RAI treatment has been reported to be missed in approximately 17% of cases (Read et al. 2004). In the present study, the thyroid status of the patients was monitored by blood samples and a questionnaire at 1-3 years’ intervals. Patients were classified as hypothyroid when the symptoms and biochemical evidence suggested hypothyroidism and resulted in the initiation of permanent thyroxine replacement therapy. The register-based follow-up probably increased the likelihood of detecting hypothyroidism in the present study. However, 27% of the patients were followed-up in the Tampere University Hospital district for less than one year after the RAI treatment, and the data on the thyroid function regarding these patients was not complete. The results did not change when the analyses were repeated excluding these patients (II-IV).

1.3. Hospitalization rate

The validity of hospital discharge diagnoses, especially cardiovascular diseases, obtained from the Finnish hospital discharge register has been good (90%) justifying their use in epidemiological studies (Heliövaara et al. 1984, Mähönen et al. 1997, Rapola et al. 1997, Leppälä et al. 1999, Pajunen et al. 2005). In the present study, the increased risk of cardiovascular and cancer morbidity and mortality reported in the patients treated with RAI was based on three registers (Finnish Cancer Registry, Statistics Finland and HILMO). Consistent results obtained from three independent registers support the validity of our results (II-IV).

The present morbidity data included only hospitalizations, and therefore diseases treated primarily in out-patient care were not covered. Thus, the hospitalization rates in the present study are not equivalent to the incidences of the corresponding diseases, particularly for diseases mainly treated in out-patient clinics. For example, the incidence of diabetes is probably higher than the observed
hospitalization rate due to diabetes in the present study. Furthermore, data on Graves’ ophtalmopathy was not available in HILMO, and could not be studied in this thesis.

1.4. Cancer incidence

The Finnish Cancer Registry is a population-based, nation-wide cancer registry established in 1952, with a completeness of more than 98% for solid cancers (Teppo et al. 1994). In the 1950’s, the reporting of cancers was voluntary. In 1961, the National Board of Health issued by law that all physicians, all hospitals, and pathological, cytological and haematological laboratories in Finland must send a notification to the Finnish Cancer Registry of all cases of cancer that come to their knowledge. In addition, the Statistics Finland informs the Cancer Registry of all death certificates, in which a cancer is mentioned. Finally, the Finnish Cancer Registry is regularly linked with the Population Register, where the authenticity of the personal identification number is checked, and the vital status, and a possible date of death or emigration are obtained.

1.5. Mortality

In the present study, the vital status and causes of death of the patients and the controls were obtained from the Finnish Population Register Centre and the Statistics Finland. The dates and causes of death of all Finnish citizens certified by a physician have been registered by the Statistics Finland since 1971. Several assessments of both specific causes and all causes of death have consistently indicated high completeness and reliability of the Finnish causes of death register (Leppälä et al. 1999, Mähönen et al. 1999, Lahti and Penttilä 2001).

In previous studies the observed mortality rate of hyperthyroid patients has been compared with the expected mortality rates counted from age- and sex-specific mortality rates in the United States, Sweden, or England and Wales. The present study is the first study in which frequency matching with individual age- and sex-matched controls with an equal life expectation for each patient were used instead of indirect standardization. There has been no major difference in the results obtained using either frequency matching or indirect standardization (Santos Silva 1999). The RR for mortality in our study was within the same range (RR=1.12) as in the previous studies.
There was no difference in the number of patients and controls died before 1971, when the cause of death was not recorded in the national cause-of-death database. Still, more controls than patients died abroad or their cause of death was otherwise unknown. The reason for this remained unclear. However, when the mortality analysis was repeated with the assumption that deaths from unknown causes were distributed similarly as the known causes of death, the results remained unchanged. Furthermore, overall mortality data was not affected by the incomplete information on the cause of death.

2. Major findings of the study

2.1. Cure rate and development of hypothyroidism after RAI treatment

The present study confirms that RAI treatment is effective in treating hyperthyroidism, but hypothyroidism will develop in most of the patients with Graves' disease and up to one third of the patients with a nodular thyroid disease in the median time of two years.

Patients with a toxic nodular disease have been found to be more resistant to RAI-induced hypothyroidism compared with patients with Graves’ disease, since RAI is not concentrated in the suppressed extranodular thyroid tissue outside the nodules. The cure rate after RAI treatment was identical in patients with Graves' disease and those with a nodular thyroid disease, although the incidence of hypothyroidism was higher in the patients with Graves’ disease (85%) than those with a toxic nodular disease (32%) in the present study, consistently with previous studies (Allahabadia et al. 2001, Erem et al. 2004).

The influence of antithyroid drugs on the outcome after RAI treatment has been conflicting, and the quality of evidence poor (Walter et al. 2007). A recent systematic review concluded that antithyroid drugs given within a week before or after RAI treatment increased the risk of treatment failure and reduced the risk of hypothyroidism, probably because the iodination of tyrosine residues on thyroid hormones is inhibited (Walter et al. 2007). On the other hand, previous antithyroid medication has increased the risk of hypothyroidism in patients with a toxic nodular
disease, probably because antithyroid drugs reduce nodule activity and increase 
the uptake of RAI by extranodular thyroid tissue (Nygaard et al. 1999c, Ceccarelli et 
al. 2005). In the present study, 88% of the patients received antithyroid medication 
until 4 days before RAI treatment. Antithyroid medication preceding RAI therapy 
decreased the risk of hypothyroidism in patients with Graves’ disease, but did not 
affect the cure rate.

Patients with severe hyperthyroidism have been reported to have a lower cure 
rate and a higher incidence of hypothyroidism than those with a mild disease, defined 
as the level of thyroid hormones before the initiation of treatment (Kung et al. 1990, 
Allahabadia et al. 2001, Erem et al. 2004). Males and young patients have had more 
treatment resistant hyperthyroidism compared with females and older patients, 
probably because of a larger thyroid gland and more severe hyperthyroidism 
(Allahabadia et al. 2001, Ahmad et al. 2002). In the present study, the risk of 
hypothyroidism was lower in females and decreased with age, but gender or age had 
no influence on the cure rate.

In conclusion, the associations between clinical factors and the risk of 
hypothyroidism found in our study were not strong enough to justify the use of 
individually adjusted doses of RAI or other treatment options, based on the clinical 
characteristics of the hyperthyroid patients. Because the development of 
hypothyroidism seems to be unpredictable by any clinical factors, the objective of 
RAI treatment should be to minimize the persistence of hyperthyroidism with 
the simplest possible form of treatment.

2.2. Cardiovascular morbidity and mortality

The cardiovascular effects of overt hyperthyroidism are thought to be reversed by 
effective treatment of hyperthyroidism (Klein and Ojamaa 2001, Osman et al. 2002). 
Previously, the risk of death due to cardiovascular diseases has been reported to be at 
its highest during the first year after RAI treatment and to decline with time (Hall et 
al. 1993, Franklyn et al. 1998). It has therefore been interpreted that the underlying 
cardiovascular diseases mainly account for the increased cardiovascular mortality. 
Furthermore, it has been suggested that the population of RAI-treated patients may 
have been selected to RAI treatment (and not to surgery) due to a reason impairing 
the prognosis, for example coronary heart disease. In previous studies, the results
have not been adjusted for prevalent cardiovascular disease (Goldman et al. 1988, Goldman et al. 1990, Hall et al. 1993, Franklyn et al. 1998, Franklyn et al. 2005). In the present study, the increased cardiovascular morbidity and mortality, especially due to cerebrovascular disease and arrhythmias, persisted up to 25-35 years after treatment with RAI. Furthermore, the cardiovascular morbidity and mortality was increased when adjusted for underlying cardiovascular disease, suggesting that the difference between the RAI-treated hyperthyroid patients and the control group was caused by the RAI treatment or by hyperthyroidism per se, and was not due to baseline differences in cardiovascular morbidity. The proportion of surgically treated patients has been less than 10% of all hyperthyroid patients in Tampere University Hospital district. It is therefore unlikely that selection of patients to RAI treatment would have induced significant confounding in this study.

No information was available on the traditional cardiovascular risk factors, such as smoking, hypercholesterolemia, or family history, which might have caused confounding in this study. However, the increased risk of hospitalization and mortality due to cardiovascular disease remained unchanged when adjusted for pre-existing diabetes and hypertension (II, IV). Furthermore, the lack of increased hospitalization or mortality due to ischemic heart disease in the hyperthyroid patients compared with the controls suggests that there were no major differences in the distribution of the traditional cardiovascular risk factors between the patients and the controls. However, there might be some residual confounding, for example due to differences in the socioeconomic status between the patients and the controls (Jakovljevic et al. 2001).

High doses of radiation have been shown to increase the risk of cardiovascular disease, but the doses received by the heart in RAI treatment for hyperthyroidism are too low (less than 0.1Gy) to affect the risk of cardiovascular disease (McGale and Darby 2005). Thus, hyperthyroidism per se probably accounts for the increased cardiovascular morbidity and mortality after RAI treatment of hyperthyroidism. The present long-term follow-up study confirms the results of recent reports suggesting that the cardiovascular effects of hyperthyroidism, especially susceptibility to arrhythmias, sustain after an effective treatment of hyperthyroidism (Flynn et al. 2006, Osman et al. 2007, Siu et al. 2007). It has been previously suggested that one third of the hyperthyroid patients develop a chronic dilated cardiomyopathy (Siu et al. 2007). In this study, the risk of heart failure, hypertension, and diseases of cerebral
and other arteries and veins sustained decades after the treatment of hyperthyroidism. Thus, the results of the present and previous studies suggest that some essential effects of hyperthyroidism on the cardiovascular system are permanent.

Previously, only Franklyn et al. (1998) have specified the cardiovascular diseases increasing mortality after RAI treatment of hyperthyroidism. In their study, cerebrovascular diseases and ischemic heart disease explained most of the increased cardiovascular mortality. In the present study, cerebrovascular diseases accounted for most of the increased risk of death due to cardiovascular diseases, but ischemic heart disease did not cause any excess deaths.

In view of the present results, cerebrovascular disease and AF are common and serious complications of hyperthyroidism. The magnitude of the effect of hyperthyroidism on cerebrovascular morbidity is comparable to an increase in systolic blood pressure by 10mmHg or LDL-cholesterol by 1mmol/l shown in previous studies (Turnbull 2003, Collins et al. 2004). Approximately 75% of strokes are first-ever strokes (Hankey 2005). Thus, primary prevention is the most effective way of reducing cerebrovascular morbidity and mortality in hyperthyroid patients. AF accounts for up to one-sixth of all ischemic strokes (Hankey 2005). Hyperthyroidism is a well-known risk factor for AF (Auer et al. 2001), and acute cardioembolic stroke is a well-described manifestation of AF in hyperthyroid patients (Presti and Hart 1989, Squizzato et al. 2005). In order to prevent cardioembolic strokes in hyperthyroid patients, electrocardiogram (ECG) should be taken at least at diagnosing hyperthyroidism, and four months after restoring euthyroidism, since AF persisting beyond four months after effective treatment of hyperthyroidism is highly unlikely to revert to sinus rhythm spontaneously (Nakazawa et al. 1982, Shimizu et al. 2002). If a patient reports palpitation, ECG should be repeated also later on during the follow-up. If AF is observed, an anticoagulant therapy should be initiated according to the general guidelines on the treatment of AF. After restoring euthyroidism, an international normalized ratio (INR) should be maintained at 2.0-3.0 with warfarin for at least three weeks before and four weeks after successful cardioversion (Singer et al. 2004). Until reverting to sinus rhythm, the control of heart rate can be achieved with β-blockers (Shimizu et al. 2002).

In the present study, the increased cerebrovascular morbidity in hyperthyroid patients was not fully explained by the increased prevalence of AF. Thus, AF leading to cardioembolic stroke is probably not the only underlying pathological mechanism.
of acute cerebral ischemia in hyperthyroidism. Acute hyperthyroidism represents a hypercoagulable state characterized by an increased hematocrit, enhanced thrombin and plasmin activity, and dehydration (Hofbauer and Heufelder 1997, Erem et al. 2002), but it is not known whether any of these changes persist after restoration of euthyroidism. In any event, blood pressure, serum cholesterol, and glucose should be checked and properly treated in all hyperthyroid patients after restoring euthyroidism, since the treatment of hypertension, hypercholesterolemia, and diabetes effectively decrease the risk of stroke (Hankey 2005). Furthermore, all patients should be encouraged to quit smoking, as smoking increases the risk of both cardiovascular disease and cancer (UNSCEAR 2000, Hankey 2005). Furthermore, smoking has immunomodulatory effects with an adverse impact on the course of Graves’ disease (Quadbeck et al. 2006).

In conclusion, considering the present and previous reports of increased cardiovascular morbidity and mortality in hyperthyroid patients treated with RAI, hyperthyroidism can no longer be considered a reversible disorder without long-term consequences. The present study adds to the current knowledge that hyperthyroidism increases especially morbidity due to cerebrovascular diseases and AF, and the excess risk is sustained decades after treatment. Patients treated for hyperthyroidism are likely to benefit from preventive interventions aimed at reducing cardiovascular risks, as recently concluded on the basis of the present study (Vanderpump 2007). However, further controlled trials to specify the long-term cardiovascular risk related to hyperthyroidism and its treatments and the mechanisms behind these risks are needed.

2.3. Cancer incidence and mortality

The present study reports a significantly elevated incidence of cancer, especially stomach, breast and renal cancer, in hyperthyroid patients treated with RAI compared with the control population. Furthermore, mortality due to gastroesophageal cancer and overall cancer mortality were higher in the patients than in the controls. Diet and smoking are potential confounding factors affecting cancer risk that could not be controlled in the present study. Furthermore, no information was available on reproductive factors, which are the main determinants of breast cancer risk. We did not have any data on hereditary predisposition to cancer of the subjects in the present study. Yet, confounding could account for our results only if there were a strong
correlation between RAI-treated hyperthyroidism and hereditary factors contributing to cancer risk. For example, the proportion of breast cancer attributable to hereditary factors in the Finnish population has been estimated to be 5-10% (Holli 1995, Syrjäkoski et al. 2000). Therefore, confounding could account for our results only if there were a ten-fold prevalence of inherited factors among the patients relative to the control group.

Ionizing radiation probably caused the small but significant increase in cancer risk in hyperthyroid patients treated with RAI in the present study. Three facts justify this statement. Firstly, cancer risk increased with the cumulative dose of RAI. Secondly, there was a latent period following the RAI treatment before the cancer incidence started to increase among the patients, suggesting that the difference between the RAI-treated hyperthyroid patients and the control group seen in the present study was caused by RAI treatment and was not due to baseline differences. The median latent period from RAI treatment to the cancer diagnosis was 12 years. Moreover, adjusting for prevalent cancer did not change the results. Thirdly, the increased cancer incidence was seen in organs known to concentrate iodine or to be sensitive to radiation-induced cancer, namely stomach, breasts, and kidneys. Moreover, an increased risk of stomach (Holm et al. 1991, Hall et al. 1992a), breast (Ron et al. 1998, Chen et al. 2001, Rubino et al. 2003) and renal cancer (Hall et al. 1991, Rubino et al. 2003) has been previously reported in patients treated with high-dose RAI for thyroid carcinoma or low-dose RAI for hyperthyroidism.

Consistently with the present study no increase in the risk of thyroid malignancies has been observed in patients treated with RAI for hyperthyroidism in most of the published long-term follow-up studies (Goldman et al. 1988, Holm et al. 1991, Angusti et al. 2000). Given that the mean latency time for the development of thyroid malignancy in radiation-exposed patients has been 10-20 years with the minimum time to appearance being between 5-9 years (Rivkees et al. 1998), the statistical power of the present study or the previous ones (Hoffman et al. 1982b, Ron et al. 1998, Franklyn et al. 1999) was insufficient for detecting an increased risk of thyroid malignancies at least in children and young adults.

Earlier reports of the long-term cancer risk in patients treated with RAI for hyperthyroidism have been conflicting (Hoffman et al. 1982b, Holm et al. 1991, Hall et al. 1992a, Franklyn et al. 1999). A summary of the previous studies on cancer incidence and mortality in hyperthyroid patients treated with RAI are presented in
The conflicting results of the present study and the previous ones concerning cancer risk after RAI treatment for hyperthyroidism in different populations may reflect differences in the sensitivity to radiation-induced cancer depending on e.g., the age at exposure, diet, and baseline cancer rates. The excess risk for solid tumors can be observed most readily when the treated patients reach the age when underlying cancer incidence rates are high. The older median age at treatment in the present study (62 years) compared with the previous ones (57 years) (Hoffman et al. 1982b, Holm et al. 1991, Franklyn et al. 1999) and the long follow-up time in the present study may have contributed to recognizing the increased cancer risk in RAI-treated patients. In the American study, the patients with a malignancy before RAI treatment were excluded (Hoffman et al. 1982b). This may have removed from the population the persons at risk who would also have developed cancer after RAI treatment. In the present study, the results were adjusted for prevalent cancer in contrast to any of the previous studies (Hoffman et al. 1982b, Holm et al. 1991, Franklyn et al. 1999).

Compared to the effective dose received from a computerized tomography of the thorax (5.1mSv), the dose received from a 10mCi dose of RAI is 1700 times higher. The treatment of hyperthyroidism with RAI should therefore be taken into account in radiation protection and calculation of the life-long cumulative dose of radiation. In recent years, the use of RAI treatment for hyperthyroidism has been increasingly recommended also for younger patients (Hennemann et al. 1986, Wartofsky 1996, Välimäki 1998, Rivkees and Dinauer 2007). However, children and young adults up to 35 years old are more sensitive to cancer risk caused by ionizing radiation (Hall 2002). For this reason, surgery is a safer treatment option for children (Lee et al. 2007) and probably also for young adults (< 35 years) with recurrent hyperthyroidism after antithyroid treatment.

An increased risk of cancer does not necessarily mean that screening of the cancer would be worthwhile. Screening for cancer is recommended if it is cost-effective and decreases mortality or improves the quality of life (Hakama 2007). National screening programs for breast cancer (50-69 year old women), colorectal cancer (60-70 year old men and women), and uterine cervical cancer (25-60 year old women) are available in Finland (Hakama 2007). Screening for stomach cancer has not been considered warranted in Finland, because of the decreasing incidence of this
Table 4. Summary of the long-term follow-up studies concerning prognosis after RAI treatment for hyperthyroidism

<table>
<thead>
<tr>
<th>Study</th>
<th>Overall Mortality, SMR</th>
<th>Circulatory diseases, SMR</th>
<th>Cancer, SMR</th>
<th>Circulatory diseases, SIR</th>
<th>Cancer, SIR</th>
<th>N</th>
<th>Follow-up, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoffman et. 1982a*</td>
<td>1.0 (0.9-1.2)</td>
<td>0.9 (0.7-1.1)</td>
<td>0.8 (0.5-1.0)</td>
<td></td>
<td></td>
<td>1,005</td>
<td>15</td>
</tr>
<tr>
<td>Hoffman et al. 1982b*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1,005</td>
<td>15</td>
</tr>
<tr>
<td>Goldman et al. 1988†</td>
<td>1.3 (1.2-1.9)</td>
<td>1.4 (1.3-1.6)</td>
<td>0.9 (0.7-1.1)</td>
<td>0.9 (0.8-1.1)</td>
<td></td>
<td>1,762</td>
<td>17</td>
</tr>
<tr>
<td>Goldman et al. 1990a</td>
<td>1.4 (1.2-1.6)</td>
<td>1.5 (1.3-1.7)</td>
<td>1.1 (0.8-1.4)</td>
<td></td>
<td></td>
<td>873</td>
<td>15</td>
</tr>
<tr>
<td>Ron et al. 1998‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>35,593</td>
<td>21</td>
</tr>
<tr>
<td>Holm et al. 1991</td>
<td>1.09 (1.03-1.16)</td>
<td></td>
<td></td>
<td>1.06 (1.01-1.11)</td>
<td></td>
<td>10,552</td>
<td>15</td>
</tr>
<tr>
<td>Hall et al. 1991</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10,552</td>
<td>15</td>
</tr>
<tr>
<td>Hall et al. 1993</td>
<td>1.47 (1.43-1.51)</td>
<td>1.65 (1.59-1.71)</td>
<td>1.09 (1.03-1.16)</td>
<td></td>
<td></td>
<td>10,552</td>
<td>15</td>
</tr>
<tr>
<td>Franklyn et al. 1998</td>
<td>1.1 (1.1-1.2)</td>
<td>1.2 (1.2-1.3)</td>
<td></td>
<td></td>
<td></td>
<td>7,209</td>
<td>14</td>
</tr>
<tr>
<td>Franklyn et al. 1999</td>
<td></td>
<td></td>
<td>0.90 (0.82-0.98)</td>
<td>0.83 (0.77-0.90)</td>
<td></td>
<td>7,417</td>
<td>10</td>
</tr>
<tr>
<td>Franklyn et al. 2005</td>
<td>1.14 (1.04-1.24)</td>
<td>1.19 (1.05-1.35)</td>
<td>0.99 (0.82-1.20)</td>
<td></td>
<td></td>
<td>2,668</td>
<td>5</td>
</tr>
<tr>
<td>Nyirenda et al. 2006</td>
<td></td>
<td></td>
<td>1.42 (1.20-1.67)</td>
<td></td>
<td></td>
<td>1780</td>
<td>N.A.</td>
</tr>
<tr>
<td>Flynn et al. 2006‡</td>
<td>1.00 (0.74-1.33)</td>
<td>0.89 (0.53-1.41)</td>
<td>0.92 (0.46-1.65)</td>
<td>1.15 (0.88-1.48)</td>
<td></td>
<td>3,888</td>
<td>5</td>
</tr>
<tr>
<td>The present study‡</td>
<td>1.12 (1.03-1.20)</td>
<td>1.19 (1.07-1.32)</td>
<td>1.29 (1.07-1.57)</td>
<td>1.12 (1.03-1.21)</td>
<td>1.23 (1.08-1.46)</td>
<td>2,793</td>
<td>9</td>
</tr>
</tbody>
</table>

SMR = standardized mortality ratio (95% confidence interval), SIR = standardized incidence ratio (95% confidence interval)

*Relative risk of women treated with RAI for hyperthyroidism compared with the surgically treated women

†80% of patients treated with RAI

‡65% of patients treated with RAI

§Percentage of RAI-treated patients not known

‡Rate ratio of patients treated with RAI compared with the age- and sex-matched controls
type of cancer. There is no reasonable tool for the screening of renal cancer (Hakama 2007). The patients with hyperthyroidism treated with RAI are likely to benefit from attending the national cancer screening programs, and should be encouraged to take part in them. However, additional mammography or gastroscopy screening cannot be recommended for patients treated with RAI for hyperthyroidism on the basis of the present study.

2.4. Other diseases

Our finding of an increased risk of hospitalization due to fractures in the RAI-treated postmenopausal women is consistent with previous studies, in which a past history of hyperthyroidism has been associated with an increased risk of fracture (Franklyn et al. 1998, Murphy and Williams 2004). An appropriate thyroid hormone replacement therapy has not been associated in an increased risk of fracture in postmenopausal women (Murphy and Williams 2004). In addition to an impaired bone quality, the risk of falling is an important determinant of fracture risk (Brown and Josse 2002). In the present study, the more frequent cardiovascular diseases may have increased the risk of falling of the hyperthyroid patients.

The increased risk of hospitalization due to infectious diseases seen in this study probably reflects susceptibility to infections due to the more frequent cardiovascular diseases and malignancies among RAI-treated hyperthyroid patients. The increased mortality from respiratory infections in hyperthyroid patients has been presumed to result from the immunosuppressive effect of antithyroid medication (Hall et al. 1993). Antithyroid drugs may cause agranulocytosis in 0.2-0.5% of patients. However, there is no evidence of other immunosuppressive effects of antithyroid drugs, although they are suggested to suppress the autoimmune responses related to Graves’ disease by decreasing serum concentrations of TSab, interleukin 2 and 6 receptors and intracellular adhesion molecule 1, and the number of helper T-cells and natural killer cells (Cooper 2005). Furthermore, the medication given before the RAI treatment hardly explains the increased risk of infectious diseases sustained up to 20 years after the treatment in the present study.

The impact of infectious diseases on mortality has been difficult to interpret in previous studies (Hall et al. 1993). In analyses based on the ICD, infectious diseases
have been suspected to explain the increased mortality due to respiratory diseases (Hall et al. 1993). When the ICD is used, only systemic infections, contagious or epidemic diseases are classified as infectious diseases. In the present study, the hospitalizations and deaths due to all infections of the central nervous, respiratory, genito-urinary, and gastrointestinal systems were classified as infectious diseases. Mortality from infectious diseases was not increased in the hyperthyroid patients treated with RAI compared with the controls. Moreover, infectious diseases did not explain the increased mortality from respiratory diseases in the present study.

Hyperthyroidism may increase the risk of death from pulmonary diseases by increasing the consumption of oxygen (Klein and Ojamaa 2001). In most studies, including the present one, data on smoking habits was not available. In the only study involving smoking habits, overall mortality of RAI-treated patients was elevated in both smokers and non-smokers, compared with the general population (Goldman et al. 1988).

2.5. Variables affecting prognosis after RAI treatment for hyperthyroidism

The main novelty value of this study was the evaluation of the effects of various clinical factors and follow-up data on the prognosis after RAI treatment for hyperthyroidism. In multivariate analyses, RAI-treated hyperthyroidism and age increased the risk of cardiovascular morbidity, cancer, and death, while the development of hypothyroidism decreased these risks. In addition, a nodular thyroid disease increased the risk of hospital admission due to cardiovascular disease. Previously, increased cardiovascular morbidity has been reported in patients with Graves’ disease and those with a nodular thyroid disease (Nyirenda et al. 2005). Also patients with Graves’ disease would be expected to have an increased cardiovascular morbidity in this study, since Graves’ disease is associated with other autoimmune diseases increasing the risk of thrombosis, such as diabetes and antiphospholipid syndrome (Perros et al. 1995, Hofbauer and Heufelder 1997). The patients with a nodular thyroid disease were older and were treated in earlier decades, but were followed-up as long as those with Graves’ disease in the present study. The excess risk for cardiovascular diseases can be observed most readily when the treated patients reach the age when the incidence of cardiovascular events is high. Furthermore, patients with a nodular thyroid disease received a higher cumulative
dose of RAI. Because of the less sensitive methods of diagnosing hyperthyroidism, patients treated in earlier decades, who were mostly those with nodular thyroid disease, may have suffered from a more prolonged hyperthyroidism before an effective treatment.

Hypothyroidism has been suggested to contribute to the elevated risk of death by causing hypercholesterolemia, diastolic hypertension and left ventricular dysfunction (Cappola and Ladenson 2003). Most previous studies lack the follow-up data on the development of hypothyroidism (Hoffman et al. 1982a, Goldman et al. 1988, Hall et al. 1993). In the present study, levothyroxine-treated hypothyroidism after RAI treatment seemed to protect against cardiovascular morbidity and death instead of predisposing to them, consistently with a previous five-year follow-up study (Franklyn et al. 2005). This may reflect the effective cure of hyperthyroidism and encourages the use of RAI doses high enough, despite the risk of hypothyroidism. Furthermore, the patients developing hypothyroidism after RAI may be more properly examined and treated for other diseases, as the permanent levothyroxine treatment requires regular medical follow-up. It is also possible that the younger and healthier patients live long enough after RAI to develop hypothyroidism, and the development of hypothyroidism is an inevitable consequence of RAI treatment unless one dies before developing it.

3. Impact of the present study on current treatment strategies

The treatment options for patients with hyperthyroidism have not changed over half a century, and their aim is to inhibit, destroy, or remove the thyroid gland. Current research is directed towards genetic and molecular approaches to find the causes of Graves’ disease (Weetman 2000), and should ultimately produce targeted treatments that will cure Graves’ disease non-invasively, without toxicity or permanent damage to the thyroid gland, or a long-term cancer risk. Currently, RAI treatment, long-term antithyroid drug therapy and surgery are the only treatment options for hyperthyroidism.

It is not possible to definitely distinguish between the effects of RAI treatment and those of hyperthyroidism on the basis of the present study. No cancer incidence or mortality data were available on the patients treated with surgery in the present study. During the past decade, the average number of patients treated surgically for
hyperthyroidism has been approximately five per year, while RAI has been chosen for ca. 100 patients per year in our hospital district. Because of the small number of surgically treated patients in our hospital district, the power of the study would have been too low to detect a potential difference in cancer incidence and mortality between the surgically and RAI-treated patients. To compare the prognosis of surgically and RAI-treated patients, we would need surgically treated patients from several Finnish centres. However, perfect comparability of patients with different treatments cannot usually be achieved in non-randomized studies, because both patient and disease characteristics affect the choice of treatment and may induce confounding by indication. It is therefore not possible to distinguish between the effects of treatment and those of the disease, unless an untreated patient group is used as a reference. However, a study with an untreated hyperthyroid control group would be impossible to conduct for ethical reasons.

The increased cancer risk associated with RAI treatment needs to be balanced against the low remission rates after medical therapy (Allannic et al. 1990, Berglund et al. 1991, Benker et al. 1998, Abraham et al. 2005), adverse effects of surgery (Sosa et al. 1998, Palit et al. 2000, Bellantone et al. 2002), and the simplicity and cost-effectiveness of RAI therapy (Ljunggren et al. 1998, Patel et al. 2006). RAI is therefore the primary treatment option for most patients with hyperthyroidism, except for pregnant women and those with severe Graves’ ophthalmopathy. In addition, long-term antithyroid drug treatment and surgery might be a safer choice for children and young adults, since they are more sensitive to the effects of ionizing radiation (Hall 2002). Long-term treatment with carbimazole up to 10 years is a viable and safe alternative, if the thyroid function is controlled at least every 6 months (Azizi et al. 2005). Thyroidectomy in experienced hands guarantees a definitive treatment of hyperthyroidism with no risk of a relapse or an increased cancer incidence (Sridama et al. 1984, Berglund et al. 1991, Franklyn et al. 1991).

The present results do not imply any major need to change the present strategies in the treatment of hyperthyroidism. However, this study emphasizes the need to centralize the treatment of hyperthyroidism not only for selecting the best treatment individually, but also for organizing the life-long follow-up. The goals of the life-long follow-up of the patients treated with RAI for hyperthyroidism should be an early detection and treatment of hypothyroidism and cardiovascular diseases.
SUMMARY AND CONCLUSIONS

The present study adds to current knowledge a large cohort study of patients treated with RAI for hyperthyroidism with long-term follow-up. The results of this study are based on four registers of high quality. This study confirms the increased cardiovascular mortality and morbidity of hyperthyroid patients shown in previous studies. The increased risk of cardiovascular morbidity and mortality, especially cerebrovascular disease and atrial fibrillation, is sustained decades after the effective treatment of hyperthyroidism. Furthermore, the present study clarifies the conflicting data on cancer risk after RAI-treated hyperthyroidism. The RAI treatment of hyperthyroidism increases cancer incidence and mortality, but the risk is small. The development of hypothyroidism is a common side-effect of RAI treatment at least in patients with Graves’ disease. However, when treated with levothyroxine hypothyroidism decreases the morbidity and mortality, probably because it is a sign of good treatment response. The summary of the major findings results in comparison with the previous studies is represented in Table 4.

The patients treated with RAI for hyperthyroidism need a life-long monitoring of their thyroid function, and of the possible risk factors and signs of cardiovascular complications and cancer. Continuing the maintenance of the computerized register of the patients treated with RAI for hyperthyroidism at the Tampere University Hospital is suggested to facilitate the recognition of hypothyroidism. Furthermore, a standardized follow-up in the primary care is suggested for patients treated with RAI for hyperthyroidism, as represented in Figure 6. All patients should be followed in the endocrine clinic for 1-4 months after the RAI treatment to ensure an effective treatment of hyperthyroidism. When a patient is in a stable hypothyroid or euthyroid state, he/she will be discharged from the endocrinological clinic, provided that no complications, such as severe eye disease, are present. The follow-up should be continued every 3 months for the first year after treatment, and every 12 months thereafter. At discharge, each patient should receive a standardized letter stating that he/she has received RAI treatment for hyperthyroidism and therefore needs lifelong annual monitoring including evaluation of the thyroid function and the risk factors for cardiovascular diseases. Patients are encouraged to attend the national cancer screening programs. Furthermore, a copy of the medical record is sent to the physician responsible for the further follow-up, with the permission of the patient.
Hyperthyroidism is a well-known risk factor for AF. However, the observation and treatment of AF is not commonly recommended in current clinical guidelines for the treatment of hyperthyroidism. In order to prevent cardioembolic strokes in hyperthyroid patients, anamnesis on cardiac arrhythmias and an ECG should be taken at least when diagnosing hyperthyroidism, and 2-4 months after restoring euthyroidism. If AF is observed, an anticoagulant therapy should be initiated, and cardioversion performed after an effective anticoagulant treatment of at least 3 weeks. The control of heart rate can be achieved by β-blockers and digitalis. In addition, the traditional risk factors of cardiovascular diseases should be effectively screened for and treated.
Figure 6. Suggested standardized follow-up program during the first year after RAI treatment for hyperthyroidism
ACKNOWLEDGEMENTS

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Tampere, September 2007
Saara Metso
REFERENCES


Long-term follow-up study of radioiodine treatment of hyperthyroidism

Saara Metso*, Pia Jaatinen*, Heini Huhtala†‡, Tiina Luukkaala†‡, Heikki Oksala* and Jorma Salmi*
*Department of Internal Medicine and ‡Research Unit, Tampere University Hospital, and †Tampere School of Public Health, University of Tampere, Tampere, Finland

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Summary

OBJECTIVE To determine the cumulative incidence of hypothyroidism during long-term follow-up in patients treated for hyperthyroidism by radioactive iodine I\(^{131}\) (RAI) therapy, the significance of clinical factors in predicting the development of hypothyroidism, and the outcome after a fixed 7 mCi (259 MBq) dose of RAI.

DESIGN Prospective cohort study of patients treated for hyperthyroidism by RAI.

PATIENTS AND MEASUREMENTS Since 1965, details on 2043 patients treated by RAI therapy in Tampere University Hospital were entered into a computerized register. Following RAI treatment, thyroid status was monitored every 1–3 months during the first year, and subsequently at 1–3-year intervals until June 2002 or until the patient died or moved out of the Tampere University Hospital district.

RESULTS The cumulative incidence of hypothyroidism in patients with Graves’ disease and toxic multinodular goitre at 1, 10 and 25 years was 24% vs. 4%, 59% vs. 15% and 82% vs. 32%, respectively. In a Cox regression model, previous partial thyroidectomy [risk ratio (RR) = 1.63 in patients with Graves’ disease and RR = 1.59 in those with toxic multinodular goitre] and age at the first RAI treatment (RR = 0.998 and RR = 0.996 per year) were statistically significantly associated with the development of hypothyroidism both in patients with Graves’ disease and in those with toxic multinodular goitre. Antithyroid medication preceding RAI therapy (RR = 0.47) decreased and female gender (RR = 1.53) increased the risk of hypothyroidism only in patients with Graves’ disease. Administration of a single dose of RAI resulted in the control of hyperthyroidism in 75% of patients, while two to six RAI treatments were needed in 25% of patients to achieve either a hypothyroid or a euthyroid state in both groups. None of the clinical factors studied was associated with the remission rate either in patients with Graves’ disease or in those with toxic multinodular goitre. The remission rate did not differ between the patients who received a dose of RAI calculated according to the uptake of RAI and thyroid size and those who received an empirical dose of RAI. The fixed 7 mCi (259 MBq) dose of RAI cured 80% of patients.

CONCLUSION RAI treatment is effective in treating hyperthyroidism in patients with Graves’ disease, but hypothyroidism will develop in 82% of patients in 25 years. Because the development of hypothyroidism seems to be inevitable and unpredictable by any clinical factors, the objective of RAI treatment should be to minimize the persistence of hyperthyroidism with the simplest possible form of treatment. We recommend a fixed 7 mCi dose of RAI to be used as the first empirical dose in the treatment of hyperthyroidism, at least in Graves’ disease.

Hyperthyroidism affects approximately 2% of women and 0.2% of men (Tunbridge et al., 1977). Radioactive iodine I\(^{131}\) (RAI) has been used to treat the condition for more than six decades (Chapman, 1983), and has proved clinically efficient, safe and cost-effective in comparison with other therapeutic alternatives, that is long-term antithyroid medication and surgery (Wartofsky, 1997). RAI has been used as a first-line therapy for hyperthyroidism, especially in the elderly (Gittoes & Franklyn, 1998), but the use of RAI is also increasing among younger patients, that is 18 years old or older (Wartofsky, 1996; Gittoes et al., 1998). However, RAI is contraindicated in children, in pregnancy and in breastfeeding mothers (Wartofsky, 1996; Gittoes et al., 1998). Administration of RAI to patients with active Graves’ ophthalmopathy may cause an exacerbation of the eye symptoms, which might be prevented by the administration of glucocorticoids (Bartalena et al., 2000).

In previous studies, 6–15% of patients given low doses (<185 MBq) of RAI (Sridama et al., 1984; Turner et al., 1985; Goolden & Stewart, 1986; Watson et al., 1988) and 50–60% of those receiving high doses (>350 MBq) became hypothyroid.

Correspondence: Saara Metso, Department of Internal Medicine, Tampere University Hospital, PO Box 2000, FIN-33521 Tampere, Finland. Tel.: + 358 3311 611; Fax: + 358 3311 64362; E-mail: saara.metso@pshp.fi

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during the first post-treatment year (Kendall-Taylor et al., 1984; Ahmad et al., 2002). In the longest follow-up studies, the cumulative incidence of hypothyroidism 20–25 years after the first RAI therapy has been 42–72% (Holm et al., 1982; Franklyn et al., 1991). Over the past few decades, much attention has been focused on achieving euthyroidism and avoiding hypothyroidism by adjusting the RAI dose. However, while it is possible to deliver a relatively precise dose of radiation to the thyroid gland, the biological response of the gland remains unpredictable (Catargi et al., 1999). Despite the numerous associations found between hypothyroidism or cure rate and different pretreatment variables, no single variable or combination of variables has been shown to predict the outcome after RAI therapy with sufficient confidence to justify the use of a mathematical formula in determining the dose individually (Turner et al., 1985; Jarlov et al., 1995; Catargi et al., 1999; Leslie et al., 2003). Thus, hypothyroidism has become an expected outcome of RAI treatment. Many clinics prefer a fixed dose regimen in RAI treatment (Nordyke & Gilbert, 1991; Gittoes et al., 1998; Allahabadia et al., 2001; Kalinyak & McDougall, 2003). As concluded recently, no consensus exists regarding the ideal first dose of RAI in the treatment of hyperthyroidism (Kalinyak & McDougall, 2003).

The aims of our study were to provide data on the cumulative incidence of hypothyroidism during long-term follow-up after RAI treatment for hyperthyroidism, to determine the significance of different clinical factors in predicting development of hypothyroidism, and to evaluate the outcome after a 7 mCi (259 MBq) dose of RAI, which has been administered as a fixed dose to most hyperthyroid patients in our hospital since 1990.

Patients and methods

Patients

The data were collected between January 1965 and June 2002. The details of all patients treated for hyperthyroidism with RAI in Tampere University Hospital were entered into a computerized register. The follow-up period commenced at the time of the first RAI treatment and continued until June 2002 or until the patient died or moved out of the Tampere University Hospital district. Patients who did not participate in the follow-up in Tampere University Hospital after RAI treatment for at least 12 months were excluded due to missing follow-up data. The flow chart of the study is shown in Fig. 1. The ethics committee of the Pirkanmaa Hospital District approved the systematic gathering and presentation of the data. The study was undertaken in accordance with the Declaration of Helsinki.

Methods

Hyperthyroidism was diagnosed when classical symptoms and signs of hyperthyroidism coexisted with biochemical evidence,
that is high total T4 or free T4 associated with decreased levels of TSH (Gittoes et al., 1998). The aetiology of hyperthyroidism was determined by clinical examination. The diagnosis of Graves’ disease was made if a diffuse goitre was present. The diagnosis of toxic nodular goitre was made if examination of the neck revealed nodularity within an enlarged thyroid. Toxic thyroid adenoma was diagnosed if a solitary nodule within an otherwise normal thyroid gland was present. If the cause of hyperthyroidism was not apparent by clinical examination, thyroid antibodies were measured. Furthermore, the aetiology was verified by thyroid scintigraphy in 72% of cases. The aetiology of hyperthyroidism was classified according to the Finnish version of the ICD (International Classification of Diseases) codes into three classes: Graves’ disease, toxic multinodular goitre and toxic adenoma.

According to a common policy in Tampere University Hospital, most patients were given antithyroid drug therapy in order to achieve euthyroidism before treatment with RAI. The drug of choice was carbimazole unless the patient was allergic to it. The RAI treatment was given for most patients unless they were pregnant or breastfeeding or had severe eye symptoms of Graves’ disease. Young patients as well as patients with eye symptoms of Graves’ disease usually received long-term antithyroid drug therapy, and RAI was chosen only for those who suffered a relapse of Graves’ disease after long-term antithyroid treatment. Surgical treatment was chosen if a patient had a very large multinodular or diffuse goitre causing symptoms of compression in the neck, or if there was a suspicion of a malignancy in the thyroid gland. Patients were informed to discontinue antithyroid drug treatment 4 days before RAI treatment and continue it again 4 days after RAI treatment. Subsequently, they gradually reduced the dose of antithyroid medication according to instructions until they discontinued it 4 weeks after RAI treatment.

Following the RAI treatment, the thyroid status of the patients was monitored by blood samples every 1–3 months during the first year, and subsequently at 1–3-year intervals. In addition, the patients completed a questionnaire on the symptoms of hypothyroidism, and reported their present medication for the thyroid illness (thyroxine or antithyroid drugs) and when the medication had been started. Patients were classified as hypothyroid when symptoms and biochemical evidence (i.e. low total T4 or free T4 associated with an elevation of TSH) suggested hypothyroidism and resulted in the initiation of thyroxine replacement therapy. Transient hypothyroidism after RAI therapy was not recorded. Patients were classified as having relapsed hyperthyroidism when symptoms and biochemical evidence (i.e. high total T4 or free T4 associated with decreased levels of TSH) necessitated repeated RAI therapy or continuous antithyroid medication lasting more than 1 year after the RAI therapy. The remission rate was determined as the proportion of patients who became euthyroid and hypothyroid after a single RAI treatment.

Statistical analysis

We used statistical software Stata 7.0 to calculate the incidence of hypothyroidism according to person-years after the first RAI treatment for hyperthyroidism. Other statistical analyses were performed using SPSS for Windows, version 11.0. A P-value less than 0.05 was considered statistically significant. The cumulative incidence of hypothyroidism was determined by Kaplan–Meier life-table analysis. Normality of the distribution of the variables studied was tested by Kolmogorov–Smirnov test. The distribution of all continuous variables was skewed. The values of continuous variables are expressed as median (minimum, maximum). Categorical variables are expressed as frequencies. Association between two continuous variables was estimated with Spearman’s correlation coefficient. According to the number of categorical variables, the Mann–Whitney test or Kruskal–Wallis test was used to assess the relationship between continuous and categorical variables. The χ²-test was used to determine whether an association seen between two categorical variables was statistically significant. Cox regression analysis was performed to evaluate the significance of different clinical factors in predicting hypothyroidism. An event was the development of hypothyroidism and the covariates were gender, the aetiology of hyperthyroidism (Graves’ disease, toxic multinodular goitre or toxic adenoma), previous partial thyroidectomy (yes or no), preceding antithyroid treatment (yes or no), duration of antithyroid treatment (< 3 months, 3–6 months or > 6 months), remission of hyperthyroidism after the first dose of RAI (yes or no), age at the first RAI treatment (years), 24-h uptake in thyroid scintigraphy (%), and the first dose of RAI (MBq). Patients who did not develop hypothyroidism were censored in June 2002 or when they died or moved out of the Tampere University Hospital district.

Results

During the past 37 years (January 1965 to June 2002) a total of 2795 patients suffering from hyperthyroidism were treated with RAI in Tampere University Hospital and included in the computerized register. Twenty-seven per cent of these patients did not participate in the follow-up for 1 year and were excluded. Figure 1 shows the number and follow-up times of the remaining 2043 patients according to different end-point groups. During the follow-up, hypothyroidism was diagnosed and treated in 38% of the patients. The median time to the development of hypothyroidism was 2 years (minimum 1 month, maximum 25.4 years).

The clinical characteristics of the patients according to different aetiological groups are presented in Table 1. In the whole population, the most common cause of hyperthyroidism was Graves’ disease (53%). However, the distribution of the aetiology varied according to the decade studied. In the 1960s, toxic multinodular goitre was the most common cause of hyperthyroidism.
(70%), while the proportion of diffuse goitre increased to be the major cause of hyperthyroidism in the 1990s (73%, aetiological group vs. decade studied, \( P < 0.001 \)). The patients with Graves’ disease were slightly younger than the patients with toxic multinodular goitre or adenoma (Table 1). In the whole population, the proportion of patients who were treated before or at the age of 40 increased during the decades studied: 3% of the patients were less than 40 years old at the 1960s, 5% at the 1970s, 14% at the 1980s and 19% at the 1990s. Only 11 patients were less than 20 years old, and all of them had Graves’ disease.

**The incidence of hypothyroidism**

Summarized follow-up times of all patients studied resulted in 15 251 person-years at risk of hypothyroidism after RAI treatment. The incidence of hypothyroidism was 50/1000 person-years at risk in all patients. In patients with Graves’ disease the incidence of hypothyroidism was 103/1000 person-years at risk, in patients with toxic multinodular goitre 18/1000 and in patients with toxic adenoma 17/1000. In Fig. 2 the cumulative incidence of hypothyroidism and the number of patients at risk at 5-year intervals are shown in different aetiological groups. The cumulative incidence of hypothyroidism in patients with Graves’ disease and those with toxic multinodular goitre or toxic adenoma were 24% vs. 4%, 59% vs. 15% and 82% vs. 32% at 1, 10 and 25 years, respectively.

---

Table 1 Clinical characteristics of the patients according to different aetiological groups

<table>
<thead>
<tr>
<th></th>
<th>Graves’ disease (53%, ( n = 1086 ))</th>
<th>Toxic multinodular goitre (37%, ( n = 749 ))</th>
<th>Toxic adenoma (10%, ( n = 208 ))</th>
<th>All (( n = 2043 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18 (199)</td>
<td>13 (94)</td>
<td>16 (33)</td>
<td>16 (326)</td>
</tr>
<tr>
<td>Female</td>
<td>82 (887)</td>
<td>87 (655)</td>
<td>84 (175)</td>
<td>84 (1717)</td>
</tr>
<tr>
<td>Antithyroid drug*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>88 (958)</td>
<td>82 (616)</td>
<td>75 (156)</td>
<td>85 (1730)</td>
</tr>
<tr>
<td>No</td>
<td>8 (91)</td>
<td>15 (111)</td>
<td>22 (45)</td>
<td>12 (247)</td>
</tr>
<tr>
<td>Duration of antithyroid treatment*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3 months</td>
<td>34 (373)</td>
<td>31 (230)</td>
<td>36 (75)</td>
<td>33 (678)</td>
</tr>
<tr>
<td>3–6 months</td>
<td>34 (365)</td>
<td>23 (170)</td>
<td>19 (39)</td>
<td>28 (574)</td>
</tr>
<tr>
<td>&gt; 6 months</td>
<td>26 (286)</td>
<td>33 (249)</td>
<td>27 (57)</td>
<td>29 (592)</td>
</tr>
<tr>
<td>Post-operative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12 (127)</td>
<td>12 (90)</td>
<td>13 (26)</td>
<td>12 (243)</td>
</tr>
<tr>
<td>No</td>
<td>78 (849)</td>
<td>81 (603)</td>
<td>83 (173)</td>
<td>80 (1625)</td>
</tr>
<tr>
<td>Remission after first dose of RAI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>76 (827)</td>
<td>74 (555)</td>
<td>77 (161)</td>
<td>75 (1543)</td>
</tr>
<tr>
<td>No</td>
<td>24 (259)</td>
<td>26 (194)</td>
<td>23 (47)</td>
<td>25 (500)</td>
</tr>
<tr>
<td>First dose of RAI (MBq)*</td>
<td>222 (55, 555)</td>
<td>259 (56, 740)</td>
<td>222 (55, 555)</td>
<td>222 (55, 740)</td>
</tr>
<tr>
<td>Total dose of RAI (MBq)*</td>
<td>259 (55, 2664)</td>
<td>259 (56, 2368)</td>
<td>259 (55, 1443)</td>
<td>259 (55, 2664)</td>
</tr>
<tr>
<td>Age at first RAI (years)*</td>
<td>56 (13, 90)</td>
<td>67 (25, 93)</td>
<td>65 (36, 84)</td>
<td>62 (13, 93)</td>
</tr>
<tr>
<td>24-h uptake in thyroid scintigraphy (%)*</td>
<td>68 (8, 99)</td>
<td>57 (12, 99)</td>
<td>49 (13, 87)</td>
<td>61 (8, 99)</td>
</tr>
</tbody>
</table>

Values are % (\( n \)) or median (min, max). \(^{*}\)Statistically significant difference between the aetiological groups. The \( \chi^2 \)-test was used for two categorical variables, and the Kruskal–Wallis test for continuous and categorical variables.
In order to evaluate the significance of different clinical factors in predicting the development of hypothyroidism, Cox regression analysis was undertaken with hypothyroidism as an event and the clinical characteristics presented in Table 1 as covariates. The risk ratios are shown in Table 2 separately in patients with Graves’ disease and those with toxic multinodular goitre or adenoma. Previous partial thyroidectomy and age at the first RAI treatment were statistically significantly associated with the development of hypothyroidism both in patients with Graves’ disease and in those with toxic multinodular goitre. Antithyroid medication preceding RAI therapy decreased and female gender increased the risk of hypothyroidism only in patients with Graves’ disease. The first dose of RAI did not affect the risk of hypothyroidism in patients with Graves’ disease. Surprisingly, in patients with multinodular goitre or adenoma, hypothyroidism developed more easily in the patients receiving lower doses of RAI than in those receiving higher doses of RAI; that is the risk ratio was 0.996 per MBq.

There was an inverse correlation between age at the first RAI treatment and the uptake of RAI in thyroid scintigraphy (Spearman’s correlation coefficient was −0.21 (P < 0.001) and −0.12 (P < 0.001) in patients with Graves’ disease and in those with toxic multinodular goitre or adenoma, respectively). In patients with Graves’ disease the uptake of RAI did not differ between patients who received antithyroid drugs and those who did not (P = 0.168). In patients with toxic multinodular goitre or adenoma the median uptake of RAI was slightly higher in patients who received antithyroid drugs than in those who did not (P < 0.001, 57% vs. 47%, respectively).

If the cumulative dose of RAI was included in the Cox regression analysis instead of the first dose of RAI, the cumulative dose had no influence on the risk of hypothyroidism in patients with Graves’ disease [risk ratio (RR) 0.999 per 1 MBq, 95% confidence interval (CI) 0.998–1.000, P = 0.092]. However, in patients with toxic multinodular goitre or adenoma there was an inverse correlation between the cumulative dose and the development of hypothyroidism; that is, the higher the dose needed to cure hyperthyroidism the lower the risk of hypothyroidism (RR 0.998 per 1 MBq, 95% CI 0.996–0.999, P = 0.006).

**Remission rate after RAI treatment**

To achieve either a hypothyroid or a euthyroid state, two RAI treatments were needed in 373 (18%) patients, three in 69 (3%) cases, four in 26 (1%), five in seven (0.3%) and six in four (0.2%) cases. One per cent (n = 21) of patients received antithyroid treatment for more than 1 year after the first RAI treatment to maintain a euthyroid state. The second RAI dose was given for persistent hyperthyroidism after a median of 10 months (minimum

### Table 2 Clinical factors influencing the development of hypothyroidism after RAI treatment

<table>
<thead>
<tr>
<th>Factors</th>
<th>Graves’ disease (n = 1086)</th>
<th>Toxic multinodular goitre or adenoma (n = 957)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.53</td>
<td>1.13–2.08</td>
</tr>
<tr>
<td>Antithyroid drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.47</td>
<td>0.33–0.68</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 6 months</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>3–6 months</td>
<td>0.92</td>
<td>0.70–1.22</td>
</tr>
<tr>
<td>&lt; 3 months</td>
<td>0.99</td>
<td>0.77–1.28</td>
</tr>
<tr>
<td>Post-operative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.63</td>
<td>1.24–2.14</td>
</tr>
<tr>
<td>Remission with first RAI dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.99</td>
<td>0.82–1.26</td>
</tr>
<tr>
<td>Age at first RAI therapy, RR per year</td>
<td>0.971</td>
<td>0.964–0.979</td>
</tr>
<tr>
<td>First dose of RAI, RR per MBq</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.998</td>
<td>0.998–1.001</td>
<td>0.467</td>
</tr>
<tr>
<td>24-h uptake (%) RR per %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.004</td>
<td>0.996–1.012</td>
<td>0.308</td>
</tr>
</tbody>
</table>

4 months, maximum 33 years). The number of RAI treatments needed to achieve remission did not differ between the aetiological groups ($P = 0.819$).

Administration of a single dose of RAI resulted in the control of hyperthyroidism in 76% of the patients with Graves’ disease, 74% of the patients with toxic multinodular goitre and 77% of the patients with toxic adenoma ($P = 0.484$) (Table 1). In patients with Graves’ disease ($n = 1086$), the distribution of gender ($P = 0.581$), antithyroid medication preceding RAI therapy ($P = 0.158$), duration of antithyroid medication ($P = 0.236$) and surgical treatment ($P = 0.504$) did not differ between those patients who were cured with a single dose of RAI and those who needed more than one dose of RAI or prolonged antithyroid treatment to achieve remission. Neither did the first dose of RAI ($P = 0.360$) nor the age at the first RAI treatment ($P = 0.826$) differ between the cured patients and those with persistent hyperthyroidism. The 24-h uptake in thyroid scintigraphy was slightly lower in patients who achieved remission with a single dose of RAI than those who needed several doses or prolonged antithyroid therapy (median 67% vs. 72%, $P = 0.001$). The results were similar in patients with toxic multinodular goitre or adenoma.

**The effect of an empirical 7 mCi dose vs. other doses of RAI on outcome after RAI treatment**

Until the end of the 1980s, thyroid scintigraphy with measurement of RAI uptake and the weight of the thyroid gland estimated by palpation were used to calculate the dose of RAI in Tampere University Hospital. Thereafter, the dose has been chosen empirically. The remission rate did not differ between the patients who received a dose of RAI calculated according to the uptake of RAI and thyroid size ($n = 1477$) and those who received an empirical dose of RAI ($n = 566$) either in patients with Graves’ disease ($P = 0.128$) or in those with toxic multinodular goitre or adenoma ($P = 0.337$).

Since 1990, a fixed 7 mCi (259 MBq) dose of RAI has been recommended as the first dose for all hyperthyroid patients. A total of 364 patients received the recommended 7 mCi dose. However, other empirical doses were also used: 61 patients received 5 mCi (185 MBq), 29 patients received 10 mCi (370 MBq) and 112 patients received other empirical doses; median 6 mCi (222 MBq), minimum 1.5 mCi (55 MBq) and maximum 15 mCi (555 MBq). The clinical characteristics of the patients in the different dose groups are presented in Table 3. The remission rate did not differ statistically significantly between the dose groups (80% in patients who received 7 mCi, 77% in patients who received 5 mCi and 69% in patients who received 10 mCi).

The cumulative incidence of hypothyroidism 1 year and 25 years after RAI treatment was 23% vs. 15% vs. 13% and 59% vs. 57% vs. 46% in patients given 7 mCi, 5 mCi or 10 mCi as the first empirical dose of RAI, respectively. The patients given 5 mCi as the first empirical dose of RAI had lower risk and those given 10 mCi similar risk of hypothyroidism compared with those given the recommended 7 mCi dose, when adjusted for the other clinical characteristics by Cox regression analysis.

**Table 3** Clinical characteristics of patients given 7 mCi and those given other empirical doses

<table>
<thead>
<tr>
<th></th>
<th>7 mCi</th>
<th>5 mCi</th>
<th>10 mCi</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, % ($n$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16 (60)</td>
<td>12 (7)</td>
<td>21 (6)</td>
<td>0.482</td>
</tr>
<tr>
<td>Female</td>
<td>84 (304)</td>
<td>88 (54)</td>
<td>79 (23)</td>
<td></td>
</tr>
<tr>
<td>Aetiology of hyperthyroidism, % ($n$)</td>
<td>0.275</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graves’ disease</td>
<td>81 (296)</td>
<td>72 (44)</td>
<td>86 (25)</td>
<td></td>
</tr>
<tr>
<td>Toxic multinodular goitre</td>
<td>16 (58)</td>
<td>26 (16)</td>
<td>14 (4)</td>
<td></td>
</tr>
<tr>
<td>Toxic adenoma</td>
<td>3 (10)</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Antithyroid drug, % ($n$)</td>
<td>0.030</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>97 (338)</td>
<td>95 (57)</td>
<td>86 (25)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3 (12)</td>
<td>5 (3)</td>
<td>14 (4)</td>
<td></td>
</tr>
<tr>
<td>Duration of antithyroid treatment, % ($n$)</td>
<td>0.171</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3 months</td>
<td>47 (168)</td>
<td>37 (22)</td>
<td>50 (14)</td>
<td></td>
</tr>
<tr>
<td>3–6 months</td>
<td>36 (131)</td>
<td>36 (21)</td>
<td>43 (12)</td>
<td></td>
</tr>
<tr>
<td>&gt; 6 months</td>
<td>17 (60)</td>
<td>27 (16)</td>
<td>7 (2)</td>
<td></td>
</tr>
<tr>
<td>Post-operative, % ($n$)</td>
<td>0.525</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9 (28)</td>
<td>10 (6)</td>
<td>3 (1)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>91 (270)</td>
<td>90 (51)</td>
<td>97 (28)</td>
<td></td>
</tr>
<tr>
<td>Remission after first dose of RAI, % ($n$)</td>
<td>0.354</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>80 (291)</td>
<td>77 (47)</td>
<td>69 (20)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>20 (73)</td>
<td>23 (14)</td>
<td>31 (9)</td>
<td></td>
</tr>
<tr>
<td>Age at first RAI, years, median (min, max)</td>
<td>0.051</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>59 (13, 88)</td>
<td>65 (21, 83)</td>
<td>53 (27, 84)</td>
<td></td>
</tr>
</tbody>
</table>

The $\chi^2$-test was used for two categorical variables, and the Kruskal–Wallis test for continuous and categorical variables.

Discussion
The relationship of clinical factors to the outcome after RAI treatment

There are only a few previously published long-term follow-up studies regarding RAI treatment of hyperthyroidism. In the present study, most patients with Graves’ disease eventually developed hypothyroidism. Our results are consistent with an earlier long-term follow-up study (Holm et al., 1982). In the patients with toxic multinodular goitre, however, the cumulative incidence of hypothyroidism seemed to level off at 30% 15 years after RAI treatment. The differences in the development of hypothyroidism in long-term follow-up might result from the different nature of Graves’ disease and toxic multinodular goitre. The higher rate of hypothyroidism in patients with Graves’ disease than in patients with toxic multinodular goitre might result from the protection of the suppressed normal extranodular tissue by its inability to concentrate RAI in patients with toxic multinodular goitre (Holm et al., 1982; Ahmad et al., 2002). Furthermore, Graves’ disease is an autoimmune disease of the thyroid gland caused by antithyrotrophin receptor antibodies, which may subside in the course of time and in some cases may also cause hypothyroidism (Akamizu, 2001). In fact, approximately 15% of patients who receive only antithyroid medication for Graves’ disease develop hypothyroidism after discontinuation of the treatment, reflecting the autoimmune nature of Graves’ disease (Gittoes et al., 1998).

The present long-term follow-up study did not verify earlier reports of a dose–response relationship between the radioactive dose and the rate of hypothyroidism or a positive correlation between the cure rate and hypothyroidism (Doi et al., 2001). The associations between clinical factors and the risk of hypothyroidism found in our study were not strong enough to justify the use of individually adjusted doses of RAI for treatment of hyperthyroidism. The reliability of predicting the development of hypothyroidism after RAI treatment for hyperthyroidism has also been poor (50–60% by multivariate logistic regression models) in previous studies (Turner et al., 1985; Kung et al., 1990). Thus, the objective of RAI treatment should be to achieve and maintain long-term remission with the simplest possible form of treatment.

The effect of an empirical 7 mCi dose vs. other doses of RAI on outcome after RAI treatment

Administration of empirical doses of RAI has been preferred to calculated doses in many clinics, because the need to measure the size and the RAI uptake of the thyroid gland involves considerable inconvenience to the patient and additional costs. The preparation of doses of RAI of varying sizes also means extra work. In a few randomized clinical trials, a fixed dose and a calculated dose of RAI have been compared directly in the treatment of hyperthyroidism (Smith & Wilson, 1967; Jarlov et al., 1995; Peters et al., 1997; Leslie et al., 2003). The advantages of a variety of dose calculation methods have been few and of little clinical significance (Smith et al., 1967; Jarlov et al., 1995; Peters et al., 1995; Leslie et al., 2003). Our results were consistent with these earlier studies: the remission rate did not differ between the patients who received a calculated dose of RAI and those who received an empirical dose.

There has been no consensus concerning the ideal fixed dose to be used. In previous literature doses of RAI varying between 5 and 10 mCi (185–370 MBq) have been recommended as the standard fixed dose in RAI treatment for hyperthyroidism (Watson et al., 1988; Allahabadia et al., 2001). A fixed 7 mCi (259 MBq) dose has been used as a standard treatment for hyperthyroidism since 1990 in Tampere University Hospital. In earlier studies remission rates of 67–72% with a 5 mCi dose of RAI and 85% with a 10 mCi dose have been reported (Watson et al., 1988; Allahabadia et al., 2001). There are no previous data on the remission rate after a fixed 7 mCi dose of RAI. In our study the remission rate achieved with the fixed 7 mCi dose of RAI was 80%. There seem to be no clinically significant differences in the outcome after the fixed 7 mCi dose selected in our clinic and the 10 mCi dose preferred in several clinics. However, to confirm this a randomized study comparing different empirical doses would be needed.

We conclude that RAI treatment is effective in treating hyperthyroidism in patients with Graves’ disease, but hypothyroidism will develop in 82% of patients in 25 years. Because the development of hypothyroidism seems to be inevitable and unpredictable by any clinical factors, the objective of RAI treatment should be to minimize the persistence of hyperthyroidism with an easily manageable treatment scheme with minimal costs. We recommend a fixed 7 mCi dose of RAI to be used as the first empirical dose in the treatment of hyperthyroidism, at least in Graves’ disease.

Acknowledgements

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References


Increased long-term cardiovascular morbidity among patients treated with radioactive iodine for hyperthyroidism

Short title: Long-term morbidity in hyperthyroid patients

Saara Metso\textsuperscript{1,2}, Anssi Auvinen\textsuperscript{3,4}, Jorma Salmi\textsuperscript{1}, Heini Huhtala\textsuperscript{3,5} and Pia Jaatinen\textsuperscript{1,2}

\textsuperscript{1}Department of Internal Medicine, Tampere University Hospital, FIN-33521 Tampere, Finland
\textsuperscript{2}Medical School, University of Tampere, FIN-33014 Tampere, Finland
\textsuperscript{3}Tampere School of Public Health, University of Tampere, FIN-33014 Tampere, Finland
\textsuperscript{4}STUK-Radiation and Nuclear Safety Authority, Research and Environmental Surveillance, FIN-00881 Helsinki, Finland
\textsuperscript{5}Research Unit, Tampere University Hospital, FIN-33521 Tampere, Finland

Correspondence:
Saara Metso, MD
Department of Internal Medicine
Tampere University Hospital,
P.O. Box 2000, FIN-33521 Tampere, Finland
Fax: +358 3 311 64362 Phone: + 358 3 311 64406
E-mail: saara.metso@pshp.fi

Key words: radioactive iodine, hyperthyroidism, morbidity, cardiovascular disease
Summary

OBJECTIVE Previous studies suggest that hyperthyroid patients remain at increased risk of cardiovascular morbidity after restoring euthyroidism. The aim of this study was to compare the rate and causes of hospitalization of hyperthyroid patients treated with radioactive iodine (RAI) with those of an age- and gender-matched reference population in a long-term follow-up study.

PATIENTS AND MEASUREMENTS A population-based cohort study with a median follow-up time of 9 years was conducted among 2611 hyperthyroid patients treated with RAI between 1969 and 2002 in Tampere University Hospital, and among 2611 reference subjects. Information on hospitalizations was obtained from the nationwide Hospital Discharge Registry. New events were analyzed as the main outcome, including only the first hospitalization due to a given indication.

RESULTS Rate of hospitalization due to cardiovascular diseases was higher among patients with hyperthyroidism than among the control population (637.1 vs. 476.4 per 10,000 person-years, rate ratio, RR 1.12, 95% CI 1.03-1.21). The risk remained elevated up to 35 years after the RAI treatment. Hospitalizations due to atrial fibrillation (RR 1.35), cerebrovascular diseases (RR 1.31), diseases of other arteries and veins (RR 1.22), hypertension (RR 1.20), and heart failure (RR 1.48) were more frequent in the patients than controls, while no such difference was found for coronary artery disease. Hospitalizations due to cancer, infectious and gastrointestinal diseases, and fractures were also more common in the patients than in the controls.

CONCLUSIONS Hyperthyroidism increases hospitalizations due to cardiovascular diseases. The excess risk is sustained decades after treatment. Patients treated for hyperthyroidism constitute a high-risk group for cardiovascular diseases and may benefit from preventive interventions.
Introduction

Radioactive iodine (\(^{131}\text{I}, \text{RAI}\)) has been commonly used as a first-line therapy for hyperthyroidism since the 1940’s.\(^1\) Hyperthyroidism has been regarded as a reversible disorder without long-term consequences, when treated effectively. However, long-term follow-up studies have revealed an increased cardiovascular mortality in those with a past history of hyperthyroidism treated with RAI compared with the background population.\(^2\)–\(^6\) In our recent report,\(^6\) cerebrovascular diseases accounted for most of the increased cardiovascular mortality, consistently with a previous long-term follow-up study.\(^4\) Instead of RAI treatment, hyperthyroidism \textit{per se} probably accounts for the elevated cardiovascular mortality. Hyperthyroidism is known to exert direct effects on the myocardium and the autonomic nervous system, thus predisposing the patient to cardiovascular morbidity.\(^7\), \(^8\) Recently, Flynn et al.\(^9\) reported an increased risk of arrhythmia up to 5 years after treatment of hyperthyroidism, suggesting that the cardiotoxic effects of hyperthyroidism are not fully reversed by restoring euthyroidism. Furthermore, cardiovascular morbidity increased in RAI-treated hyperthyroid patients compared with controls in a previous long-term follow-up study.\(^10\)

Hypothyroidism has been suggested to increase the risk of death by causing hypercholesterolemia, diastolic hypertension and left ventricular dysfunction.\(^11\) However, levothyroxine-treated hypothyroidism after RAI treatment has seemed to protect against death instead of predisposing to it.\(^5\), \(^6\) This might reflect the impact of an effective cure of hyperthyroidism. An initial hypothyroid state induced by effective treatment has been reported to be a predictor of successful reversion to sinus rhythm in those with AF during hyperthyroidism.\(^12\)

To date, no long-term studies have been published on the incidence of different cardiovascular diseases (CVD) or hospitalizations after RAI treatment for hyperthyroidism. The purpose of the present study was to assess the rate and causes of hospitalization after RAI treatment for hyperthyroidism, especially focusing on CVD. We also compared hospitalization due to CVD between sub-groups of patients by the etiology of hyperthyroidism, age, dose of RAI, recurrent hyperthyroidism, and the development of hypothyroidism.
Subjects and Methods

A total of 2611 patients (430 men and 2181 women) were treated for hyperthyroidism with RAI between January 1969 and June 2002 at Tampere University Hospital. Tampere University Hospital provides tertiary medical care for a population of approximately 460,000 people, and due to the public health care system available for all residents it is practically the sole provider of RAI treatment for this population. The case series therefore represents all incident cases of RAI-treated hyperthyroidism in the base population. The proportion of patients treated with thyroidectomy and long-term antithyroid drug therapy for hyperthyroidism was less than 10% of all hyperthyroid patients in the Tampere University Hospital district.

A reference group was formed by choosing an age- and gender-matched control subject for each patient from the Population Register Centre. The control subject had to be alive at the time when the patient received the first RAI treatment, but there were no other inclusion or exclusion criteria.

The causes of hospitalization as well as the diagnosis and date of hospital admission were obtained from the nationwide Hospital Discharge Register (HILMO) maintained by the Research and Development Centre for Welfare and Health (STAKES) using a computerized record linkage, with the personal identification number as the key. The HILMO database covers all dates and causes of hospitalization (hospital admission requiring an overnight stay) of the Finnish citizens since January 1969. Several assessments consistently indicated high completeness and reliability of the Finnish Hospital Discharge Register. The diagnoses have been coded according to the 8th revision of the International Classification of Diseases (ICD) between 1969 and 1986, the Finnish version of ICD-9 between 1987 and 1995, and the Finnish version of ICD-10 thereafter. A conversion between the different versions was made, and the causes of hospitalization were classified into 13 groups: infectious diseases, malignant tumors, diabetes, hematological diseases, psychiatric diseases, diseases of the central nervous system, cardiovascular diseases, asthma and chronic obstructive pulmonary disease (COPD), gastrointestinal diseases, diseases of the urinary system, musculoskeletal diseases, fractures, and complications of pregnancy. Furthermore,
seven different cardiovascular disease classes were analyzed separately: hypertension, coronary artery disease, diseases of the pulmonary circulation, arrhythmias, heart failure, cerebrovascular diseases, diseases of other arteries and veins, and other cardiovascular diseases (non-bacterial endo-, peri- and myocardial diseases, cardiomyopathy, and conduction disorders of the heart). The classification of infectious diseases used in the present study differed from that of the ICD. In our study, hospital admissions due to all infections of cardiovascular, central nervous, respiratory, genito-urinary, gastrointestinal, and musculoskeletal systems were classified as infectious diseases. Both the primary and secondary diagnoses recorded at discharge from the hospital were used in the analysis.

The follow-up of each patient started at the end of the year of the first RAI treatment. The follow-up period of the control subject started at the same time as that of the corresponding patient. The disease-specific hospitalization rate was calculated with follow-up until the first hospitalization due to that disease, regardless of any other causes of hospital admission. If the subject was not hospitalized because of that disease, the follow-up ended on the date of death, emigration, or the common closing date (December 31, 2003), whichever occurred first. For the complications of pregnancy, the person-years at risk were counted only for women in fertile age. If a subject was treated at a hospital several times because of the same disease, only the first admission was included. If a disease caused hospitalization prior to the beginning of follow-up, the patient was classified as having a prevalent disease. The rate ratios (RR) for hospitalization were adjusted using a prevalent disease as a covariate.

Information on the etiology of hyperthyroidism, previous surgical and anti-thyroid treatment, the dates and doses of RAI treatments, and the follow-up of thyroid function of the patients were recorded in the computerized register kept in the Tampere University Hospital since 1965, as described earlier.17

The study was undertaken in accordance with the Declaration of Helsinki. Informed consent could not be collected from the patients, because of the large number of participants and high proportion of deceased. The ethics committee of the Pirkanmaa Hospital District approved the study protocol. In addition, the National Research and
Development Centre for Welfare and Health gave permission to use data from the Population Register Centre and the Hospital Discharge Registry.

Statistical analysis

We used the statistical software Stata for Windows version 8.2 (StataCorp, College Station, Texas, USA) to calculate the hospitalization rates for various diseases. Cox regression analyses were performed using SPSS for Windows Version 14.0 (SPSS Inc., Chicago, Illinois, USA). A two-sided p-value less than 0.05 was considered statistically significant. Hospitalizations due to CVD and CVD-subgroups in patients and controls were illustrated by Kaplan-Meier analysis and the difference in cumulative hospitalization rates was assessed with a log rank test. In addition to the analysis of the whole RAI-treated population and controls, hospitalization rate was also counted in the following subgroups of patients using only their matched controls: etiology of hyperthyroidism (Graves’ disease, multinodular goiter or toxic adenoma), total RAI activity administered (55-258MBq, 259-369MBq, 370-2664MBq), recurrence of hyperthyroidism after the first dose of RAI (yes, no), development of hypothyroidism during follow-up (yes, no), previous partial thyroidectomy (yes, no), usage of anti-thyroid medication before RAI (yes, no), and age at the beginning of follow-up (13-49, 50-59, 60-69, and 70-98 years).

Results

The median age of the patients at RAI-treatment and the reference group at the beginning of the follow-up was 62 years (interquartile range 49-72 years for both groups). The median follow-up time was 9.0 years for the patients and 9.1 years for the controls (interquartile range 4.3-16.0 years for patients and 5.0-16.4 years for controls).

The most frequent indication for hospitalization both in the patients and in the controls was CVD. The risk of first hospital admission (adjusted for prior hospitalizations) due to cardiovascular, infective and gastrointestinal diseases, malignant tumors, and fractures was significantly higher in the patients than in the control group (Table 1). The risk of hospitalization due to CVD remained higher in
the patients than in the controls up to 35 years after the RAI treatment (Figure 1). The absolute increase in the risk (rate difference) of hospitalization due to CVD was 84 hospital admissions per 1000 patients by 10 years of follow-up.

Hyperthyroid patients had an increased risk of being hospitalized due to infectious diseases up to 20 years after the RAI treatment. However, hyperthyroidism was not an independent predictor of hospitalization due to infectious diseases when adjusted for both previous infectious disease and CVD (RR 1.08, 95% CI 0.97-1.20). Although the risk of hospital admission due to gastrointestinal diseases was slightly increased in the patients compared with the controls, there was no difference between the groups, if diseases of the upper and lower gastrointestinal tract and liver and pancreas were analyzed separately (data not shown). Hospitalizations due to fractures were more common among RAI-treated patients than among the respective controls in women (RR 1.26, 95% CI = 1.06-1.49), but not in men (RR 0.67, 95% CI = 0.40-1.12). In addition, hospitalizations due to fractures were increased only in female patients treated at the age of 50 years or older (RR 1.31, 95% CI = 1.10-1.56), but not among younger women (RR 0.83, 95% CI 0.44-1.51). However, when adjusted for both the prevalent fracture and CVD, the fracture risk related to RAI-treated hyperthyroidism was not statistically significant (RR 1.10, 95% CI 0.90-1.24). The risk of pregnancy complications did not differ between the patients and the controls.

The most frequent CVD leading to hospitalization was arrhythmia (Table 2). The risk of hospitalization due to atrial fibrillation (AF) was significantly higher in the patients than in the controls (RR 1.35, 95% CI 1.11-1.64) up to 35 years of follow-up (Figure 2). The second most common CVD leading to hospitalization was coronary artery disease, but it was not increased in the patients compared with the controls. The third most common CVD was cerebrovascular disease. Ischemic and embolic events accounted for the increased risk of hospitalization due to cerebrovascular diseases in the patients compared with the controls (RR 1.33, 95% CI 1.15-1.55), while the risk of hemorrhagic cerebrovascular events did not differ between the groups (RR 0.99, 95% CI 0.64-1.48). Adjustment for incident or prevalent AF in addition to the prevalent cerebrovascular disease did not markedly affect the increased risk of hospitalization due to cerebrovascular disease (RR 1.26, 95% CI 1.09-1.45). In addition, the effect of RAI-treated hyperthyroidism on cerebrovascular morbidity
remained materially unchanged, when adjusted for diabetes and hypertension in addition to prevalent cerebrovascular disease (RR 1.26, 95% CI 1.10-1.45).

Sixty percent of the patients had Graves' disease and 40% had a nodular thyroid disease (toxic multinodular goiter or toxic adenoma). Hospitalizations due to CVD were elevated in the patients with a nodular thyroid disease, but not in those with Graves’ disease, compared with the corresponding controls (Table 3). The mean total dose of RAI administered was 304 MBq (min 55, max 2664 MBq). A total of 2106 patients (80.7%) received a single dose of RAI, 397 patients (15.2%) were given two doses, 71 patients (2.7%) three doses, and 37 patients (1.4%) four or more doses. When the patients were divided into three groups according to the cumulative dose of RAI and compared with the corresponding control group, the risk of hospital admission due to cardiovascular disease was elevated only in the patients whose cumulative dose of RAI was 259-369MBq (Table 3). The risk of hospitalization due to CVD in patients with recurrent hyperthyroidism after the first RAI treatment was comparable to those cured with a single dose of RAI. Among patients who were known to have developed hypothyroidism during the follow-up, the relative risk of hospitalization due to CVD was lower than among those patients not developing hypothyroidism. A previous treatment with partial thyroidectomy did not affect the risk. A previous treatment with antithyroid drugs slightly reduced the risk of hospitalization due to CVD. The duration of antithyroid drug treatment before the first RAI treatment was 0-3 months in 37% of patients, 3-6 months in 32% of patients, 6-12 months in 14% of patients, 1-2 years in 8% of patients, and more than 2 years in 9% of patients. In Cox regression analysis, the patients treated with antithyroid drugs for less than 3 months (RR 1.13, 95% CI 1.00-1.28) or more than 2 years (RR 1.61, 95% CI 1.34-1.92) were at an increased risk of hospitalization due to CVD compared with the controls. The risk of hospital admission due to CVD increased with age at the time of the first RAI treatment.

In order to evaluate the role of different clinical factors in predicting the risk of cardiovascular hospitalization, the clinical characteristics were used as covariates in Cox regression analysis. In the multivariate analysis, RAI-treated hyperthyroidism (RR 1.36, 95% CI 1.14-1.63), a nodular thyroid disease (RR 1.20, 95% CI 1.07-1.35) and age at first treatment (RR 1.06, 95% CI 1.06-1.07/year) increased, and the
development of hypothyroidism decreased (RR 0.81, 95% CI 0.71-0.92) the risk of hospital admission due to CVD.

Discussion

Overt hyperthyroidism has been associated with tachycardia and arrhythmias (especially AF), systolic hypertension, changes in ventricular systolic and diastolic function, and pulmonary hypertension, \(^7,^8,^18\) but the cardiovascular effects are thought to be reversed by effective treatment of hyperthyroidism. However, we report an increased cardiovascular morbidity, especially due to cerebrovascular disease and arrhythmias, in hyperthyroid patients persisting up to 35 years after treatment with RAI. Our result is in accordance with a previous long-term follow-up study.\(^10\) Considering the reports of increased overall and cardiovascular mortality in hyperthyroid patients treated with RAI,\(^2,^4\) hyperthyroidism can no longer be considered a reversible disorder without long-term consequences.

Hyperthyroidism can aggravate an existing CVD or contribute to the development of a new CVD.\(^7,^8\) Thyroid hormone excess results in a hyperdynamic circulation because of an increase in cardiac contractility and heart rate, a decrease in systemic vascular resistance, and an activation of the renin-angiotensin-aldosterone system, all of which increase cardiac output.\(^7,^8\) Furthermore, hyperthyroid patients commonly show endothelial dysfunction.\(^19,^20\) The reported prevalence of AF at time of diagnosing hyperthyroidism has been 8-15%.\(^8,^21,^22\) The incidence of AF increases with age, irrespective of any underlying heart disease.\(^21,^22\) In the present study, increased susceptibility to AF persisting up to 35 years after the treatment of hyperthyroidism was observed. Our results are supported by a previous study reporting an increased risk of arrhythmias in treated hyperthyroid patients in a 5-year follow-up study.\(^9\) Furthermore, a recent study showed that despite the restoration of biochemical euthyroidism, previously hyperthyroid patients continue to experience palpitation, dyspnea, and AF 6-9 months after treatment of hyperthyroidism.\(^12\) Tri-iodothyronine (T3) is the biologically relevant thyroid hormone in the myocardium, where it modulates the transcription of multiple genes and affects ion channels for sodium, potassium, and calcium.\(^8\) Our results of a persistent increase in the risk of hospitalization due to AF, hypertension, and heart failure in RAI-treated hyperthyroid
patients suggest that some essential effects of hyperthyroidism on the cardiovascular system are permanent.

The magnitude of the effect of hyperthyroidism on cerebrovascular morbidity shown in the present study was comparable to an increase in systolic blood pressure by 10mmHg or LDL-cholesterol by 1mmol/l shown in previous studies.\textsuperscript{23, 24} Acute cardioembolic stroke is a well-described manifestation of AF in hyperthyroid patients.\textsuperscript{25, 26} Only 60\% of patients with AF and hyperthyroidism have been reported to revert to sinus rhythm within 8-10 weeks after the treatment of hyperthyroidism, and after 3 months only a few resume sinus rhythm spontaneously.\textsuperscript{27} There is some evidence that the rate of cardiogenic embolism in thyrotoxic AF exceeds that of non-thyrotoxic AF.\textsuperscript{25} However, there are no controlled studies on the use of anticoagulants in hyperthyroid AF.\textsuperscript{26} We found an increased cerebrovascular morbidity in hyperthyroid patients, which was not fully explained by the increased prevalence of AF. Thus, AF leading to cardioembolic stroke is probably not the only underlying pathological mechanism of acute cerebral ischemia in hyperthyroidism. Interestingly, the risk of thromboembolic diseases of other arteries and veins were also increased in the hyperthyroid patients of the present study. Acute hyperthyroidism represents a hypercoagulable state characterized by an increased hematocrit, enhanced thrombin and plasmin activity, and dehydration,\textsuperscript{20, 28} but it is not known whether any of these changes persist after restoration of euthyroidism.

Cardiovascular morbidity increased with age and in those with a nodular thyroid disease, while a good treatment response despite the development of hypothyroidism protected from hospitalization due to CVD. Previously, increased cardiovascular morbidity has been reported in patients with Graves’ disease and those with a nodular thyroid disease.\textsuperscript{10} Also patients with Graves’ disease would be expected to have an increased cardiovascular morbidity in this study, since Graves’ disease is associated with other autoimmune diseases increasing the risk of thrombosis, such as diabetes and antiphospholipid syndrome.\textsuperscript{28, 29} The patients with a nodular thyroid disease were older and were treated in earlier decades, but were followed-up as long as those with Graves’ disease in the present study.\textsuperscript{30} The excess risk for CVD can be observed most readily when the treated patients reach the age when the incidence of cardiovascular events is high. Furthermore, patients with a nodular thyroid disease received a higher
cumulative dose of RAI, which may reflect more serious hyperthyroidism. Because of the less sensitive methods of diagnosing hyperthyroidism, patients treated in earlier decades may have suffered from a more prolonged and severe hyperthyroidism before an effective treatment. Most previous studies lack the follow-up data on the development of hypothyroidism. In the present study, levothyroxine-treated hypothyroidism after RAI treatment seemed to protect against cardiovascular morbidity, consistently with a previous five-year follow-up study. This may reflect the effective cure of hyperthyroidism and encourages the use of RAI doses high enough, despite the risk of hypothyroidism.

Our finding of an increased risk of hospitalization due to fractures in the RAI-treated postmenopausal women is consistent with previous studies, in which a past history of hyperthyroidism has been associated with an increased risk of fracture, which may relate to the duration of exposure to excess thyroid hormones. In addition to an impaired bone quality, the risk of falling is an important determinant of fracture risk. More frequent CVD might have increased the risk of falling of the patients.

The increased hospitalization rate due to malignant tumors in the present study confirms the results of our previous studies showing an increased cancer incidence and mortality in the RAI-treated hyperthyroid patients. The increased risk of hospitalization due to infectious diseases probably reflects susceptibility to infections due to more frequent CVD and malignancies among RAI-treated hyperthyroid patients. Increased mortality from respiratory infections in hyperthyroid patients has been presumed to result from the immunosuppressive effect of antithyroid medication. Antithyroid drugs might cause agranulocytosis in 0.2-0.5% of patients. However, there is no evidence of other immunosuppressive effects of antithyroid drugs, although they are suggested to suppress the autoimmune responses related to Graves’ disease. Furthermore, the medication given before the RAI treatment hardly explains the increased risk of infectious diseases sustained up to 20 years after treatment in the present study. Unfortunately, data on smoking habits were not available in the present study.

Previously, the validity of hospital diagnoses has been good (90%) in the Finnish hospital discharge register justifying their use in epidemiological studies.
present and previous reports based on three independent registers (Finnish Cancer Registry, Statistics Finland and HILMO) have consistently shown increased cardiovascular and cancer morbidity and mortality in the Finnish hyperthyroid patients treated with RAI which supports the validity of our results.\textsuperscript{6, 33}

A major weakness of this study was that it was not possible to definitely distinguish between the effects of RAI treatment and those of hyperthyroidism. No morbidity data were available on patients treated with surgery in the present study. However, perfect comparability of patients with different treatments cannot usually be achieved in non-randomized studies, because both patient and disease characteristics affect the choice of treatment and may induce confounding by indication. Another weakness was the lack of information on the traditional cardiovascular risk factors, such as smoking, hypercholesterolemia, or family history, which might have caused confounding in the present study. However, the increased risk of cerebrovascular disease remained unchanged when adjusted for pre-existing diabetes and hypertension. Furthermore, the lack of increased hospitalization or mortality\textsuperscript{6} due to ischemic heart disease in the hyperthyroid patients compared with the controls suggests that there were no major differences in the distribution of traditional cardiovascular risk factors between the patients and the controls. There might be some residual confounding, for example due to differences in the socioeconomic status between the patients and the controls.\textsuperscript{32}

Because the present data included only hospitalizations, diseases treated primarily in out-patient care were not covered. Thus, the hospitalization rates are not equivalent to the incidences of the corresponding diseases, particularly for diseases mainly treated in out-patient clinics. For example, the incidence of diabetes is probably higher than the observed hospitalization rate due to diabetes in the present study.

In summary, patients treated with RAI for hyperthyroidism were found to have a persistently increased cardiovascular morbidity, especially due to cerebrovascular disease and arrhythmias. Our findings suggest that hyperthyroidism is not a reversible disorder without long-term consequences. The increased risk of cerebrovascular morbidity calls for primary and secondary prevention of cerebrovascular risk factors and arrhythmias in hyperthyroid patients.
Acknowledgements

This study was supported by a grant from the Medical Research Fund of Tampere University Hospital. We thank Lauri Pöyhönen M.D., PhD and Heikki Oksala M.D for organizing the systematic collection of data on patients treated with RAI for hyperthyroidism in Tampere University Hospital district, and Esko Väyrynen M.A. for the revision of the language in this manuscript.

References


Table 1. Number of cases and hospitalization rate per 10,000 person-years in the hyperthyroid patients and the age- and sex-matched control group

<table>
<thead>
<tr>
<th>Disease</th>
<th>Patients</th>
<th></th>
<th></th>
<th>Controls</th>
<th></th>
<th></th>
<th>Patients vs. controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Person</td>
<td>Hospitalization rate</td>
<td>Cases</td>
<td>Person</td>
<td>Hospitalization rate</td>
<td>Rate ratio (95%CI)*</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>1305</td>
<td>20,482</td>
<td>637.1</td>
<td>1092</td>
<td>22,923</td>
<td>476.4</td>
<td>1.12 (1.03-1.21)*</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>762</td>
<td>24,072</td>
<td>316.6</td>
<td>642</td>
<td>25,980</td>
<td>247.1</td>
<td>1.23 (1.11-1.37)*</td>
</tr>
<tr>
<td>Musculoskeletal diseases</td>
<td>499</td>
<td>24,403</td>
<td>204.5</td>
<td>543</td>
<td>25,222</td>
<td>215.3</td>
<td>0.93 (0.83-1.05)</td>
</tr>
<tr>
<td>Gastro-intestinal diseases</td>
<td>409</td>
<td>25,428</td>
<td>160.8</td>
<td>367</td>
<td>26,856</td>
<td>136.7</td>
<td>1.15 (1.00-1.32)*</td>
</tr>
<tr>
<td>Malignant tumors</td>
<td>375</td>
<td>26,562</td>
<td>141.2</td>
<td>305</td>
<td>28,054</td>
<td>108.7</td>
<td>1.23 (1.06-1.43)*</td>
</tr>
<tr>
<td>Fractures</td>
<td>326</td>
<td>26,656</td>
<td>122.3</td>
<td>282</td>
<td>27,718</td>
<td>101.7</td>
<td>1.18 (1.01-1.39)*</td>
</tr>
<tr>
<td>Psychiatric diseases</td>
<td>307</td>
<td>26,729</td>
<td>114.9</td>
<td>290</td>
<td>27,948</td>
<td>103.8</td>
<td>1.07 (0.92-1.26)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>275</td>
<td>26,863</td>
<td>102.4</td>
<td>229</td>
<td>28,078</td>
<td>81.6</td>
<td>1.04 (0.87-1.24)</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Disease</th>
<th>Patients Cases</th>
<th>Person years</th>
<th>Hospitalization rate</th>
<th>Controls Cases</th>
<th>Person years</th>
<th>Hospitalization rate</th>
<th>Patients vs. controls Rate ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diseases of urinary system</td>
<td>200</td>
<td>27,316</td>
<td>73.2</td>
<td>195</td>
<td>28,371</td>
<td>68.7</td>
<td>1.07 (0.88-1.30)</td>
</tr>
<tr>
<td>Diseases of central nervous system</td>
<td>171</td>
<td>27,185</td>
<td>62.9</td>
<td>194</td>
<td>28,239</td>
<td>68.7</td>
<td>0.92 (0.75-1.13)</td>
</tr>
<tr>
<td>Hematological diseases</td>
<td>147</td>
<td>27,339</td>
<td>53.8</td>
<td>137</td>
<td>28,587</td>
<td>47.9</td>
<td>1.03 (0.81-1.30)</td>
</tr>
<tr>
<td>Asthma and COPD</td>
<td>141</td>
<td>27,375</td>
<td>51.5</td>
<td>118</td>
<td>41,327</td>
<td>41.3</td>
<td>1.12 (0.88-1.43)</td>
</tr>
<tr>
<td>Complications of pregnancy</td>
<td>59</td>
<td>6,483</td>
<td>91.0</td>
<td>54</td>
<td>6,554</td>
<td>82.4</td>
<td>1.11 (0.76-1.60)</td>
</tr>
</tbody>
</table>

*Statistically significant difference between patients and controls adjusted with prevalent disease, i.e., hospitalization due to the same disease before the first dose of RAI.
Figure 1. Cumulative hospitalization rate due to cardiovascular diseases (CVD) by time since treatment in the hyperthyroid patients treated with RAI compared with the age- and sex-matched control group (p < 0.001, Log rank test).
### Table 2. Hospitalization rate caused by different cardiovascular diseases per 10,000 person-years in the hyperthyroid patients and the age- and sex-matched control group

<table>
<thead>
<tr>
<th>Cardiovascular disease</th>
<th>Patients</th>
<th></th>
<th>Controls</th>
<th></th>
<th>Patients vs. controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Person years</td>
<td>Hospitalization rate</td>
<td>Cases</td>
<td>Person years</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>643</td>
<td>24,864</td>
<td>258.6</td>
<td>397</td>
<td>27,218</td>
</tr>
<tr>
<td>Coronary artery</td>
<td>538</td>
<td>25,785</td>
<td>208.7</td>
<td>507</td>
<td>26,840</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>428</td>
<td>26,725</td>
<td>160.2</td>
<td>344</td>
<td>28,015</td>
</tr>
<tr>
<td>Other arteries and veins</td>
<td>357</td>
<td>25,917</td>
<td>137.7</td>
<td>296</td>
<td>27,219</td>
</tr>
<tr>
<td>Hypertension</td>
<td>344</td>
<td>26,276</td>
<td>130.9</td>
<td>271</td>
<td>27,716</td>
</tr>
<tr>
<td>Heart failure</td>
<td>346</td>
<td>27,141</td>
<td>127.5</td>
<td>214</td>
<td>28,650</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>86</td>
<td>27,821</td>
<td>30.9</td>
<td>61</td>
<td>28,969</td>
</tr>
<tr>
<td>Other(^†)</td>
<td>54</td>
<td>27,947</td>
<td>19.3</td>
<td>47</td>
<td>29,064</td>
</tr>
</tbody>
</table>

\(^*\)Statistically significant difference between patients and controls adjusted with prevalent disease, *i.e.*, hospitalization due to the same disease before the first dose of RAI.

\(^†\)Non-bacterial endo-, peri- and myocardial diseases, cardiomyopathy, and conduction disorders of the heart.
Figure 2. Cumulative hospitalization rate due to different cardiovascular diseases by time since treatment in the hyperthyroid patients treated with RAI compared with the age- and sex-matched control group (Log rank test).
Table 3. Hospitalizations due to CVD per 10,000 person-years in different subgroups of patients and in the corresponding controls

<table>
<thead>
<tr>
<th>Subgroup of patients</th>
<th>Patients</th>
<th></th>
<th>Controls</th>
<th></th>
<th>Patients vs. controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Hospitalization</td>
<td>Cases</td>
<td>Hospitalization</td>
<td>Rate ratio (95%CI)</td>
</tr>
<tr>
<td></td>
<td>rate</td>
<td>rate</td>
<td>rate</td>
<td>rate</td>
<td></td>
</tr>
<tr>
<td><strong>Etiology of hyperthyroidism</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graves’ disease (n=1571)</td>
<td>583</td>
<td>445.2</td>
<td>522</td>
<td>385.3</td>
<td>0.95 (0.85-1.08)</td>
</tr>
<tr>
<td>Toxic multinodular goitre or adenoma (n = 1040)</td>
<td>722</td>
<td>977.4</td>
<td>570</td>
<td>608.0</td>
<td>1.35 (1.21-1.52)*</td>
</tr>
<tr>
<td><strong>Total dose of RAI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55-258MBq (n=727)</td>
<td>402</td>
<td>546.8</td>
<td>359</td>
<td>475.1</td>
<td>0.97 (0.84-1.12)</td>
</tr>
<tr>
<td>259-369MBq (n=1532)</td>
<td>704</td>
<td>650.9</td>
<td>568</td>
<td>452.2</td>
<td>1.20 (1.07-1.34)*</td>
</tr>
<tr>
<td>370-2664MBq (n=352)</td>
<td>199</td>
<td>859.6</td>
<td>165</td>
<td>588.2</td>
<td>1.21 (0.98-1.50)</td>
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<tr>
<td><strong>Recurrence after the 1st dose of RAI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=524)</td>
<td>279</td>
<td>652.3</td>
<td>232</td>
<td>477.7</td>
<td>1.09 (0.91-1.31)</td>
</tr>
<tr>
<td>No (n=2087)</td>
<td>1026</td>
<td>633.1</td>
<td>860</td>
<td>476.0</td>
<td>1.13 (1.03-1.23)*</td>
</tr>
<tr>
<td><strong>Development of hypothyroidism</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=807)</td>
<td>364</td>
<td>376.4</td>
<td>301</td>
<td>316.2</td>
<td>1.03 (0.88-1.20)</td>
</tr>
<tr>
<td>No (n=1804)</td>
<td>941</td>
<td>870.3</td>
<td>791</td>
<td>590.1</td>
<td>1.22 (1.10-1.34)*</td>
</tr>
</tbody>
</table>

(continued)
Table 3 (continued)

<table>
<thead>
<tr>
<th>Subgroup of patients</th>
<th>Patients</th>
<th>Controls</th>
<th>Patients vs. controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Hospitalization rate</td>
<td>Cases</td>
</tr>
<tr>
<td>Previous partial thyroidectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=284)</td>
<td>162</td>
<td>547.1</td>
<td>126</td>
</tr>
<tr>
<td>No (n=2031)</td>
<td>1007</td>
<td>640.6</td>
<td>847</td>
</tr>
<tr>
<td>Anti-thyroid drug</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=2229)</td>
<td>1081</td>
<td>620.7</td>
<td>907</td>
</tr>
<tr>
<td>No (n=278)</td>
<td>167</td>
<td>716.3</td>
<td>131</td>
</tr>
<tr>
<td>Age at first treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13-49 years (n=678)</td>
<td>130</td>
<td>173.4</td>
<td>109</td>
</tr>
<tr>
<td>50-59 years (n=465)</td>
<td>215</td>
<td>440.8</td>
<td>190</td>
</tr>
<tr>
<td>60-69 years (n=662)</td>
<td>399</td>
<td>810.7</td>
<td>348</td>
</tr>
<tr>
<td>70-98 years (n=806)</td>
<td>561</td>
<td>1761.1</td>
<td>445</td>
</tr>
<tr>
<td>All (n=2611)</td>
<td>1305</td>
<td>637.1</td>
<td>1092</td>
</tr>
</tbody>
</table>

*Statistically significant difference between patients and controls adjusted with prevalent CVD, i.e., hospitalization due to CVD before the first dose of RAI.
Increased Cancer Incidence After Radioiodine Treatment for Hyperthyroidism

Saara Metso, MD,1,2 Anssi Auvinen, MD, PhD,3,4 Heini Huhtala, MSc,5,6 Jorma Salmi, MD, PhD,1 Heikki Oksala, MD,1 Pia Jaatinen, MD, PhD,1,2

1 Department of Internal Medicine, Tampere University Hospital, Tampere, Finland.
2 Medical School, University of Tampere, Finland.
3 STUK-Radiation and Nuclear Safety Authority, Research and Environmental Surveillance, Helsinki, Finland.
4 Finnish Cancer Institute, Helsinki, Finland.
5 Tampere School of Public Health, University of Tampere, Finland.
6 Research Unit, Tampere University Hospital, Tampere, Finland.

BACKGROUND. Concerns remain about risk of cancer after radioactive iodine (RAI) treatment for hyperthyroidism, especially in organs that concentrate iodine. The objective was to assess the long-term cancer risk from RAI treatment for hyperthyroidism.

METHODS. A total of 2793 hyperthyroid patients treated with RAI at Tampere University Hospital between 1965 and 2002, and 2793 age- and sex-matched reference subjects were followed for an average of 10 years through the Finnish Cancer Registry.

RESULTS. Cancer incidence among hyperthyroid patients treated with RAI was higher than in the population-based control group (118.9 vs 94.9 per 10,000 person-years, rate ratio [RR], 1.25; 95% confidence interval [CI]: 1.08–1.46). Furthermore, incidence of stomach (RR, 1.75; 95% CI: 1.00–3.14), kidney (RR, 2.32; 95% CI: 1.06–5.09), and breast (RR, 1.53; 95% CI: 1.07–2.19) cancer was increased among RAI-treated patients. The relative risk of cancer increased with higher RAI dose administered. The increase in cancer incidence was statistically significant in patients treated at the age of 50–59 (RR, 1.44; 95% CI: 1.05–1.97) or older than 70 years (RR, 1.39; 95% CI: 1.05–1.82). There was a 5-year latent period after the RAI treatment before the cancer incidence began to differ between the RAI-treated hyperthyroid patients and the control group.


KEYWORDS: radioactive iodine, hyperthyroidism, cancer incidence.
with surgery for hyperthyroidism in total cancer incidence, breast cancer, or leukemia. Although based on a small number of cases, an elevated risk of cancer was observed in the thyroid gland and other organs that concentrate RAI (salivary glands, digestive tract, kidney, and bladder). In a study of Goldman et al., the cancer incidence of 1762 hyperthyroid women (80% treated with RAI) did not differ from that of US white women. In a large population-based study of 10,552 Swedish patients who received RAI therapy for hyperthyroidism, significantly elevated overall cancer incidence was observed compared with the Swedish population. Among 10-year survivors, significantly elevated risks were seen for cancers of the stomach, brain, and kidney. In a population-based study of 7417 patients treated with RAI for hyperthyroidism in Birmingham (UK), the overall cancer incidence and mortality decreased, but the incidence and mortality of cancers of the small bowel and the thyroid gland were increased compared with expected rates.

The purpose of the present study was to evaluate the risk of cancer in Finnish patients treated with RAI for hyperthyroidism. Furthermore, we aimed to study the possible modification of such effect by etiology of hyperthyroidism, dose of RAI, recurrent hyperthyroidism, and development of hypothyroidism.

MATERIALS AND METHODS

Information on treatment, cancer cases, and vital status among 2793 patients (457 men and 2336 women) treated for hyperthyroidism with RAI between January 1965 and June 2002 were obtained from the database of the Tampere University Hospital, the Finnish Cancer Registry, and the Population Register Center. The patients’ follow-up started at the end of the year of the first RAI treatment. A reference group was formed by choosing an age- and sex-matched control subject for each patient from the Population Register Center. The control subject had to be alive at the time when the patient received the first RAI treatment. The follow-up period of the control subject started at the same time as that of the corresponding patient. For both patients and controls the follow-up ended on the date of the first cancer diagnosis, death, emigration from Finland, or the common closing date (December 2004), whichever occurred first.

Information on the etiology of hyperthyroidism, the dates and doses of all RAI treatments, and the development of hypothyroidism of all patients treated with RAI for hyperthyroidism at the Tampere University Hospital were recorded in the computerized register since 1965, as described earlier. Incident cancer cases occurring among patients and controls were identified from the Finnish Cancer Registry using computerized record linkage, with the personal identification number as the key. The Finnish Cancer Registry is a population-based, nationwide cancer registry established in 1952, with more than 98% completeness of solid cancers. The unspecified tumors include metastatic tumors with unknown or unspecified primary site. Prevalent cancers at baseline, ie, those diagnosed before the beginning of follow-up, were excluded. Site-specific cancer incidence was calculated with follow-up until the diagnosis of site-specific cancer, regardless of any other cancer diagnosed. In prostate, breast, and gynecological cancer, the person-years at risk were counted only for the sex at risk.

The ethics committee of the Pirkanmaa Hospital District approved the study protocol. In addition, the National Research and Development Center for Welfare and Health gave permission to use data from the Population Register and the Finnish Cancer Registry. The study was undertaken in accordance with the Declaration of Helsinki.

Statistical Analysis

We used the statistical software Stata for Windows, v. 8.2 (StataCorp, College Station, Tex), to calculate the cancer incidence rates. The incidence rate ratios were calculated by Mantel-Haenszel method. Other statistical analyses were performed using SPSS for Windows v. 13.0 (SPSS, Chicago, Ill). Normality of the distribution of the variables studied was tested by Kolmogorov-Smirnov test. The distributions of all the continuous variables were skewed and therefore non-parametric tests (Mann-Whitney and Kruskal-Wallis tests) were used to assess the relation between continuous and categorical variables. The chi-square test was used to determine whether an association between 2 categorical variables was statistically significant. A 2-sided P-value less than .05 was considered statistically significant. In addition to the analysis of the whole RAI-treated population and controls, incidence was also counted in the following subgroups of patients using only the corresponding controls: etiology of hyperthyroidism (Graves disease, multinodular goiter or toxic adenoma), total dose of RAI (55–258 MBq, 259–369 MBq, 370–2664 MBq), recurrence of hyperthyroidism after the first dose of RAI (yes, no), development of hypothyroidism during follow-up (yes, no), and age at the beginning of follow-up (13–50, 50–59, 60–69, and 70–98 years). Cox regression analysis was performed to evaluate the significance of different factors in predicting the risk of cancer.
RESULTS
The median age for the patients at treatment and controls at the beginning of the follow-up was 62 years (quartile range, 50 years to 75 years). The median follow-up time was 9.8 years for the patients and 10.0 years for the controls (Fig. 1). The person-years at risk were 30,878 among patients and 32,452 among controls. At least 1 cancer diagnosis after the beginning of follow-up was identified in 367 patients and in 308 controls. More than 2 different cancer types were diagnosed in 21 patients and 8 controls (Table 1).

The overall cancer incidence was higher among the patients than in the control group (rate ratio [RR], 1.25; 95% confidence interval [CI], 1.08–1.46). The absolute difference in incidence rates was 24 of 10,000, which corresponds to the number needed to harm of 418 (95% CI: 391–446, ie, 1 excess case of cancer is induced by treating 418 patients with RAI). The risk of cancers of the stomach (RR, 1.75; 95% CI, 1.00–3.14), kidney (RR, 2.32; 95% CI, 1.06–5.01), breast (RR, 1.53; 95% CI, 1.07–2.19), and unspecified site (RR, 2.22; 95% CI, 1.00–4.90) was increased in the patients compared with the control group (Fig. 2). The proportion of subjects free of cancer at 5 years of follow-up was 97.4% among the patients versus 97.5% among the controls. The difference in cancer incidence between the studied groups emerged thereafter, as illustrated with the Kaplan-Meier survival

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Patients Cases</th>
<th>Incidence (95% CI)</th>
<th>Control group Cases</th>
<th>Incidence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancer sites</td>
<td>367</td>
<td>118.9 (107.3–131.7)</td>
<td>308</td>
<td>94.9 (84.9–106.1)</td>
</tr>
<tr>
<td>Salivary glands</td>
<td>2</td>
<td>0.6 (0.2–2.6)</td>
<td>0</td>
<td>0.3 (0.0–2.2)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>5</td>
<td>1.6 (0.7–3.9)</td>
<td>1</td>
<td>0.3 (0.0–2.2)</td>
</tr>
<tr>
<td>Stomach</td>
<td>30</td>
<td>9.7 (6.8–13.9)</td>
<td>18</td>
<td>5.5 (3.5–8.8)</td>
</tr>
<tr>
<td>Intestinal</td>
<td>44</td>
<td>13.8 (10.2–18.5)</td>
<td>45</td>
<td>13.5 (10.1–18.1)</td>
</tr>
<tr>
<td>Liver and pancreas</td>
<td>39</td>
<td>12.1 (8.9–16.7)</td>
<td>36</td>
<td>10.8 (7.8–14.9)</td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>24</td>
<td>7.5 (5.0–11.2)</td>
<td>29</td>
<td>8.7 (6.0–12.5)</td>
</tr>
<tr>
<td>Thyroid gland</td>
<td>5</td>
<td>1.6 (0.6–3.7)</td>
<td>3</td>
<td>0.9 (0.1–2.8)</td>
</tr>
<tr>
<td>Bladder and urinary tract1</td>
<td>7</td>
<td>2.3 (1.1–4.8)</td>
<td>9</td>
<td>2.8 (1.4–5.3)</td>
</tr>
<tr>
<td>Kidney</td>
<td>20</td>
<td>6.2 (4.0–9.7)</td>
<td>9</td>
<td>2.7 (1.4–5.2)</td>
</tr>
<tr>
<td>Skin1</td>
<td>24</td>
<td>7.5 (5.0–11.2)</td>
<td>28</td>
<td>8.4 (5.8–12.2)</td>
</tr>
<tr>
<td>Brain</td>
<td>7</td>
<td>2.3 (1.1–4.7)</td>
<td>4</td>
<td>1.2 (0.5–3.3)</td>
</tr>
<tr>
<td>Hematopoietic</td>
<td>22</td>
<td>6.9 (4.5–10.4)</td>
<td>18</td>
<td>5.4 (3.4–8.6)</td>
</tr>
<tr>
<td>Breast</td>
<td>74</td>
<td>27.4 (21.8–34.4)</td>
<td>50</td>
<td>17.9 (13.6–23.6)</td>
</tr>
<tr>
<td>Gynecological</td>
<td>42</td>
<td>15.3 (11.3–20.8)</td>
<td>36</td>
<td>12.8 (9.3–17.8)</td>
</tr>
<tr>
<td>Prostate</td>
<td>21</td>
<td>47.2 (30.8–72.4)</td>
<td>17</td>
<td>32.7 (20.3–52.6)</td>
</tr>
<tr>
<td>Unspecified site</td>
<td>19</td>
<td>6.2 (3.9–9.6)</td>
<td>9</td>
<td>2.8 (1.4–5.3)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.
* Cancers of small intestine, colon, and rectum.
1 Cancers of urinary bladder, ureters, and urethra.
2 Malignant skin tumors (cutaneous melanoma, squamous cell carcinoma, and basal cell carcinoma).
The cancer incidence after 10 or more years of follow-up was 154.4 per 10,000 person-years in the patients and 126.4 in the control group (RR, 1.22; 95% CI, 1.00–1.53). Cancer had been diagnosed in 125 patients and 93 controls before the beginning of follow-up. When adjustment for previous cancer was used in the Cox regression analysis, the risk related to RAI treatment remained unchanged (RR, 1.27; 95% CI, 1.09–1.47).

The mean total dose of RAI administered was 305 MBq (minimum 55 MBq, maximum 2664 MBq). A total of 2243 (80.3%) patients received a single dose of RAI; 435 (15.6%) patients were given 2 doses; 76 (2.7%) patients 3 doses; and 39 (1.7%) patients 4 or more doses. When patients were divided into 3 groups according to the cumulative RAI activity received and compared with the corresponding control group, the overall cancer risk increased with the cumulative dose of RAI (Table 2). The relative risk of cancer was 1.06 of 100 MBq (95% CI, 1.03–1.09, Cox regression analysis).

The incidence of cancer was higher in the RAI-treated patients than in the control group in all age groups, but the difference was statistically significant only in 2 age groups: those who were ages 50–59 years or ages 70–98 years at the beginning of the follow-up (Table 2). The breast cancer risk decreased according to the age at the first RAI-treatment (RR, 2.17 vs 1.74 vs 1.66 vs 0.72 in subjects ages 13–49 years, 50–59 years, 60–69 years, and 70–98 years, respectively). Twenty-one patients younger than the age of 20 were treated with RAI. None of them or their controls had cancer during the follow-up (median 13 years in both patients and controls).

Hyperthyroidism recurred after the initial treatment with RAI in 20% of patients, necessitating repeated RAI therapy or continuous antithyroid medication lasting longer than 1 year. The risk of cancer in this subgroup of patients compared with the corresponding controls was higher than in those whose hyperthyroidism was cured with a single dose of RAI (Table 2). In the 831 patients known to develop hypothyroidism during the follow-up, the cancer risk was lower than in the rest of the patients (Table 2).

The hyperthyroidism was caused by Graves disease in 57% (1604) of patients and by nodular thyroid disease (toxic multinodular goiter or toxic adenoma) in 43% (1189). The patients with nodular thyroid disease were older (median age 67 years vs 57 years, \( P < .001 \)), received a higher cumulative dose of RAI (median dose of RAI, 259 vs 222 MBq, \( P < .001 \)), and were treated earlier (median year of the first RAI, 1976 vs 1991, \( P < .001 \)), but were followed as long as those with Graves disease (median follow-up time, 9 years 10 months vs 9 years 2 months; \( P = .57 \)). The overall cancer incidence was increased in the patients compared with the corresponding control group in both etiologic groups (Table 2). However, the risk of breast cancer (RR, 1.78; 95% CI, 1.07–2.95 vs 1.32; 95% CI, 0.79–2.20) and stomach cancer (RR, 2.38; 95% CI, 1.20–4.71 vs 1.31; 95% CI, 0.49–3.51) was increased only in the patients with nodular thyroid disease but not in those with Graves disease.

**DISCUSSION**

The present study reports a significantly elevated incidence of cancer in hyperthyroid patients treated...
with RAI compared with the control population. The availability of incidence rather than mortality data was a major asset, as it both increased the statistical power and allowed us to study also cancer sites with little mortality. The increasing cancer risk with the cumulative dose of RAI, and the fact that the cancer risk was not elevated in the first 5 years after RAI treatment, but only after 10 years of follow-up, ie, after a minimum latency for radiation-induced cancer, suggest that radiation might explain the excess cancer risk. However, the absolute risk of cancer was rather low, the number needed to harm being 418.

Our findings are consistent with the previous study by Holm et al.8 Earlier, Hoffman et al.5 did not find any difference in overall cancer incidence between women treated with RAI and those treated surgically for hyperthyroidism, but an increased risk of cancer was reported in organs that concentrate iodine, namely, salivary glands, digestive tract, kidney, and bladder, among patients treated with RAI. Contrary to the present results, Franklyn et al.7 reported a decreased overall cancer incidence in RAI-treated patients. Finland is known as an exceptional genetic isolate.11 Confounding due to ethnic differences between the patients and controls is very unlikely in the present study, as 98% of the Finnish population is of Caucasian origin. However, it might partly explain the conflicting results of the present study and the previous Swedish,8 English,7 and American5 ones. Furthermore, the conflicting results concerning cancer risk after RAI treatment for hyperthyroidism in different populations might reflect differences in the sensitivity to radiation-induced cancer depending on the age at exposure, thyroid disease, smoking, diet, and baseline cancer rates.12

The risk of stomach cancer was increased in RAI-treated patients compared with the untreated control group in our study, as well as in the study of Holm et al.8 Earlier, an elevated risk of stomach cancer was found in thyroid cancer patients treated with RAI, but not in those receiving other types of treatment.13 When the dose of RAI taken up by the thyroid gland is 60–100 Gy, doses to other organs are less than 10 cGy, except for nonthyroidal tissues that accumulate iodine, including the stomach (25 cGy).8,14 Furthermore, sodium-iodine symporter (NIS), an intrinsic plasma membrane protein that mediates active iodine transport into thyroid gland, has been detected in the gastric mucosa and probably mediates active iodine transport from the serum to the gastric fluid.15 Consequently, the stomach might be particularly vulnerable to RAI-induced cancer.

### TABLE 2

<table>
<thead>
<tr>
<th>Subgroup of patients</th>
<th>Patients Cases</th>
<th>Patients Incidence</th>
<th>Control group Cases</th>
<th>Control group Incidence</th>
<th>Patients vs controls Rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total dose of RAI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55–258 MBq, 39% (n = 1083)</td>
<td>162</td>
<td>113.3</td>
<td>151</td>
<td>101.7</td>
<td>1.11 (0.89–1.39)</td>
</tr>
<tr>
<td>259–369 MBq, 37% (n = 1033)</td>
<td>106</td>
<td>113.5</td>
<td>85</td>
<td>86.2</td>
<td>1.32 (1.00–1.75)*</td>
</tr>
<tr>
<td>370–2664 MBq, 24% (n = 677)</td>
<td>99</td>
<td>138.7</td>
<td>72</td>
<td>93.0</td>
<td>1.47 (1.09–1.99)*</td>
</tr>
<tr>
<td>Age at the beginning of follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13–49 y, 25% (n = 694)</td>
<td>34</td>
<td>35.6</td>
<td>23</td>
<td>23.8</td>
<td>1.49 (0.88–2.53)</td>
</tr>
<tr>
<td>50–59 y, 18% (n = 506)</td>
<td>95</td>
<td>128.2</td>
<td>68</td>
<td>89.0</td>
<td>1.44 (1.05–1.97)*</td>
</tr>
<tr>
<td>60–69 y, 26% (n = 731)</td>
<td>123</td>
<td>149.9</td>
<td>125</td>
<td>141.4</td>
<td>1.06 (0.83–1.36)</td>
</tr>
<tr>
<td>70–98 y, 31% (n = 862)</td>
<td>115</td>
<td>201.6</td>
<td>92</td>
<td>145.4</td>
<td>1.38 (1.05–1.82)*</td>
</tr>
<tr>
<td>Recurrence after the first dose of RAI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, 20% (n = 571)</td>
<td>87</td>
<td>125.7</td>
<td>63</td>
<td>89.6</td>
<td>1.40 (1.02–1.94)*</td>
</tr>
<tr>
<td>No, 80% (n = 2222)</td>
<td>280</td>
<td>116.9</td>
<td>245</td>
<td>96.4</td>
<td>1.21 (1.02–1.44)*</td>
</tr>
<tr>
<td>Etiology of hyperthyroidism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graves disease, 57% (n = 1604)</td>
<td>164</td>
<td>93.5</td>
<td>133</td>
<td>74.6</td>
<td>1.25 (1.00–1.58)*</td>
</tr>
<tr>
<td>Toxic multinodular goiter or adenoma, 43% (n = 1189)</td>
<td>203</td>
<td>152.2</td>
<td>175</td>
<td>119.7</td>
<td>1.27 (1.04–1.56)*</td>
</tr>
<tr>
<td>Development of hypothyroidism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, 40% (n = 831)</td>
<td>108</td>
<td>81.2</td>
<td>87</td>
<td>69.0</td>
<td>1.18 (0.89–1.56)</td>
</tr>
<tr>
<td>No, 60% (n = 1 250)</td>
<td>259</td>
<td>147.3</td>
<td>221</td>
<td>111.3</td>
<td>1.32 (1.11–1.58)*</td>
</tr>
<tr>
<td>All (n = 2793)</td>
<td>367</td>
<td>118.9</td>
<td>308</td>
<td>94.9</td>
<td>1.25 (1.00–1.46)*</td>
</tr>
</tbody>
</table>

RAI indicates radioactive iodine.

The incidence rate ratios were calculated by the Mantel-Haenszel method.

* Statistically significant difference between the RAI-treated patients and the corresponding controls.
Our finding with an RR of 1.75 at a dose of 0.25 Gy for stomach cancer corresponds to excess relative risk of 3 per Gy, which is higher than the estimate from atomic bomb survivors of Hiroshima and Nagasaki (0.3 per Gy).\textsuperscript{8,12,16} Atrophic gastritis is an autoimmune disorder that could be a confounding factor, given that it is related to both autoimmune thyroid diseases and stomach cancer.\textsuperscript{17–19} However, an increased risk of stomach cancer in the present study was found among patients with nodular thyroid disease but not among those with Graves disease, consistent with the study of Holm et al.\textsuperscript{8} The risk of stomach cancer might increase due to hyperthyroidism per se, because thyroid hormones inhibit gastric acid production and cause hypergastrinemia.\textsuperscript{17–19} Gastrin is a proproliferative, antiapoptotic hormone with a central role in acid secretion and carcinogenesis in the gastric mucosa.\textsuperscript{20} Diet is also a potential confounding factor that could not be controlled in the present long-term follow-up study.

Contrary to earlier studies,\textsuperscript{6,8,21} an increased risk of breast cancer after RAI treatment for hyperthyroidism was seen in the present study. Quiescent mammary glands do not concentrate iodine, and radiation doses received by the mammary glands are estimated to be low.\textsuperscript{8,14} However, there have been concerns regarding a potential increase in the incidence of breast cancer after RAI treatment, because an elevated risk of breast cancer has been observed among patients with thyroid cancer given high doses of RAI.\textsuperscript{14} Breast tissue is especially sensitive to radiation carcinogenesis, and dose fractionation does not decrease the risk of breast cancer per unit dose.\textsuperscript{12} Among atomic bomb survivors in Hiroshima and Nagasaki, the excess relative risk of radiation-induced breast cancer after exposure in adulthood has been estimated as 1.0 per Gy.\textsuperscript{16} In our study with a breast dose of 0.1 Gy and RR of 1.53 the corresponding estimate is somewhat higher (excess relative risk 5 per Gy). We had no information on reproductive factors, which are the main determinants of breast cancer risk. Therefore, we cannot exclude confounding factors as an explanation for our findings. Hereditary predisposition to breast cancer is also a potential confounding factor. Unfortunately, we did not have any data on hereditary predisposition to cancer of the subjects. Yet the proportion of breast cancer attributable to hereditary factors in the Finnish population has been estimated as 5% to 10%.\textsuperscript{22} Therefore, confounding could account for our results only if there is a strong correlation between RAI-treated hyperthyroidism and these hereditary factors (10-fold prevalence of inherited factors among patients relative to control group).

The increased risk of breast cancer in the RAI-treated patients of the present study might be explained by the association between thyroid disorders and breast cancer. Breast cancer and thyroid disease predominantly affect females and both have a postmenopausal peak incidence, suggesting that these 2 diseases share common, perhaps hormonal, etiologic factors.\textsuperscript{23–25} In the present study the risk of breast cancer was highest in the patients treated before 50 years of age and decreased according to age, suggesting that hormones can modify the radiation risk, as shown previously.\textsuperscript{12} One area in which thyroid and breast functions overlap is the uptake and utilization of dietary iodine. There are some experimental and epidemiological findings suggesting that iodine may protect from breast cancer development.\textsuperscript{23} Thus, iodine deficiency might have contributed to the development of both multinodular goiter and breast cancer. Interestingly, NIS is expressed in more than 80% of breast cancers.\textsuperscript{15}

The urinary bladder is known to accumulate iodine and express NIS.\textsuperscript{15} However, the risk of bladder cancer was not increased in our study or previous long-term studies of patients treated with RAI for hyperthyroidism.\textsuperscript{7,8} Interestingly, the risk of renal cancer was increased in the present study, consistent with the previous study of Holm et al.\textsuperscript{8} After ingestion, RAI initially concentrates in the thyroid gland. Circulating RAI is excreted by the kidneys.\textsuperscript{26} Tubular cells reabsorb up to 60% to 80% of the iodine excreted in primary urine,\textsuperscript{26} and renal distal and collecting tubules have been found to express NIS,\textsuperscript{15} which might increase the radiation exposure of kidneys after RAI treatment.

Edmonds and Smith\textsuperscript{14} reported a small but significant excess of incidence and mortality of leukemia in 258 patients treated with high-dose RAI for thyroid cancer (2960 MBq to 5550 MBq). However, no increased risk for malignancies of the hematopoietic system was found in our study, which is in agreement with earlier studies on patients treated with RAI (370 MBq to 555 MBq) for hyperthyroidism.\textsuperscript{5,7,8,27} Consistent with the present study, no increase in the risk of thyroid malignancies has been observed in patients treated with RAI for hyperthyroidism in most of the published long-term follow-up studies.\textsuperscript{5,8,28} However, in a few studies an elevated risk of thyroid cancer has been reported, although based on a small number of cases.\textsuperscript{5,7,29} The risk of thyroid malignancy after radiation exposure is higher in children than in adults.\textsuperscript{30–33} In a 36-year follow-up of 98 patients treated with RAI for hyperthyroidism under the age of 20, no cases of thyroid cancer were observed.\textsuperscript{34} In the present study, none of the 21
patients treated with RAI under the age of 20 were diagnosed with cancer during 13 years of follow-up. Given that the mean latency time for development of thyroid malignancy in radiation-exposed patients has been 10 years to 20 years, with the minimum time to appearance being 5 years to 9 years, the statistical power of the present study or the previous ones was insufficient for detecting an increased risk of thyroid malignancies in children and young adults. The statistical power in the present study could have been increased by doubling the number of controls.

In the present study the risk of stomach and breast cancer was somewhat higher among patients with nodular thyroid disease than those with Graves disease, as reported also by Holm et al.\textsuperscript{8} The patients with nodular thyroid disease were older, received a higher cumulative dose of RAI, and were treated earlier than those with Graves disease. The excess risk for solid tumors can be observed most readily when the treated patients reach the age when underlying cancer incidence rates are high.\textsuperscript{12} This may explain the higher cancer incidence in the patients with nodular thyroid disease than in patients with Graves disease. Nodular thyroid disease was the most common cause of hyperthyroidism from the 1960s until the 1980s, whereas the proportion of Graves disease increased and was the major cause of hyperthyroidism in the 1990s.\textsuperscript{9} The historically older cohort of patients with nodular thyroid disease might have been more sensitive to the carcinogenic effect of RAI compared with the patients with Graves disease, because of, eg, changes of diet and decreasing prevalence of \textit{Helicobacter pylori} infection during the past few decades.\textsuperscript{35}

The strengths of the present study are the relatively large size of the cohort, completeness of follow-up through high-quality registers, and detailed data on the amount of RAI administered and indications for treatment. However, it is not possible to distinguish between the effects of RAI treatment and those of hyperthyroidism on the basis of the present study. During the past decade the average number of patients treated surgically for hyperthyroidism has been 5 per year, whereas RAI has been chosen for about 100 patients per year in our hospital district. Surgical treatment is chosen if a patient has a very large goiter causing symptoms of compression in the neck, if there is a suspicion of a malignancy in the thyroid gland, or if the patient has recurring hyperthyroidism with severe eye symptoms of Graves disease. Unfortunately, we do not have cancer incidence data on the patients treated with surgery, and because of the small number of the surgically treated patients in our hospital district the power of the study would have been too low to detect a potential difference in cancer incidence between the surgically and RAI-treated patients. Furthermore, perfect comparability of patients with different treatments cannot usually be achieved in nonrandomized studies because both patient and disease characteristics affect the choice of treatment and may induce confounding by indication.

In summary, the risk of cancer, especially cancer of stomach, kidney, and breast, was increased in the hyperthyroid patients treated with RAI compared with the population-based control group. Our results emphasize the need for long-term vigilance concerning patients treated with RAI.

REFERENCES


Increased Cardiovascular and Cancer Mortality after Radioiodine Treatment for Hyperthyroidism

Saara Metso, Pia Jaatinen, Heini Huhtala, Anssi Auvinen, Heikki Oksala, and Jorma Salmi

Department of Internal Medicine (S.M., P.J., H.O., J.S.) and Research Unit (H.H.), Tampere University Hospital, FIN-33521 Tampere, Finland; Medical School (S.M., P.J.) and Tampere School of Public Health (H.H., A.A.), University of Tampere, FIN-33014 Tampere, Finland; and STUK-Radiation and Nuclear Safety Authority (A.A.), Research and Environmental Surveillance, FIN-00881 Helsinki, Finland

Context: Patients treated with radioiodine (RAI) for hyperthyroidism have been reported to be at increased risk for death. It is not clear whether the increased mortality is due to hyperthyroidism itself or the effect of RAI.

Objective: Our objective was to compare the mortality of hyperthyroid patients treated with RAI with that of an age- and gender-matched reference population.

Design: We conducted a population-based cohort study.

Participants: A total of 2793 patients who received RAI treatment for hyperthyroidism in Tampere University Hospital between 1965 and 2002, and 2793 reference subjects were followed for a median of 9 yr.

Results: Record linkage with Statistics Finland identified all-cause mortality of 453 vs. 406 per 10,000 person-years in the patients and controls [rate ratio (RR) 1.12; 95% confidence interval 1.03–1.20]. Cerebrovascular diseases accounted for most of the increased mortality among patients (RR 1.40), and mortality from cancer increased (RR 1.29) as well. The risk of death increased in patients older than 60 yr at treatment. Mortality increased with the dose of RAI and was elevated in patients with nodular thyroid disease, but not in those with Graves’ disease. Previous treatment with partial thyroidectomy decreased, whereas antithyroid medication did not affect mortality. In Cox regression analysis, RAI-treated hyperthyroidism (RR 1.56) and age (RR 1.10/1 yr) increased, and the development of hypothyroidism (RR 0.52) reduced mortality significantly.

Conclusions: Hyperthyroidism per se probably accounts for the increased cerebrovascular mortality after RAI treatment. Our results of increased cerebrovascular and cancer mortality emphasize the need for long-term vigilance concerning patients treated with RAI.

Radioiodine ([131I] RAI) is commonly used as first-line therapy for hyperthyroidism (1). It has been used for this purpose since the 1940s, although the long-term safety of RAI, especially in children and young adults, has been questioned (2). Mortality studies of hyperthyroid patients treated with RAI are few in number and based on three different patient cohorts: American (3–6); Swedish (7, 8); and English (9–11).

Hoffman et al. (3) at the Mayo Clinic reported no difference in overall mortality between 1005 women treated with RAI and 2141 women treated with surgery for hyperthyroidism in a continuation of the United States Public Health Service Cooperative Thyrotoxicosis Therapy Follow-up Study 1946–1964. Goldman et al. (4) observed increased standardized mortality rate for deaths from all causes, and from endocrine, circulatory, and respiratory diseases, but not from malignant tumors in 1762 hyperthyroid women treated with RAI (80%), thyroidectomy, or antithyroid drugs at the Massachusetts General Hospital compared with the U.S. women in another continuation of the Cooperative Thyrotoxicosis Therapy Follow-up Study. In the report of the whole original Cooperative Thyrotoxicosis Therapy Follow-up Study, including 35,593 patients, neither hyperthyroidism nor RAI treatment resulted in significantly increased risk of total cancer mortality (6).

In 10,552 Swedish hyperthyroid patients treated with RAI, a significant excess of overall mortality was observed compared with the expected rates. Moreover, the risk of dying of respiratory, cardiovascular, and endocrine diseases, and cancer, especially cancers of digestive and respiratory organs, was elevated (7, 8). In the study of Franklyn et al. (9, 10), the all-cause mortality and mortality due to cardiovascular, cerebrovascular, and thyroid diseases, and hip fracture was increased, but overall cancer mortality was decreased in a cohort of 7209 subjects with hyperthyroidism treated with RAI in the United Kingdom. In the latest study of 3888 hyperthyroid patients treated with RAI, thyroidectomy, or antithyroid drugs, Flynn et al. (12) reported no increase in all-cause, cardiovascular, or cancer mortality but increased risk of arrhythmias compared with the general population of Scotland.

The excess mortality seen in most previous studies may reflect an adverse influence of hyperthyroidism itself, a specific adverse effect of RAI or of subsequent hypothyroidism and its treatment with thyroxine (11). The purpose of the present study was to analyze the total mortality and specific causes of death in a Finnish population treated with RAI for hyperthyroidism, and to study the effect of the etiology of
hyperthyroidism, the dose of RAI, recurrent hyperthyroidism, and the development of hypothyroidism on mortality.

**Subjects and Methods**

Information on the etiology and previous treatment of hyperthyroidism, the dates and doses of RAI treatments, and vital status among 2793 patients (457 men and 2336 women) treated for hyperthyroidism with RAI between January 1965 and June 2002 at Tampere University Hospital were obtained from computerized databases kept in Tampere University Hospital and Finnish Population Register Centre. The follow-up period of the patients started at the end of the year of the first RAI treatment. Choosing an age- and gender-matched control subject for each patient from the Population Register Centre formed a reference group. The control subject had to be alive at the time when the patient received the first RAI treatment. The follow-up period of the control subject started at the same time as that of the corresponding patient. In both patient and control groups, the follow-up ended on the date of death, emigration, or the common closing date (December 2003), whichever was first.

The cause of death data of patients and controls was obtained from the Finnish Cause of Death Register. A computerized record linkage with personal identification number as the key. The dates and causes of death of all Finnish citizens certified by a physician are included in this register since 1971. In the present study, 55 deaths (29 patients and 26 controls) occurred before 1971, when the cause of death was not recorded in the national cause-of-death database. A total of 96 persons (10 patients and 86 controls) died abroad, or their cause of death was otherwise unknown.

In the Finnish Cause of Death Register, the causes of death have been coded according to the eighth revision of the International Classification of Diseases (ICD) between 1971 and 1986, the Finnish version of ICD-9 (Tauttiloukitus 1987) between 1987 and 1995, and the Finnish version of ICD-10 thereafter. A translation between the different versions was made, and the underlying causes of death were classified into nine groups: infectious diseases, malignant tumors, endocrine diseases, cardiovascular diseases, dementia, respiratory diseases, trauma, other causes of death, and unknown cause of death. The classification used in the present study differed from the ICD in a few details. In the ICD, the infectious diseases are classified according to the origin of infectious disease. In our study the causes due to all infections of central nervous, respiratory, genitourinary, and gastrointestinal systems were classified as infectious diseases. Because the diseases of the central nervous system consisted mainly of cerebrovascular diseases, infectious diseases, and dementia in the present study, we used these separate classes instead of the crude overall category of central nervous system diseases as in the ICD. We used the underlying cause of death in classification. In addition the mortality due to atrial fibrillation (AF) was analyzed using also the combined categories (AF and unspecified cardiac arrhythmias) to increase the event numbers. Mortality in patients among both men and women (442 of 10,000 (95% confidence interval (CI), 1.01–1.19). Mortality from cardiovascular diseases was elevated in patients among both men and women. Mortality from endocrine and respiratory diseases increased only among female patients, while mortality from malignant tumors increased only in male patients (data not shown).

Cerebrovascular diseases accounted for the increased risk of death from cardiovascular diseases in the patients compared with the control group (Table 1). The risk of death from endocardial diseases (chronic rheumatic and nonrheumatic valve diseases) and other cardiovascular diseases (conduction disorders of heart, diseases of pulmonary circulation, and unspecified cardiac arrhythmias) was also significantly higher among the patients, but they accounted only for a small fraction of the cardiovascular mortality. AF was equally common as an underlying cause of death among...
patients and controls (Table 1). However, when the contrib-
utory causes of death were included in the analysis, the
patients had increased risk of dying due to AF compared
with the controls (mortality 29.3 vs. 17.5 per 10,000 person-
years in the patients and controls; RR 1.68; 95% CI 1.20–2.34).

A total of 146 (5%) patients and 91 (3%) controls had
diabetes before the beginning of follow-up (P = 0.001). Car-
diovascular disease was diagnosed in 1000 (36%) patients
and 572 (21%) controls before the beginning of follow-up
(P < 0.001). When adjustment for previous diabetes, cardio-
vascular disease, and age was used in the Cox regression
analysis, the risk of cardiovascular death in the patients
compared with controls was not materially affected (unad-
justed RR 1.19; 95% CI 1.07–1.32; adjusted RR 1.15; 95% CI
1.03–1.27). A total of 117 patients (4%) and 112 controls (4%)
had prevalent cerebrovascular disease (P = 0.79). Adjusting
for prevalent cerebrovascular disease, diabetes, and age did
not change the patients’ risk of death from cerebrovascular
disease (unadjusted RR 1.40; 95% CI 1.16–1.69; adjusted RR
1.47; 95% CI 1.22–1.79).

The second most frequent cause of death was malignant
tumors. The increase in mortality from cancer in the patients
was mainly explained by gastroesophageal tumors (Table 1),
of which cancer of esophagus caused death in 7 patients and
2 controls, and that of stomach in 24 patients and 11 controls.
A total of 125 (5%) patients and 93 (3%) controls had cancer
before the beginning of follow-up (P = 0.03). When adjust-
ment for previous cancer, gender, and age was used in the
Cox regression analysis, the risk of cancer death was prac-
tically unaffected (unadjusted RR 1.29; 95% CI 1.07–1.57;
adjusted RR 1.36; 95% CI 1.12–1.65). The excess mortality due
to endocrine diseases in the patients was mainly attributable
to hyperthyroidism. All 15 deaths from thyroid disease oc-
curred between 1971 and 1986, and were caused by toxic
multinodular goiter or adenoma with thyroid crisis men-
tioned in the death certificate. The increased risk of death
from respiratory diseases was due to asthma and obstructive
pulmonary disease. The mortality from unknown causes was
significantly lower in the patients than in the control group.
When the mortality analysis was repeated with the assump-
tion that deaths from unknown causes were distributed sim-
ilarly as the known causes of death (i.e. similar proportion
from each cause in both known and unknown deaths), the
results remained unchanged (data not shown).

Of the patients, 57% had Graves’ disease and 43% nodular
thyroid disease (toxic multinodular goiter or toxic adenoma).
The overall mortality was elevated in the patients with nod-
ular thyroid disease, but not in those with Graves’ disease,
when compared with the corresponding controls (Table 2).
The mean total dose of RAI administered was 305 MBq
(minimum 55, maximum 2664 MBq). A total of 2243 patients
(80.3%) received a single dose of RAI, 435 (15.6%) were given
two doses, 76 (2.7%) three doses, and 39 (1.7%) four or more
doses. When the patients were divided into three groups
according to the cumulative dose of RAI and compared with
the corresponding control group, the overall risk of death
increased with the cumulative dose of RAI (Table 2). The risk
of dying in patients whose hyperthyroidism recurred after
the initial treatment with RAI was at the same level as in
those whose hyperthyroidism was cured with a single dose
of RAI. In patients who were known to develop hypothy-
roidism during the follow-up, mortality was lower than in

FIG. 1. Numbers and follow-up times of the RAI-treated
patients and the age- and gender-specific control group ac-
cording to different end points.
were repeated excluding these patients (data not shown). This study. The results did not change when the analyses regarding these patients were not complete in Hospital district, and the data on the development of hypothyroidism less than 1 yr after RAI treatment in the Tampere University Hospital district, and the data on the development of hypothyroidism. It is not possible to distinguish between the effects of treatment and those of the disease, unless an untreated patient group is used as a reference. Both patient and disease characteristics affect the choice of treatment and may induce confounding by indication. Young patients, women of child-bearing age, and patients with Graves’ ophthalmopathy are less likely to receive RAI in our hospital district. Unfortunately, we did not have the mortality data of patients treated with thyroidec- tomy and long-term antithyroid drug therapy for hyperthyroidism. However, the proportion of these patients is less than 10% of all hyperthyroid patients. Therefore, it is unlikely that selection of patients to RAI treatment would have induced confounding.

Consistent with the results of previous studies (4, 5, 8, 9, 11), the risk of death from cardiovascular diseases was higher.

**Discussion**

Our finding of a higher overall mortality in patients treated with RAI for hyperthyroidism compared with age- and sex-matched controls is consistent with previous studies (4, 5, 8, 9, 11). The strengths of the present study are the completeness of follow-up through high-quality registers, and the detailed data on the amount of RAI administered, etiology of hyperthyroidism, and development of hypothyroidism. It is not possible to distinguish between the effects of treatment and those of the disease, unless an untreated patient group is used as a reference. Both patient and disease characteristics affect the choice of treatment and may induce confounding by indication. Young patients, women of child-bearing age, and patients with Graves’ ophthalmopathy are less likely to receive RAI in our hospital district. Unfortunately, we did not have the mortality data of patients treated with thyroidec- tomy and long-term antithyroid drug therapy for hyperthyroidism. However, the proportion of these patients is less than 10% of all hyperthyroid patients. Therefore, it is unlikely that selection of patients to RAI treatment would have induced confounding.

Consistent with the results of previous studies (4, 5, 8, 9, 11), the risk of death from cardiovascular diseases was higher.

### TABLE 1. Observed number of deaths and mortality (deaths/10,000 person-years) from underlying causes of death in the RAI-treated patients and population-based control group

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Patients</th>
<th>Controls</th>
<th>Patients vs. controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Mortality</td>
<td>No.</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>95</td>
<td>31.0</td>
<td>96</td>
</tr>
<tr>
<td>Malignant tumors</td>
<td>232</td>
<td>75.6</td>
<td>187</td>
</tr>
<tr>
<td>Gastroesophageal tumors</td>
<td>31</td>
<td>10.1</td>
<td>13</td>
</tr>
<tr>
<td>Intestinal tumors</td>
<td>30</td>
<td>9.8</td>
<td>25</td>
</tr>
<tr>
<td>Tumors of liver and pancreas</td>
<td>33</td>
<td>10.8</td>
<td>33</td>
</tr>
<tr>
<td>Respiratory tumors</td>
<td>20</td>
<td>6.5</td>
<td>25</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>20</td>
<td>6.5</td>
<td>22</td>
</tr>
<tr>
<td>Genitourinary tract tumors</td>
<td>49</td>
<td>16.0</td>
<td>38</td>
</tr>
<tr>
<td>Thyroid tumors</td>
<td>1</td>
<td>0.3</td>
<td>0</td>
</tr>
<tr>
<td>Hematological malignancies</td>
<td>25</td>
<td>8.1</td>
<td>17</td>
</tr>
<tr>
<td>Unspecified malignant tumors</td>
<td>23</td>
<td>7.5</td>
<td>14</td>
</tr>
<tr>
<td>Endocrine diseases</td>
<td>33</td>
<td>10.8</td>
<td>15</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17</td>
<td>5.5</td>
<td>13</td>
</tr>
<tr>
<td>Thyroid diseases</td>
<td>14</td>
<td>4.6</td>
<td>1</td>
</tr>
<tr>
<td>Other endocrine diseases</td>
<td>2</td>
<td>0.7</td>
<td>1</td>
</tr>
<tr>
<td>Dementia</td>
<td>48</td>
<td>15.7</td>
<td>56</td>
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<tr>
<td>Cardiovascular diseases</td>
<td>794</td>
<td>258.9</td>
<td>697</td>
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<tr>
<td>Hypertensive diseases</td>
<td>25</td>
<td>8.2</td>
<td>18</td>
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<tr>
<td>Ischemic heart disease</td>
<td>352</td>
<td>114.8</td>
<td>380</td>
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<tr>
<td>Atrial fibrillation</td>
<td>12</td>
<td>3.9</td>
<td>11</td>
</tr>
<tr>
<td>Heart failure</td>
<td>60</td>
<td>19.6</td>
<td>46</td>
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<tr>
<td>Cerebrovascular diseases</td>
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<td>184</td>
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<tr>
<td>Endocardial diseases</td>
<td>26</td>
<td>8.5</td>
<td>14</td>
</tr>
<tr>
<td>Diseases of arteries and veins</td>
<td>36</td>
<td>11.7</td>
<td>26</td>
</tr>
<tr>
<td>Other cardiovascular diseases</td>
<td>36</td>
<td>11.7</td>
<td>18</td>
</tr>
<tr>
<td>Respiratory diseases</td>
<td>32</td>
<td>10.4</td>
<td>15</td>
</tr>
<tr>
<td>Trauma</td>
<td>35</td>
<td>11.4</td>
<td>49</td>
</tr>
<tr>
<td>Other diseases</td>
<td>82</td>
<td>26.7</td>
<td>72</td>
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<tr>
<td>Unknown cause of death</td>
<td>39</td>
<td>12.7</td>
<td>112</td>
</tr>
<tr>
<td>Total</td>
<td>1,390</td>
<td>453.2</td>
<td>1,299</td>
</tr>
<tr>
<td>Person-years at risk</td>
<td>30,669</td>
<td></td>
<td>31,972</td>
</tr>
</tbody>
</table>

Each subject has only one underlying cause of death shown in nine main groups. Furthermore, deaths from cardiovascular and endocrine diseases, and malignant tumors are presented according to specific subgroups.

* Statistically significant difference between patients and controls.

b Toxic multinodular goiter or adenoma with mention of thyroid storm or crisis in death certificate.

c Chronic rheumatic and nonrheumatic valve diseases.

d Conduction disorders, diseases of pulmonary circulation, and unspecified cardiac arrhythmias.

the corresponding controls. The risk of death was lower in patients previously treated with partial thyroidectomy than in the nonoperated ones. The antithyroid medication before RAI treatment did not affect the risk of death. The risk of overall and cardiovascular mortality in the RAI-treated patients compared with the controls increased significantly only in the subjects older than 60 yr at treatment (Table 2), while the risk of cancer death increased in the 50–59 (RR 1.49; 95% CI 1.21–2.31) and 70- to 98-yr-old patients (RR 1.21; 95% CI 1.00–2.26).

To evaluate the significance of different clinical factors in predicting the risk of death, the clinical characteristics presented in Table 2 were used as covariates in Cox regression analysis. The RAI-treated hyperthyroidism (RR 1.56; 95% CI 1.31–1.86) and age (RR 1.10; 95% CI 1.10–1.11 /1 yr) increased the risk of death, while the development of hypothyroidism decreased (RR 0.52; 95% CI 0.45–0.60) the risk. The same factors predicted cardiovascular and cancer mortality (data not shown). There were 752 patients who were followed for less than 1 yr after RAI treatment in the Tampere University Hospital district, and the data on the development of hypothyroidism regarding these patients were not complete in this study. The results did not change when the analyses were repeated excluding these patients (data not shown).
among the patients treated with RAI than among controls in the present study. Instead of RAI treatment, the hyperthyroidism is probably the major explanation for the elevated cardiovascular mortality. The prevalent cardiovascular disease did not explain the results. Previously, only Franklyn et al. (9) have specified the cardiovascular diseases. In their study, cerebrovascular diseases and ischemic heart disease explained most of the increased cardiovascular mortality. In our study cerebrovascular diseases accounted for the increased risk of death from cardiovascular diseases among the patients, but ischemic heart disease did not cause any excess deaths. Hyperthyroidism is known to exert direct effects on the myocardium and the autonomic nervous system, thus predisposing the patient to arrhythmia, especially AF (14–16). Hyperthyroidism may cause cerebral infarction by embolic events. There is some evidence that the rate of embolism in thyrotoxicotic AF exceeds that of nonthyrotoxicotic AF (14, 15). Recently, Flynn et al. (12) reported an increased risk of arrhythmia an average of 5 yr after treatment of hyperthyroidism, suggesting that cardiotoxic effects of hyperthyroidism are not fully reversed by restoring euthyroidism. In the present study, AF was observed more frequently as a contributory cause of death in the hyperthyroid patients than in the controls, although it only accounted for a part of the difference in cardiovascular mortality between the patients and controls. Several assessments of both specific causes and all causes of death have consistently indicated high completeness and reliability of the Finnish causes of death register (17–20). However, we cannot fully exclude confounding due to other risk factors, although the prevalent diabetes did not explain the difference in cerebrovascular mortality, and there was no difference in mortality from ischemic heart disease between the patients and controls.

Results on cancer mortality on hyperthyroid patients treated with RAI have been conflicting, reporting either increased (5, 7), decreased (10), or similar (4, 6) mortality compared with the general population. In two recent studies, Franklyn et al. (10) reported decreased cancer mortality, whereas Hall et al. (7) found an increased risk of death from cancer in patients treated with RAI compared with the expected rates. Our results are consistent with the latter one. The total dose of RAI did not differ substantially between the present study and that of Franklyn et al. (10). The patients were slightly older in the present study than in the study of Franklyn et al. (10). The conflicting results concerning cancer mortality after RAI treatment for hyperthyroidism in different populations might reflect chance, confounding, or differences in sensitivity to radiation-induced cancer depending on the age at exposure, smoking, diet, and baseline cancer rates.

Our results support those of Hall et al. (7), who concluded that RAI might have contributed to the excess stomach cancer mortality seen in their cohort of RAI-treated hyperthyroid patients. When treating hyperthyroidism with RAI, doses of radiation to nonthyroidal tissues are relatively low, i.e. less than 10 cGy, except for the organs that accumulate iodine, including the stomach (25 cGy) (21, 22). Consequently, the stomach might be particularly vulnerable to radiation-induced cancer (22). Although based on a small number of cases, an elevated risk of digestive tract cancer has been reported in the patients treated with RAI for hyperthyroidism (10, 21, 23). The latency period for solid tumors has been observed to be at least 10 yr after radiation exposure (24).

Thus, it is possible that the follow-up in the present study was not long enough to detect an increased mortality from cancers with better survival or longer latency than gastroesophageal tumors. The apparent converging of both the overall and cancer survival curves of the patients and controls seen after 25 yr of follow-up does not necessarily reflect a true disappearance of the excess risk, but a random error, due to the small number of subjects being followed up at 25 yr (214 patients and 229 controls).

The significantly elevated mortality from respiratory diseases in our study was in agreement with previous studies from the United States and United Kingdom (4, 8). Increased mortality from respiratory diseases has been presumed to result mainly from respiratory infections due to the immunosuppressive effect of antithyroid medication and the hyperthyroid state. Respiratory infections were classified as infectious disease in the present study, and respiratory diseases included only asthma and chronic obstructive pulmonary disease. However, susceptibility to infections might have contributed to the exacerbation of pulmonary diseases. Furthermore, hyperthyroidism might have increased the risk of death from pulmonary diseases by increasing the consumption of oxygen (16). Unfortunately, data on smoking habits were not available for our patients.

Hypothyroidism has been suggested to contribute to the elevated risk of death by causing hypercholesterolemia, diastolic hypertension, and left ventricular dysfunction (25). Most previous studies lack the follow-up data on the development of hypothyroidism. In the present study, levothyroxine-treated hypothyroidism after RAI treatment seemed to protect against death instead of predisposing to it, which is consistent with the previous 5-yr follow-up study of Franklyn et al. (11). This might reflect the effective cure of hyperthyroidism and encourages the use of RAI doses high

Fig. 2. Kaplan-Meier survival curves of the hyperthyroid patients treated with RAI and the controls (P < 0.001, log-rank test).
enough, despite the risk of hypothyroidism. Furthermore, the patients developing hypothyroidism after RAI may be more properly examined and treated for other diseases because the permanent levothyroxine treatment requires regular medical follow-up. It is also possible that the younger and healthier live long enough after RAI to develop hypothyroidism, and the development of hypothyroidism is an inevitable consequence of RAI treatment unless one dies before developing it.

Conclusions

The present study of patients treated with RAI for hyperthyroidism reports an increased cerebrovascular mortality in the patients treated with RAI compared with an age- and sex-matched control group, which is probably explained by the hypothyroidism. Furthermore, cancer mortality increased among the patients. Our results emphasize the need for effective treatment of hyperthyroidism despite the risk of hypothyroidism. Lifelong follow-up with careful screening of cerebrovascular risk factors and malignant diseases is recommended for patients treated with RAI for hyperthyroidism.

Acknowledgments

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Address all correspondence and requests for reprints to: Saara Metso, M.D., Department of Internal Medicine, Tampere University Hospital, P.O. Box 2000, FIN-33521 Tampere, Finland. E-mail: saara.metsos@pshp.fi.
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Disclosure Statement: The authors have nothing to disclose.

References


TABLE 2. Observed number of deaths and mortality from all causes (deaths/10,000 person-years) in different subgroups of hyperthyroid patients treated with RAI and in the age- and sex-matched population-based control group

<table>
<thead>
<tr>
<th>Etiology of hyperthyroidism</th>
<th>Patients</th>
<th>Controls</th>
<th>Patients vs. controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>Mortality</td>
<td>No.</td>
<td>Mortality</td>
</tr>
<tr>
<td>----------------------------</td>
<td>----------</td>
<td>----------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Graves’ disease, 57% (n = 1604)</td>
<td>488</td>
<td>287.1</td>
<td>461</td>
</tr>
<tr>
<td>Toxic multinodular goitre or adenoma, 43% (n = 1189)</td>
<td>902</td>
<td>659.9</td>
<td>838</td>
</tr>
<tr>
<td>Total dose of RAI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55–258 MBq, 39% (n = 1082)</td>
<td>596</td>
<td>414.0</td>
<td>582</td>
</tr>
<tr>
<td>259–369 MBq, 37% (n = 1032)</td>
<td>389</td>
<td>430.1</td>
<td>355</td>
</tr>
<tr>
<td>370–2664 MBq, 24% (n = 679)</td>
<td>405</td>
<td>560.0</td>
<td>362</td>
</tr>
<tr>
<td>Recurrence after the first dose of RAI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, 20% (n = 571)</td>
<td>299</td>
<td>433.9</td>
<td>274</td>
</tr>
<tr>
<td>No, 80% (n = 2222)</td>
<td>1091</td>
<td>458.1</td>
<td>1025</td>
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<tr>
<td>Development of hypothyroidism</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Yes, 30% (n = 831)</td>
<td>253</td>
<td>191.0</td>
<td>267</td>
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<tr>
<td>No, 70% (n = 1962)</td>
<td>1137</td>
<td>652.6</td>
<td>1032</td>
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<tr>
<td>Previous partial thyroidectomy</td>
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<tr>
<td>Yes, 12% (n = 303)</td>
<td>145</td>
<td>322.6</td>
<td>144</td>
</tr>
<tr>
<td>No, 88% (n = 2179)</td>
<td>1112</td>
<td>475.6</td>
<td>1033</td>
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<tr>
<td>Antithyroid drug</td>
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<tr>
<td>Yes, 88% (n = 2362)</td>
<td>1114</td>
<td>437.1</td>
<td>1039</td>
</tr>
<tr>
<td>No, 12% (n = 313)</td>
<td>207</td>
<td>551.0</td>
<td>196</td>
</tr>
<tr>
<td>Age at first treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13–49 yr, 25% (n = 694)</td>
<td>47</td>
<td>51.6</td>
<td>55</td>
</tr>
<tr>
<td>50–59 yr, 18% (n = 506)</td>
<td>194</td>
<td>260.0</td>
<td>180</td>
</tr>
<tr>
<td>60–69 yr, 26% (n = 731)</td>
<td>476</td>
<td>567.2</td>
<td>429</td>
</tr>
<tr>
<td>70–98 yr, 31% (n = 862)</td>
<td>673</td>
<td>1178.9</td>
<td>635</td>
</tr>
<tr>
<td>All (n = 2793)</td>
<td>1390</td>
<td>453.2</td>
<td>1299</td>
</tr>
</tbody>
</table>

* Statistically significant difference between patients and controls.


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Täytetään radiojodihoidoita varten ja lähetetään osoitteeseen TIO/Irene Jussila.

**Henkilötiedot**
Henkilö- ja osoitetiedot sekä kotikunta täytetään tai tarkistetaan aina.

- **Henkilötunnus**
- **Suku- ja etunimet**
- **Lähiosoite**
- **Postinumero**
- **Postitoimipaikka**
- **Kotikunta**
- **Täyttöpäivä**

**Edeltävä hoito**

<table>
<thead>
<tr>
<th>Edeltävä hoito</th>
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<tbody>
<tr>
<td>ei hoitoa = 0, tyreostaatti = 1, β-salpaaja = 2, 1+2 = 3, 1+T4 = 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoidon kesto ennen RJ-hoidoa</td>
<td>0-3 kk = 0, 3-6 kk = 1, 6-12 kk = 2, 1-2 v = 3, yli 2 v = 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Struuman laatu, palpaatio</td>
<td>diff.suurent. = 1, monikyhm. = 2, yksi kyhmy = 3, ei palp.struuma = 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leikkauksen jälkeinen hypertyreoosi</td>
<td>on = 0, ei = 1</td>
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<td></td>
</tr>
<tr>
<td>Silmäoireet</td>
<td>ei = 0, kyllä = 1, vaikea = 2</td>
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**Radiojodihoidotiedot**

<table>
<thead>
<tr>
<th>Isotooppilaboratorio täyttää</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoidon ajankohta</td>
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<tr>
<td>24 h uptake</td>
</tr>
<tr>
<td>131</td>
</tr>
<tr>
<td>Gammakuvan tieto</td>
</tr>
</tbody>
</table>

Lomakkeen käyttö
Lomake on tarkoitettu ilmoitukseksi seurantarekisterille aina, kun kilpirauhaspotilaalle pyydetään radiojodihoidon. Lomaketta ei täytetä, jos potilaalla on todettu kilpirauhasen syöpäriski.

Potilaan henkilö- ja osoitetiedot sekä kotikunta on **aina** täytettävä tai tarkistettava, koska rekisteri toimii näiden tietojen pohjalta.

Kuka täyttää

- **Radiojodihoidon lähetettävä lääkäri** täyttää kohdan "Henkilötiedot" ja kohdan "Edeltävä hoito".
- **Radiojodihoidon antaja** täyttää "Henkilötiedot", jos ne puuttuvat ja kohdan "Radiojodihoidotiedot".

TAYS nro L1032a 9.05

Ei liitetä potilaskertomukseen Lähetetään osoitteeseen TIO/Irene Jussila.
Olkaa hyvä ja vastatkaa kaikkiin alla oleviin kysymyksiin.
Vastatkaa tekemällä ympyrä kysymyksen kohdalla olevaan joko 'kyllä' tai 'ei' -sarakkeeseen, esim. 1 0 , kullakin kysymyksellä tarkoitetaan vastaushetkellä esiintyviä oireita ja mahdollisia muutoksia viime vuoden kuluessa.

Nimi ja henkilötunnus

<table>
<thead>
<tr>
<th>Kysymys</th>
<th>Kyttä</th>
<th>Ei</th>
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<tr>
<td>2. Esiintyykö Teillä tuntohärköitä?</td>
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<td>1</td>
</tr>
<tr>
<td>3. Oletteko lahtunut viime aikoina?</td>
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<td>1</td>
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<tr>
<td>4. Esiintyykö Teillä rasitushengenahdistusta?</td>
<td>1</td>
<td>0</td>
</tr>
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<td>5. Onko ajatustoimintanne mielestänne hidastunut?</td>
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<td>1</td>
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<tr>
<td>6. Onko äänenne muuttunut käheämäksi?</td>
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<td>1</td>
</tr>
<tr>
<td>7. Onko ruokahalunne vähentynyt?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>8. Paleletteko herkästi?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>9. Hikoletteko herkästi?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>10. Kärsittekö ummetuksesta?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>11. Viihdyttekö lämpimässä?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>12. Viihdyttekö vileässä? (ellei eroa, ei tarvitse vastata kohtiin 11 ja 12)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>13. Onko Teillä kuiva iho?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>14. Onko kuulonne huonontunut?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>15. Esiintyykö Teillä herkästi sydämen tykytystä?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>16. Onko ruokahalunne lisääntynyt?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>17. Ovatko hiuksenne muuttuneet kuivaksi?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>18. Onko painonne ollut nousussa?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>19. Hikoletteko vähemmän kuin aikaisemmin?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>20. Hermostutteko helposti?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>21. Oletteko kilpirauhassairauden tai jonkin muun sairauden vuoksi säännöllisessä lääkärin hoidossa?</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
Olkaa hyvä ja vastatkaa kaikkiin alla oleviin kysymyksiin.
Vastatkaa tekemällä ympyrä kysymyksen kohdalla olevaan joko 'kyllä' tai 'ei' -sarakeeseen, esim.  1  0 , kylläkin kysymyksellä tarkoitetaan vastaushetkellä esiintyviä oireita ja mahdollisia muutoksia viime vuoden kuluessa.

Nimi ja henkilötunnus

<table>
<thead>
<tr>
<th>Kysymys</th>
<th>Kyllä</th>
<th>Ei</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Tunnetteko voivanne yhtä hyvin kuin aikaisemmin (vuosi sitten)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2. Palelettekko nykyään herkästi?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>3. Onko Teillä herkästi kuuma tai hiki?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>4. Onko ruokahalunne huonontunut?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>5. Oletteko huomannut sormienne vapisevan?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>6. Väsyttökö tavallista enemmän?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>7. Onko painonne ollut nousussa?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>8. Esiintyykö Teillä sydämen tykkytystä?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>9. Tunnetteko itsenne jollain tavoin yleisesti hermostuneemmaksi?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>10. On oletteko itse tai joku muu huomannut, että äänenne on tullut kääheämäksi tai heikommaksi?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>11. Onko käsivarsienne tai jalkojenne iho tullut kuivemmaksi tai karkeammaksi?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>12. Ovatko huiskenesen tulleet karheksi tai lähtevätkö ne epätavallisen runsaasti?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>13. Jos struumanne on leikattu, oletteko itse tai joku muu huomannut, että kaulallenne olisi kasvanut uusi struuma tai kymhy? (ellei leikattu, ei tarvitse vastata)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>14. Jos Teille on määrätty kilpirauhasen toimintaan vaikuttavaa lääkettä, oletteko käyttänyt sitä säännöllisesti? (ellei määrätty, ei tarvitse vastata)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>15. Teille määrätty lääkehoito; montako tablettia vuorokaudessa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Thyroxin 25 mikrog</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Metimazol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Tyrazol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Propylthiouracil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16. Mistä lähtien (kk ja vuosi)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


KOHTA 15

Täyttöohje (esimerkki)

Jos Teille on määrätty Tyrazolia 1 tablette 4:stä vuorokaudessa, merkitään se asianomaiselle riville seuraavasti:

Mikäli tähän kohtaan vastaaminen tuntuu hankalalta, voitte vastata myös kirjoittamalla, mitä lääkemääräyksessä lukee.

TAYS nro L1032c 6.03

EI liitetä potilaskertomukseen

Lähetetään osoitteeseen TIO/Irene Jussila.
Täytetään potilaan siirtyessä avohoitoon ja lähetetään osoitteeseen TIO/Irene Jussila.

### Henkilötiedot

<table>
<thead>
<tr>
<th>Henkilötunnus</th>
<th>Suku- ja etunimet</th>
</tr>
</thead>
</table>

### Lähiosoite

<table>
<thead>
<tr>
<th>Postinumero</th>
<th>Postitoimipaikka</th>
<th>Kotikunta</th>
<th>Täyttöpäivä</th>
</tr>
</thead>
</table>

### Nykytilanne

<table>
<thead>
<tr>
<th>Nykyinen lääkehoito</th>
<th>ei hoitoa = 0, tyrosiini = 1, tyreostaatti = 2, 1+2 = 3, muu = 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tyroksiinin annos μg / vrk</td>
<td></td>
</tr>
<tr>
<td>Hypotyreoosi todettu</td>
<td>kuukausi ja vuosi</td>
</tr>
<tr>
<td>ST₃</td>
<td></td>
</tr>
<tr>
<td>ST₄V</td>
<td></td>
</tr>
<tr>
<td>S-TSH</td>
<td></td>
</tr>
<tr>
<td>S-TyglAb</td>
<td>1 :</td>
</tr>
<tr>
<td>S-TymsAb</td>
<td>1 :</td>
</tr>
<tr>
<td>S-TPOAb</td>
<td>1 :</td>
</tr>
<tr>
<td>Hormonitasapaino laboratoriokokeiden perusteella</td>
<td></td>
</tr>
<tr>
<td>eutyreoottinen = 0, hypotyreoottinen = 1, hypertyreoottinen = 2, epävarma = 3</td>
<td></td>
</tr>
<tr>
<td>Määrätty jatkohoito</td>
<td>ei = 0, tyrosiini = 1, tyreostaatti = 2, uusi RJ-hoito = 3, muu = 4</td>
</tr>
<tr>
<td>Seuraava jälkitarkastus seurantarekisterin toimesta</td>
<td></td>
</tr>
<tr>
<td>ei = 0, 1v = 1, 2v = 2, 3v = 3</td>
<td></td>
</tr>
</tbody>
</table>

### Lääkärin sv-numero

<table>
<thead>
<tr>
<th>Ei liitetä potilaskertomukseen</th>
<th>Lähetetään osoitteeseen TIO/Irene Jussila.</th>
</tr>
</thead>
</table>