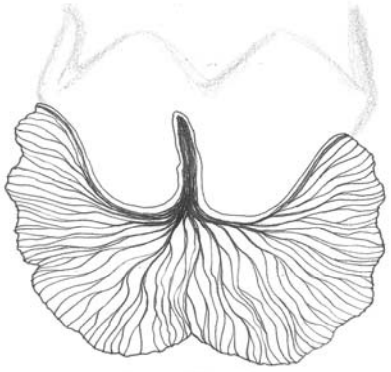
INCIDENCE AND PROGNOSIS OF DIFFERENTIATED THYROID CANCER IN SWEDEN

Catharina Ihre Lundgren



Stockholm 2006

From the Department of Medical Epidemiology and Biostatistics
and Department for Clinical Science, Intervention and Technology,
Division of Surgery, Karolinska University Hospital,
Karolinska Institutet

INCIDENCE AND PROGNOSIS OF DIFFERENTIATED THYROID CANCER IN SWEDEN

Catharina Ihre Lundgren

Stockholm 2006

Front page:
After the atomic bombing in Hiroshima, a single tree, the Gingko Bilabo, amazingly survived. The Gingko-leaf (at the front page) resembles the thyroid gland and it represents all patients with differentiated thyroid cancer, whom just like the Gingko Bilabo miraculously survived the atomic bombing. Today Gingko Bilabo is frequently used in herbal teas and in herbal medicine, one of its effects is to improve the blood flow especially to the brain.

Drawing by: Thomasine Giesecke

Printed by Universitetsservice US-AB

ISBN 91-7140-577-1

To my family

ABSTRACT

Non-medullary differentiated thyroid cancer (DTC) is a rare disorder but, nevertheless, among the most common cancers in individuals below 40 years of age. DTC consists of papillary (PTC) and follicular (FTC) thyroid cancer. The prognosis is excellent with an overall 10-year survival of 90 %. The only established risk factor for DTC is ionizing radiation. Different scoring systems are used for prognostication of DTC. Thyroidectomy is the primary treatment for patients with DTC. How the extent of surgery and postoperative treatment, mainly radioactive iodine treatment, influences the prognosis of DTC remains controversial. The aim of this study was to analyse the incidence and survival of patients with DTC in Sweden and to identify factors of prognostic importance.

From the population-based Swedish Cancer Registry we identified 5,554 individuals diagnosed with DTC during 1958-1987. The patients were followed until 31 December 1999. The relative survival ratio was used as the measure of patient survival. Within this cohort, a nested case-control study was conducted. One control, matched by age at diagnosis, sex and calendar period, was randomly selected for each case, *i.e.,* patients who died due to DTC. Information of possible prognostic factors was abstracted from the medical records. The effect of prognostic factors on DTC mortality was evaluated using conditional logistic regression.

Incidence of both PTC and FTC was higher among women than men, especially for PTC and particularly during the fertile part of life. Ten year relative survival was 99 % for patients under 40 years of age at diagnosis. Among possible risk factors for DTC, only smoking had a significantly negative influence on survival for patients with DTC. Previous radiotherapy towards the neck region had no prognostic implication. A family history of DTC influenced prognosis, although not significant due to few numbers. Patients with widely invasive FTC experienced a significantly higher mortality compared with PTC patients. Grade of differentiation significantly influenced mortality. Patients in TNM stage IV had a nine times higher mortality compared with patients in stage II. Patients with lymph node metastases experienced twice as high mortality and patients with distant metastasis a 7-fold higher risk of death compared with those with no metastases. Non-surgically treated patients had a worsened prognosis. Incomplete surgical excision was associated with higher mortality, particularly among patients in stage I. In contrast to completeness of tumour excision, surgical extent did not influence the risk of dying from DTC, neither was lymph node surgery associated with prognosis. For patients with loco-regional recurrence the risk of death was five-folded. The administration of postoperative treatment (radioactive iodine, external radiotherapy, or chemotherapy) was not associated with better survival.

The data suggest that there may exist a class of thyroid tumours that are diagnosed in women during the fertile part of life and associated with a superior prognosis. Among possible risk factors for DTC, the risk of death due to DTC was increased only for smoking patients. Clinically important prognostic factors for patients with DTC were histopathological subgroup, TNM staging including lymph node metastases and distant metastases, as well as completeness of the surgical excision, although the extent of surgery did not influence the patients' survival. Loco-regional recurrence increased the mortality significantly. Postoperative treatments were not associated with better survival.

Keywords: Differentiated thyroid cancer, papillary, follicular, nested case-control study, population-based, risk factors, prognosis, survival, TNM.

ISBN 91-7140-577-1

LIST OF ORIGINAL PAPERS

This thesis is based on the following papers, which will be referred to by their Roman numerals.

I. Lundgren CI, Hall P, Ekbom A, Frisell J, Zedenius J, Dickman PW.
Incidence and survival of Swedish patients with differentiated thyroid cancer.
Int. J. Cancer 2003;106: 569-573

II. Lundgren CI, Dickman PW, Zedenius J, Hall P.
Are possible risk factors for differentiated thyroid cancer of prognostic importance?
Submitted to Int. J. Cancer

III. Lundgren CI, Hall P, Dickman PW, Zedenius J,
Clinically important prognostic factors for differentiated thyroid cancer. A population-based nested case-control study.
Cancer, in press

IV. Lundgren CI, Hall P, Dickman PW, Zedenius J
Influence of surgical and postoperative treatment on survival for patients with differentiated thyroid cancer. A population-based nested case-control study.
Submitted to Br. J. Surg.

CONTENTS

1. INTRODUCTION

The thyroid is a complex and fascinating endocrine gland with multiple functions, including regulation of the calcium homeostasis and the basal metabolism. Thyroid nodules are frequently seen in clinical practise and the majority are benign. In non-iodine deficient areas detectable nodules occur in 4-7 % of the general population (1, 2). Thyroid nodules represent a variety of different thyroid disorders from the non-neoplastic conditions such as goitre or thyroiditis to neoplastic nodules that can be benign (follicular adenoma) or malignant. Sometimes adenomas and goitre are in combination with either hyper- or hypothyroidism. Thyroid carcinomas are rare and comprise a diverse group of malignancies ranging from the indolent papillary micro-carcinoma that hardly implies any threat to survival, to the rare anaplastic carcinoma that is the most vicious carcinoma afflicting humans. Thyroid carcinomas are often found accidentally when investigations for other thyroid disorders are performed. Because of the low incidence of the papillary and follicular thyroid carcinomas, its prolonged survival and relatively low mortality rate, prospective randomised clinical trials have not been possible to conduct. Nonetheless, patients suffer greatly from this disease, as many have recurrences and some die from persistently progressive and untreatable cancer. This is a disease that knows no boundaries, striking both young and old. Although methods to diagnose and treat patients have improved over time, there are still many questions to answer (3).

2. BACKGROUND

2.1. The Thyroid gland

2.1. I. Embryology

During the embryogenesis, the normal thyroid derives from the fusion of a median and a lateral endodermic part. The thyroid follicular cells, originating from epithelial cells, descend from the foramen cecum of the tongue to the anterior neck region and fuse with the neuroendocrine C-cells. Normal thyroid tissue can be found along the thyreoglossal duct forming a third pyramidal lobe. The thyroid accumulates and binds iodine after 11 weeks of gestation (4).

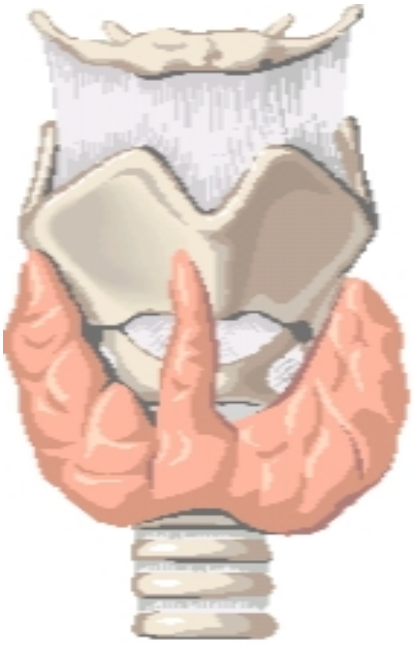


Figure 1. The thyroid gland.

2.1. II. Anatomy

Glandula thyroidea (lat), the thyroid gland, is located in the neck in front of the trachea, between the cricoid cartilage and the suprasternal notch. Macroscopically the thyroid gland is composed of two lobes connected by the isthmus. The blood is supplied mainly by the superior (which is the first branch from the external carotid artery) and inferior thyroidal arteries. The venous return empties into the brachiocephalic vein and through the internal jugular vein. Lymphatic drainage is ipsilateral and each lobe can be regarded as a separate entity, although there are some lymphatic anastomoses between the two lobes throughout the isthmus. The recurrent laryngeal nerve, a motor nerve to the intrinsic muscles of the larynx, traverses the lateral borders of the gland. Injury causes paralysis of the vocal cord on the ipsilateral side. The normal weight of the thyroid is 15-30 gram, depending on body weight and iodine supply. The four parathyroid glands are located in the posterior region of each pole of the thyroid (4).

2.1. III. Function

The functional and structural unit of the thyroid gland is the follicle. This spheric structure is lined with a single layer of epithelial cells and is filled with colloid, which is rich in the thyroid hormonal precursor thyroglobulin. Between the follicular cells are the parafollicular cells, called C-cells because they produce calcitonin, a hormone involved in the calcium homeostasis.

The synthesis of thyroid hormones, triiodothyronine (T3) and thyroxine (T4) is a complex physiologic procedure that takes place in the follicular cells. Iodine is an essential element in the thyroid physiology. It is a critical component in both T3 and T4 molecules and a key regulator of thyroid gland function. It also requires enzymatic activity by thyroxine peroxides. The mature thyroid hormones are secreted in the blood stream where they are important in the control of the basal metabolism. From the pituitary gland the thyroid stimulating hormone (TSH), or thyrotropinin, is secreted and together with thyrotropin releasing hormone (TRH) from the hypothalamus, the activity in thyroid gland is regulated by a feedback system. T3 is the biologically active hormone and T4 is converted to T3, either in the thyroid gland or in peripheral tissue cells (4).

2.2. Thyroid tumours

2.2. I. Benign

The follicular adenoma has a well-defined fibrous capsule that is grossly and microscopically complete. The size of follicular adenomas varies. It is defined as benign in the absence of vascular and capsular invasion. It is not possible to evaluate these parameters by routine fine needle aspiration and cytology (FNAC), why virtually all patients with a follicular adenoma are subjected to surgery for a careful examination of the tumour. Follicular adenomas can be sub-classified and the histological differences are striking but of no clinical importance (4). One of the frequent cytologic variant is the oxyphilic, also called oncocytic or Hürthle cell adenoma, which is composed predominantly of large cells with a granular, eosinophilic cytoplasm. Hürthle cells can be found in a number of benign conditions, including nodular goitre, hyperthyroidism and Hashimoto`s thyroiditis. The frequency of progression from adenoma to a carcinoma is controversial, but probably low (5).

2.2. II. Malignant

Thyroid cancer constitutes 1 % of all malignancies worldwide and is heterogeneous in terms of histology, clinical presentation, treatment response and prognosis. (6). They can be classified into four main groups.

Anaplastic thyroid cancer (ATC) is rare (1-5 % of all thyroid cancers) and is one of the most aggressive cancers encountered in humans. In some of the cases it represents a terminal stage in the dedifferentiation of a follicular or papillary carcinoma (4, 7). The cells in ATC do not produce thyroglobulin and are therefore not able to transport iodine and accordingly TSH

receptors are not found in their plasma membranes. ATC is rare before the age of 50 and the female/male ratio is 1.5:1 (3).

Medullary thyroid cancer (MTC) arises from the parafollicular or C cells of the thyroid and accounts for 5-10 % of all thyroid cancers. MTC can be sporadic or hereditary. The sporadic forms can arise clinically at any age but its incidence peaks during the fifth or sixth decades of life. Hereditary MTC represents 20-30 % of all MTC with an autosomal dominant pattern of transmission and a high penetrance. MTC can arise as part of a multiple endocrine neoplasia (MEN) syndrome type IIA or IIB or as a single entity in familial MTC. Both sexes are equally affected (3).

Follicular thyroid cancer (FTC) often presents as a solitary tumour that is more or less encapsulated. Depending on the degree of invasiveness, FTC is classified as minimally invasive or widely invasive FTC. It is the second most common form of thyroid cancer (10-20%) and the female/male ratio is 2.8:1 (8).

Papillary thyroid cancer (PTC) is the most common form (60-80 %) of thyroid cancer. It can be classified as micro-carcinoma (<1 cm), carcinomas limited to the thyroid gland or extending the thyroid capsule. PTC is often multifocal in one lobe and is bilateral in 20-80 % (range depends on the number of sections of thyroid tissue examined by the pathologist) (9). The female/ male ratio is 3.2:1(8).

Differentiated thyroid cancer includes MTC, PTC and FTC. The following thesis focuses strictly on non-medullary differentiated thyroid cancer (DTC) that consists of FTC and PTC.

2.3. Non-Medullary Differentiated Thyroid Cancer (DTC)

2.3. I. Epidemiology

Incidence

With the exception of Iceland and Hawaii, where thyroid cancer incidence is particularly high, incidence rates (world adjusted) from much of the world range between 1 and 2 cases per 100,000 males and between 2 and 6 cases per 100,000 females. No specific pattern in incidence rates has been discovered in Europe (10). Low rates can occur both in developed and underdeveloped countries as well as in urban or rural areas.

When comparing the incidence in the Nordic countries, the rate for Iceland was five times higher than the rest. Differences were apparent for both sexes, all age-groups, and all histological types, although the variation was widest for PTC (Figure 2, 3) (11). Proposed explanations for this geographic variation include a possible association with endemic goitre, volcanic lava, dietary patterns or differences in reporting cases. In iodine insufficient regions,

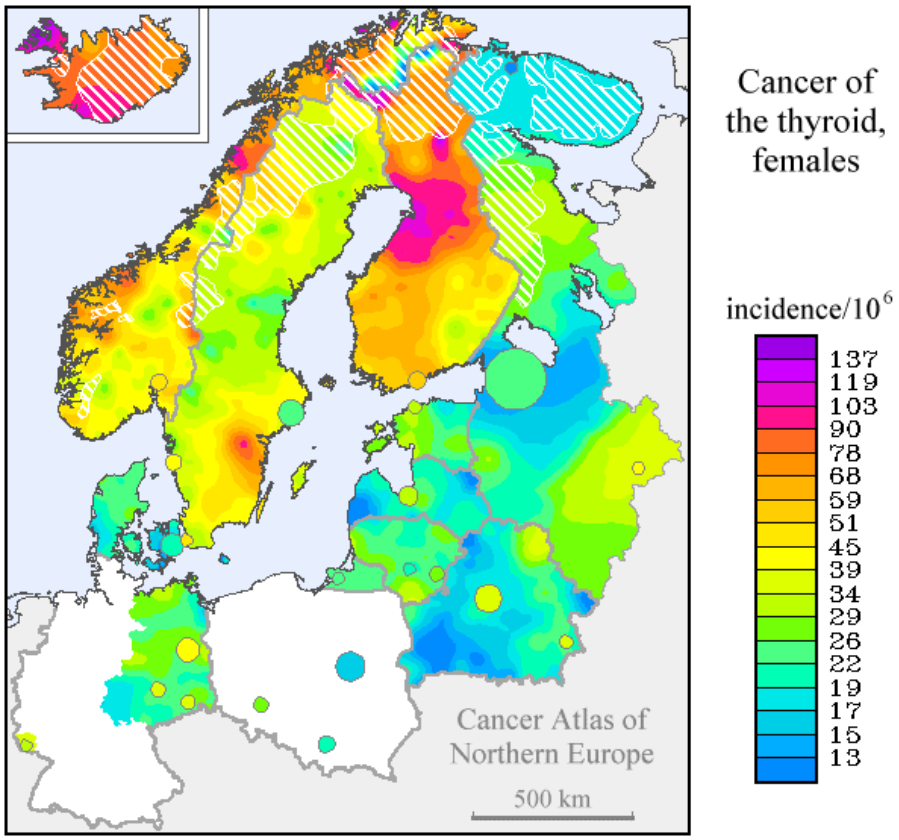


Figure 2. The incidence /1 000 000 inhabitants of thyroid carcinoma among females in northern Europe (12).

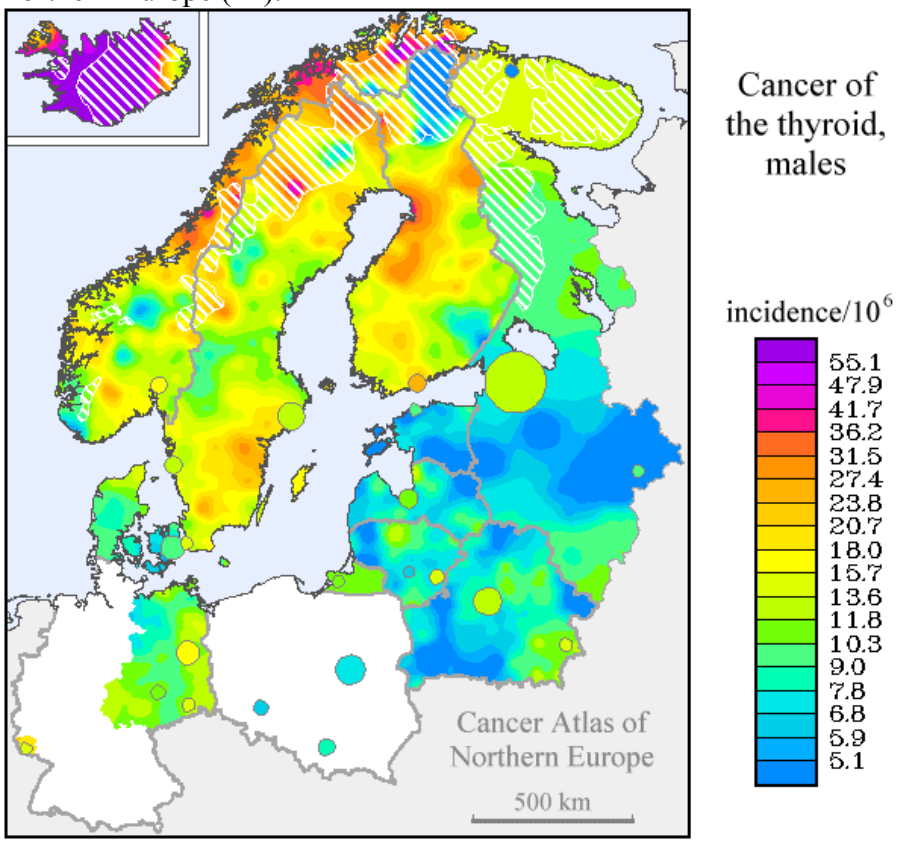


Figure 3.The incidence /1 000 000 inhabitants of thyroid carcinoma among males in northern Europe (12).

FTC is more common than PTC (13). After fall-out of radiation in the Chernobyl area, the incidence of PTC increased 3-75 fold among patients younger than 21 year. Children 5 years old or less at the time of the disaster accounted for the majority of the patients (14, 15).

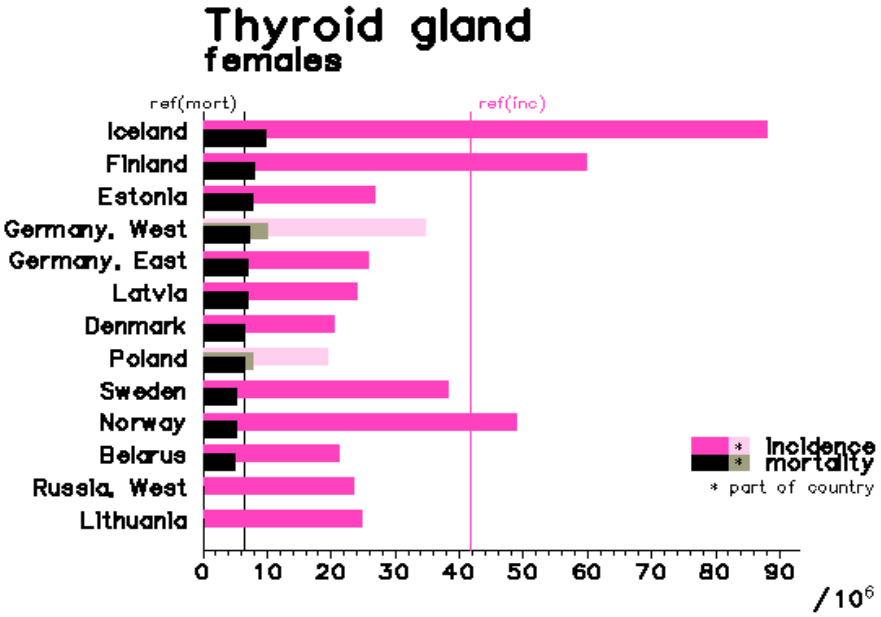


Figure 4. Incidence and mortality from thyroid carcinoma among females in northern Europe (12).

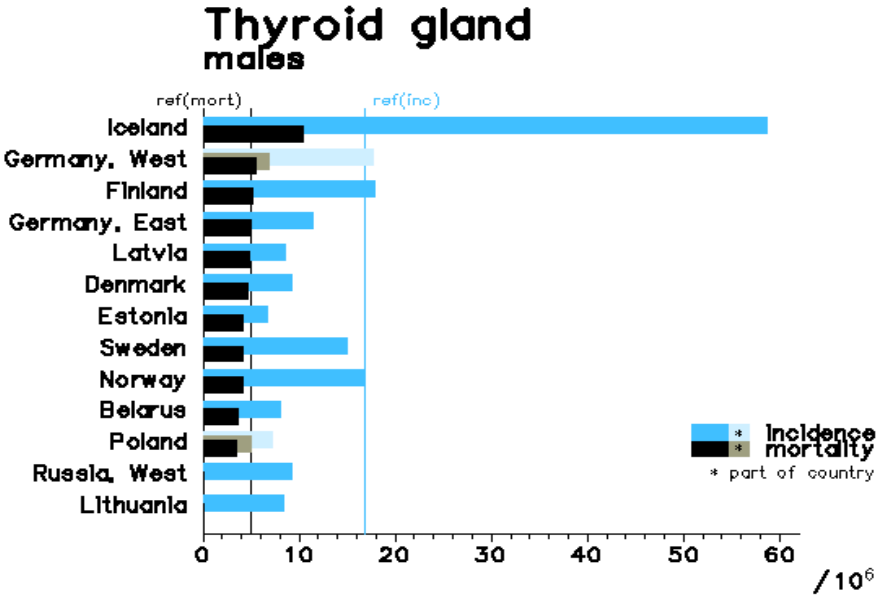


Figure 5. Incidence and mortality from thyroid carcinoma among males in northern Europe (12).

Risk factors

The only established risk factor for thyroid cancer in humans besides age and gender is ionizing radiation (16). Studies of individuals living in the Chernobyl area and of the survivors in Hiroshima and Nagasaki have shown an increased risk of particularly PTC, although so far only among those exposed as children (9). Other suggested risk factors for DTC are pre-existing benign thyroid disease (11), a family history of DTC, sex hormones (17), therapeutic or environmental ionizing radiation, iodine deficiency (18) and dietary factors, but the findings are inconsistent (17, 19-21).

Although the incidence of DTC differs in different countries, the mortality is stable and rates are comparable in most countries in Europe. As can be seen in Figure 4 and 5 there are large variations in incidence, where Island is found to have a 3-9 fold higher incidence than other European countries. In contrast, the fatal thyroid cancers are found to be equally common in the different geographical areas (Figure 4, 5).

Prognosis and scoring systems

Prognosis of DTC is known to be excellent with an overall 10-year-survival exceeding 90 % (8, 22). Comparisons are difficult due to differences in selection of patients and duration of follow-up. Local invasiveness, presence of distant metastases and increasing age at diagnosis convey a worse prognosis (23). The fact that DTC has a comparatively low incidence and generally a good long-term prognosis makes prospective randomised control trials hard to perform. Many studies have identified different prognostic factors from retrospective analyses as an attempt to find the most accurate system for classifications of patients with DTC (24). The most widely accepted system of classifying solid organ malignancies is the postoperative tumour-node-metastasis system (pTNM) which was introduced in 1987 and revised in 1992 and 2002 (25). The TNM system takes age at diagnosis, size and extension of the primary tumour, and the presence or absence of lymph nodes and distant metastases into account. Patients are classified into four risk-groups with varying cancer specific mortality (26) (Table 1).

Table 1. TNM classification for DTC

TNM	< 45 years			≥45 years		
Stage	T	N	M	T	N	M
I	any	any	0	1	0	0
II	any	any	1	2	0	0
IIIa	NA	NA	NA	3	0	0
IIIb	NA	NA	NA	1-3	1	0
IV A	NA	NA	NA	1-3	2-3	0
or				4a	any	0
IV B				4b	any	0
IV C				any	any	1

T = Tumour size
T0 = no palpable tumour
T1 ≤2 cm
T2 >2 ≤4 cm
T3 > 4cm
N = Nodal Status
N0 = no palpable cervical adenopathy
N1 = ipsilateral cervical adenopathy
N2 = contra-lateral or bilateral cervical adenopathy
N3 = fixed cervical nodes
M = Distant metastases
M0 = No distant metastases
M1 = distant metastases
T4a = any size of tumour, extending the thyroid capsule, invading surrounding tissue
T4b = any size of tumour, invading the prevertebral fascia or large vessels
NA = Not applicable

From the Mayo clinic, USA, the AGES scoring system was developed in 1987, taking **A**ge at diagnosis, tumour **G**rade, tumour **E**xtension and **S**ize of the primary tumour into account (27) for patients with PTC. In an attempt to overcome the impediment in the AGES system resulting from the lack of an accepted histologic grading system for PTC, the Mayo Clinic outcome data were reanalyzed, and a new system was designed in 1993, called MACIS, now excluding tumour grade, instead incorporating distant **M**etastases, **A**ge at diagnosis, **C**ompleteness of surgery, **I**nvasion of extra-thyroidal tissue and **S**ize of the primary tumour (28) (Table 2).

Table 2. MACIS classification of PTC

Score = 3.1 (if age < 40 years) or 0.08 x age (if age ≥40 years)
+0.3 x tumour size (cm maximum diameter)
+1 (if incompletely resected)
+1 (if locally invasive)
+3 (if distant spread)

20 year-survival by MACIS score

<6 = 99 %
6-6.99 = 89 %
7-7.99 = 56 %
≥8 = 24 %

In 1988 Cady and Rossi, created another scoring system called AMES (29). It is based on **A**ge at diagnosis, presence of distant **M**etastases, **E**xtent and **S**ize of the primary tumour. Patients were classified into a high- or low-risk group, 89 % of the patients belonged to the low-risk group with a mortality rate of 1.8 % and the remaining high-risk group had a mortality rate of 46 % (for the period 1961-1980). In the past decade DNA ploidy analysis was identified as a prognostic factor in PTC. This was added in 1992, recognized as the DAMES system (30).

Table 3. AMES scoring system for DTC.

High–risk group
All patients with distant metastases
Men > 40 and women > 50 years of age at diagnosis with:
Primary tumour extending beyond the thyroid capsule
or
Tumour size > 5 cm (primary tumour)
Low-risk group
Men ≤ 40 or women ≤ 50 years of age at diagnosis regardless of extent and size of the primary tumour.
Older patients with primary tumours < 5 cm confined to the thyroid.
No distant metastases

In 1966 the E.O.R.T.C Thyroid Cancer Co-operative Group began a registry of data on patients with thyroid cancer. Twenty-three hospitals from various countries in Europe participated and entry ended in 1977 (31). In the survival analysis of the cohort of 507 patients, all types of thyroid cancers were included. Prognostic factors of significant importance were age, sex, cell-type, clinical extent of tumour, lymph node status and number of metastatic sites. Other scoring systems have been evaluated or described (24, 32-34), most of them including tumour size, histologic type, extra-thyroidal invasion and distant metastases. Brierley et al (35) evaluated 382 patients with DTC using all of these scoring systems and found no significant difference between AGES, TNM, EORTC, MACIS and AMES systems, all of which accurately predicted the prognosis of patients with PTC.
An accurate and simple scoring system which could help predict survival and future recurrence risk for patients with DTC at the time of initial treatment, would guide treatment decisions and improve patient care.

2.3. II. Clinical symptoms and histopathological subgroups

Most DTCs present as asymptomatic single thyroid nodule. On physical examination, the nodule is firm, moves freely during swallowing and is usually not distinguishable from a benign nodule. Carcinoma should be suspected if a hard, irregular thyroid nodule is found, if ipsilateral lymph nodes are enlarged or compressive symptoms (on the airways or oesophagus) are present and if there is a history of a progressive increase in the size of the nodule. Almost all patients are clinically euthyroid and have normal serum thyrotropinin concentrations (9).

FNAC normally distinguishes between benign and malignant thyroid nodules, but follicular neoplasms are difficult to discriminate, and are therefore usually surgically removed for histopathological examination (36). Thyroid ultrasonography is useful for assessing the size of the nodule, detecting other nodules and guiding in FNAC when the nodule is small or difficult to palpate (9).

Papillary Thyroid Carcinoma (PTC)

Thyroid nodules are seen commonly in clinical practice. The majority is benign, and virtually all thyroid nodules are investigated by FNAC. Aspiration smear from PTC may reveal papillary structures and the preoperative diagnosis is based on typical nuclear and cellular characteristics. The diagnosis is confirmed by microscopical examination of the surgical specimen. The not otherwise specified PTC (classical pattern) is a mixture of neoplastic papillae and follicles. The gross appearance is a firm, opaque mass, usually poorly defined and with a granular or finely nodular cut surface. Irregular scarring is common and foci of calcification can frequently be found. Cells are larger than normal thyrocytes and are cuboidal to low columnar. Psammoma bodies are numerous (37). The cytoplasm is typically amphophilic to slightly eosinophilic. Nuclei are irregular, relatively large and ovoid and they vary in size. Nucleoli are usually close to the nuclear membranes (which makes it look thick) and much of the interior of the nucleus is “pale”, “clear” or “ground glass” in appearance. Papillae vary in size and are irregular. Lymphocyte infiltration may be seen around a papillary neoplasm (3) (Figure5).

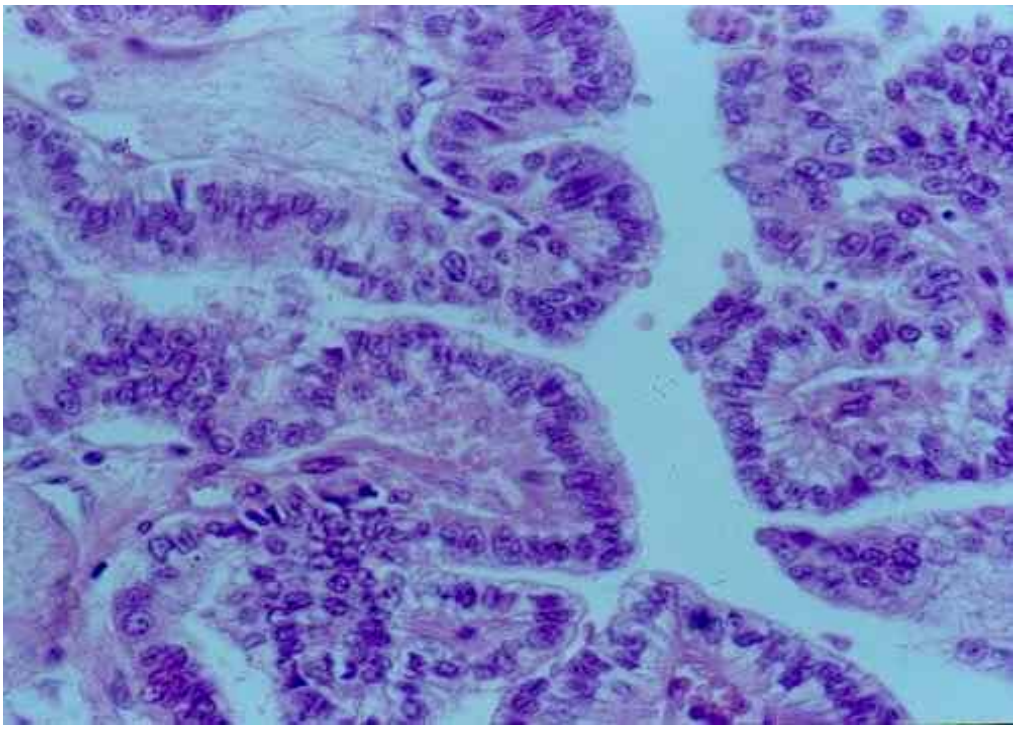


Figure 5. A histopathological view of PTC showing papillae consisting of fibro-vascular core structures, ground-glass nuclei and nuclear groves.

Multiple foci of cancer cells are common in the thyroid. PTC frequently invades lymphatic vessels, but vascular invasion is fairly uncommon.

A *follicular variant of PTC* may be diagnosed when more than 70 % of the histological pattern is composed of neoplastic follicles. Such neoplasms are often small and are usually less fibrotic than the classical PTC, but the characteristic clear nuclei are present. If the follicles are small and contain small amounts of colloid, the tumour will appear fleshy and opaque and may be misclassified as a follicular adenoma. The clinical behaviour and prognosis is similar to the classical PTC.

The *tall cell variant of PTC* is characterised by the tumour cells being twice as high as they are wide (3). It is uncommon and has a less good prognosis with a tendency to recur or metastasize (38, 39).

Columnar cell PTC is rare and occurs in adults of all ages. It is usually a solid, nodular, light-coloured mass, encapsulated or infiltrative, which contains tall, columnar cells arranged in patterns that are papillary or trabecular. It is more aggressive than the classical PTC (38, 39).

The diffuse sclerosing variant of PTC is characterized by diffuse involvement of one or both thyroid lobes, prominent fibrosis, squamos metaplasia, abundant psammoma bodies and lymphoid infiltration. It occurs mostly in children and young adults. Lymph node metastases are almost always present and lung metastases are frequent (4, 38, 39).

Occult PTC or micro-carcinoma is considered to be a harmless variant and according to the World Health Organisation (WHO) includes PTCs smaller than 1 cm in diameter (40). Usually they are found incidentally, and further treatment is not indicated (41). However, some patients with micro-carcinoma have developed metastases (42) and even died from the disease (39, 43).

Follicular Thyroid Carcinoma (FTC)

FTCs do not have the nuclear features of PTC and usually no papillae. Most classifications are based upon the degree of invasiveness of the cancer. The tumours are usually encapsulated. FTCs can be considered as *minimally invasive* or as *widely invasive* (37). Such assessment is performed after surgical resection of the tumour and requires multiple sections for the identification of malignancy (*i.e.*vascular or capsular invasion). Minimally invasive FTC has scattered tiny foci of vascular and capsular invasion at its periphery and widely invasive FTC has extensive protrusion into surrounding tissue and/or extension into multiple vessels (3). Cells of FTC are often small, with uniform round nuclei, but varying in size.

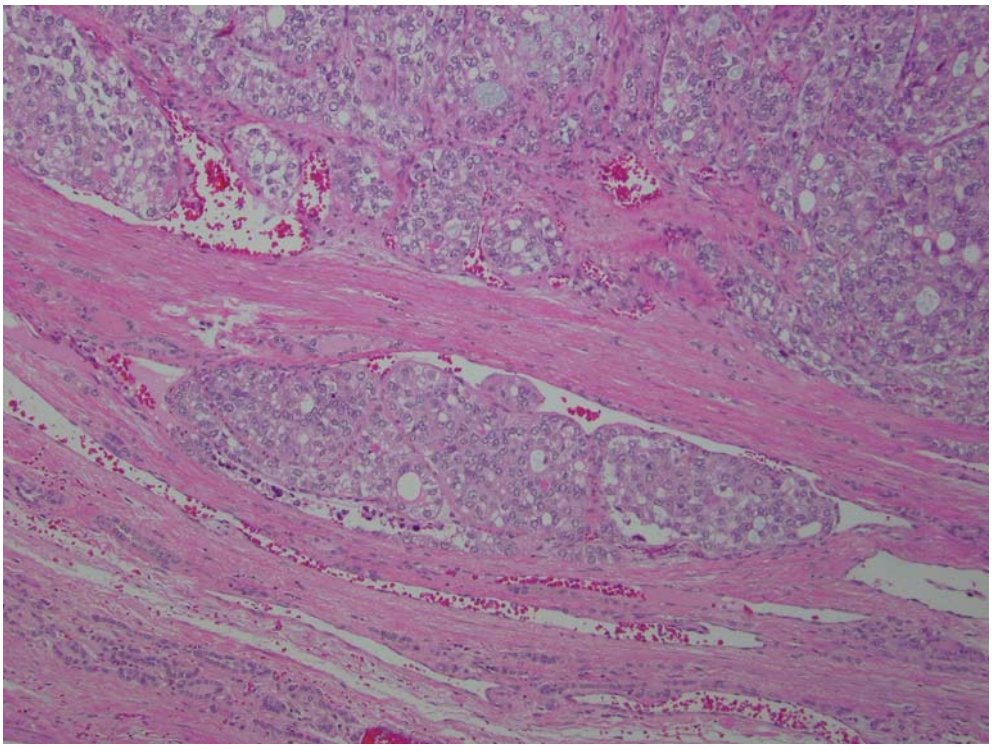


Figure 6. Histopathology of FTC with capsular and vascular invasion.

When the follicular differentiation is poor or absent, the tumour is classified as a poorly differentiated carcinoma.

Insular carcinoma is a moderately or poorly differentiated variant of FTC or PTC. Some consider it a separate entity (3).

Clear cell carcinoma is a rare variant of FTC. Glycogen accumulation or dilatation of the granular endoplasmic reticulum is responsible for the clear cell appearance (4).
Hürthle cell carcinoma (HCC) (also called oncocytic or oxyphilic variant of FTC) is a tumour composed of more than 75 % of cells with oncocytic features. Cells are eosinophilic with a granular cytoplasm rich in mitochondria. HCC presents as a solid tumour with complete or partial encapsulation. Vascular and capsular invasion are, as for FTC, the criteria of malignancy. HCC is more likely to involve regional lymph nodes than FTC but not as often as PTC. HCC produces thyroglobulin, but only few (7%) concentrate radioactive iodine (44). Based on criteria set by the WHO, this tumour of follicular origin is a subtype of both PTC and FTC, but it is more often noted as a subtype of FTC (39). HCC is often regarded as a separate category of DTC (44).

2.3. III. Treatment of DTC

Surgery should be the primary treatment for all patients with PTC and FTC. The extent of surgery is frequently debated because most patients do well whatever surgical technique is chosen (45, 46). A significant percentage of patients receive ablative dose of radioactive iodine postoperatively, which probably is beneficial to reduce the risk of recurrence for high-risk patients (22, 47). External radiotherapy to the neck is only indicated in patients with tumour residues that do not take up radioiodine (48, 49). Chemotherapy is only to be considered in patients with progressive metastatic disease (50).

Surgery

The goal of surgery is to remove all tumour tissue in the neck also including affected cervical lymph nodes. There are some controversies about the extent of thyroid surgery and over time different procedures have been performed (45, 51, 52). The most commonly described procedures are the following:
1) biopsy which refers to removal of a small piece of the tumour for histopathological classification;
2) uni- or bilateral resections (lumpectomy) which implies removal of the tumour with minimal surrounding thyroid tissue;
3) lobectomy (or hemithyroidectomy) which refers to removal of the entire lobe, whereas lobectomy and resection also includes the resection of isthmus;
4) total thyroidectomy (or near-total) is the extra-capsular removal of both lobes and isthmus, without leaving any visible thyroid tissue, which should be compared to:

5) subtotal thyroidectomy, in which some thyroid tissue may be left mainly to spare the recurrent laryngeal nerve from damage (5).

The argument against total thyroidectomy are the increased risk of surgical complications such as recurrent laryngeal nerve injuries and hypoparathyroidism (53), and the inconvenience by life-long thyroid hormone supplementation for these patients (27, 54). Arguments for total thyroidectomy are lower recurrence rates (55, 56) and that it facilitates the total ablation with radioactive iodine (9, 22) as well as follow-up using thyroglobulin as tumour marker. PTCs are frequently found to be multifocal, which speaks in favour of a total thyroidectomy (39, 57).

The frequency of lymph node metastases is related to both the histological type and extent of the thyroid tumours, to the extent of lymph node dissection. The central and lateral compartments of the neck are the areas most frequently involved. The most common lymph nodes removals strategies are:

1) node-picking which refers to an operation in which only grossly affected lymph nodes are removed;

2) the modified (or functional) neck dissection, which includes removing all fibrous and fatty tissue including the lymph nodes, but preserving the sternocleidomastoid muscle, internal jugular vein, the vagus nerve, spinal accessory nerve and sensory nerves, either unilateral or bilateral;

3) radical neck dissection, which includes the removal of all the above mentioned structures;

4) central neck dissection, which includes removing all lymph nodes pre-tracheal and adjacent to the tumour, *i.e.*, all lymph nodes between the carotid arteries (5).

In PTC patients, 35-70 % (and in children up to 80 %) have lymph node metastases, compared with FTC patients, in whom less than 20 % have lymph node metastases (4). In most patients lymph node involvement is ipsilateral, and the spread is in an orderly, defined manner from the central neck compartment to the mediastinum and lateral chains and from the lower part of the jugulocarotid chain upward. One of the arguments for lymph node dissection in patients with PTC is that it is the most efficient procedure for the treatment of lymph node metastases, although no improvement in survival has been shown (58).

Radioactive iodine treatment

The reasons to give radioactive iodine treatment postoperatively is to destroy remaining normal thyroid tissue, which increases the sensitivity of subsequent iodine-131 total body

scanning and the specificity of measurements of serum thyroglobulin for the detection of persistent or recurrent disease (9, 59). Radioactive iodine may furthermore destroy occult microscopic carcinomas, thereby decreasing the long-term risk of recurrent disease (22, 60, 61). Postoperative radioactive iodine therapy is used selectively, mainly for high-risk patients, to decrease the risk of recurrence and lower mortality rates (60, 62, 63). Four to six weeks after surgery an iodine-131 total-body scanning is performed. If any uptake of iodine-131 is detected in the thyroid bed or elsewhere, a treatment dose is given. Another total-body scan is obtained four to seven days later, and thyroxine therapy is initiated. Total ablation is verified by performing a radioactive iodine scintigraphy 6 to 12 months later.
In more than 80 % of patients who have undergone a total thyroidectomy, a total ablation is achieved (9). After less extensive surgery ablation is achieved in only two thirds of the patients. A recommendation is therefore that patients who will be treated with iodine-131 should be operated with a total or near-total thyroidectomy.

External radiotherapy

External radiotherapy to the neck and mediastinum is only indicated in patients in whom surgical excision is incomplete or impossible to perform (64). The clinical target volume is limited by the spinal cord. Potential complications include both acute (such as dysphagia, edema and dermatologic reactions) and late (tracheal compression and skin fibrosis) reactions (39). The beneficial effect of external beam radiotherapy in the treatment of selected metastatic sites (*i.e.*, brain and bone) or for palliation in cases of locally advanced inoperable disease is widely accepted (48, 49).

2.3. IV. Follow-up and recurrence

Despite the favourable clinical course of most patients with DTC, nearly half of the patients who experience recurrent thyroid cancer eventually die from this disease (39). Efforts should therefore be made to prevent recurrences. Usually recurrences are detected during the early years of follow-up but they have been detected after more than 20 years of first diagnosis (57, 58). Follow-up is therefore necessary throughout patients' lives. The risk of recurrence is higher in very young patients (<16 years of age at diagnosis) and older patients (>60 years of age at diagnosis) as well as in patients with a large tumour, especially if it extends beyond the thyroid capsule (65) and if it is poorly differentiated (66). Patients with lymph node metastases at the time of diagnosis have a higher risk of recurrence (1).

Efforts at the first time of treatment should be made to prevent recurrence by early detection and treatment, and of course complete removal of tumour in the initial operation. The postoperative treatments including iodine-131 therapy (67, 68), TSH suppression therapy and selective use of external radiation therapy in patients with unresectable cancer are also important to reduce the recurrence rate (9, 47).

Follow-up is individually planned but clinical examinations are routine procedures, although the sensitivity of neck palpation is low since lymph node metastases are not palpable when they are small and soft. With ultrasonography small (2-3 mm) lymph node metastases can be detected. A lymph node fine-needle biopsy, including cytological analysis, with guidance from the ultrasound can be performed. A measurement of thyroglobulin (Tg) is a good aid in detection of sub-clinical disease (69). However, an accurate Tg measurement is technically challenging (70). From a consensus report of the role of serum Tg as a monitoring method for low-risk patients with DTC (71), guidelines were given for patients who have undergone total or near-total thyroidectomy, radioactive iodine ablation and who have no clinical evidence of residual tumour and in whom serum Tg levels (<1µg/liter) are undetectable. TSH-stimulating Tg levels were recommended by the consensus group for follow-up, a sensitive test that could detect early recurrences or metastases for these patients (71).

For the long-term follow-up other methods such as computed tomography, iodine-131 and other variants of scintigraphy, magnetic resonance imaging and PET scanning are sometimes helpful.

Establishing optimal follow-up for patients with DTC remains challenging. It is important to detect an occult tumour that is amenable to treatment, which could be of benefit for many patients.

2.4. General epidemiological aspects

2.4. I. Validity of a study

External validity of a study reflects the generalizability of study, that is, if the results are applicable to other populations. To what degree a measurement really reveals what it is intended to, is called the internal validity. In studies of causation, it implies accurate

measurement of effects apart from random errors. Various types of biases can detract from internal validity (72).

2.4. II. Bias

The systematic deviation away from the correct value is denoted as bias and a biased measurement lacks validity. Bias or systematic errors can be defined as a process of inference producing results that depart systematically from the true values. It can be classified according to three broad categories: selection bias, information bias and confounding (72).

Selection bias is a systematic error originating from the procedures used to select study persons and from the factors influencing study participation (72). It can occur whenever the identification of individual subjects for inclusion into the study on the basis of either exposure (cohort) or disease (case-control) status differs between those who entered the study and those who would have been eligible but did not participate. Selection bias is a particular problem in case-control and retrospective cohort studies, where both the exposure and outcome have occurred at the time individuals are selected into the study. Selection bias is unlikely to occur in a prospective study because exposure is ascertained before the development of any outcomes of interest.

Information bias is any systematic error in a study caused by misclassification of exposure variables or disease outcomes. Misclassifications of exposure or outcome is a problem in every cohort study, its effect will depend on whether the misclassification was independent of the outcome. Misclassification of exposure must be considered the Achilles´ heel of epidemiology. Non-differential or random misclassification results when inaccuracies exist in the categorization of subject by exposure or disease status but these accuracies occur in similar proportions in each of the study groups. The effect of random or non-differential misclassification is to increase the similarity between the exposed and nonexposed groups, so that any true associations will be diluted or underestimated. As a result the observed relative risk estimate will always be biased towards the null. A differential misclassification is more problematic since it can exaggerate and/or underestimate an effect.
A bigger problem is normally differential misclassification. A common type of differential misclassification in case-control studies is recall bias, due to retrospective data collection.

Although recollection of past exposure should be the same for cases and controls, recall bias comes about because cases are more prone to recall than controls.

Confounding is the mixing of effect of the exposure under study with the effect of another factor, so that the estimated relative risk is biased. The confounding variable must be related to the exposure and to the outcome under study. As an example, when examining the relationship between choice of surgical procedure and death due to DTC, it would be appropriate to adjust for TNM stage in a statistical regression model, since TNM stage is associated with the exposure of interest (if surgical procedure depends on TNM stage) and is an independent risk factor for death due to DTC. In other words TNM is a possible confounding factor.

There are four types of techniques that can be used to deal with confounding when planning and analyzing a study (72):

1. *Restriction*. The whole study population is limited to subjects having the same confounding exposures, for example all in the study population is the same age.
2. *Stratified analysis*. Divides the confounding variable down to relatively narrow ranges (strata) and analyses each band separately. This is often called an "adjusted" estimate, since confounding effects have been adjusted for.
3. *Modelling*. Various statistical modelling techniques are also commonly used to remove confounding during analysis. These are not limited by the numbers of strata and these techniques are much more flexible than stratified analysis. Estimates from these analyses are called adjusted.
4. *Matching.* Subjects are matched on the potential confounding variable. If matching is employed to control confounding special statistical techniques are required to analyze data. Otherwise biased effect estimates may result.

2.4. III. Effect modification occurs when the effect of the exposure under study varies in different groups (strata) determined by another factor and when two or more causes act through the same causal mechanism. Effect modification answers the question of whether the relationship between the exposure and disease appears to be the same or different for varying levels of a factor after baseline differences in that factor are controlled. It is present when the sum of the excess risks from the separate effects is not equal to the excess risk from the joint effect and it should be described and reported, not controlled (73). Confounding and effect modification could sometimes be difficult to distinguish. Normally effect modification adds

important information while confounding distorts the results. An effect modification or interaction can be visualized by inspection of the size and pattern of the effect estimates across strata, or by tests for interaction (in studies with enough power). A given factor can be both a confounder and an effect modifier. A confounding factor is associated with both exposure and disease but not on its causal pathway and it will mislead the estimate of the effect as described above, and should be controlled for when possible.

2.4. IV. Chance or random error is another main type of error that can affect epidemiological studies. Random error is a variation in the data that we can not readily explain (72). Statistical methods are used to determine whether the observed differences are real or due to chance fluctuations. Statistical power is the probability to detect an effect if there really is one, which is influenced not only by the size of the study, but also number of cases or exposed individuals. The width of the confidence intervals and/or p-values roughly reflects the role of chance.

3. AIMS OF THE THESIS

The present thesis focuses on non-medullary differentiated thyroid cancer (DTC) which includes the papillary (PTC) and follicular (FTC) sub-types. It was aimed at studying differences in risk factors, tumour characteristics and routine treatment modalities between survivors and non-survivors of DTC.

The specific aims of the thesis were to:

- Analyse the incidence and survival in Swedish patients with DTC in relation to age at diagnosis, gender, histopathology and calendar period.

- Find out if risk factors such as smoking, reproductive factors, previous thyroid disorders and a family history of different diseases influence the prognosis for patients with DTC.

- Study how different tumour characteristics affect prognosis and if a scoring system such as TNM, is prognostically accurate for patients with DTC.

- Analyse how the surgical technique and the different postoperative treatments influence survival for patients with DTC.

4. MATERIAL & METHODS

4.1. Data sources

4.1. I. The national registration number was introduced in 1947 as a unique ten-digit (nine-digit at the introduction) personal identifier (74). The ten-digit number consists of six digits denoting the year and date of birth, two digits originally specifying the county of residents (nowadays assigned without relation to place of birth), one digit to indicate the sex of the carrier, and a check-digit which is possible to calculate given the first nine digits. It was assigned to all Swedish residents alive in January 1st, 1947 and all residents born thereafter. The national registration number makes it possible to follow every individual from birth to death.

4.1. II. The Swedish Cancer Register (SCR*)* was established in 1958, and holds records on all incident malignancies in Sweden. Reporting of incident tumours to the SCR has been mandatory for clinicians and cytologist/pathologists since 1958. The proportion of all thyroid cancers reported to the SCR for the period up to 1978 was estimated to be 98 % (75) but coverage is now considered to be close to 100 % (37). Cases detected incidentally at autopsy are included in the cancer registry but were excluded from this study. The SCR does not register tumours where the death certificate is the only source of information.

4.1. III. The Swedish Cause of Death Register was established in 1952 and provides the date of death, as well as the underlying and contributory causes of death of all deceased Swedish residents. The causes of death are classified according to the International Classification of Diseases and Related Health Problems (ICD), version 6 to 10. The completeness is estimated to exceed 99 % (76).

4.2. Study design

4.2. I. Paper I

The study was based on all thyroid cancers reported to the SCR between 1958 and 1987, with follow-up until December 31, 1999. The limitation of the period 1958-1987 was to allow for a sufficiently long follow-up time. Information on stage or treatment of the tumours is not recorded by the SCR, nor is detailed information on histopathology. The original

histopathological reports of all registered thyroid cancers were therefore examined to establish the histopathological entity of each case (13, 77). Of the 7,906 thyroid cancers reported to the registry, 1,405 (18%) patients with anaplastic and medullary thyroid cancers and 947 (12%) patients with follicular thyroid adenomas were excluded, leaving 5,554 individuals diagnosed with DTC in the study. The few HCC (n=125) did not allow detailed analyses and were therefore included in the FTC group. Tumours classified as mixed follicular and papillary were included in the PTC group.

Statistical methods

Annual incidence rates per 100,000 were calculated for 5-year age groups and 5-year calendar periods of diagnosis. The relative survival ratio, estimated from life tables, was used as the measure of patient survival. The relative survival ratio is defined as the observed survival in the patient group (where all deaths are considered events) divided by the expected survival of a comparable group from the general population, which is assumed to be free of the cancer in question. Expected survival was estimated using the Hakulinen method from Swedish population life tables stratified by age, sex, and calendar time (78). Relative survival was modelled using the life table regression model developed by Hakulinen and Tenkanen (79). The model provides estimates of excess hazard ratios (relative excess risk) (80) simultaneously adjusted for potential confounding factors. Expected and relative survival was estimated using software developed at the Finnish Cancer Registry (81). Standard errors were estimated using Greenwood's method (82) and 95% confidence intervals constructed on the log cumulative hazard scale.

4.2. II. Paper II-IV

In order to study the association between additional potential prognostic factors and patient survival, a nested case-control study was conducted within the 5,554 patients diagnosed with DTC during 1958-1987. With this study design, information on only 21 % of all patients was needed. This is an efficient study design, compared to a full cohort analysis.

Among the 5,123 patients who survived at least one year following diagnosis (of the 431 deaths during the first year, 296 were due to DTC), matching with the Swedish Causes of Death Register for the period 1959-1999 identified 693 patients with DTC (ICD-7 number 194) as the underlying cause of death. Information on potential prognostic risk factors was abstracted from the medical records of the 693 cases (see questionnaire in appendix). A group

of three specialists (a cardiologist, an oncologist and an endocrine surgeon) independently evaluated the medical records to confirm DTC as the cause of death when this was not obvious. Cause of death was reclassified for 42 (6 %) patients who died due to cardiovascular disease (n=22), other cancers (n=11), and thyroid cancer other than DTC (n=9). The cause of death for the patients classified as dying due to causes other than thyroid cancer was not routinely confirmed. Thirty-six potential cases were excluded because the medical records were not available, and 14 cases were excluded since they were diagnosed before the year of 1958, leaving a total of 601 cases.

A nested case-control study with time since diagnosis as the timescale was generated by randomly sampling one control for each case, matched by age at diagnosis (5-year age groups), sex, and 10-year calendar periods of diagnosis. Among the initially selected controls, 26 of the medical records could not be located and 26 patients never had a DTC. A second control was therefore randomly selected. A third control had to be randomly selected for an additional three cases due to missing medical records. Six of the cases were aged above 90 years at diagnosis and were excluded since no matching control could be identified, leaving 595 sets of cases and controls in the analysis.

Statistical methods

A conditional logistic regression model was used to estimate odds ratios (OR) of death due to DTC with 95 % confidence intervals. Cases and controls were matched by time since diagnosis, age at diagnosis, sex and calendar period. Effects were considered statistically significant when the 95 % confidence interval for the OR did not include 1. The multivariable analysis adjustments were made for variables such as potential risk factors, histopathological subgroups, different tumour characteristics, TNM stage, type of surgical excision and different postoperative treatments. When interactions were suspected from a clinical point of view, interaction effects were estimated.

5. RESULTS

5.1. Paper I

Incidence of both PTC and FTC was higher among women, for PTC especially during the fertile part of life, than among men. Incidence of PTC increased significantly over time, a trend that was not observed for FTC. Women experienced a superior survival compared with men. The unadjusted relative survival estimates suggested a more favourable prognosis for patients diagnosed with PTC compared with those diagnosed with FTC, although much of this effect could be explained by the confounding effect of age. In contrast to our perceptions based on clinical practise, no difference between PTC and FTC in excess mortality could be shown the first years after diagnosis (when the majority of deaths occur). The following 7-20 years after diagnosis, PTC patients experienced a lower mortality compared with FTC patients. From this study it was suggested that there may be a subgroup of thyroid tumours with superior prognosis diagnosed in women during the fertile part of life and that sex hormones may play a role in the etiology of these tumours.

5.2. Paper II

Potential risk factors such as smoking, reproductive factors, previous diseases and treatments and different family history were studied with death due to DTC as an outcome. Smoking men had a significantly increased risk of death due to DTC, a trend that was also seen for women, however not significant. Hormonal replacement therapies could not be evaluated in this study. Instead the number of children and its influence on prognosis was studied. No significant differences were found. Previous thyroid diseases, other primary malignancies and prior treatment with external radiotherapy towards the neck were studied but were of no prognostic importance. A three times higher risk of death due to DTC was seen if a relative was diagnosed with a DTC. This increase of risk was not significant due to few numbers. Except for smoking, none of the other risk factors studied had any significant influence on survival.

5.3. Paper III

Possible histopathological risk factors and stage associated prognostic factors were studied. There was an increased risk of death due to DTC for patients diagnosed with FTC compared with patients with PTC. The histopathological subgroups widely invasive FTC and unspecified FTC conferred the least favourable prognosis. Differentiation grade of the tumour

was a strong determinant of prognosis. A strong association between TNM staging and mortality in DTC was seen. Patients in TNM stage 4 had a nine times higher risk of death due to DTC compared with patients in stage 2. Incomplete surgery was associated with poor survival. The proportion of patients in whom resection was considered complete varied with TNM stage and among cases and controls. Completeness of surgery modified the prognostic effect of TNM stage. The effect of incomplete removal was most obvious in TNM stage 1 in which the tumours are small. Metastases at the time of diagnosis, regardless if they were loco-regional or distant were an indicator of worse prognosis.

The TNM classification system could accurately define subclasses of patients with less favourable prognosis, possibly in need of a more aggressive therapy. The predictive value of the TNM system would be improved if incomplete surgical excision were also considered.

5.4. Paper IV

This study was aimed at trying to identify whether different treatment modalities influenced the prognosis. The risk of death due to DTC for patients who did not undergo any operation was almost three times higher compared with those who were operated. However, the extent and type of thyroid surgery that was performed did not influence the prognosis except for patients operated with a subtotal thyroidectomy, in which a doubled risk was discovered, compared with patients with any other type of resection. In an interaction model regarding type of surgery and TNM, it was found that patients in TNM stage 3 had a 50 % increased risk of death due to DTC if operated with a subtotal thyroidectomy, compared with a total thyroidectomy. No other interactions between TNM stage and operative procedures were seen. Lymph node surgery per se was not associated with prognosis. The risk of death after a loco-regional recurrence was five-fold. No improvement in survival was seen after postoperative treatments with radioactive iodine, external radiotherapy or chemotherapy. This risk in mortality for any of the mentioned postoperative treatments remained after adjustments for the other postoperative treatments and TNM stage.

6. METHODOLOGICAL ASPECTS

6.1. Choice of study

Intervention studies or clinical trials where the exposure or the treatment is randomly allocated to the participants by the investigators, preferably in a double-blind fashion, yield the most valid effect estimates owing to the inherent control of known and unsuspected confounding. Ideally evaluation of the effects of treatments should not be based on observational data. However, due to issues of cost, feasibility and ethics, other types of studies than intervention studies are needed. For patients with DTC a randomised controlled trial would be difficult to conduct in practice, due to the low incidence, the low mortality of the disease and the need for several decades of follow-up. Cohort studies are well suited for studies of rare exposures or multiple outcomes. They are less prone to bias from selective recall of exposure, especially when information on exposure and outcome is obtained independently, through a well-functioning registry such as the SCR. The general argument that cohort studies are expensive and time-consuming does not apply to retrospective cohort studies using registry-based follow-up. Case-control studies have a number of advantages in studies of rare diseases with unknown and multiple causes. When nested in a cohort the validity of the study is comparable to a historical prospective cohort study.

6.1. I. Cohort study (Paper I)

In a cohort study individuals are followed over time and disease occurrence is registered. Two or more groups that are initially free of the disease under study differ according to exposure to a potential cause of the disease and are observed over time to compare the incidence of diseases in each group. Cohort studies are particularly useful to study multiple possible outcomes from a single exposure (83). A cohort design is limited if the incidence of the disease under study is low, since a large number of people must be followed up for a long time before results are available. This could be both time-consuming and expensive. In the first paper, all patients with thyroid cancer in the SCR were collected and an incidence and survival analysis was performed on this cohort. The main restriction to this study was the limitation of information included in the registry such as TNM stage.

6.1. II. Case-control studies (Paper II-IV)

Case-control studies compare individuals with a disease to a control without the disease, looking for differences in previous exposures. Information on exposures is usually obtained

retrospectively. Researchers must rely on memory or the completeness of medical records. The difficulty of assessment of exposure, often termed information bias, is a major limitation to case-control studies. Another challenge is the selection of controls. It is important that exposures of the control group are representative of the source population from which cases are obtained, which means that the controls should be sampled independently of their exposure status and that it is important that any control should have the possibility to become a case. The case-control study is the most efficient study design when investigating a rare outcome, such as thyroid cancer. It is cost-effective and provides the ability to simultaneously study many exposures related to an outcome, and their potential interactions (83). A case-control study of all patients that had died from differentiated thyroid cancer nested within a cohort of all patients diagnosed with differentiated thyroid cancer in Sweden was performed. A nested case-control study, unlike a standard case-control study, is not a retrospective study. After matching, the risk sets consist of subjects with the same matching factor level as the failure so that sampled case-control sets will be homogenous in the matching factor. It has the cost-efficiency associated with retrospective case-control studies but without the possibility of selection or information bias often associated with case-control studies.

7. DISCUSSION AND FUTURE STUDIES

To our knowledge, investigators in no other country have been able to study incidence and prognosis in patients with DTC in an entire population during a forty-year period. This was possible because of the access to the SCR and to the Swedish Cause of Death Registry. Hundahl et al studied approximately 50,000 thyroid cancers (1 % of total cases) during 1985-1995, from the National Cancer Data Base. This data base covers nearly 60 % of all incident cancers in the USA (84). Relative survival rates for 5 and 10 years were estimated according to histopathology, stage and surgical treatment, however due to a follow-up period of maximum 10 years, full effect of treatment and prognostic factors could not be estimated. Studies of prognosis and mortality have generally included less than 200 patients, who died of verified DTC (22, 27-29, 31, 44, 85). When evaluating factors with a possible prognostic influence, it is important to have a large number of deaths. This study consisted of 595 patients who died of DTC in Sweden during the years 1959 until 1999. During these 40 years the diagnostic methods and treatments have changed. For example, until 1980 the morphological signs of PTC had to have a papillary growth pattern but today it is sufficient that psammoma bodies or “ground-glass” nuclei are detected. In the early part of the calendar

period the proportions of falsely classified FTC were higher. Treatment modalities such as postoperative radioactive iodine treatment and type of surgical procedure chosen for patients with DTC have also varied over the time period. In the 1960s most patients were treated with lobectomy alone without adjunctive medical therapy (86). During the later time periods, most patients underwent total or near-total thyroidectomy and radioactive iodine remnant ablation and thyroid hormones suppression of TSH (87, 88) although this is still an approach not without controversy (40, 89).
In the last decade new techniques for detecting recurrences have been developed and have improved the follow-up of DTC patients. Thyroglobulin tests, computed tomography and ultrasound are some examples. How improvements in detection and treatment influence the survival for patients with DTC is a question for future studies to answer.

In the *first paper* the entire Swedish DTC-population was studied. It was discovered that survival was increased for patients diagnosed in later calendar periods, that gender was of great importance and that the most significant prognostic factor for predicting outcome in patients with DTC was age. Improved technology and more accurate and precise methods to diagnose carcinomas, can explain an increased survival for patients with DTC in later calendar periods. Why 99 % of patients younger than 40 years of age, but only 50 % of patients above 70 years of age at diagnosis survive their DTC for at least 10 years is not fully understood. One explanation could be that thyroid disorders such as hyper- or hypo-thyroidism are usually diagnosed in patients before or during middle age. During investigations incident DTC of an early TNM stage could be found. The diagnosing in the elderly patient without any symptoms is more likely to be delayed. Another possibility is that there is a subgroup of aggressive tumours that are found primarily in elderly patients.
The gender difference with a 3:1 incidence in female: male ratio, and at the same time a better survival for females, especially with PTC, indicates an influence associated with sex hormones. The carcinomas diagnosed during the fertile part of especially females life seems to be less aggressive than carcinomas diagnosed later in life. The question whether these are different entities of tumours, or if cell damages or genetics defects are more pronounced later in life, inspires to future studies.

In *Paper II* risk factors that influenced not only the incidence but also the prognosis of DTC were investigated. The risk of death due to DTC for smoking patients was increased which is contradicting some other studies (90-93). Questions were raised of a protective hormonal

factor and a possible association with a less aggressive DTC found primarily in young female patients. No association between number of births and DTC was found. Oral contraceptives and HRT were introduced during the 1960s and 1970s. Unfortunately, information on this type of exposures was missing. In a future prospective study design it would be valuable to compare the incidence and survival in women who have taken oral contraceptives and/ or HRT, with those who have not. Risk factors that, such as previous thyroid disorders, a family history of thyroid disorders and malignancies and prior radiation towards the neck did not influence survival for patients with DTC in this study, which is in contrast to previous findings (20, 94, 95).

In *Paper III* potential tumour characteristics that could influence survival of DTC were investigated. In the first paper no difference was seen between FTC and PTC after adjustments for age at diagnosis, calendar period and gender the first six years after diagnosis. However, an increased risk of death was seen for FTC patients in the nested case-control study. Patients with widely invasive FTC had a particularly bad prognosis. When matching by age at diagnosis and gender, a selection of comparatively older and a large number of male patients would be included in the nested case-control study compared with the cohort study. The incidence of PTC is especially pronounced during the fertile part of women lives; here, among cases PTCs were relatively few as were young female patients. After six years the difference in survival between FTC and PTC increases (in Paper I), showing the importance of long-time follow-up for patients with DTC.
The well-known TNM scoring system was used as a comparison. For the Swedish population this scoring system predicted the risk of death due to DTC according to stage and age at diagnosis accurately. Furthermore, TNM takes lymph node status into consideration, a feature indicated to influence survival for patients with DTC. Unfortunately, TNM lacks completeness of surgery, one of the most essential prognostic factors for DTC patients; the addition of this information would improve the system. Tumour characteristics such as differentiation grade and vascular invasion also had a prognostic influence on mortality for patients with DTC. Additional information to the TNM scoring system, of surgical completeness and of differentiation grade of the tumour, would be of great value.

In *Paper IV* the influence of surgical technique and postoperative treatments for DTC patients' prognosis were studied. Ideally, a prospective randomised controlled trial with at least 20-30 years of follow-up should provide answers to questions concerning treatment. It

has been estimated that a randomised study to detect a 10 % reduction in thyroid cancer mortality rates 25 years after radioactive iodine treatment would require 4,000 patients in each arm of the study and would take a decade or more to enrol, making results available after 35 years (96). A study of that kind would have to be conducted in a multicenter design. However, this would be both expensive and time-consuming. At present, the core information of therapy derives from large retrospective cohort studies of patients observed for decades. In this study, a nested case-control setting for comparing the effect on mortality for patients with DTC according to different types of thyroid surgical procedures was used. Treatment tradition varies around the country as well as in the rest of the world, and the debate if one should perform a hemi-thyroidectomy or a total thyroidectomy is still on-going (46, 85, 97). For patients with a tumour in TNM stage 3 operated with a subtotal thyroidectomy death due to DTC was increased. One possible explanation is that large tumours in TNM stage 3 are more likely to be resected incompletely depending on their growth pattern. Operations described as total thyroidectomies could represent tumours that respected the capsule of the thyroid. Apart from subtotal thyroidectomies for stage 3 patients, the mortality was not influenced by the surgical procedure chosen, not even after adjustment for TNM stage. One can claim that the risk for loco-regional recurrence is increased and therefore also death due to DTC if any partial resection of the thyroid is performed. An association between incomplete surgical excision, subtotal surgical procedures and loco-regional recurrence was noted, although not statistically significant.

No improvement in survival after any of the postoperative treatments such as external radiotherapy, chemotherapy or radioactive iodine was seen. The drawbacks of a nested case-control design compared with a randomised controlled trial for treatment effects, is the risk of reversed causality, *i.e.,* patients with a large or non-resectable tumour or distant spread of disease will be more likely to have postoperative treatments of the above mentioned kind. In this study nearly half of all patients were treated with radioactive iodine postoperatively, including patients in TNM stage I. As mentioned before, no randomised controlled trial has been performed which could show an effect of radioactive iodine treatment on survival. However, previous studies have showed a prolonged relapse-free period (47). To conclude, patients with the most aggressive forms of DTC will probably not survive irrespective of postoperative treatment. However, these treatments might improve the patient's quality of life and delay recurrences.

An important issue for *future studies* is the mechanism and possible association of hormones in patients with DTC. Are female patients protected by hormones such as estrogens or are the carcinomas in females, especially in younger patients, of a less aggressive type? Molecular genetic studies have already tried to explore deformities in genes such as the RET/PTC and B-Raf oncogenes and if they could explain why some tumours behave more aggressively than others (98, 99). Another approach is to investigate differences in MIB-1 index between cases and controls in the histopathological specimens. MIB-1 is an antibody directed against the proliferation factor Ki67. It has been shown that aggressive tumours have a higher MIB-1 index than less aggressive tumours (100). If all cases in the present study have a higher MIB-1 index compared with the controls, this could be very promising: MIB-1 index measured already at the time of operation could help the clinician in individualizing the postoperative treatment for each patient.

For follicular lesions FNAC is not conclusive and patients are thus referred to surgery for a conclusive histopathological examination. A multicenter study tested the usefulness of immunohistocytochemical staining for two potential malignant thyrocytes. Expression of galectin-3 and another glycoprotein (CD44v6) was tested, using monoclonal antibodies, on a thousand thyroid lesions. The sensitivity and specificity for galectin-3 alone to discriminate a benign from a malignant thyroid lesions was more than 99 % and 98 % respectively (101). Further studies would be of great importance to decide if this test method together with FNAC is sufficient as a specific indicator of FTC. Another promising marker of malignancy in follicular thyroid tumours is the detection of the fusion oncogene PAX8/PPARgamma (102). However, later studies have not been able to reach sufficient positive predictive values from neither of these tests (103).

8. CONCLUSION

The main findings of this thesis were:

- The incidence of DTC was increased for women compared with men, and at the same time women had a better prognosis.
- Age was the most important prognostic factor for survival in DTC, followed by gender and calendar period at diagnosis.
- Possible risk factors for the incidence of DTC, such as previous radiotherapy towards the neck and family history of different thyroid diseases and malignancies, did not influence the prognosis.
- Smoking increased the risk of death due to DTC.
- The TNM classification was a valid prognostic scoring system for patients with DTC. The addition of "completeness of the surgical excision" would improve the system.
- Histopathological findings such as the tumour's differentiation grade, vascular invasion and if the follicular thyroid cancer was widely invasive, were of importance for the prognosis.
- Both lymph node metastases and distant metastases increased the risk of death due to DTC.
- The surgical extent was not a prognostic factor as long as the excision of the primary tumour was complete.
- Postoperative treatments including radioactive iodine, external radiotherapy and chemotherapy did not improve survival for patients with DTC.

9. SAMMANFATTNING

För er som vill läsa den enkla, korta svenska versionen av vad jag ägnat mig åt under några år.

Sköldkörteln (*lat,* thyreoidea,) är en hormonproducerande körtel som deltar i kroppens kalkreglering och ämnesomsättning. Endast 1 % av all cancer utgår från sköldkörteln. Det finns fyra grupper av sköldkörtelcancer; papillär (PTC), follikulär (FTC), medullär och anaplastisk. PTC och FTC, vilka gemensamt kallas för differentierad sköldkörtelcancer (DTC), är de vanligaste formerna (70-90 %) och de har även bäst prognos. Inom ramen för detta avhandlingsprojekt studerades varför en del av patienterna med DTC, trots den goda prognosen avlider. För att kunna studera överlevnad krävs en lång uppföljningstid, särskilt för patienter med DTC eftersom återfall kan komma plötsligt efter 20-30 år. Tack vare våra svenska register (i denna studie, cancer- och dödsorsaksregistret) som är baserade på personnummer, kan stora befolkningsstudier genomföras.

Ur cancerregistret identifierades alla patienter med DTC, som diagnostiserades under åren 1958 (då cancerregistret startades) till och med 1987. Totalt 5 554 patienter utgjorde därmed den s.k kohorten och dessa följdes till 31/12 1999.

I det första delarbetet analyserades hur incidensen (antal nya fall av DTC/år) och överlevnaden såg ut med avseende på ålder, kön och vilket år patienterna diagnosticerades inom denna kohort. DTC var tre gånger vanligare hos kvinnor jämfört med hos män och detta framförallt för den histologiska undergruppen PTC. I överlevnadsanalysen noterades att kvinnor har en bättre prognos jämfört med män. Ålder är en viktig faktor; 99 % av alla patienter som är under 40 år vid diagnostillfället överlever i 10 år, vilket kan jämföras med de patienter som vid diagnostillfället är över 70 år, där ca 50 % dör av sin DTC.

I arbete 2, 3 och 4 studerades faktorer som kan påverka prognosen, dvs. risken att avlida i sin DTC. Ur dödsorsaksregistret, identifierades alla patienter som under perioden 1958-1987 avlidit till följd av sin DTC (vilka var 693 st). Dessa fall matchades sedan slumpmässigt mot en kontroll (av samma kön, ålder och som diagnostiserats under samma 10 års-period) ur kohorten, dvs. de som hade DTC men som inte avlidit till följd av denna (en s.k ”nested” fall-kontrollstudie). Efter noggrann journalgenomgång identifierades vissa skillnader mellan de patienter som avlidit till följd av sin cancer jämfört med dem som överlevt. Bland annat var tumörstorlek, växtsätt och spridning av tumören viktiga faktorer för överlevnaden i DTC. Däremot påverkades inte överlevnaden av om patienten hade haft andra sköldkörtelsjukdomar, en annan malignitet, om patienten fått strålning mot halsen som behandling eller om det förelåg en ärftlighet för någon av de nämnda sjukdomarna. Om kirurgen vid operation av sköldkörteln lyckades få bort hela tumören med god marginal så var prognosen avsevärt mycket bättre än om tumören inte var radikalt bortopererad. Vilken kirurgisk metod som valdes påverkade inte prognosen. Efterbehandling med radiojod, strålning eller cellgifter förbättrade inte överlevnaden. Det berodde sannolikt på att dessa behandlingar framförallt ges till de patienter som redan har en avancerad sjukdom, och därmed inte kommer överleva oavsett vilken behandling som ges.

I tidigare studier där man bedömt risk för död i DTC har högst 200 patienter som dött av DTC ingått (pga den goda prognosen för dessa patienter). Det unika med denna studie var det stora antalet fall (595 st. efter det att 98 st. exkluderades till följd av felaktig diagnos eller att journaler saknades). Det medförde att studien hade en unik styrka (s.k. ”power”). Möjligheten att värdera olika riskfaktorer och dess inverkan på överlevnaden är därmed god jämfört med de flesta andra studier. Förhoppningen är att det leder till att man på ett bättre sätt kan individualisera behandlingen för patienter med DTC. Patienter med god prognos skulle inte behöva behandlas i onödan och patienter med sämre prognos skulle kunna behandlas med de utökade rersurser som krävs.

10. APPENDIX

10.1 Definitions

Inclusion/Exclusion criteria

1) Included: patients with a DTC who died (only cases) due to their DTC. The DTC must have been diagnosed during 1958-1987.
2) Excluded: a) patients with no records of a DTC
   b) patients with another thyroid cancer (ATC or MTC)
   c) patients that were diagnosed before 1958.
   Only cases: a) if the cause of death was apparently due to another disease such as heart failure,
   b) if the DTC was not aggressive enough to cause the death.
3) Uncertainty: (only cases)
   a) when cause of death is uncertain,
   b) if the diagnosis of DTC is unclear and more medical records are needed,
   if impossible, a discussion in the specialist group, to exclude or include.

Cause of death

1) DTC: Distant metastases or primary tumours that have caused the death by for example pulmonary and/or heart failure. If a locally advanced tumour causes death by bleeding or constriction in the trachea.
2) *Not* DTC: If the patient at the time of death did not have a loco-regional recurrence or distant metastases or the DTC was apparently inactive.
3) Uncertain: More medical records needed and a discussion in the specialist group.
4) *With* DTC: The patient has an active DTC, but not very aggressive, surgery is not radical or he/she has a loco-regional recurrence or distant metastases but of less aggressive type and the patient dies due to other events such as a more fatal cancer, heart failure or trauma.

Definitions of tumour size from the histopathology report

Names/Description used in case records	Approximated size of tumour
Marbles	< 2 cm
Pea	< 2 cm
Bean	< 2 cm
Nail	< 2 cm
Nickel/ Dime	< 2 cm
Hazelnut	< 2 cm
Walnut	2-4 cm
Almond	2-4 cm
Chestnut	2-4 cm
Date	2-4 cm
Grape	2-4 cm
Golf-ball	> 4 cm
Mandarin	> 4 cm
Plum	> 4 cm
Chicken egg	> 4 cm
Fig	> 4 cm
Goose egg	> 4 cm

10.2 Protocol

THE SWEDISH PROGNOSTIC THYROID CANCER STUDY

1958-1987

Name ……..

1. **ID no.** ☐☐☐☐☐☐☐☐☐☐☐☐
2. **Hospital, code** ☐☐☐☐☐
3. **Department, code** ☐☐☐
4. **Gender** - male=1; female=2 ☐
5. **Residency, ZIP code** ☐☐☐☐☐
6. **Occupation** - no info=0; known=1 ☐

   Occupation ……..
7. **Smoker** - no info=0; yes=1; no=2; ☐
8. No. of cigarettes/day - <20=1; >20=2 ☐
9. **Children** - no info=0; yes=1; no=2 ☐
10. No. of children ☐☐
11. **Family history of thyroid cancer** - no info=0; yes=1; no=2 ☐

12. Children=1;mother=2;father=3;siblings=4;other=5 ☐
13. **Family history of cancer** - no info=0; yes=1; no=2 ☐

    Children=1; mother=2; father=3; siblings=4; other=5
14. relative ☐ type, ICD-7 code ☐☐☐☐
15. relative ☐ " " ☐☐☐☐
16. relative ☐ " " ☐☐☐☐

17. **Family history of thyroid disorder** - no info=0; yes=1; no=2 ☐

Relative: children=1; mother=2; father=3; siblings=4; other=5

Disorder: hypothyroidism=1; atoxic nodular goiter=2;
toxic nodular goiter=3; Graves' disease=4;
Hashimoto's thyroiditis=5; unkown=6

18. relative ☐ disorder ☐

19. relative ☐ disorder ☐

20. relative ☐ disorder ☐

21. **Previous thyroid disorder** - no info=0; yes=1; no=2 ☐

22. Hypothyroidism=1; atoxic nodular goiter=2; toxic nodular; goiter=3;
Graves' disease=4; Hashimoto's thyroiditis=5; unkown=6 ☐

23. **Previous thyroid disorder treatment** - no info=0; yes=1; no=2 ☐

24. Hormone replacement therapy (HRT)=1; surgery (S)=2;
^{131}I therapy=3; HRT+S=4; HRT+S+^{131}I=5; S+^{131}I=6; 1+3=7 ☐

25. External radiotherapy - no info=0; yes=1; no=2 ☐

26. **Previous cancer** - no info=0; yes=1; no=2 ☐

27. **1** Date of diagnosis ☐☐☐☐☐☐

28. Type (ICD-7) ☐☐☐☐

29. **2** Date of diagnosis ☐☐☐☐☐☐

30. Type (ICD-7) ☐☐☐☐

31. Surgery - no info=0; yes=1; no=2 ☐

32. Radiotherapy - no info=0; yes=1; no=2 ☐

33. Chemotherapy - no info=0; yes=1; no=2 ☐

34. **Previous benign disorder treated with radiotherapy at neck**
no info=0; yes=1; no=2 ☐

35. **Date of thyroid cancer diagnosis** ☐☐☐☐☐☐

36. **Cytology, no.** ☐☐☐☐☐☐☐☐☐☐

37. **Histopathological specimen, no.** ☐☐☐☐☐☐☐☐☐☐

38. ☐☐☐☐☐☐☐☐☐☐

39. ☐☐☐☐☐☐☐☐☐☐

40. **Re-examined, specimen no.** ☐☐☐☐☐☐☐☐☐☐

41. **Histology** - no info=0; unspecified follicular=1; minimally invasive follicular=2; widely invasive follicular=3; papillary=4; papillary of follicular type=5; papillary and follicular=6; other=7 ☐

42. **Uncertain histology** - no info=0; yes=1; no=2 ☐

43. **Tumor cell differentiation** - no info=0; yes=1; no=2 ☐

44. High=1; intermediate=2; low=3; 1+2=4; 2+3=5 ☐

45. **Tumor stage** - no info=0; yes=1; no=2 ☐

46. Stage 1-4 ☐

47. **Other histopathological findings** - no info=0; yes=1; no=2 ☐

48. Lymphocyte infiltration=1; Hürthle cell tumor=2; presence of connective tissue=3; vascular invasion=4 ☐

49. Free resection margins - no info=0, yes=1; no=2 ☐

50. **Preoperative diagnosis of thyroid cancer** - no info=0; cytology=1; surgery=2; clinical=3 ☐

51. Method - no info=0; yes=1; no=2; suspicion=3 ☐

52. **Date of surgery** ☐☐☐☐☐☐

53. **Thyroid surgery** - no info=0; yes=1; no=2 ☐

54. Biopsy=1; unilateral resection=2; bilateral resection=3; lobectomy=4
lobectomy+ resection=5; total thyroidectomy=6;
subtotal thyroidectomy=7; not indicated=8 ☐

55. Comments ……

56. **Lymph node surgery** - no info=0; yes=1; no=2 ☐

57. No. of lymph nodes resected: no info=99; unspecified=98 ☐☐

58. No. of metastasized lymph nodes: no info=99; unspecified=98 ☐☐

59. **Type of lymph node surgery** - no info=0; yes=1; no=2 ☐

60. Radical neck dissection=1; bilateral modified neck dissection=2;
unilateral modified neck dissection=3; node picking=4 ☐

61. **Radical surgery performed** - no info=0; yes=1; no=2;. ☐

62. if No, reason: tracheal growth=1; vascular growth=2
soft tissue=3; other=4 ☐

63. **Distant metastases at diagnosis** - no info=0; yes=1; no=2 ☐

64. Localization: lung=1; liver=2; skeleton=3; other=4 ☐

65. **Chemotherapy** - no info=0; yes=1; no=2 ☐

66. **External radiotherapy** - no info=0; yes=1; no=2 ☐

67. **^{131}I-treatment** - no info=0; yes=1; no=2 ☐

68. Date ☐☐☐☐☐☐

69. T_{24} % ☐☐☐

70. **Total no. of treatments** ☐☐

71. **Total ^{131}I amount, mCi** ☐☐☐☐☐

72. **Local recurrence 1** - no info=0; yes=1; no=2 ☐

73. Date of recurrence ☐☐☐☐☐☐

74. Treatment: no info=0; surgery=1; ext. radiotherapy=2;

^{131}I=3; 1+2=4; 2+3=5; 1+2+3=6 ; 1+3=7 ☐

75. **Local recurrence 2 -** no info=0; yes=1; no=2 ☐

76. Date of recurrence ☐☐☐☐☐☐

77. Treatment: no info=0; surgery=1; ext. radiotherapy=2;

^{131}I=3; 1+2=4; 2+3=5; 1+2+3=6; 1+3=7 ☐

78. **Distant metastases -** no info=0; yes=1; no=2 ☐

79. **Date of diagnosis** ☐☐☐☐☐☐

80. Localization 2: lung=1; liver=2; skeleton=3; other=4 ☐

81. Localization 3: lung=1; liver=2; skeleton=3; other=4 ☐

82. **Deceased -** no info=0; yes=1; no=2 ☐

83. Date ☐☐☐☐☐☐

84. Cause of death register, ICD-code ☐☐☐☐

85. Because of thyroid cancer - no info =0; yes=1; no=2, uncertain=3

with thyroid cancer =4 ☐

86. **Re-examination, histology -** no info=0; unspecified follicular=1;
minimally invasive follicular=2; widely invasive follicular=3;
papillary=4; papillary of follicular type=5;

papillary and follicular=6; other=7 ☐

87**.** Date of re-examination ☐☐☐☐☐☐

88. **Patient -** included=1; excluded=2; control=3;

re-examination=4 ☐

89. **Comments:** ……..……

……..

Signature of abstractor ……Date …….

11. ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to everyone who has supported and assisted me in so many different ways. In particular I wish to thank:

Per Hall, my supervisor, for guiding me into the world of epidemiology, for genuine and continuous encouragement, for a lot of enthusiasm, laughter, tough fights in squash and good friendship.
Jan Zedenius, my co-supervisor and colleague, a talented teacher of endocrine surgery, for your careful, detailed and very useful criticism, but most of all for being a generous and dear friend. A special thanks to **Inger** for your patience, when I occupied your kitchen table night after night with my computer and papers.
Paul Dickman, my co-supervisor, for all the hours you guided me towards statistical analysis, you managed with persistence and talented pedagogic strategies to lead me into the world of STATA and sometimes, against all odds, I enjoyed it.
Jan Frisell, my clinical tutor and mentor, my dear friend, who inspired me to work with breast and endocrine surgery, for making it possible to work, do research and still enjoy my family. For always believing in me and supporting me, no matter what.
Hans-Olov Adami, for your friendly encouragements and for giving me the opportunity to work and study at the Department of Epidemiology and Biostatistics.
Anders Ekbom, for introducing me to this project and for a great "epi-school" for clinicians.
Martin Bäckdahl, **Bo Angelin and Jörgen Larsson** for your interest in my thesis and for providing financial support throughout the years.
Bertil Hamberger for great support and interest in my work as well as nice friendship.
The "specialist group" **Göran Lundell**, **Jörgen Nordenström** and **Thomas Flodin** for helping me to decide who did or did not die in the study. A special thanks to Göran for always answering my clinical questions that were not to be found in the literature. And to Jörgen, my colleague, for introducing me into the world of PBL, EBM and teaching and for sharing important issues such as "stackars".
Milka Krestelica, for excellent technical support and for never giving up finding all the medical records, deep down in every archive. Most of all thanks for being such a great and caring friend.
Jan Eriksson for invaluable help with reading and re-evaluating the histopathological reports.
Elisabeth Bjurstedt for great secretarial support when starting the project.
Gunilla Sonnebring for marvellous help in proofreading this work.
To all fascinating people, representing almost the whole world, at MEB, especially my former room mate **Kjell Bergfeldt**, my friends in the corridor **Lena Rosenberg, Michaela Proschazka** and my present room mate **Mikael Hartman,** for sharing the ups and downs of epidemiology and biostatistics and celebrating every little step forward.
To my dear colleagues and very good friends (not already mentioned) at the Breast and Endocrine unit at Karolinska; **Catharina Eriksen, Fuat Celebioglu, Magnus Kjellman, Per Mattsson, Hanna Fredholm, Eva Reihner, Kerstin Sandelin, Leif Perbeck, Lars-Ove Farnebo, Göran Wallin** and **Birgit Stark,** for making work enjoyable and great. Also thanks to "**Agneta`s girls**" for keeping the friendly smiles and warm atmosphere.
Anders Somell, for being a brilliant teacher of endocrine surgery, and for showing me how it should be performed.
To all my **former** and **present colleagues** at Södersjukhuset, Södertälje sjukhus, Karolinska Universitetssjukhuset (Huddinge and Solna) for your support, interest and many laughs.
To all the **clinicians** throughout Sweden who provided medical records and patient data for this study.

To all my dear friends, for sharing so many fun memories and great moments together. A special thanks to **Anette** who encouraged me to find my way to Karolinska Institutet and for everything we shared since then, to **Anders** for always offering a helping hand, especially with IT-support and giving me a break in the sound of music, to **Goody** for all years of never ending laughter, lunches, talks and close friendship, to **Petra** for close and sincere friendship including everything from the yacht in Greece to the weekly non-stop-talk-power-walks.
To my dear and sweet cousin **Thomasine,** for drawing the front page.
To my four great parents in-law **Berit** & **Robert, Bengt** & **Barbro**, for invaluable help with the children, broken cars or just refilling our food supplies.
To my brothers **Jan** and **Henrik**, and their wonderful families for great moments especially at Rödsten.
To my father **Thomas**, who with your great personality, your humour and enthusiasm inspired me to become a surgeon, for reading my first drafts and for your and my mother **Gunilla's** endless support, love and friendship, for your never-failing belief and interest in my work and life.

To **Robert**, the love of my life, for your constant love and care, for your marvellous way of challenging me and making me achieve new goals. For your encouragement in my work and for sharing all that I love outside work that makes our life together exceptional.
And finally to my precious, **Susanna, Niklas** and **Michaela,** the brightest stars of the universe, for being my inspiration, my life, my everything.

This thesis was financially supported by the Swedish Cancer Foundation, the Cancer Society in Stockholm and the Åke Wiberg Foundation.

12. REFERENCES

1. **Mazzaferri EL**. Management of a solitary thyroid nodule. N Engl J Med 1993;328(8):553-9.
2. **McCaffrey TV**. Evaluation of the thyroid nodule. Cancer Control 2000;7(3):223-8.
3. **Wartofsky L**. Thyroid Cancer
A Comprehensive Guide to Clinical Management. Totowa, New Jersey: Humana Press; 1999.
4. **Schlumberger M, Pacini F**. Thyroid Tumors. second ed: Nucleon; 2003.
5. **Clark OH, Duh QY**. Textbook of Endocrine Surgery. 1 st ed. United States of America: Sunders Company; 1997.
6. **Parkin DM, Muir CS, Whelan SL, Gao YT, Ferlay S, J P**. Cancer incidence in five continents. Lyon, International Agency for Research on Cancer: IARC Scientific Publication; 1997.
7. **McIver B, Hay ID, Giuffrida DF, Dvorak CE, Grant CS, Thompson GB, et al.** Anaplastic thyroid carcinoma: a 50-year experience at a single institution. Surgery 2001;130(6):1028-34.
8. **Lundgren CI, Hall P, Ekbom A, Frisell J, Zedenius J, Dickman PW**. Incidence and survival of Swedish patients with differentiated thyroid cancer. Int J Cancer 2003;106(4):569-73.
9. **Schlumberger MJ**. Papillary and follicular thyroid carcinoma. N Engl J Med 1998;338(5):297-306.
10. **Ron E**. Thyroid Cancer. In: Schottenfeld D, editor. Cancer epidemiology and Prevention. p. 1000-1021.
11. **Fransilla KO, Saxen E, Teppo L, et al**. Incidence of different morphological types of thyroid cancer in the Nordic countries. APMS 1981;89;49-55.
12. **Pukkala**. Cancer Atlas of Northern Europe. In. Publication NO 62 ed. Helsinki: Cancer Society of Finland; 2001.
13. **Pettersson B, Coleman MP, Ron E, Adami HO**. Iodine supplementation in Sweden and regional trends in thyroid cancer incidence by histopathologic type. Int J Cancer 1996;65(1):13-9.
14. **Pacini F, Vorontsova T, Demidchik EP, Molinaro E, Agate L, Romei C, et al.** Post-Chernobyl thyroid carcinoma in Belarus children and adolescents: comparison with naturally occurring thyroid carcinoma in Italy and France. J Clin Endocrinol Metab 1997;82(11):3563-9.
15. **Nagataki S, Nystrom E**. Epidemiology and primary prevention of thyroid cancer. Thyroid 2002;12(10):889-96.
16. UNSCEAR 2000. The United Nations Scientific Committee on the Effects of Atomic Radiation; 2000 Sep.
17. **Negri E, Dal Maso L, Ron E, La Vecchia C, Mark SD, Preston-Martin S, et al.** A pooled analysis of case-control studies of thyroid cancer. II. Menstrual and reproductive factors. Cancer Causes Control 1999;10(2):143-55.
18. **Gyory F, Balazs G, Nagy EV, Juhasz F, Mezosi E, Szakall S, et al.** Differentiated thyroid cancer and outcome in iodine deficiency. Eur J Surg Oncol 2004;30(3):325-31.
19. **Negri E, Ron E, Franceschi S, Dal Maso L, Mark SD, Preston-Martin S, et al.** A pooled analysis of case-control studies of thyroid cancer. I. Methods. Cancer Causes Control 1999;10(2):131-42.
20. **Nikiforov Y E, Fagin JA**. Risk Factors for Thyroid Cancer. TEM 1997;8(1):20-25.
21. **Lundgren CI, Dickman PW, Zedenius J, Hall P**. Are possible risk factors for differentiated thyroid cancer of prognostic importance? Submitted.
22. **Mazzaferri EL, Jhiang SM**. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 1994;97(5):418-28.

23. **Baloch ZW, LiVolsi VA**. Prognostic factors in well-differentiated follicular-derived carcinoma and medullary thyroid carcinoma. Thyroid 2001;11(7):637-45.
24. **Dean DS, Hay ID**. Prognostic indicators in differentiated thyroid carcinoma. Cancer Control 2000;7(3):229-39.
25. **Sobin LH**. TNM, sixth edition: new developments in general concepts and rules. Semin Surg Oncol 2003;21(1):19-22.
26. **Loh KC, Greenspan FS, Gee L, Miller TR, Yeo PP**. Pathological tumor-node-metastasis (pTNM) staging for papillary and follicular thyroid carcinomas: a retrospective analysis of 700 patients. J Clin Endocrinol Metab 1997;82(11):3553-62.
27. **Hay ID, Grant CS, Taylor WF, McConahey WM**. Ipsilateral lobectomy versus bilateral lobar resection in papillary thyroid carcinoma: a retrospective analysis of surgical outcome using a novel prognostic scoring system. Surgery 1987;102(6):1088-95.
28. **Hay ID, Bergstralh EJ, Goellner JR, Ebersold JR, Grant CS**. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. Surgery 1993;114(6):1050-7; discussion 1057-8.
29. **Cady B, Rossi R**. An expanded view of risk-group definition in differentiated thyroid carcinoma. Surgery 1988;104(6):947-53.
30. **Pasieka JL, Zedenius J, Auer G, Grimelius L, Hoog A, Lundell G, et al.** Addition of nuclear DNA content to the AMES risk-group classification for papillary thyroid cancer. Surgery 1992;112(6):1154-9; discussion 1159-60.
31. **Byar DP, Green SB, Dor P, Williams ED, Colon J, van Gilse HA, et al.** A prognostic index for thyroid carcinoma. A study of the E.O.R.T.C. Thyroid Cancer Cooperative Group. Eur J Cancer 1979;15(8):1033-41.
32. **Yildirim E**. A model for predicting outcomes in patients with differentiated thyroid cancer and model performance in comparison with other classification systems. J Am Coll Surg 2005;200(3):378-92.
33. **Hadjieva T**. Scoring patients' risk in differentiated thyroid cancer. Onkologie 2001;24(6):561-8.
34. **Ortiz S, Rodriguez JM, Parrilla P, Perez D, Moreno-Gallego A, Rios A, et al.** Recurrent papillary thyroid cancer: analysis of prognostic factors including the histological variant. Eur J Surg 2001;167(6):406-12.
35. **Brierley JD, Panzarella T, Tsang RW, Gospodarowicz MK, O'Sullivan B**. A comparison of different staging systems predictability of patient outcome. Thyroid carcinoma as an example. Cancer 1997;79(12):2414-23.
36. **Sherman SI**. Thyroid carcinoma. Lancet 2003;361(9356):501-11.
37. **Hedinger C, Williams E, Sobin L**. Histological typing of thyroid tumours WHO, international histological classification of tumours: Springer-Verlag; 1988.
38. **Sywak M, Pasieka JL, Ogilvie T**. A review of thyroid cancer with intermediate differentiation. J Surg Oncol 2004;86(1):44-54.
39. **Caron NR, Clark OH**. Well differentiated thyroid cancer. Scand J Surg 2004;93(4):261-71.
40. **Hay ID**. Papillary thyroid carcinoma. Endocrinol Metab Clin North Am 1990;19(3):545-76.
41. **Ito Y, Tomoda C, Uruno T, Takamura Y, Miya A, Kobayashi K, et al.** Papillary microcarcinoma of the thyroid: how should it be treated? World J Surg 2004;28(11):1115-21.
42. **Ito Y, Kobayashi K, Tomoda C, Uruno T, Takamura Y, Miya A, et al.** Ill-defined edge on ultrasonographic examination can be a marker of aggressive characteristic of papillary thyroid microcarcinoma. World J Surg 2005;29(8):1007-11; discussion 1011-2.

43. **Lundgren CI, Hall P, Dickman PW, Zedenius J**. Clinically important prognostic factors in patients with differentiated thyroid cancer. A population-based nested case-control study. Cancer; in press.
44. **D'Avanzo A, Treseler P, Ituarte PH, Wong M, Streja L, Greenspan FS, et al.** Follicular thyroid carcinoma: histology and prognosis. Cancer 2004;100(6):1123-9.
45. **Kebebew E, Clark OH**. Differentiated thyroid cancer: "complete" rational approach. World J Surg 2000;24(8):942-51.
46. **Udelsman R, Shaha AR**. Is total thyroidectomy the best possible surgical management for well-differentiated thyroid cancer? Lancet Oncol 2005;6(7):529-31.
47. **Tsang RW, Brierley JD, Simpson WJ, Panzarella T, Gospodarowicz MK, Sutcliffe SB**. The effects of surgery, radioiodine, and external radiation therapy on the clinical outcome of patients with differentiated thyroid carcinoma. Cancer 1998;82(2):375-88.
48. **Mazzarotto R, Cesaro MG, Lora O, Rubello D, Casara D, Sotti G**. The role of external beam radiotherapy in the management of differentiated thyroid cancer. Biomed Pharmacother 2000;54(6):345-9.
49. **Brierley JD, Tsang RW**. External-beam radiation therapy in the treatment of differentiated thyroid cancer. Semin Surg Oncol 1999;16(1):42-9.
50. **Haugen BR**. Management of the patient with progressive radioiodine non-responsive disease. Semin Surg Oncol 1999;16(1):34-41.
51. **Kebebew E, Duh QY, Clark OH**. Total thyroidectomy or thyroid lobectomy in patients with low-risk differentiated thyroid cancer: surgical decision analysis of a controversy using a mathematical model. World J Surg 2000;24(11):1295-302.
52. **Shaha AR**. Thyroid Cancer:Extent of Thyroidectomy. Cancer Control 2000;7(3):240-245.
53. **Rosato L, Avenia N, Bernante P, De Palma M, Gulino G, Nasi PG, et al.** Complications of thyroid surgery: analysis of a multicentric study on 14,934 patients operated on in Italy over 5 years. World J Surg 2004;28(3):271-6.
54. **Shaha AR, Shah JP, Loree TR**. Low-risk differentiated thyroid cancer: the need for selective treatment. Ann Surg Oncol 1997;4(4):328-33.
55. **Hay ID, Grant CS, Bergstralh EJ, Thompson GB, van Heerden JA, Goellner JR**. Unilateral total lobectomy: is it sufficient surgical treatment for patients with AMES low-risk papillary thyroid carcinoma? Surgery 1998;124(6):958-64; discussion 964-6.
56. **Hay ID, Bergstralh EJ, Grant CS, McIver B, Thompson GB, van Heerden JA, et al.** Impact of primary surgery on outcome in 300 patients with pathologic tumor-node-metastasis stage III papillary thyroid carcinoma treated at one institution from 1940 through 1989. Surgery 1999;126(6):1173-81; discussion 1181-2.
57. **Mazzaferri EL, Kloos RT**. Clinical review 128: Current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metab 2001;86(4):1447-63.
58. **Lundgren CI, Hall P, Dickman PW, Zedenius J**. Influence of surgical and postoperative treatment on survival for patients with differentiated thyroid cancer. A population-based nested case-control study. Submitted.
59. **Verburg FA, de Keizer B, Lips CJ, Zelissen PM, de Klerk JM**. Prognostic significance of successful ablation with radioiodine of differentiated thyroid cancer patients. Eur J Endocrinol 2005;152(1):33-7.
60. **DeGroot LJ, Kaplan EL, McCormick M, Straus FH**. Natural history, treatment, and course of papillary thyroid carcinoma. J Clin Endocrinol Metab 1990;71(2):414-24.
61. **Simpson WJ, Panzarella T, Carruthers JS, Gospodarowicz MK, Sutcliffe SB**. Papillary and follicular thyroid cancer: impact of treatment in 1578 patients. Int J Radiat Oncol Biol Phys 1988;14(6):1063-75.

62. **Samaan NA, Schultz PN, Hickey RC, Goepfert H, Haynie TP, Johnston DA, et al.** The results of various modalities of treatment of well differentiated thyroid carcinomas: a retrospective review of 1599 patients. J Clin Endocrinol Metab 1992;75(3):714-20.
63. **Sawka AM, Thephamongkhol K, Brouwers M, Thabane L, Browman G, Gerstein HC**. Clinical review 170: A systematic review and metaanalysis of the effectiveness of radioactive iodine remnant ablation for well-differentiated thyroid cancer. J Clin Endocrinol Metab 2004;89(8):3668-76.
64. **Tubiana M, Haddad E, Schlumberger M, Hill C, Rougier P, Sarrazin D**. External radiotherapy in thyroid cancers. Cancer 1985;55(9 Suppl):2062-71.
65. **Andersen PE, Kinsella J, Loree TR, Shaha AR, Shah JP**. Differentiated carcinoma of the thyroid with extrathyroidal extension. Am J Surg 1995;170(5):467-70.
66. **Mazzaferri EL**. Long-term outcome of patients with differentiated thyroid carcinoma: effect of therapy. Endocr Pract 2000;6(6):469-76.
67. **Haugen BR**. Patients with differentiated thyroid carcinoma benefit from radioiodine remnant ablation. J Clin Endocrinol Metab 2004;89(8):3665-7.
68. **Ladenson PW, Braverman LE, Mazzaferri EL, Brucker-Davis F, Cooper DS, Garber JR, et al.** Comparison of administration of recombinant human thyrotropin with withdrawal of thyroid hormone for radioactive iodine scanning in patients with thyroid carcinoma. N Engl J Med 1997;337(13):888-96.
69. **Fernandes JK, Day TA, Richardson MS, Sharma AK**. Overview of the management of differentiated thyroid cancer. Curr Treat Options Oncol 2005;6(1):47-57.
70. **Spencer CA, Takeuchi M, Kazarosyan M**. Current status and performance goals for serum thyroglobulin assays. Clin Chem 1996;42(1):164-73.
71. **Mazzaferri EL, Robbins RJ, Spencer CA, Braverman LE, Pacini F, Wartofsky L, et al.** A consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma. J Clin Endocrinol Metab 2003;88(4):1433-41.
72. **Rothman JK, Greenland s**. Modern Epidemiology. 2nd ed. Philadelphia: Lippincott Williams &Wilkins; 1998.
73. **Hennekens CH, Buring JE**. Epidemiology in Medicine. First ed. Philadelphia: Lippincott Williams & Wilkins; 1987.
74. **Lunde AS, Lundeborg S, Lettenstrom GS, Thygesen L, Huebner J**. The person-number systems of Sweden, Norway, Denmark, and Israel. Vital Health Stat 2 1980(84):1-59.
75. **Mattsson B, Wallgren A**. Completeness of the Swedish Cancer Register. Non-notified cancer cases recorded on death certificates in 1978. Acta Radiol Oncol 1984;23(5):305-13.
76. National Board of Health and Welfare. Stockholm; 2001.
77. **Pettersson B, Adami HO, Wilander E, Coleman MP**. Trends in thyroid cancer incidence in Sweden, 1958-1981, by histopathologic type. Int J Cancer 1991;48(1):28-33.
78. **Hakulinen T**. Cancer survival corrected for heterogeneity in patient withdrawal. Biometrics 1982;38(4):933-42.
79. **Hakulinen T**. On long-term relative survival rates. J Chronic Dis 1977;30(7):431-43.
80. **Hakulinen T, Tenkanen L**. Regression analysis of relative survival rates. Appl Stat 1987(36):309-17.
81. **Hakulinen T, Abeywickrama KH**. A computer program package for relative survival analysis. Comput Programs Biomed 1985;19(2-3):197-207.
82. **Greenwood M**. The errors of sampling of the survivorship table. London; 1926.
83. **Grisso JA**. Making comparisons. Lancet 1993;342(8864):157-60.
84. **Hundahl SA, Fleming ID, Fremgen AM, Menck HR**. A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995 [see commetns]. Cancer 1998;83(12):2638-48.
85. **Kim S, Wei JP, Braveman JM, Brams DM**. Predicting outcome and directing therapy for papillary thyroid carcinoma. Arch Surg 2004;139(4):390-4; discussion 393-4.

86. **Cady B, Cohn K, Rossi RL, Sedgwick CE, Meissner WA, Werber J, et al.** The effect of thyroid hormone administration upon survival in patients with differentiated thyroid carcinoma. Surgery 1983;94(6):978-83.
87. **Hundahl SA, Cady B, Cunningham MP, Mazzaferri E, McKee RF, Rosai J, et al.** Initial results from a prospective cohort study of 5583 cases of thyroid carcinoma treated in the united states during 1996. U.S. and German Thyroid Cancer Study Group. An American College of Surgeons Commission on Cancer Patient Care Evaluation study. Cancer 2000;89(1):202-17.
88. **Sherman SI, Brierley JD, Sperling M, Ain KB, Bigos ST, Cooper DS, et al.** Prospective multicenter study of thyrois]carcinoma treatment: initial analysis of staging and outcome. National Thyroid Cancer Treatment Cooperative Study Registry Group. Cancer 1998;83(5):1012-21.
89. **Cady B**. Hayes Martin Lecture. Our AMES is true: how an old concept still hits the mark: or, risk group assignment points the arrow to rational therapy selection in differentiated thyroid cancer. Am J Surg 1997;174(5):462-8.
90. **Galanti MR, Hansson L, Lund E, Bergstrom R, Grimelius L, Stalsberg H, et al.** Reproductive history and cigarette smoking as risk factors for thyroid cancer in women: a population-based case-control study. Cancer Epidemiol Biomarkers Prev 1996;5(6):425-31.
91. **Galanti MR, Granath F, Cnattingius S, Ekbom-Schnell A, Ekbom A**. Cigarette smoking and the risk of goitre and thyroid nodules amongst parous women. J Intern Med 2005;258(3):257-64.
92. **Rossing MA, Cushing KL, Voigt LF, Wicklund KG, Daling JR**. Risk of papillary thyroid cancer in women in relation to smoking and alcohol consumption. Epidemiology 2000;11(1):49-54.
93. **Mack WJ, Preston-Martin S, Dal Maso L, Galanti R, Xiang M, Franceschi S, et al.** A pooled analysis of case-control studies of thyroid cancer: cigarette smoking and consumption of alcohol, coffee, and tea. Cancer Causes Control 2003;14(8):773-85.
94. **Malchoff CD, Malchoff DM**. The genetics of hereditary nonmedullary thyroid carcinoma. J Clin Endocrinol Metab 2002;87(6):2455-9.
95. **Sigurdson AJ, Ronckers CM, Mertens AC, Stovall M, Smith SA, Liu Y, et al.** Primary thyroid cancer after a first tumour in childhood (the Childhood Cancer Survivor Study): a nested case-control study. Lancet 2005;365(9476):2014-23.
96. **Wong JB, Kaplan MM, Meyer KB, Pauker SG**. Ablative radioactive iodine therapy for apparently localized thyroid carcinoma. A decision analytic perspective. Endocrinol Metab Clin North Am 1990;19(3):741-60.
97. **Haigh PI, Urbach DR, Rotstein LE**. Extent of thyroidectomy is not a major determinant of survival in low- or high-risk papillary thyroid cancer. Ann Surg Oncol 2005;12(1):81-9.
98. **Busnardo B, De Vido D**. The epidemiology and etiology of differentiated thyroid carcinoma. Biomed Pharmacother 2000;54(6):322-6.
99. **Kjellman P, Learoyd DL, Messina M, Weber G, Hoog A, Wallin G, et al.** Expression of the RET proto-oncogene in papillary thyroid carcinoma and its correlation with clinical outcome. Br J Surg 2001;88(4):557-63.
100. **Kjellman P, Wallin G, Hoog A, Auer G, Larsson C, Zedenius J**. MIB-1 index in thyroid tumors: a predictor of the clinical course in papillary thyroid carcinoma. Thyroid 2003;13(4):371-80.
101. **Bartolazzi A, Gasbarri A, Papotti M, Bussolati G, Lucante T, Khan A, et al.** Application of an immunodiagnostic method for improving preoperative diagnosis of nodular thyroid lesions. Lancet 2001;357(9269):1644-50.
102. **Kroll TG, Sarraf P, Pecciarini L, Chen CJ, Mueller E, Spiegelman BM, et al.** PAX8-PPARgamma1 fusion oncogene in human thyroid carcinoma [corrected]. Science 2000;289(5483):1357-60.

103. **Dwight T, Thoppe SR, Foukakis T, Lui WO, Wallin G, Hoog A, et al.** Involvement of the PAX8/peroxisome proliferator-activated receptor gamma rearrangement in follicular thyroid tumors. J Clin Endocrinol Metab 2003;88(9):4440-5.