Risk and prognostic factors for differentiated thyroid cancer

Abstract

Papillary and follicular carcinomas, commonly referred to as follicular cell-derived differentiated thyroid carcinomas (DTC), account for 90% of all thyroid carcinomas. The prognosis of DTC is generally good, depending on the biologic behavior of the tumor and on the appropriate initial treatment which includes total thyroidectomy and ablation by radioiodine-131. However, a considerable number of patients, approximately 30%, as shown after 30 years of follow-up, have recurrent disease. It is thus of utmost importance to evaluate the prognostic factors, as derived from retrospective studies, and identify high risk patients. Age of more than 45 years or less than 25 years is a particularly strong independent prognostic factor; on the contrary gender is a poor prognostic factor. Histological type of the cancer especially tall cancer cells and columnar cancer cells, as well as increased vascular invasion of the tumor, lymph-node and distant metastases, are all considered as risk factors that can lead to poor prognosis. Combined prognostic factors have been used to form scoring systems (SS) such as AGES, MACIS, AMES, EORTC and TNM for a more precise description of high or low risk patients. However, prognostic significance of the SS is limited, since they do not take into consideration the clinical status or the treatment procedure during the course of the disease. Molecular factors such as rearrangements of genes RET/PTC, RAS mutations and fusion of, paired box and 8/peroxisome proliferator-activated receptor gamma (PAX8/PPARγ) are also involved in thyroid cancer prognosis, while some others: human Pituitary- Tumor Transforming Gene (e.g. MIB-1, hPTTG) have been reported as additional prognostic factors. In this review we describe the risk and the prognostic factors of DTC as related to management and the outcome of DTC.

Hell J Nucl Med 2006; 9(3): 156-162

Leonidas Duntas[1], **Brigitte Maria Grab-Duntas**[2]

1. *Endocrine Unit, Evgenidion Hospital, University of Athens*
2. *Department of Nuclear Medicine, Medical Center of Athens, Greece*

Keywords: Differentiated thyroid cancer – Prognostic factors – Radioiodine-131 – Molecular factors – Scoring system

Correspondence address:
Leonidas Duntas, M.D.
Professor of Endocrinology, University of Ulm, Germany & Endocrine Clinic Evgenidion Hospital, University of Athens, 20 Papadiamantopoulou Street, 11528 Athens, Greece
Tel: 0030 210 6748 878,
Fax: 0030 210 67 56 718
E-mail: ledunt@otenet.gr

Received:
11 August 2006
Accepted revised:
18 November 2006

Introduction

The term differentiated thyroid carcinoma (DTC) defines papillary (PTC) and follicular thyroid carcinomas (FTC) and accounts for about 90% of all thyroid carcinomas. Patients with DTC have generally a good prognosis. However, a subgroup of these patients has a fatal outcome due to clinical and histological aggressive tumor course [1]. The recognition and evaluation of prognostic factors (PF) combined with data from molecular factors that evaluate the risk of recurrence and may stratify DTC patients, have been used for the selection of specific treatment modalities [2-4].

The risks of metastases, recurrence and of fatal outcome are related to several parameters, that have recently been summarized by the American Joint Committee on Cancer and International Union Against Cancer and by the National Cancer Comprehensive Network (AJCC/UICC and NCCN) (Table 1), [5]. However, it should be emphasized that a multivariate analysis is required for the determination of the independent prognostic value for each parameter [6].

This review aims to examine risk and PF in relation to management and the outcome of DTC.

Risk factors for DTC

Ionizing radiation is considered the predominant risk factor for inducing thyroid cancer. The thyroid gland is sensitive to external and internal radiation and strong dose-response relationship between the incidence of thyroid cancer and radiation absorbed dose has been reported [7]. The introduction between 1920 and 1950 of X-ray therapy in children with head and neck and with skin diseases and the consequent increase in thyroid cancer revealed that children are especially sensitive to radiation. Radiation treatment administered in infancy and childhood is considered a strong independent risk factor for the development of

Table 1. *Prognostic factors for metastases, risk of recurrence and death from DTC*

Patients related
Age < 15 years or > 45 years
Male gender
Familial history of thyroid cancer
Tumor related
Tumor diameter > 4 cm
Bilateral localization
Tumor extension beyond the thyroid capsule
Tumor subtypes: tall and columnar cell, Hürthle cell
Accentuated nuclear atypia, tumor necrosis
Vascular invasion
Cervical or mediastinal lymph nodes
Distant metastases
Low or no iodine uptake by the tumor or the metastases

DTC. This is likely due to the rapid cell proliferation in childhood. Indeed, the recent reporting that thyroid cells proliferate activity is decreased with age, documents a plausible explanation for the higher risk of radiation-induced thyroid cancer in children as compared to adults [8].

Radiation exposure due to nuclear fallout has also been identified as a major risk factor for inducing DTC, particularly in children. There is ample evidence indicating an increased incidence of thyroid cancer among atomic bomb survivors, more pronounced in young females [9]. Data from 4091 Hiroshima and Nagasaki survivors showed that thyroid gland displayed one of the highest solid tumor risk estimates [10, 11]. A significant linear dose-response relationship was observed for both malignant and benign thyroid nodules and it was estimated that about 37% of malignant tumors, 31% of benign nodules, and 25% of cysts, were associated with radiation exposure at a mean and median dose of 0.449 and 0.087 Sv, respectively [11].

The nuclear power plant accident in Chernobyl, Ukraine, increased the incidence of thyroid cancer from $1/10^6$ to $100/10^6$ in children in this region [12]. Those exposed to radioactive iodine-131 (^{131}I) have shown an increased risk of thyroid cancer for a wide range of doses and a linear dose-response from 0.1 to 1.2 Gy [13]. It is notable that two thirds of the population living in contaminated regions around the core of the accident, received doses lower than 1 mSv, whereas only one third received doses between 1 and 10 mSv [13]. However, twenty years after the accident, apart from the sizable increase in thyroid cancer incidence in children and adolescents, there is not a statistically proved radiation-related risk increase or rate increase in other cancers [14, 15]. Nevertheless, taking into consideration the doses received and the very large number of subjects exposed, it is expected that the number of thyroid cancers will rise and strict monitoring to detect them is mandatory [14]. Of course in cases of irradiation of the thyroid especially during childhood, a long-term follow-up is required.

In cases of nodular goiter, the age, sex, but not the multi nodular thyroid gland, accumulate for determining cancer risk. In a study of 5637 patients with nodular thyroid disease it was shown that the rate of malignancy was smaller in patients between 40-60 years and greater in patients younger than 30 years or older than 60 years [16]. The risk of a secondary malignancy in the forthcoming years in young women with DTC should also be considered. In a retrospective cohort study of 10,932 women with PTC, it was shown that they were at increased risk of in situ breast cancer, kidney cancer, and melanoma [17].

The high incidence of aggressive FTC as well as of anaplastic thyroid carcinomas in areas with iodine deficiency and of PTC in areas with high iodine intake, suggests that iodine intake may be involved in the pathogenesis of the disease and may invert the ratio between FTC and PTC [18]. However, the role of other nutritional factors, like selenium, has not yet been fully determined and therefore will not be considered [19].

Finally, family history is another risk factor for developing PTC. Epidemiological studies have shown that 5% of patients who develop thyroid cancer and especially those with PTC, have at least one relative with DTC [6]. An increased incidence of PTC has also been reported in patients with familial adenomatous polyposis coli and with its subtype, Gardner's syndrome [6, 20].

Table 2. *Survival studies in DTC (from ref. 60, modified)*

Author	Number of patients	Follow-up (y)	Survival	Prognostic factors
Tubiana M, 1985[25]	546	8-40	No data	Age, staging
Simpson WJ, 1988[83]	1074	6.5 (4-24)	20 y: PTC: 95%, FTC: 81%	Age, T4, M1, N1 differentiation
Akslen LA, 1991[84]	2479	2 (2-16)	5 y: 74.9% ♂, 81.9% ♀	Age, gender, T stage
Samaan NA, 1992[85]	1599	11 (2-43)	No data	Initial treatment
Shah JP, 1992[86]	931	No data	10 y: 87%	Histology, T_4, gender
Hay ID, 1993[87]	1779 (PTC)	12.7	10 y: 96%, 20 y: 95%	MACIS
Mazzaferri EL, 1994[32]	1355	15.7 (0.5-47)	10 y: 94.7%, ♂ ♀ 20 y: 89.9%	Age, gender, TNM stage
Hundahl SA, 1998[88]	49450	10	10 y: 85-93%	T stage, age

Clinical and histopathology prognostic factors

Age and gender

Age has been considered since 1925, an important PF for DTC [21]. Later, Crile and Hazard (1953) stressed the impact of age on natural history and prognosis of patients with thyroid cancer [22]. For patients below the age of 40, mortality rate at the time of diagnosis is low and increases progressively after the age of 40. Older than 65 years as compared to patients younger than 40 years, often develop locally aggressive tumors and have clinical recurrences [23, 24]. In a recent study, multivariate analysis revealed that age at the time of diagnosis was the most important factor in determining total expected survival [25]. In contrast, histological features of the DTC are unrelated to age [26]. Important studies indicating age as a prognostic factor for DTC are shown in Table 2.

Gender is of poor prognostic significance, since women with DTC show a slightly better survival than men [27].

Size

The risk of recurrence and DTC-related death is proportional to the increase in size of the primary tumor [6, 27]. The size of PTC varies from less than 1cm, defined as micro carcinoma, to large tumors predictive of recurrence and short survival time. When considering the tumor diameter at diagnosis, the cumulative risk for extra thyroidal infiltration and for proximal lymph node (LN) metastases is higher for PTC than for FTC. For distant metastases and for tumors of equal size, the risk is the same for both PTC and FTC [28].

Tumor localization and infiltration beyond the thyroid capsule

PTC is often presented with multiple foci in one or both lobes of the thyroid gland. It has been shown recently that multi locality of tumors is more likely to represent separate tumors than intra-thyroidal metastases of one tumor clone [29].

Tumor extension beyond the thyroid capsule is generally associated with poor prognosis and large studies have demonstrated via multivariate analysis that it represents an adverse PF [30, 31]. In this line of evidence, it has been reported from Greece in a retrospective analysis of 832 patients with DTC, that the extent of the disease at the time of diagnosis combined with male sex, tumor size, and age > 60 years, significantly decreased the remaining survival rate [32].

Tumor subtypes:

a. PTC

Patients with PTC exhibit a longer survival rate, mainly due to their younger age, as compared to those with FTC, with a ten-year survival up to 95% and 80%, respectively [33]. However, these figures may change depending on other related prognostic factors. The tall cell variant of PTC reported in 1976, is characterized by typical elongated tumor cells [34, 35]. This PTC variant is usually present in large tumors, over 5 cm of diameter in older male patients, and is associated with extra thyroidal manifestations and cancer related death, in up to 25% of the patients. Columnar cell carcinoma is a rare PTC variant with aggressive behavior, distant metastases and fatal outcome [36]. Finally, the diffuse sclerotic variant of PTC which affects children and adolescents, induces diffuse sclerosis of the thyroid gland, tumor related lymphocyte infiltrates, and lung metastases in up to 25% of the patients [37].

b. FTC

Hürthle cell carcinoma is a variant of FTC consisting of cancer cells, characterized by trans-capsular and/or vascular invasion, proximal LN metastases, and poor outcome [34, 38].

FTC manifests: a) in the minimal invasive form, with only capsular invasion, associated with good prognosis, and b) in the vascular invasive form, with hematogenous metastases to bones and lungs, causing death in up to 50% of the patients within a 10-year follow-up [34, 39].

In a nested case-control cohort study of 5123 patients with DTC, who survived at least one year after diagnosis, the PF of highest clinical significance were, histopathology subgroup, staging, including metastases and the completeness of surgery [40].

Encapsulated carcinoma, papillary, follicular or mixed, has a good prognosis.

Vascular invasion

In both PTC and FTC, histological detected vascular invasion of the tumor is a sign of tumor aggressiveness, leading to hematogenic invasion, distant metastases, and consequent poorer prognosis [41]. It has been demonstrated that DTC tumors with intra- and/or extra -thyroidal vascular invasion are prone to local recurrences and distant metastases, more frequent in FTC [42].

Metastases

Proximal LN metastases are more frequent in patients with PTC. In conjunction with age these metastases constitute a highly PF of tumor recurrence and cancer-related death [43]. However, limited proximal LN metastases have been shown not to influence survival rate [44]. In a recent study aiming to assess the prognostic impact of the extent of LN involvement and tumor extension beyond the thyroid capsule, 148 patients with DTC and LN metastases were investigated. [45]. Significant risk factors for persistent and recurrent DTC disease were found to be: the number of LN metastases, the extra capsular extent of the tumor, the site of location of LN metastases, combined with a tumor size of >4 cm, and the increase of the Tg level determined at 6-12 months after treatment.

In a study assessing survival in 172 DTC patients with loco-regional recurrences (LRR) it was demonstrated that age > 45 years, follicular histology, thyroid capsular infiltration, no radioiodine ablation of thyroid remnants, the presence of distant metastases as well as absence of radioiodine uptake, and thyroid bed location of the LRR, were associated with significantly reduced survival [46].

DTC patients with distant metastases have poor prognosis and considerably increased tumor-specific mortality. Additionally, the number, the size, and the specific location of

metastases are of importance. Patients with pulmonary micro metastases have a better survival rate than those with macro metastases, while the latter have a better survival rate than patients with skeletal metastases [47, 48]. Distant metastases have a worse outcome, especially if aged over 70 years [49]. Although the patients may live for long periods their overall survival is significantly influenced [50].

It is well known that patients affected by poorly differentiated DTC often exhibit lesions with increased metabolic activity, evidenced by enhanced glucose uptake, that usually have lost their ability to concentrate ^{131}I. The recent fusion of positron emission tomography and computerized tomography (PET/CT) imaging systems, offers considerable advantages over PET alone, related to a better anatomical localization of the hyper-metabolic lesions of metastases [51]. A study from the Memorial Sloan Kettering Center of 125 patients with DTC followed-up for forty months, showed that patients over 45 years, with distant metastases detected by PET, high rates of ^{18}F-fluorodeoxyglucose (FDG), ^{18}F-FDG uptake, and high volume of FDG-avid disease (> 125 ml) are associated with reduced survival [52]. The multivariate analysis demonstrated that the strongest predictor of survival was the volume of ^{18}F-FDG-avid disease [52].

Tumor cell nuclear DNA content

Although not used in clinical practice, the tumor grade based on the tumor cell nuclear DNA content is, especially in PTC, one of the best PF [53]. DNA ploidy pattern is an independent PF in multivariate analysis for PTC and Hürthle cell carcinoma [38]. In contrast, its importance has not been established in FTC.

Prognostic scoring systems

Several scoring systems (SS) assigning patients to low- and high-risk groups and based on multivariable regression analysis of the PF, have been developed. These SS represent the current staging classifications of DTC as follows: AGES was assigned in 1987 at the Mayo Clinic taking into account age, grade, tumor extent, and the size of the primary tumor [54]. Score of less than six constituted a low risk while higher than six a high risk [54]. This system has been modified by removing the factor of tumor grade and is currently based on metastases, age, tumor size, and extra-thyroidal extent (MACIS). Both these systems are based on the data from 1938 patients [55]. AMES SS was developed in the Lahey Clinic in 1988 and is based on age, distant metastases, the extent, and the size of the primary thyroid tumor [56, 57]. Patients are divided into two groups: younger than 45 years with excellent prognosis and older than 45 years with poor prognosis [34, 57]. The SS of the European Organization for Research on Treatment of Cancer (EORTC) is based on age, gender, histological type, extra thyroidal invasion, and distant metastases [58].

The TNM system has since 1987 been recognized as the international staging system; it was reviewed in 1992 and 2002 [38, 59]. It is based on the extent of the primary tumor (T), the presence or absence (N1 or N0) of lymph node metastases, and the presence or absence (M1 or M0) of distant metastases. The 1992 revision defines four stages of increasing risks of cancer-related death, while the 2002 revision has produced a more complicated and less clinically applicable classification system [6]. The most significant alteration of the last edition of the 2002 revision was the re-classification of tumor staging. This revision divides tumors according to the degree of extra-thyroid extension and therefore, it might be of assistance predicting more accurately different outcomes in patients with extra-thyroid extension of the DTC [60]. The TNM system is nevertheless the most popular staging system. This is mainly due to the fact that AJCC/UICC TNM classification is universally available and widely accepted [61]. In a cohort study of DTC patients, the multivariate analysis showed that TNM at stage T4 and also age and distant metastases, are associated with increased risk for thyroid cancer related death [62].

Nevertheless, in a comparative study all SS were able to discern a low-risk DTC group [63]. In this study the relevance of the TNM system was improved by pooling stages I and II. This SS could probably be further improved by the insertion of the extent of surgery. However, the application of these SS to determine the risk of recurrence is inevitably limited, since they do not take into consideration the clinical status or timely diagnosis and treatment, as related to the course of the disease.

Molecular factors

Tyrosine kinase receptor genes, such as RET, are known to be involved in the pathogenesis of PTC through gene rearrangement. The rearrangement of the RET protein, via three activating genes (H4, R1a and ELE1), activates the RAS/RES/MAP kinase signaling pathway, resulting in genetic instability and formation of the RET/PTC oncogene [34,64]. The RET/PTC and TRK re-arrangements are specific and common genetic alterations in PTC. There are at least 10 different types of RET/PTC. RET/PTC1 is commonly expressed by sporadic PTC, whereas PTC3 is up to 80% expressed by solid, aggressive, radiation induced PTC, such as those observed as a result of the Chernobyl accident [65]. Positive RET immune reactivity is more common in radiation-related cancers than in those from patients without exposure to radiation [66].

Several genes have been studied for mutations in both PTC and FTC. Following point mutations, the mutated RAS gene stimulates cell division and inhibits cell differentiation, thus leading to genomic instability and further mutagenic cascades [67]. The frequency of RAS mutations is lower in PTC than in FTC.

The systematic search for mutations in the RAS/RAF/MEK/ERK signal transduction cascade, an important mediator of cell proliferation and differentiation, revealed somatic point mutations in the BRAF gene in PTC [68]. All BRAF mutations involved a thymine-to-adenine tranversion at the 1796 nucleotide and are unique genetic anomalies found in a

percentage of 38% in PTC. BRAF mutations have been associated with advanced age and a more aggressive subtype of PTC [68]. Even though additional rearrangements, such as RET/PTC and/or mutations in the RAS gene may be present in PTC while no overlap has been observed with BRAF mutations, pointing out that activation of BRAF is directly related to the thyrocytes transformation to PTC cells [69]. Recently, it has been reported that the somatic point mutation of the BRAF gene (V600E), which is considered as the most common genetic event in PTC, has a prevalence of about 38-40% and was found more often in older age than in childhood or in adolescence but without any association with aggressive clinical behavior [70, 71].

Genetic alterations are the driving force for thyroid tumor genesis and the BRAF mutations may prove to have an important impact on thyroid cancer. Novel treatment approaches may well be developed based upon this finding [72].

Recently, a translocation involving the fusion of the PAX8 gene and peroxisome proliferator-activated receptor γ (PPARγ) have been detected in FTC [73]. The presence of this re-arrangement is likely to be highly suggestive of malignancy. Currently the RAS and PPARγ have been considered as the two most important oncogenes, although other unidentified genes may also be involved in the pathogenesis of FTC [74,75]. There is evidence that the detection of various molecular factors may improve accuracy of preoperative diagnosis and staging of the disease.

The sodium-iodide symporter (NIS) is a glycoprotein, essential for iodine uptake and thyroid hormone synthesis and is expressed by the thyroid at the basolateral cell border [76]. NIS is expressed by PTC and FTC. However, data are as yet insufficient to conclusively establish whether NIS expression in tumor patients has an impact on clinical outcome. It has been hypothesized that failure to detect NIS by immuno-staining, in thyroid tumors might be associated with the need for a higher radioactive iodine dose and an inversed recurrence risk [77]. In the same study it was reported that undetectable NIS expression in children and adolescents, is associated with distant metastases and recurrence of the PTC or the FTC [77].

In a retrospective study of 225 patients with PTC and FTC, the immunohistochemical detection of P53 protein was found to be a significant and independent prognostic indicator of recurrence and death [78]. Thus, immunohistochemical detection of P53 in the tumor, might be an independent PF and of value in the treatment planning of patients with DTC [78].

It has recently been reported that a monoclonal antibody (MIB-1) can recognize the antigen Ki-67, an index of cell proliferating activity expressed on the nucleus of all proliferating cells [79]. The MIB-1 index, which includes the Ki-67 index, given as the percentage of MIB-1 positive cells, was positively associated with the clinical course of PTC. A value of MIB-1 index of 1.9% or higher, appeared to be the optimal cut off value to distinguish malignant tumors [79]. Although overlap limits its clinical testing, elaborating this index it may be helpful by providing valuable information on proliferation activity that could be added to other established PF.

Recently in DTC an over-expression of the human pituitary transforming gene (HPTTG), which is regulated through the cell cycle and is peaking at mitosis, has been demonstrated [80]. Moreover, an increased pre-translational HPTTG mRNA expression in FTC and in PTC has been reported [81]. In a more recent study examining the expression of HPPTG in 95 patients thyroidectomized for DTC, a significant association between HPPTG and nodal or distant metastases and between HPPTG over-expression and decreased radioiodine uptake, has been documented [82]. Therefore, the immunohistochemical analysis of HPPTG might be of value in evaluating the aggressiveness of DTC.

In conclusion, there is sufficient evidence suggesting that: age at diagnosis, histologic type, and tumor stage, including metastases, are important PF in DTC; they are of value identifying patients at increased risk for persistent disease, recurrence, and thyroid cancer related-death, and consequently should be taken into consideration in the treatment planning and follow-up of these patients. Imaging methods like ^{18}FDG-PET scanning and also gene expression, will enhance the predictability of prognosis and establish new prognostic indicators.

Bibliography

1. DeGroot LJ, Kaplan EL, McCormick M, Straus FH. Natural history, treatment, and course of papillary thyroid carcinoma. *J Clin Endocrinol Metab* 1990; 71:414-424.
2. Mazzaferri EL. Papillary thyroid carcinoma: factors influencing prognosis and current therapy. *Sem Oncol* 1987; 14: 315-332.
3. Shaha AR. Thyroid carcinoma: implications of prognostic factors. *Cancer* 1998; 83: 401-402.
4. Cady B. Papillary carcinoma of the thyroid gland: treatment bared on risk group definition. *Surg Oncol Clin N Am* 1998; 7: 633-644.
5. NCCN and AJCC/IUCC thyroid carcinoma practice guidelines. In: http://www.nccn.org/physician_gls/f_ guidelines.html 2003.
6. Schlumberger M, Pacini F. Thyroid Tumors. 2nd edn, *Nucleon* 2003; 111-125.
7. Somerville H, Steinbeck K, Delbridge L, Stevens M. Thyroid cancer after neck irradiation during childhood. *Lancet* 2005; 366: 805.
8. Saad AG, Kumar S, Ron E, et al. Proliferative activity of human thyroid cells in various age groups and its correlation with the risk of thyroid cancer after radiation exposure, *J Clin Endocrinol Metab* 2006; 91: 2672-2676.
9. Nagataki S, Shibata Y, Inoue S, et al. Thyroid disease among atomic bomb survivors in Nagasaki. *JAMA* 1994; 272: 364-370.
10. Takeichi N, Ezaki H, Dohi K. A. review of forty-five years study of Hiroshima and Nagasaki atomic bomb survivors. Thyroid cancer: reports up to date and a review. *J Radiat RES* 1991; (Suppl-32) 180-188.
11. Imaizumi M, Usa T, Tominaga T, et al. Radiation dose response relationships for thyroid nodules and autoimmune thyroid diseases in Hiroshima and Nagasaki bomb survivors 55-58 years after radiation exposure. *JAMA* 2006; 9: 1011-1022.
12. Radiological consequences of Chernobyl accident: UN scientific Committee on effects of atomic radiation confirms earlier IAEA assessments. *Sci Total Environ* 2000; 258: 209.
13. Grammaticos P. Some of the statements of the International Committee on Nuclear Technology (ILK) about the impacts of the Chernobyl accident after twenty years. *Hell J Nucl Med* 2006; 9: 2-4.
14. Cardis E, Howe G, Ron E, et al. Cancer consequences of the Chernobyl accident 20 years on. *J Radiol Prot* 2006; 26: 127-140.
15. Cardis E, Krewski D, Boniol M, et al. Estimates of the cancer burden in Europe from radioactive fallout from the Chernobyl accident. *Int J Cancer* 2006; 119: 1224-1235.

16. Bjarnason O, Michie W. Thyroid cancer in an iodine rich area. A histopathological study. *Cancer* 1977; 39: 212-222.
17. Canchola AJ, Horn-Ross PL, Purdie DM. Risk of second primary malignancies in women with papillary thyroid cancer. *Am J Epidemiol* 2006; 163: 521-527.
18. Belfiore A, La Rosa GL, La Porta GA, et al. Cancer risk in patients with cold thyroid nodules: relevance of iodine intake, sex, age, and multinodularity. *Am J Med* 1992; 93: 363-369.
19. Duntas LH. The role of selenium in thyroid autoimmunity and cancer. *Thyroid* 2006; 16: 455-460.
20. Bell B, Mazzaferri EL. Familial adenomatous polyposis (Gardner's syndrome) and thyroid carcinoma. A case report and review of the literature. *Dig Dis Sc* 1993; 38: 185-190.
21. Craver LF. Cancer of the thyroid and its present-day treatment. *Ann Surgery* 1925; 82: 833-853.
22. Crile GJ, Hazard JB. Relationship of the age of the patient to the natural history and prognosis of carcinoma of the thyroid carcinoma. *Ann Surgery* 1953; 138: 33-38.
23. Cunningham MP, Duda RB, Recant W, et al. Survival discriminants for differentiated thyroid cancer. *Am J Surg* 1990; 160: 344-347.
24. Ward LS, Assumpção LVM. Câncer diferenciado da tiróide: fatores prognósticos e tratamento. *Arq Bras Endocrinol Metab* 2004; 48: 126-136.
25. Ronga G, Filesi M, Montesano T, et al. Death from differentiated thyroid carcinoma: retrospective study of a 40-year investigation. *Cancer Biother Radiopharm* 2002; 17: 507-514.
26. Tubiana M, Schlumberger M, Rougier P, et al. Long-term results and prognostic factors in patients with differentiated thyroid carcinoma. *Cancer* 1985; 55: 794-804.
27. Mazzaferri EL, Kloos RT. Current approaches to primary therapy for papillary and follicular thyroid cancer. *J Clin Endocrinol Metab* 2001; 86: 1447-1463.
28. Machens A, Holzhausen HJ, Dralle H. The prognostic value of primary tumor size in papillary and follicular thyroid carcinoma. *Cancer* 2005; 103: 2269-2273.
29. Sugg SL, Ezzat S, Rosen IB, et al. Distinct multiple RET/PTC rearrangements in multifocal papillary thyroid neoplasia. *J Clin Endocrinol Metab* 1998; 83: 4116-4122.
30. Shaha AR, Loree TR, Shah JP. Prognostic factors and risk group analysis in follicular carcinoma of the thyroid. *Surgery* 1995; 118: 1136-1138.
31. Hay ID, Bergstrahl EJ, Goelner JR et al. 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: 1050-1058.
32. Tzavara I, Vlassopoulou B, Alevizaki C, et al. Differentiated thyroid cancer: a retrospective analysis of 832 cases from Greece. *Clin Endocrinol* 1999; 50: 643-654.
33. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med* 1994; 97: 418-428.
34. Baloch ZW, LiVolsi VA. Prognostic factors in well-differentiated follicular-derived carcinoma and medullary thyroid carcinoma. *Thyroid* 2001; 11: 637-645.
35. Hawk WA, Hazzard JB. The many appearances of papillary carcinoma of the thyroid. *Clev Clin Q* 1976; 43: 207-216.
36. Evans HL, Columnar-cell carcinoma of the thyroid. A report of two cases of an aggRESsive variant of thyroid carcinoma. *Am J Clin Pathol* 1986; 85: 77-80.
37. Chan JKC, Tsui MS, Tse CH. Diffuse sclerotic variant of papillary thyroid carcinoma. A histological and immunohistochemical study of three cases. *Histopathology* 1987; 11: 191-201.
38. Chen H, Nicol TL, Zeiger Ma, et al. Hurthle cell neoplasms of the thyroid: Are there factors predictive of malignancy? *Ann Surg* 1998; 227: 542-546.
39. Brennan MD, Bergstrahl EJ, van Heerden JA, Mc Conahey WM. Follicular thyroid cancer treated at the Mayo Clinic: 1946 through 1970: initial manifestations, pathologic findings, therapy and outcome. *Mayo Clin Proc* 1991; 66: 11-19.
40. Lundgren CI, Hall P, Dickman PW, Zedenius J. Clinically significant prognostic factors for differentiated thyroid carcinoma: a population-based nested case-control study. *Cancer* 2006; 20: 524-531.
41. Falvo L, Catania A, D'Andrea V, et al. Prognostic importance of histologic vascular invasion in papillary thyroid carcinoma. *Ann Surg* 2005; 241: 640-646.
42. Gardner RE, Tuttle RM, Burman KD et al. Prognostic importance of vascular innocence in papillary thyroid carcinoma. *Arch Otolaryngol Head Neck Surg* 2000; 126: 309-312.
43. Hughes CJ, Shaha AR, Shah JP, Loree TR. Impact of lymph node metastasis in differentiated carcinoma of the thyroid: A matched-pair analysis. *Head Neck* 1996; 18: 127-132.
44. Lin JD, Liou MJ, Chao TC, et al. Prognostic variables of papillary and follicular thyroid carcinoma patients with lymph node metastases and without distant metastases. *Endocrine-Related Cancer* 1999; 6: 109-115.
45. Leboulleux S, Rubino C, Baudin E, et al. Prognostic factors for persistent and recurrent disease of papillary thyroid carcinoma with neck lymph node metastases and/or tumor extension beyond the thyroid capsule at initial diagnosis. *J Clin Endocrinol Metab* 2005; 90: 5723-5729.
46. Rouxel A, Hejblum G, Bernier MO, et al. Prognostic factors associated with the survival of patients developing loco-regional recurrences of differentiated thyroid carcinomas. *J Clin Endocrinol Metab* 2004; 89: 5362-5368.
47. Clark OH. Predictors of thyroid tumor aggRESsiveness. *West J Med* 1996; 165: 131-138.
48. Maxon HR III. The role of 131I in the treatment of thyroid cancers. *Thyroid Today* 1993; 16: 1-9.
49. Haq M, Harmer C. Differentiated thyroid carcinoma with distant metastases at presentation: prognostic factors and outcome. *Clin Endocrinol (Oxf)* 2005; 63: 87-93.
50. Clark JR, Lai P, Hall F et al. Variables predicting distant metastases in thyroid cancer. *Laryngoscope* 2005; 115: 661-667.
51. Nanni C, Rubello D, Fanti S, et al. Role of 18FDG-PET and PET/CT imaging in thyroid cancer. *Biomed Pharmacother* 2006; 60: 409-413.
52. Wang W, Larson SM, Fazzari M, et al. Prognostic value of [18F] fluorodeoxyglucose positron emission tomographic scanning in patients with thyroid cancer. *J Clin Endocrinol Metab* 2000; 3: 1107-1113.
53. Hay ID. Papillary thyroid carcinoma. *Endocrinol Metab Clin North Am* 1990; 19: 545-576.
54. 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* 1988; 102: 1088-1095.
55. Hay ID, Goellner JR, Ebershold 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: 1139-1147.
56. Cady B, Rossi R. An expanded view of risk-group definition in differentiated thyroid carcinoma. *Surgery* 1988; 104: 947-953.
57. Kuriakose AM, Hics WL Jr, Lore TR, Yee H. Risk group-based management of differentiated thyroid carcinoma. *J R Coll Surg Edinb* 2001; 46: 216-223.
58. Byar DP, Dor P, Williams ED, et al. A prognostic index for thyroid carcinoma: A study of the EORTC Thyroid Cancer Cooperative Group. *Eur J Cancer* 1979; 15: 1033-1041.
59. Loh KC, Greenspan PS, Gee L, et al. Pathological tumor-node metastases (pTNM) satging for papillary and follicular thyroid carcinomas: a retrospective analysis of 700 patients. *J Clin Endocrinol Metab* 1997; 82: 3553-3562.
60. Wada N, Nakayama H, Suganuma N, et al. Prognostic value of the sixth edition AJCC/UICC TNM classification for differentiated thyoid carcinoma with extrathyroid extension. *J Clin Endocrinol Metab* 2006; Epub ahead of print.
61. Brierley JD, Panzarella T, Tsang RW, et al. A comparison of different staging systems predictability of patient outcome. Thyroid carcinoma as an example. *Cancer* 1997; 79: 2414-2423.

62. Eustatia-Rutten CFA, Crossmit EPM, Biermasz NR, et al. Survival and death causes in differentiated thyroid carcinoma. *J Clin Endocrinol Metab* 2006; 91: 313-319.
63. Jukkola A, Bloigu R, Ebeling PS, et al. Prognostic factors in differentiated thyroid carcinomas and their implications for current staging classifications. *Endocr Relat Cancer* 2004; 11: 571-579.
64. Fusco A, Griego M, Santoro M, et al. A new oncogene in human papillary carcinomas and their lymphoidal metastases. *Nature* 1987; 170-172.
65. Nikiforov YE. RET/PTC rearrangement in thyroid tumors. *Endocr Pathol* 2002; 13: 3-16.
66. Collins BJ, Chiapetta G, Schneider AB, et al. RET expression in papillary thyroid cancer from patients irradiated in childhood for benign conditions. *J Clin Endocrinol Metab* 2002; 87: 3941-3946.
67. Hara H, Fulton N, Yashizo T, et al. N-RAS mutation: an independent prognostic factor for aggressiveness of papillary thyroid carcinoma. *Surgery* 1994; 116: 1010-1016.
68. Kimura ET, Nikiforova MN, Zhu Z, et al. High prevalence of RES mutations in thyroid cancer: genetic evidence for constitutive activation of the RET/PTC-RAS-RES signaling pathway in papillary thyroid carcinoma. *Cancer* 2003; 63: 1454-1457.
69. Nikiforova MN, Kimura ET, Gandhi M, et al. RES mutations in thyroid tumors are restricted to papillary carcinomas and anaplastic or poorly differentiated carcinomas arising from papillary carcinomas. *J Clin Endocrinol Metab* 2003; 88: 5399-5404.
70. Fuggazzola L, Puxeddu E, Avenia N, et al. Correlation between B-RAFV600E mutation and clinocopathologic parameters in papillary thyroid carcinoma: data from a multicentric Italian study and review of the literature. *Endocr Relat Cancer* 2006; 13: 455-464.
71. Sapio MR, Posca D, Troncone G, et al. Detection of BRAF mutation in thyroid papillary carcinomas by mutant allele-specific PCR amplification (MASA). *Eur J Endocrinol* 2006; 154: 341-348.
72. Xing N. RAS mutation in thyroid cancer. *Endocr Relat Cancer* 2005; 12: 245-262.
73. Nikiforova MN, Biddinger PW, Caudill CM, et al. PAX/8-PPRAγ rearrangement in thyroid tumors: RT-PCR and immunohistochemical analyses. *Am J Surg Pathol* 2003;26: 1016-1023.
74. Dwight T, Srinivasan RT, Foukakis T, et al. Involvement of PAX/peroxisome proliferator activated receptor γ rearrangement in follicular thyroid tumors. *J Clin Endocrinol Metab* 2003; 88: 4440-4445.
75. Karger S, Berger K, Eszinger M, et al. Evaluation of peroxisome proliferator-activated receptor-γ expression in benign and malignant thyroid pathologies. *Thyroid* 2005; 15: 997-1003.
76. Ajjan RA, Kamaruddin NA, Crisp M, et al. Regulation and tissue distribution of the human sodium symporter gene. *Clin Endocrinol (Oxf)* 1998; 49: 517-523.
77. Patel A, Jhiang S, Dogra S, et al. Differentiated thyroid carcinomas that express sodium-iodide symporter have a lower risk of recurrence for children and adolescents. *Ped Res* 2002; 52: 737-744.
78. Godballe C, Asschenfeldt P, Jorgensen KE, et al. Prognostic factors in papillary and follicular thyroid carcinomas: p53 expression is a significant indicator of prognosis. *Laryngoscope* 1998; 108: 243-249.
79. Kjellman P, Wallin G, Hoog A, et al. MIB-1 index in thyroid tumors: a predictor of the clinical course in papillary thyroid carcinoma. *Thyroid* 2003; 13: 371-380.
80. Ramos-Morales F, Dominguez A, Romero F, et al. Cell cycle regulated expression and phosphorylation of hpttg proto-oncogene product. *Oncogene* 2000; 19: 403-409.
81. Boelaert K, McCabe CJ, Tannahill LA, et al. Pituitary tumor transforming gene and fibroblast growth factor-2 expression: potential prognostic indicators in differentiated thyroid cancer. *J Clin Endocrinol Metab* 2003; 88: 2341-2347.
82. Saez C, Martinez-Brocca A, Castilla C, et al. Prognostic significance of hpptg. Immunohistochemical expression in differentiated thyroid cancer. *J Clin Endocrinol Metab* 2006; 91:1404-1409.
83. Simpson WJ, Panzarella T, Carruthers JS, et al. Papillary and follicular thyroid cancer: impact of treatment in 1578 patients. *Int J Radiat Oncol Biol Phys* 1988; 14: 1063-1075.
84. Akslen LA, Haldorsen T, Thoressen SO, et al. Survival and causes of death in thyroid cancer: a population-based study of 2479 cases from Norway. *Cancer Res* 1991; 51: 1234-1241.
85. Samaan NA, Schultz PN, Hickey RC, 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; 75:714-720.
86. Shah JP, Loree TR, Dharker D, et al. Prognostic factors in differentiated carcinoma of the thyroid gland. *Am J Surg* 1992; 164: 658-666.
87. Hay ID, Bergstralh EJ, Goellner JR, et al. 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; 114:1050-1057.
88. Hundahl SA, Fleming ID, Fremgen AM, et al. A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995. *Cancer* 1998; 83:2638-2648.