[Frontiers in Bioscience 11, 2206-2212, September 1, 2006]

Surgical treatment of differentiated thyroid carcinoma: a retrospective study

Pasquale Sperlongano [1], Domenico Parmeggiani [1], Donatella Pisaniello [1], Massimo De Falco [1] , Ignazio Sordelli [1], Marina Accardo [2], Vincenzo Cuccurullo [3], Luigi Mansi [6], Gian Paolo Tartaro [4], Alfonso Barbarisi [5], Nicola Avenia [6] and Umberto Parmeggiani [1]

[1] Department of Anaesthesiological, Surgical and Emergency Sciences, Vth Unit of Surgery and Advanced Surgical Procedures, Second University of Naples, Piazza Miraglia, Naples, Italy, [2] Department of Morphopathology Second University of Naples., [3] Nuclear Medicine Second University of Naples, [4] IXth Unit of Biotechnology Applied to Surgery, Second University of Naples, [4] Department of Head and Neck Surgery, Second University of Naples, [5] Department of Head and Neck Surgery, Hospital of Terni, Italy

TABLE OF CONTENTS

1. ABSTRACT

A retrospective study was carried out to assessed reliability of the prognostic factors (histology, age, sex, and stage), and standard procedures for the surgical treatment of differentiated thyroid cancers (DTC). From the 144 DTC cases reviewed with follow-up ranging from 1 to 25 years (m=6.33 years), total mortality for cancer was found to be 55% (8 patients), with a predictive positive value for recurrence of 95.4% and 91.8% at 12 and 24 months, respectively. Median survival was 8.8 years (range 1 to 25 years). The multivariate analysis showed that factors such as age > 45 years, histology of intermediate malignancy, size up to 1.5 cm, and presence of metastases, significantly worsened the prognosis, regardless of the intervention that was carried out. We suggest total thyroidectomy for the treatment of benign pathologies and confirmed or susepected cases of cancer. We reserve loboisthmectomy for the treatment of benign pathologies confined to one lobe or those with FNAB suggesting a follicular neoplasm.

2. INTRODUCTION

The term differentiated thyroid cancers (DTC) refers to the most frequent and differentiated forms of thyroid cancers originating from the follicular epithelium. By a retrospective analysis of DTCs encountered in our experience, we intended to assess the easily known and reliable prognostic factors (histology, age, sex, and stage) and to identify, where possible, standard procedures for the appropriate surgical treatment.

In differentiated thyroid cancers there are several prognostic factors that gave rise to the various score staging systems (Ages, Ames, Macis etc.) (1, 2, 3). Although they are all prognostically reliable, nonetheless appropriate treatment cannot be selected solely on these systems. Some parameters for the score are valuable only after surgery (histology, T stage). Thus there is ample reason to prefer total thyroidectomy, mainly based on the possibility of a more effective and efficient follow-up (4).

Table 1. Surgical Cases: Differentiated Thyroid Carcinoma (1978 – 2003)

Patients	**144**
Follow-up	1 – 25 years (average 7.3 years)
Drop out – N° and % of patients lost to follow-up	20 cases (13.8 %)
Overall Mortality	8 cases[1] / 124 (6.45 %)
Overall Survival	114 cases/ 124 (91.93 %)
Overall Survival free from disease	110 cases/124 (88.70 %)

[1] One patient died of cardiovascular disease and one died of acute leukemia

Table 2. Cases divided by surgical procedure

Surgical procedure	**Number of cases**	**Lymphectomy**
Total Thyroidectomy	117	18
Initial total	95	11
Second step total thyrodectomy	15	4
Total thyroidectomy in patients already treated elsewhere	7	3
Subtotal Thyroidectomy	20	
Lobo-Histhmectomy	7	

In spite of an increased accuracy of pre-operative diagnostic tools (ultrasound-guided FNAB, color and power Doppler, nuclear medicine with sesta-MIBI indicator) (5, 6, 7), only less than half of cancers are diagnosed pre-operatively; 10-15% have doubtful cytological diagnosis, and about 40% are given a generic diagnosis of mutinodular goiter. Still two main issues are of concern. Surely, there are cases in which conservative surgery (loboisthmectomy or subtotal thyroidectomy) followed by opotherapy is able to ensure the same therapeutic result of total thyroidectomy. This is a matter of knowing if and what are the prognostic parameters of success that can direct the indications. The second issue, strictly related to the first, is to consider as resolutive only two main interventions: total thyroidectomy or lobo-isthmectomy. To answer our first question, we chose to evaluate our own experience on the basis of variables of greater prognostic weight, trying to identify acquirable preoperative data able to influence the surgical choice . The second question finds an answer in the improvement of preoperative diagnostics, able to provide a more refined study of the thyroid ultrastructure.

3. PATIENTS AND METHODS

Our personal experience relies on 144 cases of DTC (39M, 105F), operated during more than 25 years (1978-2003) (table 1); we carried out 95 total thyroidectomies, 11 of them associated with laterocervical lymphoadenectomy and two associated with laterocervical and upperclavear lymphoadenectomy; seven totalizations in patients who underwent previous surgery elsewhere, four of them associated with lymphadenectomy, 20 subtotal thyroidectomies, two of them followed by lymphoadenectomy and 22 loboistmectomies; among these patients,12 of them accepted totalization, three were totalized with respective laterocervical lymphadenectomy, three refused the operation, and in four of them loboisthmectomy was considered radical surgical treatment (table 2).

All the data of the prognostic variables examined make it clear that:

3.1. Age

It is known that DTC found over 40 years of age shows a worse prognosis than in younger patients (8, 9, 10) with adverse effects increasing decade by decade. We accepted the age of 45 as staging preliminary discriminant.

3.2. Gender

The variable of gender seems to have a prognostic role lower than that of age. Although the statistical analysis assign to males a reliable predictive meaning, its weight is still doubtful.

3.3. Histotype and grading

The definition itself of follicular and papillary neoplasm traditionally has a prognostic meaning that gives papillary forms a better prognosis (80-90% survival after 10 years) than follicular ones (65-75% survival after 10 years). However these differences disappear when groups of patients of the same age and stage are compared (8 – 16). Therefore the main difference is that, as a rule, follicular cancers are discovered in advanced age and stages.

We adopted the classification proposed by the pathologists Carcangiu and Rosai that tests and classifies the histological form according to morphological methods of prognostic valence. This classification divides all cancer arising from the follicular epithelium into three fundamental groups (17).

1. Low malignancy (78% of cases), including all the typical forms of papillary carcinoma, the follicular variations of papillary carcinoma, the forms of sclerosing carcinoma, the differentiated Hurtle's cell cancer.

2. Intermediate malignancy (15.2% of cases), including all the forms of solid cancer, trabecular cancer, the widespread sclerosing forms, the forms with high columnar cells, the insular forms, the less differentiated cancer Hurtle's cells cancer, and the differentiated forms with undifferentiation areas.

Table 3. Relapse of disease and mortality of DTC correlated to the stage at primary treatment and at the surgical stage

Gender	Age	Stage	Histology	1st surgery	Recurrence	2nd surgery	Follow-up
F	34	T1N0M0	Papillary ca.	Loboisth.	N+ after 9 years	Tot Thyr+ Lymphad.	Aliveand d.f. after 10 years
F	38	T2N0M0	Follicular ca. with atyical features	Subtot. Thyroidect.	N+ after 6 years	Totalization + Lymphad.	Alive and d.f. after 2 years
F	38	T2N0M0	Papillary ca.	Tot. Thyroid+loboisthm.	N+ at 1 y	Lymphad	Alive and d.f. after 2 years
M	60	T4N1M0	Papillary ca with atypical features	Tot. Thyroid-lymphad	M+ after 8 years	Radioiodine	Alive m+
M	49	T3N0M0	Papillary ca.	Tot Thyroidectomy	M+ after 5 years	Radioiodine	Dead after 10 years
M	52	T3N1M0	Follicular ca.	Tot Thyroidectomy + Lymphad	M+ after 2 years		Dead after 2 years
M	53	T2N0M1	Folliculare ca. with atypical features	Tot. Thyroidectomy	N+ after 1 years		Dead after 1 year
M	60	T4N0M1	Follicular ca. with atypical features	Tot Thyroidectomy		Radioiodine	Dead after 4 years
F	76	T4N1M0	Infiltrating papillary ca.	S.T. + Tracheotomy + Lymphad	N+ at 1 year M+ after 4 years		Dead at 4 years (tracheal involvement)
F	58	T4N1M0	Papillary ca. with atypical features	Tot Thyroidectomy+ Lymphad			Dead after 10 years (tracheal involvement)
M	76	T3N1M1	Infiltrating follicular ca.	Tot Thyroidectomy+ Lymphad		Radioiodine	Dead after 1 year m+
F	63	T3N0M0	Follicular ca with atypical features	Tot Thyroidectomy	M+ after 3,5 years N+ after 2,5 years	Radioiodine	Dead after 4,5 years m+

Papillary ca: papillary carcinoma, Follicular ca: follicular carcinoma, Tot. Thyroidectomy: Total thyroidectomy, Lymphad: Lymphadenectomy, D.F.: disease free, M+: Metastasis

3. HIGH MALIGNANCY (6.8% OF CASES), INCLUDING ALL FORMS OF ANAPLASTIC CARCINOMA

A perspective study might suggest verifying whether or not being included in the first or second group really has a prognostic value, which is different for age and staging. Large perspective and retrospective studies have fixed the maximum of 1.5 cm as the critical diameter, with worse prognoses for larger sizes. However the exact cut-off size able to influence the prognosis and thus the therapeutic choice, is extremely variable. According to some AA., the limit would be 5 cm (12), according to others 4 cm (16 – 18), and fewer studies would identify as 2 cm or 1 cm the prognostic limit (19 – 22).

3.4. Nodules

It is unquestionable that the involvement of latero-cervical lymph nodes worsens the stage (23), but the appearance of N+ in younger patients (<30 years old) does not change the prognosis, substantially favorable, both in terms of metastases, and of survival (24, 25). There are still authors who state that nodal involvement would negatively affect the prognosis (26), although they suppose that it's significant only for unfavorable histology (17).

3.5. Metastasis

There is a sure correlation between the effect on the prognostic staging of metastases M, which is,in fact, the cause of the decrease of survival rate from 53% after 5 years to 38% after 10 years, and to 30% after 15 years (18 – 22). The localization of metastases would have a prognostic value also, but always negative in comparison with any variables; similarly, extra-thyroid invasion has a particularly unfavorable prognostic mean (28, 29).

Statistical analysis used the Kaplan-Meyer method for the disease-free survival rate and the overall survival evaluations and the Mann – Withney's test for the comparison of different clinico-pathological characteristics.

4. RESULTS

Statistical analysis brought to light that in 144 cases examined with a follow-up from 1 to 25 yearrs (m= 7.3 years) and with a drop out of 20 cases (13.8%), total mortality for cancer has been of 8 cases (5.5%) besides one death for cardiovascular pathology and one death six months after surgery because of acute lymphoblastic leukemia, with a median disease-free survival of 4.2 years (range 10 months to 25 years) and with negative predictive value of 95.4% and 91.8 % at 12 and 24 months respectively . The median survival was found to be 8.8 years (range 1 to 25 years) and with an estimation of overall survival rate at 24 and 48 months of 97.6% and the 94.4% respectively (table 3).

In table 3 mortality seems to be strictly correlated to the presence of distant metastases at the time of surgery (three cases), with their appearance during the follow-up (four cases), and with the local aggressiveness of the tumor (acute respiratory distress from massive tracheal invasion) in two cases with unfavorable histology (wide undifferentiated areas), while the evidence of lymph-node metastasis does not seem to affect the prognosis (1st, 2nd , 3 rd cases).

In the 1st case of table 3, the long survival time seems to be independent from the primary treatment (loboisthmectomy) and not conditioned by the evidence after nine years of loco-regional nodal metastases. In any case, the importance of a secondary treatment must be considered with totalization and lymphadenectomy to ensure an easier follow-up. Also in the 2nd case, only histology (intermediate malignancy) suggests some careful consideration.

The 3rd case is quite peculiar: the primary treatment seemed adequate, but required a latero-cervical lymphadenectomy on the opposite side one year after surgery, thus confirming that indeed there is no set standard lymphadenectomy in the treatment of DTC.

As for mortality, it must be considered that the 7th, 8th, and 11th cases belong to the histopathologic group of intermediate malignancy (Carcangiu-Rosai) and that one of them (the 7th) already presented brain metastases at primary treatment; the aggressiveness is confirmed by the low grading, the high T and the type of metastasis that ensure a rapid and unfavorable prognostic evolution. It is not casual that the most unfavorable cases are males aged over 45 years.

4.1. Age

In our experience, the age variable shows a correlation with the sex and T variables, thus rendering doubtful the suggested link between survival and disease recurrence. With regard to age, mortality for cancer is predominant in patients over age 45 and in patients over 30 with disease recurrence. Out of 124 patients screened, we found disease recurrence in only three (all lymphnodal, 5%) , among 60 patients <45 years old; two had received a partial primary treatment, so had to be completed by totalization and lymphoadenectomy after six and nine years, while the only patient who had already received total thyroidectomy underwent locoregional lymphadenectomy after one year. All of them are alive and free from disease (follow-up range 2-20 years). Among the 64 patients >45 years old there were nine recurrences (14%): three were nodal , associated with extranodal spread (trachea) and five were associated with distant metastases; unfortunately among these nine, only one is still alive (M+ after 8 years, treated by radioiodine therapy) (tables 4, 5).

4.2. Gender

Little statistical difference was found in gender, although the statistical interpretation of the phenomenon is doubtful. Males appear to show poorer prognostics with regard to other variables (histology, stage, and age). Out of the 89 female patients there were only six recoveries (6.7%) with three deceased and three still alive, and with disease-free-survival comprised between 2 and 17 years. In the group of 35 male patients there were six cases of disease relapse (17.1%), five of whom died (tables 4, 5).

4.3. Histology and grading

Another significant datum seems to be the histology and the grading that is found to be statistically independent from the variables of age, sex, and family history even when correlated with T; in fact the group of cancers with intermediate malignancy presents more deaths and recoveries. In the low malignancy group (81 cases), we found four recoveries (4.95%): three patients currently alive who had a disease-free survival ranging from a minimum of four to a maximum of 17 years and one death after 10 years. In the intermediate malignancy group (43 cases) instead, we recorded eight recoveries (18.6%), with six dead patients, two still alive and with a disease-free survival comprised between five months and six years

4.4. Tumor

In our experience related to the size of the cancer we found that with cancers smaller than 1.5 cm (43 cases), we had one recovery (2.32%): the patient is alive 18 years after the primary treatment. With cancers between 1.6 cm and 2.5 cm of size (34 cases) we had three recoveries (8.8%): two patients died after one year and one is alive after 10 years. With cancers larger than 2.5 cm (45 cases) we had eight recoveries (17.7%), seven deceased, and one alive after nine years follow-up. A multivaried analysis has shown a remarkable level of correlation with the other variables (sex, age, family, and histology).

4.5. Nodules

A doubtful datum arises from the distribution of the survival rate correlated with loco-regional lymph-node metastases: only four patients relapsed N+ (12) died, while eight of them are still alive.

4.6. Metastasis

With regard to the relapse with distal metastases, the datum reveals a reasonable prognostic role; in fact among M+ patients there are seven deceased patients and only one still alive. These data are in correlation with the variables of T and grading.

5. DISCUSSION

The prognostic role of surgical treatment is a tricky problem, because of surgical preference and difference in the extension of the operation; in second place, even in series that include standard behaviors for every cancer, at every stage, the result is sometimes of over- or under-treatment. In more eclectic records of cases, usually a paradox-effect is seen and those forms with worst prognosis may have received larger treatments. There must be then a naturally conceptual objection: that the operation should adapt itself to the cancer prognosis and not the contrary. If there is a chance to gain prognostic certainties, many studies should try and acquire them. The analysis of our work leads to a combination of characteristics that represent the portrait of the patient with more unfavorable prognosis: male gender, age>45 years, with cancer larger than 1.5 cm in size, and histological forms of intermediate malignancy. In our records this group includes 19 cases, six of them with relapse (31.5%) five deceased, one still alive, but with recurrence within one year. Which therapeutic choices do these considerations suggest? In the treatment of the most aggressive cancers even a hard-line surgical strategy is unable to control the tumoral dissemination and it needs to be improved by a preventive strategy and the knowledge of more and deeper biological and genetic mechanisms.

On the other hand, there is the group with the more favorable combination: female gender, age < 45 years old, cancers smaller than 1.5 cm, histological forms of low malignancy. In our record of cases this group includes 41cases with only one case of recurrence of disease, still surviving.

Because of our prevalent option for total thyroidectomy in the treatment of the benign thyroid pathology, most of these cases are often incidental and have received this kind of treatment independent from the definitive histological diagnosis and, even when the primary treatment has been a loboisthmectomy, our tendency has always been to proceed to a totalization of second resort, because we prefer to manage the follow-up of a patient without thyroid tissue in the anatomic seat. In these cases loboisthmectomy is not considered under-treatment. The same is valid for typical adenomas, all of accidental importance and all treated in our experience by total thyroidectomy of the first resort, which assumes a more preventive than a curative meaning particularly in the multifocal forms. Thus, in these cases we never expected any therapy other than opotherapy with substitutive dosages.

Certainly, further advantages could come from the evaluation of the prognostic incidence of unfavorable factors that concern local invasion, present in 10% of cases, but the value of the presence of multicenter neoplasia is still doubtful. Looking at seriate and complete histological selection, in over 80% of cases, also other factors have been proposed with limited testing, such as ploidy and cell content in DNA (29) as well as evaluation of tumor angiogenesis. In fact, the unfavorable prognostic meaning of a high content of DNA and a high index of tumor angiogenesis seems to be confirmed. Even without the same confirmation, the presence of some proliferative markers has a similar meaning, in for example the expression of 27 KIP, KI 67/mib1, and growth factors (valued like expression of ciclina D1) (31, 32).

The identification of a family form of microcarcinoma (5.9% of carcinomas) has an unfavorable prognostic meaning in spite of the low level of T (33). The proposal relevant to other factors such as those caused by the tissue environment in which the cancer develops, have been disappointing (lectine, laminine, collagenasis, K1 anti-tripsine). The presence of peritumoral lymph cell infiltrates has dubious meaning: it is irrelevant in European studies, while protective in the United States and Japanese analyses. More interesting perspectives come from the integration of the biomolecular research with the gene typification RET/PTC in un- and differentiated thyroid neoplasia (34, 35) and from that of the oncogenes RET/PTC1 (36) and RET/PTC3 (37). Their phenotypic expression does not affect the prognosis. Other interesting perspectives come from immunohistochemical research on malignant neoplasia markers such as CD44v6 and galectina-3 by FNAB. The application by FNAB of more advanced methods of genic determination would permit us to reach an optimal level of pre-operative information, allowing the most effective surgical strategy. Recent studies have brought to light the possibility of biomolecular determination by FNAB, using not a semi-quantitative-PCR but a real-time quantitative reverse transcription-PCR for mRNA of oncofetal-fibronectine like marker of thyroid neoplastic undifferentiation . Today, the choice of the surgeon can be guided by additional information concerning the nature and ultrastructure of cancer, thus rendering the surgical behavior linked with tumor biology. The modern aspirating needle cytology, the selection of diagnostic immunohistochemical prognostic markers, and the methodologies of intraoperative echo and radio-control allow the surgeon to "see and palpate" the glandular ultrastructure preoperatively.

6. REFERENCES

1. Asakawa H, T. Kobayshi , Y. Konoike, Y. Tanaki , Y. Matsuzawa & M. Monden: Prognostic factors in patients with recurrent differentiated thyroid carcinoma. *J Surg Oncol.* 64(3), 202-206 (1997)

2. Mazzaferri E.L: Radiodiodine and other treatment and outcomes. Prognostic features. In: The Thyroid, Eds: Braverman L.E., Utiger R.D., Werner and Ingbar's The Thyroid IV edition, Lippincott Co., Philadelphia 1139-1143 (1991)

3. Patey M., D. Menzies, S. Theobald., MJ. Delise, J.B. Flament & M. Plecot: Anatomo-clinical prognostic factors of papillary carcinoma of thyroid. Multivariate analysis: report of 52 cases. *Ann Pathol*. 18(1), 10-15 (1998)

4. Thomush O, A. Machens, C. Sekulla, J. Ukkat, H. Lippert, I. Gastinger & H. Dralle: Multivariate analysis of risk factors for postoperative complications in benign goiter surgery: prospective multicenter study in Germany. *World J Surg* Nov. 24 (11), 1335-1341 (2000)

5. Agrawal S: Diagnostic accuracy and role of fine needle aspiration cytology in management of thyroid nodules. *J Surg Oncol* 58,168-172 (1995)

6. Bogazzi F, E. Martino & A. Pinchera: Role of conventional ultrasonography and color flow doppler sonography in predicting malignancy in "cold" thyroid nodules. *Eur J Endocrinol* 138, 141 (1998)

7. Alonso O, F. Mut, G. Lago, A. Aznarez, M. Numez , J. Canepa & G. Tonya: Tc 99 m-MIBI scanning of the thyroid gland in patients markedly decreased pertechnetate uptake. *Nucl Med Commun* 19(3), 257-261 (1998)

8. Mazzaferri EL: Radioiodine and other treatment and outcomes. Prognostic features. In: The Thyroid, Eds: Braverman L.E., Utiger R.D., Werner and Ingbar's The Thyroid IV edition, Lippincott Co., Philadelphia , 1159-1161 (1991)

9. Donohue J.H., S.D.Goldfien, T.R..Miller, J.S. Abele & O.H. Clark: Do the prognosis of papillary and follicular thyroid carcinomas differ entiated. *Amer J Surg* 148, 168 (1984)

10. Mazzaferri EL & R.L.Young: Papillary thyroid carcinoma. A 10 year follow up report of the impact of therapy in 576 patients. *Amer J Med* 70, 511 (1981)

11. Ruegemer JJ, I.D. Hay, E.J. Bergstralh, J.J. Ryan, K.P. Offord & C.A. Gormon: Distant metastases in

differentiated thyroid carcinoma: a multivariate analysis of prognostic variables. *J Clin Endocrinol Metab*, 67, 501 (1988)

12. Rao RS, H.K. Parikh, V.H. Deshmane, D.M. Parikh, S.S. Shrikhande & R. Havaldar: Prognostic factors in follicular carcinoma of thyroid: a study of 198 cases. *Head Neck* Mar- Apr, 18 (2), 118-124 (1996)

13. Zidan J, S. Kassem & A. Kuten: Follicular carcinoma of thyroid gland: prognostic factors, treatment and survival. *Amer J Clin Oncol* Feb. 23(1), 1-5 (2000)

14. Beasley NJ, P.G. Walfish, I. Witterick & J.L. Freeman: Causes of death in patient with well differentiated thyroid carcinoma. *Laringoscope* Jun 111(6), 989-991 (2001)

15. Sebastian SO, J. M. Gonzalez, P.P. Paricho, J.S. Perez, D. P. Flores & A.P. Madrona: Papillary thyroid carcinoma: prognostic index for survival including the histological variety. *Arch Surg* Mar 135(3), 272-277 (2000)

16. Shaha A.R., J.P. Shah & T.R. Loree: Risk group stratification and prognostic factors in papillary carcinoma of thyroid. *Ann Surg Oncol* Nov 3(6), 534-538 (1996)

17. Carcangiu ML, G. Zampi, A. Pupi. & J. Rosai: Papillary carcinoma of the thyroid. A clinicopathologic study of 241 cases treated at the University of Florence, Italy. *Cancer* 55, 805-828 (1985)

18. Saadi H, P. Kleidermacher & C.Jr. Esselstyn: Conservative management of patients with intrathyroidal well differentiated follicular thyroid carcinoma. *Surgery* Jul,130(1), 30-35 (2001)

19. Kebebew E & O. H.Clark: Differentiated thyroid cancer: complete rational approach. *World J Surg* Aug 24(8), 942-951 (2000)

20. Melliere D, D. Berrahal, E. Hindie, J.P. Becquemin & F. Lange: Differentiated thyroid cancer. 20 years results of a protocol based on simple prognostic criteria. *Presse Med* Sep. 20 26(27),1276-1283 (1997)

21. Melliere D, D. Berrahal, E. Hindie, C. Jeanguillaume, J.P. Becquemin & F. Lange: Surveillance after treatment of differentiated thyroid cancer. *Ann Chir* Nov 125(9), 856-860 (2000)

22. Bellantone R., C.P. Lombardi, M. Boscherini, A. Ferrante, M. Raffaelli & F. Rubino: Prognostic factors in differentiated thyroid carcinoma: a multivariate anlysis of 234 consecutive patients. J *Surg Oncol* Aug 68(4), 237-241 (1998)

21. Sato N, M. Oyamatsu, Y. Koyama, I. Emura., Y. Tamiya & K. Hatakeyama: Do the level of nodal disease according to the TNM classification and the number of involved cervical nodes reflect prognosis in patients with differentiated carcinoma of the thyroid gland? *J Surg Oncol* Nov 69(3),151-155 (1998)

22. Visset J, A. Hamy, E. Mirallie & J. Paineau: Locoregional recurrence of differentiated thyroid cancers: diagnosis-treatment. *Ann Chir* Jan 127(1), 35-39 (2002)

23. Tscholl-Ducommun J & C.E.Hediger: Papillary thyroid carcinoma : morphology and prognosis.*Virchows Arch* 19(A), 396 (1982)

24. Sugitani I, Y. Fujimoto: Symptomatic versus asymptomatic papillary thyroid microcarcinoma: a retrospective analysis of surgical outcome and prognostic factors. Endocr J Feb 46(1), 209-216 (1999)

25. Tubiana M, M. Schlumberger., P. Rougier, A. Laplauche., E.Benhamon & P. Gardet: Long term results and prognostic factors in patients with differentiated thyroid carcinoma. *Cancer* 55, 794- 804 (1985)

26. Steinmuller T, J.Klupp, N. Rayes, F.Ulrick, S..Jonas, K.J. Graf & P. Neuhaus: Prognostic factors in patient with differentiated thyroid carcinoma. *Eur J Surg* Jan 166(1), 29-33 (2000)

27. Tachikawa T, H. Kumazawa, R. Kyomoto, H. Yukawa, T. Yamashita & M. Nishikawa: Clinical study on prognostic factors in thyroid carcinoma. *Nippon Jibiinkoka Gakkai Kaiho* Feb 104(2), 157-64 (2001)

28. Onaran Y, S.Tezelman, N. Gurel, T. Terzioghe, H. Oguz, R. Taakol & Y. Kapran: The value of Dna content in predicting the prognosis of thyroid carcinoma in an endemic iodine deficiency region. *Acta Chir Belg* Feb 99(1),30-35 (1999)

29. Ishiwata T, Y.Lino, H. Takei, T.Oyama &Y. Morishita: Tumor angiogenesis as an independent prognostic indicator in human papillary thyroid carcinoma. *Oncol Rep* Nov-Dec 5(6),1343-1348 (1998)

30. Tallini G, G.Garcia-Rostan, A. Herrero, D. Zelterman, G.Viale, S. Bosari & M. Carcangin: Down regulation of p27KIP1 and Ki67/Mib1 labeling index support the classification of thyroid carcinoma into prognostically relevant categories. *Amer J Surg Pathol* Jun 23(6), 678-685 (1999)

31. Lupoli G, G.Vitale, M.Caraglia, M.R.Fittipaldi, A. Abbruzzese, P.Tagliaferri & A.R. Bianco: Familial papillary thyroid microcarcinoma: a new clinical entity. *Lancet* Feb 20; 353 (9153), 637-639 (1999)

32. Chiappetta G, P.Toti, F.Cetta, A.Giugliano, F.Pentimalli & I. Amendola:The RET\PTC oncogene is frequently activated in oncocytic thyroid tumors (Hurthle cell adenomas and carcinomas), but not in oncocytic hyperplastic lesions. *J Clin Endoc Metab* Jan 87(1), 364-369 (2002)

33. Santoro M, M. Papotti, G. Chiappetta, G. Garcia-Rostan, M. Volante, C. Johnson, R.L. Camp, F. Pentimalli, C. Monaco, A. Herrero, M.L. Carcangiu, A. Fusco & G. Tallini**:** RET activation and clinical pathologic

differentiated thyroid tumors. *J Clin End Metab* Jan 87(1), 370-379 (2002)

34. Basolo F, R. Giannini, A. Togniolo, R. Casalone, F. Pacini & P. Miccoli: Establishment of a non tumorigenic papillary thyroid cell line carrying the RET\PTC1 rearrangemente. *Int J Cancer* Feb 10 97(5), 608- 614 (2002)

35. Portella G, C. Borselli, M. Santoro, D.Gerbasio, J.F. Dumont & A. Fusco: Human papilloma virus 16 E7 oncogene does not cooperate with RET\PTC 3 oncogene in the neoplastic trasformation of thyroid cells in transgenic mice. *Oncol Res* 12(8), 347-354 (2000)

36. Bartolazzi A, A. Gasbarri, M. Capotti, G. Bussolati, T. Lucante & A. Khan: Application of an immunodiagnostic method for improving preoperative diagnosis of nodular thyroid lesions. *Lancet* May 26 357(9269), 1644-1650 (2001)

37. Takano T, A.Miyauchi, T. Yokozawa, F. Matsuzuka, I. Maeda & K. Kuma: Preoperative diagnosis of thyroid papillary and anaplastic carcinomas by Real-Time quantitative reverse transcription- polymerase chain reaction of oncofetal fibronectin messenger RNA. *Cancer Research* Set 15, 59, 4542-4545 (1999)

Key Words: Differentiated Thyroid Carcinoma, Prognostic Factors In Thyroid Carcinoma, Total Thyroidectomy, Cancer, Tumor, Neoplasia, Treatment

Send correspondence to: Dr. Pasquale Sperlongano, Vth Unit of Surgery and Advanced Surgical Procedures, Second University of Naples, Piazza Miraglia, 80134 Napoli Italy, Tel.: 39-081-5665234, Fax: 39-081-5665237, E-mail: pasquale.sperlongano@unina2.it

http://www.bioscience.org/current/vol11.htm