Surgical treatment of differentiated thyroid carcinoma: a retrospective study

M. DE FALCO, G. OLIVA, M. RAGUSA[1], C. MISSO JR[1], D. PARMEGGIANI,
P. SPERLONGANO, F. CALZOLARI[1], E. PUXEDDU[2], C. MISSO[3], L.A. MARZANO[3],
A. BARBARISI[4], U. PARMEGGIANI, N. AVENIA[1]

SUMMARY: **Surgical treatment of differentiated thyroid carcinoma: a retrospective study.**

M. DE FALCO, G. OLIVA, M. RAGUSA, C. MISSO JR,
D. PARMEGGIANI, P. SPERLONGANO, F. CALZOLARI, E. PUXEDDU,
C. MISSO, L.A. MARZANO, A. BARBARISI, U. PARMEGGIANI,
N. AVENIA

Introduction. *We carried out a retrospective analysis of our experience in the management of Differentiated Thyroid Carcinoma (DTC), in order to better define prognostic factors (age, gender, histological type, stage) and outline a standard procedure, where it's possible, for surgical treatment.*

Patients and methods. *Patient population consisted of 432 cases, operated from 1978 to 2003. We carried out 285 operations of total thyroidectomy of which 39 associated to some kind of lymphadenectomy, 66 totalization (21 pts had been operated in other institutes), 60 subtotal thyroidectomies and 21 lobo-isthmectomies. Survival and mortality curves for age, sex, histological type, grading and staging have been calculated. Kaplan-Meyer statistical elaboration for disease-free interval and Mann-Withney test for the comparison of different clinical and pathological data have been employed.*

Results. *The statistical analysis puts in evidence that on 432 cases examined, with a follow-up from 1 to 25 ys (median = 6.33 ys) and with a drop-out of 60 cases (13.8 %), total mortality for cancer has been of 24 cases (6,4%), with a median interval free by disease of 4.2 ys (range 5 months to 25 ys), and a probability to stay free by disease at 12 and 24 months respectively of 95.1% and 91.6%. The median survival is resulted of 5.8 ys (range 1 to 25 ys) with a probability of survival at 24 and 48 months respectively of 97.5% and 94.3%. The multivariate analysis evidences the most important variables, i.e. age > 45 ys, tumor of intermediate malignancy, with size 1.5 cm, operative M+, significantly condition the prognosis, noticeably getting worse it, indipendently by the kind of carried out operation.*

Conclusion. *Our present therapeutic choises are: 1. total thyroidectomy in the treatment of the apparently benign pathology when bi-*

RIASSUNTO: **Trattamento chirurgico del cancro differenziato della tiroide: studio retrospettivo.**

M. DE FALCO, G. OLIVA, M. RAGUSA, C. MISSO JR,
D. PARMEGGIANI, P. SPERLONGANO, F. CALZOLARI, E. PUXEDDU,
C. MISSO, L.A. MARZANO, A. BARBARISI, U. PARMEGGIANI,
N. AVENIA

Introduzione. *Viene riportata un'analisi retrospettiva della nostra esperienza nel trattamento del cancro differenziato della tiroide, per definire al meglio i fattori prognostici (età, sesso, tipo istologico, stadio) e proporre una procedura standard, dove possibile, per il trattamento chirurgico.*

Pazienti e metodi. *Trattasi di 432 casi operati tra il 1978 ed il 2003; presentiamo 285 tiroidectomie totali, di cui 39 associate a linfoadenectomie, 66 totalizzazioni (21 pazienti sono stati operati in altri istituti), 60 tiroidectomie subtotali, 21 loboistmectomie. Le curve di sopravvivenza e mortalità sono state calcolate in base a età, sesso, tipo istologico, grading e stadio: sono stati utilizzati l'elaborazione statistica di Kaplan-Meyer per l'intervallo libero di malattia e il test Mann-Withney per comparare i differenti dati clinici e patologici.*

Risultati. *L'analisi statistica mette in evidenza che su 432 casi esaminati, con un follow-up da 1 a 25 anni (media = 6,33 anni) e con un drop-out di 60 casi (13.8%), la mortalità totale per cancro è stata di 24 casi (6,4%) con un intervallo medio libero da malattia di 4,2 anni (range 5 mesi-25 anni) e una probabilità di essere liberi da malattia tra 12 a 24 mesi rispettivamente del 95,1% e del 91,6%. La sopravvivenza media è risultata di 5,8 anni(range 1-25), con una probabilità di sopravvivenza a 24 e 48 mesi rispettivamente del 97.5% e del 94,3%. L'analisi multivariata evidenzia le più importanti variabili, ovvero età >45 anni, grado di malignità intermedia, dimensione maggiore di 1,5 cm, presenza di metastasi all'atto dell'intervento, condizionanti significativamente la prognosi, che peggiora notevolmente, indipendentemente dal tipo di intervento effettuato.*

Conclusioni. *Le nostre attuali scelte terapeutiche sono: 1) tiroidectomia totale nel trattamento della patologia apparentemente benigna, con estensione bilaterale; il rilievo all'esame istologico di un cancro inci-*

Second University of Naples
V Unit of Surgery and Advanced Surgical Procedures
(Chief: Prof. U. Parmeggiani)
[1] University of Perugia, Endocrine Surgical Unit
(Chief: Prof. N. Avenia)
[2] Internal Medicine Department
(Chief: Prof. F. Santeusanio)
[3] Federico II University of Naples
Department of General and Endocrine Surgery
(Chief: Prof. L.A. Marzano)
[4] Second University of Naples,
IX Unit of Surgery
(Chief: Prof. A. Barbarisi)

laterally with spread; the checking at the final histological exam of a cancer makes however think adequate the carried out operation; 2. lobo-isthmectomy in the treatment of unilateral benign pathology or with suspect FNAB for follicular neoplasm; the histological checking of a cancer makes think the operation adequate only in presence of favourable prognostic parameters, but in presence even of just one unfavourable variable, we consider necessary the totalization; 3. total thyroidectomy in presence of a certain or strongly suspected preoperative diagnosis of cancer.

dentale fa comunque ritenere adeguata questa operazione; 2) loboistmectomia nel trattamento di patologia benigna unilaterale o di sospetto FNAB per neoplasia follicolare; il rilievo all'esame istologico di un cancro fa ritenere comunque adeguata questa operazione solo in presenza di parametri prognostici tutti favorevoli, mentre in presenza anche di una sola variabile sfavorevole consideriamo necessaria la totalizzazione; 3) tiroidectomia totale in presenza di una diagnosi preoperatoria certa o fortemente sospetta di cancro.

Introduction

Differentiated Thyroid Cancer (DTC) represents the most frequent thyroid cancer, originating from the follicular epithelium and accounting for 90% of all thyroid carcinoma (1). Part of these tumors occurs in low-risk patients that may benefit of less aggressive management strategies. However, the characterization of low-risk patient is still confusing and we lack adequate markers to tell apart patients that may present a troublesome progression of the disease (2).

Different score staging systems (AGES, AMES, MACIS, TNM, etc.) attempted to define reliable prognostic factors, with encouraging results, but no conclusive data have emerged, able to guide the choice of treatment, also because some essential elements for the score are obtainable only at surgery (e.g., histology, T stage) (3-5).

The problem rises when these methods concern daily routine; here in fact, also where there is a refined pre-operating diagnostics, less than half of cancers reaches the treatment with a diagnosis of cancer, and it means that the 10-15% has doubtful cytological diagnosis and that nearly 40% reaches the treatment under the apparent spoils of a mutinodular goitre. We have to consider that FNAB (Fine-Needle Ago-Biopsy), even if carried out by expert hands, points out on important results, a checking of false-negative from 1.7% to 4% and of false-positive from 0.5% to 2% (6); ultrasound guide offers some possibilities of improvement of the methodology, as well color power-Doppler for vascular intralesional signal (7, 8) and from nuclear medicine for determination of hyper-seeding lesions to positive sesta-MIBI tracer (9).

Total thyroidectomy (TT) is the technique of choice for several reasons, above all an easier and more efficient follow-up, with acceptable surgical morbidity if the procedure is performed in qualified Centers (10-12). At the time of surgery only 50% of cancers has been diagnosed, despite the improvements in diagnostic workup (ultrasonography, nuclear medicine, pathology). In 10-15% of cases there is diagnostic uncertainty, and in the remaining 30-40% cancer is found within a multinodular goiter (6).

Aim of this study was to highlight the most reliable prognostic factors through a retrospective analysis of our experience, and possibly identify the optimal surgical strategy for such disease. Two basic questions are open:

a) in which cases lobo-isthmectomy (LHY) or subtotal thyroidectomy (STT), followed by opotherapic treatment, can be judged a definitive cure?

b) is it correct to consider as appropriate treatments only LHY or TT?

We retrospectively examined our surgical experience aiming to partially address these important questions that remain unanswered and need to be addressed by the current generation of thyroid-dealing physicians.

Patients and methods

A total of 432 cases of DTC (117 male, 315 female) was operated on by our groups in the period 1978-2003 (Tab. 1). Procedures are summarized in Table 2. We carried out 306 total thyroidectomies, 39 of them associated with laterocervical lymphadenectomy, 21 totalizations in patients who underwent previous surgery elsewhere, 12 of them associated with lymphadenectomy, 60 subtotal thyroidectomies and 66 loboisthmectomies; about these latter patients, 36 of them have accepted totalization, 9 have been totalised with laterocervical lymphadenectomy, 9 have refused the operation and in 12 of them loboisthmectomy has been deliberately considered radical surgical treatment.

Concerning the prognostic variables taken into consideration data were searched for

Age

It's enough evident the effect of the age on survival and it's known for a long time that DTC discovered over 40 years olds have worse prognosis than DTC discovered in younger patient (13-15) and that the pejorative effect increases years by years after

TABLE 1 - DIFFERENTIATED THYROID CARCINOMA: SURGICAL EXPERIENCE (1978 – 2003).

Cases (n)	432
Follow-up	1 – 25 years (median 6.3 years)
Drop out, n (%), patients lost to the follow-up	60 cases (13.8%)
Overall mortality	24 cases (6,45%)
Overall survival at 24 and 48 months	97.5% and 91.6%
Median survival	5.8 ys (range 1-25)
Median disease-free interval	4.2 ys (range 10 months-25 ys)

TABLE 2 - SURGICAL PROCEDURES.

Surgical procedure	Case (n)	Lymphadenectomy (n)
Total thyroidectomy	**306**	**39**
"D'emblèe"	219	11
Totalization our patients	45	8
Totalization patients treated somewhere else	21	12
Subtotal thyroidectomy	**60**	
Lobo-isthmectomy	**66**	
Not accepted	3	
Deliberated	4	

these registry limit, both about resumption and as cause of death (16-18). DTC in patients over 40 years old seems to have a worse outlook than in younger subjects, such phenomenon increasing decade after decade. In agreement with the UICC 1997 Statement, we accepted the age limit of 45 years staging discriminant.

Gender

A variable that apparently has a weaker prognostic significance than age. Females apparently fare better than their male counterpart (16).

Histological type and grading

Classification of the neoplasm as papillary or follicular entails different prognosis, with the best outlook for papillary lesions (80-90% survival at 10 years) compared to follicular neoplasms (65-75% survival at 10 years) (19). However such differences disappear if groups of patients are matched for age and stage, indicating that follicular tumors are usually diagnosed in a more advanced stage of disease (20, 21). We applied the classification of Carcangiu and Rosai, based on morphological data, that divides the lesions of the follicular epithelium basically into three groups:

1. low malignancy (78%), including all typical forms of papillary carcinoma, the follicular varieties of papillary carcinoma, sclerosing carcinomas, the differentiated variety of Hürthle's cell tumor;
2. intermediate malignancy (15.2% of cases), including all solid cancers, trabecular cancer, widespread sclerosing forms, high-columnar cell type, insular forms, less-differentiated Hürthle's cell variety, differentiated lesions with areas of de-differentiation;
3. high malignancy (6.8% of cases), including all forms of anaplastic carcinoma.

Now, although the anaplastic carcinoma is not, as it's right, to be included in the DTC, the simple identification of a form with it's characteristic automatically assigns it to the worse prognostics class.

About the first two groups, instead, it seems suggestive proposing a perspective study to verify if inclusion between the forms of the first or the second group really signs a prognostic destiny, different for the same age and classification staging, accepted by us to include them between the malign with low aggressiveness neoplasias, with survivals nearby the 100% (22). All this can be even more censured in the more and more diffused choice to limit to a lobo-isthmectomy the therapy of an incidental differentiated thyroid cancer which is T1N0M0, independently by age, sex, familiarity, histology; if this choice can appear daring, the conjecture of modulating the surgical strategy in relation to one or more variables is not so singular, in particular if we consider factors like dimensions, grading and histology.

T stage

Large perspective and retrospective studies have fixed at 1.5 cm the critical diameter, with worse prognosis for larger sizes (23). About such dimensional cut-off, however, there is no unanimity, with some authors placing the limit at 4-5 cm and others at 1-2 cm. Extrathyroid invasion indicates a grim outlook (24, 25).

N stage

Laterocervical nodal involvement shortens life-expectancy, although in younger patients (< 30 years old) such statement may not be true. There are still authors who record a negative effect of N on the prognosis (13, 26, 27), although they suppose that it's significant only for unfavourable histological type (28, 29).

M stage

M+ stage has a negative influence on prognosis (53% survival at 5 years, 38% at 10 years, 30% at 15 years) (30). The localization of metastases would have a prognostic value too, but always negative in comparison with any variables (31, 32); similarly, extrathyroid invasion has a particulary unfavourable prognostic mean (33-35).

Statistical data have been obtained by Kaplan-Meyer method for disease-free interval and survival, and by Mann-Withney test for comparison of different clinical and pathological characteristics; p< 0.05 has been considered significative.

Results

The statistical analysis puts in evidence that on 432 cases examined, with a follow-up ranging between 1 and 25 years (median 6.33 years) and with a drop-out incidence of 60 cases 13,8%, total mortality for cancer was 6.4% (24 cases), besides two deaths for cardiovascular pathology and one death six months after surgery for acute lymphoblastic leukemia. The median disease-free interval was 4.2 years (range: 10 months to 25 years), with a probability of being free from disease at 12 and 24 months from surgery respectively of 95.1% and 91.6%. Median survival was 5.8 years (range: 1 to 25 years), with a probability of surviving at 24 and 48 months respectively of 97.5% and 94.3% (Tab. 1).

Mortality appears to be strictly related to the presence

of metastases at the time of primary treatment (9 cases), or with their occurrence during follow-up (12 cases), and to local aggressiveness of the tumor (acute respiratory distress from massive tracheal invasion) – in 6 cases, with unfavourable histological type (extensive undifferentiated areas). Lymph node metastases, on the other hand, doesn't seem to significantly alter the prognosis.

Standing to the resumption of disease look interesting the 3 cases, where the long surviving time seems independent from the primary treatment (lobo-isthmectomy) and not conditioned by the evidence after years of loco-regional lymph node metastasis. Must, anyway, to be considered the importance of the secondary treatment with the totalization and the lymphadenectomy to ensure an easier follow up. Only the histologic type (intermediate malignancy) suggests some more careful consideration. Absolutely particular look 3 cases, where the primary treatment seems adequate, also if requires after 6 months to 2 years a latero-cervical lymphadenectomy on the same side and on the opposite side, confirming that doesn't exist an ideal "d'emblèe" lymphectomy in the treatment of DTC.

Standing to the mortality, must be considered that 6 cases belong to the histologic type group with intermediate malignancy (Carcangiu-Rosai) and that 3 of them arrived to the primary treatment already with cerebral metastasis; the aggressiveness is confirmed by the low grading, the high T and the type of metastasis that ensures a fast and unfavourable prognostic evolution. It's not casual, overall, that the most unfavourable cases are male and >45 ys old.

Concerning the single prognostic variables, from our data the following considerations can be drawn.

Age

In our experience, the variable age showed correlation with variables sex and T, making difficult the interpretation of results that anyway seems to evidence a suggestive link with surviving and resumption of disease. As regards the age, the mortality for cancer is prerogative of >45 ys old patients (pts) and the resumption of disease of >30 ys old pts. We find, on 372 patients screened, from 180 pts <45 ys old, only 9 resumptions of disease (all of them lymph nodal, 5%); 6 had received a partial primary treatment, so had to be completed by totalization and lymphadenectomy after 6 to 9 ys, while the only 3 patients who had already received a total thyroidectomy, underwent to a locoregional lymphadenectomy after maximum 1 year. All of them are alive and free from disease (follow up range 2-20 ys). From the 192 pts > 45 ys old we have 27 recurrence (14%), 9 were lymphnodal associated to tracheal invasion and 15 were associated to distal metastasis; unfortunately of 27, 24 are deceased and only 3 are still alive

(M+ after some ys, treated by radioiodine therapy).

Gender

In our revision, there is the difference between male and female gender, although the statistical interpretation of the phenomenon is doubtfull, because of then remarkable level of dependence. The prognostic weight of the gender seems to negatively modulate, for male pts, the influence of other variables (histologic type, stage and age). In a group of 267 female patients we find only 18 recoveries (6,7%) with 9 dead patients, 9 still living and with disease-free interval included between 2 and 17 ys; in the group of 105 male pts, we find 18 resumption of disease (17,1%), of which 15 pts deceased and only 3 alive.

Histology and grading

Another particulary significant data seems to be the histologic type and the grading that, although in correlation with T, results statistically indipendent by variables like age, sex, and familiarity; in fact the group of cancers with intermediate malignancy presents more deaths and recoveries. In the group with low malignancy (243 cases), we have examined 12 resumptions (4,9%): 9 patients actually living with an interval free by disease from a minimum of 4 to a maximum of 17ys and 3 deceased after 8-10 ys. In the group with intermediate malignancy (129 cases) instead 24 resumptions (18,6%), with 18 dead patients and 6 still living and with a free-disease-interval included between 5 months and 6 ys.

T stage

In our experience in cancer < 1,5 cm (129 cases), we have 3 resumptions (2,3%): the patients are alive after 9 to 18 ys from the primary treatment. With cancers of dimensions including between 1,6 cm and 2,5 cm (102 cases), we have 9 resumptions (8,8%), 6 deads at 1 year and 3 patients alive after 6 to 10 ys. With cancers of dimensions > 2,5 cm (135 cases), we have 24 resumptions (17,7%), 21 deads, 3 alive after 9 to 12 ys follow-up. Although this datum can look suggestive, the multivaried analysis has shown a remarkable level of correlation with the others variables (sex, age, family, and histology).

N stage

A doubtful data appears from the distribution of the survival in relation to the loco-regional lymph node metastasis: only 12 patients who have shown resumption N+ (36) are dead, 24 of them are still living.

M stage

As regards the resumption with distal metastases, the data reveals a reasonable prognostic weight; in fact,

between M+ patients there are 21 dead patients and only 3 still living. These last two dates, although they shown a good level of independence, are in correlation with variables like T and grading.

Discussion

The prognostic role of surgical treatment in the management of DTC is difficult to define: available studies are retrospective, biased by surgical habits, different technical aspects, non-standardized extent both on the gland and on the lymphatic line (36-38). Furthermore, in any case-population study, it is conceivable to expect over-treated or under-treated cases. Finally, sometimes a paradoxical effect may be observed, with tumors in advanced stage receiving under-treatment or vice-versa locally diffused low risk tumors receiving over-treatment (39, 40).

The statistical evaluation of our data allowed us to define the hypothetical portrait of a patient with unfavourable prognosis: male, age >45 years, affected by a tumor of >1,5 cm in diameter, histologically classified as intermediate malignancy; in our record of cases this group includes 57 cases with 18 resumptions (31,5%) with 15 dead patients and 3 still living, but with resumption within 1 year. What's the message for such class of patients? Aggressive initial treatment seems not to be sufficient, complementary therapies are needed, along with better knowledge of the biological and genetic mechanisms of disease. On the other hand, there is the group with the most favourable combination: female gender, age > 45 years, with a neoplasm <1,5 cm in diameter, histologically classified as low-grade malignancy; in our record of cases this group includes 123 pts with only 3 cases of resumption of disease, anyway still living.

Because of our prevalent option for total thyroidectomy in the tratment of the thyroid benign lesions, most of these often accidental cases have received this type of treatment independently by the definitive histological diagnosis and, even when the primary treatment has been a lobo-isthmectomy, our tendency has always been proceeding to a totalization of second re-

sort, because we however consider preferable managing the follow-up of a patient without thyroid tissue at all. We however don't consider, about these cases, that lobo-isthmectomy is a under-treatment. The same speech, even more so, is valid for a typic adenomas, all of accidental importance, all treated in our experience with a total thyroidectomy of first resort, that particularly in the multiple focus forms, of a probable family origin, assumes a more preventive than curative meaning. For this reason we have never expected for these cases another post-operative therapy that is not a opotherapy with substitutive dosages.

Other aspects may be of prognostic significance, such as local (extrathyroid) invasion, or multifocal neoplasia (such occurrence may be frequent if adequately searched on surgical specimens), or aneuploidy and DNA cellular content, and ultimately tumor angiogenesis index.

We stress the prognostic value of histological analyses of proliferative markers such as expression of 27 KIP, Ki 67/mib1, and growth or cell cycle related factors (cyclin D1) (41, 42).

The identification of a familial form of papillary microcarcinoma (5.9% of carcinomas) has an unfavourable prognostic significance, in spite of the low T score (43). The role of other potential cell markers as useful tools in prognosis or management of DTC have turned out disappointing (laminine, collagenase, K1 antitrypsin) (44, 45).

The presence of peritumoral lymph cells infiltrates should have a doubtful meaning: irrelevant in the European experience, with protective meaning in United States and Japanese analyses.

At last, an interesting perspective may stem from integration of biomolecular studies and gene typing (46-49) with immunohistochemical determinations on FNAB. Surgical planning could be improved adding to morphologic studies on FNAB specimens biomolecular determinations based on real time quantitative reverse transcription for mRNA of the oncofetal-fibronectin-like marker of thyroid neoplastic differentiation (50). Anatomic and microscopic data could receive an additional insight on ultrastructural patterns, in order to improve surgical decision making.

References

1. Weber T, Schilling T, Buchler MW. Thyroid carcinoma. Curr Opin Oncol, 2006;18:30-5.

2. Ward LS, Marrone M, Camargo RY, Watanabe T, Tincani AJ, Matos PS, Assumpcao LV, Tomimori E, Kulcsar MA, Nunes MT, Nogueira CR, Kimura ET. Low-risk differentiated thyroid carcinoma--literature review and management guidelines. Arq Bras Endocrinol Metabol, 2006;50:550-7.

3. Asakawa H, Kobayshi T, Konoike Y, Tanaki Y, Matsuzawa Y, Monden M. Prognostic factors in patients with recurrent differentiated thyroid carcinoma. J Surg Oncol 1997;64(3): 202-6.

4. Mazzaferri EL. Radiodiodine and other treatment and outcomes. Prognostic featurs. In: Braverman LE, Utiger RD, editors. Werner and Ingbar's IV edition. Philadelphia: Lippincott

Co. 1991; 1139-61.

5. Patey M, Menzies D, Theobald S, Delise MJ, Flament JB, Plecot M. Anatomo-clinical prognostic factors of papillary carcinoma of thyroid. Multivariate analysis: report of 52 cases. Ann Pathol 1998;18(1):10-5.

6. Chao TC, Lin JD, Chao HH, Hsueh C, Chen MF. Surgical treatment of solitary thyroid nodules via fine-needle aspiration biopsy and frozen-section analysis. Ann Surg Oncol, 2007; 14:712-8.

7. Bogazzi F, Martino E, Pinchera A. Role of conventional ultrasonography and color flow doppler sonography in predicting malignancy in "cold" thyroid nodules. Eur J Endocrinol 1998;138:41.

8. Cerbone S, Spiezia S, Colao A, Di Sarno A, Assanti AP, Lucci R, Siciliani M, Lombardi G, Fenzi G. Power Doppler improves the diagnostic accuracy of color Doppler ultrasonography in cold thyroid nodules: follow up results. Horm Res 1999; 52(1): 19-24.

9. Alonso O, Mut F, Lago G, Aznarez A, Numez M, Canepa J, Tonya G. Tc 99 m-MIBI scanning of the thyroid gland in patients markedly decreased pertechnetate uptake. Nucl Med Commun 1998;19(3):257-61.

10. Antonaci A, Anello A, Aucello A, Consorti F, Della Rocca C, Giovannone G, Scardella L. Microcarcinoma and incidental carcinoma of the thyroid in a clinical series: clinical behaviour and surgical management. Clin Ter 2006;157:225-9.

11. Danila R, Andriescu L, Grigorovici A, Dragomir C, Galusca B, Vulpoi C, Ungureanu C, Mogos V. Differentiated thyroid cancer--peculiar morphological and clinical forms. Rev Med Chir Soc Med Nat Iasi 2005;109:71-6.

12. Duntas L, Grab-Duntas BM. Risk and prognostic factors for differentiated thyroid cancer. Hell J Nucl Med 2006;9:156-62.

13. Gyory F, Lukacs G, Nagy EV, Juhasz F, Mezosi E, Szakall S, Math Y, Balazs G. Differentiated thyroid carcinoma: prognostic factors. Magy Seb 2001;54(2):69-74.

14. Rao RS, Parikh HK, Deshmane VH, Parikh DM, Shrikhande SS, Havaldar R. Prognostic factors in follicular carcinoma of thyroid: a study of 198 cases. Head Neck 1996;18(2):118-24.

15. Zidan J, Kassem S, Kuten A. Follicular carcinoma of thyroid gland: prognostic factors, treatment and survival. Am J Clin Oncol 2000;23(1):1-5.

16. Mishra A, Mishra SK. Total thyroidectomy for differentiated thyroid cancer: primary compared with completion thyroidectomy. Eur J Surg 2002;168(5):283-7.

17. Hermanek P, Sobin LH. TNM classification of malignant tumors. Berlin: Springer-Verlag, 1987.

18. Beahrs OH, Henson VE, Hutter RVP. Manual for staging of cancer. American Joint Commission on Cancer. 3rd edition. Philadelphia: JB Lippincott, 1988.

19. Mazzaferri EL. Radioiodine and other treatment and outcomes – Prognostic features- From Werner and Ingbar's The Thyroid – LE Braverman, RD Utiger eds. 4th edition Philadelphia J.B.Lippincott Co. 1991, pag. 1139-61.

20. Donohue JH, Goldfien SD, Miller TR, Abele JS, Clark OH. Do the prognosis of papillary and follicular thyroid carcinomas differ Am J Surg 1984;148:168.

21. Ruegemer JJ, Hay ID, Bergstralh EJ, Ryan JJ, Offord KP, Gormon CA. Distant metastases in differentiated thyrid carcinoma: a multivariate analysis of prognostic variables. J Clin Endocrinol Metab 1988;67:501.

22. Shaha AR, Shah JP, Loree TR. Risk group stratification and prognostic factors in papillary carcinoma of thyroid. Ann Surg Oncol 1996;3(6):534-8.

23. Carcangiu ML, Zampi G, Pupi A, Rosai J. Papillary carcinoma of the thyroid. A clinicopathologic study of 241 cases treated at the University of Florence, Italy. Cancer 1985;55:805-28.

24. Kebebew E, Clark OH. Differentiated thyroid cancer: complete rational approach. World J Surg 2000;24(8):942-51.

25. Melliere D, Berrhal D, Hindie E, Jeanguillaume C, Becquemin JP, Lange F. Surveillance after treatment of differentiated thyroid cancer. Ann Chir 2000;125(9):856-60.

26. Bellantone R, Lombardi CP, Boscherini M, Ferrante A, Raffaelli M, Rubino F et al. Prognostic factors in differentiated thyroid carcinoma: a multivariate anlysis of 234 consecutive patients. J Surg Oncol 1998;68(4):237-41.

27. Sugitani I, Fujimoto Y. Symptomatic versus asymptomatic papillary thyroid microcarcinoma: a retrospective analysis of surgical outcome and prognostic factors. Endocr J 1999;46(1):209-16.

28. Torre GC, Ansaldo GL, Varaldo E, Meola C, Franceschi A, Bottaio MP et al. Il carcinoma differenziato della tiroide: invasione linfatica e sopravvivenza, quale rapporto? In: Romano M, Lo Monte A. La chirurgia della tiroide e delle paratiroidi oggi. Napoli, G. De Nicola Ed, 1999; pp 45-54.

29. Tubiana M, Schlumberger M, Rougier P, Laplauche A, Benhamon E, Gardet P, et al. Long term results and prognostic factors in patients with differentiated thyroid carcinoma. Cancer 1985;55:794-804.

30. Saadi H, Kleidermacher P, Esselstyn C. Jr. Conservative management of patients with intrathyroidal well differentiated follicular thyroid carcinoma. Surgery 2001;130(1):30-5.

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

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

33. Campana F. Relazione 103°Congresso Nazionale della Società Italiana di Chirurgia Bologna, 28-31 Ottobre 2001.

34. Beasley NJ, Walfish PG, Witterick I, Freeman JL. Causes of death in patient with well differentiated thyroid carcinoma. Laringoscope 2001;111(6):989-91.

35. Sebastian SO, Gonzalez JM, Paricho PP, Perez JS, Flores DP, Madrona AP, et al. Papillary thyroid carcinoma: prognostic index for survival including the histological variety. Arch Surg 2000;135(3):272-7.

36. Cushing SL, Palme CE, Audet N, Eski S, Walfish PG, Freeman JL. Incidence and characteristics of facial nerve stimulation in children with cochlear implants. Laryngoscope 2004;114:2110-5.

37. 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;86:3668-76.

38. Ward LS, Assumpcao LV. Thyroid cancer: prognostic factors and treatment. Arq Bras Endocrinol Metabol 2004;48:126-36.

39. Shaha AR. Implications of prognostic factors and risk groups in the management of differentiated thyroid cancer. Laryngoscope 2004;114:393-402.

40. Sywak M, Pasieka JL, Ogilvie T. A review of thyroid cancer with intermediate differentiation. J Surg Oncol 2004;86:44-54.

41. Ishiwata T, Lino Y, Takei H, Oyama T, Morishita Y. Tumor angiogenesis as an indipendent prognostic indicator in human papillary thyroid carcinoma. Oncol Rep 1998;5(6):1343-8.

42. Tallini G, Garcia-Rostan G, Herrero A, Zelterman D, Viale G, Bosari S, Carcangin M. Down regulation of p27KIP1 and Ki67/Mib1 labeling index support the classification of thyroid carcinoma into prognostically relevant categories. Am J Surg Pathol 1999;23(6); 678-85.

43. Lupoli G, Vitale G, Caraglia M, Fittipaldi MR, Abbruzzese A, Tagliaferri P, Bianco AR. Familial papillary thyroid microcarcinoma: a new clinical entity. Lancet 1999;20;353(9153):637-9.

44. Lekmine F, Feracci H, Milhaud G, Treilhou-Lahille F, Jeanne N. Expression of laminin-2 by normal and neoplastic rat C cells during the development of medullary thyroid carcinoma. Virchows Arch. 1999;434(4):325-32.

45. Pisani T, Pantellini F, Centanni M, Vecchione A, Giovagnoli MR. Immunocytochemical expression of Ki67 and laminin in Hurthle cell adenomas and carcinomas. Anticancer Res 2003; 23:3323-6.

46. Chiappetta G, Toti P, Cetta F, Giugliano A, Pentimalli F, Amendola I et al. 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 2002;87(1):364-9.

47. Santoro M, Papotti M, Chiappetta G, Garcia-Rostan G, Volante M, Fusco A et al. RET activation and clinical pathologic differentiated thyroid tumors. J Clin End Metab 2002;87(1): 370-9.

48. Barone MV, Sepe L, Melillo RM, Mineo A, Santelli G, Monaco C et al. RET\PTC 1 oncogene signaling in PC Cl3 thyroid cells requires the small GTP-binding protein Rho. Oncogene 2001;20(48):6973-82.

49. Basolo F, Giannini R, Togniolo A, Casalone R, Pacini F, Miccoli P et al. Establishment of a non tumorigenic papillary thyroid cell line carrying the RET\PTC1 rearrangemente. Int J Cancer 2002;97(5):608-14.

50. Takano T, Miyauchi A, Yokozawa T, Matsuzuka F, Maeda I, Kuma K et al. Preoperative diagnosis of thyroid papillary and anaplastic carcinomas by Real-Time quantitative reverse transcription- polymerase chain reaction of oncofetal fibronectin messenger RNA. Cancer Research 1999;59:4542-45.