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Advanced thyroid carcinoma: An experience of 385 cases

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Abstract

Aims: To report clinical outcomes of a large series of cases with advanced thyroid cancer.
Study design: Three hundred and eighty-five patients at the UICC stages III and IV were selected for the study with thyroid cancer.
Results: Papillary carcinoma and sclerosing carcinoma have better survival than the Hürthle cell and insular types. Lymphatic metastasis does not appear to worsen the prognosis. All the tumour forms offer the chance of long survival.
Conclusions: Surgical treatment is the primary treatment of thyroid carcinoma. The combined treatments of surgery, metabolic beam therapy, suppressive hormone therapy, radiotherapy and chemotherapy cure a high percentage of patients with the tumour at an advanced stage.

Keywords: Thyroid carcinoma; Advanced lymphatic metastasis; Haematic metastases; Papillary carcinoma; Metabolic beam therapy; Surgery; Chemotherapy; Radiotherapy; Follow-up

Introduction

In the most advanced stages of follicular thyroid carcinoma (TC) surgery alone cannot achieve complete cure. Metabolic radiotherapy and thyroid hormone suppression improve outcomes.

We report the natural course of this neoplasm and the survival rate of the patients and describes the results, obtained through surgical treatment and other types of therapy, in 385 patients with thyroid cancer at advanced stages (stages III and IV of the UICC classification): these are the carcinomas that had already metastasized or had breached the glandular capsule at the time of diagnosis.

Materials and methods

The hospital files of 747 patients with thyroid cancer of the follicular type were studied, among those who came to the Nuclear Medicine ward of Careggi Hospital in Florence (from several surgeons) for follow-up treatment from 1965 to 2000. Three hundred and eighty-five patients at the UICC stages III and IV were selected for the study. One hundred and sixty three patients were affected by extraglandular TC and 222 patients from intrathyroid tumours with lymphatic (LM) and/or haematic metastases (HM) at the time of diagnosis.

Of 385 patients, 108 were men and 277 women, between 15 and 94 years of age, a mean of 45 years and 2 months. All the patients were followed up for 24–371 months (average 100 ± 9). Zampi's and coll. histological classification at 1988 is used (see in Carcangiu et al., Cancer, 1985[1]).

Treatment

Surgical treatment

In all 385 cases, a total or near-total (i.e. with a residual thyroid tissue lower than 5%) thyroidectomy was performed

Abbreviations TC, thyroid carcinoma; LM, lymphatic metastasis; HM, haematic metastasis; PC, papillary carcinoma; RT, radiotherapy.

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at the initial operation or shortly after operations that had proved to be incomplete.

In patients with the cancer having spread outside the thyroid, the thyroidectomy was extended to the muscles, and in three cases to the trachea.

In all the patients with cervical node metastases diagnosed before or during the operation, functional cervical lymphadenectomy (unilateral or bilateral neck dissection) was performed.

Post-surgery treatment

After surgery, all patients underwent to total body scintiscans with ^{131}I to check the existence of thyroid residue or additional metastases.[2,3]

Thyroid residue was eliminated through the administration of ^{131}I in appropriate doses (90–100 mCi).[2,3]

Most of the cases of additional lymph node metastasis or haematic (bone, liver) metastasis were treated with appropriate doses of ^{131}I (120–150 mCi); in the other cases the lesions were surgically removed.[2,4,5] Subsequently all patients entered a regime of suppressive TSH therapy with levothyroxine.[4,5]

Risk stratification and follow-up

The patient group was subdivided into high-risk and low-risk. Groups including low-risk patients were the males under 40 years of age and females under 50 years of age, patients with encapsulated carcinoma, expansive growth, high differentiation, a diameter below 1.5 cm, and negative total body scintiscans. All the other patients were considered-high-risk.[6]

All patients were submitted to follow-up procedures, based on clinical examination, plasma thyroglobulin level, total body scans with ^{131}I and image diagnostic techniques, ultrasounds, bone and lung X-rays, CT scan.[6,7] Clinical tests were performed every 6 months on the high-risk patients and every 12 months on low-risk patients. A total body scan was done once or twice a year on high-risk patients, and every 3–5 years on low-risk patients.

Treatment of recurrence

Patients having recurrent tumours underwent treatment of the neoplastic foci.

Metabolic radiotherapy was by far the most widely employed, having been applied in all noted tumour recurrences characterized by iodine captation, and in six cases of scarce iodine captation.

Surgery was used in 20 patients affected by several and voluminous lymphatic cervical metastases, in five patients with clinically evident local recurrence, and in three cases for metastasis in the lung, the rachis, and the brain, respectively.

External radiotherapy (used for absent captation or for non-feasible surgery) was used for 22 patients.[8] Chemotherapy was used in four cases, while radiotherapy supplemented with chemotherapy was applied in six patients;[9,10] all were cases of serious recurrence.

Statistical analysis

Fisher's exact test, the chi-square test, one-way analysis of variance, and the Kaplan–Meier method for post-operative survival with the log-rank test were used for statistical comparisons. The relative importance of various prognostic factors for post-operative recurrence and survival was analysed with Cox's proportional hazard model with the forward stepwise method. Assumptions of proportional hazards were tested. Two-sided p values of less than 0.05 were considered to represent statistical significance.

Results

The incidence of various histological types shows that the sclerosing and insular types are significantly more frequent in advanced tumours. Out of 315 papillary tumours, 178 was intraglandular with metastases and 137 extraglandular. The Hurthle cell carcinomas (13) was, respectively, five (intra) and eight (extra). Sclerosing tumours (30) indeed was intraglandular in 23 cases and extraglandular only in nine patients. Among the 25 insular advanced cancers nine was extraglandular while both anaplastic tumours observed reached the extrathyroideal tissues.

Extraglandular thyroid tumours

The predominant areas of propagation were the perithyroid stroma and muscles (136), the trachea (17) and the oesophagus (2). Propagation to the others structures (recurrent laryngeal nerve, internal jugular vein, carotid artery, etc.) was verified in 11 cases. All these patients underwent metabolic beam therapy.

In three patients tracheal resection was performed, in 13 patients the tumour was simply detached from the trachea; in the last case tracheal disobstruction was performed by laser associated with the insertion of a definitive stent. In 13 patients the last check-up did not reveal signs of tracheal invasion, including two of the three patients who had undergone resection of some of the tracheal rings.

Any patient, who had cancer spread to oesophagus, has undergone oesophagus resection, while metabolic RT that definitively cured the neoplastic foci of the oesophagus.

Metastatic tumours

The frequency of metastases, according to sex, age, capsule histology, and type of growth, is reported in Tables 1 and 2 (In Zampi's thyroid cancer classification[1]

Table 1
Frequency of metastases development and type of growth, according to sex, age, capsule presence or absence

Feature		*N* total	With metastases, *N*	Extraglandular, *N*
Sex				
Men	$p<0.01$	108	97	11
Women		277	207	70
Age				
<50 years of age	$p<0.01$	230	198	32
≥50 years of age		155	106	49
Type of growth				
Infiltrating	$p>0.05$	113	72	41
Espansive		54	43	11
Tumoral capsule				
Present	$p<0.05$	26	26	–
Incomplete		38	30	8
Absent		90	60	30

insular type includes all follicular tumours with the exception of the papillary variant of follicular carcinoma).

The destinations of early haematic metastases were: bone (17), lungs (12), lungs in association with bone (3), lungs in association with bones and liver (1), and the brain (1). The destinations of all HM observed (at diagnosis and in follow-up period) were: lungs (54), bone (20), lungs in association with bone (7), lungs with bone and brain (1), lungs with bone and liver (1), liver (1), lungs in association with the brain (1).

Disease recurrence

Most cases of disease recurrence occurred within 12 months of surgery (161/240). 73.2% of the tumour recurrence was observed in the 2 years following surgery. In the subsequent 3 years up to the 5th year of follow-up, the rate varied from 2.7 to 3.1% of the total recurrence observed. Important to note is that over 18% of the disease recurrence was verified after 5 years of follow-up. Also, 12 patients with papillary carcinoma recontracted the disease 15 years after surgery.

At a minimum follow-up period of 24 months from surgery we observed that 86 patients did not have signs of disease recurrence. Of these, 68.6% had LM and 1.2% HM at the time of surgery. Only three patients showed local recurrence of the disease. In such individuals, extraglandular invasion associated with lymphatic metastatization was present at the operation performed approximately 2 years prior. In 109 patients LM was found. The disease had spread to the lymph nodes at the initial operation in 91.7% of such patients. Seventy-nine patients had haematic metastases: in 31 cases such lesions were already present at the time of diagnosis.

Included in the results are deaths from the disease, patients living with the disease and disease-free patients at a minimum follow-up period of 24 months from surgery.

Specifically, the overall mortality rate for papillary carcinoma was 15/315 patients (4.8%): in men 7/84, in women 8/231, patients under 50 years of age 1/199 and patients over 50 years of age 14/116. For this group the following data resulted regarding the type of metastases: no deaths with non-metastatic extraglandular tumour; only one death among patients with LM (death of 65-year-old woman after 155 months from surgery due to mediastinic syndrome); deaths among patients with haematic metastatization (at 8, 23, 26, 36, 54, 72, 72, 72, 74, 86, 108, 140, 216 and 252 months from surgery).

In the 70 carcinomas of the remaining histologic variants (insular, sclerosing, Hürthle cell and anaplastic carcinomas), total mortality for the disease was 16 out of 70 cases (22.9%). In males it was 6/24, in females 10/46, patients under 50 years of age 6/31 and patients over 50 years of age 10/39. The following was found as concerns survival according to the stage of the disease: no deaths involving non-metastatic extraglandular tumours in patients with exclusively LM; 16 deaths among patients with haematic metastatization of the disease (at 12, 14, 24, 24, 24, 28, 48, 48, 48, 72, 74, 108, 144, 144, 183 and 306 months from surgery).

A study of the histological variants, in relation to the prognosis, shows how papillary and sclerosing carcinomas present higher survival rates than the Hürthle cell and insular types (Fig. 1, $p<0.01$). Another survival curve (Kaplan–Meier method) shows the significant prognostic difference between carcinomas with and without haematic metastases, whether or not diagnosed at the time of surgery or in the follow-up period (Fig. 2).

Table 2
Type of metastases present at diagnosis (A) and in the follow-up (B) related to histology

Metastases	Papillary	Sclerosing	Insular	Hürthle	Anaplastic	Total
A						
Lymph nodes	227	25	4	5	1	262
Haematica	19	4	14	5	–	42
Total	246	29	18	10	1	304
B						
Lymph nodes	199	23	3	3	–	228
Haematica	67	6	18	9	1	101
Total	266	29	21	12	1	329

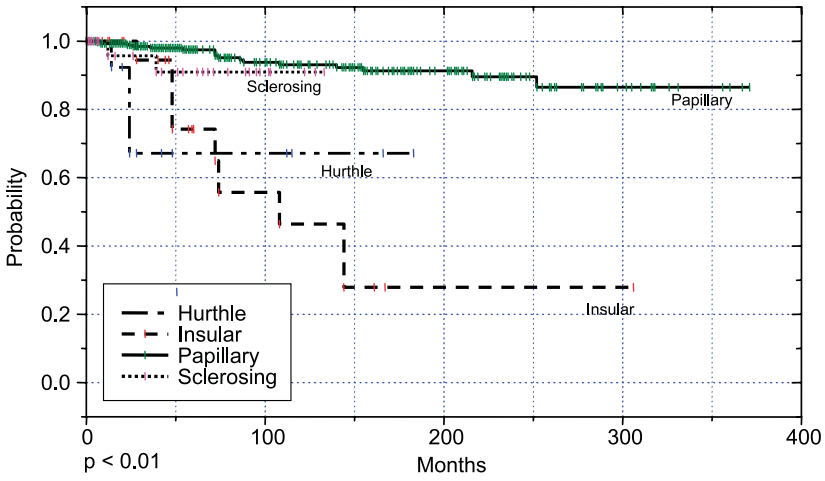

Figure 1. Advanced thyroid cancers: actuarial survival related to histological variants (Kaplan–Meier).

Discussion

The scarce biological aggression of thyroid cancer and the several therapeutic approaches offer many cases of recovery and very long survival periods, even at the most advanced stages (UICC stages III and IV).[4,5,11,12]

Studying patients with metastatic intraglandular thyroid carcinoma and with the cancer having spread outside the thyroid led to considerations both of an anatomic-pathological and clinical-prognostic nature.

Sex and age

There is evidence, and in our study too, that sex and age of the patients influence prognosis:[1,13,14] in males and in 'over fifty' patients advanced cancers are more frequent and mortality higher. In older patients the ratio of locally advanced tumours to metastatic tumours (1:2.2) is much higher than in younger patients (1:6.2). This may signify, as other authors admit,[1] that in older individuals the tumour is locally more aggressive, although this may also be attributable to later diagnosis.

Morphologic aspects and types of neoplastic growth

With regard to the morphologic aspects of the disease, it has been noted that in intraglandular metastasized tumours the tumoral capsula is absent or incomplete in the majority of the cases and complete in few cases. In extraglandular tumours the capsula is much more frequently totally absent. A study of the histological variants, in relation to the prognosis, shows how papillary and sclerosing carcinomas present higher survival rates than the Hürthle cell and insular types. This data is documented, although at times comparison between different types of histopathologic classifications is difficult.[1,13,15]

Significant differences are found between the type of metastases and the histology of the tumour. In less

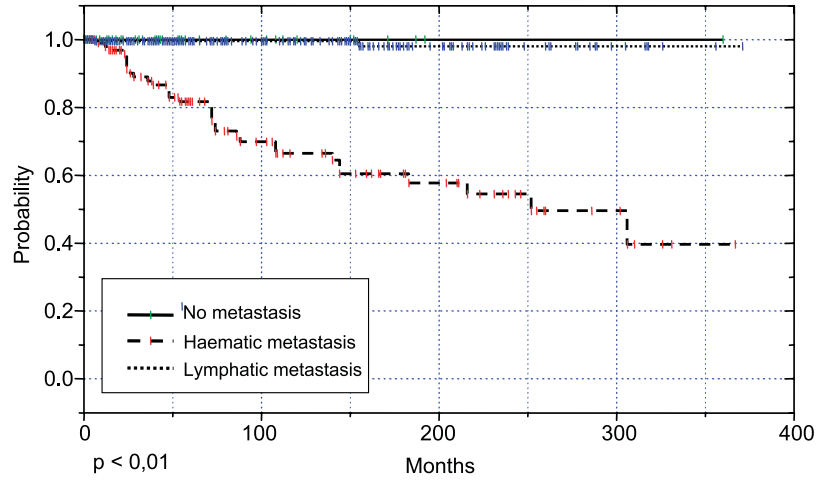

Figure 2. Advanced thyroid cancers: actuarial survival related to evidence of haematic or lymph-nodes metastasis (Kaplan–Meier).

Table 3
Deaths and disease recurrences vs state of disease at time of surgery

State of tumour at operation	Patients	Deaths	No recurrence (24-month minimum follow-up period)	Disease recurrence or persistence in any follow-up period
Only extraglandular tumour	75	6	26	23
Lymph-nodes metastases	262	11	59	175
Haematic metastases	42	12	1	40
Insufficient data	6	2		
Total	385	31	86	222

$p < 0.001$.

differentiated cancers (insular and Hürthle cell), haematic metastatization is much more frequent than in papillary and sclerosing carcinomas. Moreover, HM resulting in well-differentiated cancers is not only more frequent, but also occurs later.[11]

It is interesting to note that the ratio of patients with exclusively LM to those with haematic repetitions, at the time of diagnosis, is approximately 6:1. During the follow-up period this ratio drops considerably to approximately 2:1, due to a significant increase over time in the number of distant metastases cases (Table 2, A and B).[2]

Moreover, in the papillary variant, the tendency to develop HM in the follow-up period is greater for the extraglandular forms as compared to the intraglandular forms (13.4 vs 8.0%). Such difference, which is also confirmed by other statistics,[11,13,16] appears even more evident (17.0%) in the cases of extraglandular growth associated with the presence of lymph-node metastases. In our experience as well, the growth of HM in the follow-up period demonstrated the considerably unfavourable prognostic criteria.[11,13,17]

Also the recurrence or persistence of the disease is clearly higher in tumours that were metastatic at the time of surgery with respect to the exclusively extraglandular ones[2,13] (Table 3).

Also about 1/5 of the patients in our studies presented recurrence after 5 years from surgery. This data, together with the observation of extremely late recurrence, suggests that a long follow-up period is required for patients operated for thyroid cancer, especially at the advanced stage.[5,18]

Type of treatment

Once again surgery has a prominent role in the treatment of advanced tumours. Total or near-total thyroidectomy at the first or second operation is the predominant choice and was adopted in our cases as well.

There are no doubts over the primary importance of surgery in directly contributing to diagnostic precision and determining the local stages of the tumour.[2,14,16]

The cases of TC with invasion of local structures, such as the larynx, trachea, or oesophagus, present particular management difficulties. In situations with limited involvement of the larynx or trachea, there is controversy over whether a 'shave excision' that may leave microscopic disease at the site or a complete resection that includes removal of a portion of these structures is the better approach.[19]

With regard to managing the lymph nodes, the general view is that a preventive (prophylactic) lymphadenectomy is not justified even for locally advanced tumours.[1,2,20] A lymphadenectomy is considered necessary only for the exeresi of macroscopically positive lymph nodes at surgery, as it is possible to later treat any residual micro-metastases using other methods with excellent results.[1,2,20]

Surgery is used for distant metastases depending on the nature, site, infiltration and ability to concentrate radioactive iodine. In the case of lung metastases, which has an excellent response to radioactive iodine, surgery is used for single or multiple lesions, without captation, located at a single pulmonary lobe. In bone metastases, surgery is increasingly used to cure or palliate as a result of the relative resistance to treatment with ^{131}I. Brain metastases generally capture iodine; however, when possible, surgery is generally opted for in order to reduce the severe neurological symptoms.[21,22]

According to current medical literature metabolic beam therapy, used on almost all our patients, is the most effective post-surgical treatment for curing the primary tumoral foci, local recurrences, and particularly lymphatic and haematic metastasis.[15,21,22] We found, as example, that 1/3 of patients with early HM treated with radioactive iodine (at a minimum follow-up period of 24 months) is now disease-free.

External radiation therapy has a secondary role with respect to metabolic RT and is used for the scarcely captating tumours and those that are resistant to radioactive iodine treatment at the usual doses.[2,3,8,9]

Supplemental chemotherapy is used infrequently and with scarce results.[3,9,10]

Suppressive thyroid hormone therapy is attributed much importance by all. The differentiated neoplastic cells have the property of strongly depending on TSH for functioning and growth. Hence the suppression of this hormonal stimulus using levothyroxine, at doses from 2.5 to 3.0 γ/kg/die, is considered a valid anticancer treatment and should always be used in patients with thyroid carcinoma, especially at the advanced stages.[23]

Conclusions

Factors who affect prognosis of advanced thyroid cancers are the male sex, age of over 50 years at the time of diagnosis, histologic type (insular) and haematic metastatization.

Lymphatic metastasis does not appear to negatively change the prognosis of this type of tumour, although it is linked to a higher incidence of haematic metastasis in the follow-up period.

Even when the tumour is at an advanced stage, all the tumour forms present long survival possibilities.

Surgical treatment has a primary role in the treatment of thyroid carcinoma and the associated treatments (metabolic beam therapy, suppressive hormone therapy, and subsequently RT and chemotherapy) presently used are able to cure a high percentage of patients with the tumour at an advanced stage and to assure most diseased patients very long survival periods associated with a good lifestyles.

References

1. Carcangiu ML, Zampi G, Pupi A, Castagnoli A, Rosai J. Papillary carcinoma of the thyroid. A clinicopathologic study of 241 cases treated at the university of Florence. *Cancer* 1985;**55**:805–28.
2. Tsang RW, Brierley JD, Simpson WJ, Panzarella T, Gospodarowicz MK, Sutcliffe SB. The effects of surgery, radioiodine, and external radiation therapy on the clinical outcome of patients with differentiated thyroid carcinoma. *Cancer* 1998;**82**(2):375–88.
3. Harmer CL. Radiotherapy in the management of thyroid cancer. *Ann Acad Med Singapore* 1996;**25**(3):413–9 [Review].
4. Sugino K, Ita K, Mimura T, Ozaki O, Kawano M, Kitamura Y. The enucleation of thyroid tumors indeterminate before surgery as a papillary thyroid carcinoma: should immediate reoperation be performed? *Jpn J Surg* 1994;**24**:305–8.
5. Cady B. Presidential address: beyond risk groups—a new look at differentiated thyroid cancer. *Surgery* 1998;**124**(6):947–56.
6. Cady B. Papillary carcinoma of the thyroid. *Semin Surg Oncol* 1991;**7**: 81–9.
7. Grunwald F, Cristian M, Fimmers R, Zamora PO, Biersack HJ. Prognostic value off thyroglobuline after thyroidectomy before ablative radioiodine therapy in thyroid cancer. *J Nucl Med* 1996; **37**:1962–4.
8. Kim TH, Yang DS, Jung KY, Kim CY, Choi MS. Value of external irradiation for locally advanced papillary thyroid cancer. *Int J Radiat Oncol Biol Phys* 2003;**55**(4):1006–12.
9. The Japanese Society of Thyroid Surgery. Chemotherapy Committee Intensive chemotherapy for anaplastic thyroid carcinoma: combination of cisplatin, doxorubicin, etoposide and peplomycin with granulocyte granulocyte colony-stimulating factor support. *Jpn J Clin Oncol* 1995; **25**(5):203–7.
10. Pak H, Gourgiotis L, Chang WI, Guthrie LC, Skarulis MC, Reynolds JC, et al. Role of metastasectomy in the management of thyroid carcinoma: the NIH experience. *J Surg Oncol* 2003;**82**(1): 10–18.
11. Hay ID, Bergstralh EJ, Grant CS, McIver B, Thompson GB, Van Heerden JA, et al. Impact of primary surgery on outcome in 300 patients with pathologic tumor-node-metastasis stage III papillary thyroid carcinoma treated at one institution from 1940 through 1989. *Surgery* 1999;**126**(6):1173–82.
12. Scheuemann GFW, Gimm O, Wegener G. Surgery of locoregional recurrence and linfonode metastasis in papillary thyroid carcinoma. *Eur J Surg Oncol* 1994;**20**:286–9.
13. Laszlo A, Rosset A, Hermann F, Ozsahin M, Zouhair A, Mirimanoff O. T.i.d accelerated radiotherapy alone or alternating with chemotherapy in patients with a locally advanced ORL cancer: analysis of late toxicity. *Cancer Radiother* 2001;**5**(2):130–7.
14. Yang CC, Lee CH, Wang LS, Huang BS, Hsu WH, Huang MH. Resectional treatment for thyroid cancer with tracheal invasion: a long-term follow-up study. *Arch Surg* 2000;**135**(6):704–7.
15. Pacini F, Cetani F, Miccoli P, Mancusi F, Ceccarelli C, Lippi F. Outcome of 309 patients with metastatic differentiated thyroid carcinoma treated with radioiodine. *World J Surg* 1994;**18**:600–4.
16. Lerch H, Schlober O, Kuwert T. Survival of differentiated thyroid carcinoma studied in 500 patients. *J Clin Oncol* 1997;**15**:2067–75.
17. Tenvall J, Biorklund A, Meller T. Prognostic factors of papillary follicular and medullary carcinomas of the thyroid gland. *Acta radiol Oncol* 1985;**25**:17–24.
18. Gagel RF, Goepfert H, Callender DL. Changing concepts in the pathogenesis and menagement of thyroid carcinoma. *Cancer J Clin* 1996;**46**:261–83.
19. Gillenwater AM, Goepfert H. Surgical management of laryngotracheal and esophageal involvement by locally advanced thyroid cancer. *Semin Surg Oncol* 1999;**16**(1):19–29.
20. Grebe SKG, Hay ID. Thyroid cancer nodal metastases: biologic significance and therapeutic considerations. *Surg Oncol Clin North Am* 1996;**5**:43–63.
21. Schlumberger M, Tubiana M, De Vathaire F, Hill C, Gardet P, Travagli JP. Long-term results of treatment of 238 patients with lung and bone metastases from differentiated thyroid carcinoma. *J Clin Endocrinol Metab* 1986;**63**:960–4.
22. Maxon HR, Smith HS. Radioiodine-131 in the diagnosis and treatment of metastatic well differentiated thyroid cancer. *Endocrinol Metab Clin North Am* 1990;**19**:685–9.
23. Samaan NA, Schultz PN, Haynie TP, Ordonez NG. Pulmunary metastasis of differentiated thyroid carcinoma: treatment results in 101 patents. *J Clin Endocrinol Metab* 1985;**60**:376–81.