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Long term outcome in thyroid cancer with intermediate differentiation following systematic total or near-total thyroidectomy plus high dose radioactive iodine therapy

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ABSTRACT

The prognosis and management of thyroid cancer with intermediate differentiation have been established according to reviews and small series. The aim of the present study was to determine the long-term outcome of thyroid cancer with intermediate differentiation following standardized therapy. Thirty patients (study group) with palpable tall-cell, columnar cell, diffuse sclerosing, insular and Hurthle cell variants of thyroid carcinoma, as well as 45 follicular and 99 pure papillary controls, underwent systematic total or near-total thyroidectomy followed by at least one high dose of radioactive iodine. After a mean follow-up of 12 years, the recurrence rate was very elevated (37%) in the study group ($p<0.001$ versus controls), even in Stage I or Stage II subjects ($p<0.001$), but the disease-specific mortality in the same cohort (7%) was comparable to that of the follicular carcinoma group ($p>0.28$) and better than that of previous studies. Essentially, insular histology was associated with a poor outcome (recurrence 83%, mortality 33%). The recurrence was only locoregional in diffuse sclerosing carcinoma, whereas distant metastases (lung, mediastinum, bone, brain) were observed in all cases of recurrent insular, tall-cell and Hurthle cell carcinoma. In all metastatic cases, the iodophile status was permanent and no cases of dedifferentiation of metastases were described. Despite the aggressive behavior of thyroid cancer with intermediate differentiation, early and intensive surgical and isotopic therapy may ameliorate the prognosis.

KEYWORDS: thyroid cancer, intermediate differentiation, radioactive iodine, long-term follow-up

INTRODUCTION

Well-differentiated carcinoma is the most common histological form of thyroid carcinoma (TC), comprising nearly 90 per cent of cases and including papillary TC and follicular TC. Medullary TC arises from the calcitonin secreting thyroid C-cells with a frequency of 5 - 9 per cent of all TC, and the remaining 1 - 2 per cent are anaplastic or poorly differentiated TC [1].

Classical papillary TC and follicular TC follow a relatively indolent course in most cases. However, subtypes of these tumors have been described as presenting with more aggressive behavior and have been labeled TC with intermediate differentiation (intermediate TC). These include the tall cell variant of papillary TC (tall-cell TC), the columnar cell variant of papillary TC (columnar TC), the diffuse sclerosing variant of papillary TC (sclerosing TC), insular TC and Hurthle cell (oncocytic,

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oxyphilic) TC (Hurthle TC). These intermediate variants are not uncommon, their prevalence being estimated at between 10 and 15 per cent of all TC [2]. However, case reports and small series have primarily been reported in the literature and questions arise regarding the real prognosis and management of these tumors.

The aim of the present study was to determine the clinical characteristics, histological aspects and long term evolution after standardized initial treatment of intermediate TC and to compare them with those of follicular TC and pure papillary TC (papillary TC).

MATERIALS AND METHODS

Patient and control groups

Between January 1990 and December 2006, all newly diagnosed cases, older than 16 years of age, of palpable tall-cell, columnar, sclerosing, insular, Hurthle and follicular TC in our tertiary care institution were enrolled in this long-term comparative study. From January 1994, 100 consecutive patients older than 16 years of age and with palpable papillary TC were assigned to a control group. The exclusion criteria for the follicular TC and papillary TC cohorts were as follows: nonpalpable tumor, incidentally found on imaging procedure and presence of a non-well-differentiated component on histological analysis. A total of 46 cases of follicular TC and 30 cases of intermediate TC were recruited.

All study and control patients underwent total or near-total thyroidectomy (thyroidectomy with an examined thyroid remnant less than or equal to 1 gram and/or thyroid postoperative 24-hour iodine uptake less than 5 per cent), one-month postoperative diagnostic whole body scan, and received at least one treatment of radioactive iodine (RAI). This therapeutic strategy enabled good interpretation of the whole body scans and thyroglobulin examinations that were routinely performed and regularly repeated during the follow-up. Systematic prophylactic lymph node dissection was not performed in our study. Therapeutic unilateral or bilateral modified radical neck dissection was performed when metastatic lymph nodes were detected on preoperative imaging procedures or diagnosed during the thyroidectomy. Sometimes bilateral central lymph node dissection was performed in cases of regional metastases limited to Level VI. When RAI treatment was administered, a one-week post therapy whole body scan was always performed. The minimal first dose of RAI was 30 millicuries (mCi) in papillary TC subjects and 100 mCi in follicular TC and intermediate TC individuals. The dose of the first RAI treatment and the indications for following therapies were determined according to the MACIS (presence of *metastasis* at diagnostic whole body scan, patient *age*, *completeness* of resection, *invasion* degree, and tumor *size*) prognostic model [3]. The Institutional Review Board approved the study. In all patients, permanent thyroid-stimulating hormone (TSH) suppressive therapy by L-thyroxine was prescribed and informed consent was obtained.

The data were prospectively documented in all subjects and retrospectively analyzed in 30 intermediate TC, 45 follicular TC and 99 papillary TC cases, while the rest of the patients were lost to follow-up. The intermediate TC group included six tall-cell TC, one columnar TC, eight sclerosing TC, six insular TC and nine Hurthle TC cases with a female/male proportion and a mean age of six/zero, one/zero, six/two, five/one, and six/three, and 47, 39, 48, 57, and 50 years, in each subgroup respectively. Between 1990 and 2006 approximately 350 TC cases, 80 per cent of them papillary, tall-cell, columnar or sclerosing TC, were examined at our institution.

Histological definitions and patient classification

The histological definitions of papillary, follicular, tall-cell, columnar, sclerosing, insular and Hurthle TC in our study were in agreement with those in previously published pathology data [1, 4, 5]. The slides were carefully read and analyzed by a committee of experts in thyroid pathology. In tall-cell TC, the maximal thyroid cell dimension was two to three times the normal cell height and abundant eosinophilic cytoplasm was observed. In cases of markedly elevated cellular height with nuclear pseudo-stratification, the diagnosis of columnar TC was established. The diagnosis of sclerosing TC was made if extensive fibrosis, squamous metaplasia and a significant amount of lymphocytes were present. In Hurthle TC, large polygonal eosinophilic cells with big, dark nuclei

were accompanied by capsular and/or vascular invasion and/or metastatic disease. In all the insular TC cases, a solid pattern of growth was recognized in most of the tumor. In three cases, a papillary component was observed. In the other three cases, convoluted nuclei, high mitotic activity or tumor necrosis were not described. In the insular TC cohort, necrosis and vascular invasion were reported in one case and four cases, respectively. Subjects with the follicular variant of papillary carcinoma, carcinoma with a scirrhous growth pattern, medullary or anaplastic carcinoma were excluded from the study.

Following surgery and a postoperative whole body scan performed after a high dose of RAI (30 to 250 mCi), the patients underwent pathologic tumor node metastasis (pTNM) grouping according to the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC). In the present article, the new classification (2003) was taken into account, which categorizes tumors as: tumor less than or equal to 2 cm in greatest dimension [pT1]; tumor greater than 2 cm, but less than or equal to 4 cm in greatest dimension [pT2]; and tumor greater than 4 cm in greatest dimension [pT3] [6]. In cases of tumors with thyroid capsular effraction [pT4], the degree of local invasion was specified: perithyroidal adipose tissue only or extensive extrathyroidal spread (conjunctive tissue, muscle, perineurium, larynx-trachea or spine invasion). Unifocal tumors were considered as Ta and multifocal tumors as Tb. In Tb tumors, whether malignancy was present in one or two thyroid lobes was stated precisely. The presence of thyroid vascular invasion and the absence-existence of regional lymph node metastasis [N0-N1] or distant metastasis [M0-M1] were also accurately determined in all study groups. The patients were further classified according to the AJCC staging: age less than 45 years: M0 = Stage I, M1 = Stage II; age greater than or equal to 45 years: pT1 = Stage I; pT2-pT3 = Stage II; pT4 or N1 = Stage III; M1 = Stage IV [3].

The criteria to evaluate the response of therapy were as follows:

Complete remission was achieved when the RAI whole body scans (post therapy and diagnostic) were without any evidence of RAI accumulation and serum thyroglobulin level was less than 1 ng/ml in the presence of TSH greater than 30 mU/l.

Stable persistent disease was defined as persistent uptake in the same areas on follow-up RAI whole body scans, combined with a constantly high serum thyroglobulin level.

Progressive disease was defined as the appearance of new TC lesions on RAI whole body scan or other imaging procedures.

Laboratory tests

Thyroid function tests were performed by microparticle enzyme immunoassays (Abbot Diagnostic Division, Abbot Park, IL).

The titers of thyroglobulin, anti-thyroglobulin and antithyroid peroxidase autoantibodies were determined by immunometric assays: IMMULITE thyroglobulin, IMMULITE Anti-TG Ab, IMMULITE Anti-TPO Ab (Diagnostic Products Corporation, Los Angeles, CA). The respective sensitivities, intra- and inter-assay coefficients of variation were: thyroglobulin: 0.9 ng/ml, 4.2 to 10 per cent, 7.0 to 8.8 per cent; Anti-TG Ab: 10 IU/ml, 2.3 to 3.9 per cent, 4.2 to 9.1 per cent: Anti-TPO Ab: 7 IU/ml, 3.5 to 5.6 per cent, 7.8 to 10.5 per cent.

Statistical analysis

Comparisons between the study groups were carried out using the non-parametric Mann-Whitney U Test. Differences between proportions were analyzed by the two-tailed Chi Square Test. Statistical significance was accepted at $p<0.05$. All values are expressed as mean ± standard error (SE). All statistical calculations were performed by the Statistica® Release 5 software (Statsoft, Tulsa, OK).

RESULTS

Patient characteristics before thyroidectomy

The presenting features of patients and control subjects are presented in Table 1. Gender, age at thyroidectomy and body mass index were similar in all study groups. Except for one papillary TC and two follicular TC cases, all subjects were older than 18. Twenty-four follicular TC, 10 intermediate TC, and 45 papillary TC patients

Table 1. Presenting features before thyroidectomy.

Feature	FTC (n = 45)	TCID (n = 30)	PPTC (n = 99)
Age (years), mean ± SE	44 ± 2	48 ± 3	44 ± 1
Gender (female/male)	36/9	24/6	82/17
BMI (Kg/m^2), mean ± SE	27 ± 1	27 ± 1	28 ± 1
Cold nodule/warm nodule (scintigraphy)	43/2	29/1	97/2
Single/multiple nodules (palpation and/or US)	34/11	15/15	66/13
Hyperthyroidism: subclinical/clinical	0/3	0/3	1/5
Hypothyroidism: subclinical/clinical	1/0	0/0	4/0
Positive thyroid autoantibodies (TGAA/TPOAA)	2/4	0/0	3/10
Prior irradiation	3	1	5
Extrathyroidal malignancy	5	2*	4
Percentage of malignant FNAB	29%	74%†	79%†

*Breast cancer seven years before thyroidectomy in one case of insular thyroid carcinoma; Hodgkin's disease 21 years before thyroidectomy in one case of diffuse sclerosing variant of papillary thyroid carcinoma. †$p<0.001$ as compared with FTC.
FTC, follicular thyroid carcinoma; TCID, thyroid carcinoma with intermediate differentiation; PPTC, pure papillary thyroid carcinoma; BMI, body mass index; US, ultrasound scan; TG, thyroglobulin; TPO, thyroid peroxidase; AA, autoantibodies; FNAB, fine needle aspiration biopsy.

were younger than 45. External irradiation was described in anamnesis in three follicular TC (two for breast carcinoma, and one cranial radiotherapy for tenia capitis), one intermediate TC (for Hodgkin's Disease in a sclerosing TC case), and five papillary TC patients (three irradiations for tenia capitis, one for Hodgkin's disease and one after the Chernobyl disaster). Eleven patients were previously treated for non-thyroidal cancer: five follicular TC (renal carcinoma, small bowel leiomyosarcoma, and three cases of breast carcinoma), two intermediate TC and four papillary TC (non-Hodgkin's lymphoma, breast carcinoma and two cases of Hodgkin's disease). In most cases of intermediate TC and papillary TC, one-time total or near-total thyroidectomy was performed according to the malignancy signs that were present at fine needle aspiration biopsy. However, malignancy signs were absent in 71 per cent of follicular TC cases: Hemithyroidectomy plus isthmectomy was first performed in these patients because of hard tumor consistency, nodule enlargement or local compression symptoms. The patients were referred to a second intervention to complete the thyroidectomy if the first surgical pathology revealed follicular carcinoma. The two interventions were performed in our institution in all follicular TC, intermediate TC and papillary TC cases with two-times thyroidectomy.

pTNM classification

Pathological classification regarding tumor characteristics and the presence of lymph nodes and/or distant metastases is summarized in Tables 2 and 3.

Extensive extrathyroid spread was described in the intermediate TC group. This locally aggressive behavior was less observed in the other two cohorts. As classically described, vascular invasion was more often reported in follicular than in papillary TC. However, this type of dissemination was statistically more frequent in intermediate TC than in papillary TC.

The percentage of N1 patients, as well as the number of involved lymph nodes, was similar in the intermediate TC and papillary TC groups, and slightly lower in the follicular TC cohort. The proportion of M1 cases was similar in the intermediate TC and follicular TC groups, and

Table 2. pTNM classification: tumor characteristics, number of cases (%).

pTNM classification	FTC (n = 45)	TCID (n = 30)	PPTC (n = 99)	TCID vs FTC*	TCID vs PPTC*	FTC vs PPTC*
pT1	5 (11%)	8 (26%)	38 (38%)	0.09	NS	< 0.001
pT2	10 (22%)	3 (10%)	35 (35%)	NS	0.01	NS
pT3	3 (7%)	2 (7%)	1 (1%)	NS	0.06	NS
pT4	27 (60%)	17 (57%)	25 (25%)	NS	< 0.01	0.0001
Perithyroidal adipose tissue only	25 (56%)	13 (43%)	23 (23%)			
Extensive extrathyroidal spread	2 (4%)	4 (13%)	2 (2%)	NS	0.01	NS
Ta	35 (78%)	21 (70%)	66 (66%)			
Tb	10 (22%)	9 (30%)	33 (33%)	NS	NS	0.07
Unilobar	1 (2%)	1 (4%)	12 (12%)			
Bilateral	9 (20%)	8 (26%)	21 (21%)	NS	NS	NS
Vascular invasion	22 (49%)	6 (20%)	0 (0%)	NS	< 0.001	< 0.0001

*p value.

pTNM, pathologic tumor node metastasis; FTC, follicular thyroid carcinoma; TCID, thyroid carcinoma with intermediate differentiation; PPTC, pure papillary thyroid carcinoma; pT1, tumor ≤2 cm in greatest dimension; pT2, tumor >2 cm but ≤4 cm in greatest dimension; pT3, tumor >4 cm in greatest dimension; pT4, tumor with thyroid capsular effraction; Ta, unifocal lesion; Tb, multifocal tumor.

Table 3. pTNM classification: lymph nodes and distant metastases.

No of cases (%)		FTC (n=45)	TCID (n=30)	PPTC (n=99)
N0		38	24	70
N1		7 (16%)	6 (22%)*	30 (30%)
	Solitary lymph node	2 (5%)	2 (7%)	8 (8%)
	2 to 5 lymph node	5 (11%)	2 (7%)	17 (17%)
	>5 lymph node	0 (0%)	2 (7%)	5 (5%)
M0		40	26	96
M1		5 (11%)	4 (15%)†	3 (3%)
	Lung	0	4	2
	Mediastinum	0	0	1
	Lung + mediastinum	2	0	0
	Liver	1	0	0
	Bone	1	0	0
	Bone + lung + mediastinum	1	0	0

*p = NS as compared with FTC, p = NS as compared with PPTC. †p = 0.01 as compared with PPTC.

FTC, follicular thyroid carcinoma; TCID, thyroid carcinoma with intermediate differentiation; PPTC, pure papillary thyroid carcinoma; N0, no regional lymph node metastasis; N1, existence of regional lymph node metastasis; M0, no distant metastasis; M1, existence of distant metastasis.

significantly lower in the papillary TC cohort. Essentially, chest metastases (lung and/or mediastinum) were observed in the three groups. Bone metastases were described only in the follicular TC group.

Outcome prediction

Staging, proportion of male patients and subjects older than 45 years, as well as tumor size in the various study groups are presented in Table 4. Apart from a lower number of Stage IV subjects and a slightly higher number of Stage I individuals in the papillary TC group, the staging was similar in the three cohorts. The proportion of patients older than 45 years was higher in the intermediate TC group. No other factor of bad prognosis was observed in this cohort.

Follow-up

The mean follow-up duration was 12 and a half years in the follicular TC group, 12 years in the papillary TC group and 11 and a half years in the intermediate TC cohort (Table 4). The percentages of patients that were monitored for a minimum of five years and for at least 10 years were as follows: follicular TC: 100 per cent and 77 per cent; intermediate TC: 93 per cent and 60 per cent; papillary TC: 100 per cent and 69 per cent; whole cohort: 98 per cent and 70 per cent.

At the time our manuscript was submitted for publication, eight cases of death were reported: two in the intermediate TC group, two in the papillary TC group and four in the follicular TC group. However, only three cases of death were related to the thyroid disease: two intermediate TC patients and one follicular TC patient, the cause-specific survival rates being 100 per cent, 98 per cent and 93 per cent, in the papillary TC, follicular TC and intermediate TC cohorts, respectively. This relatively good prognosis seems to be due to the extension of the surgical procedure and the degree of the RAI therapy that was slightly more intensive in the intermediate TC cohort than in the other two groups (Table 4).

No case of bilateral laryngeal nerve injury was observed in our study. The number of patients with permanent unilateral vocal palsy and permanent postoperative hypoparathyroidism was three and seven, zero and nine, zero and four in the papillary TC, follicular TC and intermediate TC groups, respectively. Among the three cases of

Table 4. Outcome prediction, follow-up duration and cumulative radioiodine dose.

Histologic group	FTC (n = 45)	TCID (n = 30)	PPTC (n = 99)
Staging[*]			
Stage I	22 (49%)	14 (46%)	62 (62%)
Stage II	6 (13%)	5 (17%)	13 (13%)
Stage III	13 (29%)	8 (27%)	23 (23%)
Stage IV	4 (9%)	3 (10%)	1 (1%)
Patient age at TY ≥45 years[*]	21 (47%)	20 (67%)[†]	54 (54%)
Male gender[*]	9 (20%)	6 (20%)	17 (17%)
Tumor size (mm)[‡]	36 ± 3[§]	25 ± 4	20 ± 1
Follow-up duration (years)[‡]	12.5 ± 0.9	11.5 ± 1.0	12 ± 0.5
Cumulative radioiodine dose[‡]			
mCi	137 ± 12	219 ± 39[‖]	133 ± 12
GBq	5.1 ± 0.4	8.1 ± 1.4	4.9 ± 0.4

[*]Number of cases (%). [†]p = 0.09 as compared with FTC. [‡]mean ± SE. [§]p = <0.01 as compared with TCID. [‖]p = NS as compared with PPTC.
FTC, follicular thyroid carcinoma; TCID, thyroid carcinoma with intermediate differentiation; PPTC, pure papillary thyroid carcinoma; mCi, millicuries; GBq, gigabecquerels.

vocal cord palsy and the 20 cases of hypoparathyroidism, only one case and three cases respectively underwent neck dissection. The four cases of hypoparathyroidism in the intermediate TC cohort were one tall-cell TC, one columnar TC and two Hurthle TC.

In the follicular TC group, complete remission was observed in 42 patients, the disease-free survival rate being 93 per cent. At diagnosis, six N1 M0 cases and four N0 M1 cases were reported in the follicular TC cohort, whereas one N1 M1 case was described. In five N1 M0 patients and three N0 M1 subjects, the lesions disappeared following RAI therapy. One N1 M0 patient (male, age at thyroidectomy: 69 years, Stage III) showed stabilization of cervical metastases. One N1 M1 patient (male, age at thyroidectomy: 53 years, Stage IV) showed stabilization of bone, lung and mediastinal metastases, following orthopedic debulking of a sacral bone metastasis and RAI therapy. In one N0 M1 patient (male, age at thyroidectomy: 46 years, unifocal TC with extensive extrathyroidal spread without vascular invasion, Stage IV), exacerbation of bone metastases was reported and death occurred 12 years following thyroidectomy, despite RAI treatment and cobalt therapy.

In the papillary TC group, complete remission was observed in 94 patients, the disease free survival rate being 95 per cent. Among the 30 N1 cases, disappearance of the cervical metastatic lymphadenopathies was reported in 28 patients. In the other two patients (female), lung metastases appeared and were stable following RAI therapy. Age, histological features at thyroidectomy and date of metastasis diagnosis after thyroidectomy were respectively: 58 years, unifocal pT4 tumor with adipose perithyroidal tissue invasion without vascular invasion, two years; and 61 years, unilateral multifocal pT4 tumor with extensive perithyroidal tissue invasion without vascular invasion, 12 years.

Complete remission was observed following RAI treatment in the three patients initially classified as having M1 disease. No metastatic lymph nodes were described in these subjects whose gender and age at thyroidectomy were respectively: male, 69 years; female, 27 years; and female, 40 years.

Among the 66 N0 M0 patients with papillary TC, recurrence of the disease was reported in three women. In the first, cervical metastatic lymph nodes appeared, and in the other two, lung metastases were diagnosed. Age, histological features at thyroidectomy and date of metastasis diagnosis after thyroidectomy were respectively: 19 years, unifocal tumor pT2 without vascular invasion, one year; 64 years, unifocal tumor pT1 without vascular invasion, eight years; and 53 years, unilateral multifocal tumor pT2 without vascular invasion, 11 years. Following RAI therapy, the metastases disappeared in the first two cases and were stable in the third patient.

Data concerning the intermediate TC group follow-up are summarized in Table 5. Complete remission was described in 19 patients, the disease free survival rate being 63 per cent ($p<0.0001$ as compared with the papillary TC group and $p<0.001$ as compared with the follicular TC group). No case of stable persistent disease was observed. Progressive disease was reported in 11 subjects (37 per cent of cases). This recurrence rate was more elevated than in the papillary TC and follicular TC groups ($p<0.0001$ and $p=0.0001$, respectively). Among the 11 intermediate TC patients with progressive disease, five were classified as Stage I following thyroidectomy, the number of Stage II, Stage III and Stage IV patients being one, three and two, respectively. The follicular TC case with progressive disease was Stage IV and the five papillary TC cases with progressive disease were two Stage I, one Stage II and two Stage III. The recurrence rate in TC patients with Stage I or Stage II was 32 per cent in the intermediate TC group ($p<0.001$ as compared with papillary TC or follicular TC). In all intermediate TC, papillary TC and follicular TC patients with progressive disease, the metastases were visible on RAI whole body scan and no case of TC metastatic dedifferentiation was reported during the follow-up. Among the intermediate TC patients with distant metastases at diagnosis ($n=4$) or during follow-up ($n=4$), the numbers of subjects with unifocal, multifocal unilateral, or bilateral lesions at postoperative histology were three, zero, and one cases and four, zero and zero cases, respectively. Among these eight patients, two showed vascular invasion and two others

Table 5. Thyroid carcinoma with intermediate differentiation (TCID): patient follow-up (number of cases).

Initial histology (n = 30)		Evolution of initial lesions			New onset lesions	
		Complete remission	Stable disease	Progressive disease	Cervical lymph nodes	Distant metastases
Intrathyroidal (pT1 pT2 pT3 N0 M0) (n = 12)						
Unifocal (3 TCVPTC, 1 DSVPTV, 4 HCTC)	8	5	-	3	1[*]	2[†,‡]
Multifocal unilateral (1 HCTC)	1	1	-			
Bilateral (1 TCVPTC, 2 DSVPTC)	3	2	-	1	1[§]	
Local invasion (pT4 N0 M0) (n = 9)						
Adipose tissue only(1 TCVPTC, 1 CCVPTC, 1 DSVPTC, 2 ITC, 2 HCTC)	7	5	-	2		2[‖,¶]
Extensive spread (2 ITC)	2	1	-	1		1[**]
Regional extension (N1 M0) (n = 5)						
Solitary lymph node (1 HCTC)	1	1	-			
2 to 5 lymph nodes (2 DSVTC)	2	1	-	1	1[††]	
>5 lymph nodes (1 TCVPTC, 1 DSVPTC)	2	1	-	1	1[‡‡]	
Distant metastases (M1) (n = 4)						
Lung (1 DSVPTC, 2 ITC, 1 HCTC)	4	2	-	2		2[§§,‖‖]
Liver	0					
Bone	0					

[*]Cervical unilateral lymph node metastases 4 years after TY (neck dissection was not performed); the metastases disappeared following RAI treatment (cumulative RAI dose: 380 mCi) (DSVPTC, pT1, female patient, age at TY – 68 years). [†]Lung and mediastinal metastases 18 years after TY; the metastases disappeared on RAI-WBS and PET-CT following RAI treatment (cumulative RAI dose 450 mCi) (HCTC, pT3, male patient, age at TY – 47 years). [‡]Mediastinal metastases 17 months after TY, the metastases disappeared on RAI-WBS and PET-CT following RAI treatment (cumulative dose: 250 mCi) (TCVPTC, pT1, female patient, age at TY – 60 years). [§]Bilateral cervical lymph node metastases 24 months after TY (neck dissection was not performed); the metastases disappeared following RAI treatment (cumulative RAI dose: 250 mCi) (DSVPTC, pT2, female patient, age at TY – 44 years). [‖]Lung metastases, costal bone metastases and cervical vertebral metastases 16 months, four years and six years after TY, respectively (cumulative RAI dose: 750 mCi) (ITC with vascular invasion, female patient, age at TY – 57 years). [¶]Cervical metastases and lung metastases 1 year and 7 years after TY, respectively; stable disease following RAI treatment (cumulative RAI dose: 600 mCi) (ITC without vascular invasion, male patient, age at TY – 50 years). [**]Lung metastases two years after TY, death four years after TY despite RAI treatment and external cervical radiotherapy (cumulative RAI dose: 450 mCi) (ITC with vascular invasion, female patient, age at TY – 78 years). [††]New unilateral cervical lymph node metastases three years after TY, although neck dissection was performed; the metastases disappeared following RAI treatment (cumulative RAI dose 400 mCi) (DSVPTC, female patient, age at TY – 42 years). [‡‡]New bilateral cervical lymph node metastases 28 months after TY, although neck dissection was performed; the metastases disappeared following RAI treatment (cumulative RAI dose: 550 mCi) (DSVPTC, male patient, age at TY – 28 years). [§§]Tracheal metastases four years after TY, and brain and skull metastases six years after TY (cumulative RAI dose 700 mCi) (ITC with vascular invasion and tumor necrosis, female patient, age at TY – 68 years). [‖‖]Pelvic bone metastases and new lung metastases three years after TY, death four years after TY despite RAI treatment and external pelvic radiotherapy (cumulative RAI dose: 500 mCi) (ITC with vascular invasion, female patient, age at TY – 49 years).

pT1, tumor ≤2 cm in greatest dimension; pT2, tumor >2 cm but ≤4 cm in greatest dimension; pT3, tumor >4 cm in greatest dimension; pT4, tumor with thyroid capsular effraction; N0, no regional lymph node metastasis; N1, existence of regional lymph node metastasis; M0, no distant metastasis; M1, existence of distant metastasis; TCVPTC, tall cell variant of papillary thyroid cancer; CCVPTC, columnar cell variant of papillary thyroid cancer; DSVPTC, diffuse sclerosing variant of papillary thyroid cancer; ITC = insular thyroid cancer; HCTC: Hurthle cell thyroid cancer; TY, thyroidectomy; RAI, radioactive iodine; mCi, millicuries; WBS, whole body scan; PET-CT, positron emission tomography – computerized tomography.

showed vascular invasion plus extensive extrathyroidal spread (data not shown). The interval between thyroidectomy and onset of new metastases in the 11 intermediate TC cases and the five papillary TC patients with progressive disease was 46 ± 17 months (mean ± SE) and 82 ± 27 months, respectively.

Among the eight patients with sclerosing TC, four underwent neck dissection according to the intraoperative lymph node inspection and palpation, the signs of malignancy being confirmed by frozen section. In these patients, resection of all level VI lymph nodes was performed and levels I, II, III, IV, and V lymph nodes were excised on the side of the dominant thyroid tumor (bilateral central and unilateral modified radical neck dissection). Locoregional recurrence occurred in four cases of sclerosing TC [positive RAI whole body scan, negative ultrasonography (US)], two patients who underwent neck dissection and two patients who did not undergo lymph node resection.

The rate of progressive disease in the insular TC subgroup was 83 per cent. Despite this high recurrence rate, the mortality percentage was only 33 per cent. In the insular TC cohort, all cases of death or recurrence occurred less than four years after thyroidectomy.

In summary, the various study groups and subgroups may be classified by the severity order, according to recurrence rate (locoregional and/or distant) and the disease specific mortality rate, which were respectively as follows: papillary TC: 5 per cent and 0 per cent; follicular TC: 2 per cent and 2 per cent; intermediate TC: 37 per cent and seven per cent; columnar TC: 0 per cent and 0 per cent; Hurthle TC: 11 per cent and 0 per cent; tall-cell TC: 17 per cent and zero per cent; sclerosing TC: 50 per cent and 0 per cent; insular TC: 83 per cent and 33 per cent. The recurrence rate was only 25 per cent in the non insular intermediate TC cases (p=0.01 as compared with the insular TC group). The disease specific mortality rate in follicular TC and intermediate TC was similar (p>0.28).

DISCUSSION

The main finding of this long-term controlled study is the possibility of controlling the evolution of intermediate TC, despite its aggressive behavior, by intensive and early surgical and isotopic therapy.

Little clinical data is available concerning the long-term evolution of intermediate TC, generally described in case reports, reviews [1], meta-analyses [2] or small series. To the best of our knowledge, this study is the first report comparing intermediate TC with the papillary TC and follicular TC with a patient follow-up extending over such a long period of time. In previous reports, intermediate TC was compared with poorly differentiated TC [7] or with papillary TC [8] with a mean follow-up of five years [7, 9]. In our study, follicular TC patients were included and the mean follow-up reached 10 years, an important condition in thyroid tumors because of their relatively long evolution.

Our results concerning the prognosis of intermediate TC appear to be better than those published in previous series [2, 8, 10-13]. These controversial results may be related to the bias connected with the selection of patients who are not always referred to a tertiary care center, the histologic definitions of insular TC and poorly differentiated TC, which sometimes overlap, and the difficulty in enrolling a high number of patients for long-term follow-up.

In our study, the three groups were similar in terms of gender, age and follow-up duration. The relatively good prognosis of intermediate TC observed in our study could not be related to a lower percentage of male patients or a lower proportion of subjects older than 45 years. As follicular TC and intermediate TC staging at thyroidectomy were comparable, the relatively good outcome of intermediate TC in our study could not be due to an earlier diagnosis.

According to the literature, the estimated prevalence of tall-cell TC, columnar TC and sclerosing TC is respectively 3 to 12 per cent [2, 12], 0.15 to 0.2 per cent, [1] and 2 to 6 per cent [1, 2] of all papillary thyroid cancers. The frequency of insular TC and Hurthle TC have been reported to be respectively 2 to 6 per cent of all TC [2], and 3 per cent of well differentiated TC [10, 11] in countries with iodine-sufficient diets, like Israel. Apart from a somewhat low prevalence of tall-cell TC in our research, the frequency of all subgroups is in keeping with that of previous studies.

The tall-cell TC histologic type is considered per se to be an independent factor of poor prognosis as compared with papillary TC [2, 8, 14-16]. The 10-year recurrence and disease specific mortality rates in tall-cell TC have been reported to be 25 to 33 percent and 10 to 13 per cent, respectively [8, 12], higher than in our report where the corresponding percentages were 17 per cent and 0 per cent, respectively. However, total or near-total thyroidectomy was not systematic [8, 12], the role of RAI was not always studied [12] and a high proportion of patients older than 55 years [12] was sometimes included in the tall-cell TC study groups. Similar to our study, other reports have suggested that high-dose RAI therapy is an important prognostic factor for survival in cases of tall-cell TC [7].

As most papillary TC cases generally follow an indolent course [1], it is not surprising that the outcome in tall-cell TC appeared poor in most previous studies, where comparisons were made between tall-cell TC and papillary TC [8, 14, 15]. Despite the difficulty of enrolling follicular TC cases in iodine-sufficient countries, we included a number of follicular TC patients in our research, which allows comparisons between intermediate TC and aggressive well-differentiated TC. The recurrence and disease specific mortality rates (37 per cent and 7 per cent, respectively) found in our intermediate TC group are similar to the corresponding percentages described in the historical cohort including 1355 papillary and follicular TC cases during a mean follow-up of 15 years (30 per cent and 8 per cent) [17].

Our study confirms the female predominance of columnar TC and the relatively good prognosis in cases of encapsulated or minimally infiltrative tumors [1, 18]. However, very aggressive cases have been reported [2] and our therapeutic approach is also recommended by other authors [1, 8]. Unfortunately, the very small number of published columnar TC cases [2, 7, 8, 14, 18] does not allow for sufficiently powered comparative studies.

In our report, a relatively high recurrence rate was observed in sclerosing TC patients, but in all cases the metastases were only found in cervical lymph nodes. The high female/male ratio described in our research was also reported in previous studies as well as the high proportion of cervical metastatic lymph nodes, at presentation (68 to 80 per cent) or during follow-up (13 to 33 per cent) [2, 13]. For some authors, the high frequency of lymph node involvement justifies systematic neck dissection in sclerosing TC [1]. Like others [13], we performed neck dissection only if positive lymphadenopathies were found. Neck dissection did not always prevent locoregional recurrence in our study. Some authors recommend systematic compartmental lymph node dissection in cases of locoregional recurrence [19]. As no lymph node enlargement was observed at US in our four cases of recurrent sclerosing TC with positive RAI whole body scans, only high dose RAI was prescribed. Like in our report, RAI sensitivity has been reported to be relatively high in sclerosing TC with a disease specific mortality rate of less than 7 per cent over a mean follow-up period of 10 years [13].

Hurthle TC is sometimes considered as a subgroup of follicular TC [11, 20]. However, the recurrence and disease specific mortality rates in Hurthle TC have been reported to be 53 to 60 per cent and 40 to 51 per cent, respectively, after a follow-up of 10 years [10, 11], compared to 25 per cent and 20 per cent, respectively in follicular TC during the same follow-up period [10]. Because of this prognostic difference and an RAI uptake by metastatic lesions of less than 38 per cent [10, 11], Hurthle TC is classified in the intermediate TC group by some authors [1, 10].

Our study confirms the poorer outcome in Hurthle TC patients of male gender [10, 21]. The relatively low rate of recurrence in our Hurthle TC subjects may be due to the high proportion of female individuals and the high percentage of intrathyroidal tumors at presentation [10, 11]. In addition, all patients underwent total or near-total thyroidectomy, this surgical procedure increasing the disease free survival rate in Hurthle TC [1, 20]. The systematic 100 mCi RAI administration in all patients may be another explanation for the relatively good outcome in our Hurthle TC subjects. Indeed, the prognosis has been reported to be better if RAI is given immediately after surgery, compared with no RAI treatment or treatment in the event of disease relapse [11]. Moreover, delay in RAI administration has been associated with dedifferentiation of metastases [11].

Our study confirms the relatively poor prognosis of insular TC [7, 22-26]. This subgroup of tumors is classified into the intermediate TC group or the poorly differentiated TC group according to the proposal by Sakamoto [27] and the Japanese Society of Thyroid Surgery [12], the World Health Organization (WHO) classification [12], or the Turin consensus conference [28]. In our study, we used the Turin criteria for the poorly differentiated TC diagnosis, which include the presence of a solid/trabecular/insular pattern of growth, absence of the classical nuclear features of papillary TC, and the presence of at least one of the following features: convoluted nuclei, high mitotic activity and tumor necrosis. As suggested by the WHO, vascular invasion at histology seems to be a significant factor of bad prognosis in insular TC. All our insular TC patients with vascular invasion developed recurrence and the two cases of death in our intermediate TC cohort were insular TC cases with vascular invasion. However, RAI uptake by the tumor was observed in 83 per cent of the insular TC patients in our study and complete remission was described in one subject with extensive extrathyroidal spread. Recurrence and disease specific mortality rates have been estimated to be respectively, 64 per cent and 32 per cent in insular TC after a six-year follow-up period [2], and 75 per cent and 40 per cent in poorly differentiated TC (Turin classification) after a 10-year follow-up period [12]. In our study, the recurrence rate in the insular TC cohort was higher than that previously reported in poorly differentiated TC, but the mortality rate in the insular TC group was comparable to [2], or even lower than [23], that reported in the literature in the same insular TC tumors. Limited data in this study and in previous reports [9, 23, 29, 30], suggests that insular TC patient survival improved following systematic RAI therapy.

Total or near-total thyroidectomy rather than thyroid lobectomy seems to be advised in intermediate TC [1] and palpable well differentiated TC [21]. Our complication rates of 1.7 per cent laryngeal nerve injury and 11.5 per cent hypoparathyroidism are similar to those of other surgical teams operating on malignant disease [1, 11].

In summary, our data suggest that total or near-total thyroidectomy followed by early and intensive RAI therapy should be more systematically prescribed in intermediate TC. Under these conditions, the disease specific mortality rate of intermediate TC may be closer to that of follicular TC, at least in the non insular TC cases.

ABBREVIATIONS

TC, thyroid carcinoma; RAI, radioactive iodine; mCi, millicuries; TSH, thyroid-stimulating hormone; pTNM, pathologic tumor node metastasis; US, ultrasonography; UICC, International Union Against Cancer; AJCC, American Joint Committee on Cancer

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