Long-Term Outcome of Patients with Insular Carcinoma of the Thyroid

The Insular Histotype Is an Independent Predictor of Poor Prognosis

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BACKGROUND. Insular thyroid carcinoma was described originally as a tumor with aggressive behavior. However, whether a predominant insular component is an independent factor for poor prognosis is unclear.

METHODS. The authors compared the clinical behavior of tumors in three groups of patients with thyroid carcinoma—13 patients with insular thyroid carcinoma, 18 patients with follicular thyroid carcinoma, and 26 patients with papillary thyroid carcinoma—who were selected based on similar tumor size and similar age. Disease free survival and disease specific deaths were assessed in the three groups with a Kaplan–Meier analysis and were compared using the log-rank test. Cox regression analysis was used to evaluate the influence of histotype and other prognostic factors on the occurrence of distant metastases and disease specific death.

RESULTS. Patient follow-up ranged from 5.2 months to 190.0 months. At last follow-up, only 1 of 13 patients (7.7%) with insular carcinoma, compared with 8 of 18 patients (44.4%) with follicular carcinoma and 12 of 26 patients (46.1%) with papillary carcinoma, were disease free. The disease specific death rate was 61.5% among patients in the insular carcinoma group compared with 16.7% and 15.4% among patients in the follicular carcinoma group ($P = 0.006$) and the papillary carcinoma group ($P = 0.025$), respectively. At multivariate analysis, the insular histotype was the only variable that was related independently to disease specific death (hazard ratio = 4.27; $P = 0.005$). Distant metastases occurred in 84.6% of patients in the insular carcinoma group compared with 50% and 19.2% of patients in the follicular carcinoma group ($P = 0.039$) and the papillary carcinoma group ($P = 0.0003$), respectively. All metastases from patients with insular carcinomas ($n = 11$ patients) showed radioiodine uptake, but a clinical benefit from this treatment was observed only in 1 patient.

CONCLUSIONS. Patients with insular thyroid carcinoma have a poorer outcome compared with patients of similar age who have differentiated types of thyroid carcinoma with tumors of a similar size. Because radioiodine rarely is effective in the treatment of patients with metastatic insular thyroid carcinoma, novel and possible multimodal therapies should be explored for the treatment of patients with these aggressive tumors. ***Cancer* 2002;95:2076–85.**

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KEYWORDS: thyroid, insular carcinoma, outcome, prognosis.

Insular carcinoma of the thyroid was described first in 1984 by Carcangiu et al. as a distinctive clinicopathologic entity.[1] Histologically, this neoplasm is characterized by well-defined nests (insulae) that are comprised of relatively small, uniform cells and are associated sometimes with small, thyroglobulin-containing follicles. It has

been reported that insular carcinomas have an aggressive behavior, often leading to the patients' death. Therefore, this tumor histotype was classified into a variety of poorly differentiated thyroid carcinomas, morphologically and biologically intermediate between the well-differentiated thyroid tumors (papillary and follicular) and the fully undifferentiated thyroid tumors.[1–3]

However, because insular carcinomas are relatively infrequent (2–4% of all thyroid carcinomas), their biologic and clinical behavior still is not well defined. Subsequent reports have confirmed the high aggressiveness of this tumor,[1–17] with a recurrence/metastasis rate ranging from 20% to 60% and with a 10-year mortality rate that ranges from 13% to 41%.[1–4,6] However, in a recent study, no significant difference in prognosis was observed between patients with insular thyroid carcinoma and patients with widely invasive follicular thyroid carcinoma.[18] In a different study, it was found that the presence of an insular component (up to 90%) in either follicular tumors or papillary tumors did not have an adverse affect on prognosis.[19] Furthermore, a minor insular component has been recognized as a feature of the macrofollicular variant of papillary thyroid carcinoma; however, it does not appear to affect the excellent prognosis of patients with these tumors.[20] These discrepant findings may be explained by the observation that insular thyroid carcinomas often occur in patients with advanced age and present with a large tumor size. Because both advanced age and large tumor size are major factors for an adverse prognosis, the aggressiveness of insular thyroid carcinomas observed in some studies may be explained by these factors.[21–23] For all of the reasons stated above, it is unclear whether the insular histotype per se is a phenotipic characteristic of a tumor with intrinsically increased aggressiveness.

This issue is relevant to the treatment of patients with thyroid carcinoma. Insular thyroid carcinomas usually maintain some of the functional characteristics of the follicular thyroid cells, such as iodine uptake and thyroglobulin (Tg) production. Therefore, when their tumors become metastatic, patients with these tumors can be treated with radioiodine, like patients with well-differentiated thyroid tumors.[24–28] However, it has not been established whether patients who have insular carcinoma should be managed more aggressively compared with patients who have papillary/follicular carcinoma.

To clarify whether the insular histotype is an independent prognostic variable in patients with thyroid carcinoma, we studied a group of 13 patients with insular carcinoma. Tumor outcome was compared with the outcome in two groups of patients of similar age with tumors of similar size who had either papillary carcinoma (n = 26 patients) or follicular carcinoma (n = 18 patients).

Our study confirms that insular carcinomas have peculiar biologic characteristics that justify classifying these tumors as a separate clinicopathologic entity with an aggressive behavior. Moreover, although, in all patients with metastatic insular tumors, radioiodine uptake was comparable to that of patients with well-differentiated tumors, patients who had insular tumors had a significantly worse outcome compared with similarly treated patients who had either papillary or follicular tumors, suggesting that insular carcinomas require a more aggressive therapeutic approach.

MATERIALS AND METHODS

Patients

Thirteen patients underwent surgery for insular thyroid carcinoma at our center during the period 1982–1999. Three more patients with insular thyroid carcinoma that contained small anaplastic areas were excluded. All patients were age $\geq$ 45 years and had tumors that measured $\geq$ 5 cm. Patients with insular thyroid carcinoma represented 2.1% of all patients with thyroid carcinoma who were referred to us during this period.

Among the patients who underwent surgery for differentiated thyroid carcinoma during the same period, 44 patients (18 patients with pure follicular carcinoma and 26 patients with papillary carcinoma) could be matched to the patients with insular carcinoma, because they were of similar age (age $\geq$ 45 years) and had tumors of similar size ($\geq$ 5 cm). These patients were used as control groups.

Histopathologic Evaluation and Tumor Staging

All patients studied underwent total thyroidectomy plus paratracheal lymph node dissection. Laterocervical lymph nodes were dissected when they were involved macroscopically or in the presence of extensive invasion of the central lymph nodes.

For each patient, all histologic slides were reviewed by a pathologist who was unaware of the clinical data, and diagnoses were graded according to the criteria for thyroid malignancy from the World Health Organization classification system.[29] The diagnosis of insular carcinoma was based on previously described criteria.[1–3] Microscopically, these tumors were characterized by neoplastic cells arranged in solid nests or insulae with occasional microfollicles, surrounded by hyalin stroma and, occasionally, by thick, fibrous tissue and artificial clefts (Fig. 1A). The insular component was predominant ($>$ 70%) in all patients. The neoplastic cells were usually small with scanty, pale, eosinophilic cytoplasm and with rather uniform mor-

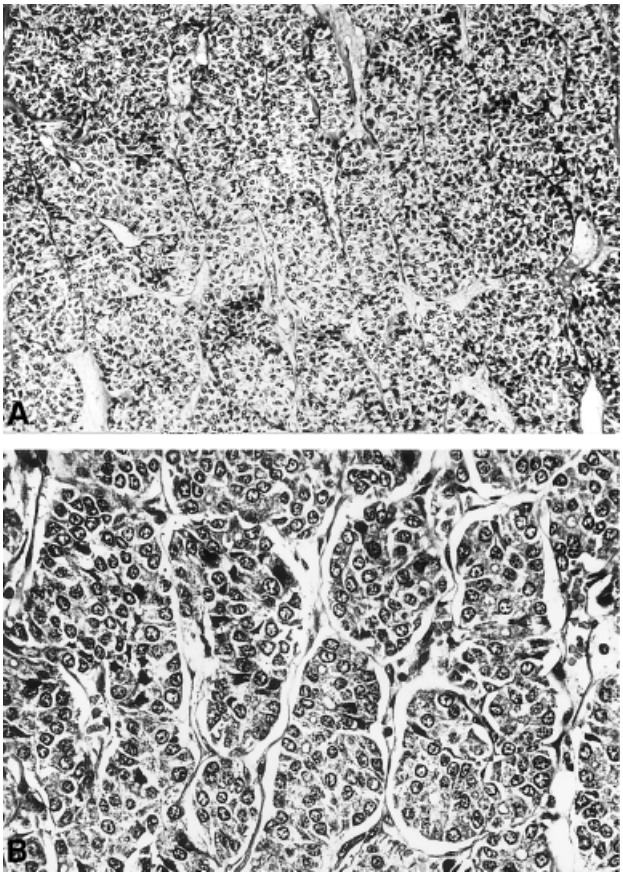

FIGURE 1. (A) Typical insular thyroid carcinoma structure showing well-defined nests and islets of small neoplastic cells with rather uniform morphology surrounded by thin fibrovascular septa with artifactual clefts. (B) High-power magnification of insulae surrounded by a rim of hyalinized collagen. Typically, neoplastic cell nuclei are small and round with chromatin arranged in small clumps. Hematoxylin and eosin [H&E] staining; original magnification $\times$ 60 (A); $\times$ 125 (B).

phology. Nuclei showed finely granular chromatin and nonprominent nucleoli (Fig. 1B). Grooved nuclei and nuclear inclusions were absent. Mitoses usually were observed in the range of 1–10 per 10 high-power fields. Necrosis was a frequent finding. Tumor stage was assessed according to the pTNM system,[30] in which T status (extent of the primary tumor) and N status (regional lymph node metastases) were determined on the basis of pathologic data, and M status (evidence of distant metastases) was based on the finding at first ^{131}I whole-body scan (WBS).

Postoperative Follow-Up

Postoperative evaluation was carried out as described previously.[31] Residual or metastatic malignant tissue was considered present when WBS was positive and/or serum Tg levels were $>$ 10 μg/L (up to 1989, as measured by radioimmunoassay) or $>$ 5 μg/L (after 1989, as measured by immunoradiometric method) when the patient was off L-Trytokine (L-T) L-T4 treatment. The presence of distant metastases at WBS always was confirmed by at least one additional imaging test (standard X-ray, computed tomography [CT] scan, or magnetic resonance imaging [MRI]). Nonsurgically removable distant metastases were treated with ^{131}I (3700–5550 megabecquerels [MBq]) every 8–12 months. A diagnosis of regional lymph node recurrence was made when either radioiodine uptake or the finding of either neoplastic epithelial cells and/or high Tg levels in fine-needle aspirates confirmed ultrasound evidence of suspicious lymph nodes. Local recurrences also were confirmed by ultrasound or CT imaging plus cytologic examination. Disease progression was defined as the enlargement of metastases or tumor masses in the neck (as evaluated by WBS and/or CT imaging plus serum Tg increase) and/or the appearance of new metastatic foci.

Statistical Analysis

The distribution by pathologic stage and other variables in the patients with insular thyroid carcinoma and the control groups was compared by logistic regression analysis. The time to metastases occurrence and the time to disease specific death were calculated from the date of surgery. The cumulative rates of metastases and disease specific death were compared using Kaplan–Meier plots. The log-rank test was used to evaluate the differences between curves. The following clinical and histopathologic variables were analyzed for correlation with the occurrence of metastases: patient age (40–50 years or $>$ 50 years), gender, familial thyroid disease, living in an iodine-deficient area, multifocal or bilateral disease, vascular invasion, jugular vein invasion, tracheal invasion, lymph node metastases at surgery, and histotype. The same variables plus disease stage according to pTNM status or the presence of distant metastasis at presentation were analyzed for correlations with disease specific death. Univariate and multivariate analyses of prognostic variables were carried out according to the Cox proportional hazards model. Only variables that were identified as potentially significant in the univariate analysis were included in the multivariate model to evaluate their independent effect. A P value < 0.05 was considered significant. Data analysis was performed using the SPSS statistical package for Windows (release 8.0; SPSS, Inc., Chicago, IL).

RESULTS

Tumor Characteristics at Presentation

Clinical and histopathologic characteristics at the time of presentation for patients with insular, follicular, or papillary thyroid carcinomas are shown in Table 1.

TABLE 1
Presentation Characteristics of Patients with Insular Thyroid Carcinomas Compared with Control Groups of Patients with Either Follicular or Papillary Carcinoma Histotypes

Characteristic	Insular	Follicular	Papillary	*P* value[a]
No. of patients	13	18	26	—
Patient age (yrs)				
Range	43–73	42–83	42–86	—
Median	64.3	56.7	61.5	—
Gende				
Female:male	11:2	12:6	15:11	N.S.
Percent female	85.4	66.7	57.7	—
Greatest tumor dimension (cm)				
Range	5.0–10	5.0–10	5.0–10	—
Median	6.0	6.5	6.0	—
Tumor stage (%)				
I	0.0	2 (11.1)	4 (15.4)	—
II	3 (23.1)	4 (22.3)	7 (26.9)	—
III	4 (30.8)	6 (33.3)	11 (42.3)	—
IV	6 (46.1)	6 (33.3)	4 (15.4)	N.S.
Multifocal (%)	0	1 (5.6)	3 (11.5)	N.S.
Bilateral (%)	0	0	4 (15.4)	N.S.
Extrathyroid extension (%)	9 (69.2)	11 (61.1)	19 (73.1)	N.S.
Vascular invasion (%)	10 (76.9)	10 (55.5)	6 (23.1)	0.007
Jugular vein invasion (%)	4 (30.8)	1 (5.6)	0	N.S.
Tracheal invasion (%)	2 (15.4)	1 (5.6)	4 (15.4)	N.S.
Lymph node metastases (%)	4 (30.8)	1 (5.6)	8 (30.8)	N.S.
Distant metastases (%)	7 (53.8)	6 (33.3)	3 (11.5)	0.029
Iodine-deficient area (%)	2 (15.4)	2 (11.1)	1 (3.8)	N.S.
Familial thyroid disease (%)	1 (7.7)	2 (11.1)	4 (15.4)	N.S.
Follow-up (months)				
Range	5.2–190.0	11.6–157.3	20.8–173.0	—
Median	45.7	67.5	49.3	—

N.S.: not significant.
[a] Statistical significance was calculated by logistic regression analysis.

Lymph node metastases were observed frequently at the time of presentation in both patients with insular or papillary thyroid carcinoma (≈ 30%) and less frequently in patients with follicular thyroid carcinoma (≈ 6%). This difference, however, did not reach statistical significance (Table 1). Invasion of adjacent soft tissues was frequent in all patients (approximately 70%) (Table 1). Vascular invasion was significantly more frequent in patients with insular carcinoma (10 of 13 patients; 76.9%) and in patients with follicular carcinoma (10 of 18 patients; 55.5%) compared with patients who had papillary carcinoma (6 of 26 patients; 23.1%; $P = 0.007$) (Table 1). Neoplastic invasion with thrombosis of the jugular vein was common in the insular carcinoma group (4 of 13 patients; 30.8%), infrequent in the follicular carcinoma group (1 of 18 patients; 5.6%), and absent in the papillary carcinoma group (Table 1). There was a trend toward more advanced tumor stage in the insular carcinoma group compared with the follicular carcinoma group or the papillary carcinoma group; this difference, however, was not significant. Distant metastases at the time of presentation occurred more frequently in patients who had insular carcinoma (7 of 13 patients; 53.8%) and follicular carcinoma (6 of 18 patients; 33.3%) compared with patients who had papillary carcinoma (3 of 26 patients; 11.5%; $P = 0.029$) (Table 1). The variables tracheal infiltration, bilateral or multifocal tumors, an association with familial thyroid disease, and living in an iodine-deficient area did not differ statistically among the three groups (Table 1).

Patient Outcome

Follow-up ranged from 5.2 months to 190.0 months and was similar for the three groups (Table 1). Locoregional lymph nodes were an important site of disease recurrence in patients with insular and papillary thyroid carcinoma (Table 2). The cumulative rate of lymph node metastases was significantly higher in patients who had insular and papillary thyroid carcinoma (84.6% and 73.1%, respectively) compared with patients who had follicular thyroid carcinoma (27.8%) (Table 2, Fig. 2A). During follow-up, new metastases at distant sites developed more frequently in patients

TABLE 2
Locoregional and Distant Metastases in Patients with Insular Thyroid Carcinoma and in Patients with Either Follicular or Papillary Thyroid Carcinoma

	Thyroid carcinoma type					
	Insular (n = 13 patients)		Follicular (n = 18 patients)		Papillary (n = 26 patients)	
Metastases	No.	%	No.	%	No.	%
Locoregional metastases						
At presentation	4	30.8	1	5.6	8	30.8
New diagnoses at follow-up	7	53.8	4	22.2	11	42.3
Total[a]	11	84.6	5	27.8	19	73.1
Distant metastases						
At presentation	7	53.8	6	33.3	3	11.5
New diagnoses at follow-up	4	30.8	3	16.7	2	7.7
Total[b]	11	84.6	9	50.0	5	19.2

[a] Insular vs. follicular carcinoma, $P = 0.035$; insular vs. papillary carcinoma, $P = 0.621$; follicular vs. papillary carcinoma, $P = 0.049$ (log-rank test).
[b] Insular vs. follicular carcinoma, $P = 0.039$; insular vs. papillary carcinoma, $P = 0.0003$; follicular vs. papillary carcinoma, $P = 0.107$ (log-rank test).

with insular thyroid carcinoma (4 of 13 patients; 30.8%) compared with the two control groups (follicular carcinoma group: 3 of 18 patients [16.7%]; papillary carcinoma group: 2 of 26 patients [7.7%]) (Table 2). The cumulative frequency of distant metastases was significantly higher in the insular carcinoma group compared with the frequency in each of the two control groups (Table 2, Fig. 2B).

Lung metastases were most frequent among patients in the insular carcinoma group (7 of 13 patients; 53.8%) and less frequent among patients in the papillary carcinoma group (3 of 26 patients; 11.5%) and the follicular carcinoma group (4 of 18 patients; 22.2%). Bone metastases were most frequent among patients in the insular carcinoma group (4 of 13 patients; 30.8%) and the follicular carcinoma group (7 of 18 patients; 38.9%) compared with the papillary carcinoma group (4 of 26 patients; 15.5%). Remarkably, distant metastases at unusual sites, including the liver, kidney, ovaries, skin, and retroperitoneum, occurred more frequently among patients in the insular carcinoma group (5 of 13 patients; 38.5%) compared with the control groups (follicular carcinoma group: 2 of 18 patients [11.1%]; papillary carcinoma group: 0 of 6 patients) and were a sign of poor prognosis. All of these patients died. Significant radioiodine uptake in metastatic tissue was present in all patients. The cumulative individual dose of radioiodine administered ranged from 100 mCi to 1290 mCi (range, 3700–47,730 MBq; median, 207 mCi) among patients in the insular carcinoma group, 35–1250 mCi (range, 1295–46,250 MBq; median, 200 mCi) among patients in the follicular carcinoma group, and 30–900 mCi (range, 1110–33,300 MBq; median, 130 mCi) among patients in the papillary carcinoma group. No patient with distant metastases was cured by radioiodine treatment. How-

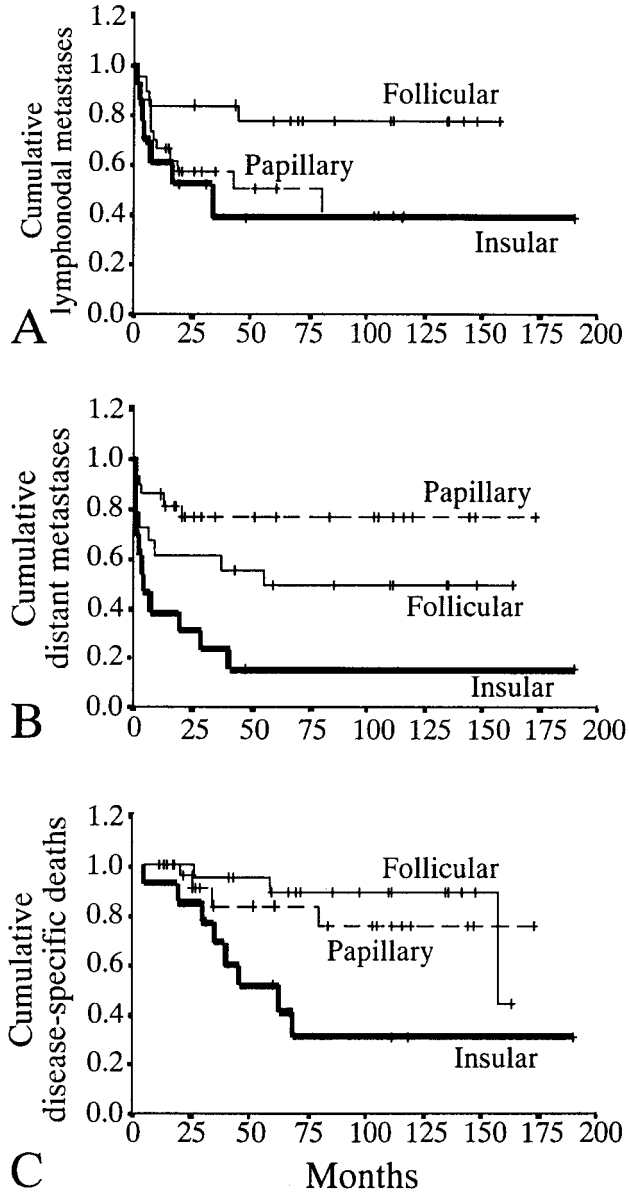

FIGURE 2. Cumulative risk of metastases or disease specific death (Kaplan–Meier plots) in patients with different histotypes of thyroid carcinoma but with similar age and tumor size at presentation. (A) Lymph node metastases (insular vs. follicular carcinoma, $P = 0.035$; insular vs. papillary carcinoma, $P = 0.621$; follicular vs. papillary carcinoma, $P = 0.049$). (B) Distant metastases (insular vs. follicular carcinoma, $P = 0.039$; insular vs. papillary carcinoma, $P = 0.0003$, follicular vs. papillary carcinoma, $P = 0.107$). (C) Disease specific death (insular vs. follicular carcinoma, $P = 0.061$; insular vs. papillary carcinoma, $P = 0.025$; follicular vs. papillary carcinoma, $P = 0.549$). P values were calculated with a log-rank test.

TABLE 3
Outcome of Patients with Insular Thyroid Carcinoma and Patents in the Control Group with Either Follicular or Papillary Thyroid Carcinoma

	Thyroid carcinoma type					
	Insular (n = 13 patients)		Follicular (n = 18 patients)		Papillary (n = 26 patients)	
Patient follow-up status	No.	%	No.	%	No.	%
Alive	5	38.5	15	83.3	22	84.6
Disease free[a]	1	7.7	8	44.4	12	46.1
With disease	4	30.8	7	38.9	10	38.5
Progressive disease	3	—	5	—	—	—
Distant	2	—	4	—	—	—
Distant and local	1	—	1	—	—	—
Stable disease	1	—	2	—	10	—
Local	—	—	—	—	6	—
Distant	—	—	—	—	2	—
Distant and local	—	—	1	—	—	—
Elevated Tg	1	—	1	—	2	—
Dead[b]	8	61.5	3	16.7	4	15.4

[a] Insular vs. follicular carcinoma, P = 0.109; insular vs. papillary carcinoma, P = 0.061; follicular vs. papillary carcinoma, P = 0.338 (log-rank test).
[b] Insular vs. follicular carcinoma, P = 0.006; insular vs. papillary carcinoma, P = 0.025; follicular vs. papillary carcinoma, P = 0.549 (log-rank test).

ever, 2 of 11 patients in the insular carcinoma group, 1 of 9 patients in the follicular carcinoma group, and 2 of 5 in the papillary carcinoma group had some benefit from radioiodine treatment, as indicated by disease stabilization and/or the reduction of tumor tissue (as assessed by circulating Tg levels, ^{131}I WBS, X-rays, CT scans, and MRI). Only one patient with insular carcinoma who had diffuse lung metastases showed a mass reduction of the metastatic localization and a decrease of circulating Tg. This patient had a tumor with an unusually high radioiodine uptake level due to an activating mutation of the thyroid-stimulating hormone (TSH) receptor (TSH-R), as previously reported.[32] Recurrent local invasion was more frequent among patients in the insular carcinoma group (7 of 13 patients; 53.8%) compared with the control groups (follicular carcinoma group: 3 of 18 patients [16.7%]; papillary carcinoma group: 2 of 26 patients [7.7%]; P = 0.003; Fisher exact test).

At the time of last follow-up, the number of disease specific deaths was significantly higher among patients in the insular carcinoma group (8 of 13 patients; 61.5%) compared with the control groups (follicular carcinoma group: 3 of 18 patients [16.7%]; papillary carcinoma group: 4 of 26 patients [15.4%]) (Table 3, Fig. 2C). Disease specific deaths were related directly to distant metastases in 5 of 13 patients in the insular carcinoma group, in 3 of 18 patients in the follicular carcinoma group, and in 2 of 26 patients in the papillary carcinoma group. Three patients with insular carcinoma (23.1%) and 2 patient with papillary carcinoma (7.7%) died because of progressive disease in the neck and/or in the mediastinal area. When patients were stratified for the presence of distant metastases at the time of diagnosis, cumulative disease specific deaths still were associated significantly with the insular histotype (P = 0.004; log-rank test). In patients with no metastases at the time of diagnosis, the mean survival was 79.7 months ± 27.6 months among patients in the insular carcinoma group compared with 153.6 months ± 8.5 months among patients in the control groups (P = 0.045; log-rank test) (Fig. 3A). In patients with distant metastases at the time of diagnosis, survival among patients in the insular carcinoma group was 62.4 months ± 17.3 months compared with 101.8 months ± 18.9 months among patients in the control groups. However, this difference did not reach statistical significance (P = 0.477; log-rank test) (Fig. 3B). Among surviving patients, only 1 patient (7.7%) in the insular carcinoma group, 8 patients (44.4%) in the follicular carcinoma

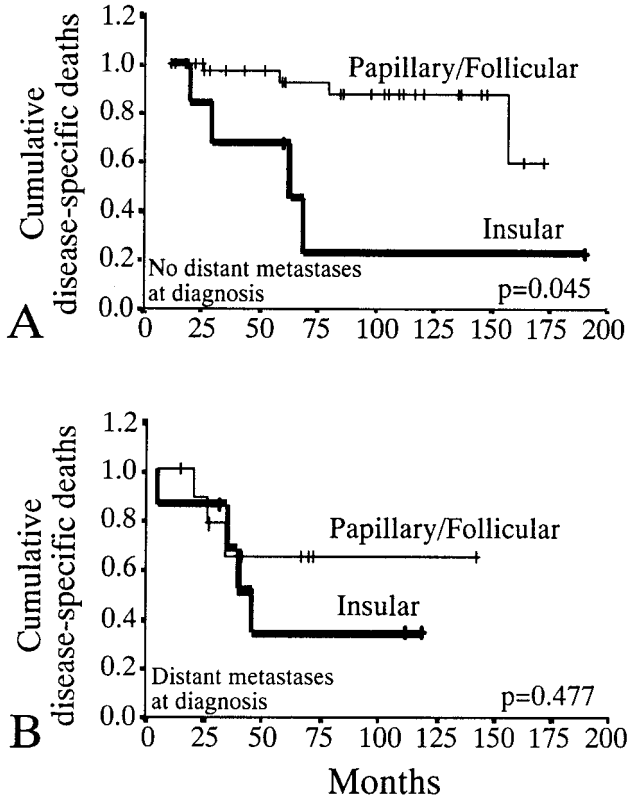

FIGURE 3. Cumulative disease specific death (Kaplan–Meier plots). (A) Patients without distant metastases at presentation (insular vs. papillary or follicular carcinoma, P = 0.045). (B) Patients with distant metastases at presentation (insular vs. papillary or follicular carcinoma, P = 0.477). P values were calculated with a log-rank test.

TABLE 4
Univariate Analysis (Cox regression model) of Patients with Thyroid Carcinoma Using Distant Metastases as the End Point

Variable	Hazard ratio	95% confidence interval	*P* value
Age (yrs)			
40–50	1.00	—	—
+50	4.21	0.98–17.15	0.044
Vascular invasion			
No	1.00	—	—
Yes	1.61	0.73–3.55	0.241
Jugular vein invasion			
No	1.00	—	—
Yes	4.72	1.66–13.41	0.004
Lymph node metastases			
No	1.00	—	—
Yes	1.44	0.66–3.11	0.357
Tracheal invasion			
No	1.00	—	—
Yes	2.43	0.90–6.57	0.079
Extrathyroidal invasion			
No	1.00	—	—
Yes	1.56	0.67–3.11	0.367
Histotype			
Papillary/follicular	1.00	—	—
Insular	3.46	1.57–7.63	0.002

group, and 12 patients (46.1%) in the papillary carcinoma group remained disease free (Table 3).

All patients with persistent disease in both the insular carcinoma group and the follicular carcinoma group had distant metastases. In contrast, among patients in the papillary carcinoma group, only 40% of patients with persistent disease had distant metastases (Table 3). Residual disease was progressive in 3 of 4 patients with insular thyroid carcinoma, in 5 of 7 patients with follicular thyroid carcinoma, and in 0 of 10 patients with papillary thyroid carcinoma (Table 3).

Univariate and Multivariate Cox Analyses for the Development of Distant Metastases and Disease Specific Death

Univariate analysis

Univariate Cox analysis was carried out to correlate the risk of developing distant metastases and disease specific death with several clinical and histopathologic variables, as specified above (see Materials and Methods). The cumulative rate of distant metastases was associated with the insular histotype ($P = 0.002$), jugular vein invasion ($P = 0.004$), and age $>$ 50 years ($P = 0.044$) (Table 4). Disease specific death was associated with the insular histotype ($P = 0.005$), lymph node metastases ($P = 0.055$), and distant metastases at presentation ($P = 0.038$) (Table 5). Hazard ratios and 95% confidence intervals are provided in Tables 5 and 6.

TABLE 5
Univariate Analysis (Cox regression model) of Patients with Thyroid Carcinoma Using Disease Specific Death as the End Point

Variable	Hazards ratio	95% confidence interval	*P* value
Age (yrs)			
40–50	1.0	—	—
+50	2.61	0.57–11.03	0.236
Vascular invasion			
No	1.00	—	—
Yes	1.14	0.41–3.15	0.802
Jugular vein invasion			
No	1.00	—	—
Yes	2.73	0.76–9.87	0.124
Lymph node metastases			
No	1.00	—	—
Yes	2.86	0.98–8.38	0.055
Tracheal invasion			
No	1.00	—	—
Yes	2.69	0.74–9.79	0.132
Stage			
I–II	1.00	—	—
III–IV	3.04	0.85–10.91	0.088
Distant metastases at presentation			
No	1.00	—	—
Yes	3.07	1.06–8.85	0.038
Histotype			
Papillary/follicular	1.00	—	—
Insular	4.27	1.54–11.85	0.005

TABLE 6
Multivariate Analysis (Cox regression model) of Patients with Thyroid Carcinoma According to Clinical and Histopathologic Variables Using either Distant Metastases or Disease Specific Death as the End Point

Histotype	Hazards ratio	95% confidence interval	*P* value
Distant metastases			
Papillary/follicular	1.00	—	—
Insular	3.46	1.57–7.63	0.002
Disease specific death			
Papillary/follicular	1.00	—	—
Insular	4.27	1.54–11.84	0.005

Multivariate analysis

According to the multivariate Cox proportional hazards model, only the insular histotype was associated independently with the development of distant metastases ($P = 0.002$) and with disease specific death ($P = 0.005$) (Table 6).

DISCUSSION

Insular thyroid carcinoma is an infrequent histotype, accounting for $<$ 5% of all thyroid carcinomas.[1,18,19] Previous studies have classified this tumor as a distinct clinicopathologic entity that is intermediate biologically between well-differentiated and fully undif-

ferentiated thyroid tumors.[1–3] Many authors have reported a high aggressiveness and mortality rate in these tumors, although others have not evidenced a poor prognosis in patients who have tumors with a minor insular component.[20] Moreover, it has been emphasized that insular carcinomas have high iodine uptake and produce Tg, both typical features of the normal thyroid cell and of well-differentiated thyroid carcinomas.[24–28] Because of the relatively rarity of this histotype, many reports included only small numbers of patients and made no direct comparison with patients who had noninsular, differentiated carcinomas. Finally, because many insular carcinomas occur in older patients who frequently have large tumors at the time of initial diagnosis, it is uncertain whether the high aggressiveness is related more to these variables rather than to tumor histotype. Therefore, the biologic behavior of insular thyroid carcinomas and the optimal therapeutic approach for the treatment of patients with these tumors are unclear.

To our knowledge, this is the first study that compares the prognosis of patients who have follicular thyroid carcinoma with the prognosis of patients who have papillary thyroid carcinoma after controlling for tumor size and patient age at the time of diagnosis. To determine whether the insular histotype is an independent prognostic factor, we examined the clinical outcome of 13 patients with insular thyroid carcinomas and compared it with the outcome of age-matched and tumor size-matched patients who had either follicular or papillary thyroid carcinomas who underwent surgery during the same period.

With respect to patients with either follicular or papillary thyroid carcinoma, a less favorable outcome was observed in patients with insular thyroid carcinoma, as judged by the development of distant metastases, the rate of persistent disease, and disease specific death. The cumulative rate of distant metastases was approximately 85% in patients with insular thyroid carcinoma compared with approximately 50% in patients with follicular thyroid carcinoma and 19% in patients with papillary thyroid carcinoma. Patients with insular thyroid carcinoma, as previously reported, characteristically developed metastases both at locoregional lymph nodes and at distant sites,[1–3] whereas patients with follicular thyroid carcinoma, predominantly developed distant metastases, and patients with papillary thyroid carcinoma predominantly developed lymph node metastases. It is interesting to note that five patients with insular thyroid carcinoma had distant metastases at unusual sites, including the liver, kidney, ovaries, skin, and retroperitoneum. All of these patients died of disease.

Disease specific death also was significantly more frequent in the group of patients with insular thyroid carcinoma (approximately 60%) compared with the other two groups (approximately 15%). At multivariate analysis, the insular histotype was the only variable that was associated significantly with the risk of disease specific death (hazard ratio, 4.27; $P = 0.005$). In accordance with previous studies,[21] older patients with either papillary or follicular tumors had similar mortality rates.

At last follow-up only, 1 patient (7.7%) in the group with insular carcinoma was disease free; in contrast, approximately 45% of patients were disease free in the other two groups. Distant metastases were present in all patients with persistent disease, both in the group with insular thyroid carcinoma and in the group with follicular thyroid carcinoma but only in 40% of patients with papillary thyroid carcinoma who had persistent disease.

A review of the patients reported in the literature (Table 7), shows that, on average, the occurrence rate for recurrences/distant metastases is approximately 50% (range, 36–83%), and the disease specific mortality rate is approximately 30% (range, 9–75%). Sasaki et al.[14] also reported that the insular component was associated with a 2.7-fold increased risk of mortality in a Cox multivariate analysis. Those authors did not match patients for age and tumor size, but they found that advanced age and large tumors were associated with 2.0-fold and 1.2-fold risks of mortality, respectively.

Because the molecular mechanisms underlying the insular structure of thyroid tumors have not been clarified, the mechanisms leading to the increased aggressiveness of this tumor histotype also are unclear. Recently, using molecular analysis by polymerase chain reaction–single-strand conformation polymorphism analysis, Pilotti et al.[18] demonstrated the presence of point mutations of the *ras* gene family in five of eight insular carcinomas analyzed, with a high proportion of CAA → AAA transversions at codon 61 of the N-*ras* gene. This abnormality, however, was not specific to insular carcinoma but also was present with similar frequency in the widely invasive variant of follicular carcinoma.

It also has been found that the p53 gene is mutated frequently (38% of patients) in patients with insular carcinoma,[33] and p53 overexpression frequently is present in areas of insular histotype with respect to surrounding areas of well-differentiated carcinoma. However, this finding was not confirmed by others.[34] Moreover, mutations of the p53 gene are not specific and have been found commonly in the anaplastic carcinoma histotype.[35,36] In a patient who had metastatic insular carcinoma with hyperfunction due to an activating mutation of the TSH-R gene, we found no alteration of the genes coding for gsp, ras,

TABLE 7
Rates of Disease Recurrence and Mortality in Patients with Thyroid Carcinoma

Study	No. of patients	Recurrences metastases		Mortality		Follow-up (months)	
		No.	%	No.	%	Mean	Range
Carcangiu et al., 1984[1]	25	18	72	11	44	42	12–96
Flynn et al., 1988[2]	4	3	75	3	75	24	12–24
Limbert et al., 1985[7]	12	8	67	5	42	66	2–240
Justin et al., 1991[24]	5	3	60	0	0	23	6–31
Papotti et al., 1993[3]	31	15	60	5	16	54	2.4–192.0
Ashfaq et al., 1994[19]	28[a]	11	39	5	18	48	12–144
Sasaki et al., 1996[4]	44	19	43	17	39	10.9 ± 0.76[b]	—
Hassoun et al., 1997[15]	2	1	50	1	50	26.5	22–31
Van den Brekel et al., 1997[16]	22	8	36	2	9	41	0.4–168
Albareda et al., 1998[6]	6	5	83	1	17	57.6 ± 44.4[b]	NA
Lam et al., 2000[34]	16[a]	7	44	7	44	47.8 ± 61.2[b,c]	NA
Machens et al., 2001[17]	7[d]	4	57[e]	NA	NA	NA	NA
Current study	13	12	92	8	61	62	5.2–190

NA: not available.
[a] Only patients with follow-up were included.
[b] Values shown are the mean standard deviation.
[c] Survival time.
[d] Only primary tumors were included.
[e] Patients with distant metastases at the time of diagnosis.

PTC/ret, trk, or met.[32] The activating mutation was present both in the primary tumor and in lymph node metastases but not in the normal contralateral tissue. It was reported previously that mutations at codon 633 of the TSH-R gene constitutively activated the cyclic AMP cascade. This TSH-R gene-activating mutation, in addition to be responsible for the autonomous hyperfunction of the tumor, also may have a role in the initiation or progression of thyroid carcinoma, as described previously in patients with autonomous functioning thyroid adenomas. However, determining the role of activating mutations of the TSH-R gene in the course of insular thyroid carcinoma will require further study.

Although metastases from insular thyroid carcinomas usually retain the ability to uptake radioiodine,[20–24] it is uncertain whether radioiodine therapy at the dosage and timing used for the treatment of patients with differentiated thyroid carcinoma is an effective treatment for patients with insular tumors, given the aggressive course of these tumors. In our series, a clear clinical benefit from radioiodine treatment was observed only in the patient who had an activating TSH-R gene mutation and an unusually high radioiodine uptake level. This observation suggests that a higher radioiodine dosage may be beneficial in patients with these tumors.

In conclusion, the current study indicates that thyroid carcinomas with insular structure are more aggressive and are associated with a poorer patient outcome compared with the outcome of patients of a similar age who have tumors of similar size with either follicular or papillary histotype. Insular carcinomas, therefore, warrant an initial aggressive treatment, including total thyroidectomy plus central lymphadenectomy followed by prophylactic radioiodine therapy. When distant metastases are present, radioiodine therapy may help; however, at the standard dosage, it is clinically effective only in a minority of patients; in most patients, the tumor rapidly progresses despite repeated radioiodine administration. An aggressive therapeutic approach with combined modalities, including cytoreductive surgery, higher doses of and/or more frequent radioiodine administration, external radiotherapy, and chemotherapy, should be evaluated. Novel therapeutic approaches also are needed and should be explored in patients with this carcinoma histotype.

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