Multivariate Analysis of Clinicopathologic Parameters for the Insular Subtype of Differentiated Thyroid Carcinoma

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Hypothesis: Insular carcinoma represents a more aggressive subtype of differentiated thyroid cancer on multivariate analysis after controlling for various clinicopathologic parameters.

Design: Retrospective analysis.

Setting: Tertiary referral center at a university hospital.

Patients: One hundred twenty-seven consecutive patients having a histological diagnosis of the follicular variant of papillary thyroid carcinoma or follicular thyroid carcinoma.

Main Outcome Measure: A logistic regression model was used to examine the relationship between various clinicopathologic parameters and the insular subtype.

Results: The insular subtype involved 14 of 127 tumors. Unlike extrathyroidal extension and nodal metastasis, primary tumor diameter (>40 mm vs ≤40 mm; \(P = .008\)) and distant metastasis (\(P = .003\)) correlated with the insular subtype. Both parameters were interrelated since tumors greater than 40 mm displayed distant metastasis more often (30% vs 8%; \(P = .008\)) than tumors measuring 40 mm or less.

Conclusions: These findings suggest that an unidentified somatic event may induce an accelerated proliferation of the transformed thyrocytes, which may ultimately result in enhanced rates of distant metastasis with increasing tumor volume.

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SINCE THE seminal description of insular carcinoma by Carcangiu et al in 1984, \(^1\) no universal consensus has been reached as to the biological aggressiveness and prognostic relevance of this comparatively rare subtype of thyroid cancer. Some authors have identified significant correlations between insular carcinoma and the occurrences of extrathyroidal growth and nodal metastases. \(^2\) These observations are awaiting confirmation by investigations that include an unselected noninsular control group. Many literature reports in this field have been hampered by the lack of such a noninsular control group. Because of the rarity of insular carcinoma—accounting for only 3.8% (27/720) to 6.2% (41/657) of thyroid tumors \(^1-^3\)—recruiting enough patients with insular carcinoma has posed difficult problems.

More recent publications have addressed the issue of biological aggressiveness by comparing patients with insular carcinoma with control groups composed of patients with more invasive forms of differentiated thyroid carcinoma. These controls have had neoplasms as diverse as widely invasive follicular carcinoma, \(^2,^4\) the tall cell, and diffuse sclerosing variants of papillary carcinoma. \(^5,^6\) Owing to the unavailability of an unselected noninsular control group, this approach does not allow one to draw definitive conclusions about the unique oncological properties of the insular subtype. To resolve the issue of biological aggressiveness of insular carcinoma, our institutional investigation was conducted in an unselected cohort of 127 consecutive patients with differentiated thyroid cancer.

See Invited Critique at end of article

RESULTS

UNIVARIATE ANALYSES OF CLINICOPATHOLOGIC PARAMETERS GROUPED BY OPERATIVE STATUS

A total of 14 (5 FVPTCs, 9 FTCs) insular tumors (11%) were identified among the 127 patients with FVPTC and FTC (Table 1). Of these, 7 were both primary...
PATIENTS AND METHODS

PATIENT SELECTION

From November 1994 through October 1999, a total of 256 consecutive patients at our institution underwent surgery for papillary thyroid carcinoma (PTC) (n = 171) or follicular thyroid carcinoma (FTC) (n = 85). These operations were performed by means of bipolar forceps coagulation and optical magnification using the technique described previously. Of the 171 PTCs, 42 tumors were of the follicular variant of papillary thyroid carcinoma (FVPTC). In keeping with the literature, none of the remaining 129 PTCs exhibited a characteristic pattern consistent with insular carcinoma. To create a more homogenous control group, this investigation was limited to the 42 patients with FVPTCs and the 85 patients with FTCs only, resulting in a study population of 127 patients. Of these, 32 patients had undergone primary surgery and 95 patients had undergone reoperations. Patients whose thyroid tumors harbored undifferentiated components were excluded from this investigation.

PATHOLOGICAL ANALYSIS

All surgical specimens had been subjected to pathological analysis and staged according to the current TNM classification (International Union Against Cancer) (except for the distinction by patient age) as stage I, T1N0M0; stage II, T2-4N0M0; stage III, any T N1M0; and stage IV, any TNM1. Insular carcinoma was diagnosed according to the criteria of Carcangiu et al., based on evidence of solid clusters (insulae) of small and uniform tumor cells containing a variable number of small follicles. All tumors stained negative for calcitonin. Particular attention was given to the relationship between the thyroid tumor and the surrounding thyroid gland, the adjoining parathyroidal soft tissue, and the surgical margins. From the adjacent soft tissue, every isolated lesion, be it visible or palpable, was embedded separately. Slides were stained with hematoxylin-eosin. Nodal metastases suspected on conventional staining were, in ambiguous cases, confirmed subsequently by cytokeratin and thyroglobulin immunohistochemistry using the standard avidin-biotin complex peroxidase method. In reoperative tumors, pathology reports were obtained from the primary institution to allow for assessment of the T category and primary tumor diameter.

STATISTICAL ANALYSIS

Patients with insular tumors were compared with their noninsular counterparts, who served as controls. Associations between categorical, ordinal, and metric parameters were tested using the 2-tailed Fisher exact test and the Mann-Whitney Wilcoxon rank sum test, respectively. Appropriate adjustments were made using the Bonferroni method. A multivariate logistic regression model was used to examine the relationship between the various clinicopathologic parameters and the insular subtype. The level of significance was set at .05.

LOGISTIC REGRESSION ANALYSIS FOR THE INSULAR SUBTYPE

Considering the findings of the univariate analyses (Table 1), a logistic regression analysis was used to identify the individual parameters that correlate with the insular subtype. The following 6 dichotomized variables were initially entered into a multivariate model as independent parameters: primary tumor diameter (>40 mm vs ≤40 mm), extrathyroidal tumor extension (pT4 vs pT1-3), nodal (pN1 vs pN0) and distant metastasis (M1 vs M0), tumor entity (FVPTC vs FTC), and surgical status (primary operation vs reoperation). Of the 127 study patients, 24 patients had to be excluded because of missing information on primary tumor diameter, leaving a total of 103 patients for multivariate analysis. The goodness of fit (93%) of this logistic regression model was not compromised by the withdrawal of surgical status as a parameter from the analysis because extrathyroidal extension (pT4) significantly correlated with surgical status (44% in primary vs 12% in reoperative patients; P = .001). As shown in Table 2, only categorized primary tumor diameter (P = .008) and distant metastasis (P = .003) correlated with the insular subtype. These 2 parameters were interrelated since tumors greater than 40 mm more often (30% vs 8%; P = .008) displayed distant metastasis than tumors measuring 40 mm or less. Neither tumor entity (FVPTC, FTC) nor surgical status (previous operation) were confounding factors in this multivariate analysis (data not shown).

COMMENT

This institutional multivariate analysis provides evidence that the insular subtype of thyroid carcinoma significantly correlates with both categorized primary tumor diameter and distant metastasis but not with extrathyroidal tumor extension (pT4) or nodal metastasis (pN1). In the logistic regression model, distant metastasis was a function of primary tumor diameter since both parameters correlated with each other. This suggests that a hitherto unidentified somatic mutation may induce an accelerated proliferation of the transformed thy-
SOMATIC MUTATIONS IN INSULAR CARCINOMA

The role of these hypothesized genetic events in the unique growth pattern and metastatic potential of insular carcinoma remains to be ascertained. Potential candidate genes for such somatic events are the ras gene family or the p53 gene. In 5 of 8 cases of insular carcinomas and also in widely invasive FTC, somatic point mutations were detected in the H-RAS and N-RAS histotypes by single-strand conformation polymorphism analysis following amplification by polymerase chain reaction. Intriguingly, 3 of the 5 ras mutations identified in insular carcinoma involved the CAA→AAA transversion at codon 61 (glutamyl transpeptidase domain) of the N-RAS gene. Transversion mutations (substitution of a purine for a pyrimidine or vice versa) obviously predominate in undifferentiated thyroid tumors as opposed to transition mutations (substitution of a purine for a pyrimidine or vice versa) which prevail in differentiated thyroid carcinomas. In follicular, poorly differentiated, and undifferentiated thyroid carcinomas, point mutations in the ras oncogene were significantly associated with the appearance of hemogenous metastases (40% vs 6%; P = .03) and bone metastases (54% vs 5%; P = .003) on univariate analysis. This observation suggests a role of ras gene activation in the process of distant metastasis. Molecular analysis of exons 5, 6, 7, and 8 of the p53 gene revealed that 14 of 46 insular carcinomas harbored somatic mutations in these exons. Considering these molecular data and the current clinicopathologic findings, insular carcinoma seems to represent a subtype rather than an entity in its own right within the spectrum of thyroid tumors. In agreement with this interpretation is the recent view that the insular subtype represents a higher grade of an existing thyroid carcinoma. The poorer survival rates in insular carcinoma are accounted for by the significant correlation we found between insular carcinoma and distant metastasis. This finding underscores the importance of having an unselected control group and of controlling for primary tumor size and the T, N, and M categories.

CLINICAL IMPLICATIONS

The surgical strategy for insular carcinoma should aim at achieving local control. To this end, a systematic dissection of the cervicocentral lymph nodes is advocated, since approximately half of insular carcinoma cases display nodal metastases by the time of diagnosis according to the literature and our data (Table 1). In

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### Table 1. Univariate Analysis of Clinicopathological Parameters Grouped by Operative Status

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of Patients</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>T classification, % ‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>20</td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>T2</td>
<td>36</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>T3</td>
<td>4</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>T4</td>
<td>40</td>
<td>23</td>
<td>0.01</td>
</tr>
<tr>
<td>Median tumor diameter, mm (25%-75% quartiles)</td>
<td>22 (13-30)</td>
<td>26 (18-40)</td>
<td>0.001</td>
</tr>
<tr>
<td>Nodal metastasis (N1 vs N0)</td>
<td>32</td>
<td>18</td>
<td>0.03</td>
</tr>
<tr>
<td>M1, %</td>
<td>12</td>
<td>11</td>
<td>0.01</td>
</tr>
<tr>
<td>FTC, %</td>
<td>48</td>
<td>73</td>
<td>0.19</td>
</tr>
</tbody>
</table>

* ras indicates follicular thyroid carcinoma.
† Two-tailed Fisher exact test and exact Mann-Whitney Wilcoxon rank sum test, respectively.
‡ Tumor classification according to the International Union Against Cancer.
§ P < .05 after Bonferroni adjustment.
† Including pulmonary M1 diagnosed by postoperative scintigraphy.
view of the high rates and prognostic significance of lung and bone metastases in this condition—this series, 7 and 5 of 14 patients, respectively—all patients should undergo early postoperative scintigraphy. When distant metastases appear on scintigraphy, radioiodine therapy should be initiated for distant control. A similar approach should be pursued in children and adolescents. Bone metastasis of the vertebral column may require palliative stabilization to keep the involved vertebral body from collapsing and impinging on the spinal cord to prevent transverse palsy, which could not only decrease quality of life, but overall survival. This was the case in one of our patients who had been followed up at an outside institution for vertebral metastasis of an insular thyroid carcinoma. While radioiodine therapy may occasionally cure patients with insular thyroid carcinoma and pulmonary metastases, dedifferentiated clones of distant metastases will evolve in some patients following several courses of radioiodine treatment. In this series, one such instance was noted in 14 patients with insular carcinoma. These tumors are particularly challenging because of their failure to take up radioiodine. The role of chemotherapy is questionable since insular carcinomas are frequently unresponsive to most cytotoxic agents in vitro and in vivo.

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REFERENCES


Invited Critique

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ince the original description of poorly differentiated or insular thyroid cancer in 1984, case reports and small series have confirmed the position of this histologic variant as intermediate in prognosis between well-differentiated thyroid cancer and anaplastic thyroid cancer. This retrospective analysis of 127 patients with FVPTC or FTC identified 14 patients who met the criteria for an insular lesion. There was a significant difference in survival between these 14 patients with poorly differentiated lesions and the remainder, as well as differences in size and metastasis at time of diagnosis determined by univariate and logistic regression analysis. Unfortunately, as is the case with other published reports, the number of patients in the insular category was small—too small, probably, from which to draw meaningful conclusions. The age of the patient, size of the tumor, and presence of metastases, however, are still important predictive variables. Do these findings indicate altering treatment of patients with thyroid cancer, as the term poorly differentiated would suggest? Probably not, since the important information would seem to be contained in the traditional TNM, AMES, AGES, and MACIS staging systems. Still, I suspect that we all will be a little more cautious in our treatment of and follow-up with patients when our pathologist calls 2 days postoperatively to advise us that the lesion was an “insular thyroid tumor.”

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