COMPUTERIZED MORPHOMETRIC STUDY OF THYROID FOLLICULAR CARCINOMA IN CORRELATION WITH KNOWN PROGNOSTIC FACTORS

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This study investigates the correlation between computer-assisted nuclear morphometry and known prognostic factors in thyroid follicular carcinoma. Thirty-six patients with thyroid follicular carcinoma who underwent surgery between 1991 and 2001 were grouped according to sex, age, size of the primary lesion, the presence of vascular invasion, and metastases. Four nuclear parameters were measured and analyzed: mean nuclear area, mean nuclear perimeter, largest to smallest diameter ratio of the nuclei, and coefficient of variation of the nuclear area. Our results indicated that none of the chosen nuclear variables were significantly correlated with the prognostic factors studied. In conclusion, nuclear morphometry does not seem to correlate with known prognostic factors and cannot serve as an additional predicting factor for biologic behavior.


Follicular carcinoma is a malignant epithelial tumor showing evidence of follicular cell differentiation that does not belong to any other distinctive type of thyroid malignancy. It is more prevalent in women than men and occurs in patients about 10 years older than those with papillary carcinoma. The criteria for the diagnosis of follicular carcinoma are strict and include the presence of capsular and/or vascular invasion. Cellular morphologic features are not included in the diagnostic criteria.

Cytologic slides can be morphometrically studied to evaluate nuclear characteristics but this plays a limited role in follicular carcinoma due to the strict histopathologic diagnostic criteria [1]. In many other tumors, morphometry can enhance the interpretation of morphologic features and, combined with clinical data and the experience of the pathologist, can lead to greater accuracy and precision in surgical pathology diagnosis. The application of nuclear morphometry in predicting prognosis has been evaluated in other malignancies [2–4].

Sex, age, size of the primary lesion, the presence of vascular invasion, and metastases are all traditional prognostic factors in thyroid follicular carcinoma. In this study, we used computerized morphometric analysis of four nuclear parameters on paraffin sections of follicular carcinoma stained with hematoxylin and eosin and correlated the results with known prognostic factors. We determined the role of image morphometry of follicular carcinoma in predicting prognosis and hoped to show that morphometric study was valuable in predicting biologic behavior in thyroid follicular carcinoma.

MATERIALS AND METHODS

Patients
We studied 36 patients with thyroid follicular carcinoma...
who underwent lobectomy or total or subtotal thyroidectomy between 1991 and 2001. Patient age ranged from 15 to 82 years (mean, 44.9 years), and the male-to-female ratio was 1:5 (6 males, 30 females). Ten of these follicular carcinomas were categorized as widely invasive and 26 as minimally invasive. The mean maximum tumor dimension was 4.5 cm (range, 2.1–7.2 cm). Four patients were clinically confirmed to have distant metastases at the same time of diagnosis, including three with widely invasive disease and one with minimally invasive disease. Patients were grouped according to age (≥ 45 years and < 45 years), tumor size (≥ 4.0 cm and < 4.0 cm), the presence of vascular permeation, and the presence of metastases.

All resected specimens were sent for histopathologic examination. Formalin-fixed, paraffin-embedded sections were prepared from each tumor and stained with hematoxylin and eosin. These paraffin sections were evaluated and the diagnosis of follicular carcinoma was agreed upon by two pathologists (SLW and CYC).

Morphometry

The hematoxylin and eosin slides were examined under a standard microscope connected to a computerized video system. Using a ×100 oil immersion lens, five to seven fields of vision were sampled randomly and photographed using a Nikon E400 digital microphotography system (N150, Nikon Co, Tokyo, Japan). A minimum of 100 nuclei per case were selected by image analysis using a Pentium III with Image-Pro Plus version 4.5 software (Media Cybernetics Inc, Silver Spring, MD, USA) to estimate the various quantitative nuclear features (Figure). Four nuclear parameters were calculated: mean nuclear area, mean nuclear perimeter, ratio of the largest to smallest diameter of the nuclei (LS ratio), and the coefficient of variation of the nuclear area (NACV). Correlations between the parameters and known prognostic factors were analyzed.

Statistical analysis

Statistical differences were determined using Student’s t test. Values of p less than 0.05 were considered statistically significant.

Results

The Table presents the mean values of all measured nuclear parameters according to patient age, gender, metastases, tumor size, and vascular permeation. There were no significant differences between any of the chosen nuclear parameters and the thyroid prognostic subgroups. That is, no selected parameter had prognostic significance.

Discussion

Research has been done into the application of morphometric image analysis in follicular neoplasms of the thyroid [5,6]. The diagnostic role of computer-assisted image analysis in thyroid follicular neoplasm has also been evaluated [7,8]. Some researchers have tried to establish nuclear morphometry by computerized image analysis as an additional tool in the differential diagnosis of thyroid follicular neoplasms [9]. Although the results of these studies showed equivocal findings, most observed that computer-assisted image analysis might support clinical evaluation in the assessment of thyroid follicular neoplasms. The most frequently selected nuclear morphometric parameters included area, perimeter, LS ratio, and NACV.

Prognostic factors in follicular carcinoma have been addressed in several studies and include older age at diagnosis, male gender, large tumor size, extensive vascular invasion, and extracapsular extension [10,11]. Studies using multivariate analysis have identified an age of at least 45 years, extrathyroidal extension, distant metastases, and tumor size of at least 4 cm as independent prognostic factors in follicular carcinoma [12]. We chose five of these prognostic factors as parameters in this study and attempted to determine their association with nuclear morphometry.
From a prognostic point of view, the role of nuclear morphometry in predicting biologic behavior has been studied in many tumors [2,3,13]. Morphometry is now increasingly applied to histologic sections, as in the prognostic study of lesion thickness in malignant melanoma and the diagnostic study of glandular architecture in colonic adenoma. The correlation between morphometric features and prognosis has been investigated, and risk groups with statistically significant differences created in cancer types such as prostate, breast, and urothelial [4,14,15]. The prognostic value of morphometry in thyroid cancer, focusing on papillary carcinoma, has also been evaluated. The results showed that nuclear morphometry in association with patient follow-up could represent an important prognostic index for papillary thyroid carcinoma [16]. Some researchers believe that morphometric analysis may significantly contribute to the role of histopathology in the evaluation of papillary thyroid carcinoma and may also provide information regarding prognosis not obtained by standard methods [17].

In our study, we tried to correlate specific nuclear parameters with known prognostic factors and investigated the value of morphometric study in thyroid follicular carcinoma. None of the nuclear morphometric parameters (area, perimeter, NACV and LS ratio) showed a significant difference among thyroid prognostic subgroups, suggesting that there is no relationship between nuclear features and the aggressiveness of thyroid follicular carcinoma. This may be because the degree of cellular pleomorphism is usually low in follicular carcinoma and may reflect the fact that the nuclear character is not included in the diagnostic criteria for follicular carcinoma. The histopathologic grade cannot provide information about prognosis, which is analogous to the conclusion in a previous study [18]. Although nuclear size was recently found to have prognostic significance in breast cancer and in a series of thyroid carcinomas, the value of nuclear morphometry in predicting the prognosis of follicular carcinoma was not established [14,16,17]. Clinical parameters (sex, age, tumor size, vascular permeation, and distant metastases) potentially correlated with prognosis did not have any relationship with the selected nuclear parameters.

**CONCLUSION**

Nuclear morphometry is a useful tool in the assessment of some tumors and can provide reliable parameters for

| Table. Mean nuclear parameters of tumor cells according to traditional prognostic factors |
|-----------------------------------|---|---|---|---|
| Age                              |       |       |       |
| < 45 yr                          | 20   | 35.32 | 21.26 | 23.99 | 1.33 |
| ≥ 45 yr                          | 16   | 36.05 | 21.55 | 24.56 | 1.32 |
| p*                               | NS   | NS    | NS    | NS    | NS    |
| Sex                              |       |       |       |
| Male                             | 6    | 33.15 | 20.70 | 21.40 | 1.30 |
| Female                           | 30   | 36.14 | 21.53 | 24.81 | 1.30 |
| p*                               | NS   | NS    | NS    | NS    | NS    |
| Distant metastases              |       |       |       |
| No                               | 32   | 36.04 | 21.50 | 24.36 | 1.33 |
| Yes                              | 4    | 32.42 | 20.48 | 23.33 | 1.32 |
| p*                               | NS   | NS    | NS    | NS    | NS    |
| Tumor size                       |       |       |       |
| < 4.0 cm                         | 26   | 35.23 | 21.23 | 24.50 | 1.32 |
| ≥ 4.0 cm                         | 10   | 36.61 | 21.81 | 23.57 | 1.35 |
| p*                               | NS   | NS    | NS    | NS    | NS    |
| Vascular permeation              |       |       |       |
| No                               | 19   | 35.65 | 21.39 | 24.24 | 1.33 |
| Yes                              | 17   | 36.63 | 21.71 | 22.88 | 1.33 |
| p*                               | NS   | NS    | NS    | NS    | NS    |

* t test. NACV = coefficient of variation of the nuclear area; LS ratio = ratio of the largest to smallest diameter of the nuclei; NS = no significant difference between groups.
diagnosis and prognosis. In our study, the nuclear parameters did not significantly correlate with known prognostic factors and, therefore, cannot serve as additional predictors of biologic behavior in thyroid follicular carcinoma.

**References**

甲狀腺濾泡細胞癌之電腦輔助形態測定研究
與預後因子之關係

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本研究主要探討在甲狀腺濾泡細胞癌中腫瘤細胞之電腦輔助形態測定研究與預後因子之關聯性。36 例甲狀腺濾泡細胞癌依據病人性別、年紀、腫瘤大小、是否有血管侵犯與是否有遠處轉移這些傳統上臨床使用的預後因子來分組。先利用數位顯微照相系統隨意選取至少 100 個細胞核，同時選定細胞核之面積大小、周長、最大徑與最小徑比、細胞核面積之變異係數當作形態測定研究的變數，利用電腦輔助程式計算出每個病例相對應的變數值再與不同預後因子之組別分別做統計上的分析。我們的研究結果並未顯示不同預後因子之組別與選定的形態測定研究的變數之關聯性有統計上的意義。因此我們認為，電腦輔助形態測定研究法並不適合用來評估甲狀腺濾泡細胞癌的預後情形。

關鍵詞：形態測定法，濾泡細胞癌，預後因子
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