

Tumor Characteristics and Clinical Outcome of Tubular and Mucinous Breast Carcinomas

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Purpose: To comprehensively characterize the clinical and biologic features of tubular and mucinous carcinomas in a large cohort of patients and to relate this to clinical outcome and management.

Patients and Methods: The clinical and biologic features of 444 patients with tubular and 1,221 patients with mucinous carcinomas were compared with those of 43,587 patients with infiltrating ductal carcinoma, not otherwise specified (NOS). Disease-free survival (DFS) and overall survival (OS) for patients with tubular and mucinous carcinomas were compared with those of patients with NOS carcinomas and with age-matched sets from the general population.

Results: Tubular and mucinous carcinomas were more likely to occur in older patients, be smaller in size (tubular only), have substantially less nodal involvement, be estrogen receptor- and progesterone receptor-positive, have a lower S-phase fraction, be diploid, and be c-erbB-2- and epidermal growth factor receptor-negative compared with NOS carcinomas. Axillary node

involvement was a poor prognostic feature in mucinous but not tubular carcinomas. Mucinous carcinomas ≤ 1 cm had a $\leq 5\%$ incidence of node involvement. The 5-year DFS and OS were 94% and 88% for tubular, 90% and 80% for mucinous, and 80% and 77% for NOS carcinoma, respectively ($P < .001$ for differences among all three types for both DFS and OS). The 5-year OS of females from the general population age-matched to the patients with tubular and mucinous carcinomas was 89% and 82%, respectively, which is not different from the OS of patients with tubular or mucinous carcinomas.

Conclusion: The biologic phenotype of tubular and mucinous carcinomas is quite favorable. Consistent with this observation, the survival of patients with tubular and mucinous carcinomas is similar to that of the general population. Systemic adjuvant therapy and node dissection may be avoided in many patients with these special types of carcinoma.

J Clin Oncol 17:1442-1448. © 1999 by American Society of Clinical Oncology.

BREAST CANCER IS a heterogeneous disease with different tumors possessing different biology and natural history. Some patients have indolent disease that requires only local therapy, whereas others manifest a more aggressive and often fatal systemic disease. The identification of patients with indolent and low-risk tumors is important and would have significant implications for clinical management, with the possibility of sparing patients medically unnecessary and potentially harmful interventions. Patients with special histologic types (eg, tubular and mucinous carcinomas) might define such a phenotype.

Knowledge about the clinical outcome of tubular and mucinous tumors has been based on studies with relatively small numbers of patients.¹⁻⁴ This is not unexpected because special histologic types are not common and each constitutes less than 3% of all invasive breast carcinomas.⁵ In addition, there are little data on the biologic features of tubular and mucinous carcinomas in the context of their clinical outcome. Therefore, an extensive analysis of tubular and mucinous carcinomas in large databases would provide more precise assessment of their biologic features and clinical outcome, which could yield useful information for making clinical decisions.

Furthermore, many studies of special types have required central pathology review, most often by one highly specialized pathologist with extensive experience in breast pathology, to verify the accuracy of diagnosis. Although this may assure homogeneous classification among the cases evaluated, the results obtained from such studies may have limitations when applied to routine community practice, where the majority of patients with breast cancer are treated. The definition of special types may vary among pathologists, and the volume of breast pathology seen in clinical practice might influence the interpretation and lead to different conclusions regarding the diagnosis of special types. The evaluation of special types of carcinomas in a large database where the pathologic diagnosis is provided by a range of pathologists would determine whether such carcinomas, when diagnosed in the community, have a

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Submitted August 17, 1998; accepted December 28, 1998.

Supported by Public Health Service Medical Oncology Program Project grant no. CA 30195, Specialized Program of Research Excellence grant no. CA58183-02, and grant no. P30CA54174 (to the San Antonio Cancer Institute) from the National Institutes of Health, Bethesda, MD.

A.L. was a United States government employee while this article was being written. The views expressed in this article are those of the authors and do not reflect the official policy of the Department of Defense or other departments of the United States government.

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0732-183X/99/1705-1442

clinical outcome similar to outcomes of patients diagnosed at a single institution after pathologic review by a focused expert.

This study comprehensively characterizes the biologic and clinical features of tubular and mucinous carcinoma in a large cohort of patients and identifies subsets of patients with an exceptionally good prognosis who might be treated without axillary dissection or systemic adjuvant therapy.

PATIENTS AND METHODS

Study Population

From 50,828 patients included in the San Antonio, TX, breast cancer databases, 444 and 1,221 patients who had pathology reports concluding a diagnosis of tubular or mucinous carcinoma, respectively, and no gross metastatic disease at diagnosis were identified. These patients were compared with 43,587 patients with infiltrating ductal carcinoma not otherwise specified (NOS) in the same databases. More than 370 academic and community institutions submitted tissue and clinical data. As previously reported,^{6,7} patients are included in these databases because steroid receptors and other biologic assays were performed on tissue from the primary tumor at the time of diagnosis in a central laboratory in San Antonio. The pathologic diagnosis of special type was made by pathologists at the referring institutions. Data on time to recurrence and death were obtained by direct review of the medical records performed by the data managers of the San Antonio database or by data collection forms completed by the office of the referring physicians.

Prognostic Factors

Estrogen receptor (ER) and progesterone receptor (PgR) concentrations were evaluated by the modified dextran-coated charcoal assay.⁸ Levels ≥ 3 fmol/mg and 5 fmol/mg were considered positive for ER and PgR, respectively. S-phase fraction and DNA ploidy were evaluated by flow cytometry.^{6,7} S-phase fraction $\geq 6.7\%$ for diploid carcinomas and 11.0% for aneuploid carcinomas were considered high. *c-erbB-2* status was determined by Western blotting.⁹ The cutoff value between low and high protein expression was 1 U/ μ g protein. Epidermal growth factor receptor (EGFR) was measured by radiobinding assay, and levels ≥ 10 fmol/mg protein were considered positive.¹⁰

Statistical Methods

The clinical and biologic characteristics of tubular, mucinous, and NOS carcinomas were compared using contingency tables, χ^2 tests, and Fisher's exact test. The primary end points were disease-free survival (DFS), defined as the interval between the diagnostic biopsy and the first recurrence, and overall survival (OS), defined as the interval between the diagnostic biopsy and death from any cause. Patients who died without evidence of recurrence were censored for DFS analysis. Curves for DFS and OS were calculated according to the method of Kaplan and Meier¹¹ and compared by the log-rank test. Age-matched mortality data for females from the general population were calculated based on life expectancy tables (1994) from the *Vital Statistics of the United States*, which are published by the United States National Center for Health Statistics and available through the Library of Congress. Multivariate analyses of DFS and OS, with stepwise variables selection, were conducted using Cox proportional hazards regression.¹² Analyses were performed using SAS Version 6.11 (SAS Institute, Inc, Cary, NC).

RESULTS

Patient and Tumor Characteristics

From a total of 50,828 patients in two San Antonio breast cancer databases, we identified 1,221 patients (2.3%) with mucinous carcinomas and 444 patients (0.8%) with tubular carcinomas. The median follow-up duration was 5 years. The clinical and biologic characteristics of the tubular, mucinous, and NOS carcinomas were compared (Table 1). Tubular and mucinous carcinomas were more likely to occur in older patients, be smaller in size (tubular only), have substantially less nodal involvement, be ER- and PgR-positive, have lower S-phase fraction, be diploid, and be *c-erbB-2*- and EGFR-negative compared with NOS carcinomas. The median ages of patients with tubular, mucinous, and NOS carcinomas were 64, 71, and 62 years, respectively (tubular *v* NOS, $P = .002$; mucinous *v* NOS, $P = .0001$). The median size of mucinous and NOS carcinomas was 2 cm, and the median size of tubular carcinomas was 1.3 cm ($P = .0001$). Tubular and mucinous carcinomas were nearly twice as likely to have low S-phase fractions and be diploid compared with NOS carcinomas. More than 95% of tubular and mucinous carcinomas failed to express *c-erbB-2* or EGFR.

A similar proportion, approximately one third, of patients with tubular, mucinous, and NOS carcinomas received adjuvant endocrine therapy. However, patients with tubular and mucinous carcinomas were far less likely to receive adjuvant chemotherapy (Table 1). Only approximately 10% of patients with tubular and mucinous carcinomas received adjuvant chemotherapy compared with 32% of patients with NOS carcinomas ($P = .001$).

Axillary Lymph Node Involvement

The incidence of axillary lymph node involvement was 41% in NOS carcinomas, nearly triple the incidence found in tubular carcinoma (16%) and mucinous carcinoma (14%). The incidence of node positivity was directly related to tumor size for all three histologies (Table 2). For carcinomas ≤ 1 cm, the incidence of node involvement was 8% for tubular, 4% for mucinous, and 19% for NOS carcinomas. Tubular and mucinous carcinomas ≤ 2 cm with positive ERs had 11% and 6% incidence of node positivity, respectively. Tubular and mucinous carcinomas ≤ 2 cm with low S-phase fraction had 11% and 5% incidence of node positivity, respectively.

DFS and OS

DFS was significantly better for tubular and mucinous carcinomas compared with NOS carcinomas, with a 5-year DFS of 94% for tubular, 90% for mucinous, and only 80%

Table 1. Clinical and Biologic Characteristics of Tubular and Mucinous Versus NOS Carcinomas

| Characteristic | Tubular | | Mucinous | | NOS Carcinoma | | P (Tubular v NOS) | P (Mucinous v NOS) |
|----------------------------|---------|----|----------|----|---------------|----|-------------------------|--------------------------|
| | No.* | % | No.* | % | No.* | % | | |
| Age ≥ 50 yr | 444 | 82 | 1,221 | 88 | 43,575 | 74 | .001 | .001 |
| Size (cm) | 421 | | 1,177 | | 41,446 | | | |
| ≤ 1 | | 36 | | 12 | | 12 | | |
| 1.1-2 | | 48 | | 42 | | 40 | | |
| 2.1-5 | | 14 | | 40 | | 41 | .001 | .59 |
| > 5 | | 2 | | 6 | | 7 | | |
| Nodes | 398 | | 1,048 | | 40,445 | | | |
| 0 | | 84 | | 86 | | 59 | | |
| 1-3 | | 13 | | 11 | | 26 | .001 | .001 |
| > 3 | | 3 | | 3 | | 15 | | |
| ER-positive | 439 | 91 | 1,207 | 92 | 43,107 | 82 | .001 | .001 |
| PgR-positive | 431 | 75 | 1,162 | 68 | 42,287 | 61 | .001 | .001 |
| S-phase fraction | 351 | | 985 | | 32,022 | | | |
| Low | | 89 | | 83 | | 50 | | |
| Intermediate | | 7 | | 10 | | 20 | .001 | .001 |
| High | | 4 | | 7 | | 30 | | |
| Diploid DNA ploidy | 392 | 81 | 1,065 | 78 | 37,771 | 44 | .001 | .001 |
| EGFR-negative | 26 | 96 | 64 | 97 | 1,754 | 81 | .05 | .001 |
| c-erbB-2-negative | 22 | 95 | 52 | 96 | 1,584 | 79 | .16 | .009 |
| Adjuvant endocrine therapy | 408 | 29 | 1,067 | 33 | 39,515 | 33 | .11 | .77 |
| Adjuvant chemotherapy | 409 | 10 | 1,068 | 10 | 39,521 | 32 | .001 | .001 |

*Total number of patients with available data for each analysis.

for NOS carcinomas ($P < .001$ for tubular v NOS and mucinous v NOS; Fig 1A). The 5-year OS was 88% for tubular, 80% for mucinous, and 77% for NOS carcinomas ($P < .001$ for tubular v NOS, $P = .088$ for mucinous v NOS; Fig 1B). The fact that OS was substantially worse than DFS for patients with tubular and mucinous carcinomas strongly suggests that a significant proportion of patients with tubular and mucinous carcinomas are dying from causes other than their breast cancer. To further explore this possibility, we evaluated the expected OS in aged-matched female sets from the general population. The 5-year OS of a general population with an age distribution similar to that of patients with tubular carcinomas is 89%, which is not significantly different than the 88% 5-year OS for patients with tubular carcinomas. The 5-year OS of a general population with age distribution similar to that of patients with mucinous carcinomas is 82%, which is not significantly different than the 80% 5-year OS for patients with mucinous carcinoma. However, the 5-year OS of a set from the general population with

age distribution similar to that of patients with NOS carcinomas is 90%, which is significantly different from the 77% 5-year OS for patients with NOS carcinomas. These data support that the majority of deaths in patients with tubular and mucinous carcinomas, unlike the deaths among patients with NOS carcinoma, are not related to tubular and mucinous carcinomas and that the majority of patients with tubular and mucinous carcinomas have near normal longevity.

DFS and OS for Node-Negative Patients

The outcome was especially favorable for node-negative patients with tubular and mucinous carcinomas. The 5-year DFS was 95% for tubular, 94% for mucinous, and 87% for NOS node-negative carcinomas ($P < .001$ for tubular v NOS and mucinous v NOS) (Fig 2A). The 5-year OS was 91% for tubular, 86% for mucinous, and 85% for NOS node-negative carcinomas ($P = .001$ for tubular v NOS; $P = .65$ for mucinous v NOS; Fig 2B). An exploratory subset analysis was performed on node-negative patients based on whether adjuvant systemic therapy was given. The DFS for node-negative tubular and mucinous patients who did not receive treatment was 95% and 93%, respectively, compared with 97% and 95%, respectively, for patients who did receive adjuvant systemic therapy. However, because the patients were not randomized, firm conclusions about the effect of adjuvant therapy cannot be drawn from this analysis.

Table 2. Relationship Between Tumor Size and Nodal Status for Tubular, Mucinous, and NOS Carcinomas

| Tumor Size (cm) | Patients With Negative Nodes | | | | | |
|-----------------|------------------------------|-----|----------|----|--------|----|
| | Tubular | | Mucinous | | NOS | |
| | No. | % | No. | % | No. | % |
| ≤ 1 | 127 | 92 | 111 | 96 | 3,771 | 81 |
| 1.1-2 | 152 | 86 | 404 | 92 | 10,581 | 68 |
| 2.1-5 | 31 | 57 | 327 | 80 | 7,787 | 49 |
| > 5 | 8 | 100 | 39 | 59 | 705 | 29 |

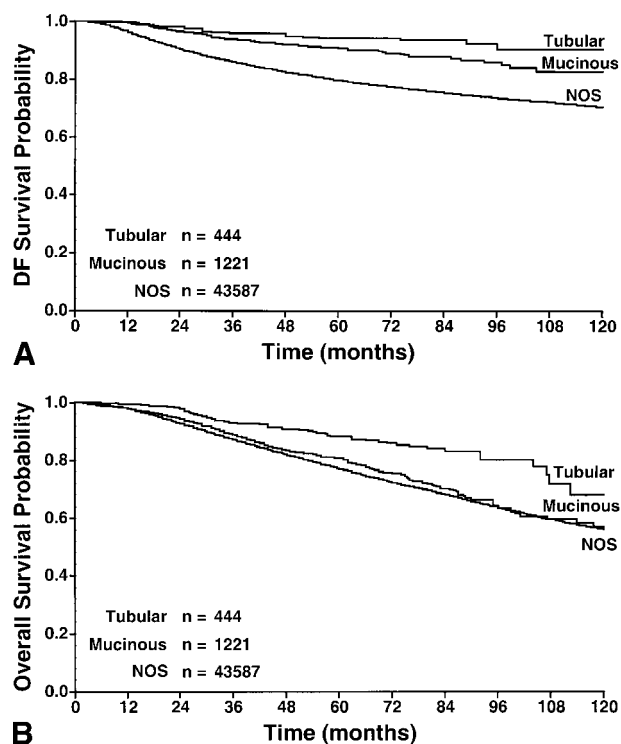


Fig 1. (A) DFS for all patients. The 5-year DFS for patients with tubular carcinoma, mucinous carcinoma, and NOS was 94%, 90%, and 80%, respectively ($P < .001$ for tubular v NOS and mucinous v NOS). (B) OS for all patients. The 5-year OS for patients with tubular carcinoma, mucinous carcinoma, and NOS was 88%, 80%, and 77%, respectively ($P = .001$ for tubular v NOS; $P = .088$ for mucinous v NOS).

DFS and OS for Node-Positive Patients

Tubular carcinomas had an excellent prognosis even when the axillary lymph nodes were involved, with a 5-year DFS of 94%; the prognosis was significantly better than that of node-positive NOS carcinomas patients, who had a 5-year DFS of 68% ($P = .0001$; Fig 3A). However, node positivity for mucinous carcinomas conferred a substantially worse prognosis, with a 5-year DFS of 76%, similar to the prognosis for node-positive NOS carcinoma patients ($P = .14$). The 5-year OS for node-positive patients was 92% for tubular, 81% for mucinous, and 69% for NOS carcinomas ($P = .0004$ for tubular v NOS; $P = .58$ for mucinous v NOS; Fig 3B). The 5-year DFS for tubular and mucinous patients who did not receive adjuvant systemic therapy was 100% and 89%, respectively.

Prognostic Factors for DFS and OS in Tubular and Mucinous Carcinomas

To determine whether traditional prognostic factors would be of value in patients with tubular and mucinous carcinomas, univariate and multivariate analyses of DFS were performed on 277 patients with tubular and 704 patients with mucinous carcinomas in whom all the following

variables were available: tumor size, number of involved nodes, age, ER, PgR, S-phase fraction, and adjuvant therapy (Table 3). Univariate and multivariate analyses of tubular carcinomas showed that none of these variables, including adjuvant systemic therapy, was significant for DFS. In the univariate analysis of mucinous carcinoma, a number of factors (Table 3), including adjuvant systemic chemotherapy, were associated with improved DFS. However, in the multivariate analysis, only tumor size, nodal status, ER, and age maintained their independent prognostic value, whereas adjuvant systemic chemotherapy lost its significance. Adjuvant chemotherapy and endocrine therapy were not independently associated with improved DFS or OS (data not shown) in either tubular or mucinous carcinomas. This supports the concept that the favorable natural history of tubular and mucinous carcinomas is probably related to their intrinsic biologic characteristics rather than to higher-than-expected benefit from adjuvant systemic therapy.

DISCUSSION

There is a paucity of large studies characterizing the clinical and biologic features and the natural history of tubular and mucinous carcinoma. To our knowledge, this is

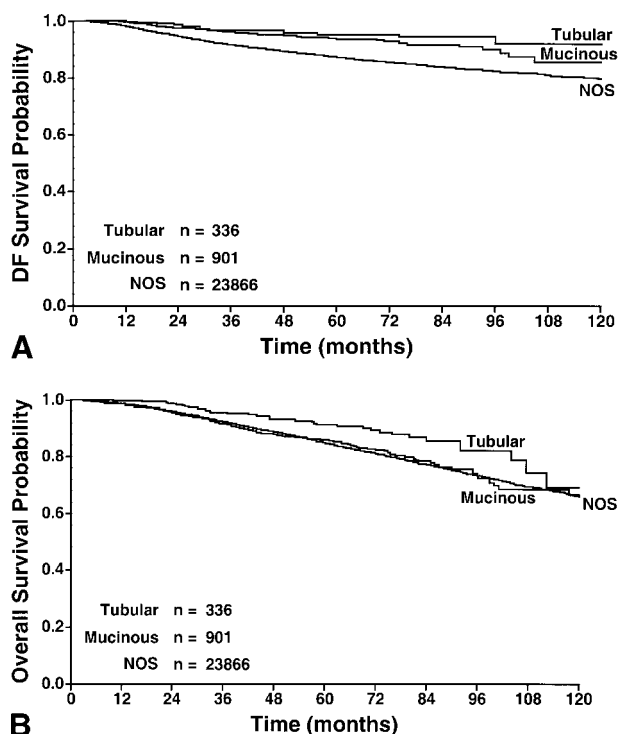


Fig 2. (A) The 5-year DFS for node-negative patients with tubular carcinoma, mucinous carcinoma, and NOS was 95%, 94%, and 87%, respectively ($P < .001$ for tubular v NOS and mucinous v NOS). (B) The 5-year OS for node-negative patients with tubular carcinoma, mucinous carcinoma, and NOS was 91%, 86%, and 85%, respectively ($P = .001$ for tubular v NOS; $P = .65$ for mucinous v NOS).

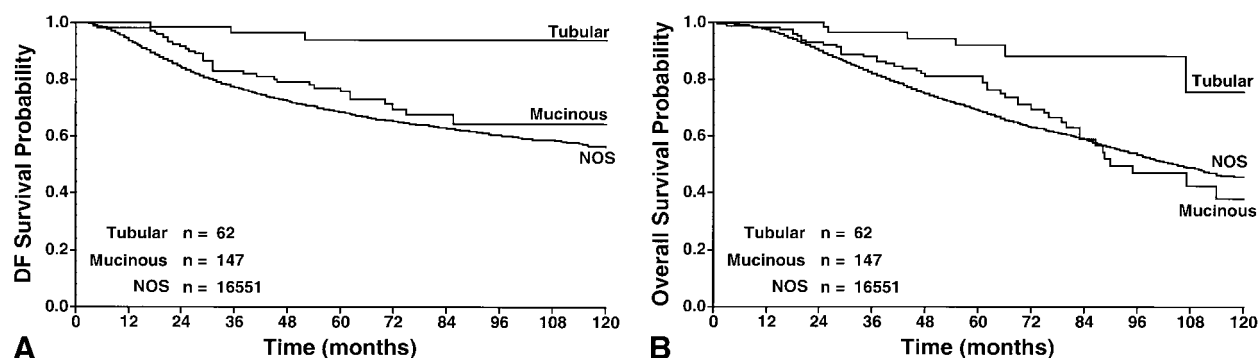


Fig 3. (A) The 5-year DFS for node-positive patients with tubular carcinoma, mucinous carcinoma, and NOS was 94%, 76%, and 68%, respectively ($P = .0001$ for tubular v NOS; $P = .14$ for mucinous v NOS). (B) The 5-year OS for node-positive patients with tubular carcinoma, mucinous carcinoma, and NOS was 92%, 81%, and 68%, respectively ($P = .0004$ for tubular v NOS; $P = .58$ for mucinous v NOS).

the largest published report on tubular and mucinous carcinomas that comprehensively evaluates their biologic characteristics and clinical outcomes. The large number of patients and the multi-institutional nature of the study population enhance the reliability of the results and permit extrapolation of the findings to routine clinical practice. The incidence of tubular (0.8%) and mucinous (2.3%) carcinomas in these databases is almost identical to the incidence of these carcinomas (0.8% for tubular and 2% for mucinous) in the Surveillance, Epidemiology, and End Results (SEER) program database,⁵ which indicates that this patient population is representative of the breast cancer patient population in general.

An important finding of this study is that the survival of patients with tubular and mucinous carcinomas is not significantly different from that of the general population. To our knowledge, this is the only large study to show that patients with tubular and mucinous carcinomas have longevity similar to that of the general population. This has significant implications for the clinical approach to the management of these patients. This finding suggests that many patients with tubular and mucinous carcinomas would

derive little survival benefit from adjuvant therapy and can be spared the side effects and the cost of such therapy. The decision to use systemic adjuvant therapy should therefore take into consideration the favorable natural history of these special types of carcinomas.

This study also found that even patients with node-positive tubular carcinomas have excellent prognoses. The lack of prognostic value of node involvement in tubular carcinomas has also been observed in another study.¹³ Although the majority of node-positive patients have received adjuvant therapy, this therapy was not independently associated with improved DFS or OS in the multivariate analyses. Additionally, none of the patients with node-positive tubular carcinomas who did not receive adjuvant therapy has relapsed, which indicates that this favorable outcome is probably related to the intrinsic biology of the disease rather than to higher-than-expected benefit from systemic adjuvant therapy. When all the evidence is considered, systemic adjuvant therapy in node-positive tubular carcinomas may not provide significant benefit, especially in regard to chemotherapy.

Another important implication of this study on the clinical management of these carcinomas is that the majority of patients with tubular and mucinous carcinomas might be spared axillary lymph node dissection. In this study, less than 15% of patients had involvement of axillary nodes, which is in general agreement with the low incidence of involved axillary nodes reported in other studies.^{1,3,5,13-15} Because node involvement in tubular carcinomas does not seem to provide prognostic information (as previously discussed) and because nodes are infrequently involved, axillary node dissection is not helpful in tubular carcinomas. In mucinous carcinomas, however, node involvement was associated with a significantly worse 5-year DFS and OS. Therefore, it is important to identify subsets of patients with mucinous carcinomas expected to have a low incidence of node positivity who might be spared axillary node dissec-

Table 3. Univariate and Multivariate Analyses of DFS for Tubular (n = 277, 14 events) and Mucinous Carcinomas (n = 704, 52 events)

| Variable | Tubular | | Mucinous | |
|----------------------------|--------------|----------------|--------------|-------------------------|
| | Univariate P | Multivariate P | Univariate P | Multivariate P (RR, CI) |
| Tumor size | .07 | NS (> .05) | .0001 | .009 (1.8, 1.2-2.8) |
| Node | .69 | NS (> .05) | .0001 | .0001 (3.8, 2-7.2) |
| Age | .27 | NS (> .05) | .001 | .046 (0.5, 0.3-0.99) |
| ER | .28 | NS (> .05) | .0004 | .012 (0.39, 0.2-0.8) |
| PgR | .49 | NS (> .05) | .08 | .83 |
| S-phase | .51 | NS (> .05) | .13 | .14 |
| Adjuvant chemotherapy | .73 | NS (> .05) | .0001 | .83 |
| Adjuvant endocrine therapy | .16 | NS (> .05) | .78 | .56 |

Abbreviations: RR, relative risk; CI, confidence interval.

tion. Mucinous carcinomas ≤ 1 cm and those that were ≤ 2 cm with a low S-phase fraction had $\leq 5\%$ chance of involved nodes, and axillary dissection might be avoided in these patients.

Another characteristic of tubular and mucinous carcinomas is the older age of patients when compared with NOS carcinomas. Older age for patients with mucinous carcinomas has been reported in other studies,⁵ but several small studies of tubular carcinomas have suggested that age might not be different for NOS carcinoma.^{1,15} However, the present study indicates that tubular carcinomas do occur more often in older patients compared with NOS carcinoma.

Tubular, but not mucinous, carcinomas were smaller in size at diagnosis compared with NOS carcinomas. Most studies of tubular carcinomas agree that they are smaller at presentation.^{1,2,13} However, the literature on the size of mucinous carcinomas is less consistent, with some studies indicating that they might be larger than NOS carcinomas at presentation^{14,16,17}; other studies suggest that they have a similar size at diagnosis.^{3,5,15} The present study and another large study from the SEER program establish that mucinous and NOS carcinomas have no significant size differences at diagnosis.⁵

Because only a few scattered studies have addressed the biologic features of tubular and mucinous carcinomas, one of the main objectives of this study was to comprehensively characterize these biologic features. This study extends the findings of other smaller studies¹⁸⁻²² indicating that tubular and mucinous carcinomas are significantly more likely to be steroid receptors-positive than NOS carcinomas. This study also shows that tubular and mucinous carcinomas are more likely to have low S-phase fractions and to be diploid. The evaluation of S-phase fractions in tubular and mucinous carcinomas in other published studies has been limited to extremely small numbers of cases, preventing any definitive conclusions; one study evaluated three cases with tubular carcinomas and found that they had low S-phase fractions,²¹

whereas another study evaluated seven cases and found that tubular and NOS carcinomas had similar percentages of cells in S phase.²⁴ A recent relatively large study published in abstract form indicated that tubular and mucinous carcinomas are more likely to have low proliferation rates compared with NOS carcinomas.²⁵ As expected, special-type carcinomas are unlikely to overexpress *c-erbB-2* and EGFR, two known deleterious growth factor receptors. However, because of the small number of patients with known *c-erbB-2* and/or EGFR status, studies with larger number of patients are needed to confirm the *c-erbB-2* and EGFR findings of this study.

One limitation of this study is that breast tumors were included in the San Antonio databases because they were sent to laboratories for biochemical corticosteroid receptor assays and/or DNA flow cytometric analyses. This represents a potential selection bias because these assays cannot be performed on small carcinomas. However, although small tumors are underrepresented in these databases, the same limitation applies to NOS carcinoma as to tubular or mucinous carcinomas, and the already excellent overall prognosis of these carcinomas would have been even better had smaller carcinomas been involved.

In conclusion, tubular and mucinous carcinomas have favorable biologic characteristics and an excellent prognosis. Axillary node dissection might not be beneficial in tubular carcinomas regardless of size or in mucinous carcinomas ≤ 1 cm. With the already favorable prognosis of tubular and mucinous carcinomas, adjuvant therapy might not provide a clinically significant benefit, and decisions about adjuvant therapy should be made in this light.

ACKNOWLEDGMENT

We thank Gary Chamness and Carole Elledge for reviewing the manuscript.

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