

Tubular Carcinoma of the Breast; a Single Institution's Experience of a Favorable Prognosis.

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Introduction:

Breast cancer is the most commonly diagnosed cancer in women worldwide, and the leading cause of cancer mortality. It is estimated in the United States, 231,840 women were diagnosed with invasive breast cancer in 2015, with 40,290 women dying from the disease (1). Based on current incidence rates, a woman's average lifetime risk of developing breast cancer is 12.4% (2). Of these cases of invasive cancer, invasive ductal is the most commonly diagnosed type. Tubular carcinoma is a rare subtype of invasive breast cancer, accounting for approximately 1-4% of cases. It has been previously established that tubular carcinoma follows a more indolent course than that of typical invasive ductal carcinoma, with lower rates of local and distant recurrences, as well as cancer related deaths. In a recent series at Brigham and Women's, Javid et al demonstrated low rates of local recurrence and distant metastasis, suggesting that lesions under one centimeter need not undergo axillary staging (3). A series by Rekha et al illustrated that compared to low grade invasive ductal carcinoma, tubular carcinoma was more likely to be detected on mammographic screening, despite smaller median size. Additionally, these lesions were more amenable to wide local excision, and were less likely to demonstrate lymphovascular invasion on pathologic examination (4).

The current National Comprehensive Cancer Network (NCCN) guidelines for management of invasive breast cancer recommend that for clinical stage I, IIA or IIB lesions, the patient undergo breast conservation therapy or mastectomy with surgical

axillary staging, along with post-surgical endocrine treatment and radiation therapy to whole breast or partial breast when patients qualify. For patients that are ER/PR positive, systemic endocrine therapy is indicated for patients with tumors over 3cm, with consideration given to tumors over 1cm (5). However, treatment algorithms within the field of breast oncology change rapidly as research in the field improves our knowledge regarding the aggressiveness of each individual tumor. Recommendations regarding adjuvant chemotherapy and endocrine manipulation may be adjusted based on a number of factors including the patient's individual and familial risk factors, Oncotype DX recurrence score, and unique biology of each cancer (i.e., ER/PR/Her2/Ki67 status). The NCCN does not differentiate tubular carcinoma as a less aggressive cancer compared to invasive ductal cancer, with the same algorithm applying to both subtypes. For tubular carcinoma of the breast, surgical resection and axillary staging, followed by whole breast radiation is the current standard of care.

This study aims to further elucidate the nature and appropriate management of tubular breast carcinoma in an effort to provide physicians the information required to reassure their patients that this rare subtype of breast cancer has favorable prognosis when managed accordingly.

Methods:

A retrospective chart review from the Jacqueline Wilentz Comprehensive Breast Center at Monmouth Medical Center, Long Branch, New Jersey was conducted. All records of patients diagnosed with tubular carcinoma of the breast from January 2000 to March 2015 were gathered, giving a total of fifty-seven patients over this sixteen-year

span. Data was collected for each patient with respect to medical history, mode of detection of lesion (i.e., on screening mammogram or a palpable mass), tumor pathology, treatment received, and patient follow up. Further details regarding each patient's history were taken into consideration including age, gender, menopausal status, personal history of breast or other cancer, and family history of breast cancer. The characteristics of each cancer were tracked, including TNM staging, pathologic subtype, and hormonal status. Treatments were categorized as type of surgery, type of adjuvant therapy, if any, and whether radiation was included in the treatment. Types of surgery included breast conservation therapy (BCT), total mastectomy with sentinel lymph node biopsy, modified radical mastectomy (MRM), and bilateral mastectomy (BM). Patient follow up documentation provided recurrence and survival data. The primary endpoint was to determine how the 57 patients with tubular carcinoma of the breast fared with regards to disease recurrence and cancer related mortality in comparison to patients with other breast cancer subtypes and comment on differences in presentation, prognosis and treatment.

Results:

The results of this retrospective study reinforced this to be a favorable subtype of breast cancer. The average age was 60 years old and all patients were female. None of the patients had a prior personal history of breast cancer, with the tubular carcinoma being their first breast cancer. Fifteen of the 57 (26%) had a positive family history of breast cancer. Three patients had a history of another type of cancer (one lung cancer status post radiation therapy, one melanoma status post resection, and a colon cancer status post

curative resection). None of the patients were under active treatment for their prior malignancies. Thirty-eight of 57 (66%) were peri- or postmenopausal. The mean follow up of was six years, ranging from one to fifteen years.

Diagnosis was made by mammography in 49 of 57 (86%) patients. Eight cancers were clinically detected on physical examination. Interestingly, six of these eight had a concomitant pathology in their resection sample. We defined concomitant pathology as another pathology in the specimen along with tubular carcinoma, such as DCIS or invasive ductal. Of the total 57 patients 42 (74%) had concomitant cancer in their pathology with fifteen (26%) of them being pure tubular carcinoma. Of the mixed pathology types, 23 showed DCIS, two atypia, 2 LCIS, 11 invasive ductal, and four invasive lobular.

Breast cancer is treated by a multidisciplinary team with most early stage breast cancer being treated by surgical resection followed by necessary adjuvant therapy based on the individual case which can range from radiation, endocrine therapy or chemotherapy. Breast conservation therapy was the treatment in 41 of the 57 patients in this series. Eight patients underwent simple mastectomy mainly because of contraindications to breast conservation therapy, namely prior radiation therapy (XRT) (1), multicentricity (5), or strong family history of breast cancer (1). One patient had no contraindications to BCT but opted for mastectomy. Eight patients underwent bilateral mastectomy (therapeutic mastectomy with contralateral prophylactic mastectomy); three had a family history of breast cancer while five others opted for this surgery either for symmetry or desire for omission of future imaging.

In regards to adjuvant therapy, the authors encountered difficulty in obtaining

complete information for every patient. Due to the retirement of some treating practitioners and transition to electronic medical records, some charts were archived, and thus unavailable for review. This especially affected access to medical oncology and radiation oncology treatment plans. If the information could not be gleaned from the electronic medical records this portion of the patient's data was excluded. All patients were offered adjuvant breast radiation therapy; twenty-two of these had no further documentation of XRT or were lost to follow-up, therefore their treatment plans could not be ascertained. Of the remaining 35 patients, 18 underwent radiation treatment while 17 refused. Of note, one of the two recurrences was in a patient who refused XRT. All patients with hormone positive cancers were offered endocrine treatment (Tamoxifen or Aromatase Inhibitor). In twenty-five patients, the endocrine treatment plans could not be ascertained from chart review. Eighteen subjects received endocrine treatment, 3 received endocrine and chemotherapy, three received chemotherapy only, and 11 refused endocrine treatment. No patient who was offered chemotherapy refused. Of the three patients who received chemotherapy, one had concomitant invasive lobular cancer, another had DCIS and the patient received chemotherapy for the tubular carcinoma. Of the three patients who received chemotherapy and hormone treatment, one was stage I invasive lobular carcinoma, one was stage I invasive ductal carcinoma, and one was for DCIS node negative.

The majority of patients in this series were diagnosed with early-stage breast cancer. In regards to tumor size (T stage), 51 of 57 cases (89%) were T1 and the remaining six (11%) were T2. Four of the T2 patients were treated with mastectomy. A sentinel lymph node biopsy procedure was done in all patients. Only one biopsy was

positive, which was for four positive lymph nodes, she underwent a completion axillary lymph node dissection. In regards to tumor biology, all patients were endocrine positive, two only ER+, while 55 were both ER and PR+, thus all patients were offered endocrine treatment. The mean follow up was seventy-two months with a range of one to fifteen years. There were no cancer related mortalities.

The two recurrences were as follows: A 50-year-old peri-menopausal female with no family or personal history of breast cancer had a palpable mass for which she underwent a lumpectomy (T1N0M0, stage I invasive tubular cancer with DCIS). The patient was ER/PR+ and refused radiation or endocrine therapy. She recurred in an adjacent quadrant 10 months later with the same pathologic subtype, tubular carcinoma. The second recurrence was in a 60-year-old post-menopausal female who also had no personal or family history of breast cancer, with a mammographically detected breast cancer. She underwent BCT and received both endocrine and radiation therapy. She recurred 12 years later as an invasive ductal carcinoma. The mass was excised from the same quadrant as her prior cancer and was ER+ as well. However, there was no tubular component to it, which likely argues more for a new primary than a strict recurrence.

Discussion:

Tubular carcinoma of the breast represents a small percentage of invasive breast cancer that is often grouped with all other histiotypes in treatment algorithms. Given the indolent course we have confirmed with our institution's experience, we propose that perhaps these cancers could be managed less aggressively. The goal of oncology is to give patients the best survival while limiting morbidity and intolerable side effects. Gone

are the days of bilateral mastectomies with axillary dissection for early stage cancers. The ACOSOG Z0011 trial has provided evidence that in regards to breast conservation therapy, more axillary surgery does not necessarily impart an improved survival (6). The authors hypothesize that even further selectiveness can be utilized in addressing nodal status with select breast cancers. Although less concrete but equally important is the prognosis and reassurance physicians provide their patients with cancer diagnosis. Evidence-based medicine, when practiced, can reassure patients that their type of cancer is less virulent, with less of a chance of recurrence. This is information practitioners should strive to provide to their patients.

Tubular carcinoma of the breast has been shown to have a very favorable prognosis when compared to other breast cancers. The overall survival has been quoted at 5 and 10 years as even better than other types of breast cancer (7). Small series have been published comparing demographics, outcomes, and treatment of tubular carcinoma to that of other histiotypes. The largest series was a metaanalysis performed by Li et al. who found 1,983 tubular carcinomas from 11 cancer databases. The total number of cancers reviewed was 139,310; tubular carcinoma comprised 1.42% of all breast cancers. It was observed that this subtype was diagnosed at an earlier stage, at a smaller size, and had an overall lower mortality. Tubular carcinoma tended to be less aggressive based on all criteria. This cancer was less likely to be at an advanced stage at diagnosis, less likely to be node positive, less likely to be hormone negative, and more likely to have lower grade at resection. Recurrence was not quoted in this large review of tubular carcinomas (8).

The data collected from the JW Breast Center provided 57 cases of tubular carcinoma over 16 years. The authors' data mirrored that of the current literature

available for tubular carcinoma of the breast. The patients were peri- to post-menopausal women, presenting with early stage cancer. There were no cancer related deaths with a mean follow up of six years, ranging from one to fifteen years. Of these 57 patients there were only two recurrences, one of which was a recurrent tubular while the other recurred as invasive ductal carcinoma. When both are considered, the recurrence rate in the series is 3.5%. However, the recurrence rate of tubular carcinoma alone is 1.75% in this series. This shows a much lower recurrence than that quoted for all comers in breast cancer, which is a ten year recurrence of 35% with lumpectomy alone and 19% with lumpectomy and radiation (9). In their series, Vo et al had a recurrence rate of 13% for tubular carcinoma, similar to that of all comers in breast carcinoma. Vo's study did, however, show disease free and overall survival rates that were statistically better than other subtypes (7).

Javid et al presented a series of 111 patients with tubular carcinoma of the breast, with only one recurrence (0.9%). This series did cite one other ipsilateral recurrence that was an invasive type carcinoma, raising their recurrence rate to 1.8%. This series supports the notion that tubular carcinoma is a less aggressive cancer with a favorable prognosis (3). A series out of Boston based hospitals looked at 28 tubular carcinomas with a minimum follow up of 10 years. The tumors also showed favorable characteristics, as 96% were T1 and 83% were LN negative. There were no recurrences in this series (10). Overall, the literature strongly supports that tubular carcinoma of the breast as a less virulent form of breast cancer. The question remains, can it be treated differently than more common breast cancers?

The possible alterations to the current standard of care in breast cancer are four

fold; omitting axillary sampling, radiation, chemotherapy, and endocrine treatment. The Z0011 trial has already suggested against axillary lymph node dissection (ALND) when three or less sentinel lymph nodes (SLNs) are found positive in early stage tumors in patients treated with BCT (6). Since most tubular carcinomas in our series were found at an early stage, the hypothesis is that fewer will have positive lymph nodes at the time of surgery. The omission of SLN biopsy (Bx) for tumors less than one centimeter in size, as suggested by Javid et al, is taken into consideration with some hesitancy (3). The data set presented here had 8.8% of patients with positive lymph nodes on SLNBx. We consider this to be too high of a number to forgo sentinel biopsy. In a 2006 review Leikola et al found that 6/27 or nearly 25% of tubular CAs were positive upon SLNBx (11).

Fortunately, SLNBx has been proven to have a low morbidity and rate of complications. Sener et al found only 3% lymphedema during sentinel biopsy (12) and Z0011 trial quoted a 6% rate of lymphedema, along with a 3% rate of wound infection, 6% seroma, and 9% parasthesias rates (6). Although no procedure is without potential risks, the SLNBx's low complication rate suggests the benefit exceeds risk, and argues against abandoning it.

The next argument would be that of systemic therapy after resection. As noted above, the data set was not controlled for chemotherapy or hormone treatment. A retrospective analysis in 2010 found that patients with tubular carcinoma had close to a normal life expectancy. Based on this the authors suggested that medical oncology adjuvant therapy may not be necessary (4). The authors here did not have enough information to show difference in recurrence rates based on chemo or hormone therapy. In the two recurrences in our study, one recurred with tubular carcinoma after refusing

endocrine therapy and radiation. The other recurrence, that of invasive ductal type, received both endocrine and radiation therapy. For this reason, no comment can be made on the need for chemo or endocrine therapy in tubular carcinoma.

The idea to omit whole breast radiation for tubular carcinoma of the breast was suggested in an article in *The Breast Journal*, 2003, when Cabral et al looked at thirtythree patients. One of twenty-one treated without radiation recurred (without an effect on overall survival), while zero of twelve treated with radiation recurred. This led to a conclusion by their authors that radiation did not affect survival as both groups overall survival was 100% (13). This idea was refuted by a 2012 review of 115 tubular CA. Ninety four were treated with radiation of which one recurred (1.1%) while five of twenty-one (24%) not treated with radiation had recurrences. The authors argued against the de-escalation of treatment for tubular carcinoma of the breast (14).

The pitfalls of this study are like all retrospective series that is lack of control and standardization. Of the 57 patients presented, the authors could not comment on thirteen patients' radiation status, as it was not uniformly documented. Another nine lacked information on chemotherapy or endocrine treatment as well. Therefore, no definitive correlations of treatment and recurrences can be made for these patients, thus this portion of their data set was excluded.

Interestingly, the data obtained for this study showed a favorable disease free recurrence and survival for tubular carcinoma of the breast regardless of it being a pure tubular histiotype or mixed. This trend suggests that tubular histology is associated with a positive prognosis even when found with concomitant cancer subtypes.

The data available for tubular carcinoma of the breast portrays a favorable

prognosis of an early stage cancer. As is always the goal with cancer care and medicine in general, researchers strive to give their patients the best treatment while limiting any harmful side effects. This sometimes leads to a call to de-escalate treatment protocols when a disease shows an indolent course. Although the data presented here may allow the practitioner to counsel their patient with confidence about tubular carcinoma, it does not allow any alteration in standard treatment plans. Sentinel lymph nodes should continue to be sampled and radiation used to reduce local recurrence. A randomized control trial would be needed to assess the risk and benefits of treating tubular carcinoma less aggressively by eliminating radiation, systemic medical therapy, or lymph node biopsy. What can be offered is that tubular carcinoma presents as an early and fairly unaggressive subtype and when treated with standard of care, has an excellent prognosis for both survival and recurrence.

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