The evolution in management of patients with subcentimeter, node-negative, triple-negative breast cancer

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Abstract
BACKGROUND: The aim of this study was to determine the evolution in treatment recommendations and outcomes for patients with subcentimeter, node-negative, triple-negative disease.

METHODS: Patients were divided into a remote (diagnosed from 1997 to 2003) and a recent (diagnosed from 2004 to 2011) group. Demographics, tumor size, surgical treatment, use of adjuvant chemotherapy, survival, and disease recurrence were evaluated.

RESULTS: Thirty patients were placed in the remote group and 31 in the recent group. Demographics, tumor sizes, and surgical treatment were similar between groups. The use of adjuvant chemotherapy increased from 7% to 42% in the recent group (P < .002). Disease-free survival and recurrence (7%) was not influenced by the use of chemotherapy.

CONCLUSIONS: This study demonstrates that adjuvant chemotherapy is increasingly used in patients with the triple-negative phenotype, regardless of other favorable prognostic variables. The value of adjuvant chemotherapy for the subgroup of patients in our study is unclear and mandates further investigation.

Over the past several decades, improvements in breast cancer outcomes have been related to enhanced efficacy of systemic therapies. Operations have become less radical, and radiotherapy techniques have reduced morbidity, but neither local therapeutic modality has changed considerably during the past several decades. Instead, the efficacy of systemic therapies has dramatically improved. The development of more effective systemic chemotherapeutic agents such as anthracyclines and taxanes has resulted in better treatment responses and improved survival when they are given as adjuvant therapeutic agents. Endocrine therapies such as tamoxifen for premenopausal women and aromatase inhibitors for postmenopausal patients reduce risks for recurrence and are associated with breast cancer prevention of contralateral breast malignancies. Targeted biologic therapy such as trastuzumab against the human epidermal growth factor receptor 2 (HER2/neu) results in excellent treatment responses for the 20% of patients who overexpress this receptor. HER2/neu positivity is associated with increased biologic aggressiveness; therefore, having effective therapy for this subgroup helps mitigate the otherwise poorer expected prognosis. These systemic approaches have improved outcomes for these high-risk patients.
therapies and their application in the management of breast cancer have provided the most important contribution to enhancing treatment outcomes.

The decision to use cytotoxic systemic chemotherapy is based on the efficacy of the drugs and the risk for recurrence. Chemotherapy is recommended when the reduction in risk for recurrence outweighs the drug toxicity. To determine the estimated reduction, prognostic indicators are used to estimate the likelihood of risk. These prognostic factors include nodal status, tumor size, and expression of hormone and HER2/neu receptors. Patients with negative nodes and small tumors have lower recurrence rates and are less likely to have cytotoxic chemotherapy play a role in their management.

For patients who overexpress estrogen and/or progesterone receptors, the use of endocrine therapy has demonstrated improved disease-free survival. Most patients who express progesterone receptors will also overexpress estrogen receptors. Endocrine therapy is effective to treat patients with overexpression of either estrogen receptors or progesterone receptors but is not effective to treat patients with tumors that express neither. These agents (both tamoxifen and aromatase inhibitors) have the ability to reduce cancer recurrence and to prevent second contralateral cancers from developing in the opposite breast. Endocrine therapy is an essential part of the overall strategy to manage breast cancer and is used liberally because its toxicity is less common compared with chemotherapy. Despite its lower toxicity, there is no value in using endocrine therapy for tumors that are negative for both estrogen and progesterone receptors.

Patients who overexpress HER2/neu receptors can have targeted therapy in the form of trastuzumab. Trastuzumab reduces distant recurrence and enhances survival for the 20% of patients with invasive cancer who overexpress this target. The drug has more recently been shown to have a strong radiosensitizing effect and is being investigated as an adjuvant agent in the treatment of ductal carcinoma in situ (DCIS). Interestingly, high-grade comedo-type DCIS is most likely to be HER2/neu positive, thereby allowing a potential systemic agent that can reduce the risk for recurrence after breast conservation for high-risk DCIS. The ability to reduce the risk for recurrence after breast conservation for DCIS is especially important because half of local breast recurrence after breast conservation occurs in the form of invasive cancer, which puts the patient at risk for distant recurrence and a reduced overall survival.

This topic is being investigated in the current National Surgical Adjuvant Breast and Bowel Project’s B43 trial, which is currently open to patient accrual. Like endocrine therapy for patients without hormone receptors, there is no value in using trastuzumab to treat patients with tumors that are negative for HER2/neu receptors.

Current adjuvant therapy strategies provide treatment for node-positive, hormone receptor–positive, and/or HER2/neu-positive cancer patients with tumors >1 cm in size. The dramatic impact of systemic therapies on improving breast cancer treatment outcomes creates potential frustration when no treatment options are available for subgroups of patients. One such subgroup is women with tumors <1 cm in size that are node negative, hormone receptor negative, and HER2/neu receptor negative. Historically, no systemic treatment has been recommended for this subgroup of patients with breast cancer.

Recently, the poor prognosis associated with the triple-negative phenotype could challenge this recommendation against adjuvant therapy. “Triple-negative” refers to the fact that these tumors do not express receptors for estrogen, progesterone, or HER2/neu. These tumors have increased biologic aggressiveness manifested by early tumor recurrence. Triple-negative cancers are typically at an advanced stage at diagnosis with large tumor sizes and nodal involvement. However, small tumors do occur in a subgroup of triple-negative patients who are node negative. The unknown question is whether these small node-negative, triple-negative tumors are as biologically aggressive as their larger node-positive counterparts. This uncertainty led to the decision to perform this study. The goal of this study was to evaluate the current treatment recommendations and outcomes at our institution regarding the use of adjuvant systemic cytotoxic chemotherapy in the management of patients with subcentimeter, node-negative, triple-negative breast cancer.

**Methods**

We retrospectively reviewed our institution’s prospectively maintained breast cancer registry from 1997 to 2011 to identify all patients with breast carcinoma measuring <1 cm in diameter. Patients were then excluded on the basis of the use of neoadjuvant chemotherapy, noninvasive or microinvasive tumors, node-negative disease, and tumors with estrogen, progesterone, or HER2/neu receptor positivity. Estrogen, progesterone, and HER2 status was determined on the basis of immunohistochemical staining, and tumor size was based on pathologists’ measurements after gross excision. This resulted in a population of patients with invasive breast cancers that were node negative, <1 cm in size, and had a triple-negative phenotype.

This population was then divided into 2 groups, a remote group that had been diagnosed from 1997 to 2003 and a recent group diagnosed from 2004 to 2011. These dates were selected because they split the cohort into 2 equally sized groups. The study began in 1997 because that was the year when HER2/neu receptor assessment became standard at our institution for all breast cancers. The groups were divided on the basis of the number of patients in each group. Demographic data, including age at and date of diagnosis, were recorded for both groups. Also noted were the size of the tumor in millimeters after gross excision; the estrogen receptor, progesterone receptor, and HER2 status (which were all negative); the nodal status (which was negative); the extent of the primary breast surgery and axillary dissection; and whether chemotherapy was used. The breast surgery was classified as either a mastectomy or a lumpectomy and the axillary surgery as either sentinel node or complete axillary dissection.
Our institution’s electronic medical record was reviewed, and follow-up phone communication with patients was attempted to classify patients as alive with or without the disease, dead with or without the disease, or lost to follow-up. Student’s t tests were used to compare quantitative variables once normal distribution of the data was confirmed. Fisher’s exact tests were used to compare categorical data between the remote group and the recent group. P values ≤ .05 were considered statistically significant. We also noted whether patients who had suffered recurrence had received adjuvant chemotherapy.

Results

The breast cancer registry contained 1,067 patients with breast cancer tumors < 1 cm in diameter. Of these 1,067 patients, 61 had invasive breast cancer that was node negative and estrogen receptor, progesterone receptor, and HER/2 negative. The division of the patients into the remote group from 1997 to 2003 and the recent group from 2004 to 2011 resulted in 30 and 31 patients in each group, respectively.

Demographic data for the 2 groups were similar. The average age at diagnosis was 59.2 years in the remote group and 56.3 years in the recent group. This was statistically similar on the basis of Wilcoxon’s rank-sum test. The tumor size in the remote group was 5.07 mm (confidence interval, 3.89 to 6.24 mm) and the tumor size in the recent group was 6.3 mm (confidence interval, 5.6 to 7.05 mm), with no statistically significant difference. For the primary surgical therapy, 80% of the remote group had breast conservation, while 61% in the recent group had lumpectomies. This was statistically similar (P = .161, Fisher’s exact test). Finally, the number of nodes examined was 5.1 in the remote group and 4.6 in the recent group and was also statistically similar. These comparisons show that the 2 groups were evenly matched in their characteristics.

Adjuvant chemotherapy was used more frequently in the recent group (42%) than in the remote group (7%) (P = .002). Despite this increased use, adjuvant chemotherapy did not appear to affect the recurrence rate or overall survival in either group. A total of 4 patients had recurrences, 3 in the remote group and 1 in the recent group. This difference was not significant. All patients in the recent group have been recently followed; 6 patients in the remote group could not be contacted. Of the 4 patients with recurrences, 1 in the recent group and none in the remote group received adjuvant chemotherapy. The use of chemotherapy did not appear to have an impact on recurrence or overall survival in our study.

Comments

This study demonstrates that medical oncologists at our institution are using cytotoxic adjuvant chemotherapy with increasing frequency to treat patients with subcentimeter, node-negative, triple-negative breast cancer. The understanding of the poor prognosis associated with the triple-negative phenotype has likely led to this therapeutic decision. Whether women with these small node-negative tumors truly have a poorer prognosis is not clarified by the results of this study. Although there were only 4 recurrences among the 61 patients (7%), the addition of chemotherapy was not associated with a statistically significant improvement in outcomes.

The poor prognosis associated with triple-negative breast cancer has led to the justifiable increased use of adjuvant chemotherapy in this subgroup of patients, even when other prognostic variables predict good outcomes. The lack of benefit associated with the use of chemotherapy in our study call into question this decision. It would be better to gather the necessary information so that the potential unnecessary use of chemotherapy could be avoided. The identification of subgroups of patients with breast cancer who have historically received chemotherapy but have recently been discovered to derive little benefit from cytotoxic treatment is best exemplified by the use of the Oncotype DX (Genomic Health, Inc, Redwood City, CA) studies.16,38,39 Oncotype DX has been used to clarify the value of chemotherapy for node-negative, estrogen receptor–positive patients. By evaluating tumors for the 21 genes included in the Oncotype DX assessment, patients can be classified as at low, intermediate, or high risk for recurrence. Adjuvant chemotherapy trials that have retrospectively evaluated tumors with the Oncotype DX assessment tool have demonstrated that the benefits of adjuvant chemotherapy are limited to the high-risk group and that low-risk patients are effectively managed by endocrine therapy alone without chemotherapy.

The recently published result of the National Surgical Adjuvant Breast and Bowel Project’s B-28 trial demonstrates that Oncotype DX has powerful predictive ability for estrogen receptor–positive, node-positive patients and has identified a group of node-positive patients who have historically received chemotherapy who can be effectively treated with endocrine therapy only and anticipate a low risk for recurrence.40 There are no data regarding the use of molecular profiling for estrogen receptor–negative patients; therefore, nodal status, tumor size, and the triple-negative phenotype will continue to direct systemic therapies in these patients.

Only a large multicenter trial would be able to provide this information for a subset of patients that makes up only 6% of women with subcentimeter invasive breast cancer.

Similar evidence is available when considering similar patients with small node-negative, estrogen receptor–negative tumors.41 Although it is clearly recognized that patients who do not express estrogen receptor on their tumors are at a survival disadvantage, when this group is compared with a similar group of estrogen receptor–positive patients, there appears to be little difference in outcomes. In other words, the small size and negative nodal status trump the concerning finding of estrogen receptor
negativity. Perhaps the same might be true for the triple-negative patients with small tumors and negative nodes.

Our study was limited by its small size and retrospective nature. It was not undertaken to provide a definitive conclusion; instead, the study was considered important to provide some preliminary information for this small subset of patients who require treatment recommendations where none exist. In fact, the trial was born out of a discussion during a multidisciplinary breast conference with a patient with 7-mm, node-negative, triple-negative breast cancer for whom chemotherapy was recommended on the basis of the her triple-negative status. Because no evidence was provided to support this treatment recommendation, we elected to evaluate our database to determine if chemotherapy had been used for such patients and what its potential value might be. We learned that chemotherapy is being used with more frequency, with limited documented benefit, and that we would have to rely on future studies to definitively help guide the optimal therapeutic decision making for women with subcentimeter, node-negative, triple-negative breast cancer.

References

making on targeted therapy based on unique tumor biology which is determined by molecular profiling and gene assay? I would predict that within the next 3 years, that will be the standard cure in this country.

Thank you for the opportunity to review this.

Emily Wolfe, M.D. (New Orleans, LA): Thank you for your question. With respect to the oncotype testing, right now it is only approved for the ER positive node negative patients. So that being said, it may or may not apply to these patients. You mentioned the fact that the ER PR status may be false based on the staining methodology which in that case that may be true and some of these patients could possibly fall into that category.

Dr Edney: Just 1 more observation. You mentioned the oncotype test was only approved for hormone receptor positive patients and that is true, but the next generation testing is approved for ER positive, PR negative, triple negative, node positive patients and tumors up to 3 cm.

Dr Wolfe: I agree that will be the future of what is coming. Based on what we had for this particular paper, we did not have that information available; therefore we chose to treat, based on the size of the centimeter. If you go back and look at our patients that fell into the more recent group, 13 of them were treated with chemotherapy. Most of them had tumors greater than .5 cm. Our medical oncologists kind of looked at it as these are the larger size more aggressive tumors, so it is better to go ahead and treat with kind of blind eyes as opposed to going back and later learning that you should have—that means that the risk of using chemotherapy does not come without its limitations. So I think there does need to be additional investigation into the specific knowledge of markers that will make for a better treatment decision when it comes to treating these types of cancers.

Alicia Mangram, M.D. (Phoenix, AZ): Very nicely presented. I get yelled at for using the DaVinci to do a gallbladder, but that doesn’t really make sense to me. The public wants the availability of the Da Vinci as an option. But the public wants it. People say coming in to our practice that they have heard about the robot. What is driving, really driving, the increase? Forty-two percent is a really big increase to use chemotherapy and I feel like if my patient has cancer, they are going to get chemotherapy no matter what. Even in a small 1 cm, I know if it is triple negative that makes us all very worried. What do you think is really driving it, is it the public or do we really believe that these patients need chemotherapy? Even though your data is limited prior to you doing your study, what do you think was driving the oncologists? Is it financial or is it really patient related?

Dr Wolfe: I believe that what’s driving the medical oncologists more towards a systemic therapy as opposed to a local regional therapy for these patients is probably fear of recurrence in these patients. These women become hypersensitive about their breasts, every lump and bump they have, they go back to their doctor to get it examined. It provides some reassurance in the way of the psyche. If you
give these patients chemotherapy, they thought they are being treated better. I can’t speak for the medical oncologist, but having a patient come to you and saying that she is extremely worried about her breast cancer coming back and she has this aggressive type of breast cancer may push the medical oncologist to make the decision to go ahead and treat it with chemotherapy despite the small size.

Anees Chagpar, M.D. (New Haven, CT): Just because I am a breast person and I can’t resist—1 last question. One of the things that may have been driving the increased use of chemotherapy is that the NCCN guidelines changed recently so that now the guidelines are to treat (or at least consider treatment) for any woman who has a tumor >5 mm with 1 negative prognostic factor. So that may have been part of the issue. But the other thing that was interesting in your cohort is that surgical management also changed to become more aggressive. So you went from 80% breast conservation to 60% breast conservation. While that was not statistically significant, and may have been due to small numbers, what do you think drove that?

Dr Wolfe: We kind of discussed that before. We think that it is due largely to using MRI and the additional parameters that these women now know about. It is patient education, a lot of it, so they prefer to have a mastectomy over breast conservative therapy that is going to increase their chances of getting cancer again.

Dr Chagpar: That is a nice primer for the MRI debate coming up in this meeting. Thank you so much.