

Questioning the Value of Evaluating Estrogen and Progesterone Receptors on Core Biopsy Specimens of Patients with Ductal Carcinoma in Situ (DCIS)

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Abstract

Purpose: To evaluate the value of estrogen and progesterone receptors on core biopsy specimens of patients with ductal carcinoma in situ.

Introduction: The immunohistochemical determination of the estrogen receptor (ER) and progesterone receptor (PR) status is predictive of the response of patients with invasive cancer to hormonal therapy. The value of the receptor status prior to definitive surgery with either breast conservation or mastectomy for patients with ductal carcinoma in situ (DCIS) and no invasive component is less clear.

Methods: We identified through the tumor registry 344 patients with breast cancer diagnosed from 2014 through 2015. Two hundred seventy-seven patients had invasive cancer at diagnosis.

Results: Of the remaining 67 patients with DCIS or atypical hyperplasia alone on core biopsy, 15 (22%) patients were found to have invasive cancer at the time of definitive surgery.

Forty-six patients without an invasive component had definitive surgery at the study institution, of which three had a component of higher grade DCIS than on the core biopsy. Fourteen patients (30%) underwent a mastectomy.

Conclusion: A significant proportion (29%) of patients with DCIS alone on core biopsy had either an invasive component at the time of definitive surgery or a higher grade DCIS component. An additional 14/46 (30%) of patients chose mastectomy, for whom consideration of adjuvant endocrine therapy for contralateral risk reduction did not depend on the receptor status of the index DCIS.

Cost savings could be realized if the determination of ER is deferred until after definitive surgery. Determination of PR on DCIS specimens can be omitted entirely.

Keywords: ductal carcinoma in situ, estrogen receptor, progesterone receptor

1. Introduction

It is estimated that in 2018 there will be 266,210 women diagnosed with invasive breast cancer and 63,960 women will be diagnosed with ductal carcinoma in situ (American Cancer Society, 2018). Since for women with invasive cancer the immunohistochemical determination of the estrogen receptor (ER) and progesterone receptor (PR) status is predictive of the response to hormonal therapy, the American Society of Clinical Oncology and the College of American Pathologists both recommended in a joint 2010 publication that ER and PR status be determined (Hammond et al., 2010). A subsequent 2014 joint publication gave recommendations for testing human epidermal growth factor receptor-2 (HER-2) status for women with invasive cancer (Wolff et al., 2014). These recommendations were originally given regarding specimens from the definitive surgical procedures, after

breast conserving surgery or mastectomy was performed.

Although not a formal requirement, many institutions began performing ER and PR testing on all patients with either invasive carcinoma or DCIS on core needle biopsy specimens. This receptor analysis can be particularly beneficial in patients being considered for neoadjuvant chemotherapy. HER-2 testing is typically performed only for patients with invasive cancer.

While determination of hormonal receptor status is valuable for patients with invasive cancer as some of these patients may be candidates for neoadjuvant systemic therapy, usually patients with DCIS proceed directly to either breast conserving surgery or mastectomy depending on the details of their clinical situation and personal preference.

Various scenarios could arise for which the ER and PR receptor status from the core biopsy specimen becomes irrelevant. If a patient diagnosed with DCIS alone on core needle biopsy is subsequently found upon definitive surgery to have an invasive component, the receptor analysis of the invasive component then determines future therapy, and the receptor analysis performed on the DCIS component from the biopsy has no utility. Secondly, DCIS can be quite heterogeneous, and the nuclear grade determined on the definitive surgical specimen may be higher than that seen on the core needle biopsy, and the receptor status of the higher grade component is the more clinically relevant. Thirdly, although adjuvant hormonal therapy following breast conserving surgery for DCIS decreases recurrences in the breast, it has not been demonstrated to improve survival. Some patients who are offered hormonal therapy may decline it even if their DCIS is ER positive. Finally, the role for determining the PR status in patients with DCIS requires investigation.

Determining the receptor status from the core biopsy specimens could be considered valuable if it influenced the decision of breast conserving surgery or mastectomy, or if the receptor determination was more reliable from the core biopsy specimen than the definitive surgical specimen. If not, there could potentially be cost savings by determining the receptor status only on the final surgical specimen.

We consequently decided to evaluate the role of ER and PR testing for our patients who, on core biopsy, had DCIS without an invasive component.

2. Materials and Methods

Through the tumor registry, 344 patients with breast cancer were identified from 2014 through 2015. At diagnosis, 277 had invasive cancer. Of the remaining 67 patients, 15 (22%) were found on either breast conserving surgery or mastectomy to have invasive cancer. One patient had an excisional biopsy with no further treatment, and was excluded from further analysis. Three patients had their biopsy at the host institution but definitive surgery and all further follow-up evaluations were conducted elsewhere. Two patients had atypical ductal hyperplasia on their initial biopsy, one of whom had DCIS following breast conserving surgery and the other had atypical ductal hyperplasia. Both were offered endocrine therapy, and both declined it. Two patients had a focus of microinvasion seen in the biopsy specimen but not in the lumpectomy or mastectomy (one each) specimens. These two patients were kept in the analysis group.

3. Results

Of the remaining 46 patients with DCIS, 31 had their initial biopsy at the host institution. The other 15 had their initial biopsy elsewhere. Thirteen patients did not have ER or PR status determined at the time of the initial biopsy. Ten of these had their biopsy at the host institution. At the time of the initial biopsy, five were grade 1, 14 were grade 2, 13 grade 3, and 14 were unknown/not graded. Thirty-two patients chose breast conservation and 14 underwent a mastectomy.

Thirty-one of the 46 patients with DCIS were offered endocrine therapy, and 12 were not offered it (including both patients with microinvasion). For three additional patients, it is not known if they were offered endocrine therapy because they chose to be followed elsewhere. Endocrine therapy was not offered to any of the four ER negative patients. For the 39 ER positive patients, 16 of the 31 patients who were offered endocrine therapy accepted it (52%).

Three of the 47 patients with DCIS were found to have a higher grade component upon definitive surgery. Two of these patients chose breast conserving surgery, and the third patient underwent a mastectomy. Receptor assays were not repeated for any of these three patients. All three patients were offered endocrine therapy, but only the patient who underwent a mastectomy agreed to take it, presumably for contralateral risk reduction.

Our 46 patients with DCIS ranged in age from 40 to 87 years, with a mean of 61 and a median of 60 years. Six patients had multifocal DCIS. For this analysis, the largest size and highest grade was used. The highest grade

was also used whenever there was discordance between the grade assigned at biopsy and that seen in the final surgical specimen. One patient had a very small DCIS that was not able to be graded. Of the remaining 45 patients, 9 were grade 1, 20 were grade 2, and 16 were grade 3.

Two patients had DCIS too small to measure on the biopsy specimens and no residual at definitive surgery. Both patients, interestingly, had contralateral invasive breast cancer and underwent bilateral mastectomy. Of the remaining 44 patients, the average size DCIS was 13.5 mm, with a range of 0.4 to 70 mm.

Of the 46 patient specimens with DCIS, 39 were ER positive, four were ER negative, and three were unknown. Thirty-seven DCIS specimens were PR positive, six were PR negative, and three were unknown. Most of the DCIS cases were both ER and PR positive (34). Five DCIS cases were ER positive/PR negative. Four DCIS cases were negative for both ER and PR. Three DCIS cases had unknown values for both ER and PR.

The mean DCIS size for the 32 patients undergoing BCS was 12.8 mm with a maximum of 50 mm and a median of 6.5 mm. For the 14 patients undergoing mastectomy, the mean size was 13.3 mm, with a maximum of 70 mm and a median of 9 mm.

For the 32 patients having BCS, nine had grade 1 DCIS, 10 had grade 2, 12 had grade 3, and one was unknown. For the 14 patients having a mastectomy, there were no patients with grade 1 DCIS. Ten had grade 2, and four had grade 3.

For the model-based statistical analysis, we removed the three patients with unknown values for both ER and PR and the single patient with values reported only as positive, leaving 42 patients for the analysis. Since the decision for breast conserving surgery versus mastectomy was binary, we applied the logistic regression with the decision as the outcome and tested the marginal effects of tumor size, grade, patient age, ER, PR, and ER/PR status on their effect of the decision via the Wald test, respectively. The results suggested the patient age, size of the DCIS, and ER receptor status did not seem to affect the decision between mastectomy and breast conserving surgery (all p-values > 0.500). Patients with grade 2 DCIS had a marginally higher odds of choosing mastectomy over breast conservation (p-value = 0.066) compared to those with grade 1 DCIS. Progesterone receptor (PR) status was marginally related to the decision of mastectomy over breast conservation (p-value = 0.064). Patients with ER+/PR- DCIS had slightly lower odds of choosing mastectomy over breast conservation (p = 0.096) compared to patient with ER-/PR- DCIS. None of these were statistically significant at the 0.05 level.

We applied a similar logistic regression model to examine whether the tumor size, grade, patient age, ER, PR, and ER/PR status affected whether the patient's acceptance of endocrine therapy. The Wald test results suggested that none of the six factors affected the patient's acceptance of endocrine therapy in a statistically significant manner (all p-values > 0.200).

4. Discussion

The NSABP B-24 protocol randomized 732 patients with DCIS following breast conserving surgery and radiation therapy to receive either tamoxifen or placebo. Randomization was conducted without knowledge of the receptor status. The trial showed a significant reduction in local recurrence for patients with ER positive DCIS who underwent breast conserving surgery and radiation therapy and who also received tamoxifen. There was no significant benefit for patients who were ER negative. PR status did not demonstrate a significant role (Allred et al., 2012).

At the time of the 2010 consensus document regarding ER and PR status of patients with invasive breast cancer was published, the results of the NSABP B-24 trial were available only in abstract form. The panel consequently left it up to patients and their physicians to decide on receptor status testing for patients with DCIS. As neoadjuvant chemotherapy for patients with invasive breast cancer developed to allow more women to have breast conserving surgery, it became necessary to determine the receptor status for these women on the core biopsy specimens. It then became common for institutions to also determine ER and PR receptors from the biopsy specimens of patients with DCIS who did not have an invasive component. Although there is a report of administering preoperative endocrine therapy to a group of women with ER-positive DCIS (Chen et al., 2009), usually women with DCIS proceed without further therapy to either breast conserving surgery or to mastectomy.

Knowing the receptor status from the core biopsy could be important if it influenced the decision as to whether to proceed with breast conserving surgery or mastectomy. For our small group of patients this did not appear to be the case. Many factors enter into the consideration of breast conservation versus mastectomy, such as patient age, size of the DCIS on imaging, the anticipated cosmetic outcome, the availability of a reconstructive surgeon, and the patient's preference. These issues likely often outweigh consideration of the ER status.

Several studies have compared the assessment of ER from the core biopsy and the surgical excision specimen for

patients with invasive cancer, with excellent concordance (Tamaki et al., 2010; Hodi et al., 2007; Douglas-Jones, Collett, Morgan, & Jasani, 2001). These studies imply that there is no compelling need to obtain the receptor status prior to the definitive surgical procedure.

The role of the progesterone receptor requires detailed discussion. A recent analysis pooled the results from three observational studies including 1556 patients with DCIS (Zhang, Dai, Liu, Song, & Chen, 2016). It concluded that there was no significant difference in the risk of local invasive recurrence based on PR status. This report did not consider the risk of DCIS recurrence.

A Korean study examined a host of potential risk factors for recurrence in their group of 111 patients who underwent breast conserving surgery for their DCIS. The patient age, ER, PR, HER-2 status, molecular subtype, and hormonal therapy were not significantly associated with recurrence. The resection margins, tumor grade, and Ki-67 index and the absence of adjuvant radiation therapy were significantly associated with the risk of recurrence (Kim et al., 2016). Most likely the small number of patients in this study is partially responsible for the failure to demonstrate the significance of ER status and hormonal therapy use.

The value of determining the progesterone receptor was also questioned in a report from the Froedtert and Medical College of Wisconsin (Chaudhary et al., 2018), in their report of 693 patients treated with DCIS between February 2002 and March 2015, 517 of whom had breast conserving surgery and 169 had mastectomy. Patients whose DCIS was ER+/PR+ had a significantly lower local recurrence rate than those whose DCIS was ER-/PR-, but the recurrence rate was not different for those whose DCIS was ER+/PR+ and those whose DCIS was ER+/PR- again leaving the independent value of the PR status in question.

The value of knowing the ER status depends upon the subsequent utilization of endocrine therapy for those women whose DCIS was ER+. A National Cancer Database study by researchers at the Mayo Clinic examined factors influencing the use of hormonal therapy for DCIS patients. They found that endocrine therapy was offered much more often in patients receiving radiation therapy compared to mastectomy (62.7% vs, 29.1%; $p < 0.001$) (Nguyen et al., 2017). Over time, there was a decrease in the inappropriate use of hormonal therapy for patients who were ER negative or who underwent a bilateral mastectomy. None of our four ER negative patients were offered hormonal therapy. PR status was not considered in this Mayo Clinic study.

Following a mastectomy, the utilization of endocrine therapy is for risk reduction towards the development of DCIS or invasive cancer in the contralateral breast, and the hormone receptor status of the DCIS from the surgically removed index breast should not be relevant. Studies from both the Female Group Health Cooperative, which serves approximately 600,000 residents in Washington State (Nichols et al., 2016) and from the North Carolina Central Cancer Registry (Anderson et al., 2017) demonstrated that women undergoing a mastectomy were less likely to receive endocrine therapy for contralateral risk reduction when compared to women undergoing breast conserving surgery.

The cost of delivering medical care is becoming increasingly more relevant. Medicare reimbursement including the pathologist interpretation is \$176.36 for each stain. For the 15 of the original 67 patients (22%) thought to have DCIS at biopsy but were found at definitive surgery to have invasive cancer, the determination of the ER and PR status from the biopsy specimens cost \$5,290.80 and was of no value. Determining the PR status for any of the 67 DCIS patients cost \$11,816.12 and was of no value. Given that 63,960 women were estimated to be diagnosed with DCIS in the United States in 2018, over \$11 million could be saved simply by eliminating PR testing for DCIS specimens.

In August 2016 a report was published from the John Hopkins Hospital claiming that reflexively testing all breast core needle biopsy specimens showing ductal carcinoma in situ (but no invasive cancer) for both ER and PR was an unnecessary exercise that costs the United States \$35 million annually (VandenBussche et al., 2016). This figure of potential savings incorporates savings not only from eliminating PR determination, but also the unnecessary cost of the receptor analysis on the core biopsy specimens from patients found either at the time of definitive surgery to have either invasive cancer or a higher grade DCIS component.

Our study was of comparable size to that of the Johns Hopkins Hospital. They studied 58 patients with DCIS alone on core biopsy, of whom seven had invasive cancer upon definitive surgery (12%). The ER status was thought to have impacted management in at most 16/49 patients with ER positive pure DCIS (33%). We had 15/67 patients with invasive cancer (22%). We had a much higher rate of patients being offered endocrine therapy for ER positive DCIS (31/39=79%), and 16/39 accepted endocrine therapy (41%).

Our study suffers from a relatively small sample size, but it confirms the results from the John Hopkins Hospital study that a significant number of patients thought to have only DCIS on their core biopsy specimens are later

found to have either an invasive component or a higher grade DCIS component at the time of breast conserving surgery or mastectomy. Both studies question the value of determining the receptor status until after the definitive surgical specimen is obtained.

5. Conclusions

A significant proportion (29%) of patients with DCIS alone on core biopsy had either an invasive component at the time of definitive surgery or a higher grade DCIS component. An additional 14/46 (30%) of patients chose mastectomy, for whom consideration of adjuvant endocrine therapy for contralateral risk reduction did not depend on the receptor status of the index DCIS.

Cost savings could be realized if the determination of ER is deferred until after definitive surgery. Determination of PR can be omitted entirely.

Table 1. Patient Characteristics and Corresponding Number of Patients

Attribute		Median (Range)	Frequency
Age (years)		60 (46 to 87)	--
Size (mm)	Breast conservation	6.5 (0 to 50)	--
	Mastectomy	9.0 (0 to 70)	--
Focality	Single focus	--	40
	Multifocal	--	6
Grade	Grade 1	--	9
	Grade 2	--	20
	Grade 3	--	16
	Not graded	--	1
ER status	Positive:	--	39
	Negative	--	4
	Unknown	--	3
Progesterone	Positive	--	37
	Negative	--	6
	Unknow:	--	3

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