Surgery 166 (2019) 509–514

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

Evaluating patterns of utilization of gene signature panels and impact on treatment patterns in patients with ductal carcinoma in situ of the breast

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ARTICLE INFO

Article history:
Accepted 16 April 2019
Available online 20 July 2019

ABSTRACT

Background: Broad patterns of use of the gene signature panel Oncotype DX DCIS and its large-scale impact on postoperative administration of radiation therapy in women with ductal carcinoma in situ of the breast remain unclear. This study sought to evaluate the patterns of use of this gene signature panel in women with ductal carcinoma in situ and the impact of these tools on postoperative radiation therapy administration.

Methods: The National Cancer Database was queried for women with ductal carcinoma in situ treated with breast-conserving therapy who had information regarding whether a gene signature panel was performed between 2010 and 2015. Demographic characteristics, the characteristics of their ductal carcinoma in situ, and whether they received postoperative radiation therapy were compared among patients who did have a gene signature panel performed and those who did not. Patterns of radiation therapy administration were also evaluated based on the recurrence risk score by the gene signature panel.

Results: Gene signature panel use increased over time, with a sharp increase in utilization occurring in 2015 (8.0% in 2015 vs 4.4% in 2014, $P < .001$). Patients with estrogen receptor–positive ductal carcinoma in situ were somewhat more likely to have a gene signature panel ordered (3.9% estrogen receptor positive vs 1.7% estrogen receptor negative, $P < .001$), as were patients with lower-grade ductal carcinoma in situ (4.5% grade I/II vs 3.1% grade III, $P < .001$). Gene signature panel utilization was associated with a decrease in the administration of postoperative radiation therapy (48.6% gene signature panel vs 83.4% no gene signature panel, $P < .001$). Among patients in whom a gene signature panel was performed, postoperative radiation therapy was administered in 81.9%, 72.0%, and 35.9% of patients with high-, intermediate-, and low-recurrence scores, respectively.

Conclusion: Gene signature panel use in patients with ductal carcinoma in situ has increased over time and is more commonly used in women with lower-risk, clinicopathologic features to determine the magnitude of benefit afforded by radiation therapy. Gene signature panel use is associated with decreased rates of postoperative radiation therapy administration, particularly among patients with scores suggesting a low rate of recurrence.

Introduction

Gene signature panels (GSPs) that predict the likelihood of recurrence and, in certain instances, response to chemotherapy have become widely used in the treatment of invasive breast cancer.[1–4] Indeed, these tests provide information that helps to guide decision making with respect to postoperative chemotherapy and have been associated with overall decreased rates of

Presented at the 76th Annual Meeting of the Central Surgical Association, Palm Harbor, FL.

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https://doi.org/10.1016/j.surg.2019.04.044
0039-6060/

postoperative chemotherapy in patients with invasive breast cancer.[2,5–7]

In December 2011, Oncotype DX DCIS (ODX DCIS; Genomic Health, Inc., Redwood City, CA), a validated GSP designed to predict recurrence risk, became available for patients with ductal carcinoma in situ (DCIS).[8–10] The ODX DCIS generates individualized estimates of the 10-year risk of local recurrence (DCIS or invasive) when treated with lumpectomy alone.[8] This GSP generates a score from an algorithm that includes 12 genes and has been validated with 2 cohort studies of patients with DCIS treated with lumpectomy alone. By providing information about the likelihood of DCIS recurrence, this test aimed to better inform decision making regarding whether to administer postoperative radiation therapy (RT) to these patients. Specifically, patients at low genetic risk of recurrence could be spared the morbidity associated with RT without affecting their development of recurrent DCIS.[8–10]

By 2020, an estimated 1 million women in the United States will be living with a diagnosis of DCIS compared with 500,000 in 2005.[11] Because DCIS is not an obligate precursor to invasive cancer, it is important to identify tools that incorporate the biologic behavior of the neoplasm to minimize both overtreatment and undertreatment. The ODX DCIS score can, therefore, be useful in potentially identifying candidates who may not need RT and in potentially justifying the decision for RT.[12]

Although previous work has demonstrated the effect using GSPs has had on clinical decision making in an academic setting, namely in selecting patients with DCIS in whom radiation therapy can be avoided safely, the effects of broad patterns of use of such panels and their large-scale impact on postoperative RT administration remain unclear.[10] This study sought to evaluate the patterns of use of GSPs in women with DCIS and the impact of these tools on postoperative RT administration.

Methods

Data acquisition

The National Cancer Database was queried for women with DCIS treated with breast-conserving therapy, without a history of preoperative RT, who had information regarding whether a GSP was performed between 2010 and 2015. A schematic detailing the algorithm used for acquisition of the study dataset can be found in supplemental Fig 1.

Patient comparison

Patient demographic characteristics, DCIS characteristics, and whether they received postoperative RT were compared among patients who did have a GSP performed and those who did not. Demographic characteristics included age at diagnosis, ethnicity, insurance status, type of treating facility, and household income. DCIS characteristics included size in centimeters, estrogen receptor (ER) status, and DCIS grade. Receipt of postoperative RT was assessed for the entire cohort and for each DCIS grade subgroup. Patterns of RT administration and postoperative hormone therapy use were also compared among patients undergoing GSP evaluation based on recurrence risk score (<39 [low],[13] 39–54 [intermediate], and ≥55 [high]). Finally, we assessed the association between pathologic risk (with low risk defined as low or intermediate grade, tumor size <2.5 cm, and negative margins[14]) and ODX DCIS recurrence risk score.

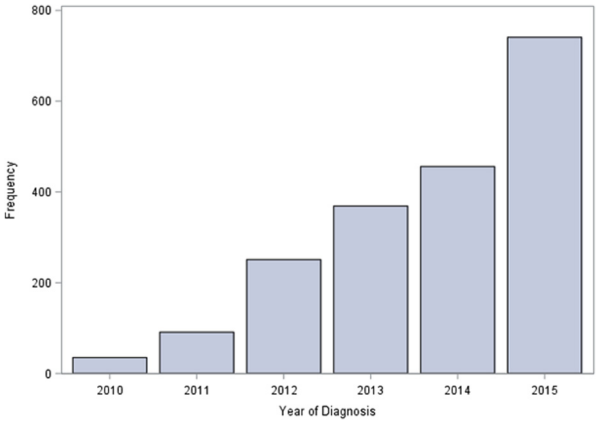

Fig 1. Multigene signature panel use for DCIS, 2010–2015.

Statistical analysis

Categorical variables were performed using χ^2 analysis or Fisher exact tests, as appropriate. Continuous variables were compared using two-tailed Student's *t* tests. All analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC).

Results

Of 55,741 women with DCIS who underwent partial mastectomy and had information regarding postoperative RT and utilization of a GSP, 1,943 (3.5%) women had a GSP performed. GSP use increased over time, with a sharp increase in utilization occurring in 2015 (8.0% in 2015 vs 4.4% in 2014, $P < .001$) (Fig 1). Patients who had a GSP performed were similar (median age 60 years with a GSP vs age 61 years with no GSP, $P < .001$) but were more likely to have private insurance (62.9% GSP vs 57.6% no GSP, $P < .001$) and have a household income >$68,000 (45.9% GSP vs 40.5% no GSP, $P < .001$) (Table I).

Regarding characteristics of DCIS, patients who underwent GSP evaluation tended to have similar-sized DCIS (7 mm GSP vs 8 mm no GSP, $P < .001$) (Table II). Patients with ER-positive DCIS were somewhat more likely to have a GSP ordered than patients with ER-negative DCIS (3.9% ER positive vs 1.7% ER negative, $P < .001$). Similarly, patients with lower-grade DCIS were somewhat more likely to have a GSP ordered than those with high-grade DCIS. GSP utilization was associated with a decrease in the administration of postoperative RT (48.6% GSP vs 83.4% no GSP, $P < .001$). On subgroup analysis by DCIS grade, GSP use was associated with the greatest decrease in RT among patients with grade II DCIS (48.6% GSP vs 73.2% no GSP, $P < .001$). Among patients in whom a GSP was performed, postoperative RT was administered in 81.9%, 72.0%, and 35.9% of patients with high-, intermediate-, and low-recurrence scores, respectively (Table III). Interestingly, postoperative hormone therapy was administered in 65%, 78%, and 80% of patients with high-, intermediate-, and low-recurrence scores, respectively.

Finally, regarding the association between pathologic risk and the ODX DCIS–derived recurrence score, among patients with low pathologic risk, 78% had a low recurrence score, 13% had an intermediate recurrence score, and only 9% had a high recurrence score. Meanwhile, 45% of patients with high pathologic risk (ie, non–low risk) had a low recurrence score, 27% had an intermediate recurrence score, and 28% had a high recurrence score.

Table I
Demographic information

	GSP ordered (n = 1,943)	No GSP ordered (n = 53,798)	*P* value
Age (y) (median [interquartile range])	60 (52–68)	61 (52–69)	<.001*
Ethnicity	*n* = 1,943	*n* = 53,269	
White	1,589 (81.8)	43,541	.16
Black	221 (11.4)	6,850	
Other	133 (6.8)	2,876	
Insurance	*n* = 1,923	*n* = 53,136	
Private	1,210 (62.9)	30,611 (57.6)	<.001
Medicare	617 (32.1)	18,584 (35.0)	
Medicaid	61 (3.2)	2,581 (4.9)	
Other government	17 (0.9)	808 (1.5)	
Uninsured	18 (0.9)	552 (1.0)	
Facility type	*n* = 1,921	*n* = 53,175	
Comprehensive community cancer program	917 (47.7)	25,436 (47.8)	.038
Academic/research program	603 (31.4)	16,197 (30.5)	
Integrated cancer network program	248 (12.9)	6,334 (11.9)	
Community cancer program	153 (8.0)	5,208 (9.8)	
Income quartile	*n* = 1,940	*n* = 53,682	
<$38,000	228 (11.8)	7,103 (13.2)	<.001
$38,000–$47,999	334 (17.2)	10,476 (19.5)	
$48,000–$67,999	487 (25.1)	14,350 (26.7)	
>$68,000	891 (45.9%)	21,753 (40.5)	

* Questionable clinical importance.

Table II
DCIS details

	GSP ordered (n = 1,943)	No GSP ordered (n = 53,798)	*P* value
Size of DCIS (mm) (median, [interquartile range])	7 (4–13)	8 (4–15)	<.001
ER positive	1,804 (92.8%)	44,911 (83.4%)	<.001
DCIS grade	*n* = 982	*n* = 23,873	
I	241 (24.5%)	4,769 (20.0%)	<.001
II	445 (45.3%)	9,826 (41.2%)	
III	296 (30.1%)	9,278 (38.9%)	

Table III
Postoperative radiation therapy details

	GSP ordered (n = 1,943)	No GSP ordered (n = 53,798)	*P* value
Postoperative radiation administered	945 (48.6%)	39,369 (73.2%)	<.001
DCIS grade			
I	62/211 (29.4%)	2,907/4,734 (61.4%)	.01
II	175/399 (43.9%)	7,103/9,758 (72.8%)	<.001
II	176/255 (69.0%)	7,623/9,216 (82.7%)	<.001

Discussion

Our study demonstrates that the use of GSPs nearly doubled from 4.4% in 2014 to 8% in 2015. In 2011, the ODX DCIS multigene assay for DCIS was made available to predict the rate of 10-year local recurrence and guide treatment decision making based on the following categories: low risk (score <39), intermediate risk (score 39–54), and high risk (score ≥55).[8] This assay was validated externally in 2013 using a cohort from the Eastern Cooperative Oncology Group E5194 study, which was a nonrandomized, prospective trial evaluating operative excision without RT for selected patients.[8] The 10-year risk of developing a local recurrence was 10.9% for low-risk, 16.1% for moderate-risk, and 15.1% for high-risk patients. In 2015, Rakovitch et al validated the ODX DCIS score in a broader population of 571 patients, with a greater score predicting both invasive and DCIS recurrence regardless of ER status (hazard ratio for local recurrence 1.68; 95% confidence interval 1.08–2.62, $P = .02$ on multivariable analysis).[9] The observed increased utilization of ODX DCIS testing seen in our study coincided with the results of the second external validation using a more clinicopathologically diverse population.

The present study also compared the characteristics of patients who received GSP testing with those who did not. There was a statistically significant increased rate of receiving a GSP for those who had private insurance and household income >$68,000. Disparities in the receipt of multigene tumor assays have also been identified for the Oncotype DX score for invasive breast cancer. Kozick et al found that Oncotype DX use for invasive breast cancer testing rose with income quartile and in patients with private insurance.[15] Bhutiani et al found that testing with a multigene signature panel for invasive cancer was obtained more frequently in young, white, and insured patients.[5]

The adoption of GSPs in DCIS patients has been slow. A survey of surgeons and radiation oncologists located in Georgia and Los Angeles showed that only about one-third of surgeons (39.3%) and radiation oncologists (35.3%) would order the ODX DCIS score to determine the risk of local recurrence.[16] One reason may be its lack of cost-effectiveness. Raldow et al utilized a Markov model simulation of the E5194 patient population to evaluate the cost-effectiveness of incorporating the ODX DCIS score into practice; although using the ODX DCIS score decreased the proportion of

patients undergoing RT, no strategy was determined to be cost-effective and very utility-sensitive, highlighting the importance of patient engagement in the decision-making process.[17] Furthermore, it is unclear how much the GSP influences decision making regarding adjuvant RT. Alvarado et al demonstrated that recommendations for RT changed in 31.3% of 115 patients after the score was obtained, with RT recommended for 73% of the patients pre-assay compared with 59.1% postassay.[10]

In this study, GSP testing was associated with a decrease in the rate of adjuvant RT (48.6% GSP vs 83.4% no GSP, $P < .001$). There is no individual-level information regarding the influence of the score on the decision-making process, but there is a marked decrease in the utilization of adjuvant RT in those patients who received the ODX DCIS test. The standard treatment recommendation for patients undergoing breast conservation treatment for DCIS is RT. This recommendation is based on 5 randomized clinical trials (NSABP B-17, EORTC 10853, SweDCIS, UK/ANZ DCIS, and RTOG 9804), all of which demonstrated a benefit in decreasing invasive and noninvasive in-breast tumor recurrence of >50% (relative risk reduction).[18] The current guidelines of the National Comprehensive Cancer Network recommend lumpectomy alone for DCIS only as a category 2B recommendation when the patient is low risk.[19] Tools such as the ODX DCIS score can assist with the decision about use or omission of RT in a multidisciplinary setting and with the patient's input.[20] But, because the test is not predictive of the benefit of RT, like Oncotype DX is for predicting the benefit of chemotherapy for invasive cancer, the information provided is only prognostic, and patients and physicians should evaluate their level of comfort with that patient's particular risk of recurrence without adjuvant radiotherapy. This inability of the Oncotype DX to provide evidence of the benefit of RT is likely why the use of oncotype DCIS is less prevalent than that for the oncotype for invasive cancer. Given the substantial evidence supporting the use of RT after lumpectomy for patients with DCIS for the prevention of local recurrence, Oncotype DX DCIS would benefit patients with low-risk lesions based on clinicopathologic criteria who preferred to avoid postoperative RT. At the present time, Oncotype DX DCIS, in our opinion, serves as an additional piece of evidence supporting a decision to omit postoperative RT in low-risk patients, where the risk of recurrence might be low enough that the costs and risks of RT would outweigh the benefits. It is important to remember, though, as pointed out by Rakovitch et al, that even the patients with low clinicopathologic risk of recurrence and a low recurrence score had a benefit from RT (10.1% [95% confidence interval 6.9–14.8] lumpectomy alone vs 6.0% [95% confidence interval 4.1–8.9] lumpectomy with RT); indeed, 74.1% of these patients had a low recurrence score and an overall recurrence rate of 13.9%.[21]

The concept of identifying low-risk DCIS patients who may avoid overtreatment is also a subject of ongoing clinical trials. The LORIS and LORD (LOw Risk DCIS) trials will provide important information about the risk of invasive cancer over time in an observed population with DCIS with the intent to also minimize overtreatment.[13,22] In the United States, the COMET (Comparison of Operative to Monitoring and Endocrine Therapy) trial is accruing 1,200 patients with hormone-positive, low-risk DCIS and randomly assigning patients to guideline-concordant care versus endocrine therapy alone.[23] These results are eagerly awaited.

The strength of our study is the ability to review a large population from institutions accredited by the Commission on Cancer to evaluate trends in the utilization of ODX DCIS scores and radiation. Still, the results of this study should be interpreted with consideration of several limitations. The data used were derived from hospital-based data reporting and thus may be subject to coding errors. Moreover, the National Cancer Database lacks GSP information in a substantial fraction of patients and may be subject to some degree of selection bias because centers using GSPs in patients with DCIS are more likely to complete that field when submitting data to the National Cancer Database. In addition, the clinical importance of some observations, despite being "statistically significant," may be of marginal clinical significance. The data do not account for several confounders, including reimbursement for ODX DCIS by insurance providers over time and variable coverage among insurers. For example, the U.S. Centers for Medicare and Medicaid Services currently covers the use of ODX DCIS, but private insurance coverage varies substantially. Finally, several of the cited studies concluded after the end of this study's time period. Therefore, this study's results, which demonstrate slow but growing utilization of ODX DCIS that falls short of ODX utilization in management of invasive breast cancer, may not reflect the most recent trends in ODX DCIS use and effects on RT administration in the United States.

In conclusion, GSP use in patients with DCIS has increased over time and is used more commonly in women with lower-risk, clinicopathologic features (ie, small DCIS size, low tumor grade, ER positive) to determine the magnitude of benefit afforded by RT. GSP use is associated with decreased rates of postoperative RT administration, particularly among patients with low recurrence scores.

Funding/Support

This work was not funded by any organizations.

Conflict of interest/Disclosure

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.surg.2019.04.044.

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Discussion

Dr Sarkis Meterissian (Montreal, QC): I would like to thank the Association for the privilege of discussing this interesting paper, and thank you, Dr. Bhutiani, for the manuscript.

I want to say that this paper is very timely, and I think people in the audience who operate on breast cancer ask themselves whether they are overtreating this disease, especially because DCIS is rapidly rising with the increasing use of mammography.

There are 3 ongoing international studies. The LORD, LORIS, and COMET trials looking at this very point—are we overtreating DCIS? In fact, in none of these trials do they use the Oncotype DX DCIS, so I will come back to that in my question. These trials are even looking at no surgery for DCIS, as you know.

When I was reading your paper, I asked myself a few questions, and I just want to limit them to maybe 3 so others can have a chance.

What is the percentage of cases where there was discordance between the clinicopathologic score, which includes the ER, PR, the grade, the size, versus the Oncotype DX score? I will give you an example. Rakovitch, from the Ontario group, published 286 patients, and in their paper, 74.1% were low risk. These are patients with low-risk pathologic factors, and 10% had a high DCIS score. So as a clinician, I think that's important. I am wondering if you can tell us where there's discordance. That's number one.

The second thing I want to ask you, since you went back to 2010—and this may be a limitation of looking at large datasets—could you look at recurrence data? In other words, you are telling us that radiation therapy had different uptakes, but does that translate into any recurrence data? Did the right decision get made when they did not give radiation?

In your paper, you looked at the use of hormone therapy. So I was wondering, could you capture any differences in the use of antihormone therapy, Tamoxifen, and the use of the Oncotype DX score?

I will throw 1 last question at you. If it's so important, why do none of the international trials incorporate the DCIS score into their algorithm. I would like to just know your thoughts about that.

Otherwise, I enjoyed your paper, and I think it's timely because more and more of us are looking at ways of not treating DCIS as aggressively as we used to.

Dr Neal Bhutiani: With respect to the discordant aspect, we have not looked at that, but we will be incorporating that into our paper. We do have all the information in the National Cancer Database.

Point number 2. Unfortunately, while recurrence is captured by the National Cancer Database, because of the number of missing data points, they do not report it in the National Cancer Database. If they did, we would have a much easier time answering a lot of these very salient questions with respect to recurrence after treatment.

Also, with hormone therapy, we didn't look specifically at whether the patients received Tamoxifen and how that plays into their Oncotype DX DCIS recurrence score. We can certainly include that in our paper.

And lastly, with respect to the trial design, like I mentioned, I think some of this has to do with the amount of data coming out very recently. More and more data is being published that's validating Oncotype DX DCIS, and large meta-analyses are demonstrating the utilization and validation of the Oncotype DX DCIS score.

I think another thing that we see in the United States has to do with, like I mentioned, insurance coverage for the tests among patients. Medicare, like I mentioned, does cover it. I don't know when CMS started doing that. There are also pathways to help patients navigate amongst their insurers. There is a genetic assistance program that provides such assistance.

However, the insurance coverage varies, I think, from region to region and with different insurers. That makes it somewhat difficult to employ it in the clinical trial.

Dr Stephen Grobmyer (Cleveland, OH): I would like to congratulate you on another great study looking at genomic signatures in breast cancer. I would like to begin by echoing our interest and many others' interest in developing new nonoperative, less-aggressive strategies for treating DCIS and add to the list of mentioned studies one that we are participating in, which involves a topical or lotion preparation of Tamoxifen that's actually applied to the breast that we think has a role in the future of preventing breast cancer, and maybe in treating DCIS.

I would like to ask you 2 questions that are related. The bigger question is, should we be doing this test at all? You observed that almost 40% of the patients in your study with a low score received radiation therapy. So it begs the question, why are tests being ordered if we are not going to act on that? Do we have a job to educate people, or are we ordering too many tests?

Dr Neal Bhutiani: With respect to should we be doing the test, I think when you look at the first slide that I presented, which is the value of radiation therapy and decreasing local recurrence in patients with DCIS, essentially, the test is set out against very strong odds, and you have to prove to yourself or give really strong evidence that a patient may not benefit from it. As a result, you have to weigh the costs and benefits of your default treatment decision, which is to radiate the patient after breast-conserving surgery, against not doing that.

So perhaps in patients with low-grade DCIS, who have low-risk clinical pathologic characteristics, I think that's the subset of patients in whom you can order the tests, and it will be easier to convince yourself to not administer radiation, so that's perhaps, in my mind, at least, the group that would benefit most from the tests being ordered.

With respect to education, I do think that plays a huge role in proper use of this test. Just like with gene signature panels and invasive breast cancer, I think there's a significant educational component to this—educating medical oncologists on its use and having a larger discussion about what's the most appropriate subset of patients in whom to use this test and then how to act on that information in multidisciplinary tumor boards and so forth—that I think would be hugely beneficial moving forward.

Dr Nicolas Ajkay (Louisville, KY): I want to also congratulate you on a wonderful presentation on genomic markers for ductal carcinoma in situ. I want to make a brief comment related to what Dr Grobmyer asked. Should we order these tests or should we not, based on the fact that we know from prior randomized clinical trials that there is a 50% reduction in the risk of local recurrences for patients with DCIS treated with lumpectomy and radiotherapy?

I think that, in practice, the test may be useful for those patients who are perceived to be at low risk of recurrence who are reluctant to have radiation. Then, you can sort out their true risk of recurrence. If they have low pathologic features and they don't want to have radiation, the test may tease out those patients that are at lower risk of recurrence without radiation, and if they are accepting of that lower risk, then they might be able to avoid radiation. Otherwise, the standard treatment continues to be radiation. Thank you very much.