ORIGINAL ARTICLE

Initial Experience with Surgical Treatment Planning in the Newly Diagnosed Breast Cancer Patient at High Risk for *BRCA-1* or *BRCA-2* Mutation

Alan J. Stolier, MD, FACS,* George M. Fuhrman, MD, FACS,† Lynnette Mauterer, MN,‡ John S. Bolton, MD, FACS,† and Duane W. Superneau, MD§

**Department of Surgery, Louisiana State University, Baton Rouge, Louisiana; and †Department of Surgery and §Section of Medical Genetics, ‡Ochsner Clinic Foundation, New Orleans, Louisiana*

■ **Abstract:** Despite an abundance of information available for dealing with patients with *BRCA-1* and *BRCA-2* mutations, little guidance is available to assist the surgeon in dealing with the genetically high-risk patient recently diagnosed with breast cancer. A retrospective review was undertaken of 170 patients who underwent genetic counseling and testing over a 3-year period from March 2000 to March 2003. Forty-three of the 170 patients tested were diagnosed with breast cancer prior to genetic testing. Nine patients (20.9%) tested positive for a deleterious mutation. Fifty-eight percent underwent genetic counseling prior to definitive cancer surgery. Five of the 25 patients who underwent lumpectomy tested positive for a deleterious mutation. Testing results became available during systemic therapy or radiation was delayed until results were known. After counseling, all five patients testing positive went on to bilateral prophylactic mastectomy and reconstruction. None had radiation therapy. Because of a strong family history, eight patients elected to undergo prophylactic mastectomy and reconstruction prior to obtaining genetic test results; and despite compelling histories, all eight tested negative for a mutation. Treatment algorithms are developed to manage patients that are first discovered to be at high risk for a *BRCA-1* or *BRCA-2* mutation at the time they are diagnosed with breast cancer. Patients diagnosed with breast cancer who are discovered to be at high risk for a genetic mutation should undergo counseling prior to definitive surgery. This maximizes the time that patients have to consider options for prophylaxis and monitoring should their test be positive. It also prevents women who would otherwise be candidates for breast preservation from undergoing unnecessary radiation therapy should they chose prophylactic mastectomy in the face of a positive test. ■

Key Words: *BRCA-1*, *BRCA-2*, breast cancer, breast reconstruction, genetic counseling, genetic testing, prophylactic mastectomy, radiation therapy, tamoxifen

Women harboring a deleterious mutation of the *BRCA-1* or *BRCA-2* gene may have as high as an 85% lifetime risk of developing breast cancer (1). Women with a strong family history of breast cancer or who have a family member who has tested positive for a mutation generally undergo genetic counseling prior to testing. For some women, however, the possibility of a *BRCA-1* or *BRCA-2* mutation is not considered until they are diagnosed with breast cancer. Because the results of genetic testing may not be available for up to 4 weeks, difficulties may arise in determining how to apply various cancer treatment options. Although unlikely to impact the oncologic approach or outcome, delays in treatment of this magnitude may add substantial anxiety to a patient already dealing with a life-threatening illness.

This retrospective study was undertaken in order to review our initial experience with genetic testing for deleterious mutations in the *BRCA-1* and *2* genes and to determine how genetic testing was incorporated into the overall cancer treatment plan as well as its possible impact on surgical therapy. It was hoped that a treatment planning algorithm might be developed for these newly diagnosed patients.

MATERIALS AND METHODS

Following approval by the Institutional Review Board, a retrospective record review was undertaken of those patients who had undergone genetic testing for deleterious mutations in the *BRCA-1* and *2* genes. All patients were tested during the 3-year period between March 2000 and

Address correspondence and reprint requests to: Alan Stolier, MD, New Orleans Cancer Institute, Suite 110C, New Orleans, LA 70115, USA, or e-mail: astoli@lsuhsc.edu.

 1075-122X/04/$15.00/0
The Breast Journal, Volume 10, Number 6, 2004 475–480

March 2003. Patients were identified from records of the Hereditary Breast and Ovarian Risk Assessment Program of the Lieselotte Tansey Breast Center at the Ochsner Clinic Foundation. All patients referred to the center undergo genetic counseling and mapping of their family pedigree by a nurse practitioner. The risks of carrying the genetic mutation are then assessed by BRCAPRO, as well as the current updated database supplied by Myriad Genetics, Inc. (www.myriad.com). A surgical oncologist or medical geneticist then evaluates this information and a recommendation is made as to whether genetic testing should be offered. After obtaining appropriate consent, all blood samples for genetic testing were sent to Myriad Genetics, Inc. (Salt Lake City, UT).

Patients testing positive then underwent further counseling, at which time all treatment, prophylaxis, and monitoring options were discussed. Risks of ovarian cancer as well as options for monitoring and prophylaxis were also covered during counseling sessions. Gynecologic oncology consultation was also routinely obtained for those patients testing positive for a mutation or with a strong family history of ovarian cancer. At the Ochsner Clinic, careful monitoring for breast cancer consisted of twice-yearly clinical examination and once-yearly mammography. Monitoring for ovarian cancer consisted of twice-yearly clinical examination as well as transvaginal ultrasound and CA-125 levels.

Individual records were analyzed for the presence or absence of genetic counseling at the time of initial diagnosis. The timing of cancer surgery in relation to prophylactic surgery, radiation, and chemotherapy was also examined.

RESULTS

From March 1, 2000 to March 1, 2003, 170 *BRCA* analyses were carried out for detection of *BRCA-1* and *BRCA-2* mutations (Table 1). Of these, 33 (19.4%) were found to have a deleterious mutation. Twenty-five patients (14.7%) underwent single-site testing, which was performed in patients with known family mutations. Twenty-five patients (14.7%) were of Ashkenazi heritage, and all had multisite testing for the three known founder mutations in the *BRCA-1* and *BRCA-2* genes. The remaining 120 patients (70.6%) underwent comprehensive *BRCA-1* and *2* analyses.

Of the 170 patients who underwent testing, 21 used numbered codes and therefore records were unavailable for review. Of the remaining 149 patients, 43 were diagnosed with breast cancer prior to genetic testing and constitute the subjects of this study.

The median age of this group of women was 47.9 years (range 24–76 years). Eight patients had a prior diagnosis of breast cancer, and for these patients it was the diagnosis of a second contralateral cancer that led to genetic counseling and testing. For the remaining 35 patients, this represented the initial breast cancer diagnosis.

Of the 43 genetic tests, 9 (20.9%) were positive for a deleterious mutation and 34 were negative. Five of the nine were positive for *BRCA-1* mutation and four were positive for a mutation in the *BRCA-2* gene. Five of the 43 patients tested were of Ashkenazi heritage. All underwent multisite testing and all tested negative for a deleterious mutation.

The timing of genetic counseling, broaching the subject of the possible hereditary nature of the patient's breast cancer, fell generally into three groups (Table 2). The first group of patients (58.1%) underwent genetic counseling prior to undergoing their initial breast cancer surgery. In most instances the subject was addressed on the same visit in which the patients learned of their cancer diagnosis. Most underwent testing either just prior to surgery or during the early postoperative period when insurance issues were being clarified. The second group (27.9%) underwent counseling either during treatment or just after all treatment (chemotherapy and/or radiation) had been completed. The third group underwent counseling at a time distant from the completion of treatment. In two instances the timing of genetic counseling could not be accurately determined.

Initial surgical therapy was lumpectomy in 25 patients, unilateral mastectomy in 8 patients, and bilateral mastectomy in 10 patients (Table 3). Of the 25 patients initially

Table 1. Genetic Tests Performed

Genetic test	Number of patients (%)
Total tests performed	170
Comprehensive	120 (70.6)
Multisite	25 (14.7)
Single-site	25 (14.7)

Table 2. The Relationship of Genetic Counseling to the Time of Definitive Breast Cancer Surgery

Timing genetic counseling	Number (%)
Prior to initial surgery	25 (58.1)
3–12 months after surgery	12 (27.9)
>12 months after surgery	6 (13.9)
Unknown	2 (4.7)

Table 3. Initial Surgical Procedure with Incidence of Prophylactic Mastectomy and Positive Genetic Testing

Initial surgical procedure	Number	Prophylactic mastectomy	Number testing positive (%)
Lumpectomy	25	5	5 (20)
Unilateral mastectomy	8	2	2 (20)
Bilateral mastectomy	10	N/A	2 (20)

undergoing breast-conserving surgery, 5 were found to have deleterious mutations. All five patients underwent repeat counseling, in which further options were discussed. These included bilateral prophylactic mastectomy and reconstruction, the National Surgical Adjuvant Breast and Bowel Project (NSABP) Study of Tamoxifen and Raloxifene (STAR) clinical trial, and monitoring. All five patients elected to undergo bilateral mastectomy. Three required chemotherapy and underwent bilateral mastectomy following chemotherapy whereas two did not require chemotherapy and underwent bilateral mastectomy shortly after the mutation was discovered. In the former three patients, results of testing became available during systemic therapy, while in the latter two patients, radiation therapy was delayed until results of genetic testing became available. All had immediate breast reconstruction. None of the patients who had lumpectomy followed by prophylactic surgery underwent radiation therapy. None of the 15 patients who tested negative underwent prophylactic surgery and all received radiation therapy to the affected breast.

Eight patients had unilateral mastectomy as their initial surgical therapy. Six tested negative and two tested positive. Of the six who tested negative, one underwent contralateral prophylactic mastectomy despite a negative test. Of the two patients testing positive, one had not completed chemotherapy at the time of this study and the other had undergone a previous mastectomy for breast cancer in the past.

Ten women underwent bilateral mastectomy as their initial surgical therapy. None of the 10 women knew the results of their genetic tests prior to surgery. Two tested positive for a deleterious mutation in the *BRCA-2* gene. Both had a history of a contralateral cancer; one diagnosed synchronously and one treated by lumpectomy 10 years prior. Indications for genetic testing in these women are noted in Table 4. Of the remaining eight women who were diagnosed with unilateral cancer and chose to undergo bilateral mastectomy prior to obtaining genetic test results, none tested positive for a deleterious mutation.

Table 4. Indications for Genetic Testing

Age (years)	Indication(s) for testing	Results of genetic test
60	Bilateral breast cancer, family history	Negative
43	Bilateral breast cancer	Positive
62	Family history	Negative
54	Family history	Negative
31	Family history, age	Negative
62	Prior ovarian cancer	Negative
54	Ashkenazi	Negative
58	Sister *BRCA-2* positive	Negative
36	Age, family history	Negative
29	Age, family history	Negative

DISCUSSION

Women who are found to have deleterious mutations in the *BRCA-1* and *BRCA-2* genes in the absence of a diagnosed breast cancer are able to undergo genetic counseling and make decisions about available options within a time frame that is suitable to their own particular needs and lifestyle. On the other hand, women diagnosed with breast cancer who have a family history suggestive of a hereditary breast cancer face a multitude of problems, not the least of which is how or even whether to incorporate this knowledge into the initial surgical approach to their breast cancer. Time constraints will generally prevent the use of genetic testing information when deciding whether to incorporate prophylaxis into the initial surgical procedure. There are exceptions. Many women who have a very strong family history of breast cancer, and after counseling, wish to have prophylactic mastectomy prior to knowing the results from genetic testing. Similarly some family histories are so compelling as to make prophylactic surgery a reasonable alternative to conventional therapy from the outset. Each of these circumstances requires evaluation on a case-by-case basis as well as genetic counseling as to estimated risks and alternatives.

For a majority of women, however, the risk of testing positive is low enough to warrant waiting for results prior to discussing options for prophylaxis or observation. In our own series of 170 tests carried out on patients with and without breast cancer, only 33 (19.4%) were positive. Similarly Shih et al. (2) reported a positive test rate of 22.6% in similar patients tested from the University of Michigan and University of Pennsylvania. This also compares favorably to a series by Frank et al. (3), reporting results from testing carried out at Myriad Genetics, in which mutations were identified in 17.2% of 10,000 tested individuals. It should also be noted that in our series, of the eight women with unilateral breast cancer who elected bilateral prophylactic mastectomy prior

knowing the results of genetic testing, none tested positive for a mutation.

In our series of 43 patients who underwent genetic testing following a diagnosis of breast cancer, 9 (20.9%) were noted to have a deleterious mutation. In the Myriad Genetics series, 4843 patients were diagnosed with breast cancer and 968 (20.0%) had a mutation (3). In most instances following a diagnosis of breast cancer, women undergo genetic testing because of a strong family history, young age, or a combination of both. In our series, three women who chose to undergo bilateral mastectomy with unilateral cancer had very compelling circumstances (Table 4). One had prior ovarian cancer and another was 29 years old at diagnosis with a strong family history. The third had a sister who had tested positive for a deleterious mutation of the *BRCA-2* gene. None of these women subsequently tested positive for a deleterious mutation. Based on these data, it would seem that in most instances it would seem prudent to wait for results of testing prior to proceeding with prophylactic surgery.

In a majority of our patients (Table 1), genetic counseling was initiated prior to the initial cancer surgery, and in most instances this occurred at the first meeting after diagnosis. There are literally hundreds of publications in the medical literature dealing with the risks and benefits of genetic counseling for hereditary breast cancer. However, most of these articles deal with counseling of high-risk patients who are cancer-free and not the patient recently diagnosed with breast cancer. Since the results of testing may take as long as 3 to 5 weeks, there are few situations in which waiting for tests results prior to initiating surgical therapy is practical. Clearly there are exceptions. One of our patients had prior ovarian cancer and five second-degree relatives with breast cancer. She was diagnosed with low-grade ductal carcinoma in situ (DCIS). After discussing the risk of invasive cancer as well as her options should she test positive, she elected to delay surgery until the results of testing were complete. When testing was positive for a *BRCA-2* mutation, bilateral mastectomy with immediate reconstruction was performed.

For those patients who are candidates for breast conservation, we recommend proceeding with breast-conserving surgery while insurance benefits are being determined and genetic testing performed (Fig. 1). If no chemotherapy is recommended, we recommend delaying radiation therapy until test results are available. If negative, one may proceed with radiation. If testing is positive, the patient can be counseled as to available options, which in our center includes careful monitoring, tamoxifen, or bilateral mastectomy with immediate reconstruction. If the patient chooses bilateral mastectomy, except for patients with more advanced disease, radiation therapy can be omitted from the treatment plan.

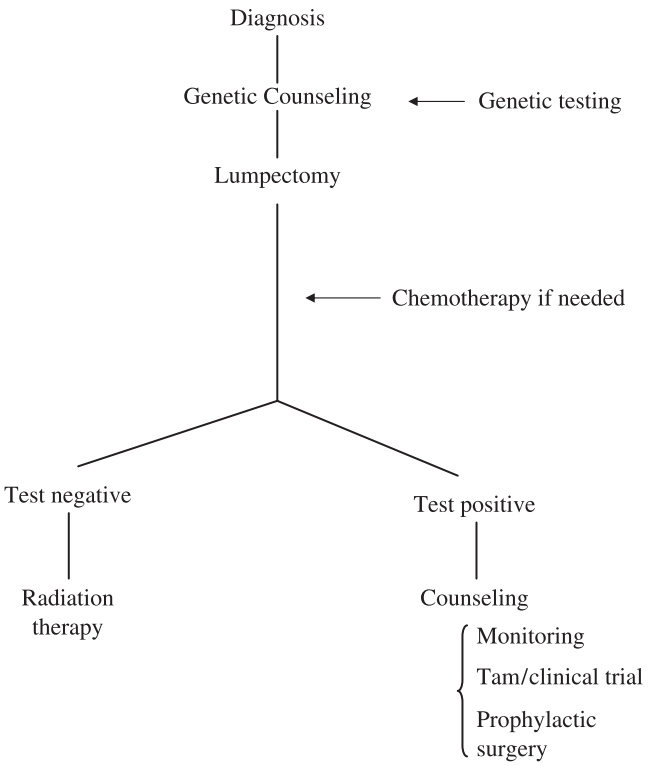

Figure 1. Algorithm for high-risk patients who are candidates for breast conservation.

Our approach to patients who are not candidates for breast-conserving surgery is somewhat more complex. In those in which silicone implant reconstruction is preferred, we recommend proceeding with unilateral mastectomy and immediate reconstruction (Fig. 2). If testing is negative, no further surgery is required. If testing is positive, further counseling is offered and the patient is presented with options for monitoring or prophylaxis. If the patient chooses to undergo prophylactic mastectomy, unilateral mastectomy and silicone implant reconstruction can be performed electively. Because reports of patients having radiation therapy after silicone implant reconstruction suggest a higher incidence of complications (4,5), we recommend delaying reconstruction until after radiation therapy in those women in whom radiation is likely to be part of the overall treatment plan.

Although there does not appear to be an increased complication rate from delayed autogenous reconstruction following radiation (6), others have reported significantly

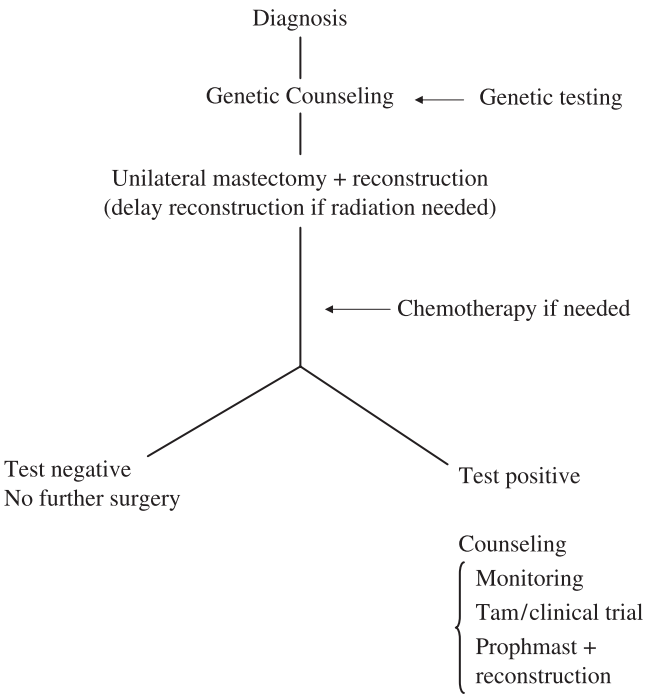

Figure 2. Algorithm for high-risk patients in whom mastectomy and implant reconstruction are planned.

poorer cosmetic results following radiation to the autogenous tissue flap (7,8). It is therefore our general recommendation that, as in silicone implant reconstruction, autogenous flap reconstruction be delayed until the completion of radiation therapy. However, these recommendations are complicated by the "single-use" nature of abdominal flaps. Use of abdominal flap reconstruction should, in most instances, not be performed in this group of patients until the results of genetic testing are available. In this situation decisions may be impacted by the degree of genetic risk and patient desires. Those with very high risk and/or very low risk tolerance may elect to proceed with prophylactic mastectomy from the outset.

A second option for autogenous reconstruction that would be applicable to those patients who are candidates for skin-sparing surgery would be a "delayed-immediate" reconstruction. Skin-sparing surgery and an expander or implant is inserted. If genetic testing is positive and the patient elects to undergo prophylactic surgery, then bilateral autogenous reconstruction can be carried out.

Based on our initial experience with *BRCA-1* and *BRCA-2* testing, and in particular, testing in the patient with a newly diagnosed breast cancer, two principles can be recommended. The first is that counseling regarding the possibility of hereditary breast cancer and genetic testing should be offered as soon as possible after the diagnosis. This allows maximum time to deal with insurance and other more personal issues. It also allows more time for education as to the various available options, as well as dealing with the profound psychological impact of this disease. The second principle is to delay radiation therapy where possible until genetic test results are known and further counseling can be obtained. Patients who choose to undergo prophylactic surgery will then have the opportunity to move rapidly once any systemic therapy is complete, eliminating the delay and cosmetic implications of breast radiation.

CONCLUSION

Many women are not found to be at high risk for a *BRCA-1* or *BRCA-2* mutation until they are diagnosed with breast cancer. In a retrospective review of our initial experience with breast cancer genetic testing, 58% of high-risk patients who are diagnosed with breast cancer undergo genetic counseling prior to definitive cancer surgery. This allows for maximum time for patients to consider options for prophylaxis should their test be positive. It also prevents women who would otherwise be candidates for breast preservation from undergoing unnecessary radiation therapy should they choose prophylactic mastectomy in the face of a positive test. In our series, eight women who were at extremely high risk for a gene mutation underwent prophylactic bilateral mastectomy prior to knowing their genetic test results. None of these women tested positive for a mutation. Except under extraordinary circumstances, it would seem prudent to withhold prophylactic surgery until genetic testing results are known.

REFERENCES

1. Ford D, Easton DF, Stratton M, *et al.* Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. *Am J Hum Genet* 1998;62:676–89.

2. Shih HA, Fergus J, Couch K, *et al.* BRCA1 and BRCA2 mutation frequency in women evaluated in a breast cancer risk evaluation clinic. *J Clin Oncol* 2002;20:994–99.

3. Frank TS, Manley SA, Olufunmilayo I, *et al.* Sequence analysis of BRCA1 and BRCA2: correlation of mutations with family and ovarian cancer risk. *J Clin Oncol* 1998;16:2417–25.

4. Panieri E, Lazarus D, Dent DM, Hudson DA, Murray E, Werner ID. A study of patient factors affecting reconstruction after mastectomy for breast carcinoma. *Am Surg* 2003;69:95–97.

5. Spear SL, Wolfe AJ. The coincidence of TRAM flaps and

prostheses in the setting of breast reconstruction. *Plast Reconstr Surg* 2002;110:478–86.

6. Disa JJ, Cordeiro PG, Heerdt AH, Petrek JA, Borgen PJ, Hidalgo DA. Skin-sparing mastectomy and immediate autologous tissue reconstruction after whole-breast irradiation. *Plast Reconstr Surg* 2003;111:118–24.

7. Rogers NE, Allen RJ. Radiation effects on breast reconstruction with the deep inferior epigastric perforator flap. *Plast Reconstr Surg* 2002;109:1919–24.

8. Netscher DT, Sharma S, Thornby J, *et al.* Aesthetic outcome of breast implant removal in 85 consecutive patients. *Plast Reconstr Surg* 1997;100:206–19.