

Hot Topics Scholarship Advocate Reports from the 2007 San Antonio Breast Cancer Symposium

Topic: Radiologic studies, including MRI

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Radiation Treatment for breast cancer: A Journey Through Time

Radiation therapy has an essential role in treatment for early stage breast cancer along with breast conserving surgery. Radiation along with lumpectomy has been an important component in the declining breast cancer mortality rate.

Dr. Lori Pierce of the University of Michigan Cancer Center attempted in her thirty minute Plenary Lecture at the 2007 San Antonio Breast Cancer Symposium to present the history of radiation therapy treatment, the changes in technology, problems, and future direction. Thirty minutes, she laughed, was far too little time to discuss the “Journey,” yet she gave a vivid presentation, enthusiastically outlining trials underway and future biological research. Radiologists will then be able to plan for optimal treatment with minimal patient short and long-term side effects.

X-rays were developed in 1895 by Roentgen, radioactivity by Becquerel and Marie Curie’s discovery of radium a few years later led to radium implants for palliative care for the patient with advanced breast cancer. The first reported cure of cancer, a basal cell epithelium (skin cancer), by this treatment appeared in the literature in 1899.

1920 saw the invention of orthovoltage which was a huge development in the cancer field. Now a dosage unit (Roentgen) and fractionated daily doses of radiation could be given rather than one massive dose which tended to cause problems to the patient. Palliation was still radiation’s goal, but scientists were beginning to see advantages for some cancers. Orthovoltage rays however could not penetrate well into deeper breast tissues and dosing was difficult to calculate. It was clear that machines capable of producing much higher energies needed to be developed in order to effectively treat cancer located below the skin surface.

Betatron followed a technique that could accelerate electrons, hitting a target and generating x-rays. Here too, major limitations with field size and dosing made this method time consuming and the radiation difficult to deliver.

A man-made radioactive isotope, cobalt, was developed in 1951 as a substitute for radium. Dr. Harold Johns' Cobalt-60 unit began "the modern era of radiation therapy." Radiologists were beginning to devise techniques to measure and best deliver radiation.

The time period deemed the "mega-voltage era" saw the high energy device, the linear accelerator, developed by Henry Kaplan and Stanford physicists, which now allowed radiation to penetrate deeply under skin with less skin damage. These first linear accelerators were cumbersome, inflexible, and needed to be manually controlled. The linear accelerator is still important in radiation therapy and it can now be computer controlled to better regulate radiation delivery. Three-dimensional targeting is even better at dosing.

As the field of radiation therapy advanced, though, "we learned that more was not always better," claimed Dr. Pierce. In one of the first studies (the Stockholm Trial) on irradiated post-mastectomy patients, serious pulmonary and cardiac toxicity were seen in patients, even years out of treatment. Lymphodema became a concern with full axillary radiation. Severe skin reactions lessened in severity since the maximum effect of the radiation occurred under the skin surface. The roentgen was replaced by the Rad, reflecting the amount of radiation absorbed by tissues rather than in the air.

New techniques began to be developed which could eliminate the problems of toxicity and more specifically target the tumor bed for precise radiation planning. Simulators now help radiologists define tumor targets. With CT-based radiotherapy planning, the area to be treated could clearly be seen. Fields could then be shaped, normal tissue damage could be minimized, and the radiologist was able to analyze beam arrangements for maximum coverage. With CT-based planning, the technician clearly sees critical organs such as heart and lung and can develop a plan for radiation. Cardiac problems, a serious side effect often causing patient death, could be dramatically decreased.

CT-based planning can lead to less toxicity as radiation is directed to the tumor mass, avoiding organs. Dosing studies can be used as estimates along with normal tissue complication

probabilities and to more accurately plan for treatment for the individual patient, avoiding poor cardiac outcomes.

The technique Active Breathing Control (ABC) can suspend a patient's breathing to help the radiologist in setting up fields without affecting the heart. This simple technique used at Dr. Pierce's institution enables radiologist to take much of the left ventricle out of the path of the x-ray beam. Taking out of the field as little as one centimeter of the heart, she claims, makes a significant difference. Problems with the size of the unit which makes it cumbersome to use, the limited availability of the machines, and the necessity of intense patient coaching before daily therapy, however, still exist.

With the advent of CT-based planning, there was also evolution from 2-D to 3-D radiation planning. Intensity Modulated Radiation (IMRT) in which radiation beams can be broken into smaller and smaller segments, gives a uniform radiation dose. Michigan is doing research comparing IMRT to 3-D planning that indicates less cardiac toxicity in IMRT, an important outcome particularly for left-sided irradiation. However, the smaller the beamlet, the longer the radiation needs to be focused, a potential cause of secondary cancers. 4-DCT is 3-D plus time which allows the radiologist to see organs moving and better plan organ sparing radiation dosing.

The University of Michigan is also working to develop techniques that can optimize radiation beam arrangements, taking into account patient anatomy and respiratory cycles. This multiple instant geometry (MIGA) should cause less potential cardiac damage in patients.

Timothy Whelen presented results of Accelerated Hypofractionated whole breast irradiation (AHWBI) on over 1,200 women who have invasive breast cancer, no node involvement, clear margins and are undergoing lumpectomy. Patients were randomized to receive standard whole breast radiation or shorter, 22 day, treatment. Results of this long-term study indicate that recurrence rates, disease free survival, overall survival, and radiation morbidity are similar. These results are encouraging for the use of partial breast radiation therapy following breast conserving surgery.

Dr. Pierce emphasized that, along with all the technical advances in radiation therapy, the biology side which has the potential of individualizing RT treatment, will make a major difference in the treatment of breast cancer.

She referred to data from Harry Barteling's group published in the New England Journal in 2002, which showed a 77 gene profile which could identify patients who might have good or poor prognoses.

Researchers from the Netherlands are trying to identify patients at higher risk of in-breast recurrence after breast conserving surgery. They are looked to see if the genetic assay could be validated. The study examined younger, high-risk patients undergoing lumpectomy, half of whom were given a larger than standard radiation boost. Most important to the future of research, samples of blood and tissues will be collected and studied in the years ahead.

Numerous abstracts and posters at this year's symposium explored technologies and genetics that Dr. Pierce highlighted in her talk. Ongoing trials look at short-term side effects, longer-term outcomes, and comparisons of standard and newer radiation techniques. The major research goal continues to be to discover the optimal way of delivering effective radiation with minimal toxicity or undesirable cosmetics.

Because breast conserving surgery (BCS) with radiation is frequently used in the treatment of breast cancer, researchers are continuing to compare whole breast to partial breast radiation. Partial breast irradiation would shorten treatment time and make it more accessible. There is a recognized decline in the number of patients choosing to have lumpectomy (BCS) and do not follow up with radiation therapy, which is a concern.

Many research presentations followed up on partial breast irradiation techniques highlighted at past symposiums. A phase II trial of brachytherapy, placing catheters in the breast near tumor areas, takes less time than WBI. By directly targeting tumors, recurrences near the site could be decreased. One study showed that the majority of local recurrence occurred in only one quadrant of the breast that would make the time consuming WBI unnecessary.

There is a continued emphasis on research and trials to develop ways to individualize radiation therapy. A large Canadian study (#4089) of over 6,000 invasive breast cancer patients who have 0-3 nodes involved, clear margins, and undergo lumpectomy, concluded after the 8 year research was analyzed, that: ER- women with breast cancer, those of young age at diagnosis, or present at stage II, have higher risks of recurrence even with WBRI and chemotherapy. This subgroup of patients has a 10-15% recurrence rate even with WBRI. This was one of several studies that showed similar results for cases where choosing the longer radiation treatment over shorter, partial breast, would be beneficial.

The time from lumpectomy to radiation therapy was investigated in several presentations. In a study from the UK, scientists looked retrospectively at 1,800 women diagnosed with breast cancer. They used the Cox model which examined age, nodal involvement, margin, hormone or chemotherapy, and date of diagnosis. By considering all factors, they were able to show that timing of radiation was not an issue for patients who do not need chemotherapy. Delay made a prognostic difference for those who need this systemic adjuvant chemotherapy. Further research suggested that radiation, if recommended, should not be initiated later than 20 weeks from breast conserving surgery.

Radiation therapy has come a long way since x-rays were discovered in 1895 and a few years later when Madame Curie's radium led to radioactive implants used to lessen the pain of advanced breast cancer. Newer, more complex accelerators have been developed that more efficiently focus radiation and cause less cardiac and skin toxicity. Radiation techniques are being compared and fine-tuned to maximize and shorten treatment time.

Research on individualizing radiation therapy to the patient based on prognostic factors and a sophisticated model is ongoing. Scientists are looking at genetics to see if they can predict who might have a radiation induced reaction or who would be at high risk for recurrence. As Dr. Pierce summed up, "The best is yet to come."

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Does the use of Hormone Replacement Therapy (HRT) increase a woman's risk of breast cancer?

Prior to the release of the Women's Health Initiative findings in 2002, the use of hormone replacement therapy was prescribed to manage common menopausal symptoms such as hot flashes, night sweats, sleep disturbances, and vaginal dryness, and was widely utilized especially in the United States. The Women's Health Initiative (WHI) findings reported that combined estrogen and progestin therapy increased the risk of breast cancer, heart disease, stroke, and blood clots, and decreased the risk of fractures and colorectal cancer [1]. The WHI also found that the use of estrogen alone (given only to women who had hysterectomies) had been linked with an increased risk of stroke and a decreased risk of fractures. These findings led to a rapid decline in the use of postmenopausal hormones in the U.S.

The incidence of breast cancer in the U.S. increased by 1.7% each year from 1990-1998. After 1998 there was a 1% decline each year until 2003 when there was a 7% drop. Dr. Peter Ravdin questioned the possible link between the decline in postmenopausal HRT and the drop in the incidence of breast cancer, and he presented his findings at the 2006 San Antonio Breast Cancer Symposium [2]. This was a major topic of discussion in the media as well as in the medical and advocacy communities. There was speculation that other factors had been overlooked, and that the decrease in the number of screening mammograms was a major contributor in the reported decreased incidence of breast cancer. The major question from an epidemiological standpoint: was this an isolated drop or would it continue long term?

This mini-symposium consisted of a series of three 30-minute lectures: 1) "A review of HRT and breast cancer in other epidemiological studies"; 2) "The women's health initiative randomized trials of menopausal hormone therapy: Results and impact on clinical practice"; and 3) "Understanding changes in breast cancer incidence - Interactions between epidemiological and clinical trial evidence". These lectures examined the question from a retrospective epidemiological perspective, clinical trials perspective, and the combination of the two, both in the United States and internationally.

Lecture #1, “A review of HRT and breast cancer in other epidemiological studies” was presented by Dr. Jack Cusick, PhD, Wolfson Institute of Preventive Medicine, London, UK. Dr. Cusick is a Clinical Trialists, Biostatistician, and Epidemiologist. He performed a review of hormone replacement therapy and the cancer epidemiologic studies related to it. He addressed the following issues: estrogen only as well as estrogen and progestin therapy, duration of risk after stopping therapy (also called recency), types of breast cancer induced by HRT, and the role of tibalone and progestin.

Dr. Cusick used three major studies: Nurses’ Health Study from Harvard University, Oxford Study (1997), and the Million Women Study. These are major research studies and the Million Women Study is the single largest cohort study of 1 million women in the United Kingdom. The conclusions reached in these trials were as follows: 1) Combined estrogen and progestin therapy has an even greater risk, compared to estrogen therapy alone. The increased risk for breast cancer returns to normal 5 years after discontinuing therapy. Women using HRT currently or those having stopped within 5 years had a clear relationship between dose and duration. The risk of short term use was very low; however there was a steadily increasing risk to 24% for those on it for 10-15 years and more than a 50% increase in risk for those on HRT for greater than 15 years. Risk was confined to current and long-term users and was calculated to be 2.3% per year of hormone replacement therapy. There was an increased risk of lobular and tubular cancers as opposed to ductal cancers; however in these studies the cancers were smaller, more favorable cancers (i.e. estrogen receptor positive). Combined HRT has a higher risk than estrogen only, a four-fold increase in risk over 5 years.

Recent updated data since the Million Women Study concluded that smaller subsequent studies are consistent with a risk of around 7.6% increase per year in current users of combined HRT therapy. The risk disappears rapidly after stopping HRT use.

Lecture #2 – “The women’s health initiative randomized trials of menopausal hormone therapy: Results and impact on clinical practice.” was presented by Dr. Roman Chlebowski, MD, PhD, Medical Oncologist and Women’s Health Initiative (WHI) investigator at UCLA. Dr. Chlebowski discussed rationale for the clinical trials for estrogen versus estrogen plus progestin

therapy to develop therapeutic guidelines for use. HRT was the most common prescription in the U.S. in the 1990's. The number of prescriptions for estrogen and progestin was 60 million in 2002. This number decreased to 25 million in 2003-2004 after the release of the WHI results.

Women's Health Initiative - Clinical trials of conjugated equine estrogen plus progestin (Prempro) versus placebo in women who have intact uterus, and conjugated equine estrogen (Premarin) versus placebo in women who have had hysterectomies. The clinical trials were started in 1993 and stopped 2.5 years early at 5.6 years of follow up, because the net harm was larger than the net benefit for estrogen plus progestin therapy. This resulted in a black box warning from the FDA for all estrogen plus progestin products for heart disease, heart attack, stroke, and breast cancer. The study also revealed that the risk for dementia doubles after 4 years of estrogen and progestin in women 65 years or older.

Conclusion of clinical trials determined that HRT is a reasonable option for short term use only. Therapy should be avoided for women who have not experienced menopause recently, and HRT should not be used to prevent coronary heart disease. There are differences in risk factors for estrogen versus estrogen plus progestin. Providers need to be aware of and support current findings. The clinical trial results revealed larger, more node positive tumors in women taking estrogen plus progestin with advanced stages. The mammographic changes caused by estrogen and progestin continue for up to one year after therapy is discontinued.

Summary of clinical trials with regard to breast cancer - Estrogen and Progestin increases the number of invasive breast cancers, increases the number abnormal mammograms, delays cancer diagnosis, and the effects are similar regardless of age. Estrogen alone – Data is less clear, neutral decrease in frequency of invasive breast cancer. Increase in mammograms requiring surgical follow-up, but not those for suspicious or highly suspicious mammograms.

Lecture #3- "Understanding changes in breast cancer incidence. Interactions between epidemiological and clinical trial evidence" presented by Dr. Peter Ravdin, MD, PhD, M.D. Anderson Cancer Center – Impact on this work in the U.S. and internationally. What other factors were examined that might also impact the incidence of breast cancer? There was a slight

decrease of 3% in the number of screening mammograms. SEER registry demonstrated a decreased risk in the incidence of breast cancer in patients 50 years or older, as well as a decreased number of estrogen receptor positive breast cancers. Within 4 months of the WHI results there was a reported 30-40% decrease in the number of women 50 or older using HRT. SEER study reported an 8.6% reduction of breast cancer by 2004, which takes the rate of incidence back to the level of 20 years ago [3].

The study by Robbins and Clarke used the cancer registry in California, which covered 3 million people and 40,000 breast cancers. It also demonstrated a 9% drop in 2002-2003 that was sustained into 2004, which correlated with the SEER study [4]. They also showed data regarding combined use therapy by county and were able to classify each county by high use, mid use and low use. They used these classifications to look at the corresponding incidence of breast cancer. There was a strong correlation between changes in hormone therapy use and breast cancer incidence, and there was no significant change in screening mammography in California during this period. They also noted that the decrease in incidence was due to a decrease in the number of estrogen receptor positive cases during the time of the study. Their conclusion was that the data strongly supported the hypothesis that changes in the use of estrogen plus progestin hormonal therapy were responsible for the significant decline in the incidence of breast cancer between 2002-2003 and sustained into 2004. Data from the Kaiser Permanente Northwest healthcare system showed decreases in breast cancer incidence mirroring the decrease in HRT as well as increasing mammography rates [5].

Does this finding hold true internationally? Results outside the U.S. are variable. This may be due to smaller populations, different patterns of use with HRT, as well as the questionable ability to measure the changes in hormonal therapy and mammography. In the Netherlands there was no significant decrease; however there was only an 11% usage of HRT in women over 50, with only 5% of the population using combined therapy. The Million Women Study was published in 2003, so the likelihood of a significant decrease would be delayed past 2004.

In conclusion: In the U.S. there is strong evidence for a link between changes in hormonal replacement therapy and changes in breast cancer incidence. Preliminary analysis of non-U.S.

data suggests that in some populations there will be a correlation; however, there will be exceptions that need to be examined carefully, as they may provide information as to what forms of hormonal therapy need to be examined in clinical trials. Some forms of hormonal therapy may have better benefit to risk ratios that need to be studied, for example. Overall, there are multiple agents, routes and dosing schedules to be studied. Epidemiological observations have identified hypotheses that have been tested in clinical trials, which have resulted in preliminary clinical evidence. This evidence has had an impact on the health behavior of the general population leading to changes in epidemiology of breast cancer in the U.S.

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Diagnosis and Treatment Issues in Breast Cancer

MRI Imaging Offers More Precise Assessment of Tumor Extent

Magnetic resonance imaging (MRI) is a non-invasive diagnostic technique used for medical imaging to visualize the structure and function of the body. It provides detailed images of the body in any plane. It is very effective at showing soft tissue contrast and is especially useful when looking at tumors. The technique is able to identify breast cancer occurring in more than one location (multifocal), or from multiple sites of origin (multicentric) as well as cancer tumors in the opposite (contralateral) breast. It works by inducing atoms in the body to emit radiowaves using a powerful magnet. When a person is in an MRI scanner, some of the hydrogen atoms (mainly in watery fluids) align with the magnetic field. A radiowave makes those atoms resonate and absorb energy. The atoms then release this energy as a very weak radiowave that can be amplified and measured by the scanner. Additional magnetic fields in different planes are used to constantly change the magnetic field and allow images of the body or a tumor to be reproduced.

Since 2002 researchers at the University of Chicago have routinely used MRI for breast cancer screening. 459 newly diagnosed patients with breast cancer underwent MRI, as well as having a clinical examination, mammogram and ultrasound imaging of the affected breast. The location, number and size of the cancers were recorded. Unsuspected lesions found on MRI were looked at a second time with mammography and ultrasound, and biopsies were performed if deemed necessary. Patients with inflammatory cancer were excluded.

Analysis of the MRI results (with pathological review) showed that secondary cancer was present in 106 patients (approximately 23% or nearly a quarter) of patients, with an average age of 51.2 years, 12% of these patients had multifocal tumors, 6% multicentric tumors, and 5% having tumors in their contralateral breast. These results clearly suggested a need for changes in treatment protocols. As a result some patients received larger lumpectomies or a mastectomy, and others received neoadjuvant chemotherapy, i.e. chemotherapy prior to surgery to shrink the tumor. In all 23% of patients, (the ones with secondary cancers), treatments were subsequently changed for the women post-diagnosis.

This study confirmed that MRI has the potential to be a very effective screening tool. It offers more precise information and detection of tumor type and extent than clinical examination, mammography or ultrasound imaging.

Shorter Radiation Schedule Just as Effective for Early Stage Breast Cancer

Women who have received breast-conserving surgery (lumpectomy) will most often receive radiation therapy. Radiation treatment, which involves high-energy X-rays, will shrink or eradicate any remaining cancer cells left behind after surgery. Until a few years ago radiation therapy, using an external beam, consisted of up to six and a half weeks of treatment. The current standard is a five-week course of treatment.

At one of the key general sessions at the San Antonio Breast Cancer Symposium, Canadian scientists presented their results from a 12-year long study in which they compared patients treated with standard breast irradiation (5 weeks or 36 days) with those that received approximately 3 weeks or 22 days of breast irradiation. This shortened period of radiation therapy is called “accelerated hypofractionated” breast irradiation and consists of 42.5 Gy (gray = unit of radiation) given as 16 fractions over a 22-day period (which includes weekends). In other words, patients are seen for 16 weekdays and receive 2.7 Gy at each treatment session. The current standard whole breast irradiation consists of 50 Gy given as 25 fractions over 36 days. Patients receive 2.0 Gy every day for 25 days of treatment. The rationale for hypofractionation is based on a radiobiologic model that predicts a larger dose per fraction given over a shorter period of time is as effective as the more traditional longer schedule. The study followed 1234 women with invasive breast cancer who were treated by lumpectomy, had clear margins after surgery, and were node negative. The study had two arms: 622 women were randomly assigned to the short treatment schedule and 612 women to the long schedule.

The primary outcome for this study was any local recurrence of invasive cancer in the treated breast. Secondary outcomes were distant recurrence of invasive breast cancer, death, breast cosmetic outcome, and delayed effects on the skin and underlying tissue, due to the radiation.

The results of this 12-year follow-up study are as encouraging as those reported in the Journal of the National Cancer Institute in 2002. The results remain practically identical. The risk of recurrence was just over 6% in both arms of the study, the overall survival was 84%, and there was little difference in the cosmetic appearance of the breast.

So the key question remains to be asked — why isn't the shorter radiation schedule used more in the United States? One of the many concerns is that the physical effects of radiation may show up ten years or more after radiation treatment. Also, women receiving radiation to the left breast may be more prone to heart damage. This study has addressed some of these issues and hopefully will be supported by favorable results from other similar studies.

In the interests of patient time, clinic resources, and health care costs, radiation oncologists may consider offering the shorter treatment regimen to breast cancer patients that have had a lumpectomy with clear margins on the right breast, and have no node involvement. Further results are needed to see if this shorter treatment works for larger tumors and whether there are adverse effects that haven't yet manifested themselves in this study.

Genes May be an Indicator for Radiation Side Effects

Common side effects of radiation therapy to breast tissue are: inflammation and reddening called erythema; skin peeling; skin shrinkage or atrophy; thickening of the underlying tissue known as fibrosis, often accompanied by an abnormal dilation of blood vessels just below the skin's surface, technically termed "telangiectasia".

Scientists at the University of Leicester, United Kingdom, have been studying patients treated with radiation therapy comparing their side effects and trying to determine if there is a genetic component that determines the severity of symptoms. Breast tissue injury due to radiation was divided into: early (acute) side effects that include skin peeling and erythema, which develops within 90 days of treatment; late effects seen from 90 days onwards and may persist through life, which include symptoms such as skin atrophy, fibrosis, and telangiectasia.

As part of this study, patients' cells were collected using mouth swabs and their DNA tested for eight genes. After at least four years of patient follow-up it was observed that patients with two

of the eight genes had a higher probability of late effects from radiation treatment namely, long term fibrosis and telangiectasia.

In the future, genetic testing may identify patients at high risk of late effects from radiation therapy. These patients should only be treated by radiation if there is no alternate treatment and warned of an increased risk of long-term side effects.

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Surgery Options for Breast Cancer Patients

There are many choices for women who have been diagnosed with breast cancer. These choices allow the newly diagnosed patients to live a quality of life far beyond what appeared to be insurmountable odds or even a death sentence, only a few years ago.

Women now have a wide-range of diagnosis and with busy life styles they want more information on their treatment options once they have been diagnosed. Whether it is which surgery (lumpectomy or mastectomy), and which node dissection will the doctor do, sentinel node biopsy or the standard of axillary node biopsy, radiotherapy, adjuvant chemotherapy what are the patients options? The patient wants maximum results from minimal invasive surgery. The medical team looks at many factors when determining the type of surgery and treatment for the patient. Among those are her age, type of biopsy performed, and location and size of the tumor. The surgeon determines if he/she will perform a sentinel node biopsy or axillary node biopsy on the patient and if axillary node, how many nodes will be dissected. Some of the factors that surgeons are discussing are if a complete axillary dissection always needed after a positive sentinel node biopsy? During the San Antonio Breast Cancer Symposium, surgeons discussed the NSABP-32 study.

Between May 1999 and February 2004, 5,611 patients were entered into the NSABP-32 trial. The patients were randomized into either Group 1 (2,807 patients) or Group 2 (804 patients). The result of this study is good news for the patient. The study determined that axillary dissection following a positive sentinel node biopsy while sometimes helpful in the prognosis and treatment planning, it is not always necessary depending on the size of the tumor and absence of lymphovascular invasion.

In another study, SEER data was looked at from 1992 through 2003 to determine the status of axillary nodes. With the introduction of SNB, the incidence of node positive women with T1/T2 breast cancer has increased significantly. There were concerns about potentially high false positives with more widespread adoption of SNB, but the data are compensated by improved pathological examinations.

It was stated that the medical team can monitor the adjusted node positivity rate for women undergoing sentinel node dissection may be a useful surrogate for determining false negatives, and this can be a quality indicator for the future. The patient will be given this information from data obtained by actual participants, someone she can relate to. This information provides the patient valuable information from which she can help to choose her surgery and treatment

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Is a new Standard of Care on the Horizon for Sentinel Node Micrometastases?

After attending the sessions on sentinel lymph node procedures, I am pleased to announce that I believe there will be alterations in the way sentinel node biopsies are currently performed. These possible changes in the standard of care will lead to more personalized, less invasive and perhaps, more effective, treatment.

The generally accepted method of testing for sentinel node micrometastases is currently a histologic evaluation. When examining a permanent sample, this method requires an experienced pathologist to evaluate the samples and determine their value in the diagnosis and staging of breast cancer. The downsides of this method are fourfold. A) There is a definite loss of tissue. B) With the method, less than 5% of the node is available for viewing. C) It is estimated that this evaluation misses 10-15% of metastases greater than 2 millimeters. D) The evaluation takes 1 to 2 days to properly complete.

If a frozen section is obtained intra-operatively, an even smaller sample size is available for evaluation. There is still loss of tissue, and the smaller sample size is more difficult to evaluate. The freezing process makes the staining of the permanent section less distinct. The sensitivity of this method is less, reportedly 40-85% versus permanent section. This method, while quicker, has not been standardized. Frozen section samples do not always detect some breast cancer types, such as lobular carcinoma. In a study at Memorial Sloan Kettering Cancer Center, which included 5298 patients, the overall sensitivity of frozen sections was 61%. (A 62% sensitivity was seen in ductal carcinoma, while only 52% of the lobular carcinomas were identified.)

GeneSearch™ BLN Assay produced a more thorough lymph node sampling (up to 50%). The test was rapid taking only 30 to 40 minutes. There was no loss of tissue. No artifacts remain on the tissue to interfere with permanent sections. This assay can be performed by a lab technician. It is objective, standardized and reproducible.

This assay used two markers: Cytokeratin 19 (CK19), which is expressed in epithelial cells, and Mammaglobin (MG), which is expressed in breast tissue. If either or both markers are positive, the result is considered positive. The cut-offs are 31.0 cycles for MG and 30.0 cycles for CK19.

The clinical trial was prospective and multi-centered (11 sites in the United States). Patients were all diagnosed with invasive breast carcinoma. Fresh lymph tissue was tested on-site at each center. The results of the assay were not used for patient management. Decisions favoring axillary lymph node dissection were based solely on histology results. All histology was reviewed by a board of centralized, expert pathologists. The Confidence Interval (CI) for this trial is 95%.

Statistical analysis, of 490 samples, produced the following results:

- Frozen sections had an 82.1% sensitivity and 97.4% specificity, while the BLN assay had a 91.0% sensitivity and 94.5% specificity.

Sensitivity, categorized by size of metastases, was calculated as follows:

- Macromets (>2.0mm): Frozen section had 90.6% sensitivity, while BLN assay had a 97.4% sensitivity (117 samples).
- Micrometastases (>0.2-2.0mm) showed 40.9% sensitivity in frozen sections and 68.2% in the BLN assay (22 samples)

The largest variance in the sensitivity of the frozen section versus the BLN assay was the ability to differentiate metastases in difficult cases.

Patient Type	N	BLN Assay	Frozen Section
Lobular	23	91.3%	65.2%
T1	43	86.0%	76.7%
Grade 1	73	87.7%	78.1%
Neo-adjuvant	3	66.6%	33.3%

The sensitivity for difficult cases was further analyzed by metastases size.

		Macro > 2.0 mm	
Patient Type	N	BLN Assay	Frozen Section
Lobular	18	94.4%	83.3%
T1	32	96.9%	87.5%
Grade 1	56	96.4%	89.3%
Neo-adjuvant	2	100%	50.0%
		Micro 0.2-2.0 mm	
Lobular	4	75.0%	0%
T1	8	63.0%	38.0%
Grade 1	14	64.0%	36.0%
Neo-adjuvant	1	0%	0%

The specificity of the assay was comparable, but not superior to the frozen section sampling, in all types, except neo-adjuvant.

Patient Type	N	BLN Assay	Frozen Section
Lobular	46	95.7%	97.8%
T1	244	95.1%	98.4%
Grade 1	223	93.7%	97.3%
Neo-adjuvant	7	100%	85.7%

The advantages of the assay include:

- Allows up to 50% of node tissue to be evaluated
- Higher sensitivity, including metastases which are difficult to detect
- Specificity is comparable
- Timing allows intra-operative use
- No loss of tissue or freezing artifacts
- Laboratory technician can perform
- Assay is a viable replacement for frozen section, or may be used as an adjunct evaluation, thus eliminating need for second surgery.

What does all of this mean in lay terms for the patient? It means that there is a better chance of detecting small metastases with the new assay. The more precise the diagnosis is, the better the medical team is able to treat the individual patient with a treatment regimen which is designed specifically for her particular situation. This avoids over-treatment and ensures that the patient is offered the appropriate treatment for their stage of disease.

The fact that the assay can be done during the surgical time in the operating room means that the patient will not likely have to undergo further surgery. Tissue is preserved. The tissue sample can be used for a further histologic evaluation without damage. Finally, because the test can be performed by a laboratory technician, it is less costly and allows the surgeon more time for the more complicated, or pressing, breast surgeries.

Coupled with the study presented that showed that patients with pN1mic disease (extremely small micrometastases of the sentinel lymph node) have a prognosis that is similar to those with node negative status, the outlook is promising. This study addressed the significance of tumor deposits. It proposes that the size of the sentinel node metastases correlates to tumor size and non-sentinel node positivity.

These studies may have a significant impact on clinical management of breast cancer. Being able to more accurately treat each individual case is a step forward for patients. The ability to offer quicker, less debilitating analysis, during one surgical procedure is a positive process.

The cause of breast cancer is still a mystery to us. With each new research project, the scientists dedicated to breast cancer research bring us closer to not only ascertaining the cause of this disease, but allow us to hope that the cure will be found within our lifetime.

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Abstract 53: *High sensitivity of a molecular assay for breast metastases in sentinel lymph node that are difficult to detect by frozen section.*

P. Blumencranz, KB Deck, PW Whitworth, P McCue, DS Reintgen, AS Chagpar, P Beitsch, TB Julian, M Mamounas, S Saha, A Giuliano, and R Simmons.

Abstract 52: *The impact of micrometastases in the sentinel nodes of patients with invasive breast cancer. Nora M Hansen, Baiba L Grube, Cynthia Ye, Roderick Turner, Meghan Brennan, James Brenner and Armando E Giuliano. Surgical Oncology, John Wayne Cancer Institute, Santa Monica, CA and St John's Hospital and Health Center, Santa Monica, CA.*

Radiologic Studies, including MRI

Magnetic Resonance Imaging (MRI) is being used more and more by physicians as a screening process for high-risk young women. Several studies on MRI were given at the San Antonio Breast Cancer Symposium this past December. One study, an update of the Dutch MRI screening study, (MRISC) was presented. This updated study, showed the ability of MRI to pick up tumors and DCIS in women who had a moderate to high susceptibility of developing breast cancer. The women in this study were given clinical breast exams (CBE), mammograms and a MRI. The MRI was used in conjunction with mammography as a screening tool. The results showed that MRI's appeared to be more sensitive than mammography in detecting tumors and/or ductal carcinoma in-situ (DCIS), in women who were at an increased risk of getting breast cancer, as opposed to the general population who didn't have this risk factor. This study took place from November 1999 to March 2006 with 2,283 women participating.

It was very noticeable the impact MRI had in finding tumors versus mammograms. For women who are carriers of the BRCA1 and BRCA2 gene, this was very significant. Because the discovery of this gene is linked to women getting breast cancer, the importance of regular screening for breast cancer is a high priority. The study found that BRCA2 patients had a higher incidence of DCIS, whereas those who had the BRCA1 gene had a lower incidence of DCIS but higher number of interval cancers.

The MRI's have demonstrated that this can be an excellent tool in the screening process. Overall, the MRI's found more tumors than conventional mammography

and cbe's in women with better than average risk factors and those who had BRCA1 and BRCA2 genes.

I found the discussion of the study on detection of enhancing lesions on contrast-enhanced MRI of the breast using real-time virtual sonography to be extremely interesting and highly informative. I would have never imagined that sonography and MRI's could be fused together to become such a powerful diagnostic tool. Eighty-five women participated in this study, which was undertaken by Japanese doctors between May 2006 and May 2007. These women had been newly diagnosed with cancer and had undergone breast surgery. Of the 85 women, 35 had invasive ductal carcinoma and were given Real-time virtual sonography (RVS). RVS is a new technology that was developed by the Japanese doctors.

The MRI's were not done in the same way they are done in the US with women lying on their stomach. Instead the women were lying on their backs in which the sonography and MRI was done simultaneously and both images were shown together. The RVS system was able to find more enhanced lesions 94% of the time, than when sonography or MRI was used alone. Another exciting factor about the RVS system was that respiratory movements did not appear to affect the outcome of the test.

In conclusion, the RVS system allowed the doctors to compare MRI and sonography images at the same time, and demonstrated excellent accuracy in picking up enhanced lesions with less radiation exposure. Again, this is not the typical the way the breast MRI exam is performed in the US, but it is interesting to see the findings that were achieved by this new technology and worth taking notice of in the future.

In some ways, this German study, MRI for diagnosing pure DCIS, expanded upon the points that were made in the previous two studies. MRI was again been proven as a very useful and powerful tool in detecting DCIS, whether alone or when used together with other screening tools. This study was done over a five-year period in which over 7,000 participated. The uniqueness of this study was that it occurred over a long time frame, and during this period, it was standard

protocol for every woman to receive a mammogram and a MRI. The basis of this study was to examine whether DCIS could be detected earlier when using a MRI along with a mammogram. It is a known factor that not all DCIS is picked up on mammograms when it is very small. So the results of the study were very positive when mammography and MRI was given as standard screening tools. Over 90% of the time, DCIS appeared on MRI images, (98% in high grade DCIS) and only 56% on mammography images. This was a significant difference, which showed the sensitivity of an MRI in finding DCIS over mammography.

During the question and answer session after the presentation, someone asked the question “how do they justify the cost of giving every woman a MRI.” The doctor responded, “We justify the cost every time it saves a life”. She stated that treatment is less expensive and women live longer when breast cancer is caught earlier. This was a very profound statement and showed how other countries use MRI to help fight breast cancer plus the added benefit of less treatment cost by finding the disease early. This presentation helped to build the case of using MRI as a screening tool and how it may help in diagnosing potentially invasive breast cancer. However, I have to note that the doctor stated that the cost of MRI’s in Germany is not nearly as expensive as it is in the US, and they have a universal health care system in place, which covers the cost of MRI for women. Perhaps it could be argued that it is also a case of supply and demand and costs will come down as more MRI’s are performed as part of the screening in the future.

The jury is still out when it comes to whether women should or should not receive an MRI. Many factors need to be looked for a doctor to make this decision. Has the women already had cancer, or does she have a strong family history of cancer. Maybe she has the BRCA1 or BRCA2 gene, or perhaps something has shown as abnormal on a mammogram and the doctor feels that an MRI could better clarify what the finding are. Also, there is the issue of whether or not the patient has insurance (at least in the U.S.) to cover the cost of the MRI, which can be very expensive. So the debate will continue in the United States at least. The American Cancer Society’s guidelines state that a young woman with a family history of breast cancer should have a mammogram plus a MRI. Let’s hope that

doctors will continue to request for the patient to have a MRI when she/he feels that it is necessary for the patient.

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