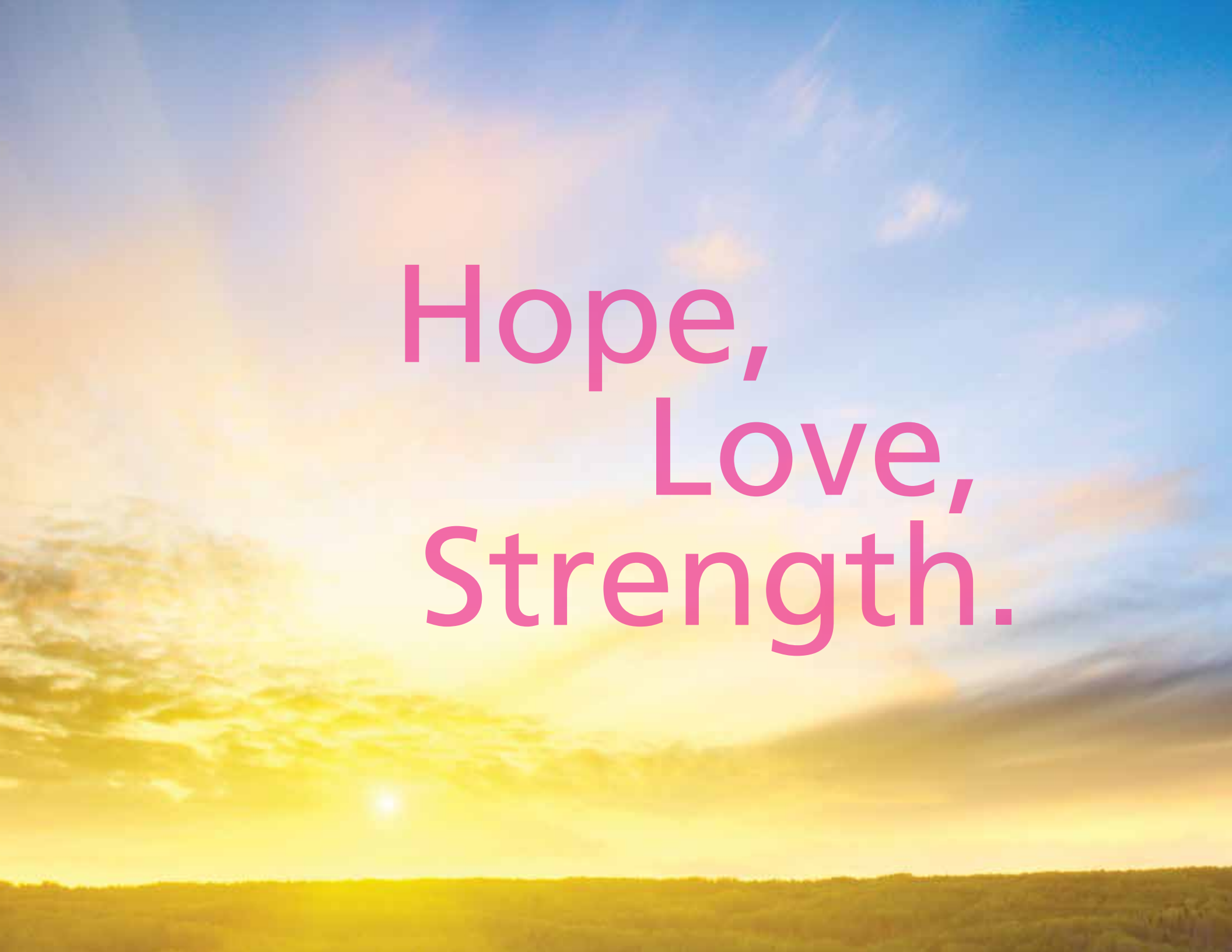
CANCER SERVICES **ANNUAL REPORT** | 2015
BREAST CANCER AWARENESS

TOGETHER, We Are...

Glendale Adventist Medical Center
Cancer Services
Adventist Health


Hope,
Love,
Strength.

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OUR **MISSION**

TO SHARE **GOD'S LOVE** WITH OUR COMMUNITY BY PROMOTING **HEALING AND WELLNESS** FOR THE WHOLE PERSON

WELCOME TO THE 2015 **CANCER SERVICES ANNUAL REPORT**

Kevin A. Roberts, President and CEO

Significant advances are being made each year in breast cancer research, early detection and treatment, but the numbers nationwide are still troubling. Approximately one in eight women in the U.S. experiences the probability of developing invasive breast cancer during her lifetime.

In 2014, nearly 232,670 new cases of invasive breast cancer were projected among women with more than 40,000 estimated deaths related to breast cancer. In 2014, breast cancer amounted to approximately 29% of reported cancers nationwide, including 20% at Glendale Adventist Medical Center (GAMC).

Is there good news? Yes, definitely. Early detection, digital mammography and continuing improvements in treatment options at GAMC are saving more lives each year. Our messages emphasizing breast cancer awareness and education, such as in the 2014 Army of Pink campaign and other cancer-related programs, have helped produce some impressive local benchmarks contrasted against the national database. Below is a table that shows GAMC's five-year survival rate compared to the nation's rate. Our award-winning Cancer Center continues to provide world-class care to our cancer patients and their families.

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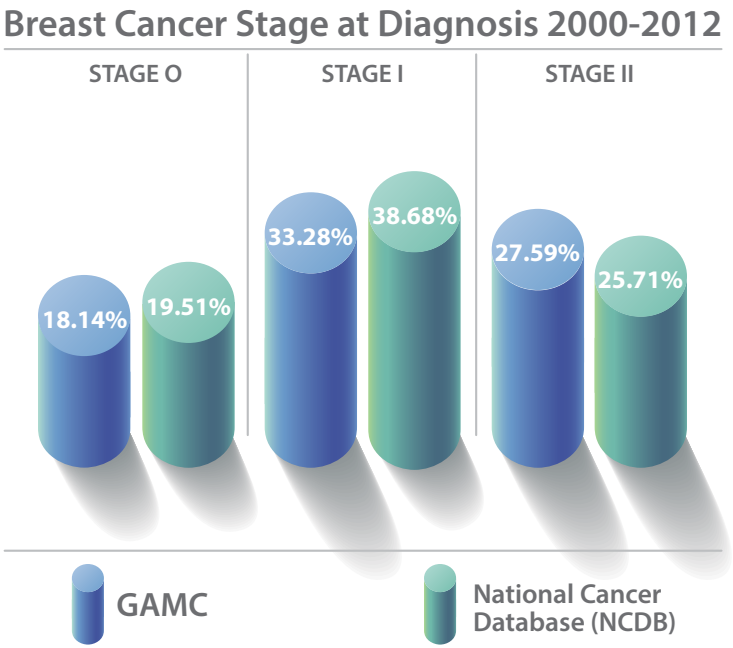


WELCOME TO THE 2015 **CANCER SERVICES ANNUAL REPORT**

At GAMC, we offer our patients an integrated breast cancer program, using a multi-disciplinary approach that unites our outstanding physicians and support associates with a single focus: providing the finest care possible. It mirrors our mission of "promoting healing and wellness for the whole person."

Since 1976, GAMC has been recognized by the American College of Surgeons (ACS) as a Comprehensive Community Cancer Program, with numerous commendations. The program continues to improve and earn additional recognitions for achieving the highest standards of patient care, including the Outstanding Achievement Award from the ACS. This prestigious honor recognizes a very select number of comprehensive community cancer programs. In addition, GAMC has been named a Pink Ribbon Facility for providing excellence in radiology services, along with exceptional commitment and support to women in the community.

We are blessed to be the recipient of hundreds of volunteer hours by members of the Cancer Care Guild, which raises funds through special events such as Laugh 4 A Cause. Proceeds and donations allow the cancer center to continue to offer free community outreach services to any patient diagnosed with cancer.

Finally, one of the indicators of an outstanding hospital is the level of satisfaction of the medical staff. Our physicians in a recent survey ranked GAMC extremely high — in the 90th percentile. Physicians have incredibly high standards, so when they exhibit this degree of confidence, that tells us we are, indeed, performing at a higher level! We join the community in expressing our deep gratitude to each member of our medical staff, particularly those who serve our cancer patients, for their exemplary work, loyalty and commitment to the mission of our hospital.

Outstanding Achievement Award

TOGETHER, We Are...HOPE

CANCER COMMITTEE **CHAIRMAN'S MESSAGE**

Boris Bagdasarian, DO, Hematology and Oncology, Chairman, Cancer Committee

As chairman of the Cancer Committee, I am pleased to introduce the annual report for 2015. Glendale Adventist Medical Center's (GAMC) oncology program continues to thrive as a leader in cancer care. We promote common interests of the nation's leading academic and free-standing cancer centers that are focused on the eradication of cancer through a comprehensive and multi-disciplinary approach. Our center of attention is based on strategic initiatives of service, evidence-based care and patient safety.

The multi-disciplinary tumor board conferences were held on a weekly basis with 100% attendance during 2014. All of the physicians in attendance were board-certified in their respective specialties, and provided ideal solutions in a collaborative and collegial fashion incorporating the latest surgical technologies, novel-agents and clinical trial options for patients.

GAMC's dedication to promote the common interests of the nation's leading academic and free-standing cancer centers was acknowledged by the Commission on Cancer in 2014, when we were granted full accreditation during survey of our program.

Several new programs were launched in 2014 including the Lung Cancer Screening Program introduced by Clayton Lau, director of radiology. There is evidence that screening persons ages 55 to 74 years who have cigarette smoking histories of 30 or more pack-years and who, if they are former smokers, have quit within the last 15 years, reduces lung cancer mortality by 20% and all-cause mortality by 6.7%.

The medical administration approved the purchase of an Endoscopic Ultrasound (EUS), which is a useful tool for staging of cancers of the esophagus, stomach, pancreas and rectum. Additionally, it can be utilized for evaluating chronic pancreatitis and other masses or cysts of the pancreas, and studying bile duct abnormalities, including stones in the bile duct or gallbladder and liver tumors.

The Rapid Quality Reporting Services (RQRS) was initiated to improve the time-frame after diagnosis and treatment submission to the National Cancer Data Base on breast and colorectal cancers.

We were successful in providing three prostate cancer screenings in 2014, under the supervision of Sze-Ching Lee, MD, urologic surgeon.

We measure our success against the highest standards set by elite cancer centers throughout the nation and are pleased to report that we have not only met, but exceeded our goals.

We thank our ACS cancer program coordinators:

- **Sam Carvajal**, MD - physician liaison
- **Melina Thorpe**, RN, - director of cancer services/quality improvement coordinator
- **Denise Cleveland**, - data manager/cancer registry quality coordinator
- **Tracey Sanders**, licensed cosmetologist, EMT - community outreach coordinator
- **Lily Villalobos**, - clinical research coordinator
- **Cynthia Klinger**, MFT - psychosocial services coordinator

Tina Parsegian, Cancer Care Guild President, 2014-15

"Where Life, Love and Hope Connect"

Glendale Adventist Medical Center's Cancer Care Guild was formed in 2011 and has since raised more than $232,000 to provide free support services at GAMC's award-winning Cancer Center. Anyone with a diagnosis of cancer, regardless of where they are being treated, can utilize these services.

The services include personal and family counseling, support groups, fitness programs such as exercise and yoga, classes in jewelry making, knitting and creative writing. Unique among all hospitals in our area is Ingeborg's Place Apart, our Positive Image Center. It is a quiet retreat for patients and also provides free wigs, hats and scarves.

Looking back over 2014, Laugh 4 A Cause, the Guild's featured comedy night, attracted an enthusiastic audience of more than 1,000 people to the Alex Theatre in October. Special thanks to comedians Vahik Pirhamzei (show producer) and K-von, along with the Allen G. Orchestra and the entire cast, for an entertaining evening.

Especially memorable was the finale when cancer survivors – mothers, daughters, aunts, grandmothers and friends – joined the ensemble and special guests on stage. It was an inspiring experience that brought tears of joy throughout the theatre.

GAMC Cancer Care Guild Committee members.

In May, the Guild hosted a membership reception and Cancer Center tour, attended by more than 70 guests and GAMC associates. We were pleased to welcome several additional volunteers to our membership.

Members of the Guild and I were also pleased to participate in and support other cancer-related activities during the year, including the hospital's Cancer Survivor Day in June and the annual youth fundraising drive.

This past year has been a wonderful experience serving as president of the Guild, working alongside a generous and compassionate group of Guild volunteers, in addition to the highly skilled staff of professionals representing the Cancer Center and Healthcare Foundation.

Massage Therapy Brings Healing Touch to Patients

When a patient is feeling a little anxious or worried, Fernando Vazquez often comes to mind to help cope with the stress. As a certified clinical massage therapist, Fernando knows that intense surgeries, radiation and medications—as well as the effects of the disease itself—can take a toll on an individual, both physically and psychologically.

Fernando's journey into massage therapy began when he was a professional soccer player and personally experienced the healing benefits of massage therapy. Graduating with an engineering degree, Fernando felt his purpose was unfulfilled until he decided to pursue formal education as a massage therapist. Fernando specialized in oncology, and completed over one thousand hours of continuing education and clinical experience before his current position here at Glendale Adventist Medical Center (GAMC).

Currently, GAMC has integrated massage therapy as a complementary therapy to the physician's treatment plan. In order to see a patient, Fernando must receive a physician referral to ensure that the patient is a good candidate for therapeutic massage therapy.

Massage therapy is an increasingly important tool in assisting with traditional medicine and the benefits are very apparent to therapists seeing clients. Massage is known to reduce stress, bolster the immune system, help remove toxins and restore energy and circulation. Fernando's knowledge of anatomy, physiology and pathology is essential for collaborating with the health care team of professionals.

"When I get that referral, I make sure to read through the patient's history and medical background. I then consult with the Disease Handbook of Massage Therapy and begin planning a safe and effective treatment plan for each patient," says Fernando. Massage therapy takes many years of clinical training and specialized certification and degrees.

"They ask me: Don't you get tired? Don't your hands hurt? No, I don't feel like I am working. This is my calling, my passion and mission," explains Fernando. He adds, "Oncology massage has become one of my favorite specialties to treat patients. The acknowledgement from patients and growing acceptance from medical professionals have been extremely satisfying."

Cynthia Klinger, Psychosocial Services Coordinator

Psychosocial Impact of Breast Cancer

Diagnosis and treatment of breast cancer presents life-changing challenges to the survivor and their loved ones. The impact breast cancer has on a survivor's life affects his/her physical body, psychological and emotional system, relationships and spirituality, as well as vocational and financial status. These challenges can lead to a breakdown of emotional stability, leading to an existential crisis. Paradoxically, the breast cancer experience can present opportunities to care for oneself, strengthen relationships, re-prioritize life and induce a spiritual awakening.

The psychological and emotional challenges brought on by a breast cancer diagnosis vary among survivors. Survivors with a strong support system and the ability to adapt and deal with loss are at an advantage in dealing with the diagnosis before, during and after treatment. Effective tools for dealing with fear of recurrence, and defense against depression and anxiety management are essential. Intervention, including individual and family counseling, breast cancer support groups, cancer education and open communication with doctors helps strengthen coping skills and reduce stress.

The physical changes that occur with breast cancer surgery, chemotherapy and radiation therapy require the ability to grieve, adjust and adapt to changes. Mastectomies, surgeries and loss of hair due to chemotherapy have an impact on self-esteem. Long-term effects of radiation therapy, bone health, onset of menopause and dealing with side effects of anti-estrogen medication, pain, fatigue, lack of sleep, nausea, chemo brain, neuropathy all affect the quality of life for survivors, as well as their relationships because patients do not look, feel, or at times, act like themselves.

The spiritual impact of being faced with a life threatening illness is transformative. The idea of death goes from a distant possibility to pervasive conscious awareness. The meaning of life is questioned and spiritual beliefs are challenged. Anxiety, worry, and the impact on families can undermine security and life as the survivor knows it. Breast cancer affects intimacy on many levels. Body image is challenged with mastectomies, scars, loss of hair

and chemotherapy infusion devices. Menopausal symptoms brought on by chemotherapy and anti-estrogen medication has an impact on marriages and self-esteem. Survivors deal with hot flashes, loss of intimacy, depression and are often too embarrassed to talk to a doctor about these personal issues, so they go untreated.

When the cancer diagnosis is given, activities of daily life are disrupted. Time off work for surgery and treatments have an impact on careers, employers and co-workers. Fear of job loss and financial strain due to medical bills becomes a heavy burden since living costs continue whether or not a survivor qualifies for sick time or disability benefits.

Families are impacted when cancer treatments, doctor appointments, lab visits and scans disrupt daily routines. Changing roles add to family stress. Spouses are pulled between caring for children, a sick family member and work. The added stress and worry put men at an increased risk for depression and anxiety.

The diagnosis of breast cancer brings challenges and stress to the individual, family, work and financial security. It is a time when survivors and their families realize their strengths and limitations. Support can be found through counseling, support groups and cancer education. Survivors that participate in yoga, exercise, meditation, cancer classes, art, knitting and dance have fun and provide mutual support for each other.

Facing cancer can strengthen the survivor spiritually, emotionally and psychologically. It is an opportunity to strengthen marriages and families as loved ones rally around the survivor. It is through these challenges that families come to realize they too are survivors.

COMMUNITY **OUTREACH**

Tracey Sanders, Positive Image Coordinator

GAMC's Cancer Services Program reaches out to our community by hosting and participating in a number of health-related activities to promote cancer awareness and provide educational resources.

Bras for a Cause, April 9, 2014

This annual Soroptimist International of Glendale-sponsored event raises money and awareness for breast cancer. Supported by Cancer Services, a group of cancer patients and survivors submitted an entry for Bras for a Cause "Celebrating Women throughout the Ages" and attended the fundraiser dinner.

Prostate Screening, June 12, 2014

A prostate cancer screening was held for the Live Well Senior Program with 19 participants. GAMC physicians who participated included Sze-Ching Lee, MD (pictured right) and the family practice residents.

Cancer Survivor Day, June 20, 2014

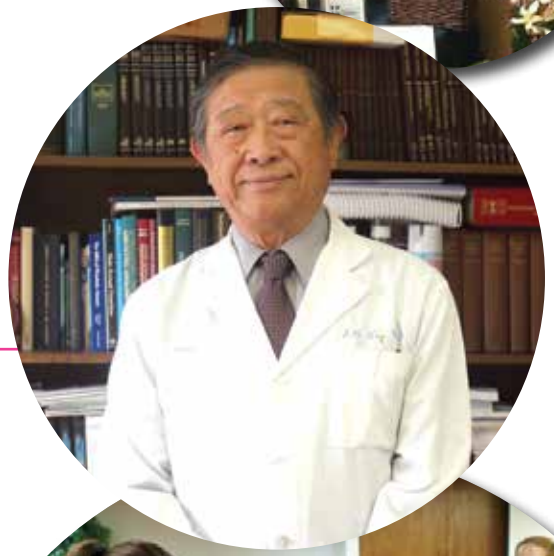
"Stars of Hope" was the uplifting theme for this event, drawing over 200 cancer survivors and their caregivers. The "Flame of Hope" awards were presented to Ryder Buck, accepted posthumously by his parents and Judy Jenson, jewelry teacher/volunteer at the Cancer Center. A special feature of this event included a performance by members of the cancer survivors' dance class, the "Can-Dancers" and featured a special performance by GAMC's President and CEO Kevin A. Roberts, on ukulele and guitar.

Community Outreach, July 24, 2014

GAMC associates, Anita McCain and Tracey Sanders (pictured right), provided education and information on GAMC's cancer resources at the Glendale Galleria.

Community Outreach, September 26, 2014

Melina Thorpe, director of Cancer Services, with Positive Image Coordinator, Tracey Sanders and Medical Oncologist, David Shin, MD hosted an educational program on lymphoma and leukemia at Crescenta Valley High School, with approximately 60 students in attendance.



Prostate Screening, October 16, 2014

A prostate cancer screening was held at the Cancer Center with 85 participants. GAMC physicians Sze-Ching Lee, MD (pictured right), Sara Kim, MD, and family practice residents participated in this program.

RELAY FOR LIFE®
American Cancer Society

Relay for Life, October 18-19, 2014

Employees, cancer survivors and patients came together to participate in this annual Relay for Life Cancer Charity Walk event.

Beauty Bus Event, October 21, 2014

A day of pampering and beauty was offered free of charge to cancer patients currently receiving cancer treatment, and their caregivers. The Beauty Bus Foundation sponsored the event with pop–up salon services such as manicures, facials, hair styling and makeup application.

ARMY OF PINK

In recognition of Breast Cancer Awareness Month in October 2014, Glendale Adventist Medical Center (GAMC) gathered an army of candidates to spread the message on breast cancer. Six prestigious men from the community were selected as brave soldiers for this biennial campaign to educate on breast cancer facts, discuss the importance of early screenings, treatment and educate on the resources available at the award-winning GAMC Cancer Center.

The Army of Pink soldiers for 2014 were **Harlan Gibbs**, MD, medical director, GAMC Emergency Department; Lt. **Tim Feeley**, Glendale Police Department; Deputy Fire Chief **Greg Fish**, Glendale Fire Department; **Archbishop Hovnan Derderian**, Western Diocese Armenian Church; **Greg Krikorian**, president of the Glendale Unified School Board; and Glendale City Manager **Scott Ochoa**, led by honorary captain **Elissa Glickman**, CEO of Glendale Arts.

Online voting took place during the month of October and Tim Feeley, along with his K-9 Yudy, was declared the 2014 Army of Pink winner! Tim and the entire police department sold special pins and T-shirts to raise money to benefit the GAMC Cancer Center and support groups available to cancer patients.

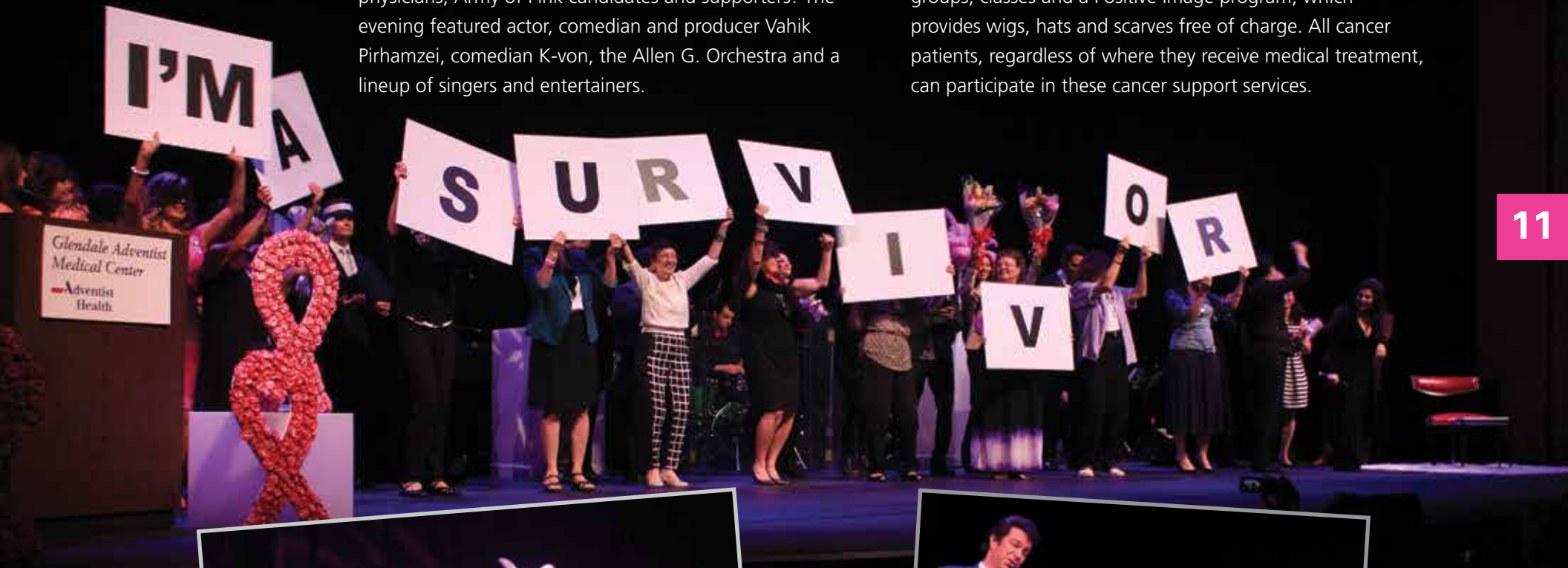
In addition, 100 low-cost mammograms were provided by GAMC to the community as a way to encourage the use of screenings as an important method of detecting cancer.

1. Campaign winner Lt. Tim Feeley (center) surrounded by GAMC physicians, executives and candidates at the announcement ceremony.
2. Sara Kim, MD; Boris Bagdasarian, DO; Ramella Markarian and Scott Ochoa, Army of Pink candidate, at the kick-off luncheon.
3. Harlan Gibbs, MD (right), campaigning around GAMC for Army of Pink votes!

Laugh 4 A Cause, October 26, 2014

The Laugh 4 A Cause comedy night at the Alex Theatre, presented by the GAMC Cancer Care Guild on October 26, attracted more than 1,000 community members, GAMC physicians, Army of Pink candidates and supporters! The evening featured actor, comedian and producer Vahik Pirhamzei, comedian K-von, the Allen G. Orchestra and a lineup of singers and entertainers.

Proceeds from the event will fund free cancer support services offered at Glendale Adventist Medical Center. These include personal and family counseling, support groups, classes and a Positive Image program, which provides wigs, hats and scarves free of charge. All cancer patients, regardless of where they receive medical treatment, can participate in these cancer support services.



Prostate Screening, November 15, 2014

Glendale Community Health Fair

GAMC supported a prostate screening at the Glendale Health Festival with 37 participants. GAMC physician, Armen Kassabian, MD, screened patients at this event.

Christmas Party, December 15, 2014

An annual Christmas party at the Cancer Center featured wonderful music, food and the opportunity to celebrate the season with staff, fellow patients and survivors. Santa Claus gladly posed for pictures with guests. The Cancer Services staff hosted this event, mindful of the joy of giving and helping our patients at Christmas and throughout the coming year.

TOGETHER,
We Are...

Chrissy Kim, American Cancer Society

Making an Impact in the Fight to End Breast Cancer

As a global grassroots force of more than three million volunteers, the American Cancer Society (ACS) is making an impact in the fight to end breast cancer and all cancers. As the largest, private, not-for-profit investor in cancer research, ACS has contributed to a 20 percent decline in overall cancer death rates in the US since the early 1990s. That means we've helped save more than 1.3 million lives during that time. The progress that's been made is remarkable, but we won't rest until we finish the fight.

During the last century, ACS has led the way in the fight against cancer by helping people stay well by showing them steps they can take to reduce their cancer risk or detect it early; helping people get well by providing resources and support to help them through every step of a cancer experience; finding cures by investing in groundbreaking research; fighting back by working with legislators to pass laws to defeat cancer; and rallying communities worldwide to finish the fight.

The American Cancer Society has played a role in nearly every major breast cancer research breakthrough in recent history including establishing mammography as the standard for breast cancer screening; discovering lifesaving treatments, such as Herceptin and tamoxifen; discovering genes that cause breast cancer; and confirming the knowledge that genetics, body weight, lack of exercise and alcohol use can increase breast cancer risk by 34 percent.

Groundbreaking breast cancer research projects are underway at institutions across the country to help understand how to better prevent, find, treat and cure breast cancer. Unlike some organizations that support only breast cancer research, ACS also funds research to find cures for all types of cancer because discoveries in one area can also help find answers in another. Since 1946, ACS has invested more than $4 billion in cancer research. Of the researchers chosen for American Cancer Society funding, 47 have gone on to win the Nobel Prize.

We know that finding breast cancer at an early stage can increase the chances of treating it successfully, so we provide screening guidelines and education for health care professionals and engage in efforts to increase public awareness about the importance of yearly mammograms. Women can sign up to receive an email that reminds them to schedule the type of breast cancer screening we recommend based on our latest guidelines by visiting Cancer.org/remindme. The Society recommends that all women 40 and older get a mammogram every year, in addition to a breast exam as part of their regular health checkups. Although there is no guaranteed way to prevent breast cancer, which is why yearly mammograms are so important, the American Cancer Society recommends steps you can take to reduce your risk.

Having cancer is hard. Finding help shouldn't be. That's why the American Cancer Society is here around the clock to guide you through every step of a breast cancer experience. In communities nationwide, ACS is helping people right now by providing transportation assistance to and from treatment, free lodging when the treatment facility is far from home and emotional support programs that connect newly diagnosed breast cancer

(continued)

patients with breast cancer survivors. Patients can receive free wigs, assistance with treatment-related physical side effects, online support network, information, answers and support through our National Call Information Center available 24 hours a day, seven days a week at (800) 227-2345 or visit us online at Cancer.org; help addressing quality of life concerns (such as pain, symptoms, stress, and other disabilities) that treat the person beyond the disease; support from person-centered care planning, communication; and informed treatment decision-making aligned with individual and family goals.

The American Cancer Society could not accomplish its lifesaving mission without the dedication of committed partners like Glendale Adventist Medical Center. Together we are creating a world with less cancer and making an impact in the fight to end breast cancer.

Through the Society's many breast cancer programs, there are numerous volunteer opportunities, such as driving patients to treatment, providing one-on-one support, helping mobilize community members to participate in Making Strides Against Breast Cancer, Relay for Life, donating and shopping at Discovery shops and much more.

GAMC Cancer Services team.

TOGETHER, There Is...SUPPORT

Lily Villalobos, Clinical Research Director

Cancer Clinical Research: Supporting the Mission

Cancer is fundamentally a disease of tissue growth regulation failure. Cancer research via clinical trials is the scientific effort to understand this disease process and discover possible therapies. Clinical trials compare proposed treatments to the best existing treatments. They may be entirely new treatments, or they may be treatments that have been used successfully in one type of cancer and are now being tested to see whether they are effective in another type. More and more, such treatments are being developed alongside companion diagnostic tests to target the right drugs to the right patients, based on their individual biology. Clinical trials conducted through Glendale Adventist Medical Center's (GAMC) Office of Integrated Research Department support the hospital's mission, "To share God's love with our community by promoting healing and wellness for the whole person."

As part of the exceptional standards that accompany the accreditation awarded to GAMC's Cancer Center by the American College of Surgeons Commission on Cancer as a Community Hospital Comprehensive Cancer Program, we are able to effectively coordinate cancer research activities. These activities involve the various applications of treatments among surgeons, medical and radiation oncologists, diagnostic radiologists, pathologists and other cancer specialists, resulting in improved patient care. Some of the most common types of cancer treated in our community are breast cancer, prostate cancer, colon cancer and brain cancer. Building relationships within the oncology research community has helped to expand our research activities, thereby offering patients treatment options that include innovative therapies targeted at reducing the burden of cancer.

Current ongoing clinical trials being conducted at GAMC include breast cancer and the study of solid tumors. Expansion of the types and number of cancer clinical trials is underway. If you are interested in participating in clinical research trials at GAMC, please contact the Office of Integrated Research at (818) 409-8009.

CONTINUING MEDICAL EDUCATION

February 5, 2014

Breast and Gynecological Cancer Screenings: How Can Less Be Better?
Anita Nelson, MD, Medical Director, Women's Health Care Programs, Harbor-UCLA Medical Center; Professor of Obstetrics and Gynecology, David Geffen School of Medicine at UCLA.

July 2, 2014

Current Strategies for the Treatment of Metastatic Renal Cell Carcinoma
Sumanta Kumar Pal, MD, Assistant Professor, Department of Medical Oncology and Therapeutics Research; Co-director, Kidney Cancer Program, City of Hope.

MULTI-DISCIPLINARY TUMOR **CONFERENCES**

Denise Cleveland, RHIT, CTR, Data Manager

Multi-disciplinary Surgical & Breast Tumor Board Conferences:

A forum that provides our cancer specialists an opportunity for meaningful discussions relating to the treatment of cancer on an individual patient basis. This forum promotes excellence in cancer patient care and outcomes.

Glendale Adventist Medical Center Tumor Board conferences are held weekly, Wednesdays, at 7AM in Committee Rooms A/B.

The Breast Tumor Board is held the first Wednesday of the month and co-moderated by a radiologist specializing in mammography, breast MRI and diseases relating to the breast.

The Surgical Tumor Boards are held on subsequent Wednesdays.

The Cancer Registry Staff gathers the information required for discussion including: medical history, pertinent pathology and radiology materials for review. Multi-disciplinary tumor boards are moderated by a surgeon, medical oncologist or radiation oncologist. Both prospective and retrospective cases are discussed. Sometimes a case may be represented for further follow-up education and to report outcomes. Physicians are encouraged to bring any and all cases they feel treatment discussion would be of benefit to them and their patients for further care.

Tumor boards provide the presenting physicians with the opportunity to obtain recommendations from the multi-disciplinary team. Physicians advise their patients accordingly of treatment recommendations.

2013 PRIMARY SITES DISCUSSED	CASES
APPENDIX	1
BLADDER	8
BRAIN	1
BREAST	12
CHORDOMA	1
COLON	5
ESOPHAGUS	1
GALLBLADDER	1
GASTRIC	5
HEAD & NECK	7
KIDNEY	4
LIVER	4
LUNG	6
LYMPHOMA	2
MESOTHELIOMA	1
PANCREAS	5
POEMS SYNDROME	1
PROSTATE	11
RECTUM/ANAL	5
SOFT TISSUE	4
THYROID	4
UTERINE	2
UNKNOWN PRIMARY	7
TOTAL:	**98**

This total reflects sites presented. Some were represented at following meetings for further discussion and outcome.

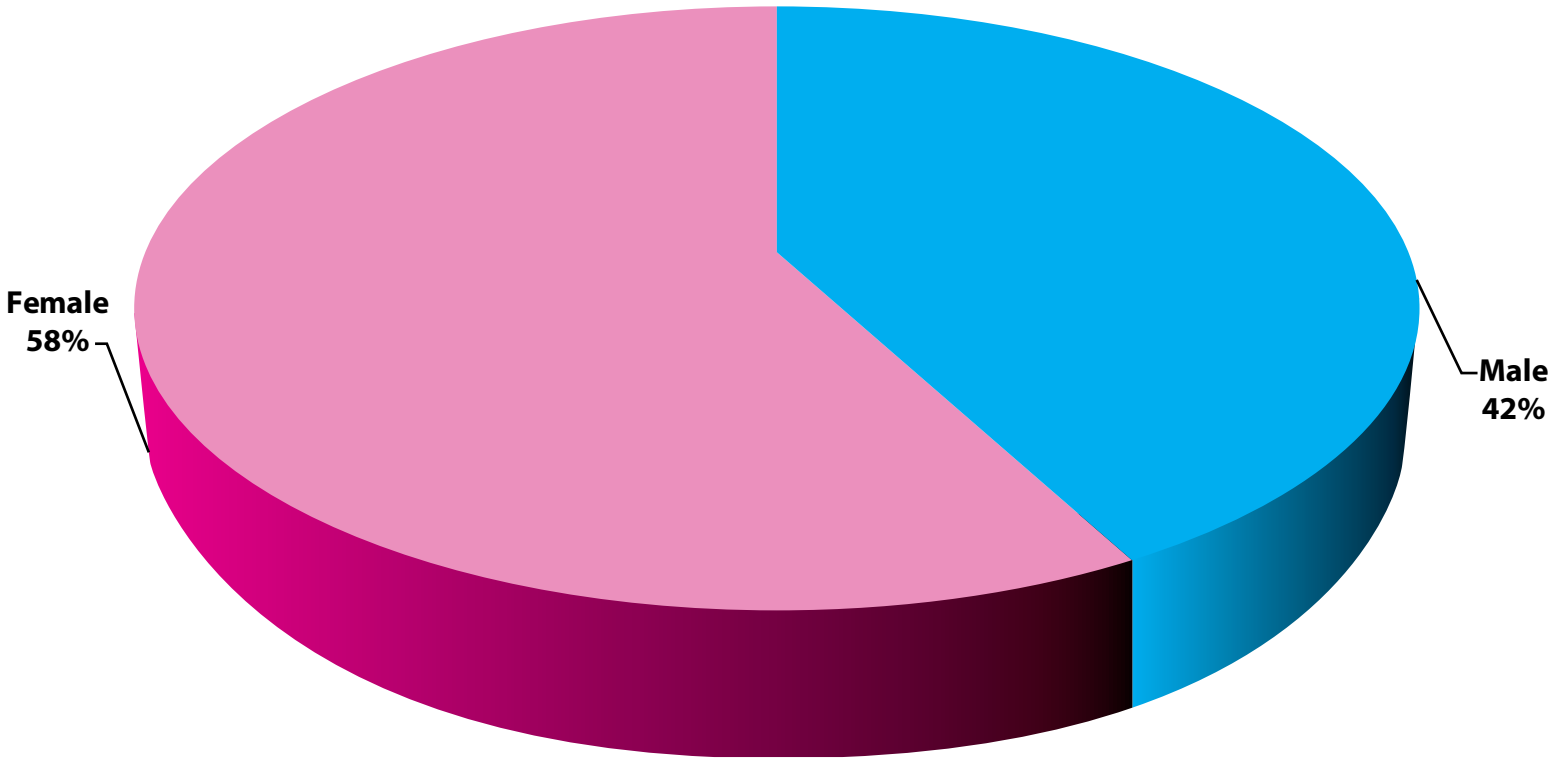
The American College of Surgeons requires that the number of cases presented annually is proportional to 15% of the analytic caseload and represents the institution's case mix. Our 2013 analytic caseload was 573 and 17% of this caseload was presented at the Tumor Board Conferences.Total cases presented at the Tumor Board are both analytic and non-analytic. Some of the analytic cases are from neighboring hospitals that may not have tumor boards.

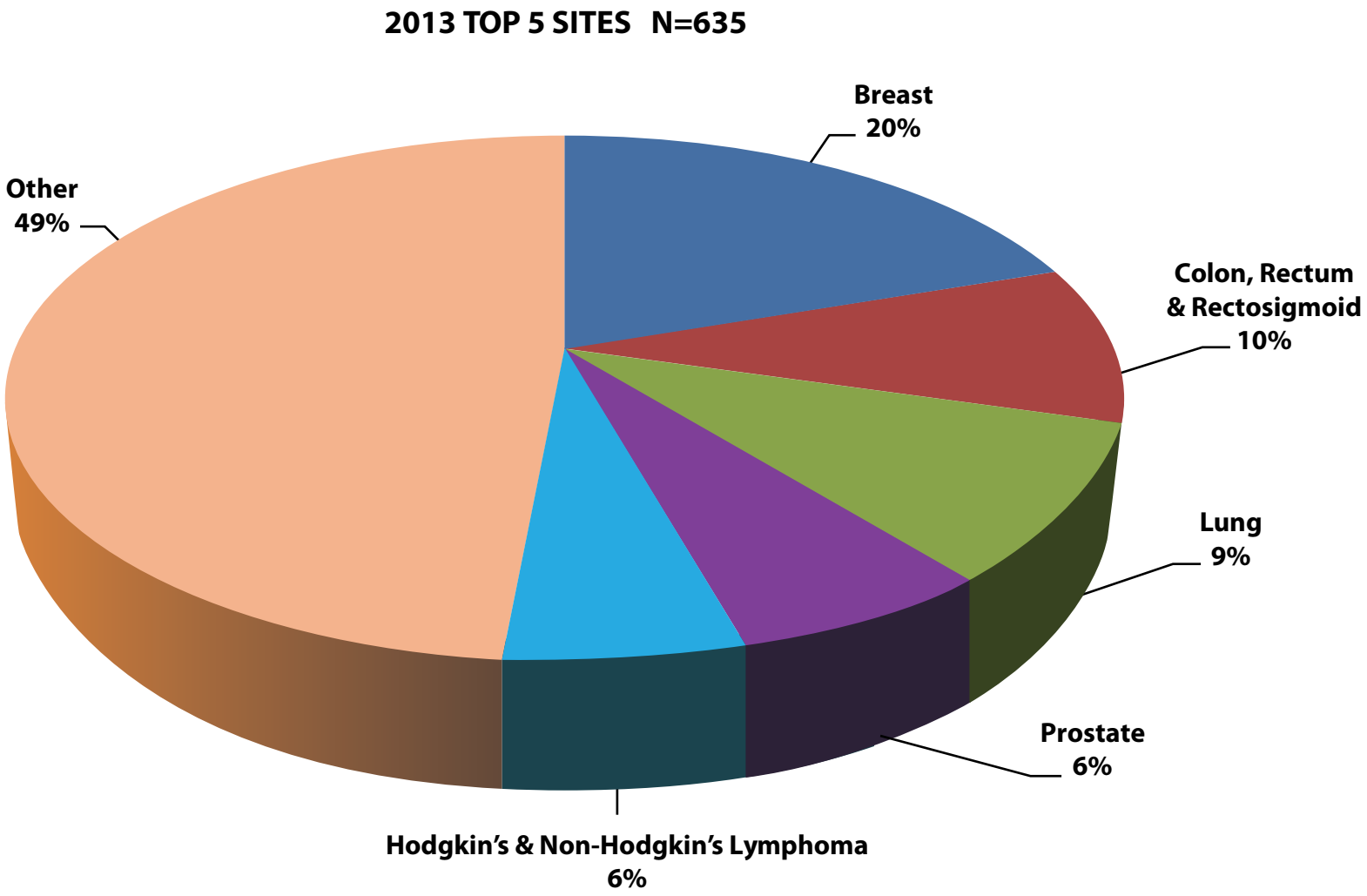
PRIMARY SITES **COMPARISON**

Primary Site	2007	2008	2009	2010	2011	2012	2013
All Sites	547	567	578	624	627	609	564
Oral Cavity/Pharynx	9	12	15	20	17	21	24
Esophagus	3	5	2	8	5	2	3
Stomach	19	11	23	18	20	17	14
Colon	46	51	55	57	56	59	44
Rectum & Rectosigmoid	21	23	23	21	16	18	18
Pancreas	15	11	16	21	14	19	14
Lung	45	53	65	82	62	63	57
Leukemia Myeloma & Hematopoietic	22	24	22	26	27	23	24
Soft Tissue	4	1	3	4	3	6	4
Melanoma of the Skin	10	7	6	7	11	14	5
Breast	88	120	101	91	120	115	103
Corpus Uteri	17	14	21	15	21	18	17
Ovary	5	11	8	10	16	17	11
Prostate	38	30	29	43	40	33	32
Bladder	30	21	25	32	40	26	32
Kidney/Renal	8	21	7	10	12	14	16
Brain/Nervous System	47	49	36	55	47	29	27
Endocrine	32	26	41	34	39	35	36
Lymphatic System	28	28	32	27	27	29	33
Unknown Primary	9	7	8	14	4	9	10

* Includes analytic cases only (diagnosed and/or received first course treatment at GAMC).

2013 MALE/FEMALE RATIO N=635




2013 TOP 5 SITES N=635
Breast
20%
Colon, Rectum
& Rectosigmoid
10%
Lung
9%
Prostate
6%
Hodgkin's & Non-Hodgkin's Lymphoma
6%
Other
49%

GAMC PRIMARY SITE **TABLE 2013**

Sorted from Most to Least Common

Site Group	Total Cases	Class		Sex		Stage					Not Applicable	Unknown
		Analytic	NonAn	M	F	Stage 0	Stage I	Stage II	Stage III	Stage IV		
ALL SITES	635	564	71	268	367	37	127	91	75	101	75	58
BREAST	125	103	22	1	124	21	29	24	18	7	0	4
COLON	48	44	4	21	27	1	7	10	11	5	0	10
LUNG/BRONCHUS-NON SM CELL	45	43	2	27	18	3	3	2	10	24	0	1
PROSTATE	40	32	8	40	0	0	5	21	4	2	0	0
NON-HODGKIN'S LYMPHOMA	35	30	5	16	19	0	12	4	3	9	0	2
BLADDER	33	32	1	27	6	8	16	5	2	0	0	1
THYROID	30	29	1	10	20	0	19	2	2	4	0	2
RECTUM & RECTOSIGMOID	19	18	1	11	8	2	4	1	0	2	0	9
STOMACH	18	14	4	13	5	0	0	1	1	5	1	6
CORPUS UTERI	18	17	1	0	18	0	3	1	5	3	0	5
KIDNEY AND RENAL PELVIS	17	16	1	12	5	0	8	2	4	2	0	0
LUNG/BRONCHUS-SMALL CELL	16	14	2	9	7	1	0	1	0	12	0	0
OTHER NERVOUS SYSTEM	16	14	2	1	15	0	0	0	0	0	14	0
PANCREAS	15	14	1	4	11	0	0	4	0	8	0	2
LEUKEMIA	15	14	1	7	8	0	0	0	0	0	14	0
BRAIN	15	13	2	4	11	0	0	0	0	0	13	0
OVARY	13	11	2	0	13	0	1	0	5	5	0	0
LIVER	12	11	1	10	2	0	3	3	1	1	2	1
UNKNOWN OR ILL-DEFINED	11	10	1	7	4	0	0	0	0	0	10	0
LARYNX	8	7	1	8	0	0	0	2	0	3	0	2
MYELOMA	8	7	1	6	2	0	0	0	0	0	7	0
CERVIX UTERI	8	7	1	0	8	0	3	0	0	2	0	2
OTHER ENDOCRINE	7	7	0	3	4	0	0	0	0	0	7	0
SOFT TISSUE	6	4	2	1	5	0	1	1	1	0	0	1

Site Group	Total Cases	Class		Sex		Stage					Not Applicable	Unknown
		Analytic	NonAn	M	F	Stage 0	Stage I	Stage II	Stage III	Stage IV		
TONGUE	5	5	0	3	2	0	2	0	2	1	0	0
SALIVARY GLANDS, MAJOR	5	5	0	3	2	0	2	1	0	1	1	0
MELANOMA OF SKIN	5	5	0	1	4	0	3	1	1	0	0	0
ANUS,ANAL CANAL,ANORECTUM	4	3	1	2	2	1	1	0	0	0	0	1
BILE DUCTS	4	4	0	3	1	0	1	0	0	0	0	3
ESOPHAGUS	3	3	0	2	1	0	0	1	0	0	0	2
SMALL INTESTINE	3	1	2	1	2	0	0	1	0	0	0	0
GALLBLADDER	3	3	0	0	3	0	0	1	1	1	0	0
OTHER HEMATOPOIETIC	3	3	0	2	1	0	0	0	0	0	3	0
HODGKIN'S DISEASE	3	3	0	0	3	0	0	1	1	0	0	1
MOUTH, OTHER & NOS	2	2	0	1	1	0	1	0	0	1	0	0
TONSIL	2	2	0	2	0	0	0	0	1	1	0	0
OTHER DIGESTIVE	2	2	0	1	1	0	0	0	0	0	2	0
PLEURA	2	2	0	1	1	0	0	0	0	1	0	1
BONE	2	2	0	1	1	0	1	0	0	0	0	1
LIP	1	1	0	1	0	0	0	1	0	0	0	0
FLOOR OF MOUTH	1	1	0	1	0	0	0	0	0	1	0	0
HYPOPHARYNX	1	1	0	1	0	0	0	0	0	0	0	1
RETROPERITONEUM	1	0	1	0	1	0	0	0	0	0	0	0
PERITONEUM,OMENTUM,MESENT	1	1	0	1	0	0	0	0	1	0	0	0
NASAL CAVITY,SINUS,EAR	1	1	0	1	0	0	1	0	0	0	0	0
OTHER RESPIR & THORACIC	1	1	0	0	1	0	0	0	1	0	0	0
KAPOSI'S SARCOMA	1	1	0	1	0	0	0	0	0	0	1	0
TESTIS	1	1	0	1	0	0	1	0	0	0	0	0

Linh Chen, MD, Diagnostic Radiology, Medical Director of Women's Imaging

In 2013, an estimated 300,000 new cases of breast cancer were expected to be diagnosed among United States women, with approximately 40,000 breast cancer deaths. Only lung cancer accounts for more cancer deaths in women. Early detection remains the primary defense against the development of life-threatening disease. Over the past few years, there have been disagreements over recommended screening schedules which have caused some confusion among many women.

For many years, the general guideline for breast cancer screening has been the following. For women younger than 40 years, monthly breast self-examination (BSE) and clinical breast exams every three years have been recommended, beginning at age 20. The most widely recommended screening approach in the United States has been annual mammography beginning at age 40 [1].

In November 2009, however, the US Preventive Services Task Force (USPSTF) changed breast cancer screening guidelines, recommending against routine mammography before age 50 as well as:

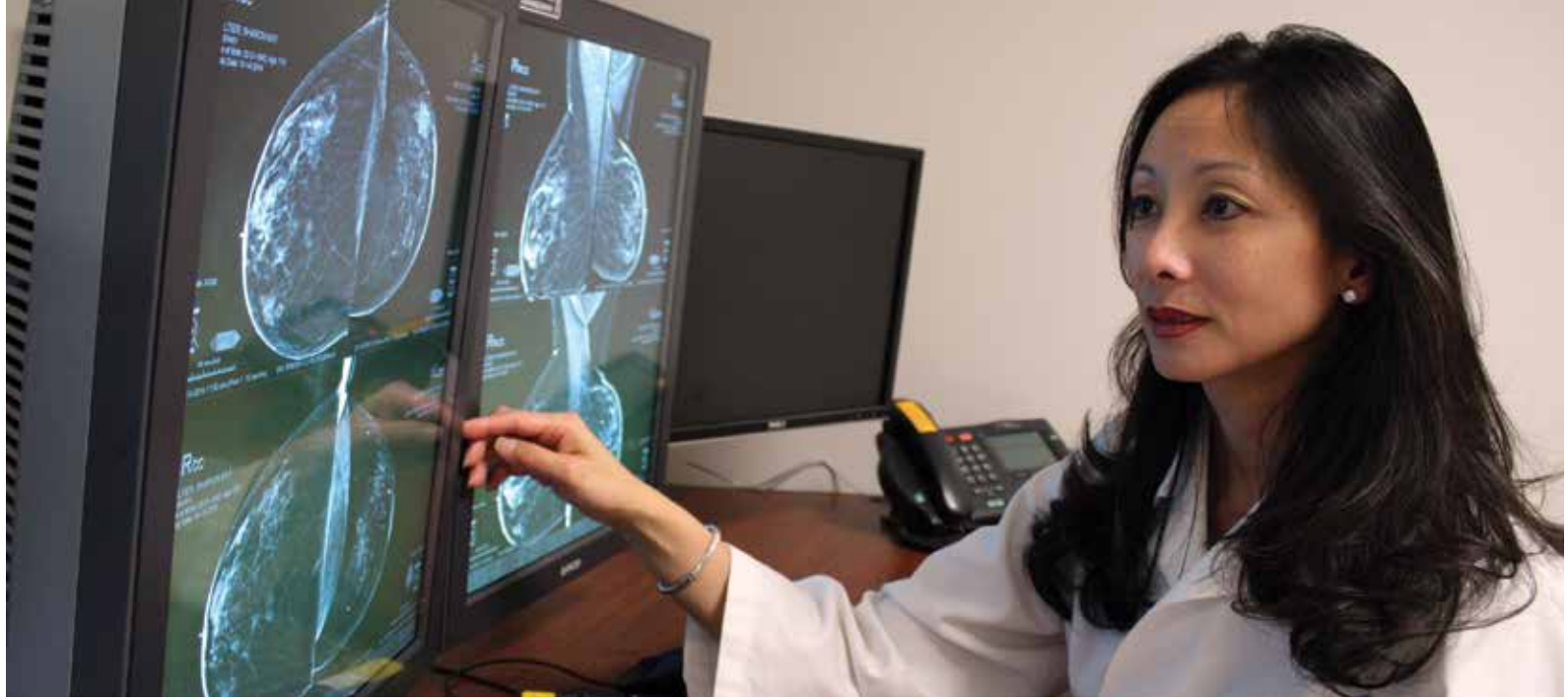
- Biennial (every two years) screening mammography for women between ages 50 and 74.
- The decision to start regular, biennial screening mammography before age 50 years should be based on individual patient history.
- No requirement for clinicians to teach women how to perform BSE.
- Insufficient evidence to assess the benefits and harms of clinical breast examination (CBE) beyond screening mammography in women 40 years or older.
- Insufficient evidence to assess the benefits and harms of screening mammography in women 75 years or older.

Despite the USPSTF recommendations, the American College of Obstetricians and Gynecologists (ACOG) continues to recommend counseling patients that BSE has the potential to detect palpable breast cancer and should be performed. ACOG also continues to recommend adherence to its current guidelines, which include the following[2]:

- Screening mammography every 1-2 years for women 40-49 years
- Screening mammography every year for women 50 years or older

Mammography

Mammography utilizes low-dose x-ray to image the breasts. Digital mammography is a mammography system in which the x-ray film is replaced by solid-state detectors that convert x-rays into electrical signals similar to those found in digital cameras. Both types of exam require breast compression. According to published results from the Digital Mammographic Imaging Screening Trial (DMIST), digital mammography performed better than film mammography for pre- and perimenopausal women under age 50 with dense breasts.



Screening mammography is the cornerstone of early detection of breast cancers because it can show small cancers up to two years before the cancers become palpable. Diagnostic mammography is used to evaluate a patient with abnormal clinical findings — such as a breast lump or pain. Diagnostic mammography may also be done after an abnormal screening mammogram in order to evaluate the area of concern on the screening exam.

Tomosynthesis

Digital breast tomosynthesis, also called three-dimensional (3-D) breast imaging, is a mammography system where the x-ray tube moves in an arc over the breast during the exposure, creating a series of thin slices which can be reconstructed into a 3-dimensional picture of the breast. Digital tomosynthesis of the breast is different from a standard mammogram in the same way a CT scan of the chest is different from a standard chest X-ray. One is 3-dimensional, the other is flat. Researchers have found that digital breast tomosynthesis (DBT) leads to reduced recall rates and an increase in cancer detection in a large breast cancer screening program.[3]

Radiation doses from digital breast tomosynthesis (DBT) is generally comparable to conventional two-view full-field digital mammography (DM). When comparing doses with the "average" breast (compressed thickness of 5 cm, 50% glandular fraction), a DBT acquisition resulted in 1.30 mGy, only an 8% higher mean glandular dose than the DM acquisition of 1.20 mGy. For a thicker breast sample (6.0 cm and 14.3% glandular fraction), a DBT acquisition was 2.12 mGy, which was 83% higher than a DM acquisition of 1.16 mGy.[4]

Ultrasonography

Ultrasonography is a useful adjunct to mammography, especially in the examination of suspicious abnormalities detected on mammography or physical examination. As a screening tool, ultrasonography is limited by a number of factors, most notably its failure to detect microcalcifications and its poor specificity (34%). Ultrasonography is used primarily to evaluate masses and to differentiate between benign cysts from solid breast masses, which may require tissue sampling. This imaging technique is also routinely used in the guidance of biopsies and the staging of the axillary lymph nodes.

Magnetic Resonance Imaging (MRI)

MRI is highly sensitive for cancer and is particularly useful in younger women at high risk who tend to have denser breast tissue. MRI does not

(continued)

replace mammography and ultrasound except in certain unusual situations and, in general, should not be performed without conventional imaging first. Contrast-enhanced MRI techniques using dedicated MRI breast coils have been found to have a high detection rate of invasive breast cancer. The technique relies predominantly on the neovascularity of the invasive tumors and their rapid uptake and washout of contrast agent relative to background breast tissue. MRI sensitivity for invasive disease is extremely high, approaching 99% in combination with mammography and ultrasound. MRI is used as an adjunct to conventional mammographic assessment because it has a lower sensitivity for ductal carcinoma in situ (DCIS), which tends have variable neoangiogenesis. Although sensitivity for high-grade DCIS is generally high because these lesions are hypervascular, MRI has low sensitivity for low-grade DCIS, which can have minimal enhancement and appear indistinguishable from benign breast tissue.

Breast MRI is not used as a general screening tool, because of significantly higher cost than mammography and poor specificity (26%), resulting in false-positives that generate significant additional diagnostic costs and unnecessary biopsies. The American College of Surgeons (ACS) recommends annual breast MRI screening in selective patients with the following risk factors:

- BRCA mutation.
- First-degree relative of BRCA carrier but untested.
- Lifetime risk approximately 20-25% or greater, as defined by BRCAPRO or other risk models.
- Radiation to chest in ages 10-30 years.

MRI is a useful adjunct diagnostic or problem solving tool. The following are current indications for MRI:

- Characterization of an indeterminate lesion after a full assessment with physical examination, mammography and ultrasonography.
- Detection of occult breast carcinoma in a patient with carcinoma in an axillary lymph node.
- Evaluation of suspected multifocal or bilateral tumor.
- Evaluation of invasive lobular carcinoma, which has a high incidence of multifocality.
- Evaluation of suspected extensive high-grade intraductal carcinoma.
- Detection of occult primary breast carcinoma in the presence of metastatic adenocarcinoma of unknown origin.
- Monitoring of the response to neoadjuvant chemotherapy.
- Detection of recurrent breast cancer.
- Determining whether silicone implants have ruptured.

Percutaneous Needle Biopsy

Percutaneous vacuum-assisted, large-gauge, core-needle biopsy (VACNB) with image guidance is the accepted method for tissue sampling of suspicious breast lesions. Needle biopsy may be performed using stereotactic, ultrasound or MRI guidance. Core needle biopsies can minimize the need for operative intervention (and subsequent scarring), and provide accurate pathologic diagnosis for appropriate management.

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BREAST CANCER SURGERY **AT GAMC**

Sam Carvajal, MD, General Surgery

Glendale Adventist Medical Center (GAMC) offers state-of-the-art breast cancer surgery. This includes biopsy, breast conservation surgery, mastectomy, neoadjuvant therapy (when appropriate) and all other forms of reconstructive surgery. Because of an efficient mammographic and MRI center, GAMC has strived to shorten the time between the first mammogram to definitive surgical treatment.

Surgical Options

Patients with a benign breast mass at GAMC are given a full range of surgical options for treatment, including vacuum-assisted rotary biopsy excision, ultrasound guided cryoablation and surgical excision. When a patient presents with microcalcifications not amenable to stereotactic biopsy or with atypical ductal hyperplasia (ADH) after core biopsy, needle localized excisional biopsy is routinely performed. When a diagnosis of ductal carcinoma in situ or invasive cancer is made, appropriate oncologic breast cancer surgery is employed. Patients are encouraged to undergo breast conservation surgery when appropriate. The majority of women undergoing breast oncologic surgery are choosing partial mastectomy with sentinel lymph node biopsy. If a patient has a positive sentinel node and otherwise fits into the criteria of the Z-11 trial, no further axillary surgery is performed. Otherwise, when a patient has a positive sentinel node, full axillary node dissection is performed. Modified radical mastectomy is routinely performed when at a patient's request or when oncologically necessary. When immediate reconstructive surgery is planned, a skin sparing technique is typically performed.

Breast Reconstruction Options

All forms of breast reconstruction surgery are offered at GAMC preferably in an immediate setting but delayed when chosen by the patient. Reconstruction options include tissue expander implant followed by permanent implant, latissimus rotation flap with implant, transverse rectus abdominis myocutaneous (TRAM) pedicle flap and TRAM free flaps. At GAMC, the majority of reconstruction operations performed are TRAM free flaps.

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Timing of Surgical Care

GAMC has strived to shorten the time from initial imaging to definitive surgical care. Protocols have been instituted to allow the mammographic radiologist to initiate, after having informed the referring physician, more detailed diagnostic imaging, including ultrasound and even performing immediate biopsy. To ensure efficiency, when surgical care is required, the radiologist will directly contact the referring physician to initiate surgical referral. The MRI is usually indicated after initial breast cancer diagnosis. MRI's are quickly performed, and, when needed, MRI-guided biopsy can be done at GAMC.

Neoadjuvant Therapy

Typically, patients who have T3 or large T2 tumors are referred for neoadjuvant chemotherapy and radiation therapy. If appropriate, breast conservation surgery can be performed after the neoadjuvant therapy. In the near future, genomic testing will be employed to determine which patients are likely to respond to neoadjuvant treatment, thereby separating out likely nonresponders for immediate surgery.

Summary

The Cancer Center oversees the surgical breast oncologic care provided at GAMC. All aspects of care are commensurate with National Comprehensive Cancer Network (NCCN) guidelines. When possible, patients are enrolled in appropriate research protocols.

"Come Unto Me"

An invitation to healing, wholeness and hope.

Come unto me all you who are weary and burdened and I will give you rest.

—Matthew 11:28

Michele Cosgrove, MD, Pathology, Department Chair and Chief of Staff

The Pathologist's Evaluation of Breast Carcinoma; Diagnostic and Theranostic Considerations

Introduction

Tissue samples from breast abnormalities are one of the most commonly encountered specimen types in the pathology laboratory. These range from tiny needle aspiration or core biopsy samples to entire breast resections (modified radical mastectomies) with underarm (axillary) lymph nodes.

Pathologic Evaluation, Gross Examination

The pathologic examination of the specimen begins with a dissection and detailed description of the specimen gross or macroscopic features—size, appearance, measurement of any visible tumor, relationship to surgical margins and enumeration of all lymph nodes. Some cases will require intraoperative examination by the pathologist to assess surgical margins or involvement of sentinel lymph nodes by tumor. This allows determination of the most appropriate extent of surgery. Documentation of fixation details—time from surgical removal to placing specimen into chemical fixative, time from fixation until tissue embedding, and type and concentration of fixative used are also recorded.

Microscopic Examination – Grading and Staging

The next step is classification of the lesion on the basis of the microscopic appearance. Many clinically worrisome breast findings will show benign pathology, most often fibrocystic changes or benign fibroadenoma. It is important that benign pathology findings are always carefully correlated with clinical and radiologic findings for confirmation. This clinical, imaging and pathology correlation has been referred to as the "triple test."

When malignancy is identified, it is further classified. The most common breast malignancy is carcinoma, although sarcomas and lymphomas of the breast can also occur. The current World Health Organization (WHO) classification of breast tumors lists over 21 subtypes of carcinoma alone.[2] The most common types are ductal and lobular carcinomas, classified based on the similarity of the tumor cells to those of the normal breast lobules or ducts. Both ductal and lobular carcinomas can exist in early, preinvasive (in-situ) or invasive (infiltrating) forms. Once classified, tumors are then assigned a histologic grade. The modified Bloom-Scarf-Richardson scoring system is a histologic grading system clinically validated for use in the most common types of breast carcinoma. A score is assigned, taking into account the architectural pattern, nuclear features and rate of cell division (mitotic activity). The pathologist's microscopic examination will also determine final status of surgical margins and extent of spread of tumor to lymphatics, blood vessels and lymph nodes.

The final pathology report on a breast cancer case will include multiple clinically validated elements that affect prognosis and treatment such as tumor type, size, histologic grade, margin status, pathologic stage and report of theranostic studies (explained below). At Glendale Adventist Medical Center (GAMC) and other facilities accredited by the American College of

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Surgeons Commission on Cancer and the College of American Pathologists, all of these findings are summarized in a synoptic format to ensure that all clinically validated elements are reported and readily available to the treating physicians.

Theranostic Evaluation

Theranostics refers to testing that is directed toward development of specific, individualized therapies for diseases. Breast carcinoma is an excellent example of a disease model where theranostic testing is well established. Determination of estrogen and progesterone hormone receptor expression (ER/PR) and Her2/neu gene expression by breast tumors is routinely used to individualize therapy, matching pharmacologic treatments according to the pattern of expression for these markers. Pathologists routinely evaluate ER and PR expression by immunohistochemistry (IHC) on invasive breast carcinomas and DCIS. If 1% or more of the tumor cell nuclei stain with antibodies to these markers, the tumor is considered "positive" for that marker. Patient's with ER and/or PR receptor positive tumors are candidates for hormonal therapies such as aromatase inhibitors, selective estrogen receptor modulators and estrogen receptor down regulators. The absence of expression of these receptors means the patient is not likely to benefit from such therapies.

Her2/neu expression is evaluated routinely in invasive breast carcinomas using either IHC, fluorescent in-situ hybridization (FISH) or both methods, according to established testing and reporting algorithms. Patients whose tumors show elevated expression of Her2/neu by IHC, FISH or both are candidates for trastuzumab therapy.

Patients whose tumors are negative for ER and PR expression and Her2/neu overexpression ("triple-negative" tumors) are not expected to benefit from hormonal therapy or trastuzumab therapy.

Another example of theranostic testing commonly used for breast cancer patients is molecular testing. There are several commercially available tests which analyze the expression of from 21-70 genes by tumor cells. These molecular "signatures" can help make predictions about the likelihood of cancer recurrence after surgery. This improves selection of appropriate

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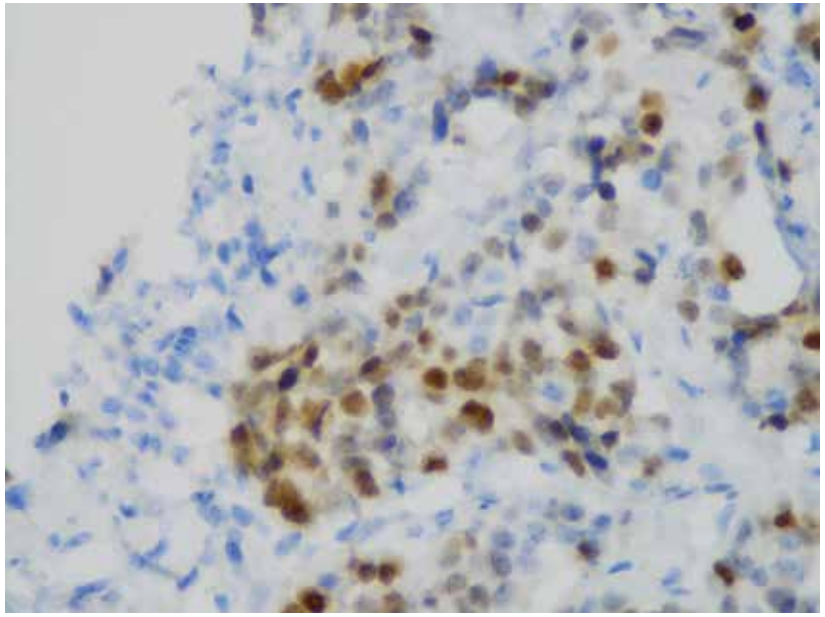

Figure 1 – Positive ER IHC, 400x magnification

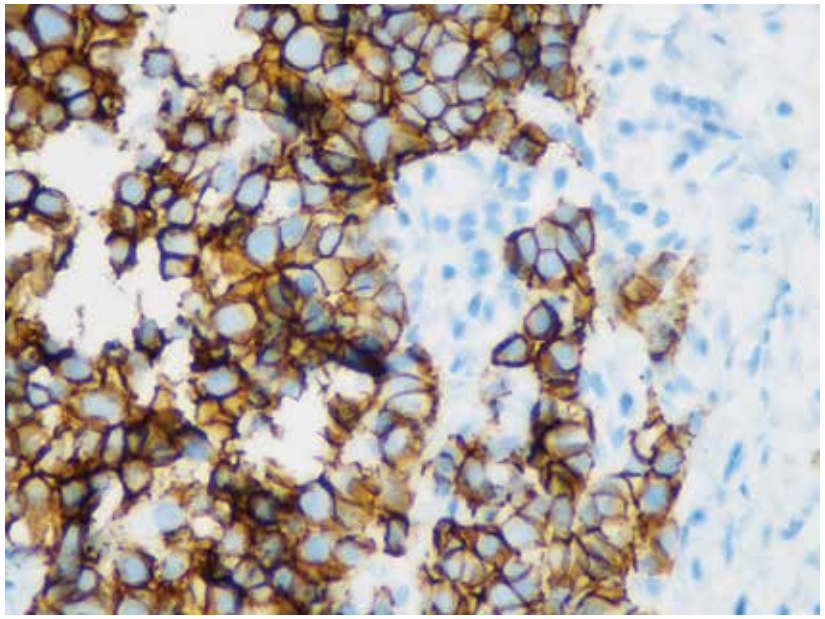

Figure 2 – Positive (3+) Her2/neu IHC, 400x magnification.

chemotherapy in patients with high recurrence risk. The proper use of these tests depends on applying them to patients with a particular disease stage and node status. The most commonly used of the commercially available tests, the 21 gene assay by RT-PCR is designed for use in patients with stage I or II node negative and ER positive tumors.

Accurate theranostic testing of the pathology sample is a crucial and technically demanding task that requires rigorously standardized protocols for specimen collection, fixation, testing and reporting. Essential components include controlling variables like cold ischemic time (time from collection to fixation), chemical fixative, selection of appropriate tissue blocks for testing, use of laboratory test systems which have been clinically validated, robust laboratory quality assurance systems and use of standardized criteria for specimen evaluation, scoring and reporting of results. Recognizing the degree to which appropriate therapy relies on these results, the American Society of Clinical Oncologists (ASCO) and College of American Pathologists (CAP) have jointly published criteria for the testing and reporting of the breast markers ER/PR and Her2/neu.[1,3] These ASCO/CAP guidelines are utilized in CAP accredited laboratories such as the one at GAMC. In addition, all of our pathologists are required to participate in on-going proficiency testing to ensure continuous competency in interpretation of these tests.

There is a need for ongoing breast cancer research, including basic pathology studies of molecular and proteomic expression to allow for further advances in personalized therapy. Through the GAMC Cancer Services Program, our Research Department reviews breast cancer cases to determine if patients might be eligible to participate in approved clinical research. One such option is for the patient to allow remnant tumor tissue which remains after completion of all necessary diagnostic and theranostic testing to be contributed for medical research. Many of our patients have chosen to participate with the hope of benefitting patients who come after them. The generosity and courage of our cancer patients are an inspiration to all of us.

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THE ROLE OF RADIOTHERAPY **FOR BREAST CANCER**

Sara Kim, MD, Radiation Oncology, Medical Director of Radiology Oncology

Radiation Therapy for Ductal Carcinoma in Situ (DCIS)

Breast Conservation Therapy (BCT) entails lumpectomy followed by radiation therapy to the breast. BCT has become the standard treatment for women with DCIS.

Mastectomy is reserved for patients with diffuse microcalcifications throughout the entire breast or large volumes of palpable disease, or when there are persistently positive surgical margins with breast-conserving surgery. The role of radiation for breast conservation therapy in patients with DCIS was defined by the National Surgical Adjuvant Breast Project (NSABP) B-17 trial, a prospective randomized clinical trial. 818 women were randomized to breast conserving surgery with or without adjuvant radiation to the breast. The overall survival at eight years was equivalent in the two treatment arms (radiation - 94% overall survival; no radiation - 95% overall survival). The addition of breast radiation reduced the 8-year overall rate of recurrence in the ipsilateral breast from 26.8% to 12.1%. Radiation not only reduced the rate of noninvasive disease recurrence but also reduced the rate of invasive disease recurrence.[1] The benefit of radiation therapy was significant for both tumors measuring 1 cm or smaller and tumors larger than 1 cm. Radiation produced a reduction in recurrences in the breast in both the patients with high-risk pathologic features and the patients with low-risk pathologic features.[2]

The results of NSABP B-17 trial were confirmed by European Organization for Research and Treatment of Cancer (EORTC) 10853 trial, a prospective randomized clinical trial which randomized more than 1,000 patients with DCIS to breast conserving surgery with or without radiation therapy. Patients treated with radiation had a lower 4 year rate of overall recurrence (recurrence of invasive and noninvasive disease) in the breast (9% vs. 16%).[3]

Radiation Therapy for Early-Stage Breast Cancer

Breast conservation therapy (lumpectomy and axillary LN assessment, followed by radiation) has been shown to have an equivalent outcome to modified radical mastectomy. This organ-preserving approach has had a profound impact on patient well-being and quality of life.[4]

NSABP B-06 trial was a prospective, randomized, phase III clinical trial comparing breast conserving surgery and radiation as an alternative to mastectomy for early-stage breast cancer. The 12-year data showed that treatment with lumpectomy and radiation was equivalent to modified radical mastectomy in terms of disease-free and overall survival.[5] The Early Breast Cancer Trialists Collaborative Group (EBCTCG) compiled the data from NSABP B-06 and six other randomized trials comparing modified radical mastectomy to breast conserving surgery plus radiation therapy for early-stage breast cancer. From the data of 3,100 women, the EBCTCG found that both treatment groups had equivalent 10-year survival of 71%.[6] After breast conservation surgery, adjuvant whole breast radiation lowers the relative risk of ipsilateral breast tumor recurrence by approximately 70% at 5 years and produces a 5% absolute improvement in 15-year overall survival.[7]

Breast Brachytherapy: Partial Breast Radiation

In appropriately selected patients with early-stage breast cancer who have undergone lumpectomy, brachytherapy or internal radiation enables delivery

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of radiation to tissues at highest risk of recurrence while minimizing radiation exposure to the normal tissues. Numerous clinical studies of both low-dose rate and high-dose rate brachytherapy for treatment of breast cancer have been conducted worldwide and show low local recurrence rates.[8-11]

Using SAVI applicator, patient typically receives a one- to-five-day treatment that is either used as primary radiation therapy or as a boost used in conjunction with external beam radiation. A catheter is implanted into the tumor resection cavity, either at the time of lumpectomy or a few weeks postoperatively. A high-dose rate remote afterloader inserts the 192Iridium source into the struts of the SAVI applicator for a few minutes to deliver the radiation to the tumor resection cavity. After the brachytherapy is completed, the SAVI applicator is removed from the patient's breast.

Post-Mastectomy Radiation Therapy

Radiation after mastectomy and chemotherapy has been shown to increase local control, disease-free survival and overall survival. Post-mastectomy radiation can improve overall survival in circumstances in which local failure can be substantially reduced. Post-mastectomy radiation is not routinely offered unless the patient has extensive lymph node involvement, tumor size greater than 5 cm, or incomplete surgery.[12-13]

The Danish 82b trial was a prospective phase III clinical trial of 1,708 pre-menopausal women with node-positive breast cancer treated with modified radical mastectomy and methotrexate-based chemotherapy who were randomized to receive post-mastectomy radiation. Patients who received post-mastectomy radiation had a decrease in local recurrence (9% vs. 32%) and increase in overall survival (54% vs. 45%).[14] A randomized prospective phase III clinical trial from British Columbia showed increase in local control (87% vs. 67%) and increase in cancer-specific survival (50% vs. 33%) in patients who received radiation after mastectomy and chemotherapy.[15]

Radiation Therapy for Inflammatory Breast Cancer

Multi-modality therapy consisting of chemotherapy, modified radical mastectomy and post-mastectomy radiation is used to treat inflammatory breast cancer. The chest wall and supraclavicular fossa are treated using the same techniques described for post-mastectomy radiation.

Hypofractionation for Whole Breast Radiation

In England and Canada, adjuvant radiation to the whole breast is given with hypofractionation (both the total dose and number of fractions are decreased compared to conventional whole breast fractionation) with excellent results.[16-17] Four randomized clinical trials in Canada and England have compared conventional whole breast radiation to hypofractionated whole breast radiation. The tumor breast local control and long term side effects between both arms were comparable for patients who satisfied certain characteristics.[18-22]

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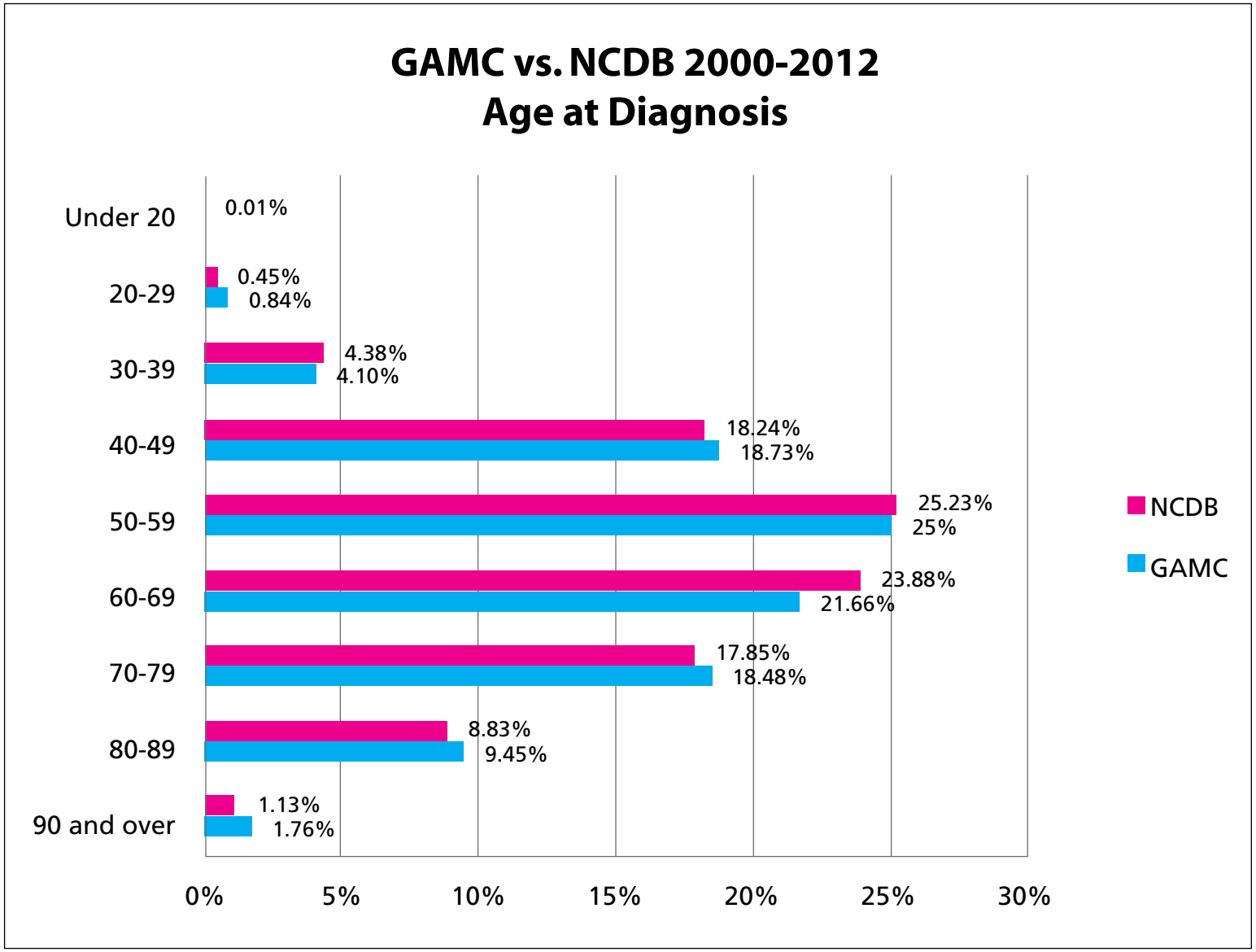
Boris Bagdasarian, DO, Hematology and Oncology, Chairman, Cancer Committee

Epidemiology of Breast Cancer

Breast cancer remains one of the most common cancers in the world. In the western industrialized countries it is the most prevalent cancer in women. In the United States, it accounts for 32% of all cancers in this group.[1] It is estimated that breast cancer develops in one of eight American women during their lifetime, assuming a life expectancy of 85 years. The risk is considerably higher for women with preexisting risk factors such as older age, strong family history of breast cancer, known mutations in breast cancer predisposition genes or personal history of histologically demonstrated precursor lesions.[2] This disease has increased steadily over the past 25 years: The annual percentage change was 3.7% between 1980 and 1987, decreasing to 0.5% between 1987 and 1999.[3] It has been hypothesized that this temporary increase in incidence was secondary to introduction of systemic use of screening mammography and lead-time. It is predicted that worldwide, more than 1.4 million new cases will be diagnosed this year. Incidences vary substantially. Worldwide, the ratio and mortality to incidence is approximately 61% for breast cancer; thus this disease is the fifth leading cause of death from cancer overall and the leading cause of cancer mortality among women (14% of cancer deaths). In the United States, an estimated 230,000 cases will be diagnosed in 2013. The five-year survival rates for breast cancer diagnosed in localized, regional and disseminated stages are 97%, 79% and 23%, respectively, in the United States. Percentage of patients with localized breast cancer is even higher among women who follow a systematic screening strategy; among these patients between 20% and 30% of cases are diagnosed in a non-invasive stage. In contrast, at least 50% of breast cancer cases in the developing world are diagnosed in Stage III or IV, because mortality for these later stages is several fold higher than for early stage disease. This high frequency of advanced stage lesions represents a substantial public health challenge for these countries.

TOGETHER, We Are...**STRONG**

GRAPH 1



Source: NCDB, Commission on Cancer, ACS, Benchmark Reports. (NCDB N=1589 Hospitals)

Approximately 49% of GAMC patients were diagnosed between the ages of 20-59, similarly 48% of the NCDB/United States were at 48% for the same age group.

Risk Factors

The incidence of breast cancer varies markedly in different groups and is influenced by certain well-established risk factors **(Table I)**. The most prominent risk factors are sex and age. Breast cancer is 100 times more common among women than men.[1] The incidence of breast cancer increases substantially with age ranging from fewer than 10 cases per 100,000 women between the ages of 20 and 30, to more than 300 cases per 100,000 over the age of 60. The rate of increase in incidence declines after menopause and especially after age 80. Mortality rates parallel this pattern although mortality from breast cancer decreases after the seventh decade of life because of the increasing frequency of other causes of death.

Familial Risk

Having close relatives with breast or ovarian cancer increases the risk of breast cancer several fold.[4] Individuals with a first degree relative (such as a mother or sister) with the disease have a substantially increased risk compared with women without such a family history. Approximately 5% to 10% of all breast cancers are associated with highly penetrant mutations in genes, such as BRCA1 and BRCA2. An additional 15% to 20% of women diagnosed with breast cancer have a positive family history, which may be due to the inheritance of several low penetrance genes that increase risk or, alternatively, share environmental exposures. The increase is greater if the first degree relative had bilateral breast cancer and if the disease was diagnosed before age 50. Both paternal and maternal sides of the family contribute to increased risk. A family history of ovarian or prostate cancer also increases the risk of breast cancer and one of the familial breast cancer syndromes.

Genetic Risk

Since the identification and cloning of BRCA1 and BRCA2, two genes associated with breast cancer (and ovarian cancer), much has been learned about the role of these genes and normal development and malignant transformation. BRCA1 and BRCA2 account for most cases of hereditary breast cancer in the United States and Europe.[5] BRCA1 and BRCA2 act as tumor suppressor genes and in association with RAD51, operate in a common DNA damage response pathway implicated in a double stranded repair.[6,7]

Breast cancer associated with BRCA1 mutations are frequently of higher grade and are hormone receptor negative. A higher percentage of cancers related to the BRCA1 mutation have atypical or typical medullary histologic features.[8,9] Breast cancers associated with mutations in BRCA2 do not defer

(continued)

Table I

Established Risk Factors for Breast Cancer

Risk Factor	Relative Risk
Sex (female vs. male)	100
BRCA1 or BRCA2 mutation	10-30
Family history of breast cancer	
First degree relative	2-7
Second degree relative	1.5-1.8
Age (>50 vs. <50 yrs.)	6.5
Benign breast disease	
Atypical hyperplasia	4.0-4.4
Hyperplasia	2.0
Breast biopsy	1.5-1.8
Nulliparity	2.0
Age at first live birth (>30 vs <20 yrs.)	1.3-2.2
Age at menopause (>55 vs. <55yrs.)	1.5-2.0
Age at menarche (<12 vs. >14 yrs)	1.2-1.5
Hormone-replacement therapy	1.0-3.0
Exposure to ionizing radiation	1.4
Alcohol consumption	1.1-2.2
(12 g/day [30 mL/day] vs. none)	
Increased body mass index	
Premenopausal women	0.54
Postmenopausal women	1.26-2.52

appreciably from sporadic cancers. No special tumor phenotype has been ascribed to ovarian cancers associated with BRCA1 or BRCA2. The lifetime cumulative risk of invasive breast cancer or individuals with BRCA1 or BRCA2 mutations ranges from 50% to 87%. For invasive epithelial cancer, the risk is 15% to 65%. Familial breast cancer, however, accounts for fewer than 10% of all breast cancers. BRCA1-related and BRCA2-related familial disease constitutes only 2/3 to 3/4 of these cases. Among women younger than 35 years old with breast cancer, 10% to 15% have BRCA1 mutation. Women with BRCA1/2 mutations already affected by the disease, have a risk, to age 70, of contralateral breast cancer that ranges between 50% to 64%. The risks of cancer of the stomach, gallbladder, bile ducts and pancreas are increased for carriers of the BRCA2 mutation and for male carriers of the mutation, the risk for breast and possibly early onset prostate cancer are increased. Other genetic abnormalities and less common familial cancer syndromes are responsible for an additional small percentage of cancers. The Li-Fraumeni syndrome is a rare, highly penetrant, autosomal dominant condition caused by mutations in the TP53 gene which plays a critical role in cell cycle control and apoptosis. Li-Fraumeni syndrome is characterized by early onset (younger than 40 years) of breast cancer, soft tissue sarcomas, leukemia, primary brain tumors and adrenocortical cancers.[4,9,10]

The cloning of BRCA1 and BRCA2 and the presumed appearance of additional molecular markers of risk, have brought the issue of genetic screening and counseling to the forefront. Both negative and positive test results are associated with a variety of emotional, legal, economic and work-related issues. Ongoing clinical trials will determine who the optimal subjects are for screening and how screening and counseling should be conducted, and what type of societal involvement is needed so that genetic screening can be used without exposing the subjected to unexpected risks and consequences.

Ethnic Background

There is much variation in incidence of breast cancer among various ethnic groups. In the United States, the highest incidence is observed in White women of European descent. Most of the current knowledge about genetic risk factors also derives from this group and the understanding of genetics is much more limited in the Black, Hispanic and American Indian populations. Results of studies of BRCA1 and BRCA2 mutations indicate a higher incidence of such mutations among women with Ashkenazi Jewish heritage. In fact, a single BRCA1 mutation (found during mutation) can be found in as many as 1% of Ashkenazi Jewish women. Founder mutations have also been identified in several other ethnic groups located in Russia, Hungary, Israel, France, Belgium and Scandinavia.

Reproductive Risk Factors

The risk of breast cancer is 30% to 50% higher for nulliparous women than it is for parous women. The earlier the age of first term pregnancy, the lower the risk. There is a 20% to 30% greater risk of breast cancer for women who have their first full-term pregnancy after age 35 as compared with nulliparous women. Early onset of menarche, late onset of menopause and greater number of years with ovulatory cycles have all been associated with an increased risk of breast cancer. Findings from some studies suggest that high parity also has a protective effect above and beyond that of an early first pregnancy.

Socioeconomic Class

Breast cancer is found more frequently among women of higher economic class than of higher educational status. This finding is probably related to lifestyle factors such as diet and age at first childbirth.

Exogenous Hormones

Current use of estrogen replacement therapy by women who have used estrogen for a long time has been associated with a modest increase in risk; use of combined estrogen and progesterone containing preparations increases the risk several fold.[11,12] However, risk decreases upon discontinuation of hormone replacement therapy and no increase in risk can be identified five years after the cessation of treatment.

(continued)

Diet

Many studies have attempted to establish a correlation between the risk of breast cancer and dietary intake of animal proteins, total calories, animal fat, fiber and micro-nutrients.[13,14] Most of the studies are more or less sophisticated epidemiologic studies of techniques, but essentially all were retrospective in nature. There are findings from some earlier studies suggesting that increased caloric and saturated fat intake might be correlated with increased risk of breast cancer. The results of more recent and definitive studies have not supported this hypothesis. The influence of dietary fiber intake on risk and the subject of several ongoing laboratory and epidemiologic studies, more than minimal alcohol intake (one or two drinks per day or 12-24 grams per day, or 30-60 ml per day) is associated with an increased risk; this linear correlation has been a reproducible finding across the majority of studies.

Ionization Radiation

Repeat exposure to radiation such as fluoroscopic chest x-rays, radiation therapy for postpartum mastitis and dermatologic or arthritic conditions is definitely linked to a greater risk of breast cancer with a demonstrated correlation with dose. The risk is 10-fold or greater for long-term survivors of Hodgkin's disease previously treated with radiation therapy. Intensive mammographic surveillance and regular physical examination of the breast is recommended for such women. However, the risk as a result of common diagnostic and radiographic procedures is minimal and of theoretical importance only.

Environmental Factors

Cigarette smoking is a controversial risk factor. Some studies have found no correlation with risk whereas others have. The findings of recent report suggested that smoking increased risk of premenopausal women but had a protective effect for postmenopausal women. There is much interest in determining whether other occupational and environmental exposures influence risk and several major prospective studies are ongoing around the world. However, no definitive correlation with any environmental factors has been documented to date.

Combinations of Factors

Each individual factor independently influences the risk of breast cancer. How these various risk factors interact and how to combine them for optimal assessment of risk is less well established. Using statistical methodology to group several risk factors, some investigators have developed modeling techniques to enhance the sensitivity and predict a value of risk assessment **(Table II).**

Table II: Risk Model and Associated Relative Risks*

Risk Factor (Code No.)	No. of Relatives with Breast Cancer	Associated Relative Risk	No. of Cases (N=2,852)	No. of Controls (N=3,146)
Age at Menarche (yrs.)				
>14 (0)	-	1,000	790	926
12-13 (1)	-	1,099	1,554	1,735
<12 (2)	-	1,207	508	485
No. of Previous Breast bxs				
Age <50 yrs.				
0 (0)	-	1,000	635	794
1 (1)	-	1,698	113	93
>2 (2)	-	2,882	66	24
Age >50 yrs.				
0 (0)	-	1,000	1,551	1,817
1 (1)	-	1,273	312	300
>2 (2)	-	1,620	175	118
Age at First Live Birth (yrs.)				
<20 (0)	0 (0)	1,000	167	285
	1 (1)	2,607	44	40
	>2 (2)	6,798	8	0
20-24 (1)	0 (0)	1,244	708	1,042
	1 (1)	2,681	208	123
	>2 (2)	5,775	25	5
25-29 or nulliparous (2)	0 (0)	1,548	986	1,106
	1 (1)	2,756	247	178
	>2 (2)	4,907	46	20
>30 (3)	0 (0)	1,927	307	291
	1 (1)	2,834	87	50
	>2 (2)	4,169	19	6

*Relative risk compared with an individual of the same age without any risk factors is estimated by determining the person's associated relative risk for the age of menarche, number of previous biopsies and the combination of age at first live birth and the number of relatives with breast cancer and multiplying these three numbers together.

Modified with permission from Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst. 1989;81:1879-1886

The modified GALE model is widely used in the United States and Western Europe for individual risk assessment and determination of eligibility for chemo prevention trials. In that context, its clinical utility has been confirmed in White North American populations, although its applicability of other ethnic groups and cultural environments has not been established. As other risk factors are validated and as molecular markers predictive of risk are developed, these models will need to be updated and have prospective validation.

Screening

In several clinical trials, screening mammography was shown to reduce the breast cancer-related mortality rates by 20% to 39% for women 50 years of age and older. In an analysis of 13 prospective randomized trials, a 26% reduction in the relative risk of breast cancer-related mortality was found with screening mammography for women 50-74 years of age.[16,17] For decades there has been controversy surrounding the standard screening recommendations for breast cancer because the published randomized trials are plagued by inconsistent quality of imaging, blood study design or execution, insufficient duration of follow-up and problems regarding leadtime bias. Unfortunately, additional randomized trials will never be performed; we are limited by current data and hand. The effect of mammographic screening on breast cancer mortality among women 40-49 over older than age 70 is less robust. An evaluation of eight randomized trials demonstrated a 50% reduction in breast cancer mortality with screening among women age 39-49, however, no strong data exists to provide a statistical benefit with screening women older than 70. The optimal interval for mammographic screening is not known. The American Cancer Society (ACS), recommends continuation of mammograms regardless of a woman's age, as long as she does not have serious, chronic health problems such as congestive heart failure, end-stage renal disease, chronic obstructive pulmonary disease and moderate to severe dementia. Age alone should not be the reason to stop having regular mammograms. ACS also supports annual imaging beginning at age 40. The recommendation is generally accepted by many experts in the field.

The sensitivity of screening mammography is somewhat lower for patients younger than 50 years as a result of the higher frequency of dense breast tissue in younger women. It is well established that mammography is less sensitive for dense breasts. Studies suggested that dense breasts are not only a function of young age but also related to hormone replacement therapy or familial or genetic components. Dense breasts represent a risk factor for breast cancer. Despite these considerations, published reports show that for breast cancers found during systematic screening of women between 40 and 49 years of age, the average tumor size is smaller and the fraction of node negative disease is greater than for unscreened controls.

These results have been advocated as reasons to propose screening even in the absence of significant reductions in the relative risk of death in randomized studies.

Advocates of screening mammography for younger women have pointed out that the incidence of breast cancer is much lower among women younger than age 50; therefore, the statistical power of published randomized trials for screening for women younger than the age of 50 was insufficient. Even after pulling all the data involving women younger than 50 years who participated in randomized trials, the power of the observation would still be insufficient to detect a 15% to 30% reduction in the relative risk of death. There is no prospective information about the effects of screening high-risk women such as patients with familial breast cancer, BRCA1 and BRCA2 mutations or the presence of other risk factors, however, because the disease tends to develop at an early age in patients with a strong family history, most experts recommend that women at high risk should begin having screening mammography at approximately age 25. Other experts have suggested that regular screening should begin five years earlier than the age at which the first case of breast cancer developed in a first degree relative. Because of the issues related to dense breasts and relative lack of sensitivity of mammography in this situation, other imaging modalities are under evaluation. Recent reports suggest that for women at high risk on the basis of family history of BRCA1 and BRCA2 mutations, MRI detects mammographically occult disease that is also undetectable by physical examination. Among patients with BRCA mutations, screening mammography can miss more than 50% of all breast cancers. Supplementing mammography with MRI has been shown to improve the sensitivity from 25-59% seen with mammography, to 80-100% when MRI is added. The specificity of combined mammogram and MRI is lower (73% -93%) than the specificity of mammography alone. Annual MRI screening among BRCA carriers has been shown to detect more interval cancers in early stage cancers compared with women not screening with MRI.

Prognostic Factors

Once the diagnosis has been established and the prognosis estimated,

(continued)

treatment planning proceeds. To a large extent, the characteristics of the tumor and patient preferences will guide the initial approach. Most early breast cancers are treated with an initial surgical intervention that is designed to remove the primary breast tumor. Axillary nodes are usually staged using either a sentinel lymph node biopsy or a level 1 and 2 axillary lymph node dissection. The size of the primary tumor in relation to the size of the breast, the presence of additional foci of cancer or mammographic abnormalities and the patient's preference for a total mastectomy or incisional biopsy determine which approach the oncologist would use.

Determinants of Local Therapy

Tumor Size

Small tumors lend themselves to partial breast excision because removal of a small tumor leaves the shape and size of the breast almost intact, therefore offering excellent cosmetic results. The size of the breast is also an important consideration, thus even relatively small tumors in very small breasts may require the excision of a substantial portion of the gland leaving unsatisfactory cosmetic results. A mastectomy is often preferable in these cases, especially when associated with breast reconstruction. Defining the size of a breast lesion is sometimes difficult, especially for tumors that are diffuse, stellate and not encapsulated. In these cases, the initial excision is often carried out with positive margins that require excision of additional tissue. Not uncommonly, these neoplasms require mastectomy anyway. High quality imaging using mammography and MRI is critical for optimal preoperative assessment and treatment planning. The administration of preoperative chemotherapy to patients with large breast cancers often result in a sufficient reduction in tumor extent to convert a mastectomy candidate into a candidate for breast conserving surgery.

Extensive Intraductal Component

An extensive intraductal component is often a manifestation of multifocal disease. In these cases, invasive and noninvasive cancers are associated. The presence of extensive intraductal cancer was proposed as an adverse risk factor for local recurrence following breast conserving surgery. More recent and definitive analysis suggested that an extensive intraductal component has

minimal or no adverse prognostic value and that all margins of resection are histopathologically tumor free.

Extensive Lymphatic Invasion

Lymphatic invasion within the breast, especially dermal lymphatic invasion, is one of the hallmarks of aggressive and diffusely growing malignant tumors such as inflammatory breast cancer. Tumors with extensive lymphatic or lymphovascular invasion seldom lend themselves to breast conserving surgery and the predominant local treatment is radiation therapy combined with total mastectomy or chemo-radiation therapy combined with total mastectomy. Extensive lymphovascular invasions are also associated with a high risk of systemic dissemination and therefore systemic therapy is an integral part of the treatment management.

(continued)

Age

Women younger than age 35 have an increased risk of local recurrence in the breast after optimally carried out breast conservation surgery. Although breast cancer in the very young is associated with various adverse prognostic indicators (ER negativity, poorly differentiated tumors, high proliferative fraction, etc.), it may serve as a surrogate marker for those indicators. In multivariate analyses, young age remains as an independent adverse prognostic factor.

Determinants of Adjuvant Therapy

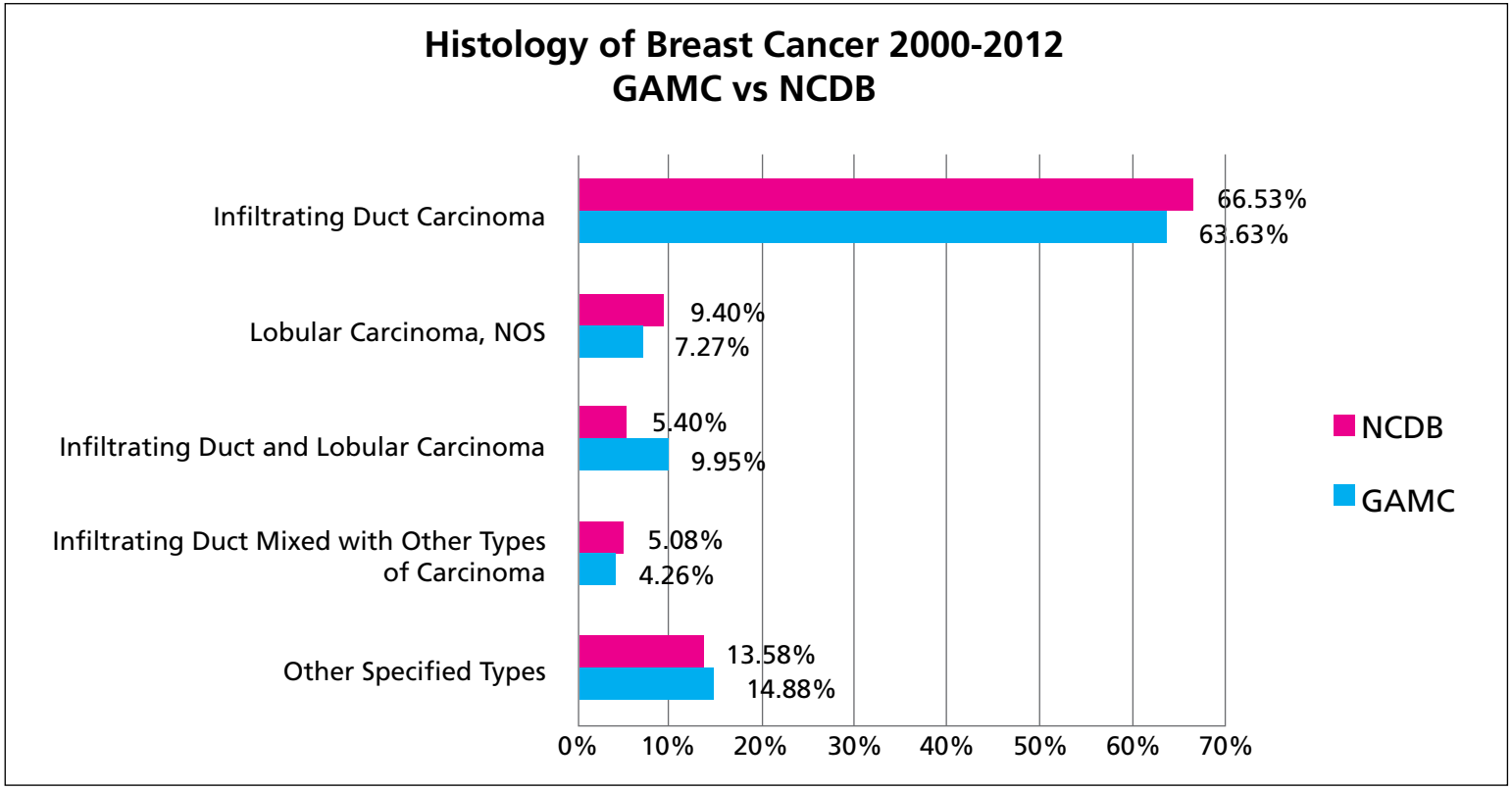
After definitive surgical resection and complete pathologic assessment, several tumor characteristics are used as the important prognostic indicator to determine the need for additional therapy.

Axillary Lymph Node Involvement

Involvement of the axillary lymph nodes still remains the most reliable and reproducible prognostic indicator for primary breast cancer. In general, 50-70% of patients with positive lymph nodes would have a relapse in the absence of systemic therapy, whereas only 20-35% of patients with negative lymph nodes are expected to relapse after local regional treatments. Each additional positive lymph node identified increases risk of recurrence and metastases by several percentage points. Thus, the risk is greater for patients

(continued)

GRAPH 2



*Source: NCDB, Commission on Cancer, ACS, Benchmark Reports. (NCDB N=1589 Hospitals)

with 4-10 lymph nodes than for patients with 1-3 lymph nodes and the probability of recurrence of metastases is more than 80% for patients with 10 or more positive nodes. The results of clinical studies have demonstrated that lymph node negativity is reliable only if at least 10 but preferably 15 axillary lymph nodes are removed and examined. Both macrometastases and micrometastases in the lymph nodes have similar prognostic significance.

The development and adoption of sentinel lymph node mapping and biopsy have changed the practice of both surgery and pathology. Patients with clinically negative lymph nodes are candidates for sentinel lymph node biopsy. With only 1-3 nodes to process, the pathologist is able to perform multiple sections of each lymph node and apply in addition to H&E stains for cytokeratin to identify small microscopic metastatic deposits. The increased number of sections and the use of immunohistochemistry contribute to the higher detection rate of micrometastases within the sentinel lymph nodes.

Tumor Size

Tumor size has prognostic significance for the determination of the potential need for adjuvant therapy. The size of the tumor is directly correlated with the risk of recurrence or metastases. Tumor size adds little to the determination of prognosis for patients with node positive breast cancer. However, for patients with node negative disease, tumor size is often one of the main prognostic indicators. The determination of tumor size should be on the basis of invasive component only and should include all three dimensions.

Histologic Type

Most invasive breast cancers are ductal type (Graph 2). The prognosis of ductal and lobular cancers are similar enough to prompt the same treatment modalities. Several less common types have more favorable prognosis. Use of histologic subtypes include pure tubular, mucinous, or colloid and papillary cancers as well as all noninvasive breast cancers.[22] These cancers are usually small and found in node negative stage. The more favorable prognosis of these histologic types supports the use of breast conserving therapy and often justifies the omission of adjuvant systemic treatment. Thus, noninvasive breast cancers do not require adjuvant systemic therapy, although adjuvant tamoxifen is offered to reduce the risk of a second primary breast cancer and tubular, colloid and papillary cancers, or cancers smaller than 3 cm are optimally treated without systemic adjuvant therapy. Pure medullary cancers also are considered to have a better prognosis than ductal cancer although not as favorable as tubular or colloid types. However, atypical medullary cancers or mixed medullary and ductal cancers have prognosis similar to prognosis for the common varieties of ductal and lobular cancers.

Histologic Grade Or Differentiation

The clear definition of histologic differentiation grades led to the recognition that those grades had reproducible prognostic significance. Nuclear grade is similarly useful, although histologic grade might be the more reliable prognostic indicator because it includes not only cellular but also tissue related criteria. Smaller tumors are more often well differentiated whereas larger tumors are frequently poorly differentiated. Poorly differentiated tumors have a greater risk of local recurrence and their association with a young age or other adverse factor may indicate that a mastectomy is a preferred local treatment. However, it is not universally accepted as a contraindication to breast conserving surgery. Tumor grade or differentiation are also associated with other prognostic indicators such as ER expression, ER estrogen receptor expression, progesterone receptor expression, HER2/neu status and S-phase fraction.

Markers Of Proliferative Capacity

Measures of proliferative rates of malignant tissues have strong prognostic value for breast cancer. The proliferative capacity of the malignant cell can be assessed by several techniques including mitotic indices, methyndamine labeling index or S-phase fractions. KI-67 has been extensively evaluated and found to correlate strongly with the results of S-phase fraction determination and therefore long term prognosis. Cyclin D1 is frequently overexpressed in breast cancer.[23] Multiple retrospective analysis and clinical trials have shown that its overexpression is correlated with an increased

(continued)

risk of relapse and death following curative treatment of primary breast cancer. Cyclin E was recently reported to be a marker of adverse prognosis for primary breast cancer. The short form of this protein was identified in both the concentration of the short form as well as the total concentration of cyclin E correlated with high risk of relapse, metastases and death.[24]

Steroid Receptors

Both the estrogen and progesterone receptors have been extensively studied in patients with primary breast cancer.[25] Both estrogen and progesterone receptors clearly have prognostic value, although their ability to discriminate between low risk and high risk patients is limited. Whereas patients with ER positive tumors tend to have better short term, disease free and overall survival rates than do patients with ER negative tumors, the difference between the two groups tends to diminish or even disappear with time. Recent analysis has suggested that the hazard rate for recurrence is greater for ER negative tumors during the first three to four years, but beyond this period of time, the hazard rate of ER positive tumors exceeds the rate for ER negative tumors. The progesterone receptor appeared in some studies to be more a value of prognostic indicator than the ER. Evaluation of both receptors previously carried out mostly by lag and binding assays is currently done by immunohistochemical or immunocytochemical methods with a high degree of reliability.

The optimal indication of steroid hormone receptors is not for determining prognosis but for predicting response after systemic therapy and therefore the selection of optimal adjuvant systemic treatments.

HER2/neu

HER2/neu is a normal gene that is amplified or overexpressed in 20-30% of breast cancers.[26] Gene amplification and protein overexpression correlates strongly, although single copy overexpressing is reported in approximately 25% of patients with breast cancer who have HER2 overexpressing tumors. The transmembrane protein P185 has intrinsic tyrosine kinase activity and belongs to the family of type 1 protein tyrosine kinase growth factor receptors. HER2 amplification overexpression is associated with an increased risk of relapse and shorter survival in most reported studies. HER2 overexpression amplification is also considered to be a marker of relative resistance to endocrine therapy with tamoxifen, radiation therapy and chemotherapy, and some reports suggest increased sensitivity to anthracyclines and perhaps taxanes. HER2/neu expression can be tested with immunohistochemical or cytochemical techniques whereas amplification is usually assayed by fluorescence in situ hybridization (FISH).

Gene Expression Signature

Differential gene expression profiling for breast cancer has produced several validated tests to assess the risk of both local and systemic disease recurrence among breast cancers with a more favorable profile (i.e. hormone receptor positive disease). They have added substantial information about prognosis for the higher risk subtypes, such as HER2/neu positive or hormone receptor negative breast cancers.

The 21 gene recurrence score known as "Oncotype DX " was developed from patients with node-negative, ER positive disease enrolled in the NSABP B 14 clinical trial which randomly assigned patients to tamoxifen adjuvant therapy or placebo. This is a widely used prognostic test in the United States.

The recurrence score is used as a continuous function and assesses residual risk of systemic recurrence among women with ER positive breast cancer treated with tamoxifen. The risk of recurrence is classified as low risk, intermediate risk and high risk. The prognostic value of this model has been validated among patients treated with Ai's and combination chemotherapy for node-negative or node-positive disease. The 21 Gene RS has also been shown to predict risk of local recurrence, regardless of administration of tamoxifen or chemotherapy. A prospective clinical trial will refine the utility of this test, especially among breast cancer classified as intermediate risk.

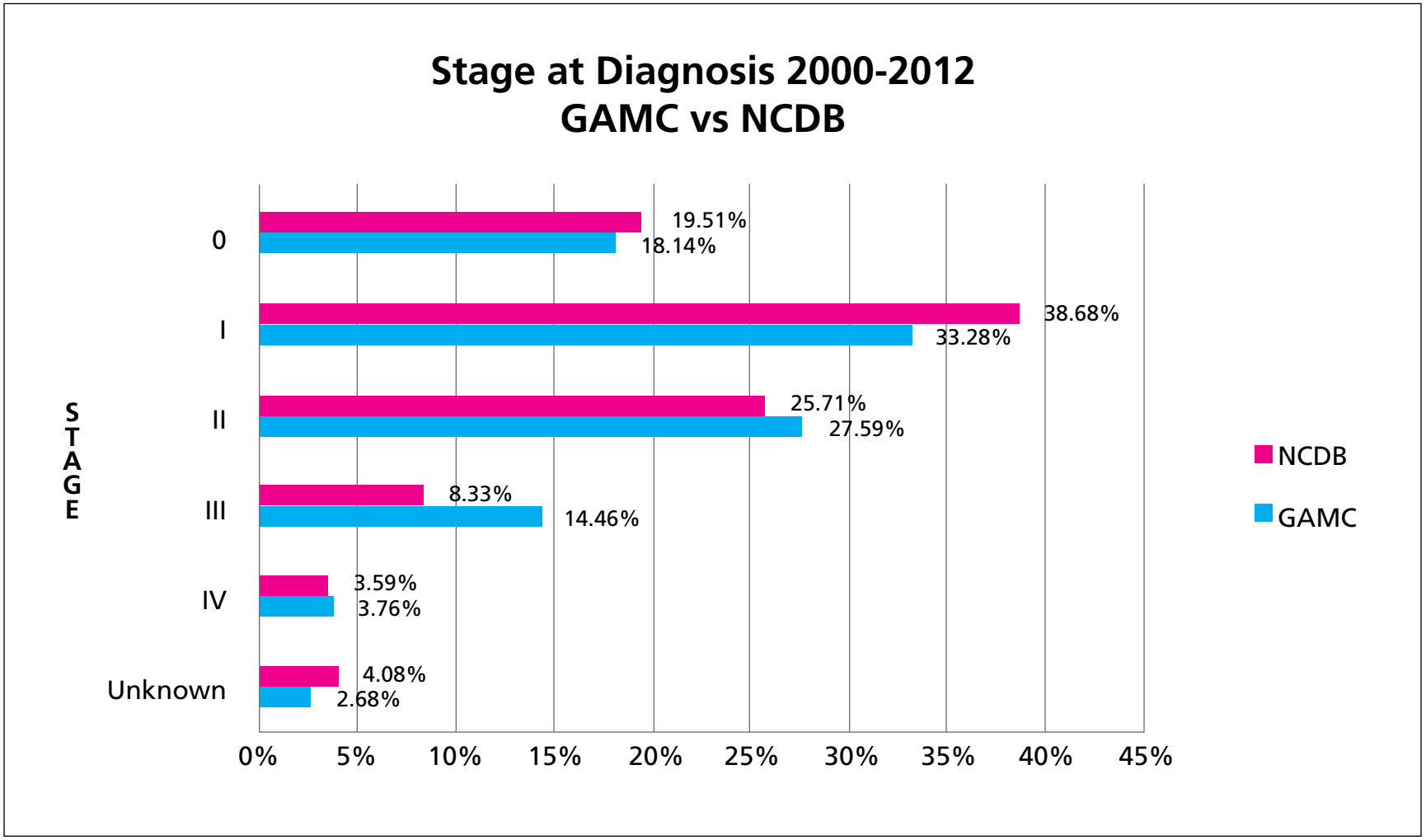
Staging

Staging classifications were designed to identify prognostically distinct subgroups of patients and to select on the basis of risk the optimal therapeutic strategy. Over the past three decades, the TNM classification system jointly developed and periodically updated by the American Joint

Commission On Cancer and the Union Internationale Contre Le Cancer was universally adapted. The TNM staging system is based entirely on anatomic imaging and histopathologic measurements and evidence of dissemination without including any of the mono prognostic factors described previously.[27]

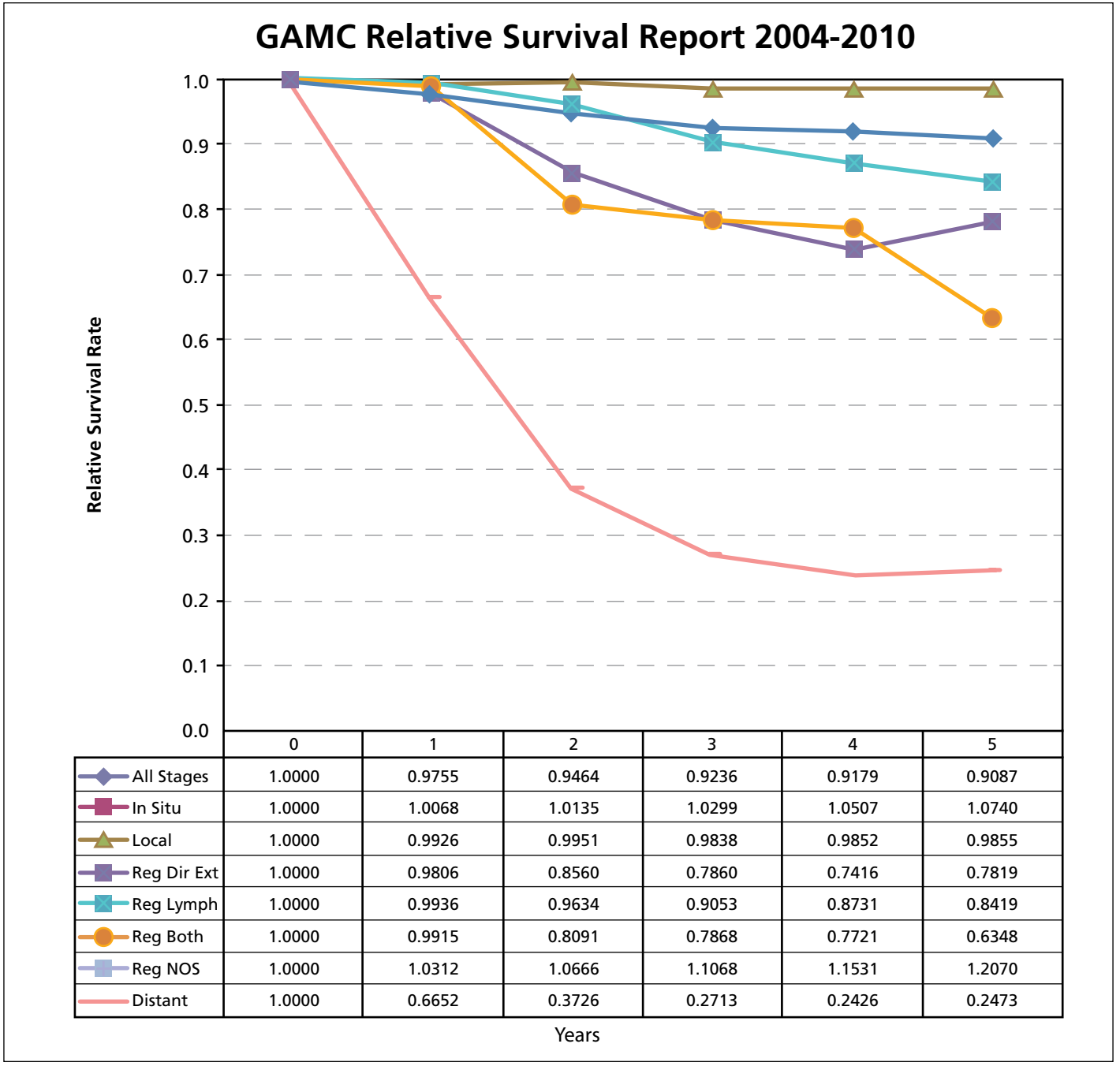
When comparing stage at diagnosis of patients at GAMC versus the United States (NCDB), we see very close similarities (Graph 3).

GRAPH 3



*Source NCDB, Commission on Cancer, ACS, Benchmark Reports. (NCDB N=1589 Hospitals)

GRAPH 4



	0	1	2	3	4	5
All Stages	1.0000	0.9755	0.9464	0.9236	0.9179	0.9087
In Situ	1.0000	1.0068	1.0135	1.0299	1.0507	1.0740
Local	1.0000	0.9926	0.9951	0.9838	0.9852	0.9855
Reg Dir Ext	1.0000	0.9806	0.8560	0.7860	0.7416	0.7819
Reg Lymph	1.0000	0.9936	0.9634	0.9053	0.8731	0.8419
Reg Both	1.0000	0.9915	0.8091	0.7868	0.7721	0.6348
Reg NOS	1.0000	1.0312	1.0666	1.1068	1.1531	1.2070
Distant	1.0000	0.6652	0.3726	0.2713	0.2426	0.2473

The five-year relative survivals (Graph 4) (CA Cancer J Clin 2015; 65:22 for United States data) at all stages was 91% at GAMC versus 89% in the United States; localized disease 99% at GAMC versus 99% in the United States, regional lymph disease 87% at GAMC versus regional 85% in the United States, distant disease was 26% at GAMC vs 25% in the United States.

Stage 0 (noninvasive disease)

Stage 0 refers to a noninvasive breast cancer or DCIS. This stage used to be diagnosed as a palpable mass; since adoption of screening mammography, DCIS is usually a mammographic finding. It can be optimally treated by performing a total mastectomy; the failure rate of treatment is less than 2%. With total mastectomy, there is a 97-98% long-term, disease-free survival for patients with noninvasive breast cancer.

When comparing stage at diagnosis of patients at GAMC versus the United States, we see very close similarities (Graph 3).

However, because more advanced invasive cancers are treated with breast conserving therapy, clinical trials were conducted to determine whether breast conserving therapy would be appropriate for DCIS. The results of the two largest randomized studies showed that lumpectomy and radiation produced long-term results identical to the results obtained after a total mastectomy. Therefore it is now generally accepted that for many cases of DCIS, a lumpectomy followed by radiation therapy to the breast represents the optimal treatment option.[28] Several studies are investigating whether radiation therapy can be omitted for patients with small, unicentric, low-grade disease with wide negative surgical margins.[29] In a large clinical trial (NSABPB24) the value of adding adjuvant tamoxifen to lumpectomy and radiation therapy was assessed. The results showed that tamoxifen reduced the risk of local recurrence in second primary breast cancer to a significant degree. Because mortality after optimally treated DCIS is rare, no effect of tamoxifen on mortality was detected.

Stage I

Most patients with Stage I disease, especially patients with unifocal neoplasms, are excellent candidates for treatment with lumpectomy combined with radiation therapy. For patients with specific contraindications for breast conserving surgery, total mastectomy is the treatment of choice. It is estimated that 50-80% of Stage I breast cancers can be treated optimally with lumpectomy and radiation therapy.[30] However, only 30-60% of patients with Stage I disease will receive that treatment in the United States, with major geographic variations occurring throughout the country. The rate of breast conserving therapy is highest in the northeast and pacific coast regions and lowest in the south and southeast regions, with an intermediate rate in other areas of the country. There are a few absolute contraindications for breast conserving therapy and the choice between it and the mastectomy is based on an acceptable tradeoff between local control and cosmesis. Some experts believe that breast conserving surgery without radiation might be a satisfactory alternative for patients, especially patients who are elderly with very small well-differentiated and ER positive tumors, if wide negative margins are obtained. However, the presumption remains to be tested in appropriately controlled clinical trials.

It is now generally agreed that Stage I breast cancers larger than 1 cm in maximum diameter are associated with a risk of recurrence that exceeds 10% and therefore systemic adjuvant treatments are warranted. If ER/PR status of the tumor is positive, endocrine therapy is clearly indicated. Tamoxifen or an aromatase inhibitor administered for five years to patients with hormone receptor positive tumors has been shown in multiple clinical trials and meta-analysis to reduce the recurrence by 50% for tamoxifen and 80% for aromatase inhibitors in postmenopausal females. The addition of adjuvant chemotherapy to the endocrine treatment for patients with ER positive invasive breast cancer larger than 1 cm in diameter is thought to increase the relative reduction and odds of recurrence by another 20%. For patients with Stage I breast cancer the absolute advantage added by chemotherapy is modest especially for older postmenopausal women. The systemic adjuvant therapy of choice for node negative ER negative tumors is a combination of chemotherapy, usually including an anthracycline.[31] There is ongoing controversy regarding the need for adjuvant systemic therapy for patients with invasive tumors smaller than 1 cm.[32]

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Stage II

Most patients with Stage II breast cancer having a single focus or a well circumscribed tumor and a favorable tumor to breast size ratio are excellent candidates for a lumpectomy and radiation therapy. It is estimated that 30-60% of patients with Stage II disease would be candidates for breast conserving therapy, although fewer than a half of the patients eligible have such therapy in the United States. For other patients with Stage II breast cancer who are not candidates for breast conserving therapy, total mastectomy represents the local regional treatment of choice. Patients with clinically palpable lymph nodes should have an axillary lymph node dissection level 1 and 2, whereas clinically node negative patients are candidates for sentinel lymph node biopsy. Should the sentinel lymph node be negative, no axillary dissection would be indicated. Radiation therapy is not necessary after total mastectomy for T2, N0 lesions or for patients who have up to three positive axillary lymph nodes. It is generally agreed that radiation therapy after mastectomy is indicated for patients with four or more positive lymph nodes.[32] Several recent clinical trials suggest that radiation therapy to the chest wall after surgery reduces local regional recurrence rate and decreases breast cancer related mortality. There is a favorable risk to benefit ratio from adjuvant systemic therapy for all patients with Stage II disease.[33] All patients with Stage II hormone receptor positive generally should receive appropriate endocrine therapy that includes tamoxifen, regardless of age or an aromatase inhibitor for five years for postmenopausal women and ovarian ablation for patients who are premenopausal. The three-year and four-year results on one trial demonstrated that Anastrozole reduced the risk of recurrence by 22% with patients with ER positive breast cancer and incremental benefit over the therapeutic effect of tamoxifen. In addition, the safety profile of Anastrozole was superior to that of tamoxifen, with fewer cases of endometrial cancer and thromboembolic events and gynecologic symptoms. However, patients who received this agent had more musculoskeletal symptoms and fractures than patients treated with tamoxifen. Estrogen deprivation would be expected to enhance bone resorption and therefore accelerate osteoporosis.[34]

All patients with Stage II hormone receptor negative breast cancer should be offered adjuvant chemotherapy. Anthracycline containing regimen is preferred, although recent studies have demonstrated a taxane based non-anthracycline protocol had similar results, however, larger studies are required to validate omission of anthracyclines in this setting. For patients with moderate to high-risk breast cancer, addition of a taxane to anthracycline based adjuvant chemotherapy regimen had demonstrated improvement in overall survival rates. Both paclitaxel and docetaxel were shown to improve the results obtained with an anthracycline based chemotherapy regimen and two agents have not been compared in the adjuvant setting. On the basis of individual trials and the results of the Oxford Overview, experts assert that the combination of chemotherapy and endocrine therapy administered sequentially presents optimal systemic treatment for women with Stage II or III breast cancer.

Postoperative adjuvant combination of chemotherapy has been shown to decrease the annual odds of recurrence by approximately 35% and the annual odds of death by 27% for women younger than the age of 50; for women older than 50 years, the corresponding figures are 20% and 11%, respectively.[31] If the chemotherapy regimen included anthracycline, additional reductions of 12% and 11% per odds of recurrence and death, respectively, were noted. If the regimen also contained a taxane, hazard reductions of 12-32% for recurrence and 14-24% for death were observed when compared with an anthracycline containing regimen without a taxane.[35] Although the precise calculations are not possible, it is probable that compared with no adjuvant chemotherapy, a regimen that contains an anthracycline plus taxane would reduce the annual odds of recurrence by approximately 50% for women under the age of 50, and by 30% for women older than 50; similarly the reductions in the odds of death would be approximately 40% for patients younger than 50 and approximately 20% for patients who are older. The effects of adjuvant chemotherapy appear greater for premenopausal women younger than 50 years of age regardless of hormone receptor status. However, chemotherapy appears somewhat more effective for women with hormone receptor negative tumors compared with the effects in hormone receptor positive cancer.

Clinical trials exploring the effect of the dose intense or high dose chemotherapy have not shown definite evidence of benefit. However, a large

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randomized trial exploring the effects of dose dense adjuvant chemotherapy suggested that anthracycline and paclitaxel based chemotherapy administered every two weeks with growth factor support significantly improved disease free and overall survival compared with the same drugs administered every three weeks following the conventional scheduling.[36] The dose dense regimen was well tolerated and after immediate follow up of over 48 months, no increase in toxicity was reported other than the added cost of hematopoietic growth factor. Adjuvant ovarian ablation also significantly lowers the annual odds of recurrence (25% +/- 7%) and death (24% +/- 7%) for premenopausal women. This effect of ovarian ablation is still of the same magnitude more than 15 years after the intervention. Permanent ovarian ablation does not appear necessary to obtain this beneficial effect because two to three years of ovarian suppression with a luteinizing releasing hormone analog also produces long-term alteration of the clinical course of hormone receptor positive breast cancer. Ovarian suppression with a luteinizing hormone releasing hormone analog given for two years produces results similar to chemotherapy.

Primary preoperative neoadjuvant chemotherapy was introduced into the treatment of operable breast cancer during the past two decades.[37,38] Primary chemotherapy followed by surgery and radiation therapy represents standard care for locally advanced breast cancer. The results of a randomized trial suggest that this strategy is safe and produces results equivalent to those of postoperative adjuvant chemotherapy with the same regimen for operable Stage I and II breast cancers. Most patients achieve reductions in tumor size; this effect is observed in both primary tumor and regional lymph nodes. This change increases opportunity for breast conserving surgery for patients with large primary tumors. Between 10% and 15% of women have a complete pathologic response in the primary tumor after three to four cycles of an anthracycline containing regimen; 20-30% of patients with biopsy proven lymph node metastases before primary chemotherapy have pathologically lymph nodes after neoadjuvant chemotherapy.[39] The pathologic complete response rate increases to 20-30% if the second cytotoxic regimen with incomplete cross resistance is also used.[40] Histologic evaluation of the effects of preoperative chemotherapy provides prognostic information that might be used to select additional systemic adjuvant treatments.

Stage III

Patients with Stage III breast cancer can be classified into two general categories. Some have large tumors without skin involvement or fixations in deeper tissues that are clearly operable. Others have neoplasms that are considered inoperable because skin involvement or fixation to the underlying chest wall precludes total resection with clean margins after a mastectomy or because extensive involvement of the regional lymph nodes makes the use of surgical intervention as the primary treatment futile. Patients with operable Stage III breast cancer, T3, N1 (some T3, N0), can be cared for in the same manner as patients with Stage II breast cancer. However, primary or neoadjuvant chemotherapy followed by surgical resection and radiation therapy is the preferred strategy.[41] Patients with inoperable Stage II disease usually have primary chemotherapy followed by surgical resection of residual disease, postoperative systemic therapy on the basis of the characteristics of the tumor and the extent of residual disease and radiation of the breast, chest wall and regional lymphatic areas. The strategy frequently used in the United States consists of administering 4-6 cycles of primary chemotherapy followed by either a modified radical mastectomy or lumpectomy and lymph node dissection; recent studies suggested administering a different cross resistant chemotherapy regimen such as a taxane might improve prognosis for both responders and non-responders to primary chemotherapy. Several larger prospective randomized trials are testing the value of additional chemotherapy both in the preoperative and postoperative setting. The results

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of three prospective randomized trials have shown that administering several cycles of two non-cross-resistant regimens preoperatively increases the pathologic remission rate to 20-30%; however, it remains to be determined whether such increases will translate into improvement in relapse or overall survival rates.[40,42] After completion of all chemotherapy, radiation therapy follows. This sequence might be altered in the case of insufficient response to primary chemotherapy when the tumor remains inoperable; such instances preoperative radiation therapy followed by surgical resection is a reasonable alternative. For patients who have locally advanced breast cancer and do not respond to primary chemotherapy, they often have a second line of preoperative chemotherapy or radiation followed by surgical resection. These patients clearly have less favorable prognosis with currently available treatments compared to patients who responded well to preoperative chemotherapy.

Stage IV (Metastatic Disease)

Patients with untreated metastatic breast cancer demonstrated considerable heterogeneity in the clinical course of the disease. Some have a fulminant clinical course with rapid development of metastases to multiple vital organs, resistant to therapy and death within a few months after detection of the first metastases.[43] Others have a more indolent disease course with a slow progression alternating with long periods of stability and metastases to soft tissues or bone. Progress in our understanding of the biology of breast cancer led to the identification of distinct biologically different subgroups that require specific therapeutic interventions for optimal results.

Metastatic disease should be considered an approach as a chronic illness. The goals of therapy are to palliate symptoms, prolong life, and if possible achieve a long-term, disease-free state. Upon diagnosis of metastases, the extent and location of metastatic disease must be assessed and on the basis of available clinical information, the likelihood of rapid progression which could cause vital organ failure or other catastrophic complications must be determined. In addition, the relevant therapeutic interventions on the basis of estrogen and progesterone receptor assays, HER2/neu status and the presence of comorbid conditions must be established. Patients are classified into low-risk and high-risk groups. People at low-risk include patients who had long disease-free interval and have limited metastatic disease, often located in the soft tissues or osseous sites. Some patients with limited visceral disease may also qualify. More often than not, low-risk patients are older and postmenopausal and the tumors are hormone receptor positive. Patients with these characteristics and positive ER or PR status are excellent candidates for hormone therapy as the first intervention for metastatic breast cancer. Patients with hormone receptor negative tumors might be treated with sequential single agent chemotherapy or trastuzumab.

Patients in the high-risk group often have the opposite characteristics: hormone receptor negative tumors, a short (less than 24 months) disease free interval and visceral dissemination. High-risk patients are candidates for cytotoxic chemotherapy. Patients with hormone receptor positive breast cancer without immediate life threatening disease should be offered endocrine therapy. Patients who are HER2/neu positive breast cancer should receive trastuzumab alone or trastuzumab containing treatments and patients with hormone receptor negative tumors should be offered cytotoxic therapy.[44]

The hormonal interventions used in early decades have been completely replaced by modern endocrine interventions that are more specific, selective and better tolerated. Major surgical ablative procedures to reduce the production of estrogens are of historic interest only, having been replaced by selective aromatase inhibitors such as anastrozole, exemestane and letrozole for postmenopausal women.

On the basis of modern prospective randomized trials, the probability of an objective response with first line endocrine therapy is 30-40% for patients with ER positive metastatic breast cancer. Disease stability is achieved in an additional 20-30% of patients during hormone therapy including a few minor responses.[45,46] Stable disease exceeding six months during endocrine therapy is associated with survival compared to that of patients who achieve an objective response. Therefore, it is customary to express the results of endocrine therapy both in terms of objective response rate (complete and partial remissions) and clinical benefit (complete and partial remission plus stable disease exceeding six months). On the basis of multiple randomized trials, selective aromatase inhibitors have become the first-line endocrine

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therapy of choice for postmenopausal patients. These agents are not known to have antitumor activity in women with intact ovarian function. Selective estrogen receptor modulators (SERMs), which until recently were considered the best choice for initial endocrine therapy, have been relegated to second-line therapy because of the improved therapeutic index of aromatase inhibitors. SERMS or some form of ovarian suppression or ablation compete for first-line endocrine therapy of metastatic breast cancer in premenopausal women. Choice of endocrine therapy for metastatic disease depends in part on the endocrine therapy used in the adjuvant setting and the interval between adjuvant endocrine therapy and detection of metastatic breast cancer. Endocrine therapies have not shown superiority in postmenopausal women over sequential use of single hormonal agents. The findings from a few small randomized trials and recent met- analysis of these studies suggest that the combination of ovarian suppression or ablation with a SERMS results in improved response rate, time to progression and survival compared with ovarian suppression alone. However, the controlled group did not receive both treatments in sequence leaving unsettled the question of the optimal use of these two endocrine approaches.

Cytotoxic chemotherapy became an integral part of management of breast cancer in the early 1970's. Several single agents produced objective responses in 20-60% of patients with previously untreated metastatic disease. The taxanes and anthracyclines are considered most effective single agents with platinum compounds, alkylating agents, vinca alkaloids and miscellaneous agents following. Response duration after a single agent therapy are short, in the range of four to six months. Combination chemotherapy regimens improves higher overall response rates exceeding 50% of the most cases with remission durations that ranged from 8-12 months and survival that approached two years. Anthracycline based combinations appeared to be more effective than CMF in several randomized trials producing not only higher overall complete remission rates but in some studies significant prolongation of survival as well. Three meta-analysis of these trials confirm the superiority of anthracycline containing regimens when

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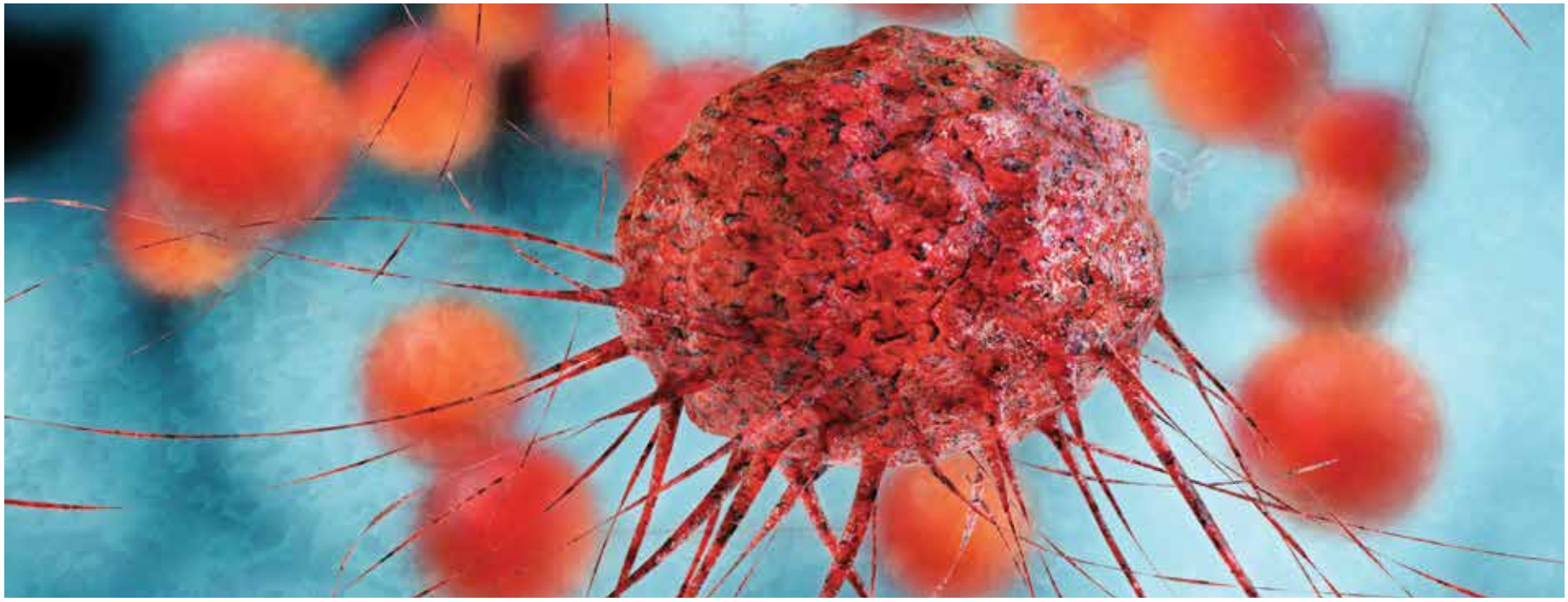

compared with CMF. Paclitaxel and docetaxel are active in previously treated patients with metastatic breast cancer producing response rates in the 30-50% range for patients with anthracycline resistant disease.[47] The activity of these agents in patients with chemotherapy naive metastatic breast cancer is equivalent or superior to that of the anthracyclines made comparable to that of several older drug combinations (CMF or FAC). Anthracycline and taxane combinations are somewhat more active than previously tested anthracycline containing combinations without taxanes producing higher overall response rates and in some trials longer times to disease progression. However, no survival benefit has been reported in the majority of randomized trials.

Combination chemotherapies associated with overall response rates ranging from 40-90%, whereas modern single agent therapies produce overall response rates to first line chemotherapy in the 20-50% range. In general, patients with good performance status, normal organ function and limited extent of disease are more likely to respond than patients with opposite characteristics. Only 15-20% of patients will achieve a complete remission, after a combination chemotherapy and a smaller percentage after single agent treatment. Progressive disease will develop within the subsequent five years for most patients who achieve a complete clinical remission but approximately 17% of all complete remissions achieved with first-line anthracycline containing regimens more than 10 years.[48] Some of these patients remain in an unmaintained complete remission for periods that now exceed 20 years.

Patients who are only candidates for chemotherapy that are asymptomatic and have nonlife threatening disease can be managed successfully with single agent therapy administered sequentially instead of using simultaneous combinations. In this manner, the benefit of each individual agent is used but overlapping added toxicity is avoided. There are many other cytotoxic options for patients who have breast cancer who do not respond to first-line therapy and for patients in whom disease progress is after an initial response period. For patients who have not been exposed to taxanes or anthracyclines in the adjuvant setting or in the front-line therapy, regimens based on these agents would be a treatment of choice. For patients who received an anthracycline containing adjuvant chemotherapy regimen, taxanes are considered an optimal therapeutic option for metastatic disease. For patients previously exposed to both anthracyclines and taxanes, other available choices include capecitabine, vinorelbine and gemcitabine either alone or in combination. Capecitabine is a remarkable addition to the treatment of breast cancer. Administered orally it is well tolerated by most patients and produces lengthy responses as well as extended periods of stability associated with excellent quality of life. Cisplatinum, carboplatin, methotrexate, and irinotecan, mitomycin-C and mitoxantrone are also available. A large number of two-drug and three-drug combinations have been reported to have substantial anti-tumor activity often comparable to leading combinations. Among these, the combination of taxanes with platinum salts also have shown activity similar to other commonly used combinations of anthracycline containing regimens.

Controversy continues regarding the optimal duration of cytotoxic therapy. Most oncologists consider it unnecessary to continue cytotoxic therapy until the onset of progressive disease. It is also known from the results of randomized trials that three cycles of chemotherapy are inadequate and that patients who receive six or more cycles have a higher response rate, longer duration response and a better quality of life than patients treated with shorter chemotherapy programs. A meta-analysis of clinical trials addressing the duration of chemotherapy suggested that treatment until the progress of disease was associated with longer time to progression and survival. It is probable in view of heterogeneity of breast cancer that there is no optimal therapy for all patients in that different patients require different durations of treatment. Many oncologists have administered chemotherapy until a maximum response is achieved and they administer a few additional cycles before discontinuing therapy. Achieving a maximum response may require only one cycle of therapy whereas some patients may need 8-10 cycles, especially patients with bone or liver metastases. Because a maximum response can be known only retrospectively, treating until maximum response usually requires four additional cycles beyond the actual number needed to achieve maximum response.

During the past 12 years, multiple clinical trials have explored the contribution of high dose chemotherapy with autologous hematopoietic stem cell support to the systematic treatment of breast cancer. Whereas uncontrolled trials suggested improved anti-tumor activity for high dose

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chemotherapy, prospective randomized control trials failed to confirm these findings. Currently there is no demonstrated indication for high dose chemotherapy for any stage of breast cancer.

Breast cancer commonly spreads to osseous structures. Bone metastases will develop during the clinical course of illness for up to 80% of patients with metastatic breast cancer. Bone metastases are a frequent source of morbidity and may cause substantial disability. Radiation therapy is commonly employed for palliation of painful metastatic deposits or to weightbearing bones with impending fractures. Patients with bone metastases also receive systemic treatments including hormone therapy and chemotherapy. Findings from several randomized clinical trials conducted during the past decade demonstrated that the combination of bisphosphonates with chemotherapy or hormone therapy delays the appearance and reduces the severity of bone related complications.

Triple Negative Disease

Triple negative breast cancer which accounts for 10-15% of all breast cancer, is more common among young and/or black women and is usually high-grade. Unlike other subtypes of breast cancer, the biology of triple negative breast cancer is such that its prognosis does not correlate as closely with tumor size or nodal involvement. Recent studies suggests that once one axillary lymph node is involved, additional axillary lymph node nodal involvement does not affect the poor prognosis associated with triple negative node positive disease. In addition, node negative triple negative breast cancer with tumor size greater than 0.5 cm has a high enough risk of disease recurrence and death to warrant a discussion of adjuvant chemotherapy. The addition of anthracyclines has improved the proportion of risk recurrence by 12% and death by 15%. These data support the use of anthracyclines for adjuvant treatment; the most commonly used combination regimen includes four cycles of Adriamycin plus Cytoxan. The addition of taxanes to anthracycline-containing regimens resulted in a 17% reduction in the relative risk of relapse and a 15% relative reduction in risk of death at five years. While there was no difference between concurrent or sequential regimens, the dose dense regimen did result in a 26% relative reduction in the risk of recurrence and 26% relative reduction in risk of death.

Elderly Patients

Because half of newly diagnosed breast cancers are detected in women age 64 and older, some special considerations for geriatric populations are in order. First, the additional life expectancy of a healthy 65-year-old in the United States is 17-1/2 years, whereas that of a similarly healthy 80-year-old woman is 8-1/2 years. Chronologic age should not be a major determinant of treatment. Comorbid conditions increase in frequency with age and tend to be the limiting factor for survival and tolerance to treatment. The 10-year survival for patients with breast cancer with no or one comorbid condition is 97%. For patients with three comorbid conditions, it is 79%. For patients with five or more comorbidities, it is 34%. Most clinical trials, whether in the adjuvant setting or for metastatic disease, were conducted with younger women, therefore, treatment decisions for geriatric patients are often made by extrapolation from the results in younger groups. The proportion of hormone receptor positive tumors increase with age; thus, endocrine therapy is equally or more successful for older patients. Chemotherapy, on the other hand, tends to have greater efficacy for younger patients or for patients with ER negative tumors. Therefore, the absolute benefit derived from chemotherapy by older patients is more modest. Older patients tend to tolerate chemotherapy well; although mild suppression is slightly more frequent and severe, infectious complications are no more common than for younger patients. Other toxic effects for chemotherapy tend to be more prominent for older patients, especially neurotoxicities and renal toxicity. Cardiac dysfunction is also more frequent among older patients, which might influence the selection of drugs. In addition, older patients have weaker social support systems and obstacles related to transportation, and lack of home caregivers are frequent. These issues are important to consider when making treatment choices.

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We Are...**Cancer Services at Glendale Adventist Medical Center**

Thank you

A special thank you to the Cancer Committee members for their dedicated leadership and tireless efforts.

Pictured at left:
Bottom Row (left to right): Melina Thorpe, RN; Sharon Feinberg, RN; Karen Brandt, RN/CNO; Cynthia Klinger, MFT; Kari Carlstrom; Jan Adduci; Allen Molina, RN; Karine Arakelyan and Irene Bourdon.
Top Row (left to right): Emillie Battig, RN; Denise Cleveland; Fernando Vazquez; Simon Keushkerian, MD; Boris Bagdasarian, DO; Sze-Ching Lee, MD; Michele Cosgrove, MD; Al Garcilazo; Tracey Sanders; Chrissy Kim; Susanna Tamazyan,RN and Linh Chen, MD.
Not Pictured: Wende Brookshire, RN; Sam Carvajal, MD; Val Emery; Juli Ji, RD; Sara Kim, MD; Arlene Matsuda, LCSW; Mark Schlesinger, MD; Lily Villalobos and Marion Watson.

Class of Case

Analytic: Cases that are first diagnosed and/or receive all or part of their first course of treatment at Glendale Adventist Medical Center.

Non-Analytic: Cases that have been diagnosed and have received their entire first course of treatment elsewhere and are first seen at Glendale Adventist Medical Center for subsequent care.

Collaboration

In order to accomplish the wide-ranging and ambitious goals involved in designing and supporting a comprehensive community cancer program, many people have contributed and continue to give their energy and expertise.

The contributions and support of the medical staff, nursing staff and many other professionals who have offered their expertise for the implementation of our cancer program throughout the year are greatly appreciated.

Special appreciation is given to all members of the Cancer Committee and the Cancer Registry for their involvement in preparing this annual report.

GLENDALE ADVENTIST MEDICAL CENTER
Telephone: **(818) 409-8000**

DEPARTMENT	EXT.
Admitting	8142
Cancer Registry	8174
Cancer Services and Radiation Therapy	8198
Clinical Trials	8009
Chaplains Office	8008
Focus on Healing	3530
Healthcare Foundation	8055
Infusion Center	8077
Ingeborg's Place Apart/Positive Image Center	8218

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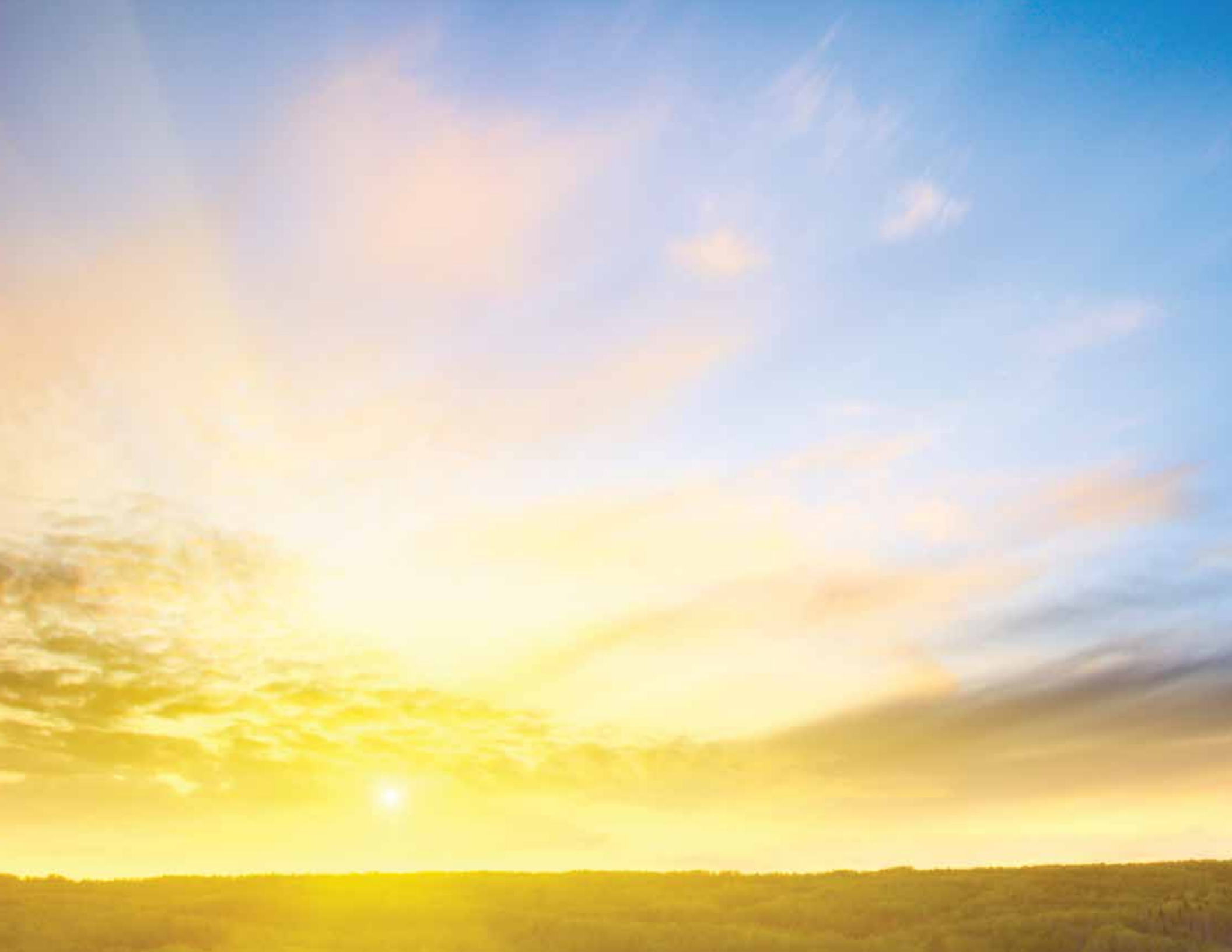

OUR **MISSION**

TO SHARE **GOD'S LOVE** WITH OUR COMMUNITY
BY PROMOTING **HEALING AND WELLNESS**
FOR THE WHOLE PERSON

Glendale Adventist Medical Center
Cancer Services
Adventist Health